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A NEW AND VERSATILE ROUTE FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED BENZENOIDS

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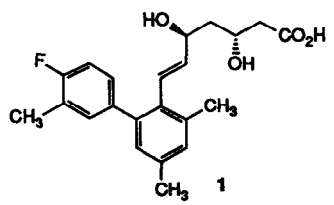
Summary: A new route for the synthesis of highly substituted benzenoids has been developed. Key steps include the conversion of unsaturated lactone **7** to carboxy substituted cyclohexenone **8** followed aromatization to give phenol **9**. The phenolic functionality provides a handle for further modification to give substituted benzenoids of type **2**.

Utilization of substituted benzenes for the synthesis of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) inhibitors, such as **1**, has been previously reported in the literature.[1] Structure-activity relationships have been limited mainly to compounds possessing a 4,6-dimethyl or 4,6-dichloro substitution pattern on the central aromatic ring, although the nature of the distal phenyl appendage has been varied extensively. Unfortunately, the utilization of many aromatic 'hydrophobic anchors'[2] have been limited by both the scope of the chemistry and the accessibility of commercially available starting materials. As part of our own program directed towards the synthesis of 7-aryl-5-hydroxyphosphinyl-3-hydroxyheptanoic acid HMGR inhibitors,[3] we were in need of a practical route for the synthesis of highly substituted aromatics such as **2**, where R^1, R^2, R^3, R^4, and R^5 may be independently chosen from a variety of alkyl or aryl substituents. Consequently, a new and versatile route for the synthesis of tri-, tetra-, and penta-substituted benzenoid aromatics has been developed and is the topic of this paper.



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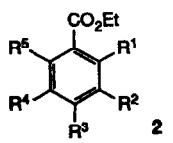
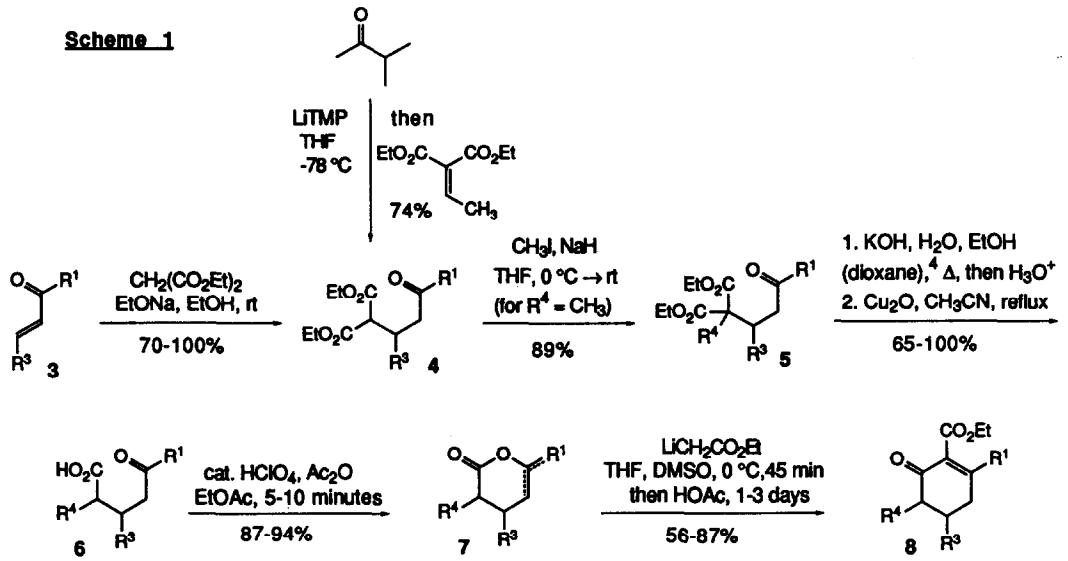


