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Regioselective synthesis of *C*-prenylated flavonoids *via* intramolecular [1,3] or [1,5] shift reaction catalyzed by acidic clays

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ABSTRACT

Prenyl side chain and dihydropyrano skeleton exists in many natural and synthetic biologically active flavonoids. A highly efficient and regioselective method for the synthesis of *C*-prenylated flavonoids *via* intramolecular [1,3] or [1,5] shift reaction of 5-*O*-prenylflavonoids catalyzed by Florisil or Montmorillonite clays is described. Florisil catalyzes intramolecular [1,5] shift reaction of 5-*O*-prenylflavonoids to obtain 8-*C*-prenylated flavonoids exclusively, Montmorillonite K10 exhibits the superior selectivity to promote intramolecular [1,3] shift reaction to obtain 6-*C*-prenylated flavonoids compared with Florisil and Montmorillonite KSF. This method provides a practical process to regioselective synthesize biologically important *C*-prenylated flavonoids in good yields using commercially available and inexpensive catalyst under mild conditions.

Introduction

C-Prenylated flavonoids are a unique class of naturally occurring flavonoids characterised by the presence of a prenylated side-chain on the flavonoid skeleton. Over the past few decades, an impressive number of bioactivities and their potential use in medicinal applications have been demonstrated for *C*-prenylated flavonoids [1,2]. *C*-Prenylflavonoids are also useful as precursors for the synthesis of naturally occurring bioactive flavonoids containing, for example, pyrano substituents [3]. *C*-prenylated flavonoids are interesting synthetic targets.

In general, the direct prenylation of flavonoids is difficult to control in terms of chemoselectivity (*C*- *vs* *O*-alkylation), regioselectivity, and number of prenyl introduced [4]. The [3,3]-Sigmatropic rearrangement (Claisen rearrangement) of *O*-prenylflavonoids provides convenient access to *para*-allyl phenols (C-8 for flavonoids) precursors to a variety of natural products, including flavonoids and coumarins [5,6]. The difficulty in preparing 2,2-disubstituted ethers often renders the Claisen rearrangement inconvenient for the preparation of terminally substituted *ortho*-allyl phenols [7]. For Claisen rearrangement of *O*-prenylflavonoids at 5-position, the chances of prenyl being rearrangement to flavonoids C-6 and C-8 are close, there is a problem of poor selectivity [8]. Catalytic use of β-diketone and rare earth metals complex catalyst [Eu(fod)$_3$], the yield of *para*-position (C-8 for flavonoid) has greatly improved, but rare earth metals are expensive and unstable [9,10]. There are certain limitations in the method of introducing prenyl group in 8-position.

In order to study the biological activities of *C*-prenylated flavonoids, a facile and efficient synthetic approach was required. The development of a straightforward and tunable entry into C-6 and C-8 prenylflavones from a common precursor would there for represent a significant addition to the field, paving the way to systematic structure-activity studies for this class of compounds.

The use of eco-friendly approaches for the synthesis of a diversity of bioactive small molecules has been increasing during recent years. Acid catalysis of organic transformations by clay aluminosilicates is an area of considerable potential and interest due to ease of handling and workup, naturally abundant, inexpensive, nontoxic, chemically versatile and recyclable [11,12]. Florisil and Montmorillonite clays, including K10 and KSF, are generally employed as effective and environmentally benign heterogeneous catalysts for several reactions, which was used to obtain dihydropyranoxanthones [13], *para*-allyl phenols, and *ortho*-allyl phenols [14,15]. Therefore, these solid catalysts seem to be an interesting green alternative to conventional chemistry practices.

In the present paper, we describe the regioselective syntheses of 8-*C*-prenylflavonoids and 6-*C*-prenylflavonoids *via* intramolecular [1,3] or [1,5] shift reaction of 5-*O*-prenylflavonoids catalyzed by acidic clay. A series of 8-*C*-prenylflavonoids **1**–**4** were synthesized under the catalysis of Florisil clay and 6-*C*-prenylflavonoids **5**–**8**

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were synthesized under the catalysis of Montmorillonite K10 clay starting from commercially available diosmetin and quercetin. Four dihydropyranoflavonoids **9**–**12** were synthesized by cyclization reaction of the prenyl group with the neighboring OH-group under acidic conditions.

