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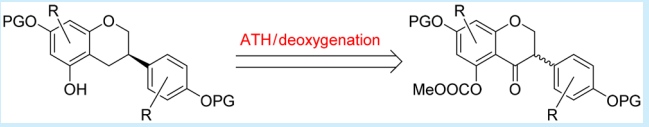
Enantioselective Total Synthesis of Natural Isoflavans: Asymmetric Transfer Hydrogenation/Deoxygenation of Isoflavanones with Dynamic Kinetic Resolution

Anton Keßberg, Tilo Lübken, and Peter Metz*

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

Supporting Information

ABSTRACT: A concise and highly enantioselective synthesis of structurally diverse isoflavans from a single chromone is described. The key transformation is a single-step conversion of racemic isoflavanones into virtually enantiopure isoflavans by domino asymmetric transfer hydrogenation/deoxygenation with dynamic kinetic resolution.



Flavonoids represent a wide range of secondary metabolites in plants with various health benefits.[1] An important subgroup of these natural products are isoflavans.

(*S*)-Equol (**1**), a potent phytoestrogenic isoflavan,[2] was first isolated from pregnant mares' urine in 1932 (Figure 1).[3] It was shown to be a selective estrogen receptor modulator,[4] and it exhibits antioxidant activity[5] and is currently being investigated as a drug for the treatment of benign prostatic hyperplasia.[6] Despite its interesting bioactivity and structural simplicity, catalytic protocols for the asymmetric synthesis of equol (**1**) are scarce.[7] Spurred by our recent success in the enantioselective synthesis of flavanones,[8] flavans,[9] and isoflavanones[7b] by means of asymmetric transfer hydrogenation (ATH), we envisioned establishing an efficient protocol for the catalytic asymmetric synthesis of isoflavans. We anticipated that a dynamic kinetic resolution (DKR) of racemic isoflavanones by means of an ATH/deoxygenation cascade might yield enantiopure isoflavans in a single step. In addition to (*S*)-equol (**1**), the isoflavans **2**, **3**, and **4** are interesting targets for this methodology. Initially isolated from *Maackia tenuifolia* by Zhu et al. in 1998,[10] manuifolin K (**2**) was later obtained from *Dalea aurea* and was shown to exhibit significant in vitro activity against the ameba *Naegleria fowleri*,[11] which triggers the rapidly fatal amebic meningoencephalitis.[12] Oh et al. reported that a number of flavonoids from *Erythrina milbraedii* effectively reduce protein tyrosine phosphatase 1 B activity.[13] Among those, isoflavan **3** was the most potent agent identified, and as such, it might prove useful for the therapy of type 2 diabetes or obesity.[14] Tanaka et al. screened plants of the genus *Erythrina* for their antibacterial activity against methicillin-resistant *Staphylococcus aureus* and found eryzerin D (**4**) to be an effective agent.[15] Further studies revealed promising activity of **4** against vancomycin-resistant enterococci.[16] The absolute configuration of the natural product **4** has yet to be determined. Except for equol (**1**), there is no synthetic access to the above-mentioned isoflavans. Herein, we report an enantioselective total synthesis of (*S*)-equol (**1**), manuifolin K (**2**), isoflavan **3**, and eryzerin D (**4**).

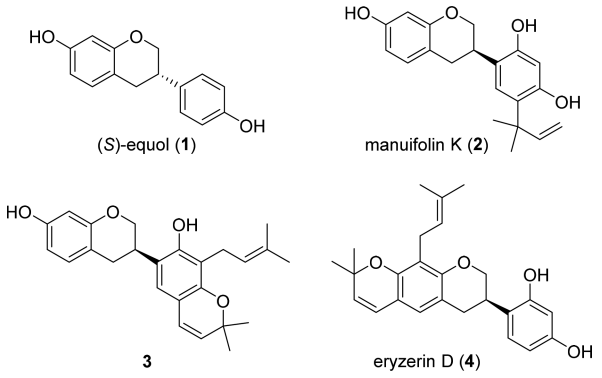


Figure 1. Structure of isoflavans **1**−**4**.