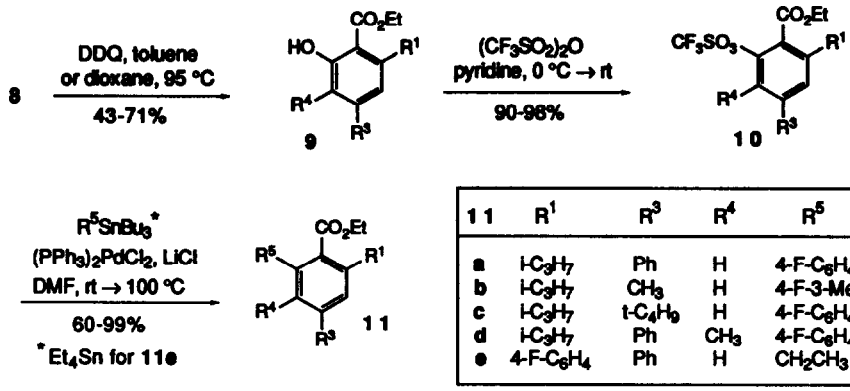
2

Scheme 1 depicts the synthetic route developed. Sodium ethoxide catalyzed Michael addition of diethyl malonate to enones **3** in ethanol gave the 5-keto diesters **4** in good yields. Enone **3** may be conveniently prepared by Claisen-Schmidt condensation of the appropriate aldehyde R^3CHO with ketone R^1COCH_3. 1,4-Addition of the kinetically formed enolate of methyl isopropyl ketone with diethyl ethylidenemalonate was found to be a more effective route for the synthesis of **4b**. In cases where R^4 = H, 5-keto diesters **4** were directly saponified with KOH in aqueous ethanol.[4] The intermediate diacids were then decarboxylated in the presence of catalytic Cu_2O in CH_3CN[5] to afford 5-keto acids **6**. The yield for this transformation was invariably >85%. In the case where substitution at R^4 = CH_3, **4d** was alkylated with methyl iodide to give **5d** and subsequently saponified and decarboxylated to give **6d** in 65% yield. The diminished yield for this particular substrate was due to base induced retro-Michael addition of **5d** during the initial stages of the reaction to give **3d**.

Scheme 1



5-Keto acids **6** underwent rapid dehydrative cyclization[6] to give the unsaturated lactones **7** in good yields. Where R^1 = isopropyl, a mixture of endo (major) and exo (minor) double bond isomers were formed, both of which were suitable subtrates for the next transformation. Reaction of **7** with two equivalents of the lithium anion of ethyl acetate (generated by the addition of ethyl acetate to LiCA in THF at -78 °C) in THF/DMSO gave an initial acyclic 3,7-diketo ester which slowly underwent intramolecular Knoevenagel condensation upon treatment with HOAc.[7,8] DDQ oxidation of the resulting carboxy substituted cyclohexenones **8** gave moderate yields of the desired phenols **9**, although TLC

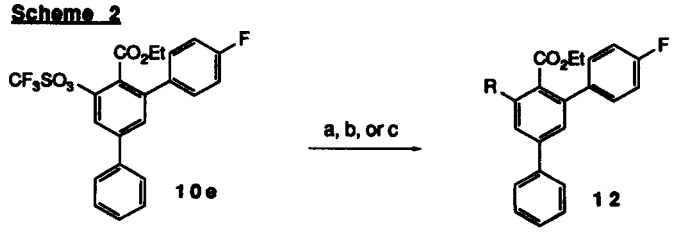


11	R^1	R^3	R^4	R^5
a	i-C_3H_7	Ph	H	4-F-C_6H_4
b	i-C_3H_7	CH_3	H	4-F-3-Me-C_6H_3
c	i-C_3H_7	t-C_4H_9	H	4-F-C_6H_4
d	i-C_3H_7	Ph	CH_3	4-F-C_6H_4
e	4-F-C_6H_4	Ph	H	CH_2CH_3

analysis of these reactions showed essentially only the product and baseline material.[9] Other methods to effect aromatization (S_8, fuse at 175 °C; Pd or Pt on carbon, decalin®, 200 °C) were found to be much less effective. Triflation of **9** consistently gave the substituted aryl triflates **10** in excellent yields. Utilizing the method of Stille,[10] triflates **10** underwent palladium catalyzed coupling with either aryl or alkyl stannanes affording **11** in usually >88% yield. A modest (60%) yield was obtained in the case of **11d**, presumably due to the reduced accessibility of the nested triflate functionality in **10d** to undergo an initial oxidative addition of palladium. Although this methodology has only been extended to the synthesis of benzoate esters where R^2 = H, it is likely that placement of a substituent at the R^2 position in **2** is feasible through the use of an appropriately substituted 5-keto diester **4**.

