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Efficient synthesis of an α-trifluoromethyl-α-tosyloxymethyl epoxide enabling stepwise double functionalisation to afford CF_3-substituted tertiary alcohols

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ABSTRACT

The efficient synthesis of an α-trifluoromethyl-α-tosyloxymethyl epoxide is reported. This highly versatile building block may be reacted sequentially with two different nucleophiles to furnish α-trifluoromethyl tertiary alcohols. Furthermore, the two enantiomers of this key intermediate have been separated using chiral HPLC and the stereochemistry shown to be conserved during subsequent chemical manipulations. Finally, an enzyme-driven desymmetrisation approach has been successfully employed to confer chirality on an intermediate in the sequence.

It has long been known that fluorinated ketones and, to a lesser extent fluorinated alcohols, can act as inhibitors of hydrolytic enzymes by mimicking the tetrahedral transition state of peptide bond hydrolysis.[1,2] Thus, due to the potential application of α-trifluoromethylated α-amino acids and their derivatives in the biochemical and pharmacological fields, there is widespread interest in the construction of stereogenic quaternary centres featuring trifluoromethyl groups under mild conditions.[3] For example, α-trifluoromethyl tertiary alcohols have featured prominantly in a new generation of glucocorticoid receptor (GR) agonists from several pharmaceutical companies.[4,5] The tertiary alcohol is believed to be involved in a critical H-bond interaction with the receptor. At least one of these agonists is being explored in development, with elegant work by Song et al. describing the formation of enantiomerically pure α-trifluoromethyl tertiary alcohols.[6] The recent explosion of interest[7] in GR agonists has prompted us to describe our work in this field.[5,8] This has been greatly enabled by a key 'doubly electrophilic' α-trifluoromethyl-α-tosyloxymethyl epoxide synthon **1** (Fig. 1) which, due to its versatility, has allowed entry into highly tractable non-steroidal GR agonists[8] such as **2** (Fig. 1) for rapid lead optimisation. The work described in this Letter may also prove of value in providing a different approach to enantiomeric derivatives featuring trifluoromethylated quaternary centres, ultimately allowing access to analogues related to α-trifluoromethylated α-amino acids.

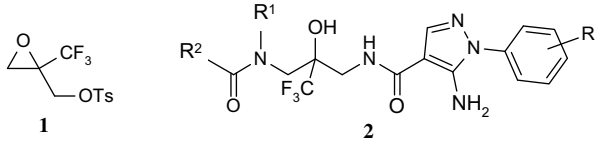

Figure 1. Structures of epoxytosylate **1** and non-steroidal GR agonist **2**.

The preparation of optically active polyfluoroalkyl epoxide synthons was reported in the literature[9] some years ago. Whilst this strategy appeared attractive and was considered for our work, it was ultimately discounted due to the necessity for the use of diazomethane in the epoxide formation and the inherent safety issues this raises for a large-scale synthesis.

Several strategies currently exist in the literature for the synthesis of α-trifluoromethyl alcohols. It is more than twenty years since Ruppert et al. disclosed the first synthesis of trimethyl(trifluoromethyl)silane.[10] Since then this has become widely established as a standard means of introducing a trifluoromethyl group into molecules via addition to carbonyl compounds (e.g.,

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ketones for the preparation of α-trifluoromethyl tertiary alcohols) In another approach used in recent years, trifluoromethyl epoxides have been employed[6,11] as intermediates permitting more diversity in the structure of the tertiary alcohol products.

A different approach involves generation of an α-trifluoromethyl oxiranyl anion by the deprotonation of commercially available 2-(trifluoromethyl)oxirane using *n*-butyllithium.[12] This has been shown to react with electrophiles to give α-substituted-α-trifluoromethyl epoxides which can further react with nucleophiles to furnish tertiary alcohols, hence offering a further level of diversification relative to other methods. One practical limitation of this methodology is that very cold temperatures (ca. −100 °C) are required to avoid possible side reactions of the anion.

We sought a complimentary approach to these methods whereby a suitably functionalised trifluoromethyl epoxide might lend itself to sequential reactions with two structurally diverse nucleophiles. A prerequisite was that the intermediate would be a stable robust entity which could be used under a range of reaction conditions. As such, an efficient five-step synthesis of the 2-trifluoromethyl-2-tosyloxymethyl epoxide **1** was developed (Scheme 1).

