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ASYMMETRIC SYNTHESIS OF HOMOISOFLAVANONE USING LIPASE-CATALYZED REACTION

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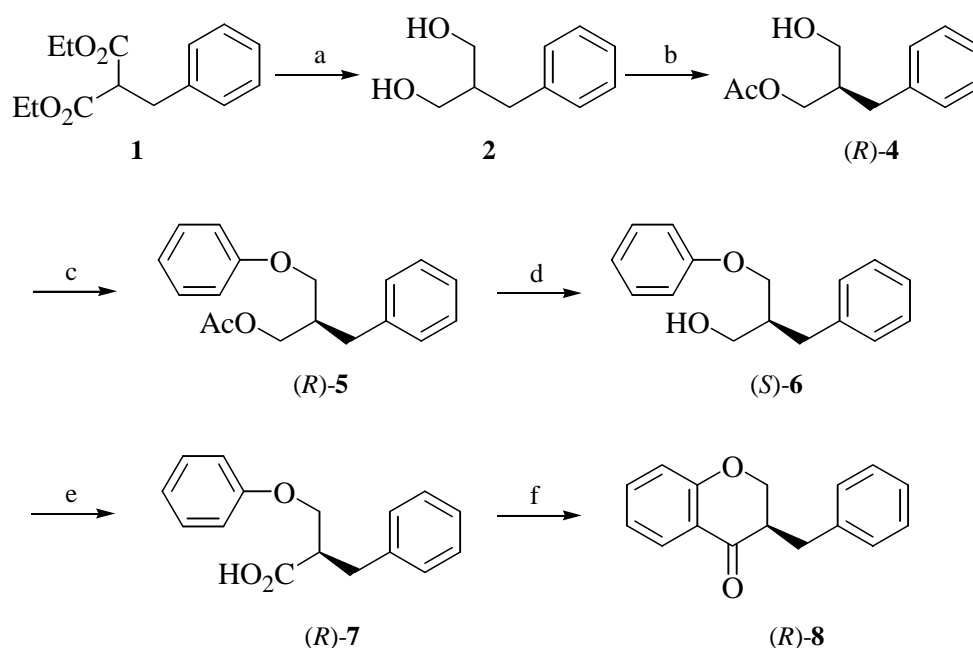
Abstract - The (*R*)- and (*S*)-enantiomers of 3-benzyl-4-chromanone (homoisoflavanone) were synthesized starting with the optically active 2-benzyl-1,3-propanediol monoacetates, which were obtained *via* the lipase-catalyzed enantioselective reaction.

Homoisoflavanones (3-arylmethyl-4-chromanones) belong to a small family of natural products¹ and have been found in several genera of Liliaceae² and Leguminosae.³ Recently, a homoisoflavanone was also isolated from *Dracaena loureiri* (Agavaceae).⁴ It is known that some of these compounds possess cyclooxygenase⁴ and phosphodiesterase⁵ inhibitory activities, antiinflammatory⁶ and antiviral⁷ activities which promoted many organic chemists to synthesize them. Although many methods to prepare racemic homoisoflavanones have been reported,⁸ there is no report of asymmetric syntheses.

We are also interested in the synthesis of flavanones or the analogues of homoisoflavanones, and have succeeded in the facile asymmetric synthesis of a flavanone.⁹ We now report the asymmetric synthesis of 3-benzyl-4-chromanone (**8**)¹⁰ from a chiral intermediate prepared by a lipase-catalyzed reaction.

First, (*R*)-**8** was synthesized according to Scheme 1. Commercially available diethyl benzylmalonate

