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A concise asymmetric route for the synthesis of a novel class of glucocorticoid mimetics containing a trifluoromethyl-substituted alcohol

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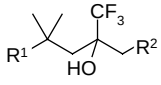
Abstract—An asymmetric route was developed for the synthesis of a class of novel glucocorticoid receptor ligand derivatives **1**. The key step of this synthesis involves a diastereoselective addition of chiral sulfoxide anion to a trifluoromethyl ketone precursor. The resulting diastereomers are readily separable and can be converted to the corresponding chiral epoxide and chiral alkyne intermediates (**2** and **3**). This sequence of reactions is suitable for large-scale preparation of these chiral intermediates and derivatives of **1**. The absolute stereochemistry of the biologically active enantiomer of these GR ligands has also been determined.

Glucocorticoids (GCs) and their derivatives such as dexamethasone and prednisolone[1] belong to a class of steroidal ligands that targets the glucocorticoid receptor (GR). These agents, which modulate GR function, have found wide use in the treatment of various inflammatory, autoimmune, and allergic disorders.[2] Recently, we have disclosed a novel series of GR ligands that belongs to the trifluoromethyl alcohol class typified by **1**.[3] To access this class we have employed epoxide **2** and alkyne **3** as key intermediates.[3] Described herein is an asymmetric route to these two synthetic intermediates and its application to the determination of the absolute stereochemistry of the biologically active enantiomer of this class of GC mimetics.



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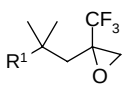

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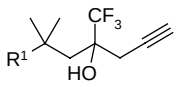

3

This chiral process can be illustrated by the synthesis of chiral epoxide **7a** and its enantiomer **7b** as outlined in Scheme 1. The key step involves a diastereoselective addition of chiral sulfoxide anion to a trifluoromethyl ketone to form the corresponding chiral β-hydroxy-β-trifluoromethyl-sulfoxide adducts. In the literature, there are limited examples of such diastereoselective addition to fluorinated ketones.[4] Thus, reaction of trifluoromethyl ketone **4** with the lithium anion of (*R*)-(+)-methyl *p*-tolylsulfoxide in THF at −78 °C afforded a mixture of the corresponding chiral sulfoxides **5a** and **b** (dr = 2.1:1). These diastereomers were easily separated by column chromatography with the faster eluting product being the major diastereomer **5a**. The optical purity was determined to be >99% de for both isomers by HPLC analyses.[5] X-ray crystallographic analysis allowed assignment of **5a** as the (*S*,*R*)-isomer (Fig. 1).[6]

Each of the separated diastereomers was then reduced using sodium iodide and trifluoroacetic anhydride in acetone at −40 °C to afford the corresponding thiol ethers **6a** and **b** in quantitative yields.[7] Treatment of the thiol ether enantiomers with trimethyloxonium tetrafluoroborate in CH_2Cl_2 followed by addition of aqueous potassium carbonate solution provided the desired chiral epoxides **7a** and **b** in optically pure form.[8] This sequence of reactions was applied to the synthesis of several other chiral epoxides (*R*)-**2** and the results are summarized in Table 1. In all cases, similar yields

Keywords: Glucocorticoid receptor; Steroid mimetics; Asymmetric synthesis.
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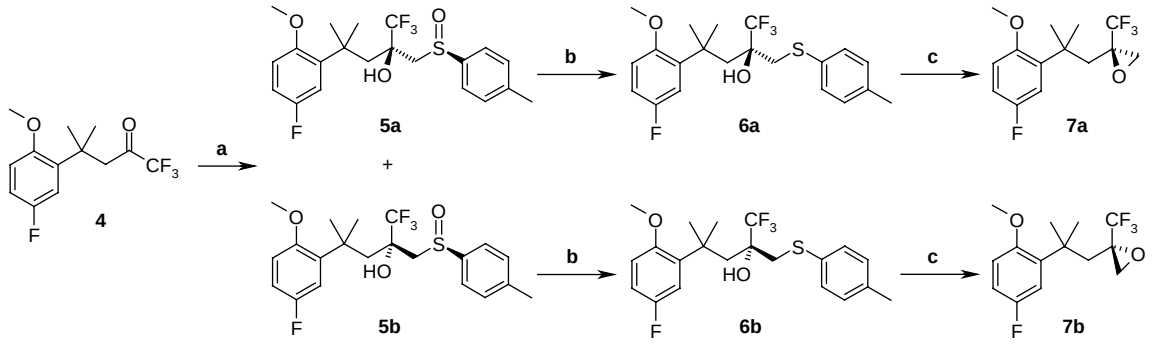


Scheme 1. Reagents and conditions: (a) lithium diisopropylamide, (*R*)-(+)-methyl *p*-tolylsulfoxide, THF, −78 °C, 91% (**5a**:**5b** = 2.1:1); (b) NaI, trifluoroacetic anhydride, acetone, −40 °C, >99%; (c) trimethyloxonium tetrafluoroborate, CH_2Cl_2, rt, then aq K_2CO_3, rt, 95%.

