Homochiral 2,5-Disubstituted 3-Fluorotetrahydrofurans carrying differently Functionalized Ring Appendages

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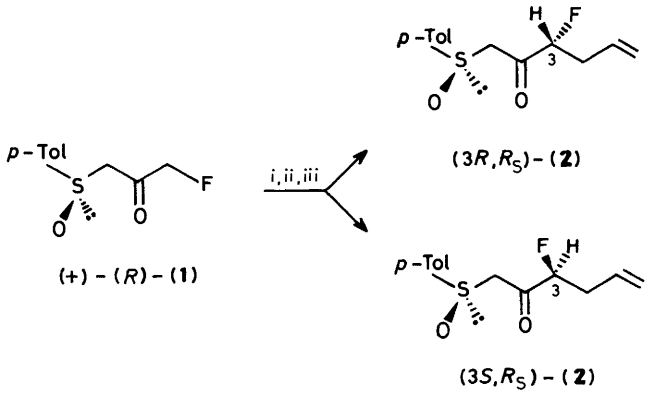
With (*R*)-1-sulphinyl-3-fluoropropan-2-one (**1**) as starting material a multistep approach is described for the asymmetric synthesis of various 3-fluorotetrahydrofurans of type (**7**)—(**12**) which carry differently functionalized 2- and 5-methyl groups.

It has been demonstrated that both (*S*)- and (*R*)-3-fluoro-1-(*p*-tolylsulphinyl)propan-2-one (**1**) are useful synthons for the preparation of monofluorinated and variously functionalized chiral and non-racemic molecules.[1–3] Since the presence of fluorine in biologically active products results in a variety of quite pronounced effects,[4] we thought it would be of interest to transform (**1**) into homochiral regio- and stereo-defined fluorinated tetrahydrofurans which are valuable synthetic intermediates for many bioactive compounds.

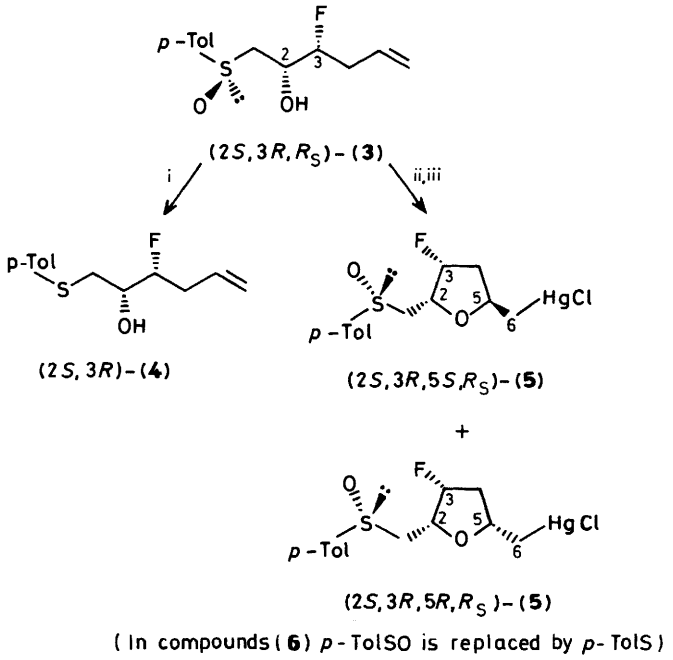
(+)-(*R*)-3-Fluoro-1-(*p*-tolylsulphinyl)propan-2-one (**1**)[5] was transformed into the two (R_S)-3-fluoro-1-(*p*-tolylsulphinyl)hex-5-en-2-ones (**2**) (68% yield; 3*S*/3*R* ratio, 6:4) (Scheme 1)



Scheme 1. i, Lithium di-isopropylamide (2.2 mmol)/THF/−78 °C; ii, allyl bromide (1.5 mmol)/THF/−78 °C; iii, chromatographic separation (pentane–diethyl ether, 4:6)

which were separately reduced to the corresponding secondary alcohols (**3**) both having the *S* absolute configuration at the oxygenated chiral centre[3] (95% yields, d.e. >95%). Single sulphinyl alcohols (**3**) gave the thio alcohols (**4**) in nearly quantitative yields upon deoxygenation of the sulphoxide group (Scheme 2). The absolute stereochemistry at the alcohol centres of (**4**) and therefore of (**3**) was established by comparing the ^{1}H chemical shifts of the esters obtained with (+)-and (−)-2-phenylpropionic acid (PP-esters)[6] while the *syn* (2*S*,3*R*) and *anti* (2*S*,3*S*) relative configurations were assigned from the ^{1}H and ^{19}F spectroscopic data as already described for many similar cases.*

Cyclization of the sulphinyl alcohols (**3**) to tetrahydrofuran systems was induced with mercury(II) salts since they are



Scheme 2. i, Sodium iodide/trifluoroacetic anhydride/acetone/−40 °C; ii, mercury(II) trifluoroacetate/THF/0 °C; iii, potassium chloride/water

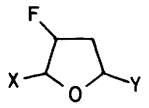
compatible with the chiral sulphoxide and require very mild reaction conditions. In this way, treatment of (2*S*,3*R*,R_S)-(**3**) with mercury trifluoroacetate in tetrahydrofuran (THF) at room temperature gave a clean *exo-trig* cyclization and upon exchanging the trifluoroacetic ion with chloride (2*S*,3*R*,5*S*,R_S)- and (2*S*,3*R*,5*R*,R_S)-5-chloromercuriomethyl-3-fluoro-2-(*p*-tolylsulphinylmethyl)tetrahydrofurans (**5**) were obtained (20:1).

