

ENANTIOSELECTIVE SYNTHESIS OF EUCOMOLS USING SHARPLESS CATALYTIC ASYMMETRIC DIHYDROXYLATION[†]

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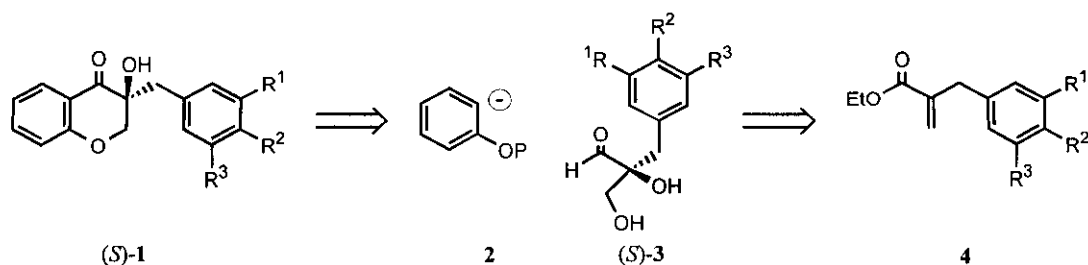
Abstract - A novel synthetic method was developed for eucomols, (*S*)-3-hydroxyhomoisoflavanones. Addition of aryllithium to aldehyde ((*S*)-**9**) obtained by asymmetric dihydroxylation of **4**, followed by the formation of cyclic ether, gave eucomols, (*S*)-3-hydroxyhomoisoflavanones (**1a-e**).

As a small family of natural products, homoisoflavanones have been isolated from several genera in *Liliaceae*¹ and *Caesalpinoideae* (*Leguminosae*).² According to their structural features, these can be classified into three types which are eucomin (3-benzylidenechroman-4-one), dihydroeucomin (3-benzylchroman-4-one) and eucomol (3-hydroxy-3-benzylchroman-4-one).^{1a} Several eucomols and the related compounds such as (*R*)- and (*S*)-5,7-*O*-dimethyleucomol,³ (*R*)-*O*-trimethylsappanone B and (+)-*O*-trimethylbrazilin,⁴ and (*S*)-8-benzyloxy-*O*-tribenzylsappanone B and (-)-haematoxylin⁵ have various important biological properties. These all compounds have one chiral center at C(3) position. Because their biological activities are dependent upon the absolute configuration,³⁻⁵ the biologically active eucomols should be obtained in chiral forms. The asymmetric synthesis of the eucomols, (*R*)- or (*S*)-3-

[†] Dedicated to the late Dr. Shun-ichi Yamada, Professor Emeritus Tokyo University

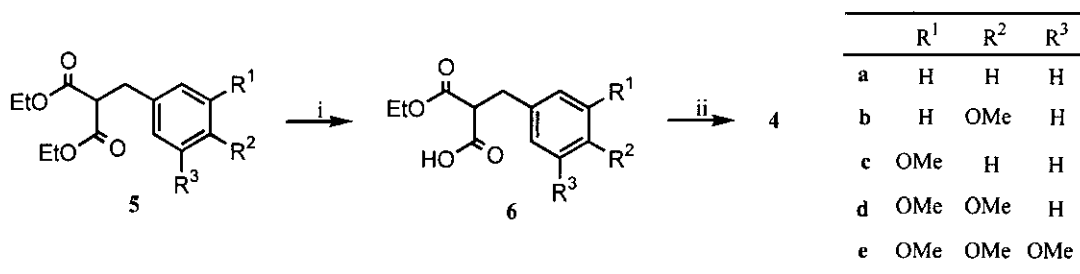
hydroxyhomoisoflavanone, was reported by asymmetric hydroxylation using (+)- or (-)-8,8-disubstituted camphorylsulfonyloxaziridines as a chiral reagent.³⁻⁵ However, the stoichiometric consumption of the chiral reagent makes that method less practical to prepare large amount of the chiral eucomols and their various derivatives. In this paper, we report a novel and practical enantioselective synthesis of eucomols by the catalytic asymmetric dihydroxylation (AD) developed by Sharpless⁶ as a key reaction.