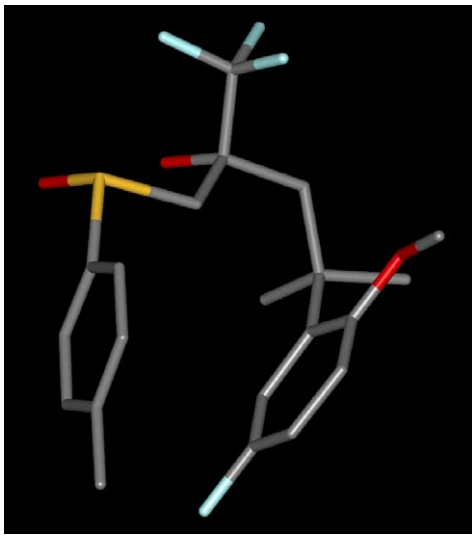
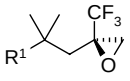
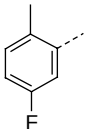
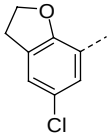
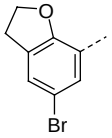


Figure 1. X-ray crystal structure of **5a**.

Table 1. Synthesis of chiral epoxides



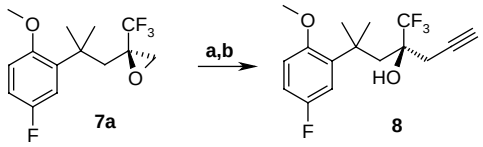
***(R)*-2**

Entry	R^1	Sulfoxide % yield (dr)	Thiol ether % yield	Epoxide % yield
1		85 (2.1:1)	>99	78
2		80 (2.2:1)	99	95
3		65 (2.1:1)	99	95

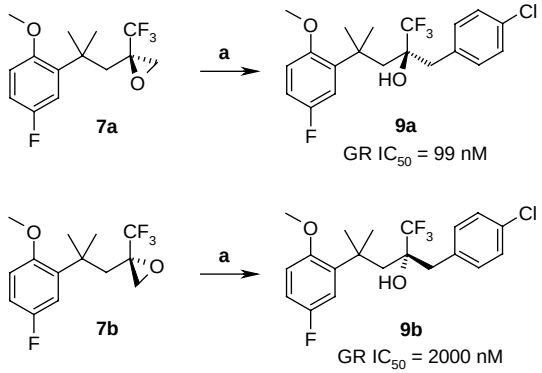
and selectivity were observed. The enantiomeric epoxides (*S*)-**2**, if desired, can be specifically targeted using (*S*)-(−)-methyl *p*-tolylsulfoxide.

These chiral epoxides can be ring-opened by various carbon, oxygen, nitrogen, and sulfur nucleophiles to afford derivatives of formula **1** or their precursors.[3] As an example, treatment of **7a** with lithium trimethylsilylacetylide in DMSO followed by desilylation afforded chiral alkyne intermediate **8** (Scheme 2). The alkyne moiety in **8** is a versatile synthetic handle and can be converted to a variety of heteroaryl groups such as indoles and azaindoles.[3]

In order to determine the absolute stereochemistry of the more biologically active enantiomer of this class of GR ligands, compounds **9a** and **b** were separately prepared from the corresponding chiral epoxides **7a** and **b** (Scheme 3) and tested in a glucocorticoid receptor



Scheme 2. Reagents and conditions: (a) lithium trimethylsilylacetylide, DMSO, rt; (b) tetrabutylammonium fluoride, THF, rt, 60% (two steps).



Scheme 3. Reagents and conditions: (a) *p*-chlorophenylmagnesium bromide, CuI, ether, rt, 28–30%.

binding assay.[9] Compound **9a** was shown to be the more potent enantiomer in this binding assay with a GR binding IC_{50} of 99 nM. In contrast, compound **9b** was less active in this assay (IC_{50} = 2000 nM).[10] It should be noted that the desired enantiomer **9a** is derived from the major sulfoxide diastereomer **5a**.

In summary, a concise asymmetric route was developed for the synthesis of a class of glucocorticoid receptor ligand derivatives **1**. The key step of this synthesis is a diastereoselective addition of chiral sulfoxide anion to a trifluoromethyl ketone precursor. The resulting diastereomers are readily separable and can be converted to the corresponding chiral epoxide and chiral alkyne intermediates. This sequence of reactions is suitable for large-scale preparation of these chiral intermediates and derivatives of formula **1**. The absolute stereochemistry of the more biologically active enantiomer of these GR ligands has also been determined.

