Stabilisation of the Thromboxane Ring System by Electron-withdrawing Substituents: Synthesis and Attempted Cyclisation of Substituted Tetrahydropyran-2,4-diols

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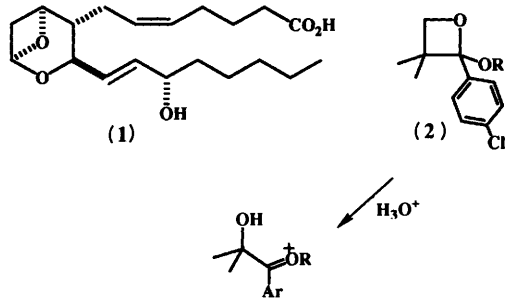
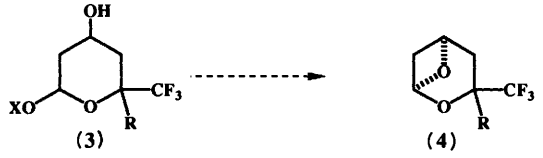
The hetero Diels–Alder reaction of trifluoromethyl ketones and 1-benzyloxy-3- trimethylsilyloxybutadiene is developed as a route to 4-hydroxytetrahydropyranyl acetal derivatives. Several 6,6-disubstituted tetrahydropyran-2,4-diols have been prepared, and their anomeric equilibria measured by ^{1}H NMR spectroscopy. Attempted cyclodehydration to 2,6-dioxabicyclo[3.1.1]heptanes (thromboxane A_2 analogues) failed under various conditions.

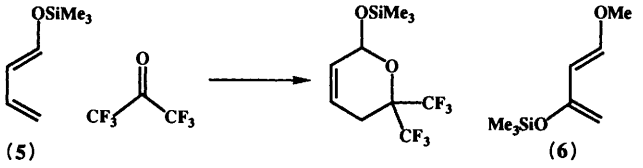
The study of the potent platelet aggregating factor and vasoconstrictor thromboxane A_2 (TxA_2; **1**) is complicated by its short lifetime—of the order of 30s under physiological conditions.[1] This is an intrinsic property of the oxetane acetal system,[2] and a severe restriction on the design of potential antagonists. As a result, several groups have made analogues with one or both of the acetal oxygen atoms replaced by carbon[3] or sulphur.[4] We are interested in stabilising the oxetane acetal ring system by appropriate substitution. Electron-withdrawing substituents like the OH groups of sugars have a large stabilising effect on tetrahydropyranyl acetals.[5] This is a result of inductive destabilisation of the developing oxocarbocation always involved in acetal cleavage. In a preliminary study we showed that the trifluoroethyl oxetane acetal (**2**; R = CH_2CF_3) is hydrolysed some 5000 times more slowly than the corresponding methoxy derivative (**2**; R = CH_3).[6]



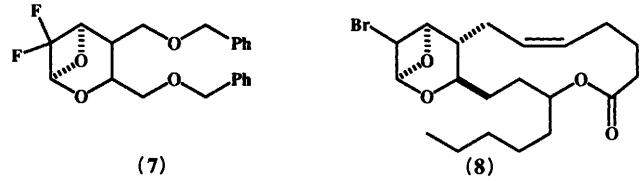
This paper describes the synthesis of a series of tetrahydropyranyl acetals (**3**) and hemiacetals (**3**; X = H), with one or two CF_3 groups in the corresponding 6 position, designed as precursors to stabilised oxetane acetals (**4**).



Our route to compounds (**3**) is based on the hetero Diels–Alder reactions of trifluoromethyl ketones with suitable alkoxy and silyloxy dienes. Ishihara and co-workers[7] have reported that hexafluoroacetone reacts with dienol silyl ethers such as (**5**), to yield the cycloadducts under very mild conditions. This observation is complemented by a great deal of work, especially by the Danishefsky group, on the cycloaddition reactions of electron-rich silyloxy dienes, such as (**6**), with aldehydes. These reactions also proceed under very mild conditions in the presence of Lewis acid catalysts.[8]



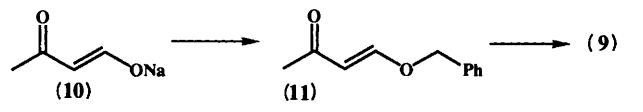
During the early stages of this work Fried and his coworkers[9] reported the synthesis of 7,7-difluoro-2,6-dioxa[3.1.1]-bicycloheptane (**7**), which is hydrolysed over 10^8 times more slowly than TxA_2. Still and his group also used the stabilising effect of a hetero-atom in their successful synthesis of TxA_2 *via* (**8**).[10]

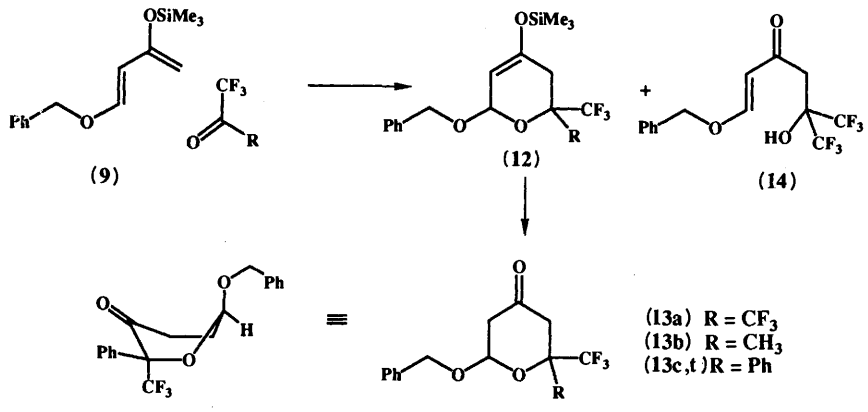


Results and Discussion

Synthesis of 2-Benzyloxytetrahydropyran-4-ones.—We chose to use the previously unreported benzyloxybutadiene (**9**), because the benzyl group is readily removed under mild conditions, and because the increased molecular weight should counteract the expected high volatility often associated with organofluorine compounds. The diene (**9**) was made by benzylation of the sodium enolate (**10**),[11] followed by reaction of the butenone (**11**) with trimethylsilyl chloride according to Danishefsky.[12]

Reaction of the diene (**9**) with hexafluoroacetone in tetra-





hydrofuran at −45 °C gave the desired cycloadduct (**12**; R = CF_3). Some 30% of the aldol addition product (**14**) was also formed, but treatment of the mixture of products with NaF in wet tetrahydrofuran converted both into the tetrahydropyran-4-one (**13a**) [overall yield 70% from (**11**)].

The ketone acetals (**13b, c** and **t**) were prepared similarly, from trifluoroacetone and trifluoroacetophenone, respectively: the cycloadditions using these less electrophilic dienophiles were carried out at room temperature. No aldol product [corresponding to (**14**)] was detected in the reaction with trifluoroacetophenone: after desilylation of the silyl enol ethers (**12**; R = Ph) a 5:1 mixture of the ketones (**13c**) and (**13t**), (with Ph and benzyloxy groups *cis* and *trans*, respectively) was obtained, in 61% yield from (**11**). These could be separated by fractional crystallisation, and the major isomer was shown by a single crystal X-ray structure analysis,[13] to have the phenyl and benzyloxy groups *cis*, as expected for *endo* addition. In the crystal (**13c**) adopts a conformation close to a classical boat, with the phenyl and benzyloxy groups both in their preferred (equatorial and axial) conformations. The trifluoroacetone adduct (**13b**) was obtained as an inseparable 2:1 mixture of diastereoisomers. We were unable to assign their stereochemistry, and these adducts were not studied further.

Reduction to 2-Benzyloxytetrahydropyran-2,4-diols.—Selectivity in the reduction of the ketone acetal (**13a**) to the mixture of diastereoisomeric alcohols (**15c**) and (**15t**) was investigated using a range of metal hydride reducing agents. Results are summarised in Table 1. Diastereoisomer ratios were calculated from the integrated ^1H NMR signals of the anomeric protons, and stereochemistries assigned on the basis of the coupling constants measured for these signals. The assignments are consistent with known reagent selectivities. L-Selectride (lithium tri-s-butylborohydride) is a bulky reagent known to be very sensitive to steric effects in the reduction of cycloalkanones,[14] and thus expected to deliver hydride from the less hindered face of (**13a**), to give predominantly the *cis* isomers (**15c**). TRIBAL (tri-isobutylaluminium), on the other hand, gives the highest yield of the *trans*-alcohol (**15t**), no doubt because complexation of the aluminium to the benzyloxy group directs hydride delivery to the more hindered face. The diastereoisomeric alcohols (**15**) were not separated: the hemiacetals produced on debenzylation will equilibrate rapidly.

Similar selective reductions were carried out on the diastereoisomeric ketones (**13c**) and (**13t**), and the results are summarised in Table 2. Assignments are again based on the ^1H NMR signals of the anomeric protons. The effect of the bulky phenyl group is to increase selectivity when hydride delivery is predominantly from the opposite face of the ring, and to reduce it when hydride is delivered from the same face.

Three of the diastereoisomeric diols were obtained free or almost free of other isomers by chromatography. Only (**17c**), formed least favourably of all, could not be obtained free from its congener (**17t**).

Table 1. Stereoselectivity in the reduction of the ketone (**13a**).

