Organic LETTERS

Letter

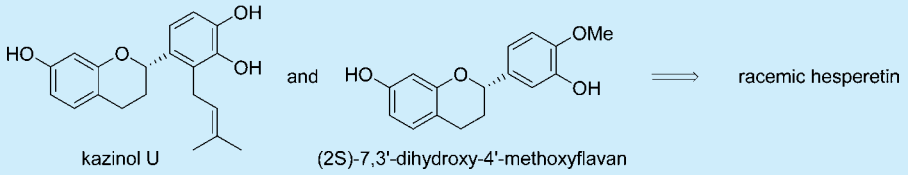
pubs.acs.org/OrgLett

Enantioselective Synthesis of 2′- and 3′-Substituted Natural Flavans by Domino Asymmetric Transfer Hydrogenation/Deoxygenation

Anton Keßberg and Peter Metz*

Fachrichtung Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany

Supporting Information

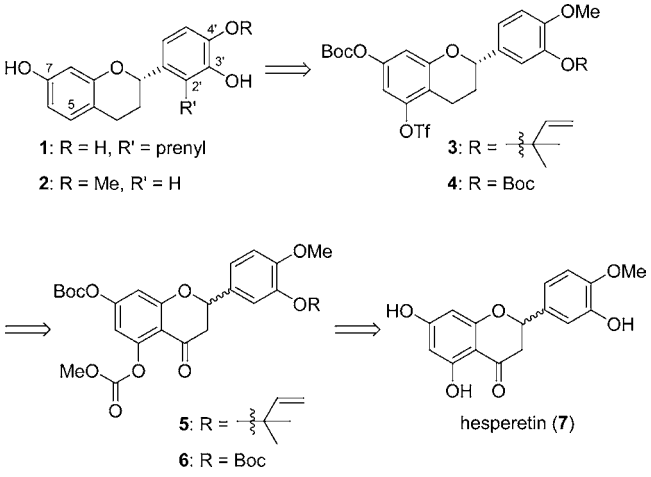


ABSTRACT: A concise and highly enantioselective synthesis of the natural flavans kazinol U and (2*S*)-7,3′-dihydroxy-4′-methoxyflavan is reported for the first time. The key transformation is a single-step conversion of a racemic flavanone to a flavan by means of an asymmetric transfer hydrogenation/deoxygenation cascade with kinetic resolution.

Flavonoids represent a highly interesting and diverse class of natural products that exhibit a wide range of bioactivities.[1] Especially prenylated derivatives are repeatedly reported to show distinct physiological effects.[2] Lately, a particularly fascinating flavan named kazinol U (**1**) was isolated from *Broussonetia kazinoki*.[3] It was shown to be a potent phytoestrogen, antioxidant, and inhibitor of nuclear factor-κB, making it a potential drug to treat menopausal symptoms and type I diabetes.[3−5] As a total synthesis of **1** has not been achieved yet, and the absolute configuration is assumed to be (*R*) but remains unknown to date, an enantioselective synthesis is highly desirable. Another valuable flavan is (2*S*)-7,3′-dihydroxy-4′-methoxyflavan (**2**). First synthesized in racemic fashion by Dick,[6] it stood out among others because of its pleasant sweet taste even when considerably diluted. Later on, the enantiomer (*S*)-**2** was isolated from various plants like *Dracaena cinnabari*, *Hippeastrum x hortorum*, *Brosimum acutifolium*, and *Terminalia argenta*.[7] Recently, flavan **2** was repeatedly patented in various compositions for improvement of sweet taste and masking unpleasant taste sensations.[8] Especially as other sweetening agents such as *Stevia rebaudiana* are suspected to have adverse side effects on the male reproductive system, alternative substances are of growing importance.[9] Although studied in the racemic series, no enantioselective route to flavan **2** has been described to date.[6,10] Herein we report the first enantioselective synthesis of the two flavans[11] kazinol U (**1**) and (2*S*)-7,3′-dihydroxy-4′-methoxyflavan (**2**).

