ORGANIC LETTERS

2006
Vol. 8, No. 22
5149−5152

De Novo Asymmetric Syntheses of SL0101 and Its Analogues via a Palladium-Catalyzed Glycosylation

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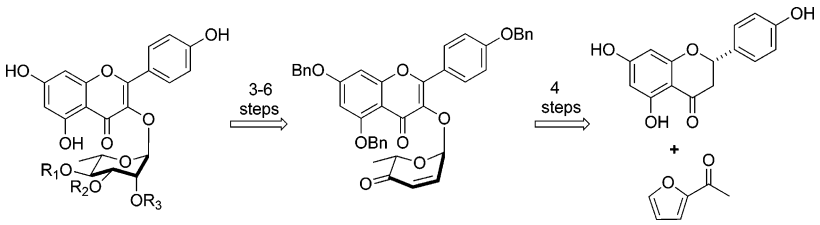
Received August 22, 2006

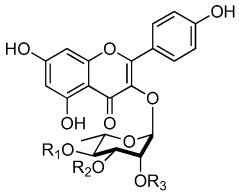
ABSTRACT



The enantioselective syntheses of naturally occurring kaempferol glycoside SL0101 (1a) and its analogues 1b–e, as well as their enantiomers, have been achieved in 7–10 steps. The routes rely upon a diastereoselective palladium-catalyzed glycosylation, ketone reduction, and dihydroxylation to introduce the *rhamno*-stereochemistry. The asymmetry of the sugar moiety of these kaempferol glycosides was derived from Noyori reduction of an acylfuran. An acetyl group shift from an axial (C-2) to equatorial position (C-3) under basic conditions was also described.

In an effort to find specific inhibitors of p90 Ribosomal S6 Kinase (RSK), Smith and Hecht screened an extensive collection of botanical extracts derived from rare plants.[1] Using a dual high-throughput screen they found only one extract that inhibited the RSK2 isoform (RSK2) without inhibiting the tyrosine kinase (FAK). The active extract was from a South American dogbane plant named *Forsteronia refracta*. More detailed bioactive fractionization revealed the active constituent to be a kaempferol glycoside, which was given the name SL0101 (Figure 1).[1] SL0101 (**1a**) is a member of a class of acylated kaempferol L-rhamnosides that occur naturally with various degrees of acylation (e.g., **1a**−**e**).[2] SL0101 sans acetyl groups (**1b**) is also known as afzelin.[2a] The kaempferol glycosides, like most flavonoids, have received a great deal of attention because they are believed to induce many positive biological effects.[3]

In addition to this unique activity, our interest in SL0101 (**1a**) was peaked by the report that it displayed activity some



	R_1	R_2	R_3	IC_{50} (Rsk2)
1a	Ac	Ac	H	89 nM
1b	H	H	H	--------
1c	Ac	Ac	Ac	--------
1d	Ac	H	H	189 nM
1e	Ac	H	Ac	580 nM

Figure 1. Kaempferol glycoside SL0101 (**1a**) and its analogues **1b**−**e** and their Rsk2 inhibitory activities.

(1) (a) Smith, J. A.; Poteet-Smith, C. E.; Xu, Y.; Errington, T. M.; Hecht, S. M.; Lannigan, D. A. *Cancer Res.* **2005**, *65*, 1027−1034. (b) Xu, Y.; Smith, J. A.; Lannigan, D. A.; Hecht, S. M. *Bioorg. Med. Chem.* **2006**, *14*, 3974−3977.

(2) For the isolation of **1a,d,e** see ref 1b and for **1a,b**, see: (a) Matthes, H. W. D.; Luu, B.; Ourisson, G. *Phytochemistry* **1980**, *19*, 2643−2650. For **1b**, see: (b) Kaouadji, M. *Phytochemistry* **1990**, *29*, 2295−2297. For **1b** and **1d**, see: (c) Masuda, T.; Jitoe, A.; Kato, S.; Nakatani, N. *Phytochemistry* **1991**, *30*, 2391−2392. For **1a** and **1e**, see: (d) Nakatani, N.; Jitoe, A.; Masuda, T. *Agric. Biol. Chem.* **1991**, *55*, 455−460. For **1c**, see: (e) Usia, T.; Iwata, H.; Hiratsuka, A.; Watabe, T.; Kadota, S.; Tezuka, Y. *J. Nat. Prod.* **2004**, *67*, 1079−1083. (f) For **1b**, see: Deng, J.-Z.; Marshall, R.; Jones, S. H.; Johnson, R. K.; Hecht, S. M. *J. Nat. Prod.* **2002**, *65*, 1930−1932.

