Flavonoids

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Utilizing an *o*-Quinone Methide in Asymmetric Transfer Hydrogenation: Enantioselective Synthesis of Brosimine A, Brosimine B, and Brosimacutin L

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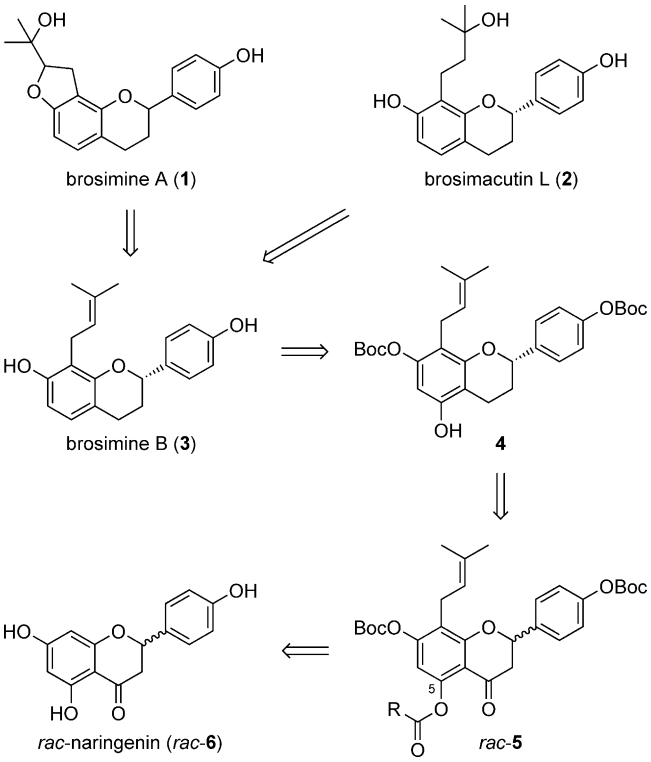
Abstract: *A concise and highly enantioselective synthesis of the flavonoids brosimine A, brosimine B, and brosimacutin L is reported for the first time. The key transformation is a single-step conversion of a flavanone into a flavan by means of an asymmetric transfer hydrogenation/deoxygenation cascade.*

Brosimum acutifolium is a tree from the genus *Moraceae*, which is distributed throughout Brazil. The extract of its stem bark is valued in traditional medicine owing to its anti-inflammatory and anti-rheumatic properties.[1] More recent investigations on its crude ground bark extract revealed promising antibacterial activity against both multidrug-resistant and ATCC strains of *Staphylococcus aureus*.[2] Intense studies towards the identification of the bioactive compounds led to the isolation of a variety of flavans, including brosimine A (**1**),[3,4] brosimacutin L (**2**),[4] and brosimine B (**3**).[3,5] Brosimine B (**3**) was recently also isolated from the leaves of *Morus yunnanensis*[6a] and from mulberry leaves.[6b] Of note, flavan **2** was shown to display significant cytotoxic activity against vincristine-resistant P388 cancer cells.[4] While the absolute configuration of flavan **2** was assigned as (*S*) on the basis of CD measurements, that of **3** is assumed to be (*S*) but this is so far unknown, and neither the relative nor the absolute configuration of **1** has yet been determined. Herein we report the first enantioselective synthesis of flavans[7] **1**–**3** by using a novel domino asymmetric transfer hydrogenation (ATH)/deoxygenation of a racemic flavanone with kinetic resolution as the key transformation.

As outlined in Scheme 1, brosimine A (**1**) might be derived from brosimine B (**3**) through a catalyst-controlled Shi epoxidation[8] followed by 5-*exo-tet* cyclization. Brosimacutin L (**2**) can also be connected to **3** by means of a regioselective cobalt-catalyzed hydration according to a method reported by Mukaiyama.[9] Flavan **3** should be attainable from compound **4** by reductive removal of the phenolic hydroxy substituent[10] and cleavage of the carbonate groups. We envisioned that enantiopure phenol **4** might be directly available from a racemic flavanone *rac*-**5** bearing a suitable 5-*O*-acyl substituent through the recently disclosed rhodium-catalyzed ATH of flavanones[11] by utilizing a catalyst developed by Noyori.[12] Similar ketone deoxygenations lacking the enantioselectivity are well known for the reaction of 5-*O*-acetyl[13] or 5-*O*-methoxycarbonyl[14] flavanones with sodium borohydride.[15] A range of ketones *rac*-**5** would be readily obtained from racemic naringenin (*rac*-**6**) in analogy to the previously reported synthesis of 8-prenylflavanones.[16]



