Chirality Transfer from the Furan Ring Transfer Reaction

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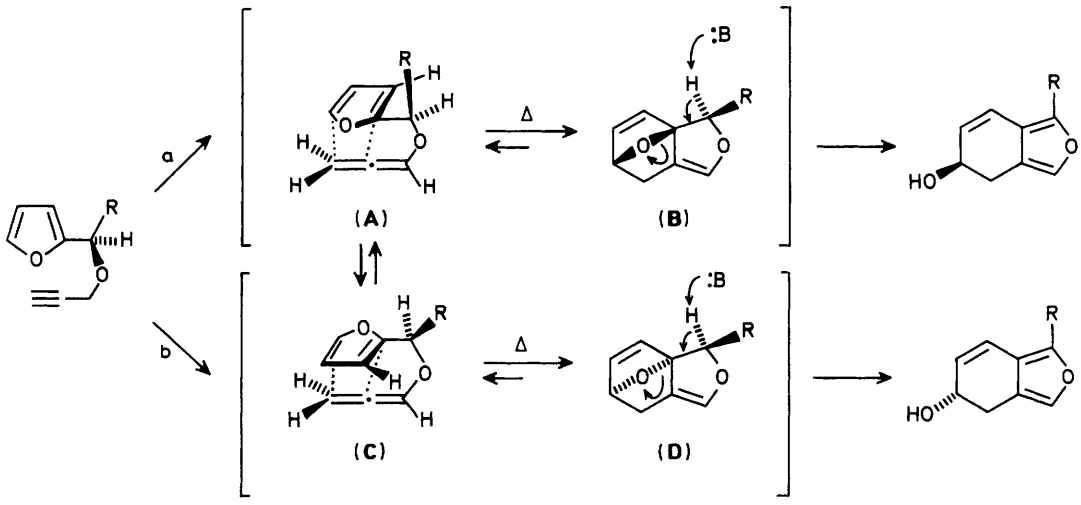
The furan ring transfer (FRT) reactions of optically active propynyl ethers [(**1**) and (**2**)] are described, facile chirality transfer from the cycloadduct to the allylic carbon of the product being observed; the stereochemistry of the product was determined by *X*-ray analysis.

Previously we have developed the furan ring transfer (FRT) reaction: a novel ring transfer reaction of furans to fused furans *via* the intramolecular Diels–Alder reaction of allenyl furfuryl ethers followed by fragmentation of the resulting cycloadduct.[1—3] This reaction has provided a facile method for the construction of fused furans and synthetically useful isobenzofurans.

The FRT reaction of propynyl ethers bearing a substituent (R ≠ H) in the furfurylic position may proceed *via* two diastereoisomeric pathways as outlined in Scheme 1. If one



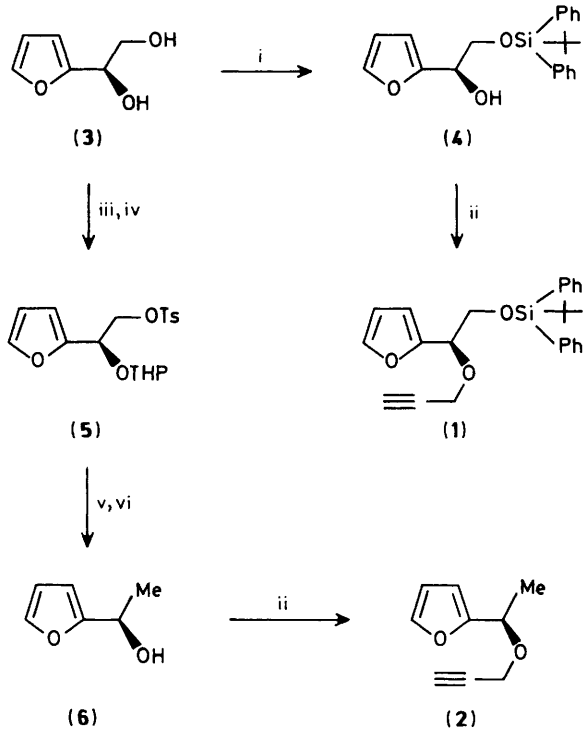
Scheme 1

pathway is favoured over the other, transfer of chirality from the substrate to the product should occur. The results of this work may provide important information about the FRT reaction pathway. Thus, we have examined the FRT reaction using optically active propynyl ethers as substrates.

