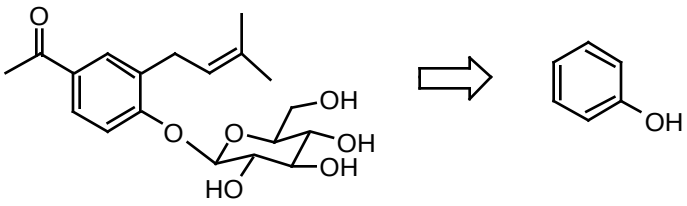
Progress towards the synthesis of an anti-inflammatory acetophenone glucoside

Matthew R. Dintzner*, Kristen M. McClelland, and Debbie Coligado

Contribution from the Department of Chemistry, DePaul University, 1036 West Belden Avenue, Chicago, IL 60614, Fax: (773)325-7421, e-mail: mdintzne@depaul.edu

Progress towards the synthesis of anti-inflammatory acetophenone glucoside 1 (3-(3-methyl-2-butenyl)acetophenone-4-O-β-glucopyranoside) from phenol is described. The synthesis features two successive intramolecular rearrangements. The first is a clay-catalyzed [1,3] sigmatropic shift of ally phenyl ether 8 to give phenol 9. The second is a regioselective Lewis acid-catalyzed Fries rearrangement of acetate 10 to give acetophenone derivative 5. Stereoselective glycosidation of 5 will generate the target β-glucopyranoside.

Acetophenone glucosides are abundant in nature and exhibit an array of physiological activity.[1] Despite their relative abundance and biological significance, however, there have been minimal reports in the literature on the synthesis of these compounds. Acetophenone glucoside **1** (3-(3-methyl-2-butenyl)acetophenone-4-*O*-β-glucopyranoside), along with several other derivatives, was recently isolated from the Mediterranean area species *Helchrysum italicum*. These compounds were shown to exhibit anti-inflammatory activity in a 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema test.[2] We report our efforts towards an efficient synthesis of **1** from commercially available phenol (Figure 1).

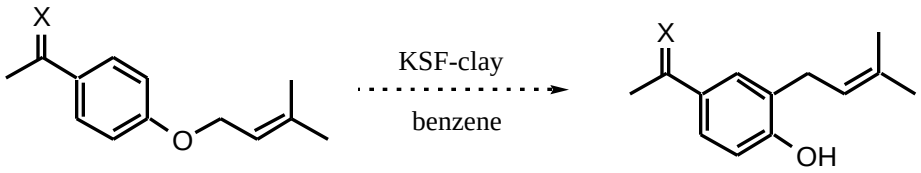


1

Figure 1. Retrosynthetic analysis of **1**

Our initial plans to synthesize **1** were based on attempted clay-catalyzed [1,3] shifts of prenylated 4'-hydroxyacetophenone derivatives **2-4** (Scheme 1), according to the method of Dauben.[3] Substrates **2-4** were synthesized straight-forwardly from commercially available 4'-hydroxyacetophenone. Attempted [1,3] shifts with **2-4** were minimally successful, typically resulting in dealkylation.

Scheme 1. Attempted [1,3] shifts

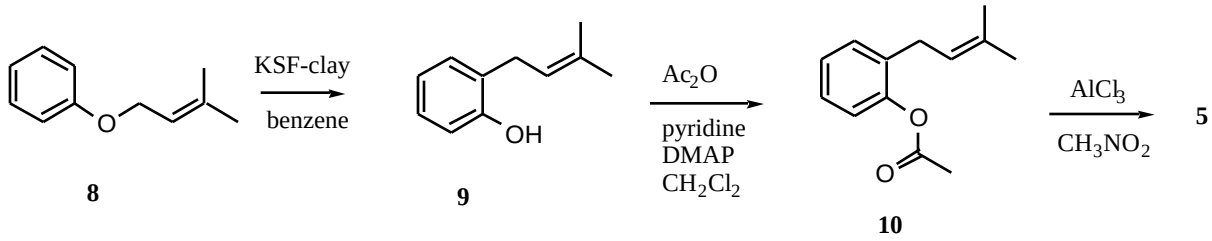


2, X = O (ketone)
3, X = -OCH_2CH_2O- (1,3-dioxolane)
4, X = -$SCH_2CH_2CH_2S$- (1,3-dithiane)