Scheme 1



Our strategy is shown in Scheme 1. Eucomol ((*S*)-1) was retrosynthesized *via* three key reactions; asymmetric dihydroxylation of **4**, addition of aryllithium (**2**) to aldehyde ((*S*)-3), and the intramolecular Mitsunobu reaction.

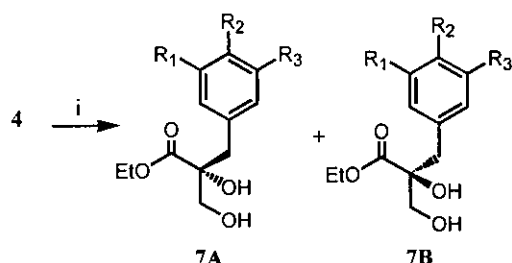
Scheme 2



Reagents and conditions: (i) KOH (1.2 eq), EtOH, rt, 3-5 h, **6a** (100%), **6b** (83%), **6c** (86%), **6d** (87%), **6e** (84%); (ii) NaH (2.1 eq), CH₂NMe₂I (1.1 eq), THF, reflux, 2-3 h, **4a** (61%), **4b** (60%), **4c** (23%), **4d** (72%), **4e** (77%).

The substrates (**4**) for AD reaction were prepared from diethyl benzylmalonates (**5**) as shown in Scheme 2. **5** was partially hydrolyzed with KOH to give **6**, which was subjected to Mannich reaction with *N,N*-dimethylmethyleammonium iodide (Eschenmoser's salt) to give **4**.

Scheme 3



Reagents and conditions: (i) AD-mix- α (chiral ligand (DHQ)₂PHAL) or AD-mix- β (chiral ligand (DHQD)₂PHAL) *t*-BuOH:H₂O = 1:1, 0 °C, 20-24 h.

Table 1

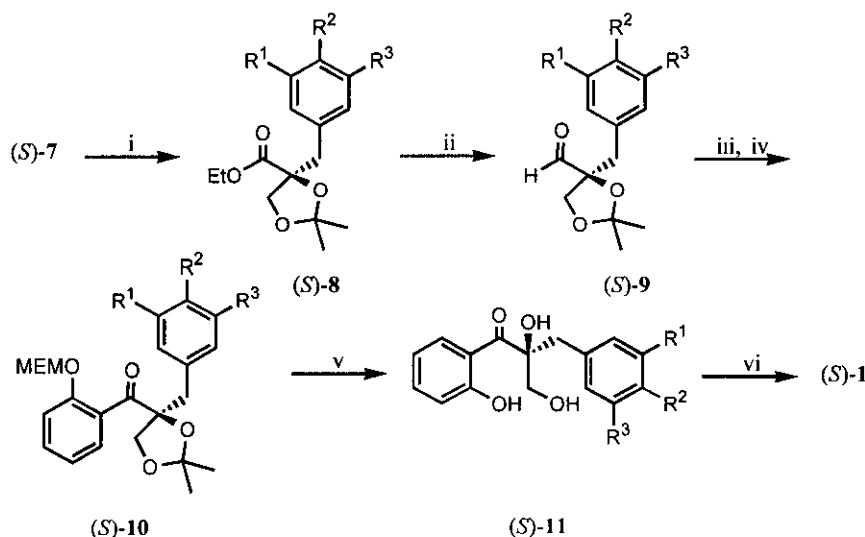
	AD-mix- α , 7A		AD-mix- β , 7B	
	% ee	% yield	% ee	% yield
a	71	85	76	90
b	63	80	80	93
c	75	82	88	97
d	83	94	90	96
e	93	83	93	97

The asymmetric dihydroxylations of **4** with AD-mix- α or AD-mix- β were performed by standard procedure to give **7A** and **7B**, respectively. The absolute configuration of **7Ba** was assigned (*S*) by comparison of the specific rotation of (*R*)-2-hydroxy-2-methyl-3-phenylpropionic acid⁷ which was obtained by the chemical transformation of **7Ba**. It was in accord with the absolute configuration expected from Sharpless model.⁶ The configurations of **7b-e** obtained from **4b-e** were assigned by the Sharpless model. The ee values were determined by the ¹H-NMR spectra of the (*S*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid esters of **7**. As shown in Table 1, the AD reactions were performed in 80-97% yields. Generally, AD-mix- β gave better results than AD-mix- α in both chemical yield and ee yield. In case of **4a-c** having de- or monomethoxyphenyl group, 63-88% ee were obtained. However, **4d** and **4e** bearing di- or trimethoxyphenyl group provided relatively better results (83-93% ee). The transformation of (*S*)-**7** to (*S*)-**1** was then carried out as in Scheme 4. The protection of diol ((*S*)-**7**) with 2,2-dimethoxypropane gave the corresponding acetonide ((*S*)-**8**), which was reduced to the corresponding aldehyde ((*S*)-**9**) with DIBALH. The addition of *o*-2-methoxyethoxymethoxyphenyllithium⁸ to (*S*)-**9**, followed by oxidation with pyridiniumchlorochromate gave (*S*)-**10**, which was treated with 2% HCl-

