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ASYMMETRIC SYNTHESIS OF HOMOISOFLAVANONE USING LIPASE-CATALYZED REACTION

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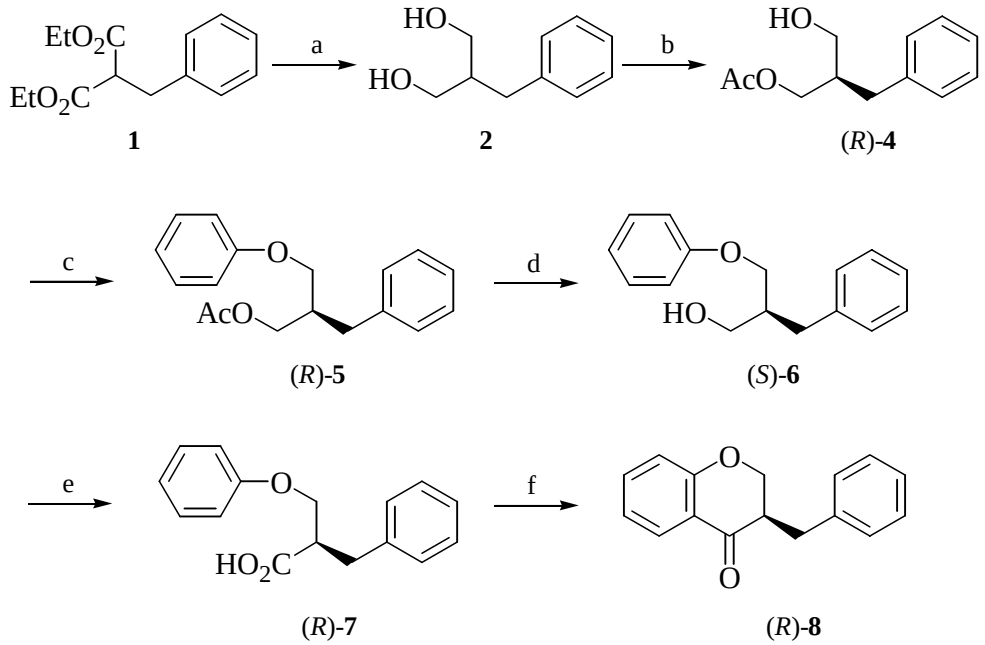
Abstract - The (*R*)- and (*S*)-enantiomers of 3-benzyl-4-chromanone (homoisoflavanone) were synthesized starting with the optically active 2-benzyl-1,3-propanediol monoacetates, which were obtained *via* the lipase-catalyzed enantioselective reaction.

Homoisoflavanones (3-arylmethyl-4-chromanones) belong to a small family of natural products[1] and have been found in several genera of Liliaceae[2] and Leguminosae.[3] Recently, a homoisoflavanone was also isolated from *Dracaena loureiri* (Agavaceae).[4] It is known that some of these compounds possess cyclooxygenase[4] and phosphodiesterase[5] inhibitory activities, antiinflammatory[6] and antivirus[7] 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

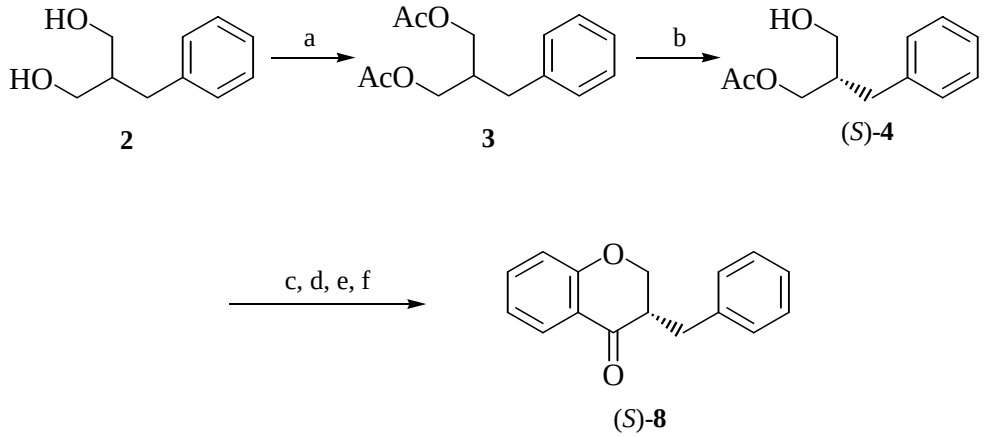
(**1**) was reduced using $LiAlH_4$ and the diol (**2**) thus obtained was subjected to the lipase (Lipase PS "Amano" from *Burkholderia cepacia*)-catalyzed transesterification in vinyl acetate, which acted not only as the solvent but also as the acetylating reagent, to afford the optically active monoacetate[11] ((*R*)-**4**) in 97% ee[12] {$[\alpha]^{22}_D$ +28.4° (*c* 1.7, $CHCl_3$)}. The absolute configuration of (*R*)-**4** was established by comparison of its optical rotation with that in the literature[13] {$[\alpha]^{25}_D$ +31.9° (*c* 1.2, $CHCl_3$), >99% 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*)-**8**[14] in 98% ee[15] {$[\alpha]^{25}_D$ -10.5° (*c* 1.0, 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 ^oC-rt (75%); d: NaOH, EtOH-H_2O, rt (77%); e: Jones oxid., rt (64%); f: TFAA, TFA, CH_2Cl_2, rt (88%)

According to the same procedure, (*S*)-**8**[14] was also synthesized in an optically active form {96% ee,[15] $[\alpha]^{23}_D$ +9.5° (*c* 1.2, MeOH)} from (*S*)-**4** (96% ee[12]) 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.



2 **3** (*S*)-**4** (*S*)-**8**

Scheme 2: **Reagents and conditions**: a: AcCl, pyridine, THF, 0 ^{o}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. ^{1}H-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.