5, X = O (ketone)
6, X = -OCH_2CH_2O- (1,3-dioxolane)
7, X = -$SCH_2CH_2CH_2S$- (1,3-dithiane)

An alternative approach to compound **5** employs two successive intramolecular rearrangements. The KSF clay-catalyzed [1,3] shift of allyl phenyl ether **8** (prepared from phenol) is a known reaction, and proceeded smoothly in our hands to give phenol **9**, along with some of the *para* isomer. Acylation of **9** with acetic anhydride in the presence of pyridine gave acetate **10** in good yield. Treatment of **10** with $AlCl_3$ in nitromethane resulted in regioselective Fries rearrangement to give phenol **5** in good yield (Scheme 2).[4]

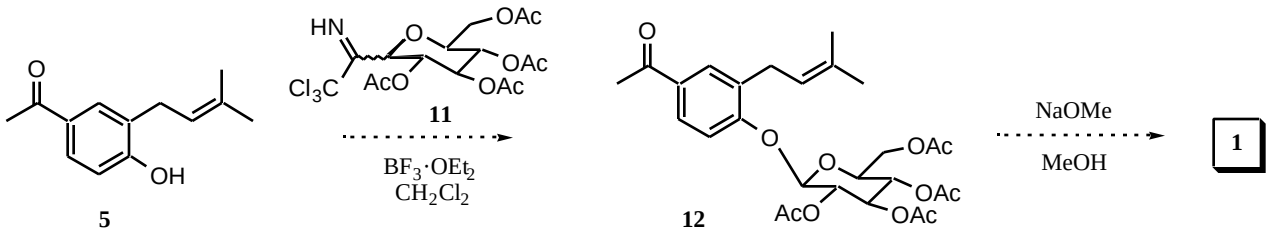
Scheme 2. Alternate approach to intermediate **5**



8 **9** **10**

The second phase of our synthesis presents a two-fold challenge in that aryl glucopyrannosides are not typically accessible via standard Fischer conditions, and the desired glycoside product is the less stable β-anomer.[5] However, treatment of **5** with 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl trichloroacetimidate **11** in the presence of $BF_3 \cdot OEt_2$ in dichloromethane is predicted to proceed selectively to give β-D-gluopyranosoide **12**, based on the method of Penverne.[6] Stereoselectivity is driven by anchimeric assistance from the 2-O-acetyl group of **11**. Finally, treatment of **12** with methanolic sodium methoxide will give the target compound **1**.

Scheme 3. Synthesis of **1**



References

1. (a) Gongora, L.; Manez, S.; Giner, R.M.; Carmen, R.M.; Gray, A.I.; Rios, J. *Phytochemistry* **2002**, *59*, 857; (b) Yoshikawa, M.; Shimada, H.; Nishida, N.; Li, Y.; Toguchida, I.; Yamahara, J.; Matsuda, H. *Chem. Pharm. Bull. Jpn.* **1998**, *46*, 113; (c) Lin., Y.; Lin. T.; Kuo, Y. *J. Nat. Prod.* **1997**, *60*, 369; (d) Jahodar, L; Kolb, I. *Pharmazie* **1990**, *45*, 446.
2. Sala, A.; Recio, M.; Giner, R.M.; Máñez, S.; Ríos, J. *J. Nat. Prod.* **2001**, *64*, 1360.
3. Dauben, W.G.; Cogen, J.M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241.
4. Cairns, N.; Harwood, L.; Astles, D. P. *Tetrahedron* **1992**, *48*, 7581.
5. Collins, P.M.; Ferrier, R.J. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; Wiley: New York, 1995.
6. Penverne, C.; Ferrières, V. *J. Chem. Ed.* **2002**, *79*, 1353.