Reducing agent	Yield (%)	Product ratio *cis* (**15c**):*trans* (**15t**)
L-Selectride	85	80:20
$NaBH_4$	80	75:25
$LiAlH_4$	92	65:35
DIBAL	94	3·:70
TRIBAL	75	15:85

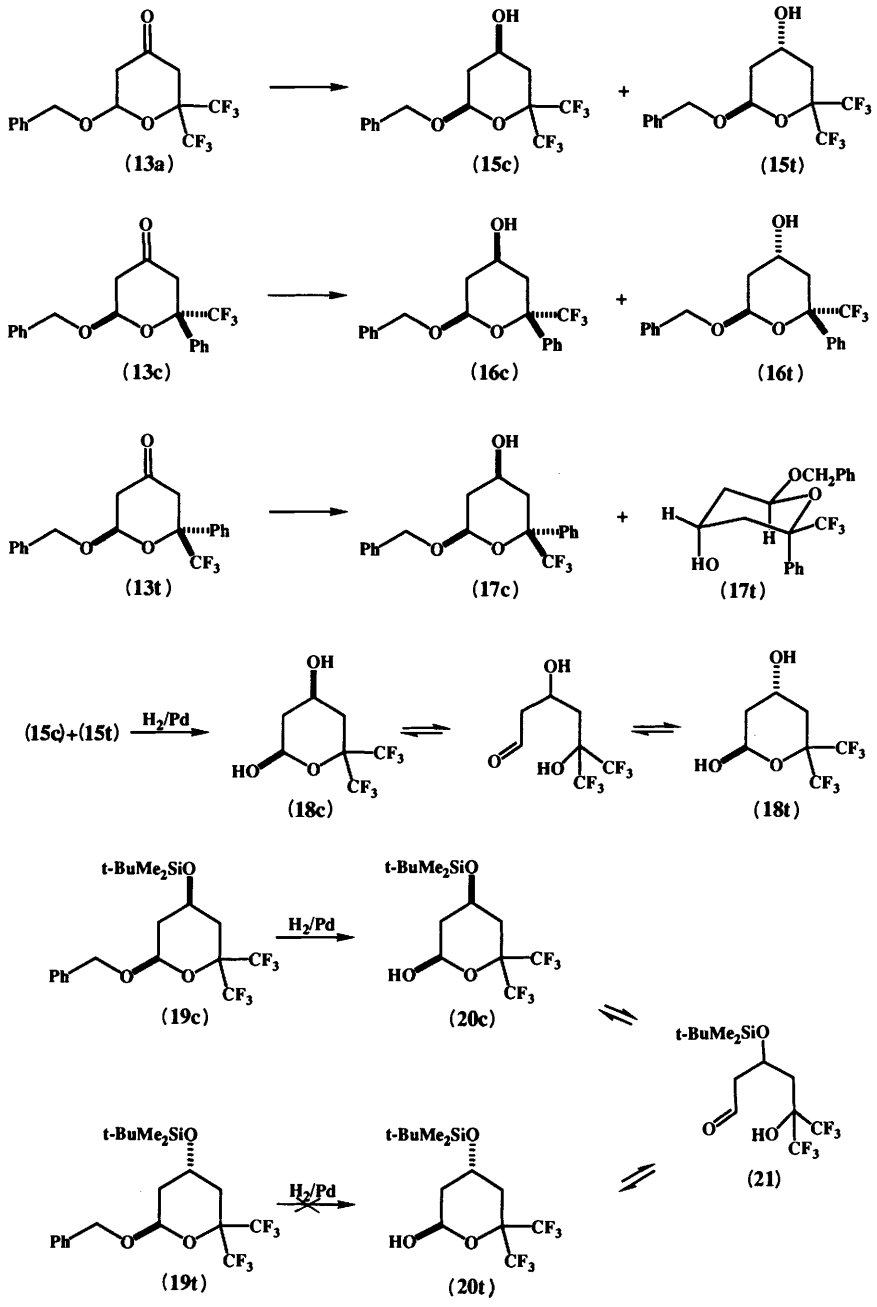
Table 2. Stereoselectivity in the reduction of ketones (**13c, 13t**)

Reducing agent	Product ratio from (**13c**) *cis* (**16c**):*trans* (**16t**)	Product ratio from (**13c**) *cis* (**17c**):*trans* (**17t**)
L-Selectride	86:14	
$NaBH_4$	80:20	60:40
TRIBAL	20:80	5:95

The ^1H NMR coupling constants indicate that when the 2-benzyloxy and 4-hydroxy substituents are *trans*-disposed, the phenyl group has a strong axial preference, sufficient to override the anomeric effect, and drive the benzyloxy substituent equatorial. The clearest example is isomer (**17t**), where the coupling constants are consistent with the anomeric proton (1H, dd, *J* 2.6, 7.7 Hz) being axial and the 4-proton being equatorial, as expected for the chair conformation shown. This conformation persists when the 4-hydroxy group is converted into the t-butyldimethylsilyl ether. Such a preference of the phenyl group for the axial orientation has been observed previously in *gem*-substituted cyclohexanes[15,16] and cyclohexanones,[17] and has been rationalised by Allinger and Tribble,[18] who point out that the orientation of an equatorial phenyl ring is restricted by geminal substitution. [The parent ketone (**13c**) does have the phenyl group equatorial, but is evidently a special case, as it ends up in a non-chair conformation.] This conformational preference of the phenyl group can clearly affect the ease of cyclisation of the corresponding 2,4-diols discussed below.

Debenzylation of Benzyl Tetrahydropyranyl Acetals.—Removal of the benzyl group by hydrogenolysis proceeded smoothly for the mixture of diastereoisomers (**15**), to give the tetrahydropyran-2,4-diols (**18**).

The ^1H NMR spectrum was complex, showing an aldehyde proton, several OH protons (signals removed on shaking with D_2O), and *six* signals in the anomeric proton region (4.8–5.6



ppm). Evidently equilibria are set up involving the open-chain form (characterised also by an IR band at 1 730 cm^{-1}) and more than just the two ring hemiacetals (**18**). Further characterisation of this mixture was unsuccessful. It is likely that the 4-OH group is involved in the equilibria, possibly in dimer formation, since silylation of this group before hydrogenolysis prevents this proliferation of anomeric proton signals.

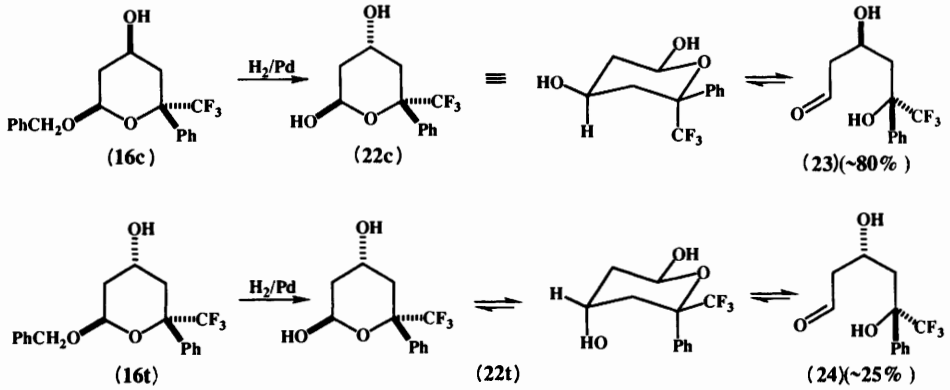
Hydrogenation of the mixture of t-butyldimethylsilyl ethers (**19**) resulted in the conversion of the *cis*-isomer (**19c**) into the hemiacetal (**20**) as an equilibrium mixture of anomers, but left the *trans* isomer (**19t**) unchanged. It could be separated from the reaction mixture and shown by ^1H NMR to exist in a conformation similar to that of the parent alcohol (**18**: *O*-benzyl axial, *O*-silyl equatorial).

The ^1H NMR in $CDCl_3$ showed a 3:2 mixture of anomers (**20c**):(**20t**), in the presence of some 20% of the open-chain form (**21**). In [$^2H_8$]-tetrahydrofuran the anomeric ratio was 1:1, and no ring-opened form could be detected.

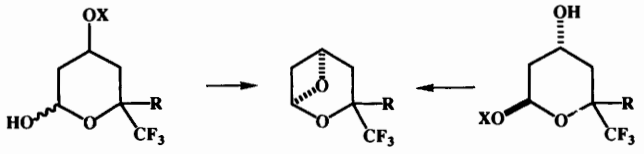
Hydrogenolysis of the benzyl tetrahydropyranyl acetals derived from the trifluoroacetophenone adducts was investigated for the two diastereoisomers (**16**), with the *O*-benzyl and phenyl groups *cis*. The ^1H NMR spectrum ($CDCl_3$) of the resulting crystalline diols can be interpreted in terms of a single hemiacetal (anomeric and C-4 protons both axial) and the open-chain isomer in each case.

More polar solvents favoured the cyclic forms: no ring-opened isomers could be detected by ^1H NMR for (**22c**) in [$^2H_4$]-methanol or for (**22t**) in [$^2H_6$]-acetone.

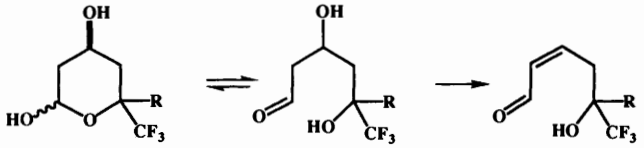
Attempted Cyclodehydration of Tetrahydropyran-2,4-diols.—The final step in our planned approach to the 2,6-dioxa-[3.1.1]bicycloheptane ring system requires the displacement of one OH group of the tetrahydropyran-2,4-diol by the other, which must therefore be *trans* to it. The alternatives are thus to convert the 4-OH into a good leaving group OX (**25**), in which case anomeric equilibration at the hemiacetal centre should



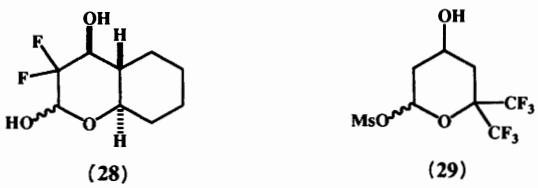
take care of the geometrical problem; or to generate the leaving group at the more reactive anomeric centre, in which case the geometry at both centres may have to be defined (**26**).