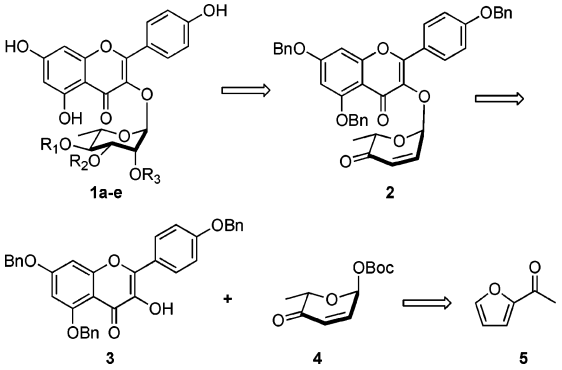
10.1021/ol062076r CCC: $33.50
Published on Web 10/06/2006

150 times greater than that of the simple aglycon, kaempferol. Similarly, we were intrigued by the importance of the specific placement of acetyl groups on the L-rhamnose and its effect on the SAR of SL0101 (Figure 1).[4] As part of an effort to elucidate the role of the sugar and acetyl portion of SL0101 to its activity, we decided to prepare both enantiomers of SL0101 (**1a**) and its analogues **1b**−**e** (Figure 1).

Not long after the isolation and structure elucidation of SL0101 (**1a**), its first synthesis was reported by Professor Hecht.[4] The Hecht synthesis derived the absolute and relative stereochemistry from rhamnose. In contrast, we were interested in the possibility of preparing all five members of this class of kaempferol glycosides **1a**−**e** via asymmetric catalysis. This de novo approach would have the additional advantage of preparing both the D- and L-enantiomers for biological testing.

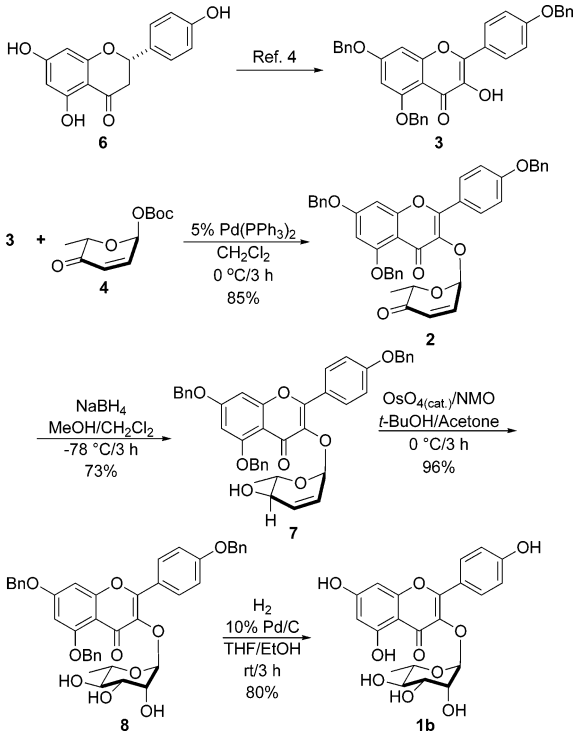
Recently we reported a diastereoselective palladium-catalyzed glycosylation reaction that used alcohols as nucleophiles and pyranones such as **4** as glycosyl donors.[5] We have also found several post-glycosylation transforms, which subsequently install the desired sugar stereochemistry.[6] This methodology also works well for other *N*-, *O*-nucleophiles, such as 6-chloropurine/benzimidizole and phenol.[7] In order to produce this class of interesting compounds for activity studies, we decided to apply this methodology toward the syntheses of the kaempferol glycosides, SL0101 (**1a**) and its analogues **1b**−**e**. In addition to providing material for biological study, this effort should also allow us study flavon-3-ol as a nucleophile in the palladium-catalyzed glycosylation.

