Kinetic Resolution

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A Practical Access to Highly Enantiomerically Pure Flavanones by Catalytic Asymmetric Transfer Hydrogenation

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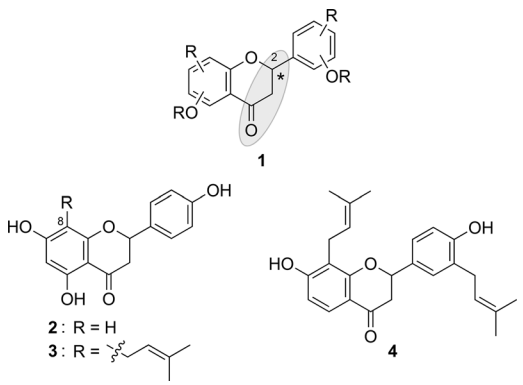
Dedicated to Dr. habil. Helmuth Tietz on the occasion of his 65th birthday

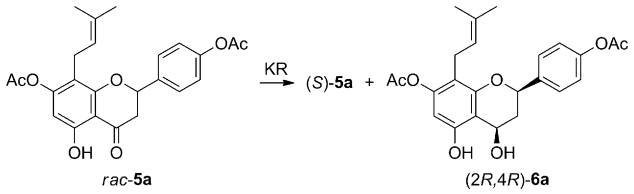
Flavonoids constitute the largest share of secondary metabolites occurring in higher plants. A subgroup of these natural products, the flavanones (**1**), features a variety of useful bioactivities such as antifungal, antibacterial, and antiviral effects (Scheme 1).[1] Particularly prenylated derivatives show pronounced physiological activities.[2] The naturally occurring



Scheme 1. Basic structure of flavanones (**1**), naringenin (**2**), 8-prenylnaringenin (**3**), and glabrol (**4**).

(2*S*) enantiomer of 8-prenylnaringenin (**3**), also known as sophoraflavanon B,[3] is currently the strongest phytoestrogen known[4,5] and additionally exhibits further interesting biological properties.[6] Similarly, the less oxygenated prenylated flavanone glabrol (**4**) displays a range of interesting biological effects. Amongst others,[7] the licorice constituent (*S*)-**4** inhibits the cancer target isoprenylcysteine carboxyl methyltransferase[8a] and shows potent activity against *Staphylococcus aureus* and *Mycobacterium smegmatis*.[8b]

While many flavanones can be isolated from plants, only the naturally occurring enantiomers are available in this way and often only with low efficiency. The enantioselective synthesis of flavanones has been explored more intensely in recent years,[9,10] but additional studies, which provide practical access to highly enantiomerically pure flavanones, are still very desirable. Here we report such a procedure[11] that gives rise to both enantiomers quickly and efficiently through the non-enzymatic kinetic resolution[12] of easily available racemic flavanone derivatives. The starting point for the development of this process was the discovery that the racemic β-chiral ketone *rac*-**5a**[4] derived in only three steps from naringenin (**2**) can be subjected to a surprisingly[13] selective asymmetric transfer hydrogenation[14] to give (*S*)-**5a** and (2*R*,4*R*)-**6a** under suitable conditions (Scheme 2).



Scheme 2. Kinetic resolution (KR) of *rac*-7,4′-*O*,*O*-diacetyl-8-prenylnaringenin (*rac*-**5a**) by asymmetric reduction.

Initially, the kinetic resolution of *rac*-**5a** was investigated using a number of chiral metal–diamine complexes (**I**–**IV**, Scheme 3)[15] in a mixture of formic acid and triethylamine (Table 1). The chiral complexes (**I**–**IV**) were generated in situ from a suitable metal precursor and the monotosylated diamine ligand and transformed into the catalytically active metal hydride under the reaction conditions of transfer hydrogenation. Only rhodium(III) complex **III**[15b–f] provided very good yields and excellent enantiomeric excesses for both products. When the (*R*,*R*)-diamine ligand was used, the (*R*) enantiomer was transfer hydrogenated highly selectively even with only 0.5 mol% of **III**, and a mixture of the nonconverted ketone (*S*)-**5a**[16] and the alcohol (2*R*,4*R*)-**6a** was obtained which was readily separated by flash chromatography. An increase of the catalyst loading to 2 mol% **III** yielded (*S*)-**5a**

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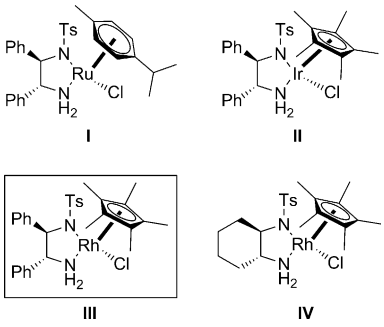


Scheme 3. Chiral metal–diamine complexes **I**–**IV**. Ts = tosyl = *p*-toluenesulfonyl.