8-*C*-Prenyldiosmetin (**1**) was isolated from Peanut Hull, which has been previously described as vasorelaxant agent [16]. Isocannflavin B (**2**) and Cannflavin B (**6**) were isolated from *Cannabis sativa L*, which has demonstrated ability to inhibit the BMP2K kinase and implied in the development of myopia [17,18]. 8-Prenyl quercetin (**3**) was found in *Desmodium caudatum* [19] with strong suppressed LPS-induced inflammation activity [2]. 6-C-Prenyldiosmetin (**5**) was obtained from cultured cells of Morus alba or Cudrania tricuspidate [20] and 3,3′,4′,7-Tetramethoxy-8-*C*-Prenylquercetin **(4)** was isolated from *Phebalium dentatum* Smith (Rutaceae) [21]. 6-*C*-Prenyl quercetin (**7**) was isolated from the sheaths of *Vellozia kolbekii* Alves, which was found to be active as 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavengers [22].

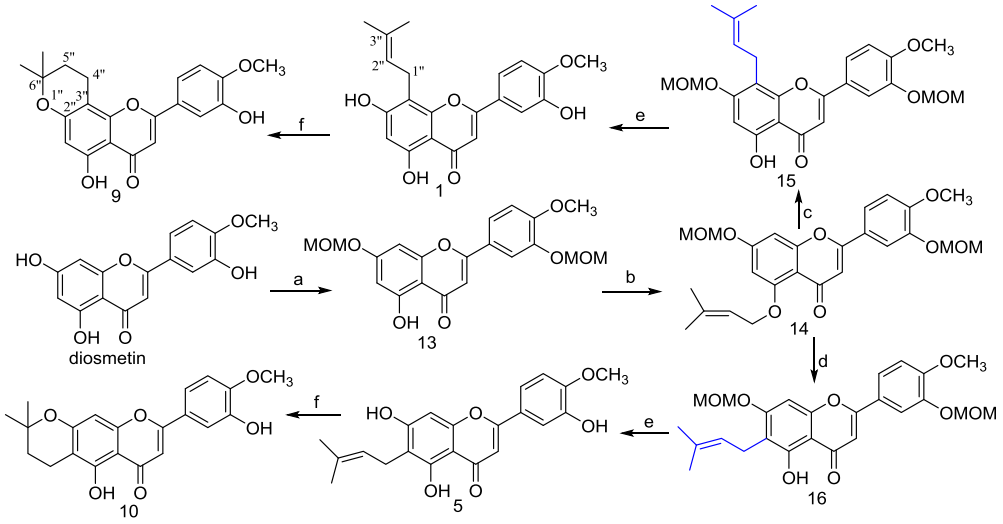
Results and discussion

As is shown in Schemes 1–3**,** staring materials diosmetin and quercetin was commercial available, luteolin was prepared from diosmentin according to literature procedures [23]. Then chloromethyl methyl ether (MOMCl), which was stable in basic conditions and easily removed by acidic treatment, was added to protect the hydroxy group of diosmetin and quercetin to obtain selectively methoxymethyl (MOM) group protected products **13** and **21**. Luteolin was successively treated with MOMCl and $(Me)_2SO_4$ to obtain 3′,7-bis-*O*-methoxymethylchrysoeriol **(17)**. *O*-Prenylation of the free 5-hydroxy group of **13**, **17** and **21** was respectively prenylated with prenyl bromide affording target prenyl ethers **14**, **18** and **22**.

