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Asymmetric synthesis of (3*S*) 3-benzoyloxymethylisobenzofuranone and its 3*R* enantiomer as analogues of α,β-butenolides

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Abstract—Both enantiomers of 3-benzoyloxymethylisobenzofuranone have been obtained in good yield in six steps from phthalaldehyde using a D-xylose derivative as a chiral protecting group. The two chiral heterocycles are γ-hydroxymethyl-α,β-butenolide analogues having a benzene ring in positions 2 and 3. The key step was the dihydroxylation using both OsO_4 and AD-mix developed by Sharpless. The asymmetric dihydroxylation using AD-mix required a double diastereoselectivity and gave excellent diastereoisomeric excess.

A number of nucleoside analogues have been found to possess antiviral activity against HIV.[1] The compounds approved by the US FDA for the treatment of HIV infection as reverse transcriptase inhibitors are AZT,[2] ddC,[3] ddI,[4] 3TC,[5] d4T [6] and ABC[7] (Fig. 1). The 2′,3′-didehydro-2′,3′-dideoxynucleosides possessing a 2′,3′ double bond on the glycone moiety have good in vitro activity[6] but a disadvantage of these nucleosides is the cleavage of the glycosidic bond by a specific phosphorylase. In our laboratory, we have developed the synthesis of d4T analogues having a benzo[*c*]furan glycone moiety (**BcF**).[8–11]

Unfortunately all of the benzo[*c*]furan derivatives synthesized in our work showed no activity against HIV reverse transcriptase except for the uracil derivative having a benzoyl group in 5′ position. In this case a modest activity was exhibited. One reason for the inactivity of the benzo[*c*]furan nucleosides in general might be due, simply, to their not being good substrates for HIV reverse transcriptase. However the activity found in the one exception might have arisen from the lactone **10***S* resulting by a glycosidic bond cleavage and not from the parent nucleoside.

This hypothesis has prompted us to investigate the synthesis of compounds related to α,β-butenolide. The chiral derivatives such as (*S*)-benzoyloxymethyl-α,β-butenolide have served as key intermediates for the elaboration into various natural products and ana-

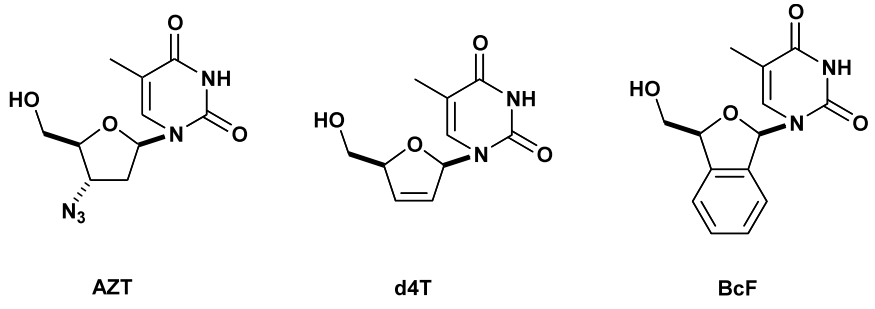

Figure 1.

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logues.[12–14] α,β-Butenolide derivatives are widely present in secondary metabolites which show interesting physiological activities as exemplified by the aglycon of ranunculin, namely, (*S*)-hydroxymethyl-α,β-butenolide[15,16] (Fig. 2).