Scheme 1 depicts the general retrosynthetic approach to isoflavans **1**−**4**. First, the natural products **1**−**4** can be traced back to the respective phenols **5a**−**c**. We envisioned that enantiopure isoflavans **5a**−**c** might be obtainable from the racemic isoflavanones **6a**−**c** in a single step through a domino ATH/deoxygenation process involving an *o*-quinone methide (**I**) as the crucial intermediate.[9] In contrast to the previously reported transformation of flavanones,[9] the isoflavanones **6a**−**c** might readily racemize under the reaction conditions and, thus, allow for a dynamic kinetic resolution.[7b] Finally, the isoflavanones *rac*-**6a**−**c** should be attainable from chromone **7**[17] by means of protecting group interchange, Suzuki coupling, and conjugate reduction.

The preparation of (*S*)-equol (**1**) is depicted in Scheme 2. Starting from chromone **7**,[17] a highly chemoselective cleavage of the 5-*O*-MOM functionality and subsequent treatment with methyl chloroformate afforded vinyl iodide **8** in excellent yield.

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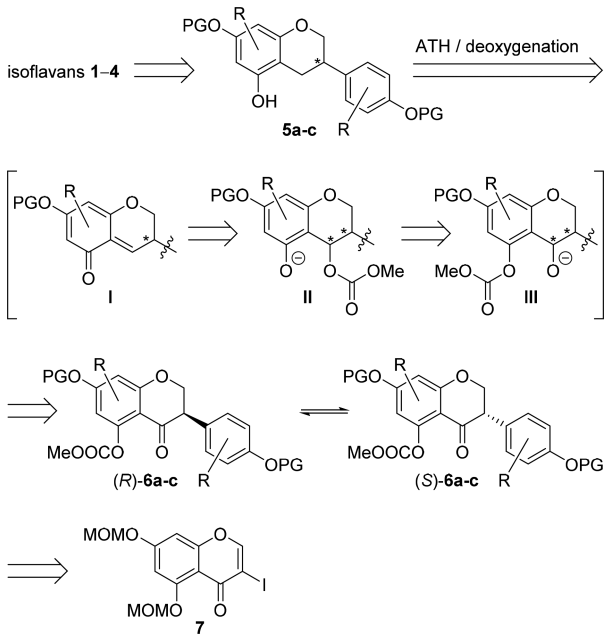
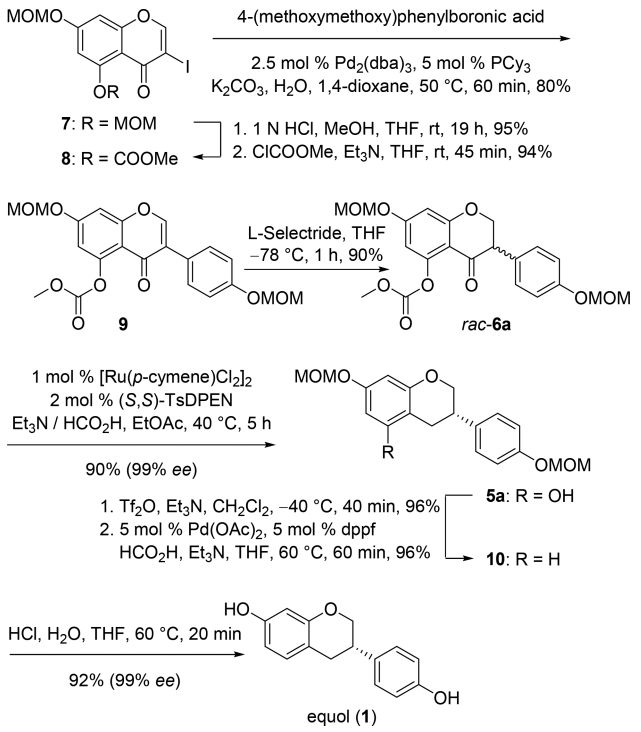
Scheme 1. General Retrosynthetic Analysis of Isoflavans 1−4