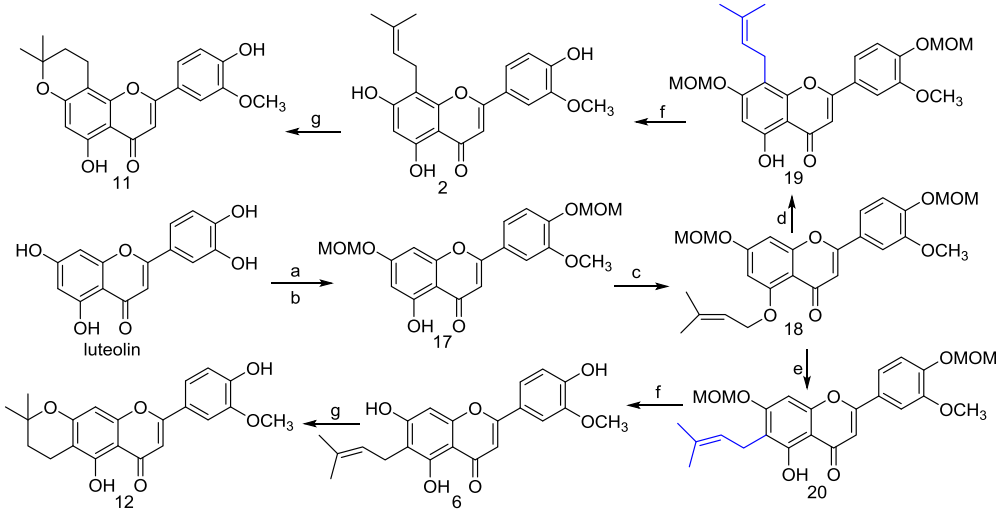
Reagents and conditions: (a) CH_3OCH_2Cl, K_2CO_3, acetone, r.t., 84%; (b) prenyl bromide, K_2CO_3, acetone, 45 °C, 70%; (c) Florisil, toluene, reflux, 92%; (d) Montmorillonite K10, toluene, reflux, 54%; (e) dilute HCl (aq.), CH_3OH, r.t., 80%; (f) H_2SO_4, CH_3OH, reflux, 85%;

Reagents and conditions: (a) CH_3OCH_2Cl, K_2CO_3, acetone, r.t.; (b) $(Me)_2SO_4$, K_2CO_3, acetone, r.t, 65%; (c) prenyl bromide, K_2CO_3, acetone, 45 °C, 72%; (d) Florisil, toluene, reflux, 88%; (e) Montmorillonite K10, toluene, reflux, 54%; (f) dilute HCl (aq.), CH_3OH, r.t., 84%; (g) H_2SO_4, CH_3OH, reflux, 90%;

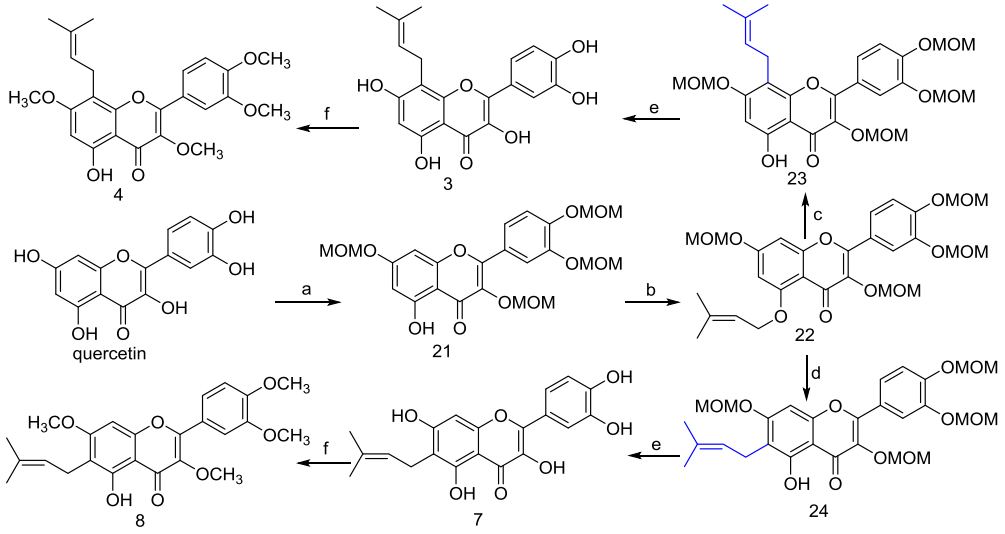
Reagents and conditions: (a) CH_3OCH_2Cl, K_2CO_3, acetone, r.t., 80%; (b) prenyl bromide, K_2CO_3, acetone, 45 °C, 85%; (c) Florisil, toluene, reflux, 86%; (d) Montmorillonite K10, toluene, reflux,



Scheme 1. Synthetic routes of *C*-prenylated flavonoids from diosmetin.