The requisite propynyl ethers (**1**) and (**2**) were prepared from readily available 2-(D-glycero-1,2-dihydroxyethyl) furan (**3**)[4,5] (Scheme 2). The primary alcohol group in (**3**) was selectively protected according to the published procedure[6] to give the t-butyldimethylsilyl ether (**4**). (*R*)-2-Furyl ethanol (**6**)† was synthesised by dehydroxylation of (**3**). The propynyl ethers (**1**) and (**2**) were obtained in high yields by treatment of (**4**) and (**6**) with n-butyl-lithium, followed by 3-bromopropyne. The structures of these compounds were confirmed by spectroscopic means.‡

When a mixture of t-butyldimethylsilyl ether (**1**) and 10 equiv. of potassium t-butoxide in Bu^{t}OH was refluxed for 20 min, (**7**) was obtained in 55% yield *via* the FRT reaction (equation 1). The structure of (**7**), which is apparent from the spectral data, resembles that of 4,5-dihydroisobenzofuran-5-ol prepared previously.[1] Similarly, compound (**2**) underwent a FRT reaction to afford (**8**).§ Products (**7**) and (**8**) showed the following optical rotations {(**7**): $[\alpha]_D^{27}$ −31.36° (*c* 1.1, MeOH); (**8**): $[\alpha]_D^{24}$ −68.25° (*c* 1.23, MeOH)}. Substantial transfer of chirality is observed from the starting material to the allylic carbon in the bicyclic alcohols.

The enantiomeric ratios of (**7**) and (**8**) were determined by Mosher's method¶ after transformation into the corresponding tetrahydo derivatives (**9**) and (**11**) (Scheme 3), because of the instability of the dihydroisobenzofuran moiety. Compounds (**9**) and (**11**) were converted into (*S*)-β,β,β-trifluoro-α-phenylpropanoates [α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters] according to Mosher's procedure[7] and the enantiomeric purity was determined by ^{1}H n.m.r. spectroscopy.¶



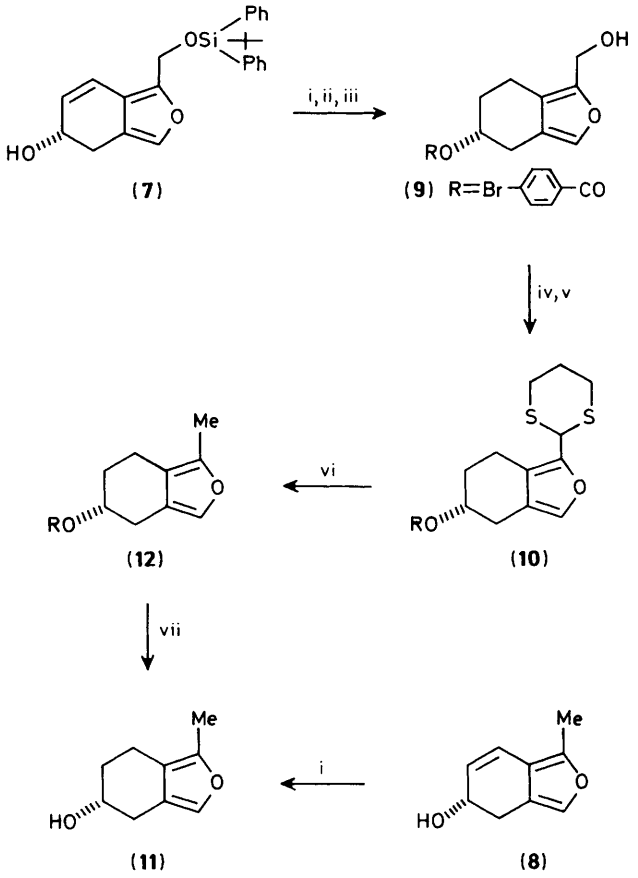
Scheme 2. *Reaction conditions:* i, Bu^t(Ph)$_2$SiCl, imidazole, dimethylformamide (DMF), 0 °C, 12 h, 84%; ii, Bu^{n}Li, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), 0 °C 1 h, then BrCH$_2$CCH, room temp., 12 h, from (**4**): 70%, from (**6**): 55%; iii, TsCl, (Ts = *p*-MeC$_6$H$_4$SO$_2$), pyridine, 0 °C, 15 h, 70%; iv, dihydropyran, pyridinium toluene-*p*-sulphonate, CH$_2$Cl$_2$, room temp., 2 days, 93%; v, LiEt$_3$BH, THF, room temp., 2 h, 75%; vi, 5% aq. HCl, MeOH, room temp., 40 min., 84%.