Table 1: Asymmetric reduction of *rac*-**5a** to give ketone (*S*)-**5a** and alcohol (2*R*,4*R*)-**6a** (see Scheme 2).[a,b]

Cat.	[mol%]	(*S*)-**5a**	(2*R*,4*R*)-**6a**
I	2[c]	56%, 64% *ee*	–[d]
I	5[e]	traces[f]	73%, 7% *ee*
II	2	72%, 15% *ee*	13%, –[f]
II	5	82%, 16% *ee*	18%, –[f]
III	0.5	50%, 97% *ee*	45%, ≥99% *ee*
III	2	43%, ≥99% *ee*	41%, ≥95% *ee*[g]
IV	2	89%, 14% *ee*	–[d]
IV	5[h]	49%, 70% *ee*	48%, 79% *ee*

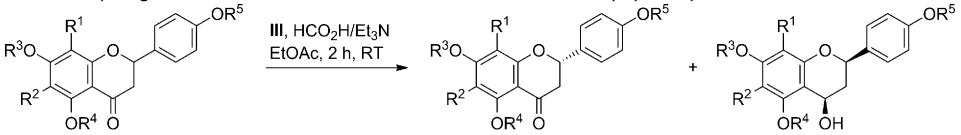
[a] HCO_2H/Et_3N, EtOAc, 2 h, RT. [b] Enantiomeric excess (*ee*) determined by HPLC on a chiral stationary phase. [c] 10 h. [d] Not isolated. [e] 14 h. [f] *ee* value not determined. [g] After oxidation to give (*R*)-**5a** determined by optical rotation. [h] 19 h.

even with ≥99% *ee*. Under analogous conditions, ruthenium(II) complex **I**[15a,d,e] showed only low enantioselectivity, and iridium(III) complex **II**[15b–e] was much less reactive than **III**. Likewise, switching from rhodium(III) catalyst **III** to **IV**[15b] resulted in decreased reactivity and selectivity.

With rhodium(III) catalyst **III**, a variety of flavanone derivatives (*rac*-**5a–i**) can be subjected to efficient kinetic resolution (Table 2). Both the ketones (*S*)-**5** and the alcohols (2*R*,4*R*)-**6** were isolated in good yields with excellent enantiomeric excesses. Besides acyl groups, also ethers and acetals are well tolerated, whereas silyl ethers are partially cleaved under these conditions. Control of conversion is not required, since the reaction stops completely after transfer hydrogenation of one enantiomer. While a loading of 2 mol% of **III** is usually sufficient to obtain almost enantiomerically pure products, in part significantly reduced catalyst loadings can be used depending on the substrate. Thus, kinetic resolution of *rac*-**5g**[17] with only 0.2 mol% of **III** provided the flavanone derivative (*S*)-**5g** with 99% *ee*, and for the preparation of (*S*)-**5b**[18] with 95% *ee* the loading could even be lowered to 0.1 mol% **III**. Only for the highly enantioselective synthesis of the anti-inflammatory[19a] and molluscicidal[19b] naringenin trimethyl ether (*S*)-**5h** as well as the methyl ether (*S*)-**5i** a higher catalyst loading was necessary.

NOESY measurements of the resulting alcohols **6** showed that only the *cis* diastereomers were formed, which was also confirmed by X-ray analysis[16] of the compounds (2*R*,4*R*)-**6f**, (2*R*,4*R*)-**6h**, and (2*R*,4*R*)-**6i**. The absolute configuration of the acetylated flavanones (*S*)-**5a**,**b**,**c**,**f** was determined by deacylation to give (*S*)-8-prenylnaringenin ((*S*)-**3**), (*S*)-naringenin ((*S*)-**2**), and (*S*)-6-(1,1-dimethylallyl)naringenin, respectively, while the absolute configuration of (*S*)-**5i** was established by crystal structure analysis[16] of (2*R*,4*R*)-**6i** using anomalous X-ray diffraction. For the flavanone derivatives (*S*)-**5d**,**e**,**g**,**h**, the absolute configuration was assigned in analogy to the five entries mentioned above and by application of the transition-state model in Scheme 4. This model is based on the attractive CH–π interactions between the methyl groups of the pentamethylcyclopentadienyl (Cp*) ligand and the aromatic part of the substrate ketone as well as on the simultaneous transfer of the rhodium hydride and the *syn* NH proton to the carbonyl group.[20] A geometry like that sketched in Scheme 4 for the unreactive (*S*)-flavanone enantiomer leads to a destabilizing interaction between the tosyl group of the rhodium complex and the aromatic substituent at C-2 of the flavanone, which does not occur in