Scheme 1. Retrosynthetic Analysis of Kaempferol Rhamnosides **1a**−**e**



Retrosynthetically, we envisioned that pyranone **2** could be derived from a Pd(0)-catalyzed glycosylation between flavonol **3** and pyranone **4** (Scheme 1). Subsequent application of $NaBH_4$ reduction and an Upjohn dihydroxylation (OsO_4/NMO)[8] would install the *manno*-stereochemistry.[9] The selective introduction of the C-4 acetyl group should occur by introducing an acylation reaction between the $NaBH_4$ reduction and dihydroxylation. All that would remain would be to differentiate the C-2 hydroxyl group from the C-3 hydroxyl group. For this, we planned to use a combination of selective orthoester hydrolysis[10] and acyl migration reactions.[11] Since pyranone **4** has been prepared in either enantiomeric form,[12] this procedure should be amenable to the preparation of both enantiomers of **1a**−**e**. Herein we describe our successful efforts at the implementation of this strategy to this class of kaempferol glycosides **1a**−**e**, which is noteworthy in that the various acetyl groups in **1a**−**e** are installed without any hydroxyl protecting groups on the sugar.

Scheme 2. Synthesis of Kaempferol Rhamnoside **1b**



Our synthesis started with the known perbenzylated kaempferol **3**, which was synthesized from naringenin **6** in three steps (Scheme 2).[4] The glycosylation was carried out with flavonol **3** and L-pyranone **4** under catalysis of 2.5 mol

(3) (a) Muir, S. R.; Collins, G. J.; Robinson, S.; Hughes, S.; Bovy, A.; Ric De Vos, C. H.; van Tunen, A. J.; Verhoeyen, M. E. *Nat. Biotechnol.* **2001**, *19*, 470−474. (b) Hertog, M. G. L.; Feskens, E. J. M.; Hollman, P. C. H.; Katan, M. B.; Kromhout D. *Lancet* **1993**, *342*, 1007−1011.

(4) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 1097−1099.

(5) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429.

(6) (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982−2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17−36.

(7) (a) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921−3924. (b) Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293−296. (c) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605−1608.

(8) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

(9) According to carbohydrate nomenclature, rhamnose is 6-deoxy-mannose.

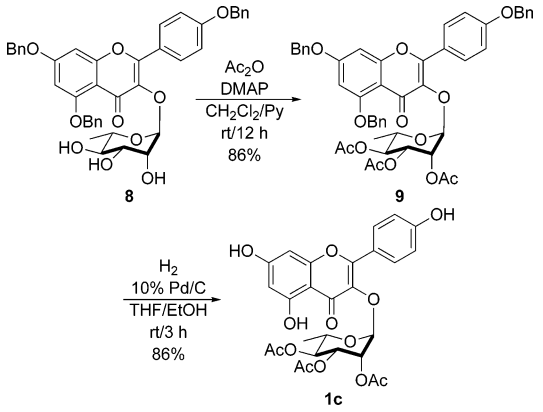
(10) For the selective acylation of an axial alcohol, see ref 6 and (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754−1769. (b) Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res.* **1994**, *251*, 33−67.

(11) (a) Doerschuk, A. P. *J. Am. Chem. Soc.* **1952**, *74*, 4202−4203. (b) Pettit, G. R.; Cragg, G. M.; Suffness, M. *J. Org. Chem.* **1985**, *50*, 5060−5063.

% $Pd_2(dba)_3$·$CHCl_3$ and 10 mol % of PPh_3 in CH_2Cl_2 at 0 °C, which afforded pyranone **2** in 85% yield with complete α-selectivity (Scheme 2). Reduction of the enone **2** by $NaBH_4$ at −78 °C in CH_2Cl_2/MeOH resulted in allylic alcohol **7** in 73% yield with excellent diastereoselectivity (dr >20:1). The *rhamno*-stereochemistry in **8** was diastereoselectively introduced upon exposure of **7** to the Upjohn conditions (OsO_4/NMO, 96%). Debenzylation of **8** using Pearlman's catalyst (10% Pd/C) in the presence of hydrogen gave kaempferol rhamnoside **1b** in 80% yield.

