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Short, convergent, stereoselective syntheses of enantiopure 2-benzopyran-5,8-quinones related to the aphid insect pigments, the protoaphins

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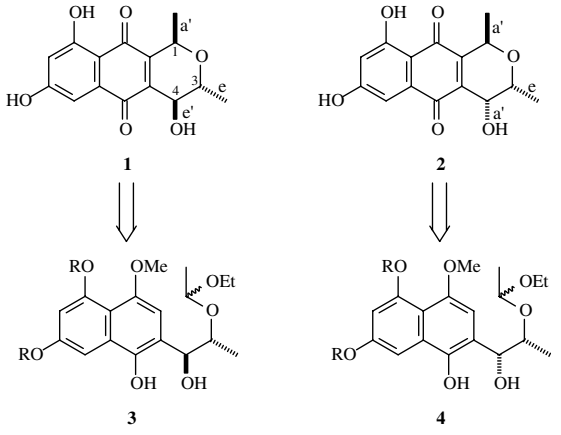
Abstract—The enantiopure (1*S*,3*S*,4*R*)-, (1*R*,3*S*,4*S*)- and (1*S*,3*S*,4*S*)-3,4-dihydro-1,3-dimethyl-4-hydroxy-2-benzopyrans **16**, **25** and **26** are prepared in two related reaction sequences, each in eight steps and good overall yield. The starting materials are 4-methoxyphenol **6** and (2*S*,1′*R* and 2*S*,1′*S*)-1′ ethoxyethoxypropanal **9**, the latter providing the source of asymmetry from the chiral pool. The three key reactions involved in each sequence are either highly or completely diastereoselective.

In seeking a short, convergent route to the derivatives quinone A **1** and quinone A′ **2** of the aphid insect pigments, the protoaphins,[1] we have previously reported[2] on the complementary diastereoselectivity achieved when titanium or magnesium naphtholates react with ethoxyethyl-protected (*R*)-lactaldehyde as the initial source of asymmetry. These reactions afford the benzyl-epimeric adducts **3** and **4**, respectively, as appropriate retrosynthetic targets for the quinones **1** and **2** (Scheme 1). It remained to establish a convenient method for the cyclization of these adducts to form the target naphthopyran skeleton through selective loss of ethanol. For both the natural derivatives **1** and **2** this cyclization would also need to be stereoselective to afford the pseudoaxial stereochemistry for the C-1 methyl group. We report here on model reactions that yield the related parent 2-benzopyrans in enantiopure form.



Scheme 1.

The ultrasonication-promoted reaction[3] of the titanium phenolate **5** of 4-methoxyphenol **6** with the cheaper ethoxyethyl-protected (*S*)-lactaldehyde **9**[4] gave the adduct **10** (Scheme 2). This product **10** was obtained in a diastereoisomeric ratio of 93:7 together with the alternative benzyl epimer **17** (see below), and was accompanied by the recovery of significant quantities of starting 4-methoxyphenol **6**. The crude reaction mixture was subsequently treated with camphorsulfonic acid and gave the enantiopure all-*cis* phenolic dioxolane **11** as the sole *cis*-4,5-diastereoisomer. This intramolecular protection step conveniently selectively expelled ethanol from the adduct **10** as required. Acetylation facilitated the careful chromatographic separation of the enantiopure acetate **12**[5] from the acetate **7** of starting material **6** and the minor quantities of the enantiopure diastereoisomeric dioxolanes **19** (see below). Acetate **12** was obtained in an overall yield of 15% over the three steps, or 52% based on consumed starting material. This represented an average yield per step of about 80%.

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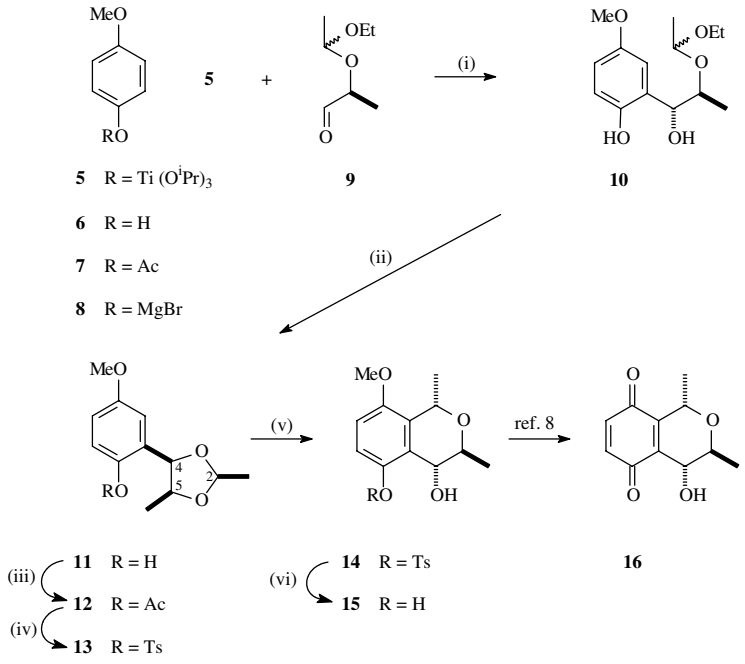