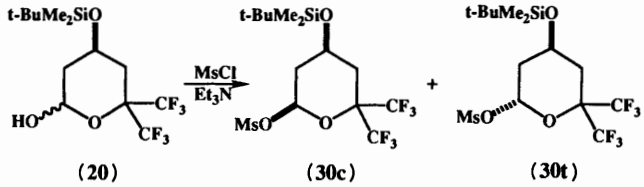
Of a large number of attempted cyclodehydrations we describe briefly those which had intelligible and instructive results. Under the modified Mitsunobu conditions (diethylazodicarboxylate/trimethyl phosphite in CH_2Cl_2) used by Still[10] in his successful preparation of 2,6-dioxa[3.1.1]bicycloheptanes, the mixture of diols (**18**) gave the dehydration product (**27**, R = CF_3) of the ring-opened form:



Other products appeared to be adducts of (**18**) and diethyl azodicarboxylate, but no bicyclic species could be detected. The reaction was repeated in tetrahydrofuran, and in dimethylformamide, since we know that the proportion of the ring-opened form is minimised in polar solvents, but the results were not significantly different. Similar results were obtained for both diols (**22**) obtained from the trifluoroacetophenone adducts, which also give the corresponding enone (**27**; R = Ph). In a variation designed to avoid enone formation, we prepared the 2-mesylates from the 4-silyl ethers (**20**). [Fried[9] reported the selective mesylation of the 2-OH group of his diol (**28**), but (**18**) and methanesulphonyl chloride, under a variety of conditions, gave only very small amounts of the diastereoisomeric mesylates (**29**)]. As with the Mitsunobu reactions, the major product was the enone (**27**; R = CF_3).



Mesylation of the hemiacetals (**20**) gave a high yield of the undesired *cis* derivative (**30c**) as the major product. Even the best conditions found (Et_3N in tetrahydrofuran) gave a 3:1 *cis:trans* mixture. The *trans* isomer (**30t**) was also found to decompose on chromatography on silica gel, so the mixture of diastereoisomers was used without purification for the next step. (Both diastereoisomers decompose within a few days at −20 °C; a reverse-Prins type of fragmentation is an obvious potential source of instability.)

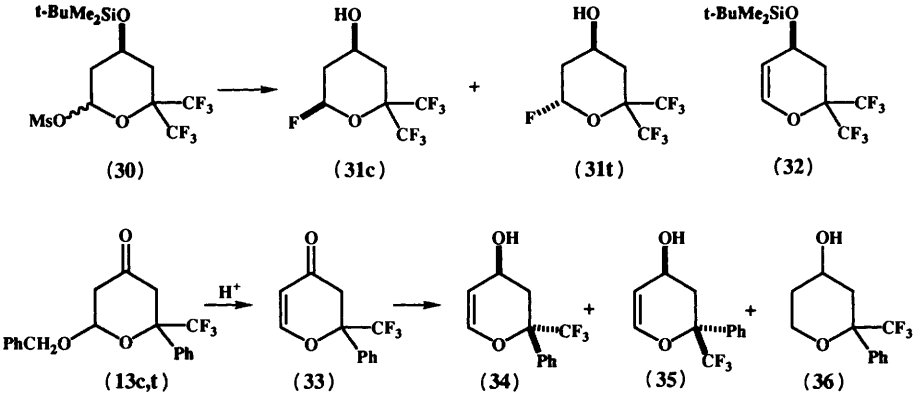


We hoped to achieve selective removal of the silyl protecting group using fluoride ion. The *trans*-4-alkoxide derived from (**30t**) should undergo intramolecular cyclisation to the 2,6-dioxa[3.1.1]bicycloheptane, while the *cis*-4-alkoxide is expected to fragment. In the event, treatment of the mixture of mesylate (**30**) with tetrabutylammonium fluoride (1.1 equiv.) in tetrahydrofuran gave the 2-fluorotetrahydropyran-4-ols (**31**) as the only identifiable products. The diastereoisomer ratio was independent of that of the starting materials, as expected for an S_N1 reaction (or for anomeric equilibration of the fluorides).

Under rigorously anhydrous conditions (CsF, tetrahydrofuran, 70 °C) the same products were obtained, together with some dihydropyran (**32**). No trans of bicyclic species, or of deprotected mesylates, was found in any of these reactions. It seems clear that displacement by fluoride at the anomeric centre is faster than the desired cyclisation process, and probably faster than desilylation also.

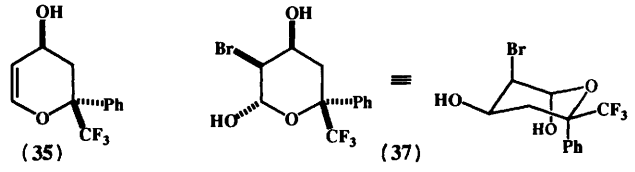
3-*Bromotetrahydropyran*-2,4-*diol System*.—In a final attempt to gain access to stabilised 2,6-dioxa[3.1.1]bicycloheptanes, and following Still,[10] we introduced bromine at the 3-position of the diol, the idea being that the substituent may promote ring-closure to the hemiacetal, as well as stabilising the oxetane acetal system electronically. The bromine should be removable after cyclisation.

The enone (**33**) could be obtained from the cycloaddition of trifluoroacetophenone and the diene (**9**) in the presence of $ZnCl_2$, according to Danishefsky,[8c,e] but only in poor yield. Our preferred route involves treating the mixture of tetrahydropyranones (**13c,t**) with refluxing trifluoroacetic acid. Reduction of the enone with $NaBH_4$ in ethanol gave a poor yield (20%) of dihydropyran-2-ols (**34**), (**35**) in a 5:1 ratio (steric development control), with predominant 1,4-addition of hydride. On the



other hand, $NaBH_4$ in the presence of Ce^{III} chloride (−78 °C in MeOH) gave an excellent yield (*ca.* 90%) of 1,2-reduction products, with the opposite selectivity (**34**):(**35**) (1:9). This is consistent with the work of Luche[21] who found that Ce^{III} promoted axial delivery of hydride. The main product (**35**) was obtained pure on recrystallisation.

After much experimentation, conditions were found (5 equiv. of *N*-bromsuccinimide in aqueous tetrahydrofuran) for the conversion of the dihydropyranol (**35**) into the bromohydrin (**37**) in reasonable yield (62%). ^1H NMR spectroscopy in $CDCl_3$ showed the diol to be present entirely in the ring-closed form, and as a single anomer. The coupling constants for 2-H, 3-H and 4-H are consistent with the conformation shown.



This was confirmed by the isolation from the reaction mixture of small amounts of the other bromohydrin, with these three protons all axial, and thus the three hetero-substituents all equatorial. The extent of the anomeric preference of (**37**) was confirmed by its conversion into the diacetate. The single diastereoisomer obtained had coupling constants for (2-, 3- and 4-H) similar to those found in the ^1H NMR spectrum of the parent diol.

Despite good expectations, all attempts at the cyclodehydration of diol (**37**), under a range of Mitsunobu conditions, only gave adducts with diethyl azodicarboxylate. Conceivably, the steric bulk of the geminal substituents at position 6 interferes with the conversion of the 2-OH into a good leaving group.

Although no 2,6-dioxa[3.1.1]bicycloheptane synthesis was achieved, this work has defined some ground rules for the formation of thromboxane analogues by the hetero Diels-Alder route. It has also developed this route as a powerful method for the introduction of the chemically and biologically interesting trifluoromethyl group into complex tetrahydropyran derivatives.

Experimental

General Procedures.—IR spectra were recorded on a Perkin-Elmer 297 spectrometer. Only strong absorbances are reported. ^1H NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker WP-80 (80 MHz) and Bruker WM-250 (250 MHz) instruments. Unless otherwise indicated the data given are taken on the 250 MHz instrument. Chemical shifts were measured relative to tetramethylsilane (δ 0.00) as internal standard. Mass spectra were recorded on an AEI MS 30: High resolution mass spectra on an AEI MS 902. UV spectra were recorded on a UVIKON 810P spectrometer.

M.p.s were measured on a Reichert hot-stage apparatus, and are uncorrected. Flash column chromatography was performed according to the method of Still, Kahn, and Mitra.[22] Analytical thin-layer chromatography was carried out on commercial plates coated with Merck Kieselgel 60 F_{254}. Benzene was distilled and stored over CaH_2. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Dichloromethane was freshly distilled from CaH_2. All other solvents were distilled before use.

The reagents diethyl azodicarboxylate (DEAD), methanesulphonyl chloride (MsCl), pyridine, triethylamine, and trimethyl phosphite, were all distilled before use. Toluene-*p*-sulphonyl chloride was recrystallised from light petroleum (b.p. 60–80 °C). *N*-Bromosuccinimide (NBS) was recrystallised from water and dried *in vacuo*. $ZnCl_2$ and CsF were dried *in vacuo* at 200 °C. Other commercially available reagents were used as received.

(E)-4-*Benzyloxybut*-3-*en*-2-*one* (**11**).—Benzyl bromide (10.3 g, 60 mmol) was added dropwise to a stirred solution of sodium acetoacetaldehyde (**10**), (6.5 g, 60 mmol) in dimethyl sulphoxide (40 ml) at room temperature. After addition was complete the mixture was stirred for a further 20 min and then taken up in CH_2Cl_2 (100 ml). This solution was washed with water (4 × 150 ml), and saturated brine (100 ml), and then dried (Na_2SO_4) and concentrated. The residue was vacuum distilled to give the title compound as an oil (4 g, 38%), b.p. 110 °C/0.2 mmHg (lit.,[23] 102–103 °C/0.1 mmHg), R_F (EtOAc–hexane, 1:3) 0.24; ν_{max}(film) 1 660 (C=O), 1 610 (C=C), and 960 cm^{-1}; δ_H($CDCl_3$, 90 MHz) 7.62 (1 H, d, *J* 13 Hz, CH_2OCH), 7.30 (5 H, br s, Ph), 5.70 (1 H, d, *J* 13 Hz, CH_3OCH), 4.88 (2 H, s, $PhCH_2$), and 2.13 (3 H, s, CH_3) (Found: M^+, 176.0839. $C_{11}H_{12}O_2$ requires 176.0838); *m/z* 176 (3%, M^+), 133 (5%, M–CH_3CO), 108 (22%, $PhCH_2OH$), and 91 (100%, $PhCH_2$). Smaller scale preparations were purified by flash column chromatography on silica gel (EtOAc–hexane, 1:3).