In order to extend the scope of this methodology, it was desired to utilize the triflate group on **10** as a handle for further modification (see Scheme 2). Thus, palladium catalyzed reduction[11] of **10e** with HCO_2H/Bu_3N effected removal of the triflate group, giving trisubstitued benzoate ester **12a** in high yield. Palladium catalyzed vinylation of **10e** gave **12b**, which may be further functionalized to the corresponding aldehyde or hydroxymethyl compound via ozonolysis or hydroboration/oxidation respectively. Reaction of **10e** with $(CH_3)_2CuLi$[12] permitted the introduction of a methyl group ortho to the ester functionality.

Scheme 2



12	R
a	H
b	H_2C=CH
c	CH_3

(a) R = H; HCO_2H, Bu_3N, $(PPh_3)PdCl_2$, DMF, 100 °C, 2 h, 97%.
(b) R = vinyl; n-Bu_3SnCH=CH_2, LiCl, $(PPh_3)PdCl_2$, DMF, 85 °C, 1.5 h, 90%.
(c) R = CH_3; $(CH_3)_2CuLi$, Et_2O, -78° → 0 °C, 52%.

Surprisingly, higher order cuprates such as $(CH_3)_2Cu(CN)Li_2$, reported to be better for this type of transformation,[13] were found to be less effective. Literature methods also exist for the conversion of aryl triflates to aryl cyanides,[14a] aryl aldehydes,[14b] aryl esters,[14c,d] aryl amides,[14c] and aryl ketones.[14e]

In conclusion, a new and versatile method for the synthesis of highly substituted benzenes has been developed. Utilization of this methodology should make easier the synthesis of a variety of benzenoid aromatics not readily accessible through the functionalization or transformation of commercially available aromatic precursors.

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2. Ables, R.H.; Nakamura, C.E. *Biochemistry* **1985**, *24*, 1364.
3. The design and utilization of hydroxyphosphinyl containing HMGR inhibitors has been presented at the X International Symposium on Drugs Effecting Lipid Metabolism, Houston, TX, November 1989; Abstract No. 233.
4. In the case of **4e**, aqueous dioxane was used as the solvent. The use of ethanol as a co-solvent effected partial displacement of the fluorine with an ethoxy group in the aromatic ring.
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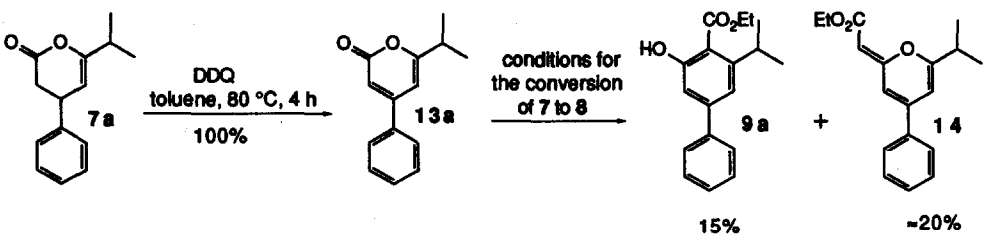
6. Hauser, F.M.; Baghdanov, V.M. *J. Org. Chem.* **1988**, *53*, 4676. In general, 5-keto acid **6** (10 mmol) was added to 40 mL EtOAc which was 0.01 M in $HClO_4$ and 1 M in acetic anhydride. After 5-10 minutes, the mixture was quenched with saturated $NaHCO_3$ and worked up in the usual manner.
7. A similar method to that used by Hauser for the conversion of 1H-2-benzopyranones to ethyl 1-hydroxy-2-naphthoates was used, see Hauser, F.M.; Pogany, S. A. *J. Het. Chem.* **1978**, *15*, 1535.
8. An alternate protocol for the synthesis of phenols **9** was attempted in which ethyl lithioacetate was added to the readily available α-pyranone **13**. Pyranone **13** was obtained in excellent yield by DDQ oxidation of the corresponding unsaturated ester. The low conversion of **13** to **9a** and the formation of unexpected by-products such as **14** lead us to abandon this route.



9. Prolonged exposure of phenols **9** to DDQ does not seem to result in a diminished yield of product. It is possible that the enolic tautomer of **8** may act as a diene in a Diels-Alder reaction with DDQ giving baseline material, although this is speculative.
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