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Synthesis of Enantiomerically Pure 7-Hydroxy-2-substituted-2,3-dihydro-1,4-benzodioxin Derivatives

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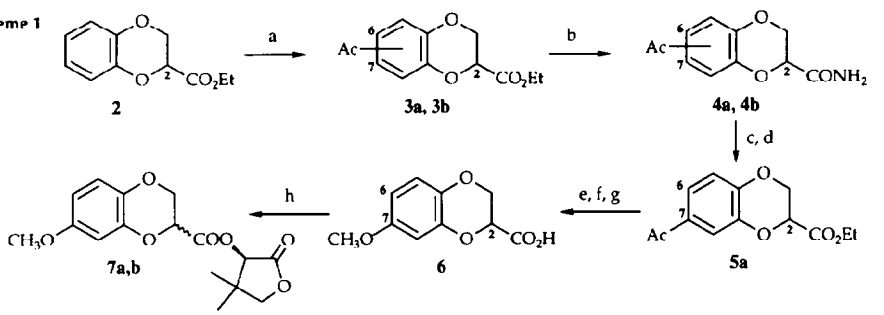
Abstract. *A rapid and simple procedure for the preparation of the two pure enantiomers of 7-hydroxy-2-substituted-2,3-dihydro-1,4-benzodioxin derivatives is described.*

The 2,3-dihydro-1,4-benzodioxin ring system has been widely used in medicinal chemistry, particularly in the design of cardiovascular agents such as α and β adrenergic antagonists.[1,2] Moreover, this system has been recently found to be useful in developing serotoninergic receptor ligands.[3] It has been shown that the absolute stereochemistry at the stereogenic center in 2-substituted-2,3-dihydro-1,4-benzodioxin derivatives is of prime importance for both affinity and selectivity for these CNS receptors. In the course of our work concerning the synthesis of derivatives exhibiting both α and β adrenergic properties, we needed to obtain the two pure enantiomeric forms of 7-hydroxy-2-carboxy-2,3-dihydro-1,4-benzodioxin **1**. Optically pure 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxins have been previously prepared from chiral buildings blocks, such as glycerol[4] or glycidol[5] derivatives. In our case, however, these methods would involve a great number of steps and the difficult separation of isomers. The enzymatic resolution of the same racemic compounds using the Amano P-30 lipase enzyme[6] could be a more attractive alternative, but two successive operations are needed to obtain satisfactory enantiomeric excess. Herein, we describe the easy resolution of the racemic 7-methoxy acid **6** via *R*-(-)-pantolactone derivatives.[7]

The required 7-methoxy derivative **6** was first prepared from the easily available ester **2**[8] as shown in scheme 1. Acetylation of **2** provided an inseparable mixture of compounds **3a** and **3b** (75:25) in 90% yield. The separation of each pure isomer was carried out *via* the isomeric carboxamides **4a** and **4b** adapting the method of Mills.[9] Indeed, the desired isomer **4a** can be separated by its insolubility in ethanol.

Scheme 1

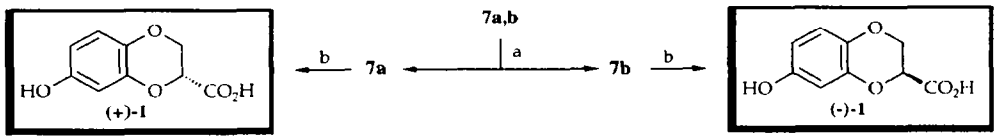


Reaction conditions: (a) AcCl, $AlCl_3$, CS_2, 0°C. (b) NH_4OH 28 % EtOH. (c) Separation. (d) EtOH, HCl reflux. (e) MCPBA, CH_2Cl_2, reflux, 18h. (f) KOH 10N then HCl. (g) KOH, Me_2SO_4 then HCl. (h) *R*-(-)-pantolactone, EDCI, DMAP, CH_2Cl_2.

