ENANTIOSELECTIVE SYNTHESIS OF EUCOMOLS USING SHARPLESS CATALYTIC ASYMMETRIC DIHYDROXYLATION†

Sang-sup Jew,* Hyun-ah Kim, Jeong-hoon Kim, and Hyeung-geun Park

College of Pharmacy, Seoul National University, San 56-1, Shillim-Dong, Kwanak-Gu, Seoul, 151-742, Korea

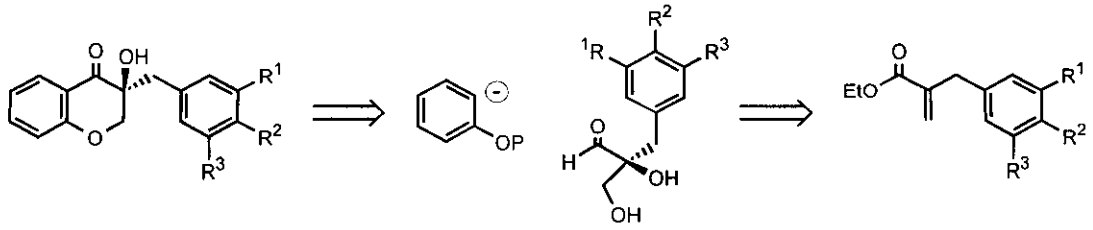
Abstract - A novel synthetic method was developed for eucomols, (*S*)-3-hydroxyhomoisoflavanones. Addition of aryllithium to aldehyde ((*S*)-**9**) obtained by asymmetric dihydroxylation of **4**, followed by the formation of cyclic ether, gave eucomols, (*S*)-3-hydroxyhomoisoflavanones (**1a-e**).

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 (-)-haematoxylin[5] 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 Sharpless[6] as a key reaction.

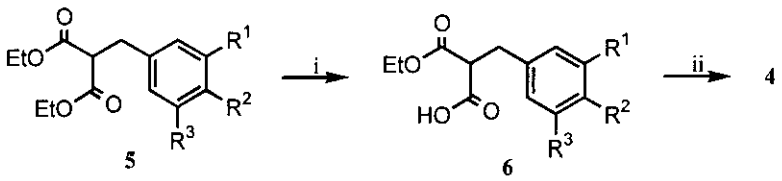
Scheme 1



(*S*)-**1** **2** (*S*)-**3** **4**

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



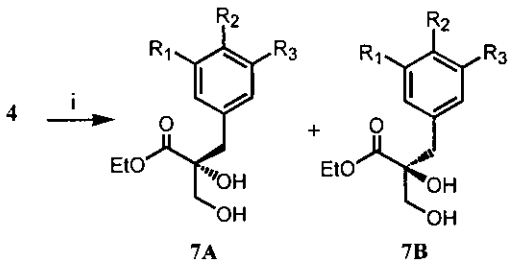
5 **6**

	R^1	R^2	R^3
a	H	H	H
b	H	OMe	H
c	OMe	H	H
d	OMe	OMe	H
e	OMe	OMe	OMe

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), CH_2NMe_2I (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*-dimethylmethyleneammonium 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:H_2O = 1:1, 0 °C, 20-24 h.

Table 1

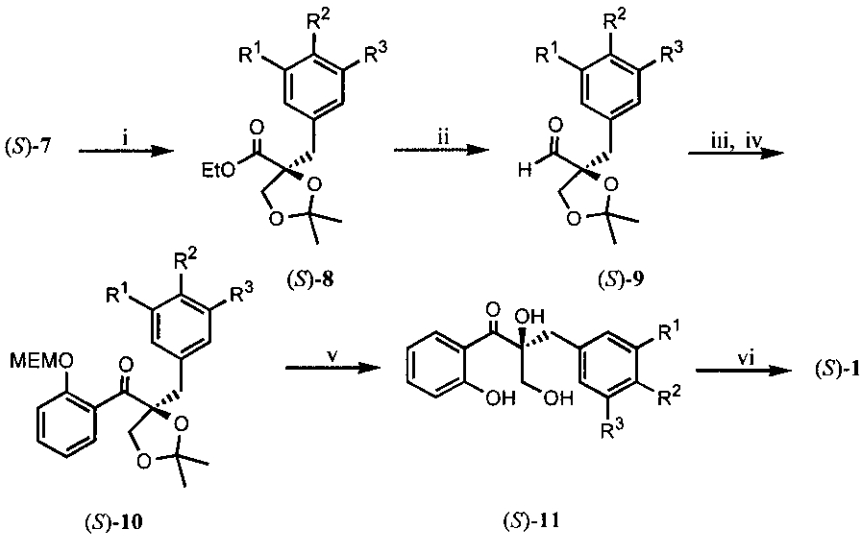
	AD-mix-α,	**7A**	AD-mix-β,	**7B**
	% ee	% yield	% ee	% yield
a	71	85	76	90
b	63	80	80	93
c	75	82	88	97
d	83	94	90	96
e	93	83	93	97

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 acid[7] 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 ^{1}H-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-methoxyethoxymethoxyphenyllithium[8] 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 reaction[9] 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*)-MEMOC$_6$H$_4$Li (1.0 eq), THF, -78 °C→rt, 3-5 h; (iv) PCC (1.5 eq), NaOAc (0.3 eq), CH_2Cl_2, 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) (C_6H_5)$_3$P (1.5 eq), DEAD (1.5 eq), THF, rt, 12 h, (*S*)-**1c** (71%), (*S*)-**1d** (81%), (*S*)-**1e** (73%).