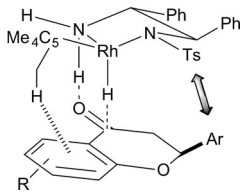
Table 2: Asymmetric transfer hydrogenation of flavanone derivatives *rac*-**5** with rhodium(III) catalyst **III**.



rac-**5a–i** (*S*)-**5a–i** (2*R*,4*R*)-**6a–i**

rac-**5**	R^1	R^2	R^3	R^4	R^5	[mol%] (*R*,*R*)-**III**	(*S*)-**5** yield [%][a]	(*S*)-**5** *ee* [%][b]	(2*R*,4*R*)-**6** yield [%][a]	(2*R*,4*R*)-**6** *ee* [%][b]
a	prenyl	H	Ac	H	Ac	0.5	50	97	45	≥99
b	H	H	Ac	H	Ac	0.1	47	95	45	≥99
c	prenyl	H	Ac	Ac	Ac	1	44	≥99	–	–
d	prenyl	H	Ac	MOM	Ac	2	41	≥99	44	≥99
e	H	H	Ac	MOM	Ac	2	42	97	47	98
f	H	1,1-dimethylallyl	Ac	H	Ac	2	48	≥99	47	≥95[c]
g	H	prenyl	Ac	H	Ac	0.2	47	99	50	–[d]
h[e]	H	H	Me	Me	Me	10	48	98	48	≥99
i	Me	H	Me	Me	Me	10	48	99	47	≥95[c]

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] After oxidation to give (*R*)-**5** determined by optical rotation. [d] Not determined. [e] At 0°C, 20 h reaction time. Prenyl = 3-methyl-2-butenyl, MOM = methoxymethyl.

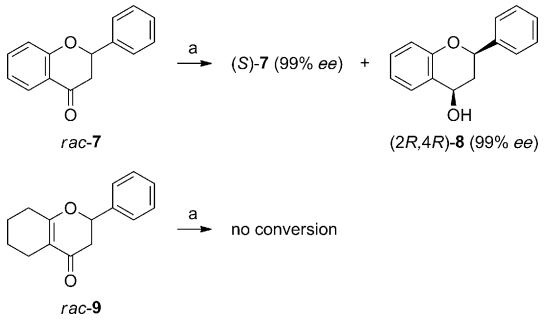


Scheme 4. Unfavorable Ts↔Ar interaction in the transition state of the asymmetric transfer hydrogenation of the unreactive (*S*)-flavanone enantiomer with the catalytically active species from **III**.

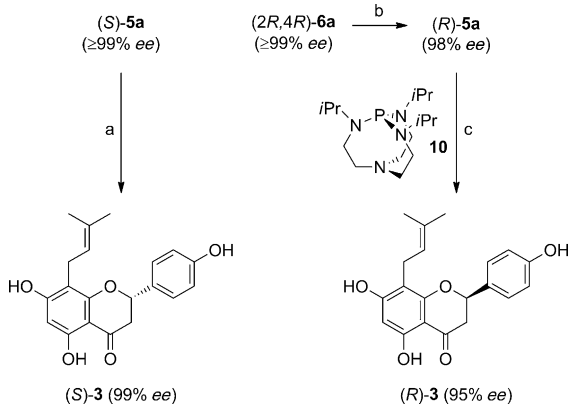
the transition state of the asymmetric transfer hydrogenation of the reactive (*R*) enantiomer.

The model depicted in Scheme 4 implies that less substituted flavanones should also undergo a highly enantioselective reduction. Indeed, the simple flavanone *rac*-**7** reacted with perfect discrimination between the two enantiomers as well to give ketone (*S*)-**7**[21] and alcohol (2*R*,4*R*)-**8**[22] in virtually enantiopure form (Scheme 5). In contrast, *rac*-**9**[23] lacking the aryl ketone moiety showed no conversion.

Scheme 6 illustrates the application of the highly enantioselective asymmetric transfer hydrogenation of *rac*-**5a** with rhodium(III) complex **III** to the synthesis of (*S*)- and (*R*)-8-prenylnaringenin (**3**). Oxidation with activated manganese dioxide[10h,22] smoothly converted the alcohol (2*R*,4*R*)-**6a** to