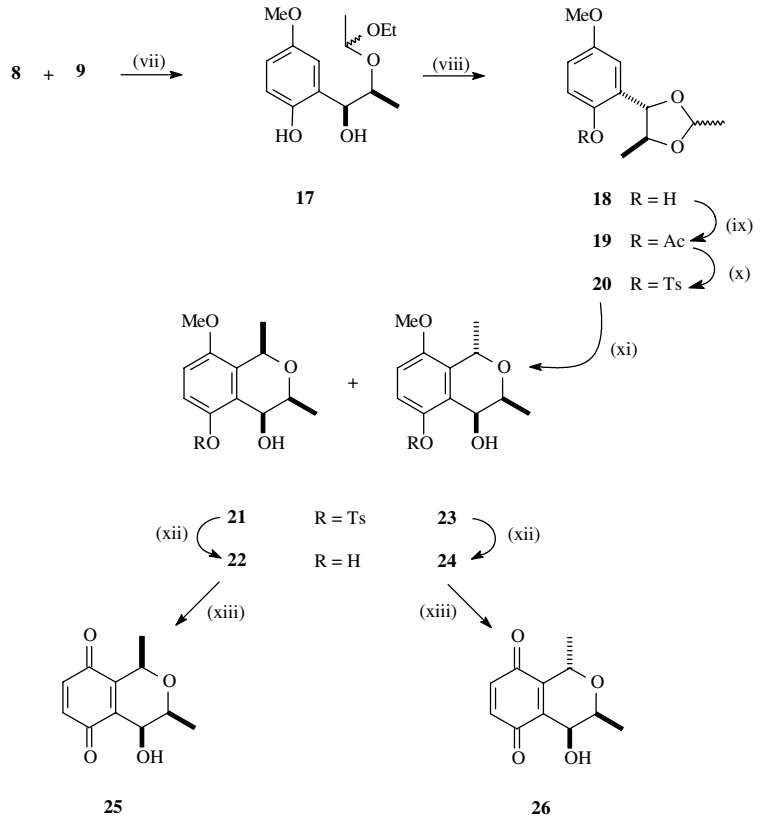
Scheme 2. Reagents and conditions: (i) **6**, toluene, Ti(O^{i}Pr)$_4$, rt, 30 min; added to **9**, 0 °C, 20 min; ultrasound, 20–40 °C, 5 h; satd aq NaF, 5 h; (ii) $CH_3CH(OEt)_2$, CSA, rt, 30 min; (iii) Ac_2O, py, 18 h, 15% overall, (52%*); (iv) KOH, MeOH, rt, 3 h; *p*-TsCl, K_2CO_3, acetone, rt, 7 h, 85%; (v) $TiCl_4$, CH_2Cl_2, −78 °C, 2 h, 44% (95%*); (vi) KOH, H_2O, MeOH, 70 °C, 4 h, 81% (*yields based on consumed starting material).

We have previously shown[6,7] that 2,5-dimethyl-4-phenyldioxolanes are isomerized in high yield to the corresponding 2-benzopyrans using titanium(IV) chloride, except where an electron releasing methoxy oxygen atom on the aromatic ring *ortho* to the dioxolanyl group led to an alternative unwanted reaction.[7] As anticipated the *ortho*-acetoxy group led to decomposition of **12** when treated with the titanium reagent. However, conversion of the acetate **12** into the enantiopure tosylate **13**[5] (in an overall yield for the two steps of 85%) provided more stable protection for, and reduced electron availability from, the *ortho*-tosyloxy oxygen atom, which effectively prevented the subsequent unwanted dioxolane ring-opening. Treatment of tosylate **13** with titanium(IV) chloride led to its clean conversion into the enantiopure 2-benzopyran **14**[5] as the sole product, although starting dioxolane **13** was recovered together with the corresponding *erythro*-diol, which was readily reconverted into the dioxolane **13** through acetalation with 1,1-dimethoxyethane and camphorsulfonic acid. The product **14** was obtained in a yield of 44%, or 95% based on the recovery of starting material **13** and diol. Hydrolysis of the tosylate **14** afforded the known[8] enantiopure 2-benzopyran-4,5-diol **15** in 81% yield and this has previously been converted through oxidative dealkylation with silver(II) oxide into the enantiopure 2-benzopyran-5,8-quinone **16** in a yield of 91%.[8] The diol **15** and the quinone **16** derived by this method were identical to those obtained previously.[8]

The alternative ultrasound-promoted reaction[3] of the bromomagnesium phenolate **8** with the same lactaldehyde **9** afforded the benzyl-epimeric adduct **17** (Scheme 3) in a diastereoisomeric ratio of 93:7 accompanied by the previous adduct **10** and considerable quantities of starting material **6**. Adduct **17** was converted, without purification as above, into the C-2 epimeric mixture of acetoxyphenyldioxolanes **19** via the phenols **18**. Careful chromatographic separation of the mixture of enantiopure dioxolanes **19** from the acetate **7** and the small quantities of the minor diastereoisomeric dioxolane **12** gave **19**[5] in an overall yield of 36% for the three steps, or 70% based on consumed phenol **5**. This represented an average yield per step of about 89%. Conversion of the C-2 epimeric mixture of acetoxydioxolanes **19** into the corresponding mixture of C-2 epimeric tosyloxydioxolanes **20**,[5] through hydrolysis and reprotection, was achieved in an overall yield of 84% for the two steps.