(E)-1-*Benzyloxy*-3-(*trimethylsilyloxy*)*buta*-1,3-*diene* (**9**).—This compound was prepared according to the method described by Danishefsky and Kitahara[12] for (*E*)-1-methoxy-3-(trimethylsilyloxy)-buta-1,3-diene (**6**). Since attempted distillation resulted in decomposition, the purification procedure was modified, as follows. The crude reaction mixture was concentrated and taken up in Et_2O (15 ml/g), filtered through Celite, and concentrated. The residue was again filtered through Celite and concentrated, and the procedure repeated twice more, to give the title compound as an orange oil (90%). ^1H NMR spectroscopy showed it to be better than 95% pure, and it was used in the cycloaddition reactions without further purification; ν_{max}(film) 1 645 (C=C) and 1 630 cm^{-1} (C=C);

$\delta_H(CDCl_3$, 90 MHz) 7.37 (5 H, br s, Ph), 6.77 (1 H, d, *J* 12 Hz, CH_2OCH), 5.50 (1 H, d, *J* 12 Hz, OCH=C*H*, 4.77 (2 H, s, $PhCH_2$), 4.13 (2 H, m, CH_2=C), and 0.27 (9 H, s, $SiMe_3$).

2-Benzyloxy-6,6-bis(trifluoromethyl)tetrahydropyran-4-one (**13a**).—The silyloxy diene (**9**), (1.6 g, 6.45 mmol) was stirred in tetrahydrofuran (2 ml at −78 °C in a flask with a wired-on septum. This flask was connected *via* a syringe needle and PVC tubing to a flask, also protected by a wired-on septum, containing phosphorus pentoxide (5 g) at room temperature. The system was evacuated and then placed under argon. Hexafluoroacetone sesquihydrate (1.87 g, 9.67 mmol) was injected rapidly (before pressure developed) onto the phosphorus pentoxide. Gaseous hexafluoroacetone (b.p. −28 °C) was released and condensed in the cooled flask. After 20 min the phosphorus pentoxide-containing flask was disconnected from the reaction flask by removing the syringe needle. The reaction mixture was stirred for 3 h, the temperature being kept below −45 °C, after which it was allowed to come to room temperature and then stirred overnight. The mixture was carefully concentrated under reduced pressure. ^{1}H NMR spectroscopy of the residue indicated that there were two main products; 2-benzyloxy-4-(trimethylsilyloxy)-6,6-bis(trifluoromethyl)-5,6-dihydropyran (**12**), (70%), $\delta_H(CDCl_3$, 90 MHz) 7.42 (5 H, br s, Ph), 5.53 (1 H, br s, 2-H), 5.00 (1 H, s, 3-H), 4.93 and 4.60 (2 H, ABq, *J* 11 Hz, $PhCH_2$), 2.57 (2 H, br s, 2 × 5-H) and 0.23 (9 H, s, $SiMe_3$); and (*E*)-1-benzyloxy-6,6,6-trifluoro-5-hydroxy-5-trifluoromethyl-hex-1-en-3-one, (**14**), (30%), $\delta_H(CDCl_3$, 90 MHz) 7.75 (1 H, d, *J* 13 Hz, CH_2OCH), 7.42 (5 H, br s, Ph), 5.87 (1 H, d, *J* 13 Hz, OCH=C*H*), 4.71 (2 H, s, $PhCH_2$), and 2.90 (2 H, br s, CH_2). The residue was taken up in tetrahydrofuran (15 ml) and water (4 ml) and stirred with NaF (0.5 g, 12 mmol) for 1 h. The mixture was concentrated under reduced pressure, and then taken up in CH_2Cl_2 (40 ml), and the solution washed with water (3 × 30 ml) and saturated brine (50 ml), dried (Na_2SO_4), and concentrated. The residue was taken up in pentane (50 ml), filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (EtOAc–hexane, 1:2) to give the *ketone* (**13a**) as a pale yellow oil (1.79 g, 81%), R_F (EtOAc–hexane, 1:2) 0.36, ν_{max}(film) 1 740 (C=O) and 1 240 cm^{-1} (C-F); $\delta_H(CDCl_3)$ 7.33 (5 H, m, Ph), 5.44 (1 H, dd, *J* 1.9 and 3.4 Hz, 2-H), 4.92 and 4.62 (2 H, ABq, *J* 12.0 Hz, $PhCH_2$) 3.28 and 2.83, (2 H, ABq, *J* 17.3 Hz, 2 × 5-H), 2.80 (1 H, dd, *J* 3.4 and 18.4 Hz, 3A-H), and 2.64 (1 H, dd, *J* 1.9 and 18.4 Hz, 3B-H) (Found: M^+, 1 342.0676. $C_{14}H_{12}F_6O_3$ requires 342.0691, *m/z* 342 (9%, M^+), 235 (15%, M − $PhCH_2O$), 147 (48%), and 107 (100%, $PhCH_2O$). Since the title compound (**13a**) was found to decompose slowly with time, it was stored under argon at −20 °C.

(2SR,6RS)- *and* (2SR, 6SR)-*2-Benzyloxy-6-phenyl-6-(trifluoromethyl)tetrahydropyran-4-ones* (**13c**), (**13t**).—The silyloxybutadiene (**9**), (4 g, 16 mmol) in tetrahydrofuran (7 ml) was stirred under argon at −78 °C. Trifluoroacetophenone (2.78 g, 16 mmol) was added dropwise to the mixture, which was then allowed to warm to room temperature after which it was stirred for a further 48 h. Tetrahydrofuran (30 ml, water (10 ml), and NaF (1.0 g) were added and the mixture stirred vigorously for 90 min. It was then concentrated under reduced pressure, taken up in CH_2Cl_2 (100 ml), extracted with water (3 × 50 ml) and saturated brine (50 ml), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:4) to give a mixture of solid diastereoisomeric ketones (**13c**) and (**13t**), (3.8 g, 10.9 mmol, 68%). ^{1}H NMR spectroscopy showed the ratio of (2*SR*, 6*RS*) to (2*SR*, 6*SR*) (**13c**) to (**13t**) to be 5:1. Separation of the diastereoisomers was achieved by fractional crystallisation from hexane. The (2*SR*, 6*RS*) isomer (**13c**), (phenyl and benzyloxy groups *cis*) crystallised as prisms, m.p. 84.5–85.5 °C (Found: C, 65.4, H, 5.15. $C_{19}H_{17}F_3O_3$ requires C, 65.1, H, 4.90%), R_F (EtOAc–hexane, 1:2) 0.43, ν_{max}(Nujol) 1 715 (C=O), and 1 220 cm^{-1} C-F); $\delta_H(CDCl_3)$ 7.64–6.91 (10 H, m, 2 × Ph), 5.51 (1 H, dd, *J* 2.3 and 4.0 Hz, 2-H) 4.58 and 4.44 (2 H, ABq, *J* 11.2 Hz, $PhCH_2$) 3.36 (2 H, ABq, *J* 16.9 Hz, 2 × 5-H), 2.86 (1 H, dd, *J* 4.0 and 18.3 Hz, 3A-H), and 2.63 (1 H, dd, *J* 2.3 and 18.3 Hz, 3B-H); *m/z* 244 (10%, M − PhCHO), 107 (65%, $PhCH_2O$), and 91 (100%, $PhCH_2$). The structure was confirmed by a single crystal *X*-ray analysis.[13] The (2*SR*, 6*SR*) isomer (**13t**), (phenyl and benzyloxy groups *trans*) crystallised as spherulites, m.p. 77–78 °C, R_F (EtOAc–hexane, 1:2) 0.50, ν_{max}(Nujol) 1 720 (C=O) and 1 200 cm^{-1} (C-F); $\delta_H(CDCl_3)$ 7.55–7.30 (10 H, m, 2 × Ph), 5.34 (1 H, t, *J* 3.0 Hz, 2-H), 5.05 and 4.68 (2 H, ABq, *J* 11.7 Hz, $PhCH_2$), 3.54 and 3.25 (2 H, ABq, *J* 16.2 Hz, 2 × 5-H), 2.54 (1 H, dd, *J* 3.0 and 17.4 Hz, 3A-H), and 2.35 (1 H, dd, *J* 3.0 and 17.4 Hz, 3B-H) (Found: M^+, 350.1143. $C_{19}H_{17}F_3O_3$ requires 350.1130), *m/z* 350 (1%, M^+), 172 35%), and 91 (100%, $PhCH_2$).

(2SR,4RS)- *and* (2SR,4SR)-*2-Benzyloxy-6,6-bis(trifluoromethyl)-tetrahydropyran-4-ols* (**15c**), (**15t**).—The stereoselectivity of several reagents was investigated since the *cis* (2*SR*,4*RS*) and *trans* (2*SR*,4*SR*) alcohols could not be separated.

(i) *Lithium tri-s-butylborohydride* (*L-Selectride*). A 1M solution of L-Selectride (0.64 ml, 0.64 mmol) in tetrahydrofuran was stirred at −78 °C under argon. The ketone (**13a**), (110 mg, 0.32 mmol) in tetrahydrofuran (2 ml) was added dropwise. Stirring was continued for 2.5 h, after which the mixture was allowed to warm to room temperature. An excess of H_2O_2 was added and the mixture stirred for a further 20 min; it was then concentrated under reduced pressure. The residue was taken up in water (15 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were washed with water (20 ml) and saturated brine (20 ml), dried (Na_2SO_4), and concentrated. Flash column chromatography of the residue on silica gel (EtOAt–hexane, 1:2) gave a mixture of the diastereoisomeric alcohols (**15c**) and (**15t**) as a pale yellow oil (94 mg, 85%). The isomer ratio was determined from the integrated ^{1}H NMR spectrum, *cis*:*trans* 80:20.