Scheme 2. Synthetic routes of *C*-prenylated flavonoids from luteolin.



Scheme 3. Synthetic routes of *C*-prenylated flavonoids from quercetin.

45%; (e) dilute HCl (aq.), CH_3OH, r.t., 80%; (f) $(Me)_2SO_4$, K_2CO_3, acetone, r.t, 82%;

Once 5-*O*-prenylflavonoids **14**, **18** and **22** were available, our attention was focused on the formation of 6-and 8-*C*-prenylated flavonoid. In our previous research, the key route of synthetic strategy of 8-*C*-prenylated flavonoid was a regioselective microwave-assisted Claisen rearrangement from 5-*O*-prenylflavonoid [5]. Although we were readily able to obtain 8-*C*-prenylated flavonoid in good yields under microwave-assisted Claisen rearrangement reaction, 6-*C*-prenylated flavonoids were unreachable. In conjunction with ongoing efforts in our laboratories, we tried to use a convenient acidic clay catalyzed intramolecular [1,3] or [1,5] shift reaction, which was originally reported by Dauben [6], to transform 5-*O*-prenylflavonoids into 6-or 8-*C*-prenylated flavonoids. In Dauben's work, Montmorillonite KSF clay was used to catalyze [1,3] shift reaction and obtained a 34% yield of *ortho*-prenyl phenol along with small amounts of *para*-prenyl phenol. Herein we present a more detailed investigation of this reaction for the conversion of 5-*O*-prenylflavonoids to 6-or 8-*C*-prenylflavonoids.

For compound **14**, Florisil (60–100 mesh), Montmorillonite K10 clay (240 m^2/g), or Montmorillonite KSF clay (20–40 m^2/g) was used to catalyze this reaction respectively (in Fig. 1). The starting material **14** was completely consumed after 4 h in the catalysis of Florisil, with a complete transformation of MOM-protected 8-*C*-prenylflavonoid **15** (yield 92%), which was confirmed by the characteristic NMR signals at $\delta = 3.42$ [d, $J = 7.0$ Hz, 2H, $-C\underline{H}_2-CH=C(CH_3)_2$], 6.47 (s, 1H, 6-H) and loss of H-8 (C-8 position). In the catalysis of Montmorillonite K10 clay, we could obtain desired MOM-protected 6-C-prenylflavonoid **16** as major products (yield 54%) [characteristic signals for the $-C\underline{H}_2-CH=C(CH_3)_2$ group at $\delta = 3.32$ (d, $J = 5.9$ Hz, 2H), $\delta = 6.65$ (s, 1H, 8-H) and loss of H-6] and MOM-protected 8-*C*-prenylflavonoid **15** (yield 25%). The treatment of **14** with Montmorillonite KSF clay also give us desired MOM-protected 6-*C*-prenylflavonoid **16** (yield 34%) and MOM-protected 8-*C*-prenylflavonoid **15** (yield 38%). The result showed that Florisil has high selective catalysis on intramolecular [1,5] shift reaction of 5-*O*-prenylflavonoids, Montmorillonite K10 clay has superior catalysis on intramolecular [1,3] shift reaction than Florisil and Montmorillonite KSF (Table 1). The possible mechanism for the synthesis of **15** and **16** showed that intramolecular [1,3] and [1,5] shift reaction were formed through an aromatic electrophilic substitution at nucleophilic aromatic position (C-6 or C-8) under the catalyzation of acidic clays (in Fig. 2).