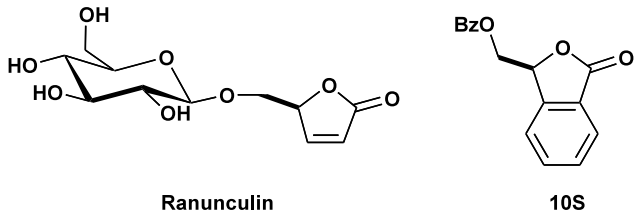
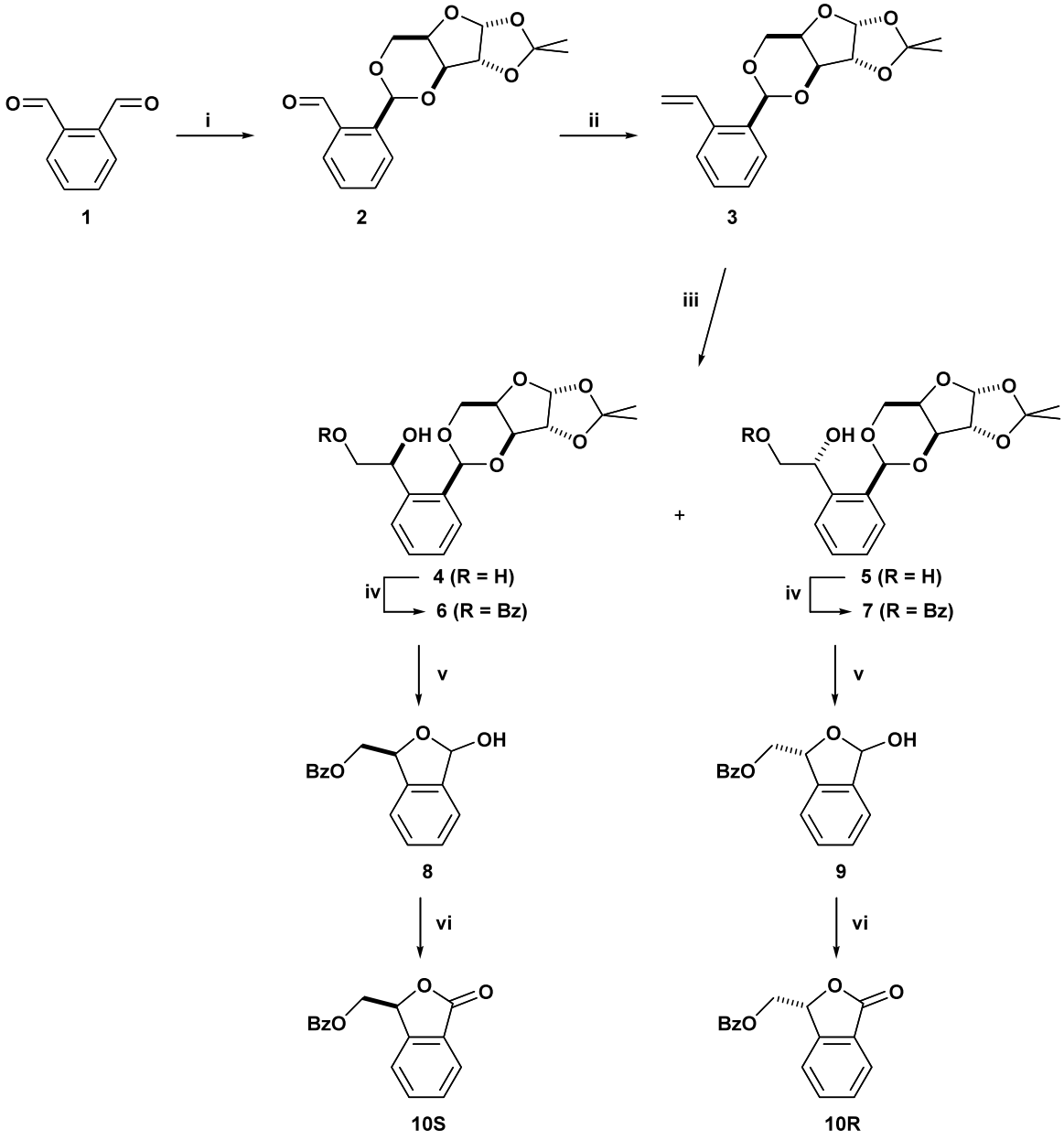
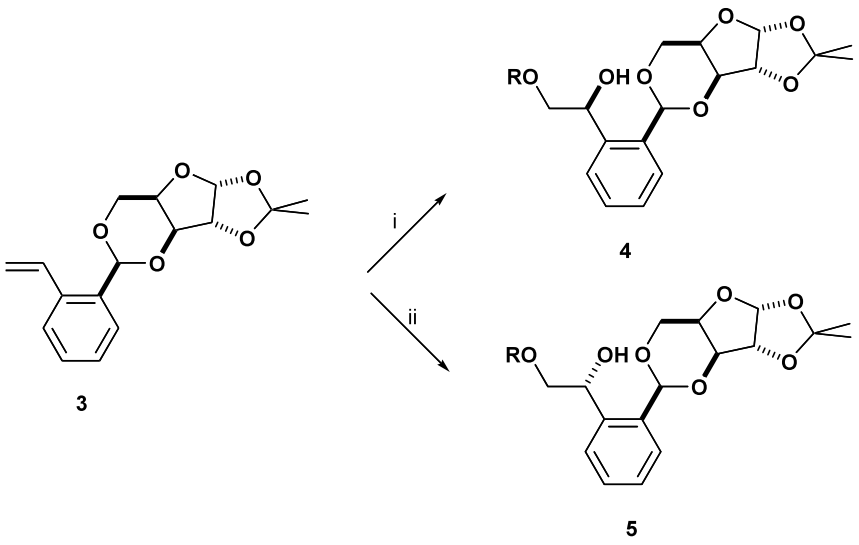


Figure 2.