Scheme 1 depicts our retrosynthesis for flavans **1** and **2**. Kazinol U (**1**) might be traced back to triflate **3** by means of Claisen rearrangement, deoxygenation at the 5-position, and release of the hydroxy groups. The key transformation of this synthesis is an asymmetric transfer hydrogenation (ATH)/deoxygenation cascade first reported for a 5,7,4′-trisubstituted flavanone[12] using a rhodium-catalyst developed by Noyori[13]

Scheme 1. Retrosynthesis of Kazinol U (1) and (2*S*)-7,3′-Dihydroxy-4′-methoxyflavan (2) Leading to Racemic Hesperetin (7)



that was recently used for the ATH of flavanones[14] to great success. Similar transformations of racemic 5-*O*-acetyl[15] and 5-*O*-methoxycarbonyl[16] flavanones using sodium borohydride[17] are well-known. An *o*-quinone methide, which is formed by initial reduction of the ketone moiety, subsequent migration of the methoxycarbonyl group, and elimination, is believed to be the crucial intermediate of this deoxygenation cascade. Reduction of the unsaturated ketone would eventually yield the desired flavan skeleton.[12,15−17] Flavan **3** should be available from racemic flavanone **5** by application of the ATH/deoxygenation cascade and subsequent treatment with triflic anhydride. Ketone **5** might be derived from commercially

Received: November 19, 2016
Published: December 7, 2016

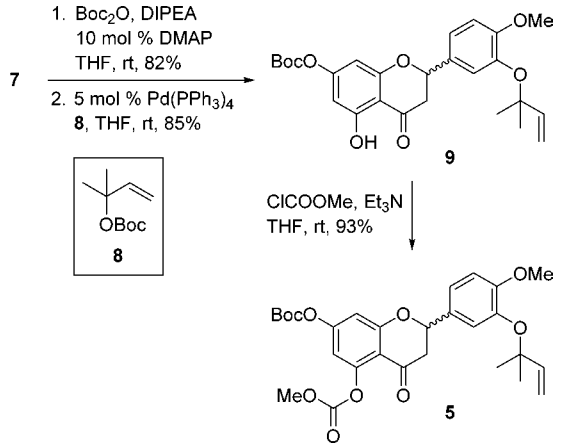
DOI: 10.1021/acs.orglett.6b03459
Org. Lett. 2016, 18, 6500−6503

available racemic hesperetin (7) by means of consecutive chemoselective Boc protection, Tsuji–Trost allylation,[18] and methoxycarbonylation.

Flavan **2** is approached in a similar retrosynthetic fashion and should be obtained from di-*O*-Boc derivative **4** through reductive removal of the trifloxy group and cleavage of the two carbonates. Enantiopure **4** in turn could be prepared through domino ATH/deoxygenation from racemic flavanone **6**. Finally, compound **6** can also be derived from racemic hesperetin (7).

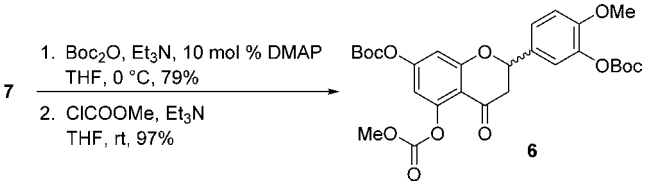
The preparation of ATH precursor **5** is depicted in Scheme 2. After chemoselective conversion of flavanone **7** to the corresponding 7-*O*-Boc derivative, flavanone **9** was obtained in good yield by the application of a method reported by Theodorakis.[18c] In accordance with the published allylation of phenols[19] using carbonate **8**,[20] we found the reaction to be reversible, making short reaction times a necessity in order to avoid regeneration of the starting material. Subsequent treatment of **9** with methyl chloroformate gave rise to ATH precursor **5** in good yield.

Scheme 2. Preparation of Flavan 5 from Hesperetin (7)



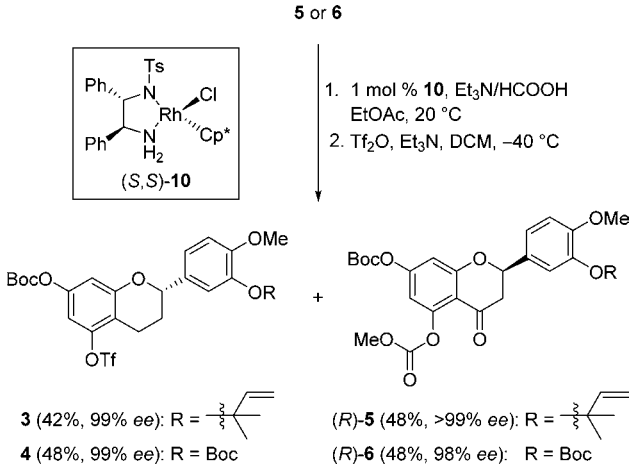
The second ATH precursor **6** was synthesized in a similar fashion (Scheme 3). Chemoselective conversion of **7** to the di-*O*-Boc derivative was followed by treatment with methyl chloroformate to furnish ATH substrate **6** in excellent yield.