Scheme 1. Retrosynthesis of brosimine A (**1**), brosimacutin L (**2**), and brosimine B (**3**) leading to racemic naringenin (*rac*-**6**).

The preparation of ATH substrates *rac*-**5a**,**b** from commercially available *rac*-**6** is depicted in Scheme 2. After chemoselective conversion of *rac*-**6** to give the di-*O*-Boc derivative *rac*-**7**, the prenyl ether *rac*-**8** was synthesized under Mitsunobu[17] conditions in excellent yield. Subsequently, a Eu-catalyzed sigmatropic rearrangement accelerated by microwave irradiation afforded the 8-prenylflavanone *rac*-**9** in only five minutes. Finally, treatment of *rac*-**9** with either acetic anhydride or methyl chloroformate gave rise to the desired 5-*O*-acyl derivatives *rac*-**5a** and *rac*-**5b**, respectively.

The crucial ATH of the flavanones *rac*-**5** with kinetic resolution was screened by using the catalyst (*S*,*S*)-**10**[12] and a mixture of formic acid and triethylamine in ethyl acetate at

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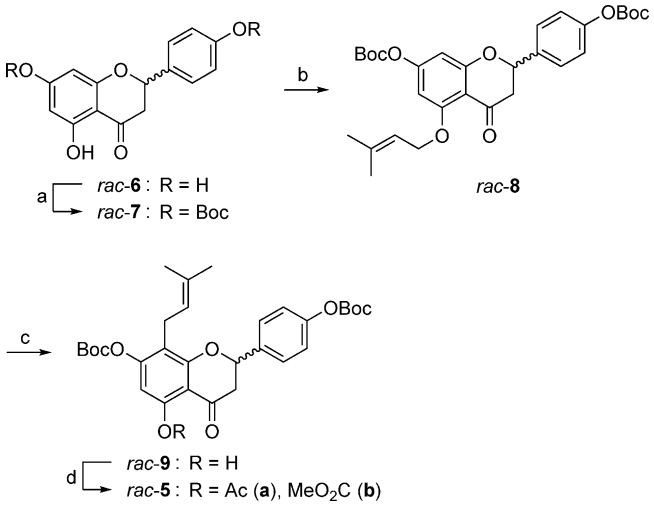
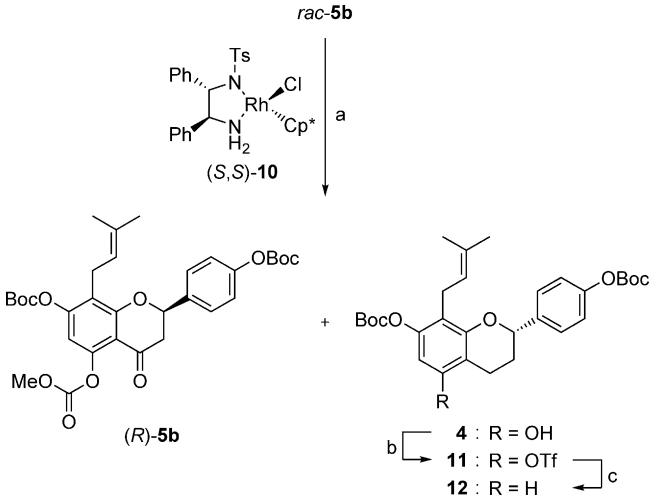