MeOH to afford the α,β -dihydroxyketone ((*S*)-11). The intramolecular Mitsunobu reaction⁹ of (*S*)-11 with triphenylphosphine and diethyl azodicarboxylate gave (*S*)-1.

In summary, eucomols, (*S*)-3-hydroxyhomoisoflavanone (1a-e) were prepared through 7 steps from 4 in overall yield 12-21% and 76-93% ee. High ee of catalytic asymmetric dihydroxylation in this procedure gave advantage for industrial application.

Scheme 4



Reagents and conditions: (i) 2,2-dimethoxypropane (2.5 eq), *p*-TsOH (0.2 eq), THF, rt, 16-18 h, (*S*)-8b (83%), (*S*)-8c (98%), (*S*)-8d (93%), (*S*)-8e (93%); (ii) DIBALH (1.2 eq), toluene, -78 °C, 20-30 min, (*S*)-9b (88%), (*S*)-9c (87%), (*S*)-9d (85%), (*S*)-9e (46%); (iii) (*o*)-MEMOC₆H₄Li (1.0 eq), THF, -78 °C→rt, 3-5 h; (iv) PCC (1.5 eq), NaOAc (0.3 eq), CH₂Cl₂, reflux, 3-4 h, (*S*)-10b (28%), (*S*)-10c (29%), (*S*)-10d (37%), (*S*)-10e (44%); (v) 2% HCl-MeOH, 50 °C, 1-2 h, (*S*)-11b (91%), (*S*)-11c (88%), (*S*)-11d (91%), (*S*)-11e (88%); (vi) (C₆H₅)₃P (1.5 eq), DEAD (1.5 eq), THF, rt, 12 h, (*S*)-1c (71%), (*S*)-1d (81%), (*S*)-1e (73%).

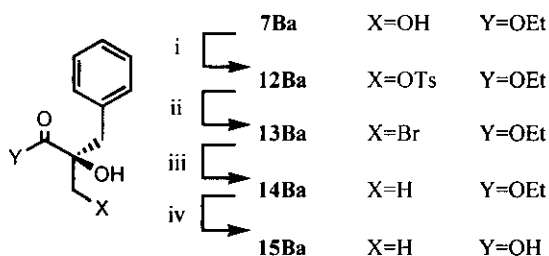
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7. (a)



Reagents and conditions: (i) TsCl (1.5 eq), pyridine (4.5 eq), CHCl_3 , rt, 24 h (87%); (ii) LiBr (3.0 eq), THF, 55°C , 40 h, (67%); (iii) Bu_3SnH (2.2 eq), AIBN (cat.), benzene, reflux, 20 min, (53%); (iv) 6N-HCl, reflux, 6 h (100%).

7Ba ($[\alpha]_D^{13} +10.43^\circ$ (c 0.86, CHCl_3)) was tosylated to give **12Ba** which was converted to bromide

(13Ba). Debromination of 13Ba, followed by hydrolysis afforded 15Ba ($[\alpha]^{20}_{\text{D}} +13.2^\circ$ (c 1.51, dioxane) *lit.*^{7b} (*R*)-2-hydroxy-2-methyl-3-phenylpropionic acid, $[\alpha]^{20}_{\text{D}} +17.0^\circ$ (c 5.60, dioxane)); (b) M.

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8. *o*-2-Methoxyethoxymethoxyphenyllithium was prepared by the treatment of *o*-2-methoxyethoxymethoxyphenylbromide with *n*-BuLi (1.1 eq)-THF at -78°C (0.5 h).

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