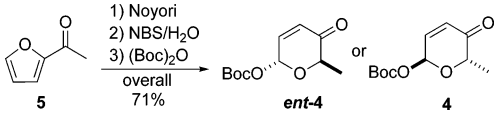
In addition to the unacylated *rhamno*-sugar **1b**, the peracylated sugar **1c** could also be easily prepared in two steps from triol **8**. Exhaustive acylation of the triol **8** with the excess acetic anhydride in presence of pyridine and 10% DMAP gave triacetate **9** in 86% yield (Scheme 3). Debenzylation of triacetate **9** by hydrogen using Pearlman's catalyst (10% Pd/C) again produced kaempferol rhamnoside triacetate **1c** in 86% yield.

Scheme 3. Synthesis of Kaempferol Rhamnoside Triacetate **1c**

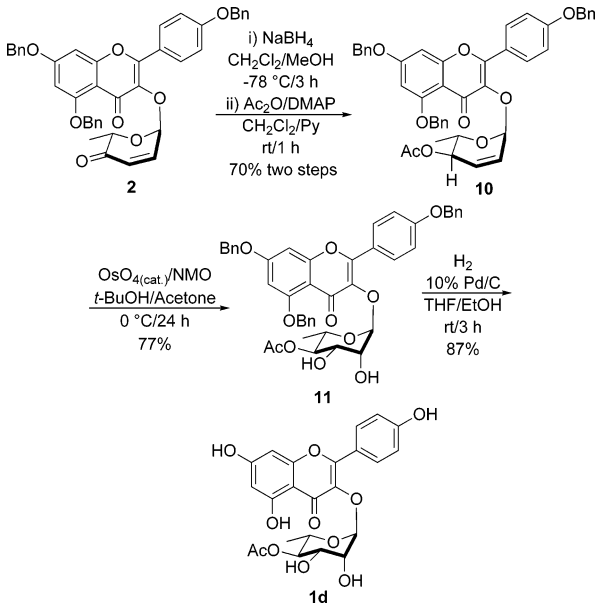


The selective installation of the C-4 acetyl group in **1d** was easily achieved without the need of additional protecting groups from the previously described allylic alcohol **7** (Scheme 2). In this route (Scheme 4), the $NaBH_4$ reduction of enone **6** was followed by an acylation of the resulting allylic alcohol with acetic anhydride in the presence of pyridine and DMAP. This two-step procedure afforded acetate **10** in 70% overall yield. Once again, dihydroxylation using the Upjohn condition stereoselectively converted allylic acetate **10** into the *rhamno*-diol **11** in 77% yield. Global deprotection was accomplished under hydrogenolysis conditions by exposure of diol **11** to 1 atm of H_2 in the presence of Pearlman's catalyst (Pd/C), which furnished kaempferol rhamnoside 4″-acetate **1d** in 87% yield.

(12) Pyranones such as **4** and its enantiomer *ent*-**4** can be prepared in three steps from achiral acylfurans such as **5** in either enantiomeric form (D/L). The pyranone asymmetry is derived from a Noyori reduction; see refs 5b, 7a, and Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005−1009.

