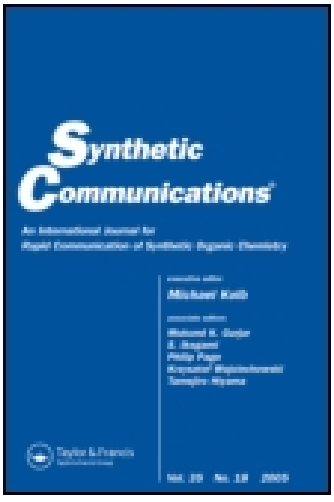

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Synthesis of Some C-4 Hydroxybenzo[c]pyrans: A New Approach

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Synthesis of Some C-4 Hydroxybenzo[*c*]pyrans: A New Approach

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Abstract: A new synthetic approach to the synthesis of some epimeric C-4-hydroxybenzo[*c*]pyrans is described. A key step in their formation is stereoisomerisation of a nonconjugated *ortho* alkenylphenylketone and -ester using palladium bisacetonitrile [bisacetonitriledichloropalladium(II)] to give the corresponding conjugated *E* stereoisomers which cyclize on treatment with *meta*-chloroperbenzoic acid (m-CPBA) to afford the target compounds.

Keywords: C-4 hydroxybenzo[*c*]pyrans, hydroxy[*c*]pyrans, *meta*-chloroperbenzoic acid, palladium bisacetonitrile

Some naturally occurring compounds contain a C-4 hydroxypyran ring (in which the hydroxyl may occupy a *pseudo*-axial or *pseudo*-equatorial position) as part of their structures. Two examples are the extended quinones, protoaphins-fb and-sl.[1] We have previously developed novel syntheses that afford such C-4 hydroxypyranquinones.[2–4] More recently, an oxidative mercury-mediated ring closure of 2-(prop-1′-enyl)phenylmethanol derivatives was reported, which afforded diastereomeric isochroman-4-ols.[5]

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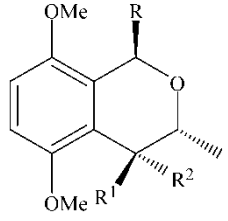
We now have developed a convenient new synthetic approach by which the diastereomeric hydroxypyran pairs **1** and **2**, as well as **3** and **4**, are available in good overall yield (Scheme 1).



