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SYNTHESIS OF RICCARDIN B BY NICKEL-CATALYZED INTRAMOLECULAR CYCLIZATION

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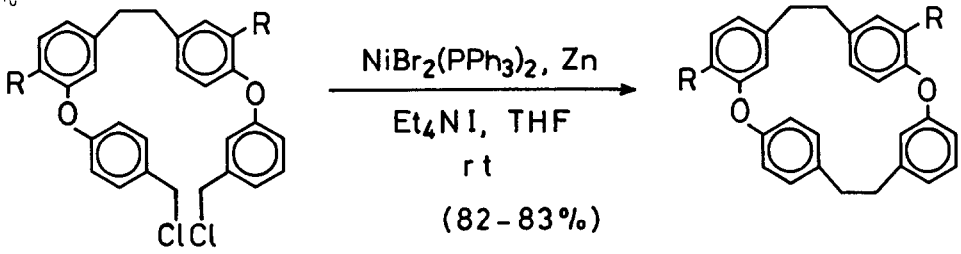
Summary: Riccardin B, a macrocyclic bis(bibenzyl) possessing cytotoxic activity, and its dehydroxy derivative were synthesized in high yields using the nickel-catalyzed intramolecular coupling of the acyclic precursors.

Riccardin B (5) is a metabolite of the liverwort *Riccardia multifida* (L.) S. Gray.[1] It is one of a relatively uncommon group of natural products having a macrocyclic bis(bibenzyl) structure. Riccardin B (5), as well as other congeners (*e.g.*, riccardin A,[1] marchantin A,[2] etc.), has been shown to exhibit cytotoxic activity against KB cells. Recently, the synthesis of marchantin A was reported by an intramolecular Wittig-Horner-Emmons reaction as the key step.[3]

We now report an efficient and short-step synthesis of riccardin B (5) and its carbon framework (2) using the nickel-catalyzed intramolecular cyclization of the acyclic precursors (1 and 3).



1: R = H
3: R = OMe

2: R = H
4: R = OMe
5: R = OH

We have recently reported the efficient reductive-coupling of alkenyl, aryl, benzyl, and phenacyl halides using the active nickel complex generated *in situ* by reduction of $NiX_2(PPh_3)_2$ with zinc in the presence of Et_4NI.[4] Although many reagents for benzyl coupling are already known, the nickel-catalyzed coupling proceeds under mild reaction conditions to give bibenzyls in good to high yields.[4b] Nickel tetracarbonyl has been employed by Corey et al. for the synthesis of macrocyclic terpenoids using the intramolecular allyl coupling.[5] However, nickel

tetracarbonyl is inapplicable to benzyl coupling because of the preferential carbonylation reaction.[6] In this communication, we show the active nickel complex generated *in situ* in the presence of Et_4NI to be an effective catalyst for the intramolecular benzyl coupling reaction.