Scheme 2. Preparation of flavanones *rac*-**5** from naringenin (*rac*-**6**). a) Boc_2O, 10 mol% DMAP, Et_3N, THF, RT, 1 h, 94%; b) Ph_3P, DIAD, 3-methyl-2-buten-1-ol, THF, RT, 14 h, 95%; c) 10 mol% [Eu(fod)$_3$], $CHCl_3$, 110°C, 5 min, microwave, 70%; d) for *rac*-**5a**: Ac_2O, Et_3N, THF, 46°C, 20 h, 80%, for *rac*-**5b**: $ClCO_2Me$, Et_3N, THF, RT, 1 h, 89%. Boc = *tert*-butoxycarbonyl, DMAP = 4-(dimethylamino)pyridine, DIAD = diisopropyl azodicarboxylate, fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate.

room temperature. Next to the substrates *rac*-**5a**,**b**, we also tested the corresponding racemic tri-*O*-Boc derivative of 8-prenylnaringenin[18] as well as *rac*-5,7,4′-*O*,*O*,*O*-triacetyl-8-prenylnaringenin. The latter compound had already been subjected to an analogous ATH reaction with the catalyst (*R*,*R*)-**10**, from which no benzylic alcohol reduction product could be isolated.[11] From this set of substrates, the methylcarbonate *rac*-**5b** turned out to be optimal and led to the most efficient flavan production (Scheme 3). While separation of



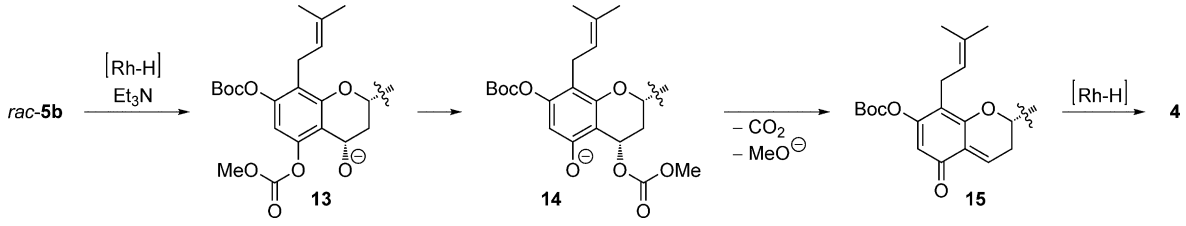
Scheme 3. ATH of *rac*-**5b** and subsequent conversion to give flavan **12**. a) 1 mol% (*S*,*S*)-**10**, Et_3N/HCO_2H, EtOAc, RT, 15 min, 44% (*R*)-**5b**, 42% **4**; b) Tf_2O, Et_3N, CH_2Cl_2, −40°C, 40 min, 91% **11** (99% *ee*), 100% (*R*)-**5b** (99% *ee*); c) $Pd(OAc)_2$, dppf, HCO_2H, DMF, 2 h, 60°C, 98%. Ts = *p*-toluenesulfonyl, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, Tf = trifluoromethanesulfonyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

the flavanone (*R*)-**5b** and the desired flavan **4** proved to be difficult, the corresponding yields could be readily determined by ^{1}H NMR integration of the product mixture. Subsequent treatment with triflic anhydride allowed the clean separation of the resultant triflate **11** from (*R*)-**5b**. Analysis by HPLC on a chiral stationary phase revealed an excellent enantiomeric excess of 99% for both flavanone (*R*)-**5b** and flavan **11**. A palladium-catalyzed deoxygenation[10] of **11** at C-5 then furnished flavan **12** in almost quantitative yield. In order to experimentally verify the absolute configuration of **4** and **5b** obtained by ATH, we synthesized the corresponding (*R*) enantiomers starting from (*R*)-8-prenylnaringenin,[11] the absolute configuration of which is well known. Comparison of the specific rotation data confirmed the anticipated (*R*) configuration of **5b** and therefore the (*S*) configuration of **4**.[18]