(ii) *Tri-isobutylaluminium*. To a stirred solution of the ketone (**13a**), (2.257 g, 6.6 mmol) in hexane (40 ml) at room temperature under argon was added a 1M solution of tri-isobutylaluminium in toluene (11 ml, 11 mmol). The mixture was stirred for 48 h, and then quenched by the slow addition of 10% aqueous sodium hydrogen carbonate (10 ml). The mixture was poured into a separating funnel and water (100 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the combined extracts were washed with saturated brine (100 ml), passed through phase-separating paper, and concentrated. Flash column chromatography as described above for the L-Selectride reaction yielded the mixture of alcohols (**15c**) and (**15t**), (1.7 g, 75%): (*cis*:*trans*, 15:85). Data for the mixture of *alcohols*: R_F (EtOAc–hexane, 1:4) 0.3, streaks, ν_{max}(film) 3 400 (OH) and 1 215 cm^{-1} (C-F); $\delta_H(CDCl_3)$. *cis*-Isomer (**15c**): $\delta_H(CDCl_3)$ 7.33 (5 H, m, Ph), 5.06 (1 H, dd, *J* 1.7 and 6.9 Hz, 2-H), 4.91 and 4.60 (2 H, ABq, *J* 11.9 Hz, $PhCH_2$), 4.15 (1 H, m, 4-H), 2.44 (1 H, dd, *J* 6.0 and 14.6 Hz, 5A-H), 2.21 (1 H, m, 3A-H), 2.05 (1 H, bs, signal removed by D_2O shake, OH), 2.01 (1 H, ddd, *J* 1.3, 10.0 and 14.6, 5B-H) and 1.80 (1 H, m, 3B-H). *trans*-Isomer (**15t**): $\delta_H(CDCl_3)$ 7.33 (5 H, m, Ph), 5.29 (1 H, dd, *J* 2.1 and 3.4 Hz, 2-H), 4.83 and 4.49 (2 H, ABq, *J* 11.8 Hz, $PhCH_2$), 4.45 (1 H, m, 4-H), 2.45 (1 H, dd, *J* 4.4 and 14.4 Hz, 5A-H), 2.20 (1 H, dm, *J* 14.8, 3A-H), 1.81 (1 H, dd, *J* 10.2 and 14.4 Hz, 5B-H), 1.68 (1 H, ddd, *J* 3.4, 10.4 and 14.8 Hz, 3B-H), and 1.63 (1 H, br, s, signal removed by D_2O shake, OH), (Found: M^+, 344.0864. $C_{14}H_{14}F_6O_3$ requires 344.0847), *m/z* 344 (8%, M^+), 253 (3%, M − $PhCH_2$), 107 (30%, $PhCH_2O$), and 91 (100%, $PhCH_2$).

Reduction with sodium borohydride, lithium aluminium hydride or di-isobutylaluminium hydride gave intermediate diastereoisomer ratios (Table 1).

6,6-*Bis*(*trifluoromethyl*)*tetrahydropyran*-2,4-*diol* (**18**).—A mixture of the diastereoisomeric alcohols (**15c**) and (**15t**), (3:1), (895 mg, 2.6 mmol) was stirred with 10% palladium on carbon (560 mg) in ethanol (60 ml). The mixture was hydrogenated at room temperature until 1 equivalent of H_2 was taken up (10 h). The reaction mixture was filtered through Celite and concentrated; flash chromatography of the residue on silica gel (EtOAc–hexane, 1:2) gave the diols (**18c**) and (**18t**) (522 mg, 79%) as an oil which when set aside for several weeks crystallised as plates, m.p. 114–117 °C (Found: C, 33.2, H, 3.20. $C_7H_8F_6O_3$ requires C, 33.1, H, 3.20%); R_F (EtOAc–hexane–MeOH, 25:75:1) 0.11, $\nu_{max}(CHCl_3)$ 3 300 (OH), 1 730 (C=O), and 1 200 cm^{-1} (CF): the relative intensity of the C=O absorption is substantially reduced when the spectrum is taken in tetrahydrofuran as solvent), *m/z* 253 (15%, *M* − H), 235 (10%, *M* − OH), 208 (60%), 190 (73%), 167 [33%, $(CF_3)_2COH$], 145 (65%), and 69 (100%, CF_3). The ^1H NMR spectrum is extremely complex: the signals do, however, fall into sensible groups: $\delta_H(CD_3COCD_3)$, aldehyde proton region; 9.77 (t, *J* 1.3 Hz); hemiacetal (OH) proton region; 7.05, 6.43, 6.24, 6.01, and 5.77 (all br s, all signals removed by D_2O shake), hemiacetal (anomeric) proton, 2-H, region; 5.59 (t, *J* 4.2 Hz, signal sharpened after D_2O shake), 5.45 [dt, *J* 5.0 (t) and 10.8 Hz], 5.35 (br s), 5.18 (br d, *J* 10 Hz), 5.01 (dd, *J* 2.5 and 10.0 Hz, signals sharpened after D_2O shake) and 4.93 [dt, *J* 4.2 (t) and 10.4 Hz); 4-H region, 4.8–4.0, at least five different multiplets; 3-H, 5-H region; 2.85 (m, simplifies to d after D_2O shake, *J* 6.3 Hz) and 2.45–1.40 (m). The integration is consistent with the proton distribution of (**18**).

(2SR,4RS,6RS)-2-*Benzyloxy*-6-*phenyl*-6-(*trifluoromethyl*)-*tetrahydropyran*-4-*ol* (**16c**).—Treatment of the (2*SR*,6*RS*)-tetrahydropyran-4-one (**13c**), (90 mg, 0.26 mmol) with L-Selectride by the method described above gave a 6:1 mixture of the corresponding tetrahydropyran-4-ols, with the title compound predominating. Flash column chromatography on silica gel (EtOAc–hexane, 1:2) gave (**16c**) as an oil (67 mg, 73%), containing a trace of the isomer; R_F (EtOAc–hexane, 1:2) 0.24; ν_{max}(film) 3 375 (OH), and 1 180 cm^{-1} (CF); $\delta_H(CDCl_3)$ 7.68–7.00 (10 H, m, 2 × Ph), 5.19 (1 H, dm, *J* 7.5 Hz, 2-H), 4.90 and 4.71 (2 H, ABq, *J* 11.9 Hz, PhCH_2), 4.26 (1 H, m, 4-H), 2.83 (1 H, ddd, *J* 1.0, 5.0, and 14.2 Hz, 5A-H), 2.28 (1 H, dm, *J* 12.8 Hz, 3A-H), 2.00 (1 H, dd, *J* 9.9 and 14.2 Hz, 5B-H), 1.61, (1 H, ddd, *J* 7.5, 9.0, and 12.8 Hz, 3B-H), and 1.57 (1 H, s, signal removed by D_2O shake, CHO*H*); *m/z* 265 (4%), 228 (6%), 206 (30%, *M* − CF_3, Ph), 107 (35%, $PhCH_2O$), and 91 (100%, $PhCH_2$).

(2SR,4SR,6RS)-2-*Benzyloxy*-6-*phenyl*-6-(*trifluoromethyl*)-*tetrahydropyran*-4-*ol* (**16t**).—Treatment of the (2*SR*,6*RS*)-tetrahydropran-4-one (**13c**) (190 mg, 0.54 mmol) with tri-isobutylaluminium by the method described above gave a 4:1 mixture of the corresponding tetrahydropyran-4-ols, with the title compound predominating. Flash column chromatography on silica gel (EtOAc–hexane, 1:2) gave the mixture of alcohols as an oil (140 mg, 74%), containing some 10% of the minor isomer (**16c**); R_F (EtOAc–hexane, 1:2) 0.31; ν_{max}(film) 3 350 (OH), and 1 180 cm^{-1} (CF); $\delta_H(CDCl_3)$ 7.69–7.01 (10 H, m, 2 × Ph), 5.28 (1 H, t, *J* 3.0 Hz, 2-H), 4.61 and 4.46 (2 H, ABq, *J* 12.2 Hz, PhCH_2), 4.20 (1 H, m, 4-H), 2.91 (1 H, dm, *J* 13.3 Hz, 5A-H), 2.10 (1 H, dm, *J* 14.0 Hz, 3A-H), 2.06 (1 H, dd, *J* 11.0 and 13.3 Hz, 5B-H), 1.74 (1 H, ddd, *J* 4.0, 10.2, and 14.2 Hz, 3B-H), and 1.56 (1 H, br s, signal removed by D_2O shake, CHO*H*); *m/z* 334 (8%, *M* − H_2O), 265 (15%), 206 (45%, *M* − CF_3), 107 (30%, $PhCH_2O$), and 91 (100%, $PhCH_2$).

(2SR,4SR,6SR)-2-*Benzyloxy*-6-*phenyl*-2-6-(*trifluoromethyl*)-*tetrahydropyran*-4-*ol* (**17t**).—Treatment of the (2*SR*,6*SR*)-tetrahydropyran-4-one (**13t**), (115 mg, 0.33 mmol) with tri-isobutylaluminium by the method described above gave the title compound after flash column chromatography on silica gel (EtOAc–hexane, 1:2), as an oil (97 mg, 83%); R_F(EtOAc–hexane, 1:2) 0.3; ν_{max}(film) 3 380 (OH), and 1 200 cm^{-1} (CF); $\delta_H(CDCl_3)$ 7.67–7.29 (10 H, m, 2 × Ph), 5.15 (1 H, dd, *J* 2.6 and 7.7 Hz, 2-H), 5.09 and 4.68 (2 H, ABq, *J* 11.7 Hz, PhCH_2), 4.45 (1 H, m, 4-H), 2.59 (1 H, dd, *J* 3.8 and 15.2 Hz, 5A-H), 2.49 (1 H, dd, *J* 4.1 and 15.2 Hz, 5B-H), 2.01 (1 H, ddd, *J* 4.2, 7.7, and 13.0 Hz, 3A-H), 1.82, (1 H, dm, *J* 13.0, 3B-H), and 1.54 (1 H, br s, signal removed by D_2O shake, CHO*H*) (Found: M^+, 352.1296, $C_{19}H_{19}F_3O_3$ requires 352.1286); *m/z* 352 (4%, M^+), 312 (15%), 206 (30%), 107 (25%, $PhCH_2O$), and 91 (100%, $PhCH_2$).