Removing the MOM protecting group of MOM-protected 6-*C* and 8-*C* prenylflavonoids **15**, **16**, **19**, **20**, **23** and **24** were achieved by stirring these compounds in 1 mL HCl (3 mol L^{-1}) and 20 mL CH_3OH for 4 h in reflux. After purification by column chromatography methods, we could obtain 8-*C*-prenylflavonoids 8-*C*-prenyldiosmetin (**1**), isocannflavin B (**2**) and 8-*C*-prenylquercetin (**3**), and 6-*C* prenylflavonoids 6-*C*-prenyldiosmetin (**5**), cannflavin B (**6**) and Gancaonin P (**7**). The cyclization reaction of compounds **1**, **2**, **5** and **6** under acidic conditions in reflux, we could obtain dihydropyranflavonoids **9**–**12** [characteristic signals for the 1″–CH_2- group at $\delta = 2.64$–2.88 (t, $J = 6.7$ Hz, 2H), 2″–CH_2- group at $\delta = 1.85$–1.89 (t, $J = 6.7$ Hz, 2H), and 3″–$2CH_3$ group at $\delta = 1.36$–1.32 (s, 6H)]. Introduction of desired methyl functionality on 8-*C*-prenylquercetin (**3**) and Gancaonin P (**7**) was accomplished by

Table 1
Intramolecular [1,3] or [1,5] shift reaction of **14** catalyzed by acidic clays respectively.

Acidic clay	Product yield (%)		
	13	**15**	**16**
Florisil	0	92	0
Montmorillonite K10	18	25	54
Montmorillonite KSF	21	38	34

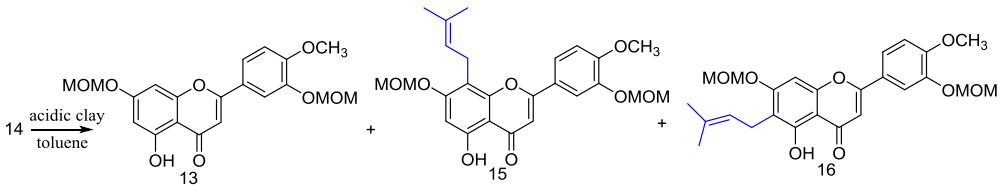


Fig. 1. Intramolecular [1,3] or [1,5] shift reaction of **14** catalyzed by acidic clays respectively.

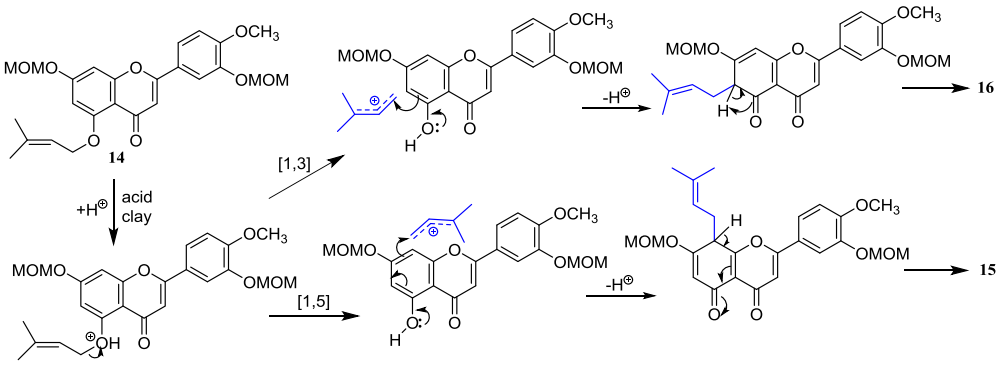


Fig. 2. Possible mechanism of intramolecular [1,3] and [1,5] shift reaction for the synthesis of 6-and 8-C-prenylated flavonoids.

using dimethyl sulfate in the presence of potassium carbonate to produce methylated prenylquercetin **4** and **8**.

Experimental section

See Supplementary materials.

Conclusion

8-*C*-prenylated flavonoids **1**–**4** and 6-*C*-prenylated flavonoids **5**–**8** were synthesized under the catalysis of Florisil or Montmorillonite K10 respectively starting from commercially available diosmetin and quercetin. The assembly of the 8-*C*-prenylated flavonoids were easily achieved *via* a intramolecular [1,5] shift reaction from 5-*O*-prenylated flavonoids with the catalysis of Florisil. Comparing with Montmorillonite KSF and Florisil, Montmorillonite K10 showed the superior selectivity on promoting intramolecular [1,3] shift reaction to transform 5-*O*-prenylated flavonoids into 6-*C*-prenylflavonoids.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151138. These data include MOL files and InChiKeys of the most important compounds described in this article.

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