1. R = CH_3; R^1 = H; R^2 = OH
2. R = CH_3; R^1 = OH; R^2 = H
3. R = H; R^1 = H; R^2 = OH
4. R = H; R^1 = OH; R^2 = H

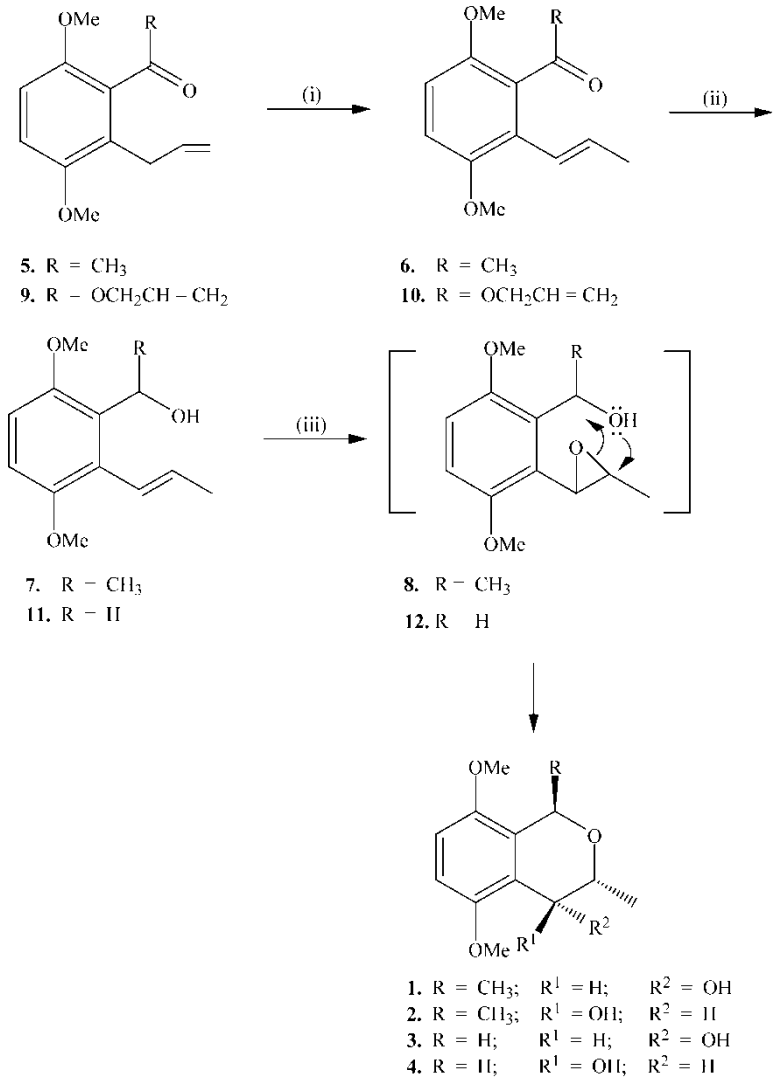
Ketone **5**[4] was smoothly converted to the conjugated *E* olefin **6**[4] (89%) on treatment with a catalytic amount of palladium bis(acetonitrile)[6] in dry dichloromethane. ^{1}H NMR integration showed the presence of some (less than 2%) of the corresponding *Z*-isomer. Our earlier work[2,3] in this regard relied entirely on base-induced conjugations employing potassium t-butoxide in THF.

Compound **6** gave alcohol **7**[4] on treatment with lithium aluminium hydride. This was followed by epoxidation of the olefinic bond of **7** using m-CPBA to give the diastereomeric C-4 hydroxypyran **1**[4] as the major product (in which the OH is *pseudo* axial) as well as pyran **2**[4] (in which the OH is *pseudo* equatorial) as their racemates in yields of 46% and 36%, respectively. The target hydroxypyrans presumably formed via cyclization of the intermediate epoxide **8**. We have found the same product distribution in our earlier[4] oxidative cylization reactions employing cerium(IV) ammonium nitrate–the product with the hydroxy in a *pseudo*-axial position being the major diastereomer.

Compound **9**[4] could also be converted to the *E* olefin **10**[5] with palladium bisacetonitrile in excellent yield (90%). This was treated as for compound **6** to afford alcohol **11**,[5] which, upon treatment with m-CPBA, gave the epimeric C-4 hydroxypyrans **3** and **4**[5] as their racemates in yields of 58% and 23%, respectively (also probably via cyclization of the intermediate epoxide **12**).

The ^{1}H NMR spectroscopic data for pyrans **1**, **2**, **3**, and **4** agreed entirely with those published earlier.[4,5]

We envisage that this new synthetic approach to C-4 hydroxybenzo[*c*]-pyrans could be employed as a model for the synthesis of naturally occurring compounds containing the C-4 hydroxypyran ring system.



Scheme 1. (i) Palladium bis(acetonitrile)/CH_2Cl_2; (ii) $LiAlH_4$/ether; (iii) m-CPBA/CH_2Cl_2.

EXPERIMENTAL

^{1}H NMR spectra were recorded using a Varian 200-MHz instrument at ambient temperature in deuterochloroform. Infrared spectra were measured as Nujol mulls on a Beckman Aculab spectrometer. High-resolution mass spectra were recorded on a modified AEI-902 spectrometer. Melting points were recorded on a Fischer-John apparatus and are uncorrected. Column

chromatography was carried out on dry columns with Merck kieselgel (silica gel) 60 (70–230 mesh) as adsorbent.

