The First Synthesis of (±)-Cycloolivil: A Highly Stereoselective Synthesis of 3-Hydroxy-1-aryltetralin Lignans Based on the Stereoselective Hydroxylation of α,β-Dibenzyl-γ-butyrolactones

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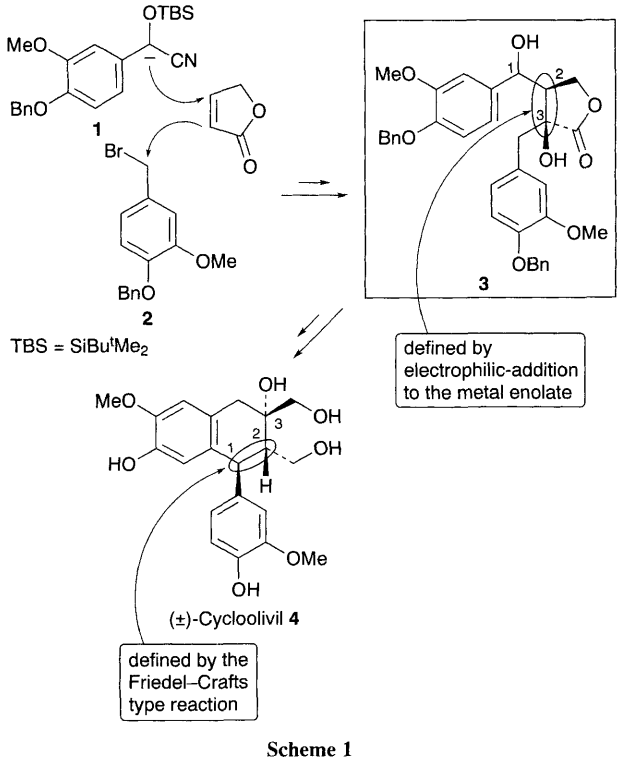
Cycloolivil, a representative example of 3-hydroxy-1-aryltetralin lignans, was stereoselectively synthesised in good yields based on the stereoselective electrophilic addition to the metal enolate of α,β-disubstituted γ-butyrolactone as a key step.

Lignans of the 3-hydroxy-1-aryltetralin series such as cycloolivil **4** have attracted recent attention because of their intriguing biological activities, *e.g.* diuretic, antiseptic, antifebrile and antirheumatic.[1,2] Only one synthetic approach to this series of lignans has been reported: α′-acetoxy-trachelogenin diacetate was synthesised by oxidation of trachelogenin diacetate with lead tetraacetate, followed by the Friedel–Crafts-type cyclisation and subsequent reduction leading to the corresponding 3-hydroxy-1-aryltetralin derivative.[3] However, this method is generally inapplicable to the synthesis of this series of lignans. In connection with our efforts in search of new compounds having interesting biological activities from lignan derivatives,[4] we now report a highly stereoselective synthesis of lignans of the 3-hydroxy-1-aryltetralin series.

Scheme 1 illustrates the main features of our synthesis of (±)-cycloolivil **4**, a representative example of the 3-hydroxy-1-aryltetralin series of lignans. The synthetic method involves the reaction of **1**, **2** and 2-butenolide, followed by the stereoselective electrophilic addition to the metal enolate **5** (Fig. 1) and subsequent conversion of **3** into (±)-cycloolivil **4**. We envisaged that the relative stereochemistry of the contiguous carbon centres of **3**, C-2 and C-3, would be defined by the electrophilic attack on the metal enolate **5** which takes place predominantly from the upper face in spite of presence of the β-substituent; the shielding of the bottom face by the phenyl group of the α-benzyl group due to the conformational rigidity induced by 1,3-allylic strain would be effective to allow the preferential attack of an electrophile from the upper face.[5,6] The C-1 and C-2 carbon centres of (±)-cycloolivil would be stereochemically defined by the Friedel–Crafts-type cyclisation reaction of **3**.[7]

On the basis of the strategy described above, we first examined the synthesis of **9** from the *O*-silylated cyanohydrin **1**. The conjugate addition of the lithium enolate of **1** to 2-butenolide at −78 °C, followed by trapping the resulting enolate with 3-methoxy-4-(benzyloxy)benzyl bromide **2** gave **6**. Without isolation of **6**, the mixture was treated with Bu_4NF to afford the *trans*-γ-butyrolactone **7** in 75% yield from **1**. Reduction of the carbonyl group of **7** with L-Selectride proceeded stereoselectively to give the alcohol **8** as a sole product in 91% yield.[8] The hydroxy group of **8** was protected by a Me_3Si group to afford **9** in 80% yield (Scheme 2).