(2SR,4RS,6SR)-2-*Benzyloxy*-6-*phenyl*-6-(*trifluoromethyl*)-*tetrahydropyran*-4-*ol* (**17c**).—Treatment of the (2*SR*,6*SR*)-tetrahydropyran-4-one (**13t**), (88 mg, 0.25 mmol) with sodium borohydride in ethanol gave a 3:2 mixture of alcohols (76 mg, 86%), with the title compound the favoured isomer. The diastereoisomer (**17c**) could not be obtained free from its isomer. The characterisation derives from the ^1H NMR spectroscopy, as follows: $\delta_H(CDCl_3)$ 7.55–7.28 (10 H, m, 2 × Ph), 5.05 and 4.68 (2 H, ABq, *J* 11.9 Hz, PhCH_2), 3.73 (2 H, m, 2- and 4-H), 2.95 (1 H, m, 5A-H), 2.06 (1 H, m, 3A-H), 2.01 (1 H, dd, *J* 10.8 and 13.1 Hz, 5B-H), 1.83 (1 H, br s, signal removed by D_2O shake, CHO*H*), and 1.65 (1 H, m, 3B-H).

(2SR,4RS)- *and* (2SR,4SR)-2-*Benzyloxy*-4-(*t-butyldimethylsilyloxy*)-6,6-*bis*[*trifluoromethyl*]*tetrahydropyrans* (**19**).—A mixture of the diastereoisomeric 4-hydroxytetrahydropyrans (**15c**):(**15t**), (3:1), (500 mg, 1.45 mmol) was placed in a flask with t-butyldimethylsilyl chloride (436 mg, 2.9 mmol) and imidazole (390 mg, 5.8 mmol). The flask was flushed with argon, dimethylformamide (1.75 ml) introduced, and the mixture stirred at room temperature. After 2 h the reaction mixture was taken up in Et_2O (40 ml) and extracted with water (2 × 40 ml) and saturated brine (40 ml), dried (Na_2SO_4), and concentrated. The residue was flash chromatographed on silica gel (EtOAc–hexane, 1:8), to yield the 4-silyloxytetrahydropyrans (**19**) as an oil (500 mg, 80%). The mixture was not separated, but the *trans*-isomer (**19t**) was obtained pure after the following reaction, and is characterised here (Found: C, 52.5, H, 6.20. $C_{20}H_{28}F_6O_3Si$ requires C, 52.4, H, 6.15%); R_F(EtOAc–hexane, 1:8) 0.6, ν_{max}(film) 1 200 cm^{-1} (CF); $\delta_H(CDCl_3)$ 7.36–7.31 (5 H, m, Ph), 5.25 (1 H, m, 2-H), 4.83 and 4.51 (2 H, ABq, *J* 12.3 Hz, PhCH_2), 4.38 (1 H, m, 4-H), 2.28 (1 H, dd, *J* 4.8 and 14.2 Hz, 5A-H), 2.06 (1 H, dm, *J* 14.0 Hz, 3A-H), 1.82 (1 H, ddd, *J* 1.3, 9.9 and 14.2 Hz, 5B-H), 1.67 (1 H, ddd, *J* 3.7, 10.7, and 14.0 Hz, 3B-H), 0.88 (9 H, s, t-butyl), 0.08 and 0.07 (3 + 3H, $SiMe_A$ and $SiMe_B$); *m/z* 458 (3%, M^+), 401 (5%, *M* − t-Bu), 351 (12%, *M* − $PhCH_2O$), 219 (100%), and 147 (100%). The *cis*-isomer (**19c**) was only characterised as the mixture with the *trans*-isomer: $\delta_H(CDCl_3)$ 7.36–7.29 (5 H, m, Ph), 4.95 (1 H, dd, *J* 3.1 and 8.3 Hz, 2-H), 4.91 and 4.59 (2 H, ABq, *J* 11.9 Hz, PhCH_2), 4.03 (1 H, m, 4-H), 2.4–1.6 (4 H, m, 2 × 3-H) and 5-H), 0.87 (9 H, s, t-butyl), 0.06 and 0.05 (3 + 3H, $SiMe_A$ and $SiMe_B$).

4-(*t-Butyldimethylsilyloxy*)-6,6-*bis*(*trifluoromethyl*)*tetrahydropyran*-2-*ol* (**20**).—The silyloxytetrahydropyrans (**19**), (500 mg, 1.09 mmol, *cis*:*trans* 3:1) were hydrogenated over 10% palladium on carbon (250 mg) in ethanol (15 ml), at room temperature and atmospheric pressure, with vigorous stirring. After one equivalent of H_2 had been taken up (2.5 h) the reaction mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc–hexane, 1:8) to yield first unchanged silyloxytetrahy-

dropyran (120 mg, 26%), which ^{1}H NMR showed to be almost exclusively the *trans*-isomer (**19t**), indicating that virtually none of this isomer had undergone hydrogenolysis. The second compound isolated was the hemiacetal (**20c**), (270 mg, 67%), which crystallised when set aside for several days to give plates, m.p. 51–52 °C (Found: C, 42.5, H, 6.00. $C_{13}H_{22}F_6O_3Si$ requires C, 42.4, H, 6.00%); R_F(EtOAc–hexane, 1:2) 0.59; ν_{max}(Nujol) 3 250 (OH) and 1 220 cm^{-1} (CF), δ_H [$^2H_8$]-THF, 1:1 mixture of anomers): *cis* anomer, 6.51 (1 H, d, *J* 6.3 Hz, signal removed on D_2O shake, OH), 5.17 (1 H, m, collapses to dd on D_2O shake, *J* 2.1 and 8.3 Hz, 2-H), 4.13 (1 H, m, 4-H), 2.33–1.50 (4 H, m, 2 × 3-H), and 5-H), 0.93 (9 H, s, t-butyl), 0.13 and 0.12 (3 + 3 H, $SiMe_A$ and $SiMe_B$); *trans*-anomer, 6.43 (1 H, dd, *J* 2.1 and 6.0 Hz, signal removed on D_2O shake, OH), 5.52 (1 H, m, collapses to t on D_2O shake, *J* 2.5 Hz, 2-H), 4.50 (1 H, m, 4-H), other signals as listed for the *cis*-anomer; δ_H($CDCl_3$) (3:2 mixture of *cis*:*trans* anomers, plus aldehyde tautomer) 9.68 (1 H, s, CHO) and 4.80 (1 H, m, CHOSi), other signals masked by those of the ring-closed forms: *m*/*z* 311 (6%, *M* − t-Bu), 267 (18%), 219 (20%), and 75 (100%).

(4SR,6RS)-6-*Phenyl*-6-(*trifluoromethyl*)*tetrahydropyran*-2,4-*diol* (**22t**).—The (2*SR*,4*SR*,6*RS*)-tetrahydropyran-4-*ol* (**16t**), (120 mg, 0.34 mmol), containing some 10% of the (2*SR*,4*RS*,-6*RS*)-tetrahydropyran-4-ol (**16c**) was hydrogenated over 10% palladium on carbon (100 mg) in ethyl acetate (5 ml), with vigorous stirring, at room temperature and pressure. After this time one equivalent of hydrogen had been taken up and the reaction mixture was filtered through Celite, concentrated, and flash chromatographed on silica gel (EtOAc–hexane, 1:1) to yield the title compound as an oil, which crystallised when set aside for several hours (56 mg, 63%), m.p. 114–116 °C, R_F-(EtOAc–hexane, 1:1) 0.22; ν_{max}(Nujol) 3 350 (OH) and 1 160 cm^{-1} (CF); δ_H([$^2H_8$]-acetone), 7.64–7.37 (5 H, m, Ph), 5.98 (1 H, d, *J* 7.0 Hz, signal removed on D_2O shake, hemiacetal OH), 4.80 (1 H, ddd, *J* 2.3 and 7.0 and 10.1 Hz, 7.0 Hz coupling disappears on D_2O shake, 2-H), 4.18 (1 H, d, *J* 5.0 Hz, signal removed on D_2O shake, 4-OH), 3.65 (1 H, m, 4-H), 2.81 (1 H, dd, *J* 3.3 and 12.9 Hz, 5A-H), 2.07 (1 H, dm, *J* 11.6 Hz, 3A-H), 1.81 (1 H, dd, *J* 11.4 and 12.9 Hz, 5B-H) and 1.44 [1 H, dt, *J* 10.1 (t) and 11.6 Hz, 3B-H] (Found: $M^+ - H_2O$, 244.0696. $C_{12}H_{13}F_3O_3 - H_2O$ requires 244.0711); *m*/*z* 244 (15%, $M^+ - H_2O$), 219 (20%), 175 (35%), 105 (100%), and 77 (43%, Ph); ^{1}H NMR in $CDCl_3$ showed a significant amount (*ca.* 25%) of the ring-opened tautomer (**24**).

(4RS,6RS)-6-*Phenyl*-6-(*trifluoromethyl*)*tetrahydropyran*-2,4-*diol* (**22c**).—The (2*SR*,4*RS*,6*RS*)-tetrahydropyran-4-ol (**16c**), (145 mg, 0.41 mmol) was hydrogenated as described above, and flash chromatographed on silica gel (EtOAc–hexane, 1:2) to yield the title compound as an oil, which crystallised when set aside for several days to give plates (49 mg, 46%), m.p. 140–145 °C; R_F(EtOAc–hexane, 1:2) 0.25; ν_{max}(Nujol) 3 380 (OH) and 1 170 cm^{-1} (CF); δ_H([$^2H_4$]-methanol), 7.80–7.31 (5 H, m, Ph), 4.55 (1 H, dm, *J* 8.7 Hz, 2-H), 3.71 (1 H, m 4-H), 2.45 (1 H, dm, *J* 14.3 Hz, 5A-H), 2.12 (1 H, ddd, *J* 1.7, 10.3, and 14.3 Hz, 5B-H), 1.73 (2 H, m, 2 × 3-H) (Found: $M^+ - H_2O$, 244.0713. $C_{12}H_{13}F_3O_3 - H_2O$ requires 244.0711); *m*/*z* 244 (3%, $M^+ - H_2O$), 204 (12%), 193 (8%, *M* − 175 (35%), 105 (100%), 77 (30%, Ph), and 69 (10%, CF_3). ^{1}H NMR in $CDCl_3$ showed a large amount (*ca.* 80%) of the ring-opened tautomer (**23**) to be present; δ_H9.74 (1 H, s, CHO), 7.60–7.31 (5 H, m, Ph), 5.28 (1 H, br s, signal removed on D_2O shake, tertiary OH), 4.13 (1 H, m, C*H*OH), 2.70 (1 H, dd, *J* 4.3 and 9.5 Hz, CH_AH_BCHO), 2.67 (1 H, dd, *J* 4.2 and 9.5 Hz, CH_AH_BCHO), 1.91–1.40 (2 H, m, CH_2Ph), and 1.56 (1 H, br s, signal removed on D_2O shake, CHO*H*).