† The enantiomeric excess (88% ee) was determined by Mosher's method.¶

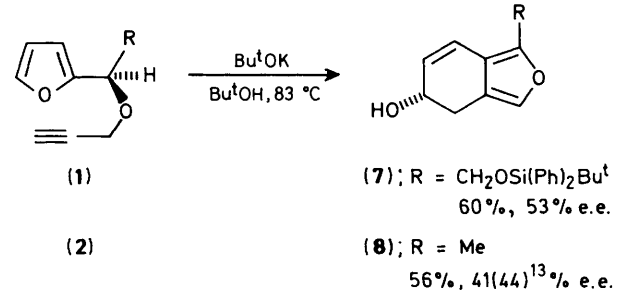
‡ All synthesised compounds have been fully characterised spectroscopically and have correct elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis.

§ The intermediates (**A**)—(**D**) could not be isolated even when subjected to controlled reaction conditions.

¶ In the 270 MHz ^{1}H n.m.r. spectra, the methylene protons in the furfurylic position of the MTPA ester prepared from (**9**) and the furyl proton of the MTPA ester prepared from (**11**) appear as base-line separated peaks. Thus, the enantiomeric purity was calculated from the relative peak areas of these signals.



Scheme 3. *Reaction conditions:* i, H_2, Pd/C (5%), MeOH, room temp., 1 h, from (**7**): 86% from (**8**): 44%; ii, *p*-bromobenzoyl chloride, pyridine, CCl_4, room temp., 10 h, 65%; iii, Bu^n_4NF, THF, room temp., 1 h, 100%; iv, MnO_2, CCl_4, room temp., 15 h, 69%; v, propanedithiol, $Mg(OTf)_2$, CH_2Cl_2, room temp., 12 h, 88%; vi, Raney Ni (W2), dioxane, room temp., 15 min, 98%; vii, 10% aq. KOH, MeOH, room temp., 40 min, 100%.



To determine the absolute configuration by *X*-ray analysis, the furfuryl alcohol (**9**) was converted into 1,3-dithiane (**10**) (Scheme 3). Treatment of (**9**) with 10 equiv. of MnO_2 gave the aldehyde in 69% yield. Dithioacetalisation of the aldehyde using propanedithiol and magnesium trifluoroacetate[8] afforded the desired crystalline 1,3-dithiane (**10**) in 88% yield. Three cycle recrystallisations from dichloromethane and ether provided the enantiomerically pure crystalline *p*-bromobenzoate (**10**) as colourless plates {m.p. 160—161 °C, $[\alpha]_D^{26}$ + 72.55° (*c* 0.86, EtOAc)}. *X*-Ray structure determination of

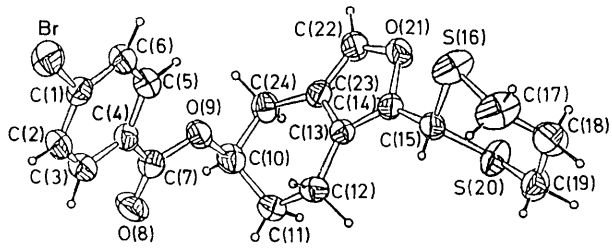


Figure 1. ORTEP drawing of *X*-ray determined structure of (**10**).

(**10**)§§ permits assignment of the *S* configuration to the newly created chiral element of (**7**) (Figure 1). The absolute configuration of (**8**) was determined by measurement of the optical rotation after transformation to (**11**) (Scheme 3).††

These experiments suggest that the FRT reaction of substrates bearing a substituent at the furfurylic position proceeds preferentially *via* both diastereoisomeric transition states (Scheme 1). The major enantiomer is formed through path b, although transition state (**A**) may be sterically favoured over (**C**) in the intramolecular Diels–Alder reaction step.[9,10] Thus, we consider that the observed stereochemical outcome may depend on the *syn*-elimination step of the resulting oxabicyclo[2.2.1]hexene ring system.[11] The origin of this selectivity is uncertain, however, the results should further enhance the utility of the FRT reaction in selective synthesis of fused furan ring systems.

We thank Dr. Nawata (Chugai Pharmaceutical Company) for performing the *X*-ray analysis.

Received, 5th July 1988; Com. 8/02670J

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§§ *Crystal data*; (**10**) $C_{19}H_{19}BrO_3S_2$, M = 439.40 orthorhombic, space group $P2_12_12_1$, a = 16.313, b = 17.373, c = 6.562 Å, Z = 4, D_c = 1.569 g cm^{-3}, λ(Cu-K_α) = 1.54184 Å, μ = 53.318 cm^{-1}. Solved by direct method R = 0.036 for 2032 reflections, Bijvoet method, [$|F_0| > 3\sigma|F_0|$]. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

†† (**11**) prepared from (**10**): $[\alpha]_D^{26}$ +26.72° (*c* 0.83, MeOH), (**11**) prepared from (**8**): $[\alpha]_D^{26}$ +15.51° (*c* 1.08, MeOH).