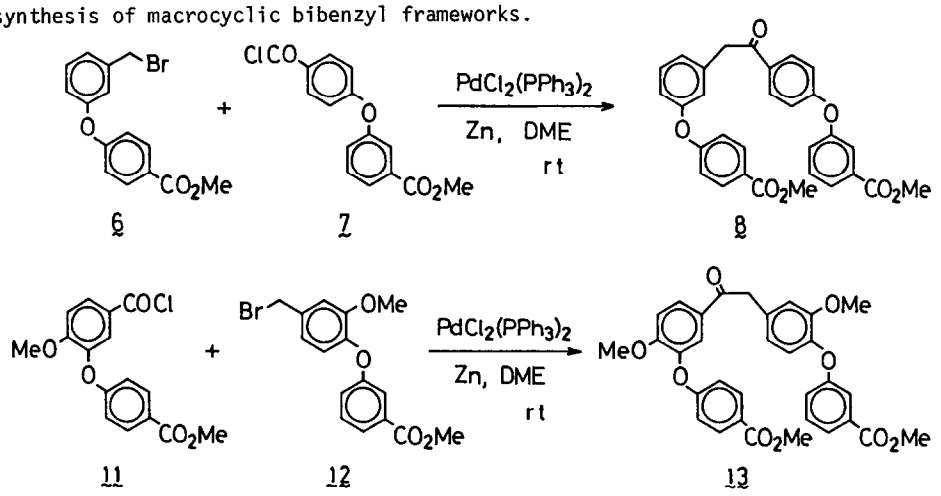
We first examined the synthesis of the carbon framework (1) which possesses the symmetrical structure (C_2-symmetry). The direct cross-coupling of benzyl bromides and acyl chlorides in the presence of a palladium catalyst and zinc powder was reported by Fujisawa et al.[7] However, in the case of *p*-methoxybenzyl bromide and benzoyl chloride, the yield of the cross-coupling product greatly decreased (13%), presumably owing to the competitive benzyl coupling of *p*-methoxybenzyl bromide. We found that this problem is easily overcome by slowly adding a solution of *p*-methoxybenzyl bromide to the reaction mixture and obtained the corresponding cross-coupling product in 67% yield. In this manner, the coupling of the bromide (6)[8] and the acid chloride (7)[9] was carried out. To a mixture of 6 (1 equiv.), $PdCl_2(PPh_3)_2$ (0.1 equiv.) and active Zn (2 equiv.) in DME was added a solution of 7 (1 equiv.) in DME over 50 min at room temperature and the mixture was stirred at the same temperature for 20 h. After the usual workup, the cross-coupling product (8, colorless needles, mp 121-122 °C) was obtained in 62% yield. Clemensen reduction of 8 with Zn-Hg / HCl afforded the diester (9, colorless oil, 83%). Reduction of 9 with $LiAlH_4$ gave the diol (10, colorless cryst., mp 88-89.5 °C, 92%), which was converted with $SOCl_2$ to the dichloride (1, colorless cryst., mp 51.5-53 °C, 70%). Although the intramolecular coupling of 1 with the active nickel complex under normal reaction conditions[4b] resulted in the formation of many polymeric substances, a successful cyclization was carried out under high dilution conditions. A mixture of $NiBr_2(PPh_3)_2$ (0.45 mmol), active Zn (4.5 mmol) and Et_4NI (0.9 mmol) in abs. THF (10 ml) was stirred for 30 min at room temperature to generate the active nickel complex. To the mixture was added a solution of 1 (0.3 mmol) in abs. THF (5 ml) over 2.5 h at room temperature. After 3 h at the same temperature, the solid was filtered off. Evaporation of the filtrate and chromatography of the residue gave the cyclic bis(bibenzyl) (2,[10] colorless needles, mp 145-145.5 °C, 82%).

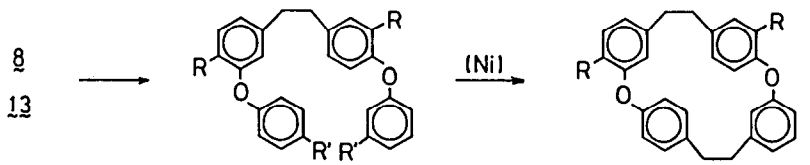
The synthesis of riccardin B (5) was successively carried out in a similar manner mentioned as above. To a mixture of 11[11], $PdCl_2(PPh_3)_2$ and active Zn in DME was added a solution of 12[12] in DME over 1.5 h at room temperature and the resulting mixture was stirred for 20 h to afford the keto-diester (13, colorless needles, mp 112-112.5 °C, 50%). Clemensen reduction of 13 (91%), followed by reduction with $LiAlH_4$ (88%) gave the diol (15, colorless oil). Treatment of 15 with $SOCl_2$ afforded the dichloride (3, colorless oil, 84%). To a suspension of the active nickel complex [prepared from $NiBr_2(PPh_3)_2$ (2 equiv.), active Zn (15 molar equiv.) and Et_4NI (4 equiv.)] was added a solution of 3 in THF over 2 h at room temperature and the mixture was stirred at the same temperature for 5 h to give riccardin B dimethyl ether (4,[1] 83%).

To complete the synthesis of riccardin B, 4 was treated with an excess of BBr_3 in CH_2Cl_2 at -78°C. The material formed (colorless prisms, mp 82-83 °C, 95%) proved to have spectral data (Mass, IR, ^1H-NMR, and ^{13}C-NMR) which nicely matched with those reported by Asakawa et al.[1]

The nickel-catalyzed cyclization of the dibromide (16) proceeded in high yield to afford

riccardin B dimethyl ether (4). The intramolecular coupling could be also carried out in benzene with 3 equiv. of $NiBr_2(PPh_3)_2$ and an excess of Et_4NI. In conclusion, the present results indicate that the intramolecular coupling using the active nickel complex is available for the synthesis of macrocyclic bibenzyl frameworks.