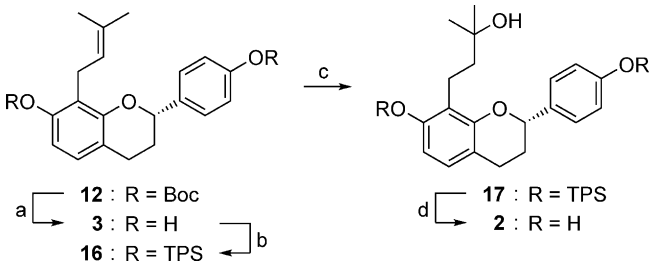
An *o*-quinone methide[19] is believed to be the crucial intermediate of the ATH shown above. In analogy to the mechanistic rationale for the deoxygenation of 5-*O*-acyl substituted flavanones[13,14] and related substrates[15] with sodium borohydride, a plausible pathway from flavanone *rac*-**5b** to flavan **4** is illustrated in Scheme 4. Initially, the ketone is converted into the benzylic alkoxide **13** in a highly enantioselective fashion. Subsequent migration of the methoxycarbonyl group to give the phenoxide **14** is followed by elimination with formation of the reactive *o*-quinone methide **15**, which eventually undergoes a conjugate reduction to afford flavan **4**.

With flavan **12** in hand, brosimine B (**3**) can be synthesized by simple cleavage of the carbonate groups (Scheme 5). While trifluoroacetic acid failed to remove the Boc moieties cleanly, lithium aluminum hydride reduction gave rise to the natural product **3** in good yield and virtually enantiopure form. Starting from brosimine B (**3**), brosimacutin L (**2**) was synthesized in three steps. Formation of the silyl ether **16** and subsequent regioselective hydration by applying Mukaiyama[9] conditions provided the tertiary alcohol **17**. In the course of the latter reaction, the enantiomeric excess dropped slightly to 98%. Finally, cleavage of the silyl ether furnished brosimacutin L (**2**). The specific rotation[20] of the synthetic products **3** and **2** confirmed the (*S*) configuration assigned to **2** from CD measurements and assumed for **3**.[3–6]

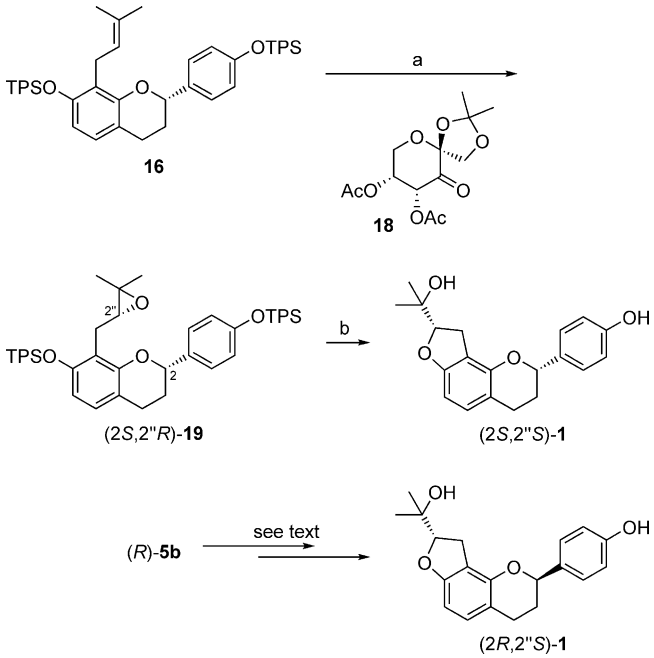
We then utilized Shi's asymmetric epoxidation protocol and a subsequent 5-*exo*-*tet* cyclization to generate flavan **1** (Scheme 6). In accordance with the reported epoxidation of various prenylated arenes featuring an *o*-silyloxy function,[21] Shi's diester **18** proved to be superior to the conventional Shi acetonide catalyst in terms of diastereomeric ratio, and the stereoisomer (2*S*,2″*R*)-**19** was obtained next to only small amounts of its C-2″ epimer. For related prenyl-substituted substrates, approach of the dioxirane derived from **18** was shown to occur from the *Re* face.[21a-c] Eventually, treatment of epoxide (2*S*,2″*R*)-**19** with tetrabutylammonium fluoride[21] furnished (2*S*,2″*S*)-**1** in almost quantitative yield and good diastereomeric purity (d.r. = 94:6). Unfortunately, separation of the two epimers by column chromatography was possible for neither epoxide **19** nor flavan **1**. Moreover, the NMR spectra of (2*S*,2″*S*)-**1** and its C-2″ epimer are very similar. Therefore, a comparison with the published data of the



Scheme 4. Possible mechanism for the deoxygenation of flavanone **5b**.