The phrase "residue obtained on workup" refers to the residue when the organic layer was separated and dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

Light petroleum refers to petroleum ether (bp 60–80°C). Palladium bisacetonitrile refers to bisacetonitriledichloropalladium(II) and m-CPBA to *meta*-chloroperbenzoic acid. All solvents and reagents were distilled before use.

2,5-Dimethoxy-6-(*trans*-1′-propenyl)acetophenone (6)

Palladium bisacetonitrile (119 mg, 0.459 mmol) in dry dichloromethane (5 ml) was added to a stirred solution of compound **5**[4] (202 mg, 0.918 mmol) in dry dichloromethane (10 ml) under nitrogen. After 18 h, the reaction mixture was thrown into water and extracted with dichloromethane. The residue obtained on workup was chromatographed (eluant 30% ethyl acetate in light petroleum) to afford product **6**[4] (179 mg, 89%) as a light yellow oil. (Found: M^+, 220.1097. $C_{13}H_{16}O_3$ requires 220.1099.) ν max 1700 cm^{-1}. δ ($CDCl_3$) 1.85 (3H, d, J 6.6 Hz, Ar-CH=CHC$\underline{H}_3$), 2.41 (3H, s, Ar-CO$\underline{CH}_3$), 3.76 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.04 (1H, dq, J 16.2 and 6.6 Hz, Ar-CH=$\underline{CH}$CH$_3$), 6. 38 (1H, dq, J 16.2 and 1.8 Hz, Ar-$\underline{CH}$=CHCH$_3$), 6.72 (1H, d, J 9.0 Hz, Ar-H), 6.80 (1H, d, J 9.0 Hz, Ar-H).

1-(Hydroxyethyl)-2,5-dimethoxy-6-(*trans*-1′-propenyl)benzene (7)

Ketone **6**[4] (168 mg, 0.765 mmmol) in dry ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (145 mg, 3.827 mmol) in dry ether (20 ml). After 20 min, saturated ammonium chloride (2 ml) was added followed by anhydrous magnesium sulphate. Workup of the filtrate gave a residue, which was chromatographed (eluant 30% ethyl acetate in light petroleum) to afford product **7**[4] (151 mg, 89%) as white crystals; m.p. 83–84°C (from light petroleum) (lit.[4] 83–84.5°C). (Found: M^+: 222.1260. $C_{13}H_{18}O_3$ requires 222.1256.) ν_{max} 3520 cm^{-1}; δ ($CDCl_3$) 1.55 (3H, d, J 6.6 Hz, Ar-C$\underline{H}_3$CHOH), 1.90 (3H, dd, J 6.6 and 2.0 Hz, CH=CHC$\underline{H}_3$), 3.75 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.22–5.36 (1H, br s, OH, D_2O exchangeable), 5.64–5.82 (1H, dq, J 16.0 and 6.6 Hz, CH=$\underline{CH}$CH$_3$), 6.35 (1H, dq, J 16.0 and 2.0 Hz, $\underline{CH}$=CHCH$_3$), 6.69 (1H, d, J 8.8 Hz, Ar-H) and 6.77 (1H, d, J 8.8 Hz, Ar-H).

(±) (1R, 3R, 4R)-3,4-Dihydro-4-hydroxy-5,8-dimethoxy-1,3-dimethyl-1H-benzo[2,3-*c*]pyran (1) and Its 4S-diastereomer (2)

The conjugated alcohol **7**[4] (206 mg, 0.928 mmol) was dissolved in dichloromethane (10 ml) and immersed in ice. m-CPBA (240 mg,

1.391 mmol) in dichloromethane (10 ml) was added dropwise to the stirred alcohol solution. After 2 h, the reaction was thrown into a sodium hydroxide solution (0.1 mol dm^{-3}). The organic components were extracted into dichloromethane. The residue obtained upon workup was chromotographed on a short column (eluant 30% ethyl acetate in petroleum ether) to afford first compound **2**[4] (74 mg, 36%) as an oil; ν_{max} (film) 3480–3100 cm^{-1}(br). (Found: M^+, 238.1182. Calc. for $C_{13}H_{18}O_4$: M, 238.1205.) This was followed by compound **1**[4] (94 mg, 46%) as white crystals; mp 113–114°C (from hexane) (lit.[4] mp 113–115°C).