Two options were considered to synthesise the ketone intermediate **4**. Attempts to introduce alcohol protecting groups by *O*-alkylating 1,3-dihydroxyacetone met with limited success, so 1,3-dibenzyloxy-2-propanol **3** was oxidised using Ley's method[13] in 83% yield. The oxidation could also be effected using sulfur trioxide pyridine complex in DMSO, or 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) along with sodium hypochlorite (13% w/v). Reaction of **4** with trimethyl(trifluoromethyl)silane employing cesium fluoride or cesium carbonate/cat. tetrabutylammonium fluoride (TBAF) in DMF gave moderate yields (25–38%) of the tertiary alcohol **5**. However, changing the solvent to THF and employing TBAF stoichiometrically[14] increased the yield markedly to over 80%. The benzyl groups were exchanged for *p*-toluenesulfonyl groups by firstly subjecting **5** to hydrogenation conditions employing 5% palladium on carbon in ethanol. The resulting triol **6** was treated with *p*-toluenesulfonyl chloride in pyridine to give the tertiary alcohol **7**. Despite using 3 equiv of the sulfonyl chloride, only the primary alcohols were functionalised. Due to the acidic nature of the alcohol, mild basic conditions effected cyclisation to afford the epoxide **1**. On a small scale, polymer-supported carbonate[15] was used for convenience but on a larger scale this became cost prohibitive, so potassium carbonate was employed.

This route is robust and has been scaled to produce kilogram quantities of **1** without issue; on this scale, the TEMPO oxidation and potassium carbonate epoxidation reaction conditions were used.

The epoxytosylate **1** is essentially doubly electrophilic and whilst both electrophilic centres are reasonably reactive, one electrophile is appreciably more reactive than the other. For example (Scheme 2), on treatment of **1** with a slight excess of benzylamine in dioxane, the epoxide is smoothly opened in preference to displacement of the tosylate. The tosylate can then be displaced with a different nucleophile such as hydroxide to give the diol **9** in 57–64% overall yield. This is a robust sequence and has been carried out on >80 g scale.

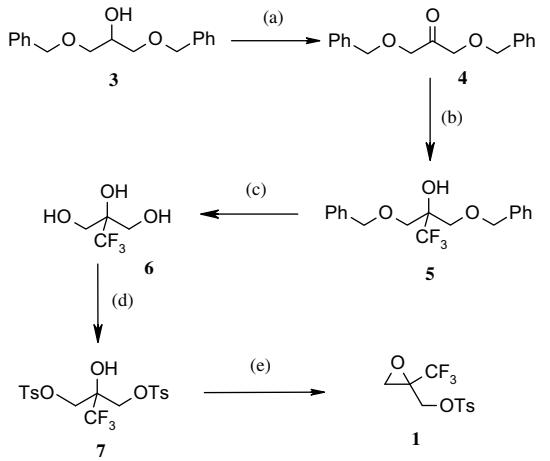
Alternatively, the epoxytosylate **1** can be treated first with the anion of ethylbenzamide generated with sodium hydride in DMF (Scheme 2). After 18 h, benzylamine may be added to react with the second electrophile to give **11** in 32% overall yield. This example illustrates the one-pot reaction of the epoxytosylate with two different nucleophiles.

In a third example, treatment of epoxytosylate **1** with dibenzylamine in the presence of excess lithium perchlorate in ether (Scheme 2) leads to isolation of the epoxide **12**. It is unclear whether this occurs by preferential displacement of the tosylate, or epoxide opening followed by ring closure of the resulting hydroxy tosylate. Epoxide **12** can then be reacted with ethylamine to provide the diamine **13** in reasonable yield.

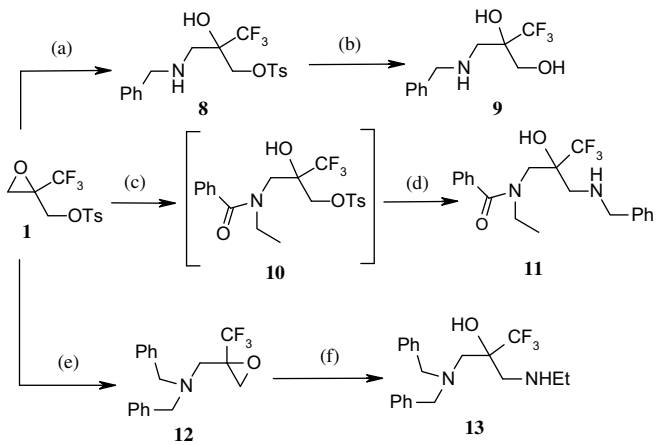
Thus, the reactivity of the epoxytosylate **1** may be manipulated by the judicious selection of nucleophiles (and reagents) to provide the product of choice.