Attempted Cyclodehydration of 6,6-*Bis*(*trifluoromethyl*)*tetrahydropyran*-2,4-*diols* (**18**; R = CF_3).—One typical procedure is described, of numerous variations on the method used by Still.[10] To dichloromethane (1.5 ml) at −5 °C was added distilled trimethyl phosphite (105 μl, 0.89 mmol) and freshly distilled diethyl azodicarboxylate (DEAD), (105 μl, 0.66 mmol). The mixture was stirred at room temperature under argon until the yellow colour of the DEAD was discharged after which it was added to a stirred solution of the diol (150 mg, 0.59 mmol) in dichloromethane (9 ml) under argon. The mixture was warmed to room temperature and stirred for 30 min. Concentration under reduced pressure followed by flash column chromatography on silica gel (EtOAc–hexane, 1:3) gave starting material (**18**), (70 mg, 47%) and (*E*)-6,6,6-trifluoro-5-hydroxy-5-(trifluoromethyl)hex-2-enal (**27**; R = CF_3), (45 mg, 21%) as an oil, R_F(EtOAc) 0.71; ν_{max} 3 300 (OH), 1 675 (C=O), 1 630 (C=C), and 1 220 cm^{-1} (CF); δ_H($CDCl_3$), 9.55 (1 H, d, *J* 7.7 Hz, CHO), 6.87 [1 H, dt, *J* 7.3(t) and 15.7 Hz, CH_2CH], 6.24 [1 H, ddt, *J* 1.2(t), 7.7 and 15.7 Hz, C*H*CHO], 4.21 (1 H, br s, OH), and 2.96 (2 H, d, *J* 7.3 Hz, CH_2) (Found: M^+, 236.0276. $C_7H_6F_6O_2$ requires 236.0272); *m*/*z* 236 (55%, M^+), 235 (45, *M* − H), 167 (42, *M* − CF_3), and 69 (100, CF_3), as well as unidentified adducts of the starting material and DEAD. Various other dehydrations of this type, varying the solvent, the proportions of reagents, the reaction time, *etc.*, gave very similar results, and in particular no indication, from TLC or ^{1}H NMR, that any 2,6-dioxabicyclo[3.1.1]heptane had been formed.

Dehydration of (4SR,6RS)-6-*Phenyl*-6-(*trifluoromethyl*)*tetrahydropyran*-2,4-*diol* (**22t**).—The diol (**22t**), (55 mg, 0.21 mmol) was treated with diethyl azodicarboxylate and trimethyl phosphite (38 μl of each) in dichloromethane (2.5 ml) by the method described above for the diol (**18**). TLC indicated a large number of products and partial separation of these by flash column chromatography on silica gel (EtOAc–hexane, 1:6) showed the enone (*E*)-6,6,6-trifluoro-5-hydroxy-5-phenyl-hex-2-enal (**27**, R = Ph) to be present: δ_H($CDCl_3$) 9.37 (1 H, d, *J* 7.2 Hz, CHO), 7.55–7.31 (5 H, m, Ph), 6.55 [1 H, dt, *J* 8.4(t) and 15.8 Hz, CH_2CH], 6.15 (1 H, dd, *J* 7.2 and 15.8 Hz, C*H*CHO), 3.23 (1 H, dd, *J* 8.4 and 14.5 Hz, CH_AH_B), 3.06 (1 H, dd, *J* 8.4 and 14.5 Hz, CH_AH_B) and 2.55 (1 H, br s, OH), as well as various unidentified adducts of the starting material and DEAD. Varying the solvent (THF, DMF) to promote ring-closure did not lead to detectable amounts of cyclodehydration product. Similar reactions using the (4*RS*,6*RS*)-diastereoisomer (**22c**) gave very similar results.

(2SR,4RS) *and* (2SR,4SR)-2-*Methylsulphonyloxy*-6,6-*bis*(*trifluoromethyl*)*tetrahydropyran*-4-*ols* (**29**.—The diol (**18**), (104 mg, 0.41 mmol), triethylamine (0.29 ml, 170 mg, 1.68 mmol), and tetrahydrofuran (2 ml) were stirred under argon at room temperature. To the mixture was added methanesulphonyl chloride (35 μl, 0.45 mmol). Stirring was continued for 30 min after which the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:2) to yield starting material (18 mg, 17%) and a mixture of products (83 mg) which was further purified by flash chromatography (CH_2Cl_2) to give the *enone* (**27**; R = CF_3), (50 mg, 51%) described above, the derived mesylate (11 mg, 10%) and the title compounds as an oil (11 mg, 8%), (*cis*:*trans*) 1:1. These were not separated, and the following data refer to the mixture of diastereoisomers. R_F(CH_2Cl_2) 0.58; ν_{max}($CHCl_3$) 3 250 (OH), 1 360 (S=O), 1 220 (CF) and 1 100 cm^{-1} (S=O), δ_H($CDCl_3$), *trans*-isomer; 6.36 (t, *J* 3.3 Hz, 2-H), 5.43 (1 H, m, 4-H), 3.11 (3 H, s, $MeSO_3$), 2.85–2.17 (4 H, m, 2 × 3-H, 2 × 5-H) and 1.55 (1 H, br s, OH): *cis* isomer; 5.91 (1 H, dd, *J* 3.2 and 8.3 Hz, 2-H), 5.10 (1 H, m, 4-H), other signals as for the *trans*-isomer; *m*/*z* 236 (3%,

$M^+ - CH_3SO_3H$), 219 (100%), 79 (45%, CH_3SO_2), and 69 (28%, CF_3).

(2SR,4RS) *and* (2SR,4SR)-4-(*t-Butyldimethylsilyloxy*)-2-*methylsulphonyloxy*-6,6-*bis*(*trifluoromethyl*)*tetrahydropyrans* (**30**).—The hemiacetals (**20**), (150 mg, 0.41 mmol) and triethylamine (82 mg, 0.82 mmol) were stirred in tetrahydrofuran (4 ml) at 0 °C under argon. To this mixture was added methanesulphonyl chloride (38 μl, 0.49 mmol) and stirring continued for 1 h. The mixture was concentrated under reduced pressure and the residue extracted with pentane. The pentane washings were passed through Celite and concentrated (172 mg, 94% crude yield), (*cis*:*trans*, 3:1 by ^1H NMR). Separation of the diastereoisomers was not possible, since the *trans* isomer was found to decompose on silica. However, the reaction was very clean and the mixture of diastereoisomers was used without further purification. Both diastereoisomers decomposed within a few days at −20 °C. cis-*Isomer:* (**30c**) R_F (EtOAc–hexane, 1:8) 0.41; ν_{max}(film) 1 380 (S=O), 1 230 (CF), and 1 120 cm^{-1} (S=O); δ_H($CDCl_3$, 90 MHz) 5.87 (1 H, br d, *J*, 10.5 Hz, 2-H), 4.17 (1 H, m, 4-H), 3.15 (3 H, s, SO_2Me), 2.30–1.52 (4 H, m, 2 × 3-H, 2 × 5-H, 0.90 (9 H, s, t-butyl) and 0.12 (6 H, br s, $SiMe_2$); *m/z* 367 (5%, $M - CH_3SO_2$), 265 (25%), 237 (44%), 235 (45%), and 219 (100%). *trans*-Isomer (**30t**): R_F(EtOAc–hexane, 1:8) 0.32; δ_H($CDCl_3$, 90 MHz) 6.32 (1 H, t, *J* 3 Hz, 2-H), 4.4 (1 H, m, 4-H), 3.05 (3 H, s, SO_2Me), other peaks as listed above for the *cis*-isomer.

Reaction of (2SR,4RS) *and* (2SR,4SR)-4-(*t-Butyldimethylsilyloxy*)-2-*methylsulphonyloxy*-6,6-*bis*(*trifluoromethyl*)*tetrahydropyrans* (**30c**), (**30t**) *with Fluoride Anion.*—(i) *Tetrabutylammonium fluoride.* A diastereoisomeric mixture of the mesylates (**30c**): (**30t**), (3:1; 99 mg, 0.22 mmol) was stirred at −78 °C in tetrahydrofuran (3 ml) under argon. Tetrabutylammonium fluoride (1M solution in tetrahydrofuran; 0.24 ml) was added, and the mixture allowed to warm to room temperature over 30 min; it was then concentrated under reduced pressure. The residue was taken up in water (10 ml) and washed with CH_2Cl_2 (3 × 5 ml). The combined organic layers were washed with saturated brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:4) to yield a 4:3 mixture of the (2*SR*,4*RS*)- and (2*SR*,4*SR*)-2-fluoro-6,6-bis(trifluoromethyl)tetrahydropyran-4-ols (**31c**), (**31t**), (43 mg, 76%): data (for the *mixture* unless stated otherwise): R_F(EtOAc–hexane, 1:2) 0.3; ν_{max}(film) 3 400 (OH) and 1 230 (CF) cm^{-1}; δ_H($CDCl_3$) *trans*-isomer: 5.94 (1 H, br d, *J* 53.6 Hz, 2-H), 4.44 (1 H, br m, sharpened on D_2O shake, 4-H), 2.6–1.5 (4 H, m, 2 × 3-H, 2 × 5-H), and 2.03 (1 H, br s, signal removed on D_2O shake, OH); *cis*-isomer: 5.84 (1 H, dt, *J* 3.4 (t) and 53.2 Hz, 2-H), 4.26 (1 H, br m, sharpened on D_2O shake (4-H), 1.65 (1 H, br s, signal removed on D_2O shake, OH); other signals as for the *trans*-isomer (Found: $M^+ - H_2O$, 238.0233. $C_7H_7F_7O_2$ requires $M^+ - H_2O$, 238.0229); *m/z* 238 (19%, $M - H_2O$), 236 (20%, M − HF), 219 (12%), 209 (35%), 187 (8%, $M - CF_3$), 145 (60%), and 69 (100%, CF_3). Altering the reaction temperature, reagent concentration, and diastereoisomer ratio of the starting material did not change the product ratio significantly.