Allyl-3,6-dimethoxy-2-(*trans*-1′-propenyl)benzoate (10)

Ester **9**[4] (209 mg, 0.798 mmol) in dry dichloromethane (10 ml) was treated with palladium bisacetonitrile (166 mg, 0.638 mmol), as for the preparation of compound **6**. Workup and chromatography (eluant 30% ethyl acetate in light petroleum) gave **10**[5] (188 mg, 90%) as a yellow oil. ν_{max} 1845 and 1700 cm^{-1}. (Found: M^+, 262.1207. $C_{15}H_{18}O_4$ requires 262.1205). δ ($CDCl_3$) 1.85 (3H, dd, *J* 6.6 and 1.8 Hz, Ar-CH=CHC$\underline{H_3}$, 3.32 (2H, dt, *J* 5.8 and 1.4 Hz, Ar-$CO_2\underline{CH_2}$CH=CH_2), 3.77 and 3.79 (3H each, s, 2 × OCH_3), 4.75–4.82 (2H, m, Ar-CO_2CH_2CH=$\underline{CH_2}$), 5.32–5.48 (1H, m, *J* 16.0 and 6.7 Hz, Ar-CH=$\underline{CH}CH_3$), 5.80–6.25 (1H, m, Ar-$CO_2CH_2\underline{CH}$=CH_2), 6.42 (1H, dq, *J* 16.0 and 1.8 Hz, Ar-$\underline{CH}$=$CHCH_3$), 6.76 (1H, d, *J* 9.0 Hz, 5-H), 6.82 (1H, d, *J* 9.0 Hz, 6-H).

[3,6-Dimethoxy-2-*trans*-(1′-propenyl)phenyl]methanol (11)

Ester **10**[5] (104 mg, 0.397 mmol) was reduced with lithium aluminium hydride (75 mg, 1.98 mmol) as for the synthesis of compound **7**. Similar workup and chromatography afforded alcohol **11**[5] (73 mg, 89%) as an oil. ν_{max} 3400, 1640, and 1600 cm^{-1} and δ ($CDCl_3$) 1.94 (3H, dd, *J* 6.6 and 1.8 Hz, Ar-CH=CH$\underline{CH_3}$), 2.28 (1H, br s, OH, D_2O exchangable), 3.78 (3H, s, 6-OCH_3), 3.83 (3H, s, OCH_3), 4.77 (2H, s, Ar-$\underline{CH_2}$OH), 5.89–6.07 (1H dq, *J* 16.0 and 6.7 Hz, Ar-CH=$\underline{CH}CH_3$), 6.48 (1H, dq, *J* 16.0 and 1.8 Hz, Ar-$\underline{CH}$=$CHCH_3$), and 6.74 (2H, s, 4- and 5-H).

(±)(3R, 4R)-3,4-Dihydro-4-hydroxy-5,8-dimethoxy-3-methyl-1H-benzo[*c*]pyran (3) and Its 4S Diastereomer (4)

Alcohol **11**[4] (152 mg, 0.729 mmol) was cyclized using a solution of m-CPBA (188.7 mg, 1.0933 mmol) as in the preparation of compounds **1** and **2**. Similar workup and chromatography gave pyran **4**[5] (35 mg, 23%); mp 61–62°C (from hexane) (lit.[5] 60–61°C); (Found: M^+ 224.1038. Calc. for $C_{12}H_{16}O_4$:

M, 224.1049.) This was followed by pyran **3**[5] (88 mg, 58%); mp 69–70°C (from hexane) (lit.[5] 68–70°C). (Found: M^+ 224.1039. Calc. for $C_{12}H_{16}O_4$: M, 224.1049.)

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