Treatment of the C-2-epimeric dioxolanes **20** with titanium(IV) chloride led to their clean conversion into the mixture of C-1 epimeric 2-benzopyrans **21**[5] and **23**[5] although, once again, starting dioxolanes **20** and *threo*-diol were also recovered. The *threo*-diol was recycled to the mixture of dioxolanes **20**. Chromatographic separation readily afforded the individual 2-benzopyrans **21** and **23** in yields of 44% and 14%, respectively, or 66% and 21%, respectively, based on consumed dioxolanes **20**. Hydrolysis of each of these gave the corresponding 4,5-diols **22** and **24**, each in a yield of 84%. The diol **22** was subjected to oxidative dealkylation with silver(II) oxide to yield the enantiopure quinone **25** and similarly the diol **24** gave the enantiopure quinone **26** in unoptimized yields of 72% and 67%, respectively.

In conclusion, a concise, convergent synthesis of the enantiopure 2-benzopyranquinones **16**, **25** and **26** is achieved from the inexpensive, commercially available



Scheme 3. Reagents and conditions: (vii) **6**, THF, $Me_2CHMgCl$, rt, 30 min; THF replaced by CH_2Cl_2 added to **9**, 0 °C, 30 min; ultrasound, 20–40 °C, 4.5 h; (viii) $CH_3CH(OEt)_2$, CSA, rt, 30 min; (ix) Ac_2O, py, 18 h, 36% overall, (70%*); (x) KOH, MeOH, rt, 3 h; *p*-TsCl, K_2CO_3, acetone, rt, 5 h, 84%; (xi) $TiCl_4$, CH_2Cl_2, −78 °C, 1.5 h, 44% (66%*) for **21**, 14% (21%*) for **23**; (xii) KOH, H_2O, MeOH, 70 °C, 3 h, 84%; (xiii) AgO, 72% for **25**, 67% for **26** (*yields based on consumed starting material).

4-methoxyphenol **6** in eight steps, and in an overall yield of 31% for quinone **16**. These quinones are three of the four possible diastereoisomers based on 3*S* stereochemistry. The previously published route[8] involving the assembly of quinone **16** was achieved in an overall yield of 11% in twelve steps from the more expensive starting material 2,5-dihydroxyacetophenone, although this latter method has the advantage of providing all four diastereoisomers of 3*S* stereochemistry.[8,9] In either sequence the corresponding enantiomers are available from *R*-lactate. The quinones **16** and **26** possess the absolute configurations that are enantiomeric to those required for quinone A **1** and quinone A′ **2** and the latter natural derivatives would therefore be assembled from *R*-lactate. A third, hitherto unreported,[10] protoaphin affords the C-3 epimer of quinone A with the same absolute configuration as that of the 2-benzopyranquinone **25**. These sequences, therefore, provide, in principle, the correct absolute stereochemistries found in the quinonoid moieties of the three known protoaphins through choice of either *R*- or *S*-lactate for the C-3 asymmetric centre.

The recovery of starting material **6** and the lack of complete diastereoselectivity in the formation of the benzyl-epimeric adducts **10** and **17** are no doubt the consequences of inadequate electron availability on the metal phenolates **5** and **8** since reaction of the lactaldehydes **9** with the more electron-rich naphtholates derived from 4,5,7-trialkoxynaphthols consumes all starting material and proceeds with complete diastereoselectivity.[2] In the reaction sequences discussed here two additional steps, acetylation of the phenolic dioxolanes **11** and **18** and hydrolysis of the derived acetates **12** and **19**, were required to separate unreacted starting material since the tosyloxyphenyldioxolanes **13** and **20** were not readily chromatographically separated from the tosylate of the starting material **6**. It is envisaged that this will not be necessary in the conversion of the known[2] benzyl-epimeric adducts **3** and **4** into the quinones **1** and **2**, and this would further shorten the synthetic sequences. Furthermore, recovery of starting dioxolanes and corresponding diols during the isomerizations of the dioxolanes **13** and **20** with titanium(IV) chloride is also ascribed to relatively poor electron availability on the aromatic ring, further attenuated by the electron withdrawing tosyloxy group, for the required intramolecular electrophilic substitution reactions.[6]

Acknowledgements

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