(ii) *Caesium fluoride.* A diastereoisomeric mixture of mesylates (**30c**):(**30t**), (3:1), (70 mg, 0.16 mmol) was heated with anhydrous CsF in tetrahydrofuran (2 ml) under argon at 70 °C for 4 h. Concentration under reduced pressure, followed by an aqueous work up as described above for the TBAF reaction, gave a residue which was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:5) to yield the 2-fluorotetrahydropyrans characterised above (12 mg, 30%) and 4-(t-butyldimethylsilyloxy)-6,6-bis(trifluoromethyl)-5,6-dihydro-4*H*-pyran (**32**), (9 mg, 16%) as an oil: R_F(EtOAc–hexane, 1:8) 0.8; ν_{max}(film) 1 620 (C=C) and 1 210 cm^{-1} (CF); δ_H($CDCl_3$, 80 MHz) 6.31 (1 H, dd, *J* 1.9 and 6.4 Hz, 2-H), 4.96 (1 H, ddd, *J* 1.3, 2.1, and 6.4 Hz, 3-H), 4.33 (1 H, br t, *J* 7.5 Hz, 4-H), 2.20 (2 H, m, 2 × 5-H), 0.85 (9 H, s, t-Bu) and 0.11 (6 H, s, $SiMe_2$); *m/z* 350 (1%, M^+), 293 (15%, M − t-Bu), 219 (100%), 169 (40%), and 69 (10%, CF_3).

6-*Phenyl*-6-*trifluoromethyl*-5,6-*dihydropyran*-4-*one* (**33**).—A diastereoisomeric mixture of the 2-(phenylmethoxy)pyran-4-ones (**13c**), (**13t**), (2.8 g, 8 mmol) in trifluoroacetic acid (30 ml) was refluxed at 80 °C for 2 h. On cooling, the mixture was concentrated under reduced pressure, flash-columned on silica gel (EtOAc–hexane, 1:4), and the resulting solid recrystallised from CH_2Cl_2–hexane to give the enone (**33**), (1.76 g, 91%) as needles, m.p. 89–90 °C (Found: C, 59.2, H, 3.80. $C_{12}H_9F_3O_2$ requires C, 59.5, H, 3.75%); R_F(EtOAc–hexane, 1:4) 0.33; ν_{max}(Nujol) 1 680 (C=O), 1 605 (C=C), and 1 200 cm^{-1} (CF); δ_H($CDCl_3$) 7.51–7.40 (5 H, m, Ph), 7.31 (1 H, d, *J* 6.1 Hz, 2-H), 5.40 (1 H, d, *J* 6.1 Hz, 3-H), and 3.28 (2 H, s, 2 × 5-H); *m/z* 242 (17%, M^+), 213 (40%), 172 (100%, $M - C_3H_2O_2$), and 104 (93%).

(4RS,6SR)-6-*Phenyl*-6-*trifluoromethyl*-5,6-*dihydro*-4H-*pyran*-4-*ol* (**35**).—The enone (**33**), (370 mg, 1.53 mmol) was stirred in methanol (10 ml) with $CeCl_3 \cdot 7H_2O$ (633 mg, 1.68 mmol) for 10 min at room temperature. The mixture was then cooled to −78 °C and sodium borohydride (64 mg, 1.7 mmol) in ethanol (4 ml) added dropwise. The resulting mixture was stirred at −78 °C for 2 h, allowed to warm to room temperature, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc–hexane, 1:2) to yield a mixture of 4-hydroxypyrans (**34**):(**35**), (1:9), (346 mg, 93%) as a solid. Recrystallisation from hexane gave the title compound as needles, m.p. 77–79 °C (Found: C, 59.8; H, 4.60. $C_{12}H_{11}F_3O_2$ requires C, 59.0, H, 4.55%); R_F(EtOAc–hexane, 1:2) 0.24; ν_{max}(Nujol) 3 250 (OH), 1 635 (C=C) and 1 200 cm^{-1} (CF); δ_H($CDCl_3$) 7.52–7.37 (5 H, m, Ph), 6.45 (1 H, dd, *J* 1.6 and 6.3 Hz, 2-H), 4.80 (1 H, m, 3-H), 3.96 (1 H, m, 4-H), 2.93 (1 H, ddd, *J* 1.7, 6.2 and 13.1 Hz, 5A-H), 2.21 (1 H, dd, *J* 10.2 and 13.1 Hz, 5B-H) and 1.49 (1 H, br s, OH) (Found: M^+, 244.0698. $C_{12}H_{11}F_3O_2$ requires 244.0711); *m/z* 244 (3%, M^+), 243 (4%, M − H), 224 (48%, M − HF), 172 (100%), 103 (95%), and 77 (38%, Ph). Concentration of the mother liquor from the recrystallisation gives a 1:1 mixture of the (4*RS*,6*SR*)- and (4*SR*,-6*SR*)-isomers. ^1H NMR of the minor isomer (**34**): δ_H($CDCl_3$) 7.56–7.36 (5 H, m, Ph), 6.59 (1 H, d, *J* 6.2 Hz, 2-H), 5.09 (1 H, t, *J* 6 Hz, 3-H), 4.15 (1 H, m, 4-H), 2.88 (1 H, d, *J* 14.9 Hz, 5A-H), 2.48 (1 H, dd, *J* 5.2 and 14.9 Hz, 5B-H), and 2.05 (1 H, br s, OH).

(3RS,4RS,6SR)-3-*Bromo*-6-*phenyl*-6-(*trifluoromethyl*)*tetrahydropyran*-2,4-*diol* (**37**).—To the dihydropyran-4-ol (**35**), (35 mg, 0.143 mmol) in tetrahydrofuran (2 ml) at 0 °C was added water (0.4 ml) and *N*-bromosuccinimide (140 mg, 5 equiv.). The mixture was warmed to room temperature and stirred for 60 min. It was then diluted with Et_2O (20 ml), extracted with saturated aqueous sodium hydrogen carbonate (2 × 20 ml), dried (Na_2SO_4), and concentrated. Flash column chromatography of the residue on silica gel (EtOAc–hexane, 2:3) gave the title compound as a solid (30 mg, 62%). Recrystallisation from CH_2Cl_2–hexane gave prisms, m.p. 136–138 °C (Found: C, 42.1; H, 3.45. $C_{12}H_{12}BrF_3O_3$ requires C, 42.3, H, 3.45%); R_F(EtOAc–hexane, 1:1) 0.36; ν_{max}(Nujol) 3 450 (OH) and 1 170 cm^{-1} (CF); δ_H($CDCl_3$) 7.63–7.36 (5 H, m, Ph), 4.58 (1 H, d, *J* 1.5 Hz, 2-H), 4.47 (1 H, m, 3-H), 3.68 (1 H, dm, *J* 11.6 Hz, signal sharpened on D_2O shake, 4-H), 2.75 (2 H, br s, signal removed on D_2O shake, 2 × OH), 2.60 (1 H, dd, *J* 4.0 and 13.2 Hz, 5A-H), and 2.40 (1 H, dd, *J* 11.6 and 13.2 Hz, 5B-H); *m/z* 271 (4%,

$M - CF_3$), 197 (15%), 172 (55%), 122 (25%, C_2H_3BrO), 105 (100%, PhCO) and 77 (35%, Ph); ^1H NMR showed that the (3*SR*,4*RS*,6*SR*) diastereoisomer was also present; $\delta_H(CDCl_3)$ 6.59 (1 H, d, *J* 7.1 Hz, signal removed on D_2O shake, 2-OH), 4.84 (1 H, dd, *J* 7.1 and 11.1 Hz, 7.1 coupling removed on D_2O shake, 2-H), 3.71 (1 H, t, *J* 11.0 Hz, 3-H), 3.63 [1 H, br m, collapses to dt on D_2O shake, *J* 4.0 (d) and 11.0 Hz, 4-H], 3.05 (1 H, dd, *J* 4.0 and 13.9 Hz, 5A-H), 2.14 (1 H, dd, *J* 11.1 and 13.9 Hz, 5B-H), and 1.64 (1 H, br s, 4-OH). This compound was not isolated.

(2SR,3RS,4RS,6SR)-2,4-*Diacetoxy*-3-*bromo*-6-*phenyl*-6-(*trifluoromethyl*)*tetrahydropyran*.—To a stirred mixture of the bromo diol (**37**), (78 mg, 0.23 mmol) in pyridine (0.5 ml), under argon at room temperature, was added acetic anhydride (0.11 ml). Stirring was continued for 1 h after which the pyridine and acetic anhydride were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:3) to yield the *diacetate* as a solid (90 mg, 92%). Recrystallisation from CH_2Cl_2–hexane gave needles, m.p. 127–130 °C, R_F(EtOAc–hexane, 1:2) 0.61; ν_{max}(Nujol) 1 750 (C=O) and 1 220 cm^{-1} (CF); $\delta_H(CDCl_3)$ 7.69–7.42 (5 H, m, Ph), 5.60 (1 H, d, *J* 1.6 Hz, 2-H), 4.76 (1 H, m, H(4), 4.40 (1 H, br s, 3-H), 2.71 (2 H, m, 2 × 5-H), 2.21 and 2.14 (2 × 3 H, AcOC(H) 2 and 4) (Found: M^+, 424.0169. $C_{16}H_{16}BrF_3O_5$ requires *M*, 424.0133); *m*/*z* 424 (5%, M^+), 243 (35%), 197 (100%), 172 (45%), and 105 (63%).

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