In the same way (2*S*,3*S*,R_S)-(**3**) gave (2*S*,3*S*,5*R*,R_S)- and (2*S*,3*S*,5*S*,R_S)-(**5**) (5:1) in 88% overall yield. The thio alcohol (2*S*,3*S*)-(**4**) reacting in a similar way, gave the corresponding (2*S*,3*S*,5*R*)-and (2*S*,3*S*,5*S*)-5-chloromercuriomethyl-3-fluoro-2-(*p*-tolylthiomethyl)tetrahydrofurans (**6**) (4.5:1) in 91% overall yield. In all cases, single diastereoisomers of the 2,5-disubstituted 3-fluorotetrahydrofurans (**5**) and (**6**) could be easily obtained pure by flash chromatography.

The fluorotetrahydrofurans (**5**) and (**6**) so prepared were then subjected to a number of transformations to investigate their synthetic potential. Thus, (2*S*,3*R*,5*S*,R_S)-(**5**) underwent reductive demercuriation to give (2*S*,3*R*,5*R*,R_S)-3-fluoro-2-(*p*-tolylsulphinylmethyl)-5-methyltetrahydrofuran (**7**) (94%). Bromination of the same diastereoisomer (2*S*,3*R*,5*S*,R_S)-(**5**) gave the corresponding (2*S*,3*R*,5*S*,R_S)-5-bromomethyl-3-fluoro-2-(*p*-tolylsulphinylmethyl)tetrahydrofuran (**8**) along with the corresponding 5*R* epimer (Table).

* In compounds (2*S*,3*R*,5*S*,R_S)- and (2*S*,3*R*,5*R*,R_S)-(**5**) the values of the $^3J_{3,4}$ (0.8 and 1.1 Hz) and in compounds (2*S*,3*S*,5*S*,R_S)- and (2*S*,3*S*,5*R*,R_S)-(**5**) the values of the $^3J_{3,4}$ (1.8 and 1.1 Hz) were diagnostic of a *trans*-relationship between these protons, thus confirming the assignment of the relative stereochemistry on acyclic compounds.

Table. Mercury-free 2,5-disubstituted 3-fluorotetrahydrofurans (**7**)—(**12**)



Compound	X	Y	Reactions conditions	Total yield [%, from (**5**)]	$[\alpha]_D^{20}$/° (*c* in $CHCl_3$)
(2*S*,3*R*,5*R*,R_S)-(**7**)	$CH_2S(O)C_6H_4Me$-*p*	Me	*a*	94	+158 (0.8)
(2*S*,3*R*,5*S*,R_S)-(**8**)	$CH_2S(O)C_6H_4Me$-*p*	CH_2Br	*b*	45	+69 (1.1)
(2*S*,3*R*,5*R*,R_S)-(**8**)	$CH_2S(O)C_6H_4Me$-*p*	CH_2Br	*b*	45	+211 (2.0)
(2*S*,3*S*,5*R*,R_S)-(**9**)	$CH_2S(O)C_6H_4Me$-*p*	CH_2OH	*c*	34	+194 (1.0)
(2*R*,3*R*,5*R*)-(**10**)	CH_2OH	Me	*a*, *d*, *e*, *f*	58	−30.3 (0.5)
(2*R*,3*R*,5*R*)-(**11**)	CO_2H	Me	*a*, *d*, *e*, *g*	77	−31.6 (0.8)
(2*R*,3*S*,5*R*)-(**12**)	$CH(OMe)_2$	CH_2OBn	*c*, *h*, *d*, *i*	71	−3.9 (0.9)

[a] Sodium borohydride/CH_2Cl_2/3M aqueous sodium hydroxide/0 °C. [b] Bromine/CH_2Cl_2/r.t. [c] Sodium borohydride/bubbling oxygen/dimethylformamide/r.t. [d] Trifluoroacetic anhydride/2,4,6-trimethylpyridine/MeCN/r.t. [e] Mercury(II) chloride/water. [f] Sodium borohydride/MeCN. [g] Sodium chlorite/2-methylbut-2-ene/potassium hydrogen phosphate/t-butyl alcohol. [h] Benzyl bromide/NaH/dimethylformamide/r.t. [i] Mercury(II) chloride/methanol.

Treatment of (2*S*,3*S*,5*R*,R_S)-(**5**) with sodium borohydride in dimethylformamide solution under a stream of oxygen gave the (2*S*,3*S*,5*R*,R_S)-3-fluoro-5-hydroxymethyl-2-(*p*-tolylsulphinylmethyl)tetrahydrofuran (**9**) (34%).