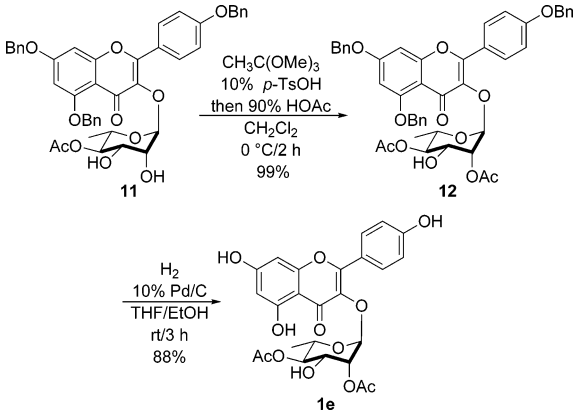


Scheme 4. Synthesis of Kaempferol Rhamnoside 4″-Acetate **1d**



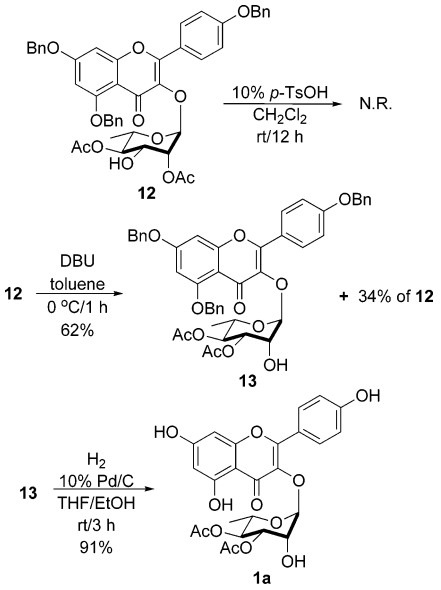
Acylation of the C-2 axial hydroxyl group of diol **11** was selectively introduced using orthoester chemistry in excellent yield (99%).[6] Exposure of diol **11** to trimethyl orthoacetate in the presence of 10% *p*-TsOH in CH_2Cl_2 was followed by hydrolysis with excess 90% HOAc/H_2O (Scheme 5). Once again, reductive debenzylation of **12** with hydrogen and 10% Pd/C produced kaempferol rhamnoside 2″,4″-diacetate **1e** in 88% yield.

Scheme 5. Synthesis of Kaempferol Rhamnoside 2″,4″-Diacetate **1e**



In contrast to the selective C-2 acylation of the axial alcohol in **11** (Scheme 5), our synthesis of SL0101 required the selective acylation of the C-3 equatorial alcohol (Scheme 6). Unfortunately all of our attempts with Ac_2O/Py at various temperature only furnished mixtures of diacetate **13** and **12**, as well as triacetate **9** (∼1:1:1). We next turned to the isomerization of the less stable axial C-2 acetate in **12** to the more stable equatorial C-3 acetate in **13**.

Scheme 6. Synthesis of SL0101 (**1a**)



All attempts to shift the axial acetyl group of diacetate **12** to the equatorial position by using 10 mol % *p*-TsOH in CH_2Cl_2 at room temperature failed to give desired diacetate **13** (Scheme 6). In contrast, more promising results were seen with basic conditions. For instance, analysis of crude ^{1}H NMR of dilute toluene solutions of **12** with 1 equiv of DBU showed clean conversion to a 2:1 mixture of **13** and **12**. In practice good yields of **13** (62%) could be obtained along with recovered starting material (34%) after SiO_2 chromatography. Finally, debenzylation of **13** under the similar condition as before produced SL0101 (**1a**) in 91% yield. Our synthetic products **1a**−**e** were physically and spectroscopically identical to the isolated natural materials in terms of melting point, optical rotation, R_f, ^{1}H NMR, ^{13}C NMR, and MS.[2,4]

In conclusion, a divergent and highly enantio- and diastereoselective procedure for the preparation of naturally occurring SL0101 (**1a**) as well as four kaempferol rhamnoside analogues **1b**−**e** has been developed. This approach provides either enantiopode of kaempferol glycosides **1a**−**e** without protecting any of the sugar hydroxyl groups. Our approach relied upon a diastereoselective palladium(0)-catalyzed glycosylation followed by a sequence of reduction/dihydroxylation reaction, as well as acylation. An acetyl group shift from an axial position to an equatorial position provided an alternative way for selective acylation of the equatorial hydroxyl group of a *cis*-diol in carbohydrate chemistry. The evaluation of the biological activities of these kaempferol glycosides is in progress.

Acknowledgment. We thank the NIH (GM63150) and NSF (CHE-0415469) for their generous support of our research program. Funding for a 600 MHz NMR and an LTQ-FT Mass Spectrometer by the NSF-EPSCoR (#0314742) is also gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062076R