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Towards the synthesis of chiral isochromanquinones. The use of Corey–Bakshi–Shibata reductions

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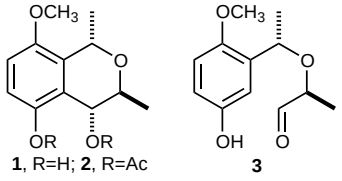
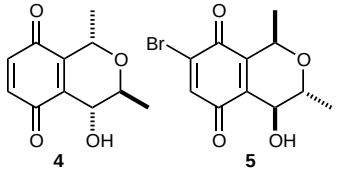
Abstract—(1*R*,3*R*,4*S*)-3,4-Dihydro-4-hydroxy-6-methoxy-1,3-dimethylisochroman-5,8-dione has been synthesized in 65% ee from (1*R*,3*R*,4*S*)-5-benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-dimethylisochroman by catalytic hydrogenolysis followed by Fremy's salt oxidation of the derived phenol. The latter isochroman was synthesized from a mercury(II) mediated oxidative cyclization of (*R*)-3-benzyloxy-4-methoxy-1-(1′-hydroxyethyl)-2-prop-1′-enylbenzene which in turn was obtained in 75% ee from the chiral reduction of 1-acetyl-3-benzyloxy-4-methoxy-2-prop-1′-enylbenzene with borane–methylsulfide complex in the presence of the Corey–Bakshi–Shibata catalyst.

Recently the synthesis of the chiral diol **1**, characterized as the more stable diacetate **2**, has been described.[1] This was achieved employing titanium tetraisopropoxide and ultrasonication on the phenolic aldehyde **3**. By this judicious choice of chelating metal ion used during the ring closure, selective synthesis of chiral 4-hydroxyisochromanquinone **4** was accomplished.[2] Related methodology has resulted in the synthesis of bromoquinone **5** and its subsequent Diels–Alder reaction with 1-methoxy-1,3-trimethylsilyloxy-1,3-butadiene has provided an entry into the synthesis of chiral naphthopyranquinones.[3]





In this paper we wish to report our preliminary findings on an alternative approach towards the synthesis of chiral isochromanquinones in which the introduction of the first stereogenic centre is generated by the use of the Corey–Bakshi–Shibata (CBS) reduction.

Allylation of the phenolic group of isovanillin followed by pyrolysis at 180°C afforded phenol **6**. This was alkylated employing the appropriate alkyl halide in hot (80°C) dimethylformamide containing potassium carbonate to produce **7**, **8** and **9** in yields of 77–80%. Treatment of these aldehydes with methylmagnesium iodide followed by oxidation with manganese(IV) oxide in boiling benzene gave the corresponding ketones **10**, **11** and **12** in yields of about 70% over two steps.

Initial attempts to reduce ketones **10**, **11** and **12** using borane dimethyl–sulfide complex and the Corey–Bakshi–Shibata catalysts[4] under a variety of conditions afforded the desired chiral alcohols in yields of only 7–8%. The major products isolated resulted from undesired addition to the olefin and were similar to those previously described by us.[5] This was overcome by conjugation of the olefinic bond of the allyl substituent in these ketones using $PdCl_2(MeCN)_2$.[6] Chiral reduction of these conjugated products as described above afforded the (*R*)-alcohols **13**, **14** and **15** in average yields of 58% and with ee values of 74–75% (Scheme 1).[7]

Keywords: chiral reduction; mercury(II) mediated oxidative cyclisation; isochromanquinones.

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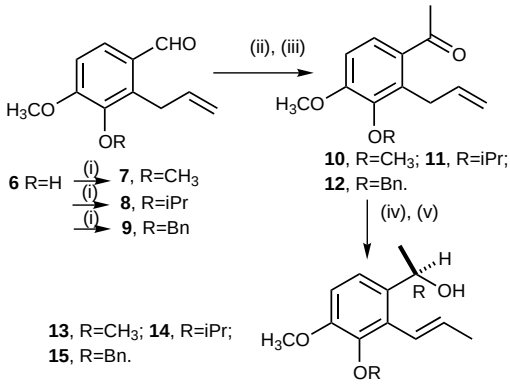
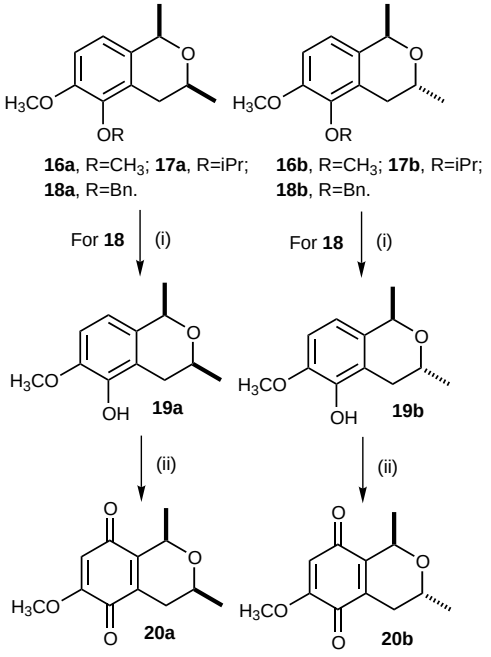


Scheme 1. *Reagents and conditions*; (i) RBr, K_2CO_3, DMF, 80°C, 24 h, 77–80%; (ii) CH_3MgI, Et_2O, 25°C, 40 min, 80–93%; (iii) MnO_2, benzene, reflux, 45 min, 57–60%; (iv) $PdCl_2(CH_3CN)_2$, CH_2Cl_2, 35°C, 72 h, 81–94%; (v) $BH_3{\cdot}(CH_3)_2S$, THF, CBS catalyst, 25°C, 30 min, 55–61%, 74–75% ee.