ACKNOWLEDGEMENT

This paper was supported by NON DIRECTED RESEARCH FUND, Korea Research Foundation, 1996.

REFERENCES AND NOTES

1. (a) W. Heller and C. Tamm, *Fortschr. Chem. Org Naturst.*, 1981, **40**, 105; (b) M. Adinolfi, G. Barone, M. Belardini, R. Lanzetta, G. Laonigro, and M. Parrilli, *Phytochemistry*, 1985, **24**, 2423; (c) L. Camarda, L. Merlini, and G. Nasini, *Heterocycles*, 1983, **20**, 39; (d) A. Tada, R. Kasai, T. Saitoh, and J.

Shoji, *Chem. Pharm. Bull.*, 1980, **28**, 1477 and 2039; (e) G. Barone, M. Belardini, R. Lanzetta, G. Laonigro, and M. Parrilli, *Rend. Accad. Sci. Fis. Mat., Naples (Ital.),* 1983, **50**, 297 [*Chem. Abstr.*, 1985, **102**, 5997g]; (f) N. Kaneda, H. Nakanishi, T. Kuraishi, and T. Katori, *Yakugaku Zasshi,* 1983, **103**, 1133; (g) M. Adinolfi, G. Barone, M. Belardini, R. Lanzetta, G. Laonigro, and M. Parrilli, *Phytochemistry,* 1984, **23**, 2091; (h) M. Adinolfi, G. Barone, R. Lanzetta, G. Laonigro, L. Mangoni, and M. Parrilli, *ibid.*, 1985, **24**, 624; (i) Y. Watanabe, S. Sanada, Y. Ida, and J. Shoji, *Chem. Pharm. Bull.,* 1985, **33**, 5358.

2. (a) M. Namikoshi, H. Nakata, and T. Saitoh, *Phytochemistry,* 1987, **26**, 1831; (b) T. Saitoh, S. Sakashita, H. Nakata, T. Shimokawa, K. Kinjo, J. Yamahara, M. Yamasaki, and T. Nohara, *Chem. Pharm. Bull.,* 1986, **34**, 2506; (c) K. K. Purushothaman, K. Kalyant, K. Subramaniam, and S. P. Shanmughanathan, *Indian J. Chem., Sect. B.* **21,** 383; (d) D. D. Mc Pherson, G. A. Cordell, D. D. Soejarto, J. M. Pezzut, and H. H. S. Fong, *Phytochemistry*, 1983, **22,** 2835.

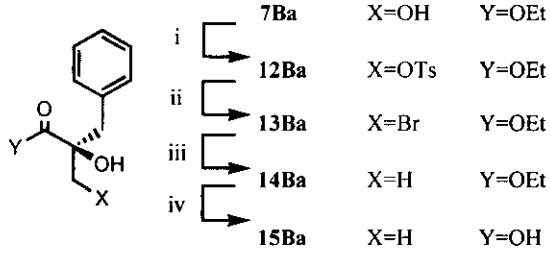
3. F. A. Davis and B.-C. Chén, *Tetrahedron Lett.*, 1990, **31**, 6823.

4. F. A. Davis and B.-C. Chen, *J. Org. Chem.* 1993, **58**, 1751.

5. A. Arnoldi, A. Bassoli, G. Borgonovo, and L. Merlini, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2447.

6. R. A. Johnson and K. B. Sharpless, 'Catalytic Asymmetric Synthesis: Catalytic Asymmetric Dihydroxylation.' ed. by I. Ojima, VCH publishers, New York, 1993, pp. 227-272.

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

(**13Ba**). Debromination of **13Ba**, followed by hydrolysis afforded **15Ba** ($[\alpha]^{20}_D$ +13.2° (c 1.51, dioxane) *lit.*[7b] (*R*)-2-hydroxy-2-methyl-3-phenylpropionic acid, $[\alpha]^{20}_D$ +17.0° (c 5.60, dioxane)); (b) M. Kobayashi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 1898.

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

9. (a) S. Bitlner and Y. Assaf, *Chem. Ind.*, 1975, 281; (b) M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, *J. Chem Soc., Perkin Trans 1*, 1975, 461.

Received, 24th February, 1997