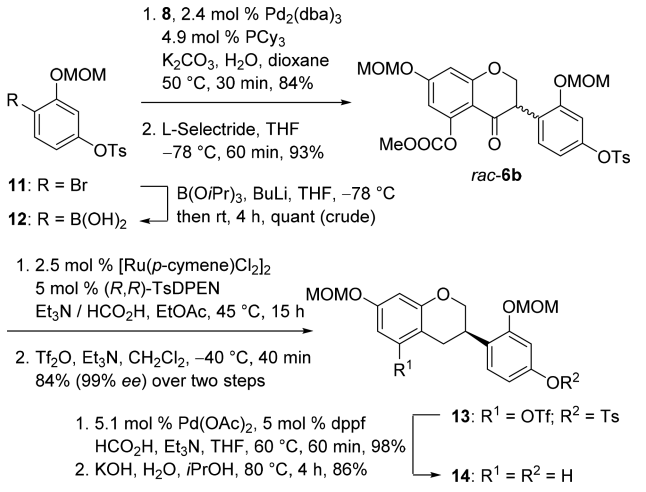
Scheme 2. Synthesis of (*S*)-Equol (1)



Construction of the isoflavanone *rac*-**6a** was achieved in two steps by Suzuki coupling[18] with 4-(methoxymethoxy)-phenylboronic acid[19] and conjugate reduction of the resulting isoflavone. The crucial ATH of ketone *rac*-**6a** was studied using a chiral ruthenium catalyst[20] and a mixture of triethylamine and formic acid as the hydrogen source. To our delight, the desired ATH/deoxygenation cascade proceeded smoothly at low catalyst loading and gave rise to the virtually enantiopure product (*S*)-**5a** in 90% yield. Reductive removal of the free hydroxyl group by treatment of compound **5a** with triflic anhydride and subsequent palladium-catalyzed deoxygenation[21] furnished product **10** in very good yield. Finally, (*S*)-equol (**1**) was obtained by simple hydrolysis of the acetal moieties with 99% enantiomeric excess.

Starting with chromone **8**, we continued our investigation on the domino ATH/deoxygenation with isoflavans **2** and **3** as the targets (Scheme 3). While initial attempts to convert aryl

Scheme 3. Synthesis of Isoflavan 14



bromide **11**[22] to the corresponding boronic acid **12** failed, an in situ quenching protocol by Li et al.[23] allowed for convenient handling and gave the best results. Suzuki coupling of **8** with **12** and subsequent treatment with L-Selectride gave rise to the ATH substrate *rac*-**6b**. In order to maintain a reasonable reaction time, a slightly higher catalyst loading was used, compared to the domino ATH/deoxygenation of *rac*-**6a**. This was largely because of the presence of the 2′-OMOM group. Subsequent treatment with triflic anhydride allowed for a convenient purification and gave rise to virtually enantiopure isoflavan **13** in good yield over two steps. Finally, deoxygenation at the 5-position and removal of the tosylate group furnished product **14**, which was further used to generate both manuifolin K (**2**) and pyrano-isoflavan **3**.

Commencing with isoflavan **14**, manuifolin K (**2**) was readily available in two steps (Scheme 4). Initially, prenyl ether **15** was synthesized under Mitsunobu conditions[24] in good yield and short reaction time. The subsequent Claisen rearrangement was carried out in acetic anhydride[25] in order to avoid an abnormal rearrangement.[26] Due to partial MOM cleavage and acetylation, the crude product mixture was submitted to solvolysis, followed by acidic deblocking in order to obtain manuifolin K (**2**) as the sole product[27] with excellent enantiomeric excess and good yield. Isoflavan **3** was also obtained from compound **14** in six steps. The prenyl groups were introduced by means of Tsuji−Trost allylation with allylic carbonate **16**[28] and subsequent europium-catalyzed rearrangement.[29,30] In comparison to the perfect regioselectivity of the Claisen rearrangement of ether **15**, this transformation exhibited moderate selectivity, favoring the 5′-position over the 3′-position due to steric constraints. However, both regioisomers were transformed to the single product **17** using the same two-step protocol once again. Thus, phenol **17** was obtained in good overall yield from isoflavan **14**. Benzopyran **18** was synthesized through oxidative cyclization using DDQ.[31] Surprisingly, no regioisomeric product was observed next to **18**. Finally, acid-promoted cleavage of the acetal moieties furnished the target compound **3** in moderate