In addition, the chiral auxiliary sulphinyl group could be removed through a Pummerer rearrangement followed by a methanolysis of the phenylthio-trifluoroacetyl intermediate to give a protected formyl group. Alternatively, hydrolysis of the same intermediate gave an aldehyde which upon reductive (sodium borohydride) or oxidative (sodium chlorite) elaboration afforded hydroxymethyl or carboxy residues respectively.

High yields (see Table) of (2*R*,3*S*,5*R*)-5-benzyloxymethyl-3-fluorotetrahydrofuran-2-carbaldehyde dimethyl acetal (**12**) were obtained when the (2*S*,3*S*,5*R*,R_S)-5-benzyloxymethyl-3-fluoro-2-(*p*-tolylsulphinylmethyl)tetrahydrofuran [obtained through benzylation of (2*S*,3*S*,5*R*,R_S)-(**9**)] was treated with trifluoroacetic anhydride–2,4,6-trimethylpyridine (other reagents we had previously employed to prepare similar entities[2] proved less effective) and (2*S*,3*R*,5*R*,R_S)-(**7**) gave (2*R*,3*R*,5*R*)-3-fluoro-2-hydroxymethyl-5-methyltetrahydrofuran (**10**) (58%) and (2*R*,3*R*,5*R*)-3-fluoro-5-methyltetrahydrofuran-2-carboxylic acid (**11**) (87%).

The structure and stereochemistry of compounds (**7**)—(**12**) followed from both analyses of their ^1H and ^{13}C n.m.r. spectra and comparison with the n.m.r. spectral data of the parent compounds (**5**) for which a very detailed study was performed. The absolute configuration at C-2 and C-3 was drawn from that of the precursor (**3**), while the assignment of the configuration at the newly formed chiral C-5 followed from n.O.e. experiments.

It should be noted that the cyclizations of bishomoallylic alcohols (**3**) by mercury trifluoroacetate is highly regioselective (only five-membered ring compounds were detected). The diastereoselection seems to be influenced mainly by the stereochemistry at the fluorinated carbon since the tetrahydrofurans (**5**) with a *trans* arrangement between the fluorine and the chloromercuriomethyl residues formed with high preference starting from both *syn* and *anti* α-fluoro alcohols (**3**).

Experimental

Synthesis of (2S,3R,5S,R_S)- *and* (2S,3R,5R,R_S)-5-*Chloromercuriomethyl*-3-*fluoro*-2-(p-*tolylsulphinylmethyl*)*tetrahydrofurans* (**5**).—A solution of mercury(II) trifluoroacetate (0.51 g, 1.2 mmol) in anhydrous THF (5 ml) was added to a solution of (2*S*,3*R*,R_S)-3-fluoro-1-(*p*-tolylsulphinyl)hex-5-en-2-ols (**2**) (0.26 g, 1.0 mmol) in the same solvent (5 ml) at room temperature and stirring was continued for *ca.* 10 min until the starting product was completely used up (t.l.c., hexane–ethyl acetate, 2:8). A solution of potassium chloride (0.12 g, 1.6 mmol) in water (1 ml) was then added after which the mixture was stirred for 30 min, diluted with water (10 ml), and extracted with dichloromethane (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Benzene (2 ml) was added to the residue and then evaporated. Flash chromatography (ethyl acetate–hexane, 9:1) gave in the order: (2*S*,3*R*,5*S*,R_S)-(**5**) (93.6% yield), m.p. 186 °C (from ethyl acetate–hexane, 9:1), $[\alpha]_D^{20}$ +70.60° (*c* 1.0, in $CHCl_3$) and (2*S*,3*R*,5*R*,R_S)-(**5**) (4.7% yield), m.p. 195 °C (from ethyl acetate), $[\alpha]_D^{20}$ +64.23° (*c* 1.0, in $CHCl_3$).

The same procedure applied to (2*S*,3*S*,R_S)-(**3**) gave a 5:1 mixture of (2*S*,3*S*,5*R*,R_S)-(**5**) (70% yield), m.p. 155 °C (from ethyl acetate), $[\alpha]_D^{20}$ +80.80° (*c* 1.0, in $CHCl_3$) and (2*S*,3*S*,5*S*,R_S)- (**5**) (14% yield), m.p. 136 °C (from ethyl acetate), $[\alpha]_D^{20}$ +98.70 (*c* 1.0, in $CHCl_3$). In the same way, the thio alcohol (2*S*,3*S*)-(**4**) gave the corresponding 5-chloromercuriomethyl-3-fluoro-2-(*p*-tolylthiomethyl)tetrahydrofurans (**6**) as a 4.5:1 mixture of (2*S*,3*S*,5*R*)-(**6**) (75.3% yield), m.p. 72 °C (from di-isopropyl ether), $[\alpha]_D^{20}$ −28.11° (*c* 1.1, in $CHCl_3$) and (2*S*,3*S*,5*S*)-(**6**) (16.7% yield) (oil), $[\alpha]_D^{20}$ + 5.98° (*c* 2.0, in $CHCl_3$).

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Received 30*th September* 1988; *Paper* 8/03902J