Scheme 3. Preparation of ATH Precursor 6 from Hesperetin (7)



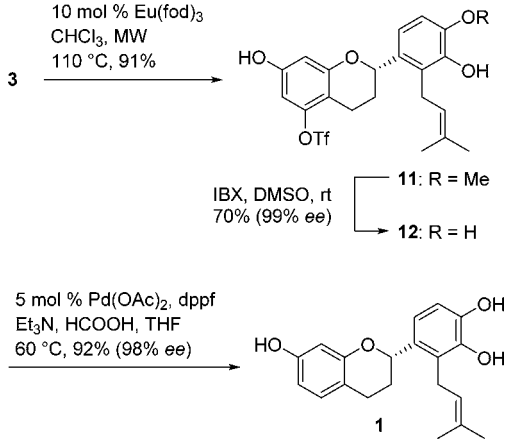
With racemic flavanones **5** and **6** in hand, the crucial ATH conditions were applied (Scheme 4). As separation of the resulting flavans and flavanones proved to be difficult, the mixture was treated with triflic anhydride, which allowed isolation of the pure products. This methodology led to efficient flavan production of 42% for **3** and 48% for **4**, where analysis by chiral HPLC revealed an excellent enantiomeric excess of 99% for both compounds. Furthermore, the corresponding *R*-configured flavanones **5** and **6** were isolated with high enantiomeric excess. In addition to these transformations, flavan *ent*-**3** was synthesized in the same fashion[21] using racemic **5** and (*R*,*R*)-**10**[13] in order to get access to both enantiomers of kazinol U (**1**), the absolute configuration of which is believed to be (*R*).[3]

Scheme 4. ATH and Subsequent Treatment with Triflic Anhydride



The synthesis of kazinol U (**1**) from **3** is depicted in Scheme 5. Europium-catalyzed sigmatropic rearrangement[22] accelerated by microwave irradiation was accompanied by complete removal of the carbonate group and furnished 2′-substituted flavan **11** in good yield. It is noteworthy that deblocking of the carbonate can be avoided in the absence of the Lewis acid europium. However, this protocol leads to a prolonged reaction time and a significant decrease in yield. Cleavage of the methyl ether proved to be rather challenging. While classic demethylation methodologies using boron tribromide[23] or aluminum chloride[24] failed to cleanly generate catechol **12**, this transformation occurred smoothly when 2-iodoxybenzoic acid[25] was applied. Importantly, the oxidative demethylation had to be done prior to deoxygenation, as the absence of the trifloxy group led to a drastic decrease in yield. With triflate **12** in hand, kazinol U (**1**) could be synthesized by palladium-catalyzed deoxygenation at C-5.[26] Compound **1** proved to be prone to racemization in the presence of Pd residues. However, optimization of the reaction and workup conditions minimized the stereochemical erosion and led to the natural product **1**

Scheme 5. Synthesis of Kazinol U (1) from Flavan 3

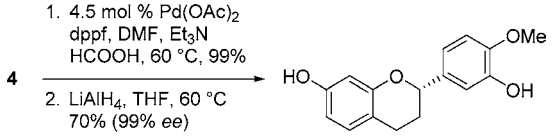


DOI: 10.1021/acs.orglett.6b03459
Org. Lett. 2016, 18, 6500–6503

with 98% *ee*. By means of the reaction sequence illustrated in Scheme 5, triflate *ent*-**3** was converted to flavan *ent*-**1** as well.[21] Comparison of the specific rotations of synthetic flavans **1** and *ent*-**1** with the literature data[3] revealed that natural kazinol U, contrary to prior assumption, possesses the *S* configuration.

Commencing with flavan **4**, reductive trifloxy removal[26] at C-5 and subsequent cleavage of the carbonate groups gave rise to the natural product **2** in virtually enantiopure form (Scheme 6). The specific rotation of synthetic product **2** confirmed the assumed *S* configuration of the natural product.

Scheme 6. Synthesis of (2*S*)-7,3′-Dihydroxy-4′-methoxyflavan (2)



2

In summary, we have accomplished the first enantioselective synthesis of kazinol U (**1**) and (2*S*)-7,3′-dihydroxy-4′-methoxyflavan (**2**) starting from commercially available racemic hesperetin. The natural products were obtained with 98% *ee* and 99% *ee*, respectively, in a concise and efficient manner. The absolute configuration of **2** was verified to be *S*, while the configuration of kazinol U (**1**) had to be revised to *S*. Furthermore, it was shown that a previously reported domino ATH/deoxygenation[12] is readily applicable to 3′-oxygenated flavanones, making it a potent strategy for the enantioselective synthesis of flavans.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03459.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: peter.metz@chemie.tu-dresden.de.

