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Development of a Preparative-Scale Asymmetric Synthesis of (*R*)-*p*-Tolyl Methyl Sulfoxide for Use in a One-Pot Synthesis of a Drug Intermediate Containing a Trifluoromethyl-Substituted Alcohol Functionality

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Abstract:

A one-pot process for the synthesis of (*S*)-1,1,1-trifluoro-4-(5-fluoro-2-methoxy-phenyl)-4-methyl-2-((*R*)-toluene-4-sulfinyl-methyl)pentan-2-ol (3) is described, which was a key intermediate for the preparation of a class of novel glucocorticoid receptor ligands. The chemistry features the preparative-scale synthesis of (*R*)-*p*-tolyl methyl sulfoxide [(*R*)-*p*TMSO] from (2*R*,4*S*,5*R*)-4-methyl-5-phenyl-3-(tolene-4-sulfonyl)oxathiazolidine-2-oxide (5) and the synthesis of 3 from 5 without isolation of (*R*)-*p*TMSO during the process.

Introduction

Recently, our discovery group disclosed a series of glucocorticoid receptor ligands of a general structure of (*S*)-**1**, which may be useful in the treatment of various inflammatory, autoimmune, and allergic disorders (Figure 1).[1] This class of compounds contains a CF_3-substituted stereogenic quaternary carbon, and very few methods have been reported for the asymmetric synthesis of this type of structure.[2a] Our discovery group has reported that the nucleophilic ring-opening of chiral epoxide **4** provided a quick access to compound **1**.[1] Gram quantities of **4** were prepared from diastereomerically pure β-hydroxy-β-trifluoromethyl sulfoxide adduct **3** (Scheme 1).[2b] The chiral alcohol center in key intermediate **3** was installed by diastereoselective addition of the lithium anion of (*R*)-*p*-tolyl methyl sulfoxide [(*R*)-*p*TMSO] to trifluoromethyl ketone **2**.

In support of toxicological studies and other drug development activities, a large amount of key intermediate **3** was needed for the synthesis of **4**. In this paper, we describe a preparative-scale synthesis of the key reagent [(*R*)-*p*TMSO] as well as a one-pot process to prepare **3** starting with norephedrine-derived oxathiazolidine-2-oxide **5** without the need to use (*R*)-*p*TMSO as an isolated intermediate during the process.

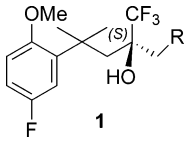

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Figure 1.

Results and Discussion

Preparation of **3** requires enantiomerically pure (*R*)-*p*TMSO. In the past two decades, chiral sulfoxides have been widely used as efficient chiral auxiliaries in the synthesis of enantiopure and biologically active molecules.[3−4] Among different chiral sulfoxides, *p*TMSO is one of the most widely employed to incorporate chirality into organic molecules.[5−7] However, the lack of an efficient method for the preparation of *p*TMSO has limited its application on industrial scales. Recently, Senanayake et al. reported a versatile chiral building block **5**, from which a variety of sulfoxides could be prepared in excellent stereoselectivity and yield by consecutive Grignard additions (Scheme 2).[8] We were interested in extending the scope of this chemistry to the production of *p*TMSO on hundred-gram scales.

The synthesis began by preparation of oxathiazolidine-2-oxide **5** from (1*R*,2*S*)-*N*-tosyl norephedrine (TNE) that is commercially available in multikilogram quantities.[8] Addition of *p*-tolyl magnesium bromide to a THF solution of **5** generated the desired intermediate **6** via selective cleavage of the more reactive S−N bond. Initially, the reaction was quenched at this stage with NH_4Cl aqueous solution, and intermediate **7** was isolated and used for synthesis of a variety of *p*-tolyl-containing chiral sulfoxides. However, slight epimerization at the sulfur center occurred when this protocol was used. To avoid this problem and to develop a more practical procedure, a one-pot process was investigated.