9: R = H, R' = CO_2Me
10: R = H, R' = CH_2OH
1: R = H, R' = CH_2Cl
14: R = OMe, R' = CO_2Me
15: R = OMe, R' = CH_2OH
3: R = OMe, R' = CH_2Cl
16: R = OMe, R' = CH_2Br

2: R = H
4: R = OMe
5: R = OH
(Riccardin B)

References and Notes

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   c) M. Iyoda, K. Sato, and M. Oda, *Tetrahedron Lett.*, in press.
   d) M. Iyoda, M. Sakaitani, A. Kojima, and M. Oda, *Tetrahedron Lett.*, in press.
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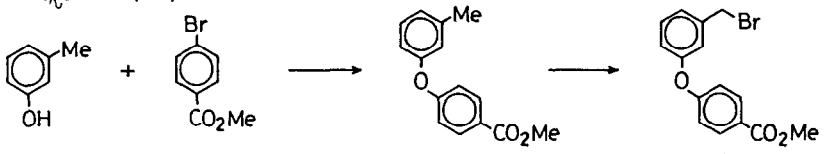
7) T. Sato, K. Naruse, M. Enokiya, and T. Fujisawa, *Chem. Lett.*, 1981, 1135.

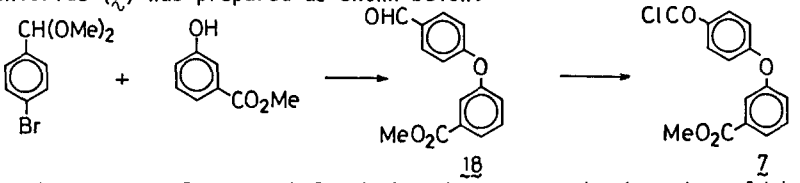
8) The bromide (6) was prepared as shown below:



17 6

The sodium salt of *m*-cresol was treated with CuCl to give the copper salt which was coupled with methyl *p*-bromobenzoate in pyridine under reflux for 20 h. After the usual workup, the coupling product (17) was obtained in 98% yield. Bromination of 17 with NBS in CCl_4 in the presence of benzoyl peroxide gave the bromide (6) in 91% yield.

9) The acid chloride (7) was prepared as shown below:

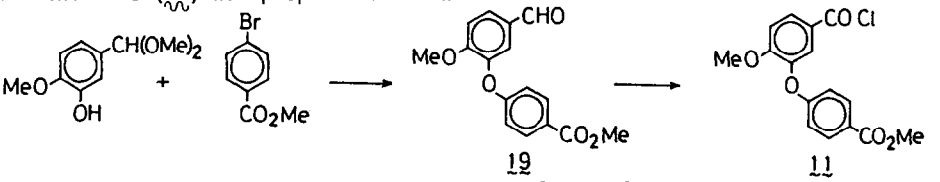


18 7

Coupling of the copper salt of methyl *m*-hydroxybenzoate and *p*-bromobenzaldehyde dimethyl acetal (pyridine, reflux, 20 h), followed by acid hydrolysis gave the coupling product (18, 63%). Jones oxidation of 18 (93%), followed by treatment with oxalyl chloride (quantitative yield) gave the acid chloride (7).

10) 2; (m/z) 392 (M^+), 287, 196; ^{1}H-NMR ($CDCl_3$) δ 7.30 (dd, J=8, 3Hz, 2H), 7.10 (dd, J=8, 1, 2H), 6.93 (dd, J=8, 3, 2H), 6.72 (d, J=9, 4H), 6.55 (d, J=9, 4H), 6.05 (dd, J=2, 1, 2H), 2.83 (br. s, 8H); ^{13}C-NMR ($CDCl_3$) δ 156.7, 154.8, 143.5, 134.2, 130.1*, 129.9, 124.8, 122.1, 119.0, 116.4*, 38.2, 37.4 (an asterisk indicates two different carbon signals overlapped).

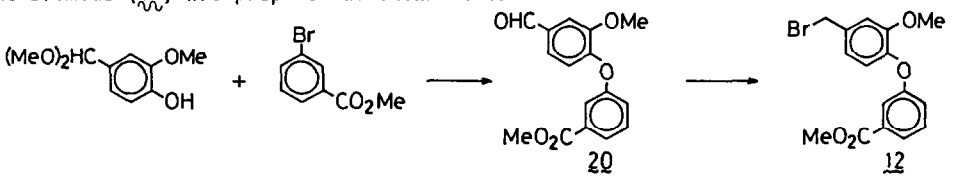
11) The acid chloride (11) was prepared as shown below:



19 11

Coupling of the copper salt of isovanillin dimethyl acetal and methyl *p*-bromobenzoate gave 19 (82%) which was converted to 11 by sequential treatment with CrO_3 and oxalyl chloride in 97% overall yield.

12) The bromide (12) was prepared as shown below:



20 12

Coupling of the copper salt of vanillin dimethyl acetal and methyl *p*-bromobenzoate, followed by acid hydrolysis gave 20 (74%) which was converted to 12 by sequential treatment with $NaBH_4$ and PBr_3-pyridine in 72% overall yield.

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