ORCID

Peter Metz: 0000-0002-0592-9850

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank B. Sc. Nils Krüger, Technische Universität Dresden, for preliminary investigations on the synthesis of racemic flavanone **6** and its reduction with sodium borohydride.

■ REFERENCES

(1) (a) Middleton, E., Jr.; Kandaswami, C.; Theoharides, T. C. *Pharmacol. Rev.* **2000**, *52*, 673−751. (b) Teixeira, A. F.; de Carvalho Alcântara, A. F.; Pilý-Veloso, D. *Magn. Reson. Chem.* **2000**, *38*, 301−304. (c) de Carvalho Alcântara, A. F.; Teixeira, A. F.; da Silva, I. F.; de Almeida, W. B.; Pilý-Veloso, D. *Quim. Nova* **2004**, *27*, 371−377. (d) Brahmachari, G. *Nat. Prod. Commun.* **2008**, *3*, 1337−1354. (e) Prasad, S.; Phromnoi, K.; Yadav, V. R.; Chaturvedi, M. M.; Aggarwal, B. B. *Planta Med.* **2010**, *76*, 1044−1063. (f) Parhiz, H.; Roohbakhsh, A.; Soltani, F.; Rezaee, R.; Iranshahi, M. *Phytother. Res.* **2015**, *29*, 323−331.

(2) (a) Barron, D.; Ibrahim, R. K. *Phytochemistry* **1996**, *43*, 921−982. (b) Torres, S. L.; Arruda, M. S. P.; Arruda, A. C.; Müller, A. H.; Silva, S. C. *Phytochemistry* **2000**, *53*, 1047−1050. (c) Botta, B.; Vitali, A.; Menendez, P.; Misiti, D.; Delle Monache, G. *Curr. Med. Chem.* **2005**, *12*, 713−739. (d) Takashima, J.; Komiyama, K.; Ishiyama, H.; Kobayashi, J.; Ohsaki, A. *Planta Med.* **2005**, *71*, 654−658. (e) Yazaki, K.; Sasaki, K.; Tsurumaru, Y. *Phytochemistry* **2009**, *70*, 1739−1745. (f) Hu, X.; Wu, J.-W.; Wang, M.; Yu, M.-H.; Zhao, Q.-S.; Wang, H.-Y.; Hou, A.-J. *J. Nat. Prod.* **2012**, *75*, 82−87. (g) Yang, Y.; Yang, X.; Xu, B.; Zeng, G.; Tan, J.; He, X.; Hu, C.; Zhou, Y. J. *Fitoterapia* **2014**, *98*, 222−227.

(3) Lee, D. Y.; Kim, D. H.; Lee, H. J.; Lee, Y.; Ryu, K. H.; Jung, B.-I.; Song, Y. S.; Ryu, J.-H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3764−3767.

(4) Bae, U.-J.; Lee, D. Y.; Song, M.-Y.; Lee, S.-M.; Park, J.-W.; Ryu, J.-H.; Park, B.-H. *Biol. Pharm. Bull.* **2011**, *34*, 1026−1031.

(5) Kim, A. Y.; Lee, C. G.; Lee, D. Y.; Li, H.; Jeon, R.; Ryu, J.-H.; Kim, S. G. *Free Radical Biol. Med.* **2012**, *53*, 1198−1208.

(6) Dick, W. E., Jr. *J. Agric. Food Chem.* **1981**, *29*, 305−312.

(7) (a) Masaoud, M.; Ripperger, H.; Porzel, A.; Adam, G. *Phytochemistry* **1995**, *38*, 745−749. (b) Wink, M.; Lehmann, P. *Bot. Acta* **1996**, *109*, 412−421. (c) Takashima, J.; Ohsaki, A. *J. Nat. Prod.* **2001**, *64*, 1493−1496. (d) Garcez, F. R.; Garcez, W. S.; Martins, M.; Lopes, F. A. *Biochem. Syst. Ecol.* **2003**, *31*, 229−232. (e) Yang, Y.; Huang, S.; Zhao, Y.; Zhao, Q.; Sun, H. *Nat. Prod. Res. Dev.* **2005**, *17*, 539−541.