Having demonstrated an efficient and robust racemic route, we then began to address the tractability of a chiral synthesis. Two questions can be raised. Firstly, can enantiomerically pure epoxytosylate be reacted sequentially with two different nucleophiles without racemisation? Secondly, can enantiomerically enriched or pure epoxytosylate **1** be prepared from the symmetrical triol **6** (or other precursor) using a desymmetrisation strategy? The latter would have the major theoretical benefit that 100% of the triol **6** could be converted into the single desired enantiomer. This stands in contrast to a resolution of the epoxytosylate (or some chiral precursor or derivative) where theoretically only 50% of the desired enantiomer can be obtained from the racemate.

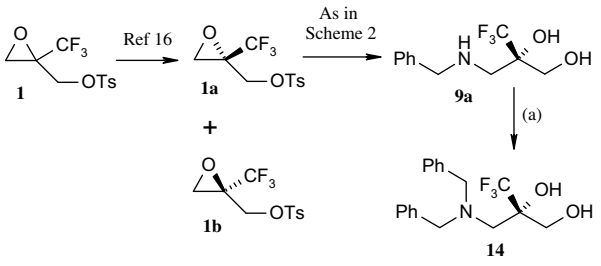
To address the first question, the epoxytosylate **1** was separated by preparative chiral HPLC[16] into its two enantiomers **1a** and **1b** (Scheme 3). Epoxytosylate **1a** (of ca. 95% enantiomeric purity)



Scheme 1. Reagents and conditions: (a) TPAP, NMO, 4 Å molecular sieves, DCM, rt, 18 h (83%); (b) $TMSCF_3$, TBAF, THF, 0 °C → rt, 18 h (81%); (c) H_2, 5% Pd.C, EtOH, rt, 24 h (98%); (d) TsCl, pyridine, 0 °C → rt, 20 h (91%); (e) PS-carbonate, DCM, 0 °C → rt, 18 h (94%).



Scheme 2. Reagents and conditions: (a) $BnNH_2$ (1.05 equiv), dioxane, rt, 18 h; (b) 2 M NaOH, dioxane, reflux, 18 h (57–64% for 2 steps); (c) PhCONHEt, NaH, DMF then **1** (1 equiv), rt, 18 h; (d) $BnNH_2$ (1 equiv), rt, 24 h (32% for two steps); (e) Bn_2NH (1 equiv), $LiClO_4$ (10 equiv), Et_2O rt, 18 h (59%); (f) $EtNH_2$ (2 equiv), THF (62%).

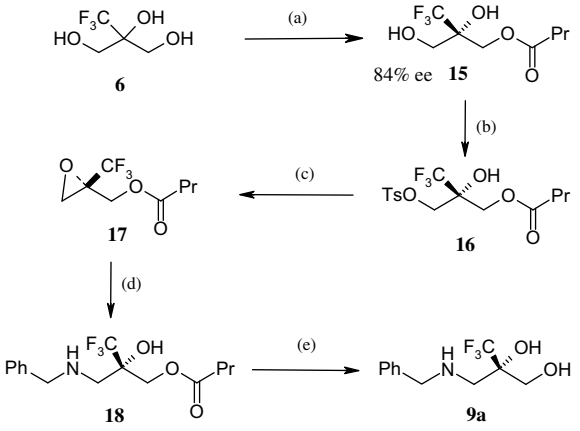


Scheme 3. Reagents and conditions: (a) PhCHO (1 equiv), $NaBH(OAc)_3$, AcOH, DCM, rt, 72 h (10%).

has been processed through to **9a** which is 95% enantiomerically pure by chiral HPLC when compared with **9**, demonstrating that the described sequence may be carried out without racemisation.[17] Compound **9a** was then reductively alkylated with benzaldehyde to give **14**, the measured optical rotation of which is the antipode of that quoted in the literature for the (*R*)-enantiomer[9] indicating the stereochemistry of **14** is therefore (*S*).