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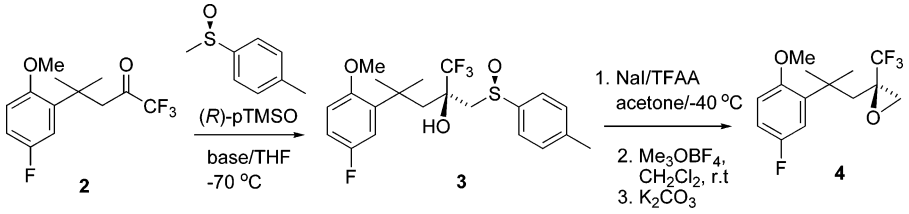
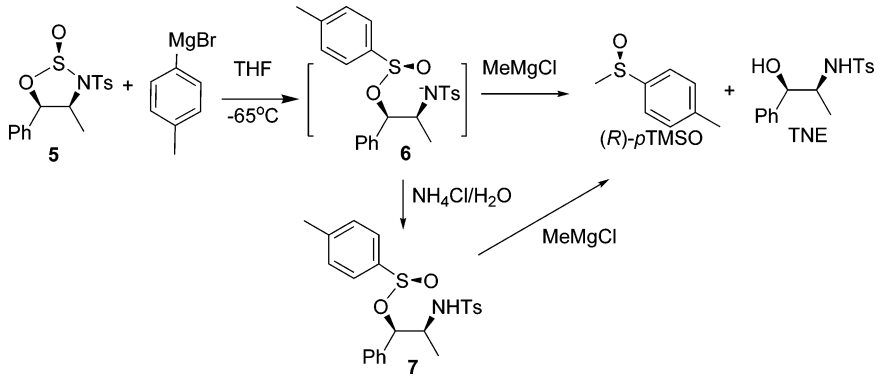
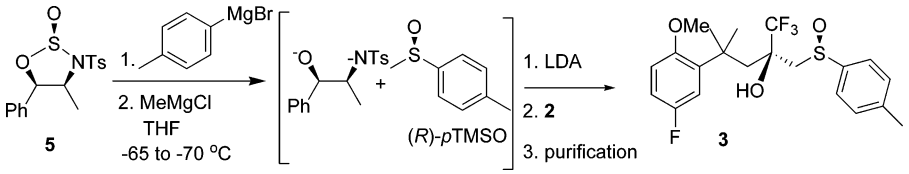
Scheme 1. **Asymmetric synthesis of epoxide 4 via (*R*)-*p*TMSO anion addition to 2**



Scheme 2. **Asymmetric synthesis of enantiomerically pure (*R*)-*p*TMSO**



Scheme 3. **One-pot process for the synthesis of 3**



It was observed that the addition rate of *p*-tolyl magnesium bromide was crucial for achieving optimum yields. Fast addition gave a low yield of the desired product due to the formation of undesired di-*p*-tolyl sulfoxide. Poor yield was also seen when the reaction was carried out at higher temperatures, with formation of other unknown impurities. An excellent yield was obtained when the reaction was performed at −65 to −70 °C with *p*-tolyl magnesium bromide being added over 2−3 h. Subsequently, MeMgCl was introduced into the reaction mixture over 30 min, and the reaction mixture was stirred for 30−60 min and then was warmed to 0 to −10 °C to complete the reaction. Standard workup afforded a mixture of the desired chiral sulfoxide and the cleaved chiral auxiliary (TNE).

Attempts to isolate (*R*)-*p*TMSO from the product mixture via crystallization were not successful. However, thanks to the large polarity difference between TNE and the target chiral sulfoxide product, (*R*)-*p*TMSO could be readily isolated by chromatographic purification on silica with a gradient elution of ethyl acetate/hexanes (from 30:70 to 100:0). Good separation was obtained when a mass ratio of 1:6 of crude product to silica was used. This one-pot protocol was very volume efficient and could be performed at a concentration of 1.2−1.5 M of **5** in THF up to 1-kg scale to give (*R*)-*p*TMSO in greater than 75% isolated yield and >99% ee.[9]

(*R*)-*p*TMSO was then treated with LDA at −70 °C in THF followed by the addition of ketone **2** to furnish the desired adducts in a diastereomeric ratio of 2:1. The two diastereomers were separated by column chromatography on silica to give **3** in 59% isolated yield and 99% de and the undesired isomer in approximately 32% yield.