We next examined the stereoselective hydroxylation of the metal enolate. The potassium enolate **5** (M = K), generated by



Scheme 1

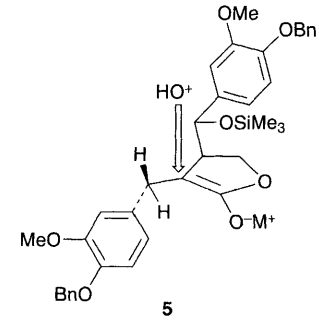
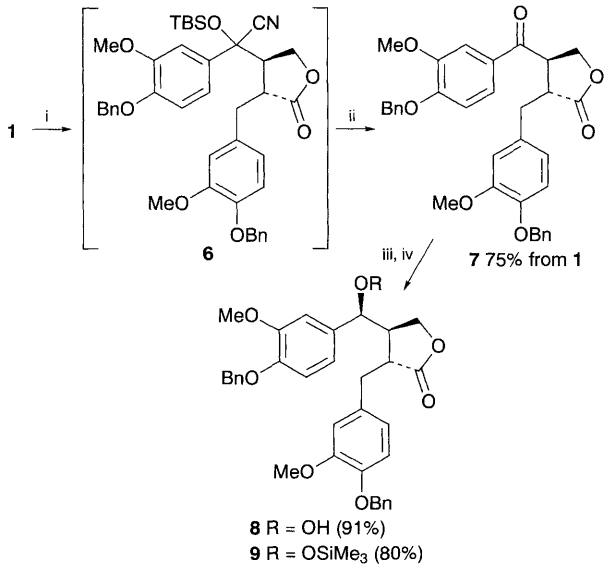


Fig. 1

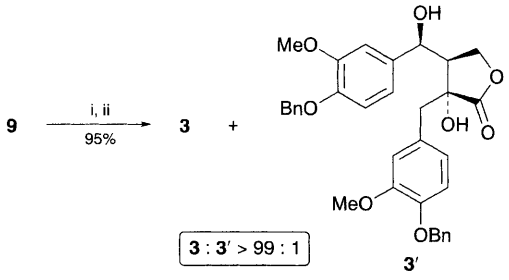


Scheme 2 *Reagents and conditions*: i, LDA–THF, −78 °C then 2-butenolide, −78 °C then **2**, −78 °C; ii, Bu_4NF–AcOH–CH_2Cl_2, 0 °C; iii, L-Selectride–THF, −78 °C; iv, Me_2SI, Et_3N–DMF, room temp.

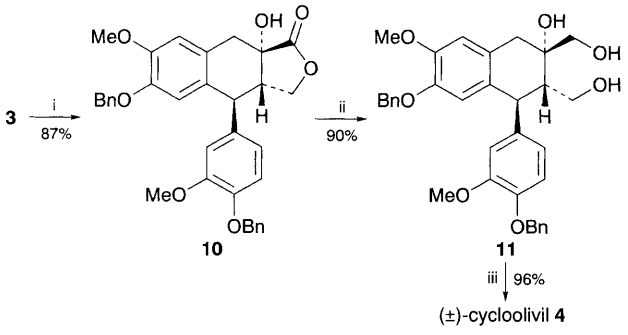
treatment of **9** with potassium bis(trimethylsilyl)amide in THF at −78 °C, was treated with oxodiperoxymolybdenum (pyridine) hexamethylphosphoramide (MoOPH), followed by treatment with Bu_4NF to furnish a mixture of **3** and its stereoisomer **3′** in 95% yield: the ratio of **3** **3′**:† being greater than 99 : 1 (Scheme 3).

The conversion of **3** into (±)-cycloolivil was then examined. Treatment of **3** with TFA in CH_2Cl_2 at 0 °C gave 3-hydroxy-1-aryltetralin lactone **10**‡ in 87% yield. Reduction of **10** with $LiAlH_4$ in THF afforded the triol **11** in 90% yield. Hydrogenolysis of **11** afforded (±)-cycloolivil **4** in 96% yield§ (Scheme 4).

As described, we have achieved a highly stereoselective synthesis of (±)-cycloolivil. This method should find wide application in the stereoselective synthesis of lignans of the 3-hydroxy-1-aryltetralin series.



Scheme 3 *Reagents and conditions*: i, $KN(Me_3Si)_2$, MoOPH–THF, −78 °C; ii, Bu_4NF–CH_2Cl_2, room temp.



Scheme 4 *Reagents and conditions*: i, TFA–CH_2Cl_2, 0 °C; ii, $LiAlH_4$–THF, room temp.; iii, H_2, Pd–C–THF–MeOH

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Footnotes

† The relative stereochemistry between the C-2 and C-3 of **3** was determined by ^1H NMR (400 MHz); the NOE (5.7%) between 2-methine proton and methylene protons of 3-benzyl group was observed.

‡ A large coupling constant (J_{ab} 12.2 Hz) observed between H-1 and H-2 in the *O*-methyl derivative of **10** (prepared by methylation of the hydroxy group of **10**) strongly suggested that the stereochemistry at C-1 and C-2 of **10** was *trans*.

§ The ^1H and ^{13}C NMR spectra of (±)-cycloolivil **4** obtained here were consistent with those of natural (±)-cycloolivil.[1,2] The structure of **4** was unambiguously confirmed by X-ray crystallography.

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