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Enantioselective synthetic method for 3-hydroxyflavanones: an approach to (2*R*,3*R*)-3′,4′-*O*-dimethyltaxifolin

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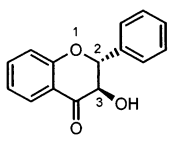
Abstract

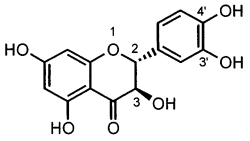
A new enantioselective synthetic method for (2*R*,3*R*)-3-hydroxyflavanone (**1a**) was developed via asymmetric dihydroxylation (ADH) and intramolecular Mitsunobu reaction as key reactions and the application to synthesis of (2*R*,3*R*)-3′,4′-*O*-dimethyltaxifolin (**1b**) is described.

Keywords: 3-hydroxyflavanone; asymmetric dihydroxylation; intramolecular Mitsunobu reaction; (2*R*,3*R*)-3′,4′-*O*-dimethyltaxifolin.

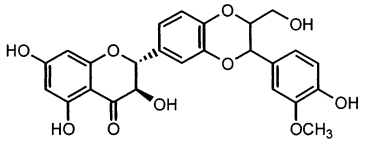
3-Hydroxyflavanone type natural products which are widely distributed in the plant kingdom show considerable and various biological activities.[1] Among them, Silybin and Taxifolin show strong hepatoprotective effect due to their strong antioxidant effect.[2]



3-Hydroxyflavanone



Taxifolin



Silybin

Two chiral centers exist at C(2) and C(3) in 3-hydroxyflavanone and the absolute configurations of the majority of naturally occurring 3-hydroxyflavanones are 2*R* and 3*R*. Onda (57–62% ee)[3] and Ferreira (20–92% ee)[4] reported the enantioselective synthesis of 3-hydroxyflavanone derivatives by using catalytic asymmetric epoxidation, but the stereoselectivity is relatively lower than the practical level. In this paper, a highly enantioselective synthetic method (99% ee) for optically pure (2*R*,3*R*)-3-hydroxyflavanones by using catalytic asymmetric dihydroxylation[5] and an intramolecular Mitsunobu reaction[6] as key reactions and the application to the synthesis of (2*R*,3*R*)-3′,4′-*O*-dimethyltaxifolin are described.

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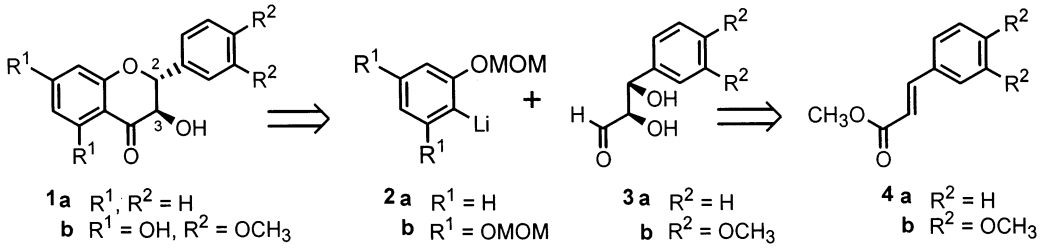
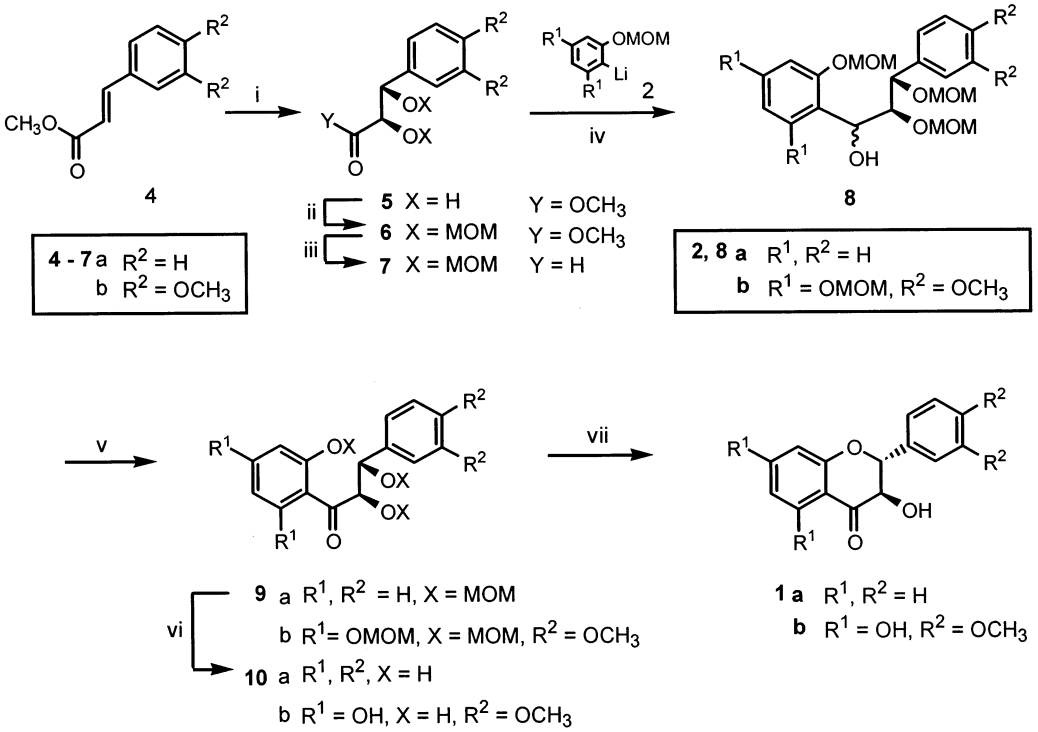
(2*R*,3*R*)-3-Hydroxyflavanones (**1a**,**b**) were retrosynthesized via three key steps; asymmetric dihydroxylation of methyl cinnamates (**4a**,**b**), addition of aryllithium (**2a**,**b**) to chiral dihydroxyaldehydes (**3a**,**b**), and intramolecular Mitsunobu reaction as shown in Scheme 1.



