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A Simple Approach to 2-Substituted-4-Furanmethanol Compounds

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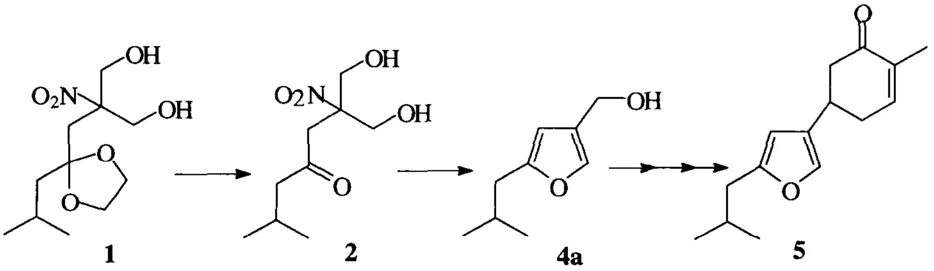
Abstract : A two step synthesis of the title compounds from easily available starting materials is reported. The method involves a Hörner-Wadsworth-Emmons reaction between β–ketophosphonates and 1,3-diacetoxy-2-propanone, followed by mild acid treatment of the γ,γ'–diacetoxyenones thus obtained.

The synthesis of 2-substituted-4-functionalized furans is a problem of current interest,[2] since an important number of natural products containing this structural subunit is known.[3]

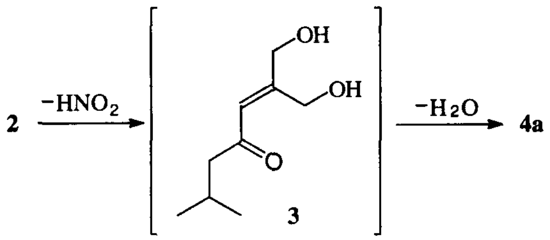
A total synthesis of the sesquiterpene bilobanone **5** from 2-isobutyl-4-furanmethanol **4a** has been reported by us previously.[4] The synthesis of **4a** involved a new method for the preparation of 2-substituted-4-functionalized furans in which the heterocyclic ring was formed by acid hydrolysis of nitroketal diol **1**, followed by base ($NaHCO_3$) treatment of nitroketone diol **2**[5] (scheme 1):

Scheme 1



Although the reaction mechanism for this transformation (**2**→**4a**) remains unknown, in our opinion it is reasonable to assume that HNO_2 elimination in the nitroketone **2** would afford an intermediate γ,γ'–dihydroxyenone **3** which cyclizes to the furan ring (scheme 2):

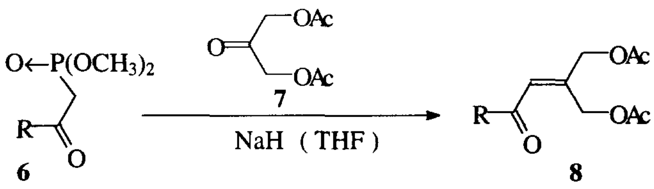
Scheme 2



Accordingly to this hypothesis, we reasoned that if intermediate dihydroxyenone **3** (or a conveniently protected derivative thereof) could be prepared by a direct method, a simple synthesis of furans such as **4** would be available. In this paper we would like to demonstrate that our expectation is correct.

Due to simplicity and generality, the Hörner-Wadsworth-Emmons reaction between β–ketophosphonate anions (obtained from **6** with NaH in THF) and 1,3-diacetoxy-2-propanone **7** as the carbonyl acceptor[6] has been chosen by us as the method of enone formation (scheme 3). The acetate carbonyls of **7** are inert under the reaction conditions and good yields of γ,γ′–diacetoxyenones **8** are obtained.[7]

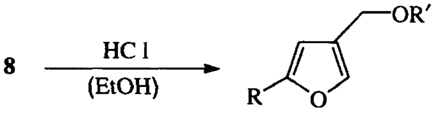
Scheme 3



a : R = $(CH_3)_2CHCH_2$, 77 %
b : R = C_6H_5 , 65 %
c : R = 2,5-$(OCH_3)_2C_6H_3$, 80 %

Although our attempts, to convert enone **8b** into the phenylfuranmethanol **4b** under basic conditions failed, in acidic medium (catalytic aqueous HCl in EtOH, 65°, 4-5 h.) the desired furan **4b** was obtained in high yield (91%) along with traces of the corresponding acetate **4c** (scheme 4):

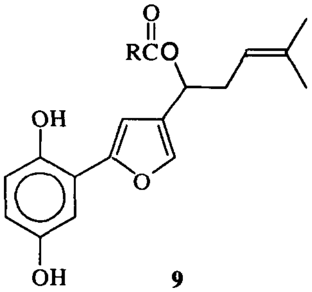
Scheme 4



4a : R = $(CH_3)_2CHCH_2$, R′ = H, 76 %
4b : R = C_6H_5, R′ = H, 91 %
4c : R = C_6H_5, R′ = Ac
4d : R = 2,5-$(OCH_3)_2$-C_6H_3, R′ = H, 52 %

Following the general protocol, furanmethanol **4a** is obtained in two simple steps and in 59% overall yield from β–ketophosphonate **6a**, a major improvement of our original procedure (≈23% overall yield over 7 steps).[4]

The interesting furanmethanol **4d** (a potential intermediate for shikonofurans[3] **9** synthesis) has also been obtained in 41% overall yield from the dimethyl 2,5-dimethoxyphenacylphosphonate **6c**.



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The application of the proposed methodology for the synthesis of **9** and other related natural products is now in progress.

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REFERENCES AND NOTES

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2. Anand, R.C.; Singh, V. *Heterocycles*, **1993**, *36*, 1333-1336 and references cited therein.

3. a) Inouye, H.; Matsumura, H.; Kawasaki, M.; Inoue, K.; Tsukada, M.; Tabata, M. *Phytochemistry*, **1981**, *20*, 1701-1705. b) Yoshizaki, F.; Hisamichi, S.; Kondo, Y.; Sato, Y.; Nozoe, S. *Chem. Pharm. Bull.*, **1982**, *30*, 4407-4411.
4. Escalona, H.; Maldonado, L.A. *Synthetic Commun.*, **1980**, *10*, 857-862.
5. Nitroketone diol **2** is a rather unstable crystalline solid; mp 104-105°; IR (KBr) 3315, 1715, 1550, 1460, 1410, 1390, 1375, 1350, 1050 cm^{-1}; ^{1}H NMR (CDCl$_3$, 90 MHz) δ 0.90 (d, J = 7 Hz, 6 H), 2.00-2.50 (m, 3H), 3.15 (s, 2H), 3.60-3.90 (broad, 2 OH), 4.05 (s, 4H).
6. Bentley, P.H.; McCrae, W. *J. Org. Chem.*, **1970**, *35*, 2082-2083. We have found that compound **7** is an easily obtained, stable, crystalline solid, highly convenient for our purposes. However, many other OH–protected 1,3-dihydroxyacetone derivatives are also conceivable candidates as carbonyl acceptors in the Hörner-Wadsworth-Emmons reaction described here.
7. Compound **7** has been previously used as substrate in Wittig-type reactions : a) Plieninger, H.; Meyer, E.; Sharif-Nassirian, F.; Weidmann, E. *Liebigs Ann. Chem.*, **1976**, 1475-1486. b) Gadir, S.A.; Smith, Y.; Taha, A.A.; Thaller, V. *J. Chem. Res. (S)*, **1986**, 222-223.

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