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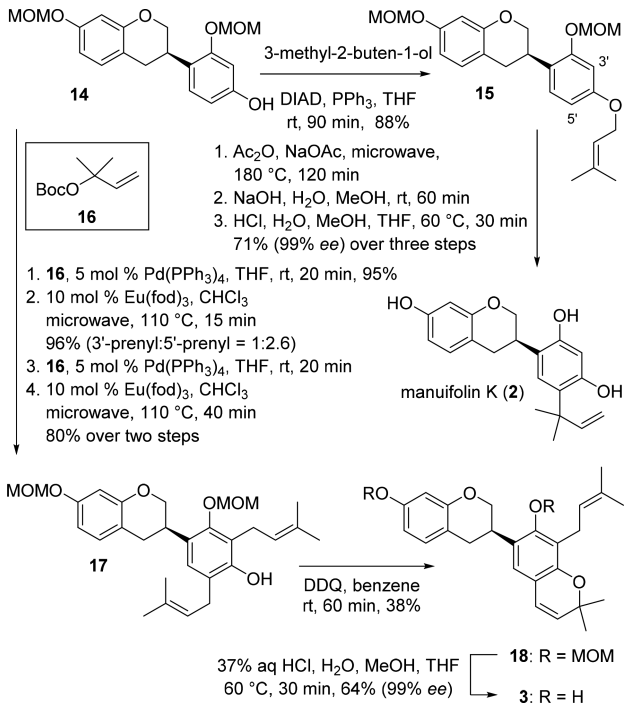
Scheme 4. Synthesis of Isoflavans 2 and 3



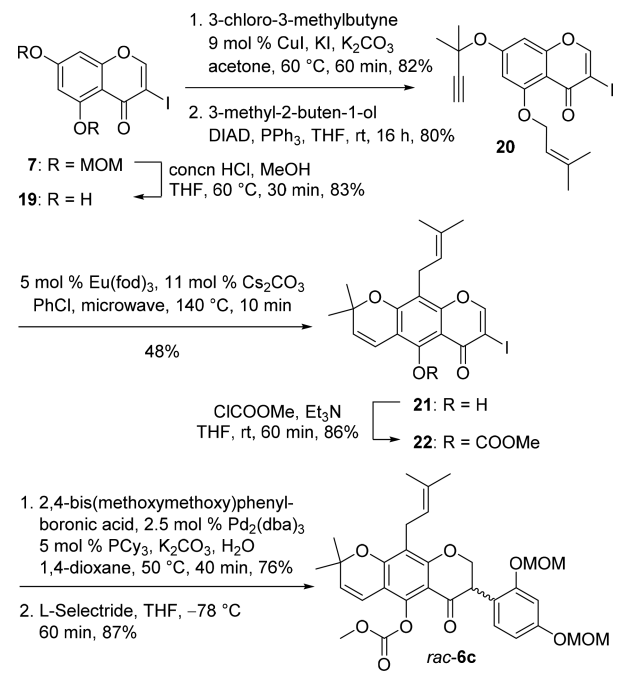
yield due to the unstable nature of structure **3**. Unexpectedly, the spectroscopic data of the synthetic sample **3** did not match the reported data.[13] A thorough review of the published information revealed that Oh et al. in fact isolated eryzerin D (**4**) rather than isoflavan **3**.

Synthesis of the structurally challenging ATH substrate *rac*-**6c**, required for eryzerin D (**4**), is depicted in Scheme 5. Starting with chromone **7**, treatment with concentrated HCl allowed the clean removal of both MOM functionalities. Ether **20** was obtained by means of a highly chemoselective propargylation[32] and subsequent prenylation under Mitsunobu conditions.[24] A cascade of domino Claisen/Cope rearrangement, followed by annulation[33] of the pyran moiety, comprising five pericyclic transformations, gave rise to chromone **21** in a single step in satisfying yield. Europium catalysis[29,30] was crucial for this reaction in order to ensure the domino Claisen/Cope process occurred first and, thus, counter to the usual regioselectivity of the annulation reaction.[34] Treatment of product **21** with methyl chloroformate gave rise to chromone **22**. Finally, Suzuki coupling of vinyl iodide **22** with 2,4-bis(methoxymethoxy)phenylboronic acid[35] and subsequent conjugate reduction furnished isoflavanone *rac*-**6c**.

