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An improved method for the synthesis of γ-DDB

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ABSTRACT

A mild and efficient method for the synthesis γ-DDB has been developed through anhydride-linker assisted intramolecular Ullmann reaction. Highly regioselective bromination of differentially protected gallate was realized by virtue of the introduction of NBS.

Families of DDB (compounds with dimethylenedioxybiphenyl group) are known for their interesting biological activities, for example, antihepatotoxic, antitumor, anti-HIV and antifungal properties.[1–4] They are also useful building blocks for access to Schisandrin-type lignans.

The synthesis of symmetrical α- or β-DDB (Fig. 1) is easily achieved through intermolecular Ullmann reaction[5] between two identical bromobenzene units.[2a,6–10] However, this approach is not suitable for unsymmetrical γ-DDB. If Ullmann coupling of the two required bromobenzene units were performed, mixtures of α-DDB, β-DDB and γ-DDB would be obtained.

A reasonable way to avoid competitive homocoupling is to build a linker between the two different coupling units, an intramolecular coupling reaction could then be realised. We previously reported an ester-linker directed intramolecular Ullmann reaction for the synthesis of γ-DDB.[11] Whilst the desired unsymmetrical product was obtained, a disappointing yield of 25% was obtained. Newman and Cella reported Ullmann reactions between coupling partners joined by an anhydride rather than ester-linker.[12] Indeed, by applying such a linker, intramolecular Ullmann reaction of **10** (vide infra) was achieved with high yield. Also, the reaction could be carried out at 60–70 °C rather than the high temperature generally required. We now report the full detail of our improved method for the synthesis of γ-DDB.

As shown in Scheme 1, regioselective bromination of 3-hydroxy-4,5-methylenedioxybenzoate **2** using 1 equiv of NBS added slowly to the reaction mixture gave bromide **3** in 79% isolated

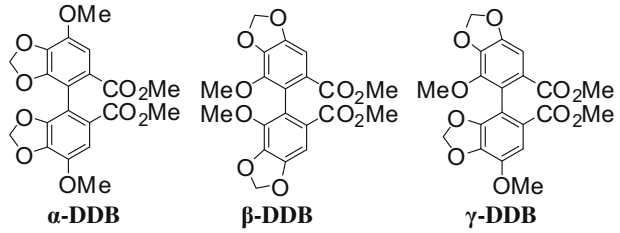
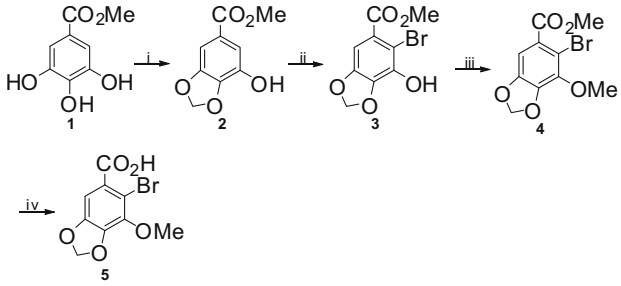


Figure 1.

yield, uncontaminated by significant amounts of the 6-brominated or dibrominated products. Methylation of the hydroxy group in **3**, followed by saponification gave **5**, the first component for the synthesis of γ-DDB. In comparison to our previous strategy for the introduction of the bromo group by application of a regioselective



Scheme 1. Reagents and conditions: (i) CH_2I_2, K_2CO_3, DMF, 40 °C, 20 h, 49%; (ii) NBS, THF, rt, 0.5 h, 79%; (iii) Me_2SO_4, K_2CO_3, acetone, reflux, 4 h, 90%; (iv) (a) KOH (aq), reflux, 5 h; (b) H^+, 95%.

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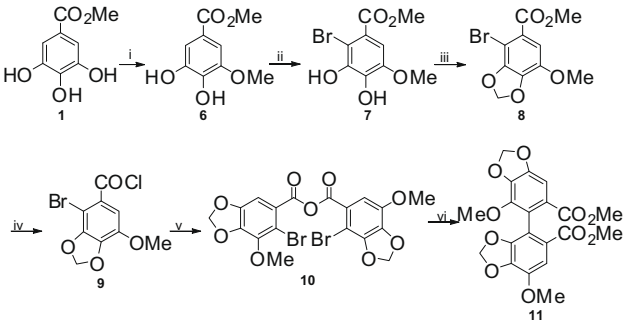

Scheme 2. Reagents and conditions: (i) Ref. 11; (ii) NBS, THF, rt, 0.5 h, 89%; (iii) CH_2I_2, K_2CO_3, acetone, reflux, 5 h, 78%; (iv) Ref. 11, 77%; (v) **5**, pyridine, THF, 0 °C, 0.5 h, 86%; (vi) (a) Cu (powder), DMF, 60–70 °C, 1.5 h; (b) KOH, MeOH/H_2O, reflux, 20 min; (c) H^+; (d) MeOH, concd H_2SO_4, reflux, 10 h, 40% over the four steps.

nitration–reduction-Sandmeyer reaction sequence,[11] use of NBS as the regioselective bromination agent gave a greatly improved yield (79% vs 18%).

Mono-methylation of triol **1** gave **6** (Scheme 2), which was brominated in the 6-position with NBS to give compound **7** in excellent yield. In the production of **3** and **7**, we observed bromination with NBS occurring regioselectively ortho to the hydroxy substituent. Similar results were also observed by Tsuboi[10] using DBDMH as the brominating agent. Following a similar strategy described for the synthesis of **5**, benzoyl chloride **9** was obtained in good overall yield from **7**. Compound **10**, the key precursor for intramolecular Ullmann reaction was then prepared by anhydride formation between **5** and **9**. Subsequent studies showed that the anhydride-linker directed intramolecular Ullmann reaction of **10** could be performed at 60–70 °C, instead of the high temperatures generally required for this reaction, and gave, after hydrolysis and ester formation, γ-DDB **11** in good overall yield.

In conclusion, we have developed a mild and efficient method for the synthesis of γ-DDB. Compared to our previous method, the yield for regioselective bromination and intramolecular Ullmann reaction, the two key steps of the synthesis, were greatly improved.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.166.

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