One problem with the preparative separation of the enantiomers by chiral HPLC was that only low loadings were possible. Thus, a desymmetrisation approach was of even greater interest. The chirality was introduced early in the synthesis by a lipase-catalysed desymmetrisation of the triol **6** (Scheme 4). A screen for triol acylation in neat vinyl butyrate using kits of commercially available lipases gave a number of hits.[18] Of these hits, the lipase from *Burkholderia cepacia* (AE012) was selected for further investigation as it produced the desired monobutyrate **15** with the best enantioselectivity (86% ee) and with little dibutyrate formation.[19,20]

In an unoptimised reaction using lipase Amano PS, the monobutyrate **15** was produced in 81% solution yield and 84% ee. Due to incomplete conversion, the unreacted triol **6** needed to be removed by column chromatography which resulted in significant loss of the monoester (42% isolated yield). In contrast, complete consumption of triol could be attained by passing a solution of triol **6** in vinyl butyrate and TBME through a plug flow reactor containing *Burkholderia cepacia* lipase immobilised on sepabeads EC-EP.[21] By allowing some conversion of monoester **15** to diester, even after the disappearance of triol **6**, an enantioenrichment of the monobutyrate **15** could be attained that resulted from further enzyme-catalysed acylation of the minor monobutyrate enantiomer to dibutyrate. In preliminary experiments using this continuous flow



Scheme 4. Reagents and conditions: (a) lipase vinyl butyrate (42%); (b) TsCl (1 equiv), pyridine (1 equiv), DCM (70–100%); (c) PS-carbonate, THF; (d) $BnNH_2$ (1 equiv) (80–100% for two steps); (e) 5 M HCl, EtOH (100%).

format, the monobutyrate **15** was furnished in 85% solution yield and 92% ee from a 10 g/L solution of triol **6** in vinyl butyrate/TBME (1:9). As the diester does not participate in the subsequent chemical step and can be removed readily at a later stage, the monoester/diester mixture resulting from the continuous reaction can be used without the need for purification steps.

A batch of desymmetrised butyrate **15** of 84% ee was converted selectively into the tosylate **16** in excellent yield (Scheme 4). The epoxy-butyrate **17** could then be prepared readily by using polymer-supported carbonate. This was smoothly reacted with benzylamine to give the aminoester **18** in excellent yield over two steps. Base hydrolysis of **18** caused *O*- to *N*-migration of the butyryl group. Although the resultant amide can be hydrolysed in acid to the diol **9a**, acid hydrolysis of the ester **18** gives the diol **9a** directly in quantitative yield in one step. Chiral HPLC analysis of **9a** showed it still to be enantiomerically enriched in the (*S*) enantiomer (ca. 83% ee) demonstrating that the route does not cause racemisation, and also assigning the absolute stereochemistry of the enzyme-mediated desymmetrisation. This sequence opened-up a route to enantiomeric analogues for lead optimisation (such as **2**) and potentially for large-scale preparation of final drug substances.

In summary, we have described the synthesis and reactivity of a versatile intermediate **1**. We have also demonstrated the preparation of enantiomerically pure **1** (and related analogues), and further shown that these can be used without racemisation.

1. Experimental for preparation of epoxytosylate 1

1.1. 1,3-Bis[(benzyl)oxy]-2-propanone 4

To a suspension of powdered 4 Å molecular sieves (30 g) in DCM (500 mL) was added 4-methylmorpholine *N*-oxide (21 g) and 1,3-dibenzyloxy-2-propanol (24.7 mL). The mixture was stirred vigorously under a nitrogen atmosphere for 1.5 h then treated with tetrapropylammonium perruthenate (1.75 g) (note: exotherm). Stirring was continued for 18 h then the mixture was filtered through a pad of Celite. The filtrate was evaporated in vacuo and the residue was purified by flash chromatography using a 0–25% ethyl acetate/cyclohexane gradient to obtain the title compound as a white solid (22.45 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31–7.40 (m, 10H); 4.59 (s, 4H); 4.26 (s, 4H).

1.2. 1,1,1-Trifluoro-3-[(benzyl)oxy]-2-{[(benzyl)oxy]methyl}-2-propanol 5

To a solution of **4** (21.94 g) in anhydrous THF (300 mL) under a nitrogen atmosphere was added trimethyl (trifluoromethyl)silane (16.8 mL). After cooling to 0–5 °C tetrabutylammonium fluoride (90 mL of a 1 M solution in THF) was added slowly maintaining the reaction temperature below 10 °C. The cooling bath was removed and stirring was continued for 18 h. The reaction mixture was partitioned between 1 M HCl (800 mL) and diethyl ether (300 mL). The layers were separated, and the aqueous phase was further extracted with diethyl ether (300 mL). The combined organic extracts were dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash chromatography using a 0–25% ethyl acetate/cyclohexane gradient to obtain the title compound as a pale yellow oil (22.37 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29–7.39 (m, 10H); 4.60 (s, 4H); 3.72 (s, 4H); 3.38 (s, 1H).