(8) (a) Wessjohann, L.; Backes, M.; Ley, J.; Jakob, P.; Paetz, S.; Reichelt, K. (Symrise GmbH, Germany). US 20100292175, 2010. (b) Hans, J.; Moldenhauer, J.; Bitzer, J.; Koepcke, B.; Roemer, E. (Symrise AG, Germany). WO 2013023891, 2013. (c) Krammer, G.; Sabater, C.; Riess, T. (Symrise AG, Germany). WO 2015189346, 2015.

(9) (a) Yamada, A.; Ohgaki, S.; Noda, T.; Shimizu, M. *Shokuhin Eiseigaku Zasshi* **1985**, *26*, 169−183. (b) Melis, J. S. *J. Ethnopharmacol.* **1999**, *67*, 157−161.

(10) (a) Xue, J.; Zhang, X.; Liang, X.; Li, Y. *Chin. Chem. Lett.* **2003**, *14*, 443−444. (b) Xue, J.; Zhang, X.; Chen, X.; Zhang, Y.; Li, Y. *Synth. Commun.* **2003**, *33*, 3527−3536.

(11) For a review, see: Mazimba, O.; Keroletswe, N. *Int. Res. J. Pure Appl. Chem.* **2015**, *8*, 112−146.

(12) Keßberg, A.; Metz, P. *Angew. Chem.* **2016**, *128*, 1173−1176; *Angew. Chem., Int. Ed.* **2016**, *55*, 1160−1163.

(13) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186−2187.

(14) (a) Lemke, M.-K.; Schwab, P.; Fischer, P.; Tischer, S.; Witt, M.; Noehringer, L.; Rogachev, V.; Jäger, A.; Kataeva, O.; Fröhlich, R.; Metz, P. *Angew. Chem.* **2013**, *125*, 11865−11869; *Angew. Chem., Int. Ed.* **2013**, *52*, 11651−11655. (b) Metz, P.; Schwab, P.; Fischer, P.; Lemke, M.-K.; Tischer, S. DE 11 2007 001 531 B4, 2012.

(15) (a) Shie, J. J.; Chen, C.-A.; Lin, C.-C.; Ku, A. F.; Cheng, T.-J. R.; Fang, J.-M.; Wong, C.-H. *Org. Biomol. Chem.* **2010**, *8*, 4451−4462. (b) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240−5246. (c) Sweeny, J. G.; Iacobucci, G. A. *Tetrahedron* **1977**, *33*, 2927−2932.

(16) Mitchell, D.; Doecke, C.; Hay, L. A.; Koenig, T. M.; Wirth, D. D. *Tetrahedron Lett.* **1995**, *36*, 5335−5338.

(17) Also see: (a) McLoughlin, B. J. *J. Chem. Soc. D* **1969**, 540−541. (b) Bell, K. H. *Aust. J. Chem.* **1969**, *22*, 601−605. (c) Stealey, M. A.; Shone, R. L.; Miyano, M. *Synth. Commun.* **1990**, *20*, 1869−1876. (d) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502−6503.

(18) (a) Kaiho, T.; Yokoyama, T.; Mori, H.; Fujiwara, J.; Nobori, T.; Odaka, H.; Kamiya, J.; Maruyama, M.; Sugawara, T. JP 06128238, 1994. (b) Kamei, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2003**, *44*, 8505−8507. (c) Chantarasriwong, O.; Cho, W. C.; Batova, A.; Chavasiri, W.; Moore, C.; Rheingold, A. L.; Theodorakis, E. A. *Org. Biomol. Chem.* **2009**, *7*, 4886−4894.

DOI: 10.1021/acs.orglett.6b03459
Org. Lett. 2016, 18, 6500−6503

(19) Sunderhaus, J. D.; McAfoos, T. J.; Finefield, J. M.; Kato, H.; Li, S.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M. *Org. Lett.* **2013**, *15*, 22−25.
(20) Ruchti, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 16756−16759.
(21) See the Supporting Information for details.
(22) (a) Gester, S.; Metz, P.; Zierau, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015−1018. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815−816.
(23) Benton, F. L.; Dillon, T. E. *J. Am. Chem. Soc.* **1942**, *64*, 1128−1129.
(24) Baddeley, G. *J. Chem. Soc.* **1944**, 330.
(25) (a) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903−2906. (b) Barontini, M.; Bernini, R.; Crisante, F.; Fabrizi, G. *Tetrahedron* **2010**, *66*, 6047−6053.
(26) (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541−5544. (b) Engler, T. A.; Lynch, K. O., Jr.; Reddy, J. P.; Gregory, G. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1229−1232.

DOI: 10.1021/acs.orglett.6b03459
Org. Lett. 2016, 18, 6500−6503