Scheme 5. Synthesis of brosimine B (**3**) and brosimacutin L (**2**). a) $LiAlH_4$, THF, 60 °C, 50 min, 90 % (99 % *ee*); b) TPSCl, imidazole, DMF, RT, 24 h, 96 %; c) 20 mol % $Co(acac)_2$, $PhSiH_3$, O_2, THF, RT, 24 h, 56 % (98 % *ee*); d) TBAF, THF, 0 °C, 10 min, 75 % (98 % *ee*). TPS = *tert*-butyldiphenylsilyl, acac = acetylacetonate, TBAF = tetrabutylammonium fluoride.



Scheme 6. Synthesis of the brosimine A stereoisomers (2*S*,2″*S*)-**1** and (2*R*,2″*S*)-**1**. a) 60 mol % **18**, Bu_4NHSO_4, DMM, MeCN, phosphate buffer pH 6, K_2CO_3, oxone, 0 °C to RT, 11 h, 66 %; b) TBAF, THF, 0 °C to RT, 30 min, 99 % (d.r. = 94:6; > 99 % *ee*). DMM = dimethoxymethane.

natural product **1** did not reveal conclusive information about its relative configuration.

With the aim of determining the relative and absolute configuration of the natural product **1**, we also synthesized the stereoisomer (2*R*,2″*S*)-**1**. Commencing with a sodium borohydride reduction of (*R*)-**5b** to give the flavan *ent*-**4**, we followed the reaction sequence established for (2*S*,2″*S*)-**1** and used the Shi catalyst **18** again. Additionally, we prepared their enantiomers (2*R*,2″*R*)-**1** and (2*S*,2″*R*)-**1** by utilizing the Shi catalyst *ent*-**18**.[18] For all four stereoisomers of **1**, the optical rotation was measured. Since the diastereomeric ratio and enantiomeric excess for these compounds were known from HPLC on a chiral stationary phase, the specific rotation of the pure isomers could be calculated from the the data obtained. Comparison of these values with the specific rotation of the natural product shows that brosimine A (**1**) possesses a (2*S*,2″*R*) configuration.[22] This assignment is in line with the fact that all three flavans (**1**–**3**) were isolated from *Brosimum acutifolium*. Hence, brosimine A (**1**) is presumably biosynthetically derived from brosimine B (**3**) and has a (2*S*) configuration.

In summary, we have accomplished the first enantioselective synthesis of the three flavans **1**, **2**, and **3**, starting from commercially available racemic naringenin (*rac*-**6**). Central to our strategy is an ATH/deoxygenation cascade that enables the single-step conversion of flavanones into flavans in a highly enantioselective fashion. Brosimine B (**3**) and brosimacutin L (**2**) were obtained with 99 % *ee* and 98 % *ee*, respectively, in a short and efficient reaction sequence, and their absolute configuration was unambiguously established. Likewise, all four stereoisomers of brosimine A (**1**) were readily synthesized with > 99 % *ee*, and our results show that stereoisomer (2*S*,2″*R*)-**1** is the natural product.

Keywords: asymmetric catalysis · domino reactions · flavonoids · kinetic resolution · natural products

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[22] Synthetic (2*S*,2″*S*)-**1**: calculated $[\alpha]_D^{25} = +5.6$ ($c = 0.75$ in $CHCl_3$) from the (2″*S*)-series of **1** and calculated $[\alpha]_D^{25} = +4.3$ ($c = 0.54$ in $CHCl_3$) from the (2″*R*)-series of **1**; synthetic (2*R*,2″*S*)-**1**: calculated $[\alpha]_D^{25} = +83.9$ ($c = 0.56$ in $CHCl_3$) from the (2″*S*)-series of **1** and calculated $[\alpha]_D^{25} = +88.4$ ($c = 0.45$ in $CHCl_3$) from the (2″*R*)-series of **1**; natural **1**:[3] $[\alpha]_D^{25} = -7.06$ ($c = 0.35$ in $CHCl_3$).

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