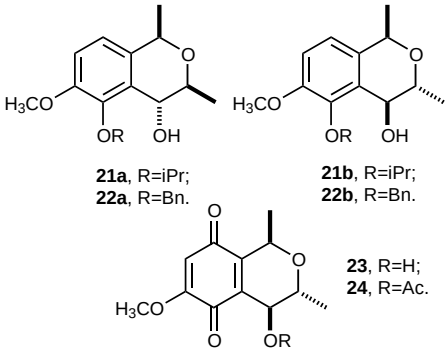
Cyclisation of the chiral alcohols **13**, **14** and **15** was effected using a mercury(II) mediated protocol.[8] In this way isochromans **16**, **17** and **18** were obtained as 1:1 separable mixtures of (1*R*,3*S*) and (1*R*,3*R*) diastereoisomers in average yields of 60%. Catalytic hydrogenolysis of the diastereoisomeric mixture of **18** over Pd/C in ethyl acetate containing a drop of concentrated HCl afforded the corresponding phenolic mixtures **19** in 97% yield.

Oxidation of this mixture with Fremy's salt[9] afforded the two chiral quinones **20a** (26%) and **20b** (28%) with ee values of 70% (Scheme 2).



Scheme 2. *Reagents and conditions*; (i) H_2, Pd/C c. HCl (one drop) EtOAc, 25°C, 15 h, 97% **19a** and **19b**; (ii) $K(SO_3)_2NO$, methanol/phosphate buffer, 25°C, 15 h, 26% **20a**, 28% **20b**.

On the other hand, treatment of the isopropoxy and benzyloxy alcohols **14** and **15** with mercury(II) acetate in the presence of oxygen[10] afforded the two diastereoisomeric pairs of the 4-hydroxy analogues **21** and **22** in yields of 40 and 63%, respectively.



Catalytic hydrogenolysis of the mixture **22a** and **22b** using the same conditions as described for **18** afforded the corresponding phenols which were oxidized with Fremy's salt to yield a stereoisomeric mixture from which one optically enriched enantiomer, (1*R*,3*R*,4*S*) **23**, was isolated in 26% yield. The quinone **23** was also converted into its acetate **24**. The ee value of **24** was determined as 65% on the addition of 10 mol% of the asymmetric lanthanide shift reagent $Eu(hfc)_3$ and observing separation of signals in the ^1H NMR spectrum. In particular, the acetate signal at δ 2.08 was deshielded and split into two signals at δ 2.86 and 2.79.

In summary, an alternative protocol is being developed for the synthesis of chiral isochromanquinones making use of the CBS reduction of an aromatic ketone functional group. There are not many examples of CBS reductions on systems containing *ortho*-substituents[11] and this study represents the first example of *ortho*-vinyl acetophenones undergoing partially enantioselective CBS reductions. Methods to improve both yields and ee's are currently under investigation.

Acknowledgements

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7. The CBS catalyst (0.1 ml, 0.05 mmol) in 0.5 M toluene was introduced under nitrogen into an oven dried three necked flask. The borane:dimethyl sulphide complex in THF (0.33 ml, 0.33 mmol) was added dropwise to this reagent, and the mixture stirred at 25°C for 5 min. The ketone (3.31 mmol) in THF (2 ml) was then introduced by syringe through one neck while additional borane:dimethyl sulphide complex in THF (1.99 ml, 1.99 mmol) was added simultaneously by syringe through the other neck over a period of 10 min. After stirring for an additional 30 min, methanol (1 ml) was added and stirring was continued for a further 10 min. The reaction mixture was extracted with dichloromethane and the residue purified by gravity silica gel column chromatography using ethyl acetate: hexane (1:4) as eluent to afford the desired products.
In this way alcohol **15** was obtained as a pale yellow oil, (61%) with the following spectroscopic data. $[\alpha]_D = +21.9°$, ($c = 0.755$, CH_2Cl_2, 25°C), ee 74% (from europium shift reagent); ν_{max} (film)/cm^{-1} 3396 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$) 1.46 (3 H, d, *J* 6.2, CH_3CH[OH], 1.89 (3H, dd, *J* 6.6 and 1.8, CH=CHCH_3), 3.87 (3H, s, OCH_3), 4.88 (2H, s, OCH_2Ph), 5.11 (1H, q, *J* 6.2, CH_3C*H*[OH]), 5.97 (1H, dq, *J* 16.0 and 6.6, CH=C*H*CH_3), 6.39 (1H, dq, *J* 16.0 and 1.8, C*H*=CHCH_3), 6.87 (1H, d, *J* 8.4, H-5), 7.32 (1H, d, *J* 8.4, H-6), and 7.38 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 19.2 (*C*H_3CH[OH]), 24.4 (C-3′), 56.0 (OCH_3), 66.5 (*C*H[OH]), 74.6 (*C*H_2Ph), 111.1 (C-2′), 120.8 (C-6), 123.7 (C-5), 128.3 (3×ArC), 128.4 (2×ArC), 131.1 (C-2), 132.4 (C-1′), 136.7 (C-1), 138.0 (ArC), 145.5 (C-3) and 152.1 (C-4).
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(ii) *o*-Methyl substituted ketones have also been reduced stereoselectively with the CBS reagent. Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835.