1.3. 2-(Trifluoromethyl)-1,2,3-propanetriol 6

A solution of **5** (21.87 g) in ethanol (400 mL) containing 5% palladium on carbon (2.2 g, wet, Degussa type E101 NO/W) was stirred under an atmosphere of hydrogen for 24 h. The reaction

mixture was filtered through a pad of Celite and the filtrate was evaporated in vacuo. The residue was evaporated twice from DCM to obtain the title compound as a white solid (10.1 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.65 (s, 1H); 4.89 (t, J = 6.0 Hz, 2H); 3.54 (d, J = 5.8 Hz, 4H).

1.4. 3,3,3-Trifluoro-2-hydroxy-2({[(4-methylphenyl)sulfonyl]oxy}methyl)propyl 4-methylbenzenesulfonate 7

A stirred solution of **6** (9.42 g) in pyridine (100 mL) under a nitrogen atmosphere was cooled to 0–5 °C. To this was added *p*-toluenesulfonyl chloride (33.67 g) to give an orange solution. The cooling bath was removed and stirring was continued for 20 h, then the reaction mixture was evaporated in vacuo. The residue was partitioned between 1 M HCl (700 mL) and ethyl acetate (300 mL). The layers were separated, and the aqueous phase was further extracted with ethyl acetate (300 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash chromatography using a 0–50% ethyl acetate/ cyclohexane gradient to obtain the title compound as a very pale yellow oil, which crystallised on standing (25.08 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.78 (d, J = 8.3 Hz, 4H); 7.38 (d, J = 8.3 Hz, 4H); 4.18 (s, 4H); 3.66 (s, 1H); 2.48 (s, 6H).

1.5. [2-(Trifluoromethyl)-2-oxiranyl]methyl 4-methylbenzenesulfonate 1

A stirred solution of **7** (27 g) in DCM (400 mL) under a nitrogen atmosphere was cooled to 0–5 °C. To this was added polymer-supported carbonate[15] (32.9 g). The cooling bath was removed and stirring was continued for 18 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo to obtain the title compound as a very pale yellow oil, which crystallised on standing (16.04 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, J = 8.3 Hz, 2H); 7.38 (d, J = 8.3 Hz, 2H); 4.26–4.45 (ab, J = 12.0 Hz, 2H); 3.14 (d, J = 4.8 Hz, 1H); 3.01 (dd, 1H); 2.47 (s, 3H).

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15. Carbonate on polymer support supplied by Fluka (capacity ~3.5 mmol/g).
16. Preparative separation of the enantiomers of **1**. Column Chiralpak AD, 2 inch × 20 cm eluting with heptane/ethanol 98:2 with a flow rate of 75 mL/min. **1 b** elutes at around 17 min and **1a** at around 21 min. Racemate loadings <200 mg are required to achieve acceptable separation of the enantiomers.
17. Analytical separation of the enantiomers of **9**. Column Chiralcel OD-H, 25 cm, eluting with 5% ethanol in heptane with a flow rate of 1 mL/min. The enantiomers appear at 8.61 and 9.98 min. The material processed to **9a** from **1a** is composed of 5% of the first eluting enantiomer and 95% of the second eluting enantiomer.
18. Using Alphamerix Screening Kits 1 and 2 (Mann Associates) hits were obtained from *C. rugosa* lipase (AE02), *Achromobacter* spp. lipase (AE04), *Alcaligenes* spp. lipase (AE05), *Burkholderia cepacia* lipase P1 (AE06), *Pseudomonas stutzeri* lipase (AE07), *Burkholderia cepacia* lipase P2 (AE012) and *Mucor javanicus* lipase (AE013).
19. The screen was monitored by TLC and product ee determined by ^{31}P NMR after derivatisation of the monobutyrate, present in crude reaction mixtures, as the mono Mosher's ester. Previous Mosher's ester derivatisation of authentic racemic monobutyrate and triol had shown that their respective ^{31}P NMR signals do not overlap. The authentic diester was inert to Mosher's ester derivatisation. All enzyme hits preferentially produced the same enantiomer.
20. Parallel screening for diacetate or dibutyrate hydrolysis activity also gave a number of hits, all of which resulted in complete hydrolysis to the triol under a variety of conditions.
21. Sepabeads EC-EP is a porous epoxy-resin support produced by Resindion–Mitzubishi.