Treating **4a** with anhydrous hydrogen chloride in refluxing ethanol gave the 7-isomer **5a** in 57% yield. Ester **5a** was hydrolyzed and the resulting acid was characterized unambiguously by comparing it to the acid previously described by Campbell *et al.*[10] Baeyer Villiger reaction followed by hydrolysis led to the hydroxy acid **1** (88%), which was converted to the required methoxy acid **6** using the Delmas method (96%).[11]

The resolution of 7-methoxy-2-carboxy-2,3-dihydro-1,4-benzodioxin *via* *R*-(-)-pantolactone derivatives is illustrated in scheme 2.

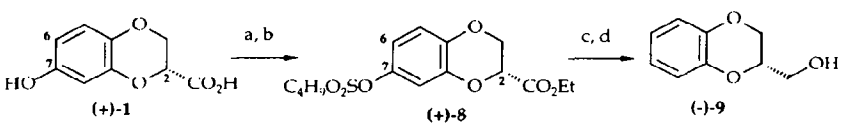
Scheme 2



Reaction conditions: (a) flash-chromatography. (b) BBr_3, CH_2Cl_2, RT.

The diastereomeric esters **7a** and **7b** derived from *R*-(-)-pantolactone were obtained in 80 % yield by adapting a known procedure[12] and were separated by flash chromatography. The diastereoisomeric purity was assayed by HPLC[13] and was determined to be greater than 99 %. Treatment of **7a** and **7b** with BBr_3 at room temperature yielded the enantiomerically pure compounds **(+)-1** and **(-)-1** respectively.[14] Enantiomeric purity and absolute configuration of each isomer were determined by converting **(+)-1** and **(-)-1** to the known 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin enantiomers **(-)-9** and **(+)-9** under non racemizing conditions (scheme 3).[5]

Scheme 3



Reaction conditions: (a) EtOH, APTS, reflux. (b) $CF_3(CF_2)_3SO_2F$, Et_3N. (c) H_2, Pd/C, MeOH. (d) $LiAlH_4$, Et_2O, reflux.

The enantiomeric purities of **(-)-1** and **(+)-1** were determined by ^{1}H-NMR (300 MHz) and HPLC analyses on the derived Mosher esters of **(+)-9** and **(-)-9**.[15] The absolute configurations can be assigned as 2*R* for **(+)-1** and 2*S* for **(-)-1**.

In conclusion, the method described is a rapid and simple procedure for the preparation of the enantiomers of 7-hydroxy-2-substituted-2,3-dihydro-1,4-benzodioxin derivatives.

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13. Zorbax Sil (250x4.6 mm) column (DuPont). Eluent. C_6H_{14}-CH_2Cl_2-CH_3OH, 95:5:0.5. Light Scattering Detection (Sedex 45).
14. **(-)-1**: $[\alpha]_D$ -55 (c = 1, CH_3OH); mp 203-205°C; ^{1}H-NMR (DMSO-d_6) δ (ppm), *J* (Hz): 6.56 (d, 1H, J_{ortho} = 9, H-5), 6.30 (d, 1H, J_{meta} = 3, H-8), 6.17 (dd, 1H, J_{ortho} = 9, J_{meta} = 3, H-6), 4.50 (dd, 1H, J_{vic} = 5, J_{vic} = 3, H-2), 4.20 (dd, 1H, J_{vic} = 3, J_{gem} = 11, H-3), 4.12 (dd, 1H, J_{vic} = 5, J_{gem} = 11, H-3'). **(+)-1**: $[\alpha]_D$ +54 (c = 1, CH_3OH); mp 203-205°C.
15. The Mosher esters of **(+)-9** and **(-)-9** were prepared by coupling with *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid using DCC/DMAP. The yields were 80% and 86% respectively. Diastereoisomers were analyzed on a Hypercarb (150x4.6 mm) column (Shandon). Eluent: CH_3OH-H_2O-TFA, 50:50:0.5. UV detection 254 nm.

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