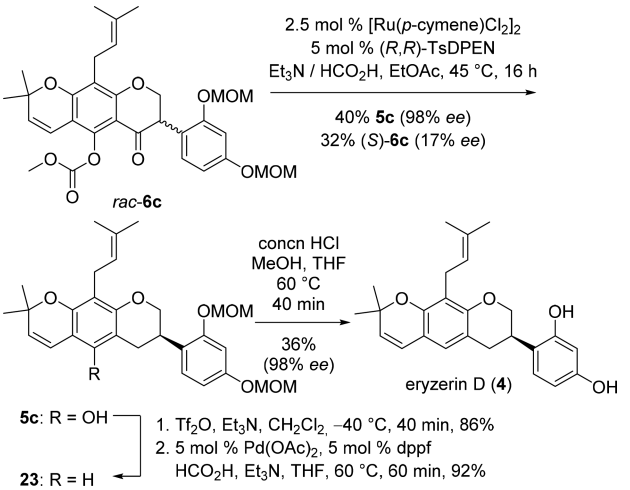
Scheme 6 illustrates the ATH/deoxygenation of isoflavanone *rac*-**6c** and the final steps toward eryzerin D (**4**). Isoflavan (*R*)-**5c** was obtained with 98% ee, applying the same reaction conditions used for the transformation of isoflavanone *rac*-**6b**. Unfortunately, in situ racemization of compound (*S*)-**6c** proved to be quite slow, and thus, complete conversion of *rac*-**6c** was not achieved. While reduction of substrate *rac*-**6c** was not impeded by the addition of Lewis and Brønsted acids or bases, racemization was not accelerated either. Nonetheless, enantioselective reduction of the highly functionalized isoflavanone *rac*-**6c** yielded 40% of the fairly unstable product (*R*)-**5c**, which was submitted to further transformation right away. Treatment of **5c** with triflic anhydride and subsequent deoxygenation gave rise to isoflavan **23** in good yield. Finally, eryzerin D (**4**) was obtained by removal of the MOM groups. In accordance with the chemical behavior of isoflavans **3** and **5c**, the combination of a pyran moiety and free phenolic hydroxyl groups led to the fairly unstable properties of **4**. With isoflavan **4** in hand, comparison of specific rotation and CD spectrum of the synthetic sample with the literature data[15] revealed the absolute configuration of eryzerin D (**4**) to be *R*. Furthermore, NMR and MS data are in good agreement with the data reported by Oh et al.[13,36]

In summary, we have accomplished the first enantioselective total synthesis of manuifolin K (**2**), eryzerin D (**4**), and isoflavan **3**. Our results verify the *R* configuration for the natural product **4**, and the absolute configuration of isoflavan **2** was unambiguously established. In addition, the published structure of compound **3** was revised to be identical to that of eryzerin D (**4**). Furthermore, a new catalytic protocol for the asymmetric total synthesis of equol (**1**) was established. Central to our

Scheme 5. Synthesis of ATH Substrate *rac*-6c



Scheme 6. Synthesis of Eryzerin D (4)



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strategy is a DKR of isoflavanones by means of a domino ATH/deoxygenation reaction. This protocol allows a single-step preparation of isoflavans from racemic isoflavanones in a highly enantioselective fashion and also tolerates substitution at the 2′-position of the substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01034.

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.

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(35) See the Supporting Information for details.

(36) While the specific rotation indicates that Oh and co-workers[13] actually isolated the enantiomer (*S*)-**4**, the reported CD spectrum is in poor agreement. Thus, information about the absolute configuration of natural compound **4**, obtained by Oh and co-workers,[13] remains ambiguous.

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