This report describes the synthesis of the 3-benzoyloxymethylisobenzofuranones **10***S* and **10***R* which are potential metabolites of the corresponding 5′-benzoylated nucleoside **BcF** and are benzoylated derivatives of hydroxymethyl-α,β-butenolide, to make available a library of novel compounds for biological evaluation. With the objective of generating an asymmetric carbon atom at one of the formyl groups of phthalaldehyde (**1**), the compound was firstly protected using a chiral group such as 1,2-*O*-isopropylidene-α-D-xylofuranose. The acetalation afforded only one diastereomer **2** (50% yield) which had the *S*-configuration, as shown by the NOE interaction between the three axial protons of the 1,3-dioxane ring.[11]



Scheme 1. *Reagents and conditions*: (i) PTSA, toluene; (ii) *tert*-BuOK, $CH_3(C_6H_5)_3P$, toluene; (iii) OsO_4, acetone, water; (iv) BzCl, $(C_2H_5)_3N$, toluene; (v) PTSA, acetone, H_2O; (vi) $NaIO_4$, $RuCl_3$, acetonitrile, ethyl acetate, H_2O.



Scheme 2. *Reagents and conditions*: (i) AD-mix α, *tert*-BuOH, H_2O; (ii) AD-mix β, *tert*-BuOH, H_2O.

Homologation of the remaining formyl group was effected by a Wittig reaction to afford the styrene derivative **3** (Scheme 1). Dihydroxylation using OsO_4 gave a mixture of two diastereomeric diols **4** and **5** in the ratio 1:1, which were separated by column chromatography and obtained in similar yields. The diols **4** and **5** were obtained in pure form after a classical purification by silica gel chromatography. It is noteworthy that the use of monoacetonexylose as chiral protecting group did not lead to any diaselectivity in the oxidation step. This lack of selectivity has already been observed in the Corey epoxidation starting from **2**.[11] This is perhaps due to the chiral protecting group being too far from the oxidation centre. Removal of the acetal from compounds **4** and **5** in an acidic medium gave the desired benzo[*c*]furan and the isochromane derivatives. A selective protection of the primary hydroxyl group was required to selectively obtain only the isobenzofurane derivative. Reaction of the diol **4** with benzoyl chloride afforded the intermediate **6** with a free secondary hydroxyl group. The monoacetonexylose was removed by treatment with acetic acid in water, which was followed by spontaneous cyclization between the hydroxyl and formyl groups to give the heterocycles **8a** (1*S*,3*S*) and **8b** (1*R*,3*S*) in the ratio 1:1. The two epimers **8** were each oxidized using different procedures to give poor yields of **10***S* and **10***R*. The best result was obtained using $RuCl_3$–$NaIO_4$[17] to give solely **10***S* in 50% yield. Compound **5** gave the enantiomer **10***R* in a similar yield.[18]

Sharpless asymmetric dihydroxylation (Scheme 2) using AD-mix α and AD-mix β afforded the diols **4** and **5** with a diastereomeric excess of 99% and 98% respectively (HPLC determination). The absolute configuration of the chiral centre in the diol **4** was determined by X-ray crystallography (*S* configuration)[19] and was in accordance with the mnemonic device developed by Sharpless[20,21] and our own asymmetric dihydroxylation study.[22]

The benzo[*c*]furanones **10***S* and **10***R* having one asymmetric carbon atom were obtained in good yields starting from the achiral phthalaldehyde. The key steps of this route were the introduction of a chiral protected group derived from D-xylose and the use of the asymmetric dihydroxylation developed by Sharpless. The antiviral evaluation of each enantiomerically pure lactones **10***S* and **10***R* is underway.

Acknowledgements

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18. (3*S*)-3-Benzoyloxymethylisobenzofuranone (**10***S*): white solid; mp 109°C; $[\alpha]_D^{28}=+35$ (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.65 (1H, dd, $J=5.9$, 12.1 Hz, H-8a), 4.83 (1H, dd, $J=3.6$, 12.1 Hz, H-8b), 5.82 (1H, m, H-3), 7.28–8.04 (10H, H-arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.1 (C-8), 79.0 (C-3), 122.7, 126.9, 128.9, 130.9, 130.3, 133.8, 134.7 (C-arom), 166.4 (CO benzoyl), 170.3 (CO lactone).
(3*R*)-3-Benzoyloxymethylisobenzofuranone (**10***R*): $[\alpha]_D^{28}=-34$ (*c* 0.4, $CHCl_3$). The physical data are identical with those of **10***S*.
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