



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.

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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 reaction⁵ 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

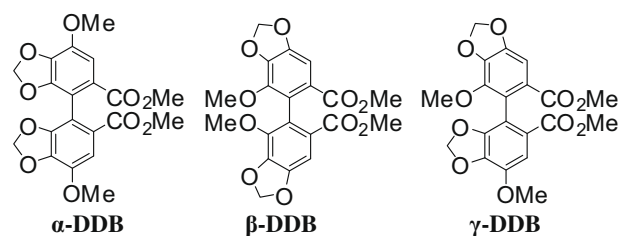
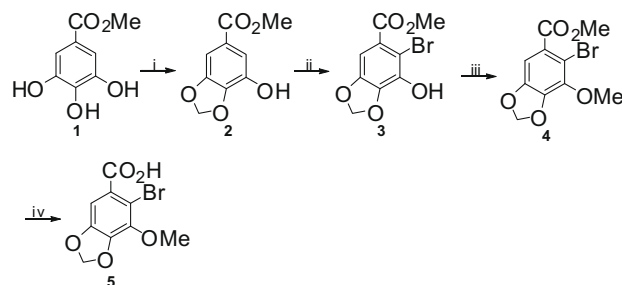


Figure 1.

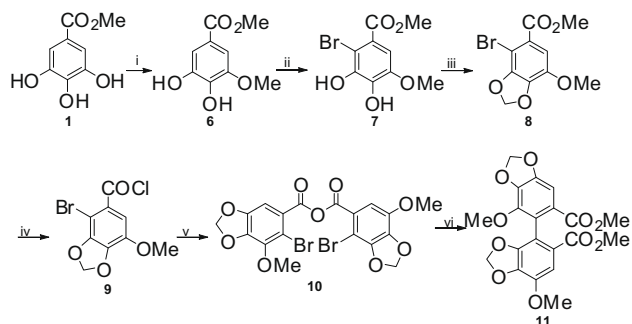
yield, uncontaminated by significant amounts of the 6-brominated or dibrominated products. Methylation of the hydroxy group in **3**, followed by saponification gave **5**, the first component for the synthesis of γ -DDB. In comparison to our previous strategy for the introduction of the bromo group 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 Tsuboi¹⁰ 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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