Scheme 1.

Sharpless asymmetric dihydroxylations of **4a** and **4b** with AD-*mix*-α[7] gave highly optically pure diols, **5a** (80, 99% ee) and **5b** (89, 99% ee), respectively (Scheme 2). The enantiomeric excess was determined by the analysis of ^{1}H NMR of the diastereomeric Mosher's esters of **5a** and **5b**.[8] The absolute configurations of C(2) and C(3) in **5a** were assigned as 2*R*,3*S* by comparison with the literature data.[9] In the case of **5b**, the absolute configuration was tentatively assigned as 2*R*,3*S* from enantioselectivity mnemonic of ADH reactions (Table 1).[5]



Scheme 2. Reaction conditions: (i) AD-*mix*-α (1.4 g/mmol), methanesulfonamide (1.0 equiv.), *t*-BuOH–H_2O (1:1) soln., 18–24 h. **5a** (80%), **5b** (89%), (ii) MOMCl (9–10 equiv.), $(i\text{-Pr})_2$NEt (2.5 equiv.), CH_2Cl_2, rt, 8–10 h, **6a** (95%), **6b** (92%), (iii) DIBAL-H (1.3 equiv.), toluene, −78°C, 1.5 h, **7a** (69%), **7b** (83%), (iv) **2a** (1.0 equiv.), THF, −78°C, 5 min then **5a** (0.78 equiv.), −78°C to rt, 1.5 h, **8a** (50%); **2b** (1.2 equiv.), THF, 50°C, 20 min, **5b** (1.0 equiv.), −50°C to rt, 30 min, **8b** (65%), (v) NMO (1.5 equiv.), TPAP (0.2 equiv.), 4 Å molecular sieve, CH_2Cl_2, rt, 1.5–2 h, CH_2Cl_2, **9a** (92%), **9b** (90%), (vi) 2% HCl in MeOH, 40°C, 2 h, **10a** (31%), **10b** (41%), (vii) PPh_3 (1.5 equiv.), DEAD (1.5 equiv.), THF, rt, 40 min, **1a** (54%), **1b** (51%)

Table 1
Asymmetric dihydroxylation of methyl cinnamates (**4**)

$$\mathbf{4} \xrightarrow{\text{asymmetric dihydroxylation}} \mathbf{5}$$

	R^2	% Yield[a]	% ee[b]	Config.	$[\alpha]_D^{20}$
a	H	80	99	2*R*,3*S*[c]	+10.6
b	OCH_3	89	99	2*R*,3*S*[d]	+2.3

[a] Isolated yields by column chromatography with silica gel.