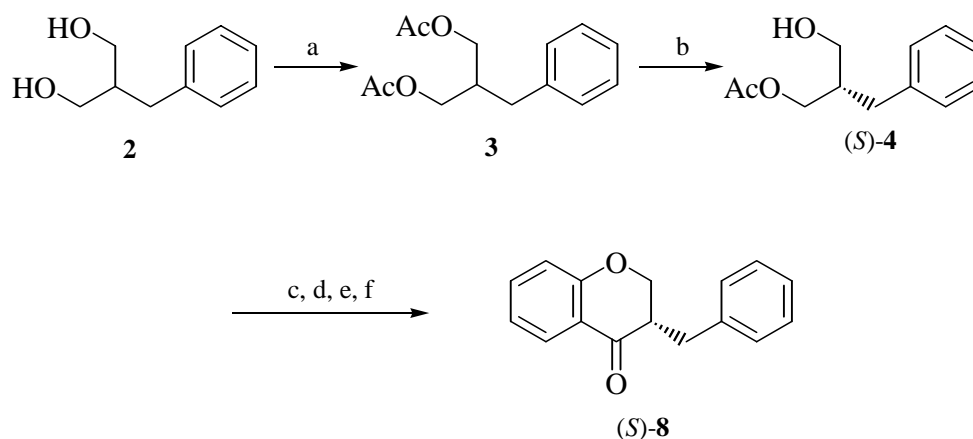
(1) was reduced using LiAlH_4 and the diol (2) thus obtained was subjected to the lipase (Lipase PS “Amano” from *Burkholderia cepacia*)-catalyzed transesterification in vinyl acetate, which acted not only as the solvent but also as the acetylating reagent, to afford the optically active monoacetate¹¹ ((*R*)-4) in 97% ee¹² $\{[\alpha]_{\text{D}}^{22} +28.4^\circ (c\ 1.7, \text{CHCl}_3)\}$. The absolute configuration of (*R*)-4 was established by comparison of its optical rotation with that in the literature¹³ $\{[\alpha]_{\text{D}}^{25} +31.9^\circ (c\ 1.2, \text{CHCl}_3), >99\% \text{ ee}, (R)\}$. Although Bertucci *et al.*¹³ reported that the Lipase PS-catalyzed transesterification of 2 in vinyl acetate yielded (*R*)-4 in >99% ee, we were not able to obtain (*R*)-4 in such a high enantiomeric excess. The coupling of (*R*)-4 and phenol with diisopropyl azodicarboxylate in the presence of triphenylphosphine gave the phenyl ether ((*R*)-5). The hydrolysis of the ester moiety of (*R*)-5 with NaOH afforded the corresponding alcohol ((*S*)-6), which was oxidized to the carboxylic acid ((*R*)-7) using Jones reagent. The intramolecular Friedel-Crafts acylation of (*R*)-7 using trifluoroacetic acid and trifluoroacetic anhydride afforded (*R*)-8¹⁴ in 98% ee¹⁵ $\{[\alpha]_{\text{D}}^{25} -10.5^\circ (c\ 1.0, \text{MeOH})\}$. Judging from their enantiomeric excesses, no racemization of the intermediates occurred during the conversion processes from (*R*)-4 to (*R*)-8.



Scheme 1: Reagents and conditions: a: LiAlH_4 , Et_2O , rt (76%); b: vinyl acetate, Lipase PS, rt (87%); c: PhOH, PPh_3 , diisopropyl azodicarboxylate, THF, 0°C -rt (75%); d: NaOH, $\text{EtOH-H}_2\text{O}$, rt (77%); e: Jones oxid., rt (64%); f: TFAA, TFA, CH_2Cl_2 , rt (88%)

According to the same procedure, (*S*)-8¹⁴ was also synthesized in an optically active form {96% ee,¹⁵ $[\alpha]_{\text{D}}^{23} +9.5^\circ (c\ 1.2, \text{MeOH})\}$ from (*S*)-4 (96% ee¹²) which was obtained by the Lipase PS-catalyzed enantioselective hydrolysis of 3,¹⁶⁻¹⁸ prepared from 2, in phosphate buffer (Scheme 2).

In conclusion, we have been able to easily synthesize the (*R*)- and (*S*)-enantiomers of 3-benzyl-4-chromanone. We are now synthesizing novel optically active 3-arylmethyl-4-chromanones and testing their biological activities.



Scheme 2: Reagents and conditions: a: AcCl, pyridine, THF, 0 °C-rt (79%); b: Lipase PS, phosphate buffer (pH 7), rt (30%); c-f: 14% in four steps.

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11. The yields of the unreacted diol (**2**) and the diacetate (**3**) produced from monoacetate (**4**) measured by GC analysis were about 0.7% and about 0.2%, respectively. We did not isolate them.
12. Determined by HPLC analysis on Chiralcel OB-H, hexane:2-propanol=7:1 (v/v), flow rate=0.5 ml/min. Retention times: (*S*)-**4**, t=17 min; (*R*)-**4**, t=19 min.
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14. ¹H-NMR and IR spectral data of the (*R*)- and (*S*)-**8** were identical to those of the racemate in the literature.^{7b}
15. Determined by HPLC analysis on Chiralcel OB-H, hexane:2-propanol=20:1 (v/v), flow rate=0.5 ml/min. Retention times: (*S*)-**8**, t=28 min; (*R*)-**8**, t=32 min.
16. The yields of the unreacted diacetate (**3**) and the diol (**2**) produced from monoacetate (**4**) measured by GC analysis were about 27% and about 32%, respectively. We did not isolate them.
17. Although **3** was also subjected to hydrolysis with other lipases, satisfactory results for the ee values of (*S*)-**4** could not be obtained. Hydrolysis of **3** with Lipase ALC (Meito) yielded (*S*)-**4** in 82% ee, while with Lipase PPL (Amano) did (*R*)-**4** in 64% ee.

18. Mori *et al.* also reported the conversion of **3** into (*S*)-**4** by other lipases. However, they could not obtain (*S*)-**4** in high ee; K. Mori and N. Chiba, *Liebigs Ann. Chem.*, 1989, 957.