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Asymmetric Synthesis of a Lignan Lactone from a *Meso* Anhydride

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Abstract: Reaction of the anhydride of a *meso*-2,3-dibenzylbutanedioic acid with (+)-α-methylbenzylamine proceeds diastereoselectively to give an acid-amide which can be converted into an enantiomerically enriched *cis*-2,3-dibenzylbutyrolactone.

Meso bifunctional compounds are of particular interest as substrates for asymmetric synthesis since they can be converted stereoselectively into compounds containing at least two chiral centres in 50-100% yield.[1] Such reactions can be brought about using chemical or enzymatic methods,[1,2] and cyclic anhydrides derived from dicarboxylic acids have proved popular substrates for such reactions.[3-13]

We have sought to use this methodology for the synthesis of lactones of the dibenzylbutyrolactone series. These compounds are valuable precursors for the synthesis of a wide variety of lignan lactones.[14] While several methods for the asymmetric synthesis of *trans*-dibenzylbutyrolactones have been developed,[15] no methods for the asymmetric synthesis of the *cis*-lactones have been reported.

The required *meso*-2,3-dibenzylbutanedioic acid anhydride **(7)** was prepared from the doubly unsaturated anhydride **(1)** as outlined in Scheme 1. Anhydride **(1)** was prepared by a route involving two consecutive Stobbe condensations starting from diethyl succinate. It was obtained as deep red crystals, m.p. 176-7°C, and its structure was confirmed by X-ray crystallography. Hydrogenation of **(1)** using a 10% palladium on charcoal catalyst at 60 p.s.i. gave the dibenzylmaleic anhydride **(2)** in 86% yield as yellow crystals, m.p. 112-3°C. However attempted further hydrogenation of **(2)** using a variety of catalysts was unsuccessful. Furthermore hydrogenation of the doubly unsaturated diester **(3)** gave the required 2,3-dibenzylsuccinate **(5)**, but as a mixture of *d/l* and *meso* isomers. We therefore converted the maleic anhydride **(2)** into the corresponding dimethyl ester **(4)** which underwent hydrogenation to give the *meso* diester **(5)** in 92% yield. The diester **(5)** was obtained as white crystals, m.p. 138-9°C, and its structure was confirmed by X-ray crystallography. Hydrolysis of **(5)** using 5M HCl in diglyme gave the diacid **(6)**, m.p. 197-8°C (62% yield), which was converted into the *meso* anhydride **(7)**, m.p. 124-5°C (60% yield), using DCCI.

Reaction of the anhydride **(7)** with (+)-α-methylbenzylamine gave the acid-amide **(8)** as white crystals, m.p. 184-6°C, $[\alpha]_D^{21}$ +56.7 (c 0.48 in CH_2Cl_2), 86% d.e., in 62% isolated yield (Scheme 2). Reaction of **(8)** with ethyl chloroformate followed by reduction with sodium borohydride gave the hydroxy-amide **(9)**, m.p. 109-111°C, $[\alpha]_D^{20}$ +19.6 (c 0.50 in CH_2Cl_2), 86% d.e. (50% yield), which on treatment with hydrochloric acid in glyme gave the *cis*-lactone **(10)**, $[\alpha]_D^{21}$ +32.3 (c 1.434 in CH_2Cl_2), in 69% yield. The absolute configuration of **(10)** was established by correlation with the (-)-*trans*-2,3-dibenzylbutyrolactone **(11)**.[14]

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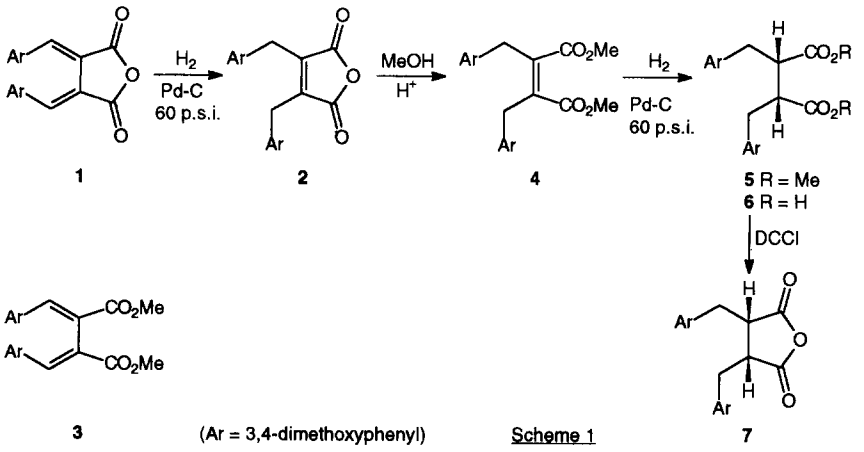
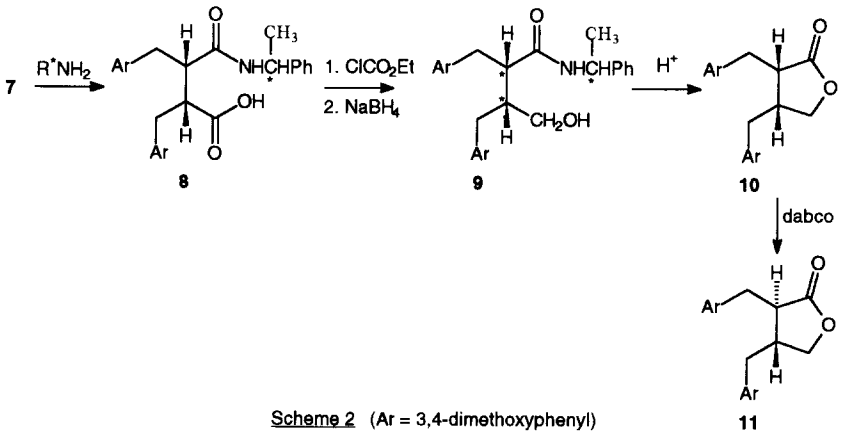


Scheme 1



Scheme 2

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