[b] The enantiomeric excess was determined by the analysis of ^1H NMR of the diastereomeric Mosher's esters[9] of **5a** and **5b**.

[c] The absolute configurations of the diols were determined by comparison of sign of optical rotation of the enantiomer (2*S*,3*R*, lit.[9] $[\alpha]_D^{20}$ −10.7, enantiomerically pure).

[d] The absolute configurations were tentatively assigned by enantioselectivity mnemonic in ADH reactions.

Protection of the C(2) and C(3) hydroxyl groups of **5a**,**b** with methoxymethylchloride (MOMCl) and *N*,*N*-diisopropylethylamine followed by reduction with diisobutylaluminum hydride at −78°C gave corresponding aldehydes, **7a**,**b**. Addition of aryllithium **2a**,**b**[10] to the aldehyde **7a**,**b** afforded secondary alcohol **8a**,**b**, respectively. Oxidation of **8a**,**b** with tetrapropylammonium perruthenate[11] and *N*-methylmorpholine *N*-oxide produced the corresponding ketone **9a**,**b** which were deprotected in acidic condition to give pentahydroxyketone **10a**,**b**. **10a** and **10b** were submitted to the intramolecular Mitsunobu reaction with triphenylphosphine and diethyl azodicarboxylate to give 3-hydroxyflavanone **1a** ($[\alpha]_D^{23}$ −25.0, CH_2Cl_2; lit.[3a] $[\alpha]_D^{12}$ −12.5, CH_2Cl_2; lit.[12] $[\alpha]_D^{23}$ −15.9, CH_2Cl_2; 59% ee) and 3′,4′-*O*-dimethyltaxifolin **1b** ($[\alpha]_D^{17}$ +12.01, CH_3OH), respectively. The absolute configurations of new stereogenic center (C(2)) of **1a**,**b** were assigned as 2*R* by the anti-relationship between C(2)H and C(3)H ($J = 11.5$ Hz), which is in accord with the SN_2 mechanism of the Mitsunobu reaction.

In conclusion, highly enantioselective synthetic method for (2*R*,3*R*)-3-hydroxyflavanones was developed via asymmetric dihydroxylation (ADH) and intramolecular Mitsunobu reaction as key reactions. By this new synthetic method, (2*R*,3*R*)-3′,4′-*O*-dimethyltaxifolin was prepared from methyl 3,4-dimethoxycinnamate in seven steps (8, 99% ee). We believe that the highly efficient synthetic method could be applied for the synthesis of other biologically active (2*R*,3*R*)-3-hydroxyflavanone type natural products.

Acknowledgements

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References

1. Bohm, B. A. In *The Flavonoids—Advances in Research Since 1986*; Harbone, J. B., Ed; Chapman & Hall: London, 1994; p. 419.

2. Cavallini, L.; Luchetti, G. *Gazz. Med. Ital.* **1976**, *125*, 365.
3. (a) Takahashi, H.; Kubota, Y.; Miyazaki, H.; Onda, M. *Chem. Pharm. Bull.* **1984**, *32*, 4852. (b) Takahashi, H.; Li, S.; Harigaya, Y.; Onda, M. *J. Nat. Prod.* **1988**, *51*, 730.
4. Van Rensberg, H.; Van Heerden, D. S.; Beznidenhoudt, B. C. B.; Ferreira, D. *J. Chem. Soc., Chem. Commun.* **1996**, 2747.
5. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. Catalytic Asymmetric Dihydroxylation. VCH: New York, 1993; pp. 227–272.
6. (a) Mitsunobu, O. *Chem. Rev.* **1981**, 1. (b) Lee, B. H.; Biswas, A.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 106. (c) Mattingly, P. G.; Kerwin, J. K.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983.
7. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
8. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
9. Asymmetric dihydroxylation of **4a** by using dihydroquinidine 4-chlorobenzoate as catalyst gave the enantiomer of **5a** (2*S*,3*R*, $[\alpha]_D^{20}$ −10.7, enantiomerically pure): Davis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957.
10. **2a** was prepared from 2-methoxymethoxybromobenzene and *n*-BuLi by lithium halogen exchange and **2b** was prepared from 1,3,5-trismethoxymethoxybenzene and *n*-BuLi by lithium hydrogen exchange.
11. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1725.
12. Tacko, I.; Satoshi, M. *J. Heterocycl. Chem.* **1995**, *32*, 1125.