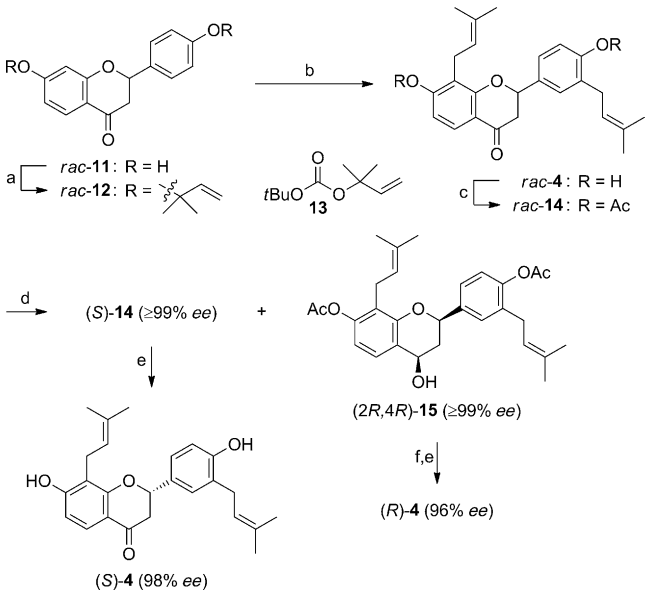
Scheme 5. Asymmetric transfer hydrogenation of substrates *rac*-**7** and *rac*-**9**. a) 1 mol% **III**, HCO_2H/Et_3N, CH_2Cl_2, 24 h, RT, 47% (*S*)-**7**, 43% (2*R*,4*R*)-**8**.



Scheme 6. Enantioselective synthesis of (*S*)- and (*R*)-8-prenylnaringenin (**3**). a) *Pseudomonas* sp. lipase, THF, BuOH, RT, 96%; b) MnO_2, CH_2Cl_2, RT, 74%; c) 5 mol% **10**, MeOH, 40°C, 64%.

the flavanone derivative (*R*)-**5a**. Similarly, oxidation with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide[24] afforded (*R*)-**5a** without racemization; however, the yield was slightly lower (64%). Deacetylation of diacetate (*S*)-**5a** to give the flavanone (*S*)-8-prenylnaringenin ((*S*)-**3**) with potassium carbonate in methanol[4] caused significant racemization. Gratifyingly, this transformation succeeded by transesterification with butanol in the presence of catalytic amounts of a lipase from *Pseudomonas* sp. (Roche) at room temperature without stereochemical erosion in high yield. Alternatively, transesterification with methanol catalyzed by the Verkade base **10**[25] (10 mol%) at 40°C could be performed, after which (*S*)-**3** was isolated in 89% yield with 92% *ee*. This non-enzymatic deblocking was further optimized for diacetate (*R*)-**5a** and led with only minimal racemization to (*R*)-8-prenylnaringenin ((*R*)-**3**).

Our approach to (*S*)- and (*R*)-glabrol (**4**) is shown in Scheme 7. Racemic **4**[26] was prepared from commercially available liquiritigenin (*rac*-**11**)[27] by formation of the double isoprenyl ether through reaction with carbonate **13**[28] followed by a highly regioselective europium(III)-catalyzed[4,29] twofold Claisen rearrangement preferably under microwave irradiation. Formation of diacetate *rac*-**14** set the stage for the crucial asymmetric transfer hydrogenation, which proceeded with excellent enantioselectivity using catalyst **III**. As yet another alternative deblocking procedure that minimizes racemization, sodium perborate[30] in methanol converted (*S*)-**14** to the natural product (*S*)-glabrol ((*S*)-**4**),[7a,31] while the



Scheme 7. Enantioselective synthesis of (*S*)- and (*R*)-glabrol (**4**). a) **13**, 1 mol% $[Pd(PPh_3)_4]$, THF, 0°C to RT, 100%; b) 5 mol% $[Eu(fod)_3]$, toluene, 2 h, 100°C, microwave irradiation (300 W), 81% or 5 mol% $[Eu(fod)_3]$, toluene, 24 h, 100°C, 67%; c) Ac_2O, Et_3N, CH_2Cl_2, 0°C to RT, 97%; d) 1 mol% **III**, HCO_2H/Et_3N, CH_2Cl_2, 24 h, RT, 46% (*S*)-**14** (≥99% *ee*), 44% (2*R*,4*R*)-**15** (≥99% *ee*); e) $NaBO_3 \cdot 4H_2O$, MeOH, RT, 47% (*S*)-**4**, 57% (*R*)-**4**; f) 15 mol% TPAP, NMO, MS 4 Å, CH_2Cl_2, RT, 98%. fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

unnatural enantiomer (*R*)-**4** was obtained from (2*R*,4*R*)-**15** after oxidation and deacetylation.

In summary, almost enantiomerically pure flavanones, in particular prenylated representatives, are available through kinetic resolution of the β-chiral ketones with rhodium(III) complex **III** in a mixture of formic acid and triethylamine in high yield. Thus, a practical enantioselective preparation of the bioactive flavanones 8-prenylnaringenin (**3**) and glabrol (**4**) was accomplished for the first time, and these compounds can now be supplied easily for further bioassays.

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