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3. (a) Bekkali, Y.; Cardozo, M. G.; Kirrane, T. M.; Kuzmich, D.; Proudfoot, J. R.; Takahashi, H.; Thomson, D.; Wang, J.; Zindell, R.; Harcken, C. H. J. J.; Razavi, H. PCT Int. Appl. WO 03/082787, 2003. (b) Bekkali, Y.; Betageri, R.; Gilmore, T. A.; Cardozo, M. G.; Kirrane, T. M.; Kuzmich, D.; Proudfoot, J. R.; Takahashi, H.; Thomson, D.; Wang, J.; Zindell, R.; Harcken, C. H. J. J.; Riether, D. PCT Int. Appl. WO 03/082280, 2003. (c) Kuzmich, D.; Lee, T. W.; Proudfoot, J. R.; Regan, J. R.; Thomson, D. S.; Hammach, A.; Ralph, M. S.; Zindell, R. PCT Int. Appl. WO 04/063163, 2004. (d) Lehmann, M.; Schöllköpf, K.; Strehlke, P.; Heinrich, N.; Fritzemeier, K.-H.; Muhn, H.-P.; Krattenmacher, R. PCT Int. Appl. WO 98/54159, 1998.
4. (a) Bravo, P.; Bruché, L.; Farina, A.; Gerus, I. I.; Kolytcheva, M. T.; Kukhar, V. P.; Meille, S. V.; Viani, F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1667; (b) Bravo, P.; Frigerio, M.; Resnati, G. *J. Org. Chem.* **1990**, *55*, 4216; (c) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227.
5. HPLC analyses were done using a Supelco SUPELCOSIL™ ABZ + Plus column (4.6 mm × 10 cm) and a gradient elution from 5% acetonitrile/95%water (+0.05% TFA) to 100% acetonitrile (+0.05% TFA).
6. CCDC 286063 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
7. Arnone, A.; Biagini, G.; Cardillo, R.; Resnati, G.; Bégué, J.-P.; Bonnet-Delpon, D.; Kornilov, A. *Tetrahedron Lett.* **1996**, *37*, 3903, These authors described an enzymatic reduction method for the synthesis of chiral β-hydroxy-β-trifluoromethyl thiol ether and its subsequent conversion to a chiral trifluoromethyl-substituted epoxide.
8. Representative procedures: synthesis of (*R*)-2-[2-(5-fluoro-2-methoxyphenyl)-2-methylpropyl]-2-trifluoromethyloxirane.
   (a) To a suspension of (*R*)-(+)-methyl *p*-tolylsulfoxide (28.2 g, 183 mmol) in 200 mL of anhydrous THF at −78 °C was added lithium diisopropylamide (LDA) mono(tetrahydrofuran) (1.5 M solution in cyclohexane, 122 mL, 183 mmol) for over 30 min. The resulting clear yellow solution was stirred for 15 min. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one **4** (46.3 g, 166 mmol) dissolved in 125 mL THF was then added via cannula over 30 min. After 1.5 h at −78 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with saturated aqueous sodium bicarbonate ($NaHCO_3$) solution, washed with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography with silica gel (eluted with 10–30% EtOAc/hexanes) afforded sequentially (*S*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-((*R*)-toluene-4-sulfinylmethyl)pentan-2-ol **5a** (44.2 g, 62%) and (*R*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-((*R*)-toluene-4-sulfinylmethyl)pentan-2-ol **5b** (20.6 g, 29%). The diastereomeric excess was determined to be >99% for both isomers (HPLC peak area).[5]
   (b) To a suspension of (*S*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-((*R*)-toluene-4-sulfinylmethyl)pentan-2-ol **5a** (44.2 g, 102 mmol) and sodium iodide (46.0 g, 307 mmol) in 600 mL of anhydrous acetone at −40 °C was added a solution of trifluoroacetic acid anhydride (72.2 mL, 511 mmol) in 200 mL of anhydrous acetone via an addition funnel dropwise over 30 min. A greenish brown mixture was formed instantaneously. After 15 min, the reaction mixture was quenched with saturated aqueous sodium sulfite (Na_2SO_3) solution, and neutralized with saturated aqueous sodium carbonate (Na_2CO_3) solution. The brown color disappeared and the crude product was concentrated to remove most of the acetone solvent. The resulting material was diluted with water and extracted with ether. The combined organic phases were washed with brine, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated in vacuo to afford (*S*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-*p*-tolylsulfanylmethylpentan-2-ol **6a** as an orange oil (42.7 g, >99%).
   (c) To a solution of (*S*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-*p*-tolylsulfanylmethylpentan-2-ol **6a** (42.7 g, 102 mmol) in 250 mL of anhydrous dichloromethane was added trimethyloxonium tetrafluoroborate (22.7 g, 153 mmol). The resulting suspension was stirred at room temperature for 4.5 h. A solution of potassium carbonate (42.4 g, 307 mmol) in 250 mL of water was then added. After 16 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography with silica gel (eluted with 0–2% EtOAc/hexanes) afforded the title compound **7a** as a pale yellow oil (28.3 g, 95%).
9. Fluorescence polarization competitive binding assays were performed to quantitate the ability of test compounds to displace ligands from GR in solution. Binding reactions were assembled in 96-well microplates and consisted of Baculovirus lysate containing GR, 5 nM tetramethyl–rhodamine conjugates of dexamethasone, and test compound dilutions in an assay buffer containing 10 mM TES, 50 mM KCl, 20 mM sodium molybdate, 1.5 mM EDTA, 0.04% w/v CHAPS, 10% v/v glycerol, and 1 mM DTT, pH = 7.4. IC_{50} values reported are means from at least two separate experiments each consisting of duplicate 11-point concentration-effect curves. The authors would like to acknowledge Dr. Richard M. Nelson and his group (Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals Inc.) for testing **9a** and **b** in this assay.

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