Stereoselective Syntheses of Benzo- and Naphtho-pyrans by Lewis Acid catalysed Isomerisation of Aryldioxolanes

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Phenyl- and naphthyl-dioxolanes are stereoselectively isomerised using titanium tetrachloride in methylene dichloride at −78 °C into benzo- and naphtho-pyrans.

Our interest in the synthesis of benzo-[1] and naphtho-pyrans[2,3] related to the aphid pigments has led us to investigate their formation by the stereoselective isomerisation of aryldioxolanes, an intramolecular version of the Mukaiyama reaction.[4,5]

Isomersation of the diastereoisomeric mixture of naphthyldioxolanes† **3**‡ and **4** (*ca.* 1 : 1 obtained by acetalation of the diol **1**, a single stereoisomer) with titanium tetrachloride (10 equiv.) in methylene dichloride at −78 °C afforded the two angular naphthopyrans **5** (13%) and **6** (39%), and the diol **1** (13%). Assignments **5** and **6** were distinguished from the alternative naphthofuran isomers **9** on the basis of a comparison of the ^{1}H NMR spectra of the former pair and those of their respective acetates **7** and **8**.[2,6] While the relative configuration at C(3) and C(4) for compounds **5** and **6** was confirmed by the coupling constant (*ca.* 1.5 Hz) observed between H(3) and H(4),[1–3] the configuration of the C(1) methyl group relative to the substituents at C(3) and C(4), and the angular ring system in each case were established by X-ray crystallography,[7] which also confirmed the spectral assignments.

Other examples supported the generality of the method. Thus, the bromodiol **2** afforded the dioxolane **10** as a single diastereoisomer. Its treatment with titanium tetrachloride as above afforded the debrominated pyran **11** (45%) as a single stereoisomer, together with the derivative **12** (18%) arising from migration of bromine, and the diol precursor **2** (14%). The stereochemical correspondence between the two pyrans **11** and **12** was confirmed by treatment of the latter with butyllithium followed by water, which gave the former (81%). The coupling constant (8.3 Hz) between H(3) and H(4) determined the *trans* relative stereochemistry at the adjacent pyran carbons, while the *trans* relationship between the two pyran methyls, and the nature of the ring system were confirmed by the conversion of **11** into the desoxy *trans*-dimethyl pyran **13** (using phosphorus tribromide followed by Raney nickel), identical with material similarly obtained from pyran **5**, and different from the *cis*-dimethyl isomer **14** derived from **6**.

Phenyldioxolanes reacted similarly and smaller amounts of the catalyst appeared to increase the yields. Thus, compound **15** with titanium tetrachloride (2 equiv.) under the above conditions afforded the two benzopyrans **16** (70%) and **17** (17%). The stereoisomeric mixture of dioxolanes **18** and **19** yielded the benzopyrans **20** (70%) and **21** (8%). From the mixed dioxolanes **22** and **23**, the benzopyran **24** (45%) was obtained, together with the chlorohydrin **25** (40%), the lower yield of the pyran with concomitant formation of product **25** being a result of the influence of the methoxy substituent *ortho* to the dioxolane ring, which promoted its alternative benzylic cleavage.

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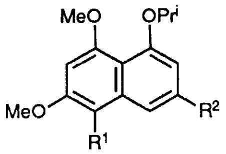
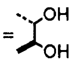
† Structures depicted as single enantiomers represent racemates.

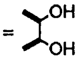
‡ New compounds gave satisfactory elemental analyses (except product **25**) and their spectroscopic data were in accord with the assigned structures.

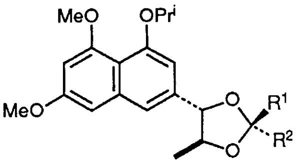


1 R^1 = H, R^2 =

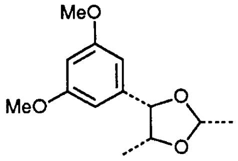


2 R^1 = Br, R^2 =





3 R^1 = H, R^2 = Me
4 R^1 = Me, R^2 = H



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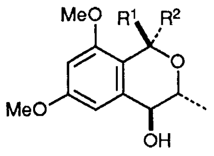
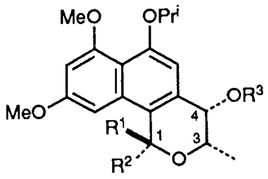
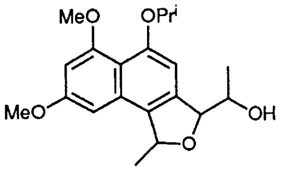


16 R^1 = Me, R^2 = H
17 R^1 = H, R^2 = Me



5 R^1 = Me, R^2 = R^3 = H
6 R^1 = R^3 = H, R^2 = Me
7 R^1 = Me, R^2 = H, R^3 = Ac
8 R^1 = H, R^2 = Me, R^3 = Ac



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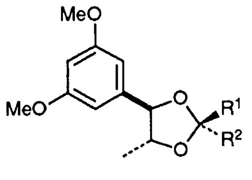
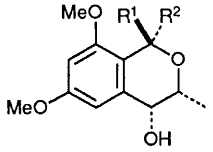
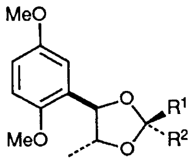


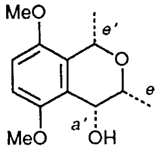
18 R^1 = Me, R^2 = H
19 R^1 = H, R^2 = Me



20 R^1 = H, R^2 = Me
21 R^1 = Me, R^2 = H



22 R^1 = Me, R^2 = H
23 R^1 = H, R^2 = Me



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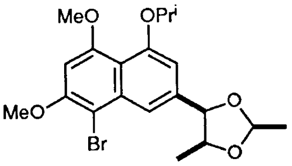

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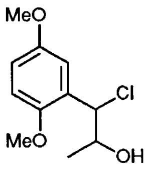
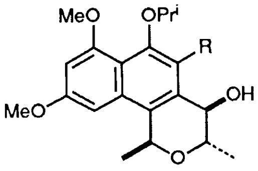
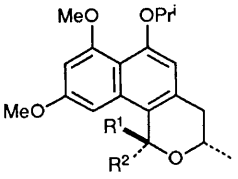


25



11 R = H
12 R = Br



13 R^1 = Me, R^2 = H
14 R^1 = H, R^2 = Me

The stereochemistry at C(1) for each of the benzopyrans was assigned using nuclear Overhauser effect spectroscopy. For compound **24**, further evidence for H(1) being pseudo-axial was obtained by its oxidation with silver(II) oxide[8] to the corresponding quinone, for which long range coupling (*J* 1.5 Hz) to the pseudoequatorial H(4) was observed.[9,10] The factors determining the stereochemistry of the C(1) methyl groups in both the benzo- and naphtho-pyrans may depend on intermediate species coordinated to titanium, and are not yet fully understood.

These results establish that, under carefully controlled conditions, naphthyl- and phenyl-dioxolanes can be stereoselectively isomerised by titanium tetrachloride to the corresponding pyrans. Other Lewis acids, such as boron trifluoride–diethyl ether, tin(IV) chloride, triisopropoxytitanium chloride and diisopropoxytitanium dichloride, are not effective. Further aspects of this process, together with details of the syntheses of the dioxolanes employed, will be reported elsewhere.

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