Although the above two-stage route could be used for preparation of **3** in sufficient amount, this process suffers from the need to use isolated (*R*)-*p*TMSO that was prepared from **5** via a tedious process. To overcome this limitation and develop a more efficient process, we envisioned a one-pot approach from **5** to **3** as shown in Scheme 3. After Grignard additions, a mixture of (*R*)-*p*TMSO and doubly deprotonated TNE was obtained. It was postulated that, without isolating the chiral sulfoxide, this crude product mixture could be used directly for reaction with trifluoromethyl ketone **2**.

Thus, the reaction for the preparation of (*R*)-*p*TMSO was performed according to the same protocol described above. At the completion of the reaction, the reaction mixture was cooled to −65 to −70 °C, and one equivalent of LDA was added over 15 min. After 30 min, ketone **2**, dissolved in THF, was added dropwise, and the resulting mixture was stirred for another 30 min. HPLC analysis showed that the reaction was complete and afforded the desired products in the same 2:1 diastereomeric ratio.

Attempts to directly isolate product **3** from the crude product mixture using crystallization were not successful. TLC analysis showed that TNE was much more polar than alcohol **3** and that they could be easily separated by chromatography.[10] Thus, the crude product mixture was first

(9) See the Experimental Section for the chiral HPLC method.

filtered through a silica pad to remove the auxiliary to afford alcohol **3** with an improved diastereomeric ratio of 4:1.[11] To further enrich the diastereomeric purity, recrystallization conditions were investigated for **3**. A combination of *n*-propanol/EtOAc was identified as the optimal solvent system, and compound **3** was obtained in satisfactory overall yield (48%) with >99% de after one crystallization.

Conclusion

In conclusion, a scaleable, one-pot process was developed for the preparation of **3** from diastereomerically pure oxathiazolidine-2-oxide, **5**. The overall process throughput was greatly improved by obviating the need to use (*R*)-*p*TMSO as an isolated intermediate.

Experimental Section

General Procedures. All reagents were commercially obtained and used as received unless otherwise noted. All reactions were performed under an atmosphere of dry nitrogen. Moisture-sensitive reactions were carried out in anhydrous solvent either purchased or pretreated with molecular sieves overnight. Purification of products was performed by flash chromatography on silica gel 60. TLC was performed on Merck 60F-254 glass plates. HPLC analysis was performed on an Agilent 1100 instrument. NMR spectra were measured on a Bruker AM-400 MHz NMR spectrometer.

Synthesis of *p*-Tolyl Methyl Sulfoxide [(*R*)-*p*TMSO]. To a solution of **5** (1.0 kg, 2.84 mol) in anhydrous THF (6−8 L) at −65 to −70 °C was added *p*-tolyl magnesium bromide (2.85 L, 1.0 M in THF) over 3−4 h. At the completion of the reaction as monitored by TLC analysis, methyl magnesium chloride (0.95 L, 3.0 M in THF) was added to the mixture in 30−60 min. The reaction mixture was warmed to 0 to −10 °C, and the reaction was monitored on TLC. At the completion of the reaction, saturated NH_4Cl aqueous solution (4−5 L) was added slowly to quench the reaction. The mixture was diluted by addition of ethyl acetate (5 L) and warmed to ambient temperature. After removing the aqueous phase, the organic phase was washed with brine (2 L × 2). Then the organic solvents were evaporated to dryness, and the residue was subjected to column chromatography eluting with a gradient of EtOAc/heptane (3:7 to 100:0, v/v) to afford TNE (820 g, 94.7%) and the desired sulfoxide (343 g) in 78% yield and 99% ee. ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.70 (s, 3H), 7.32−7.34 (m, 2H), 7.35−7.55 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 21.4, 43.9, 123.5, 130.0, 141.5, 142.4. Chiral HPLC method: column: Chiralcel OD, 250 mm × 4.6 mm; 220 nm; mobile phase: hexane/IPA (92:8); flow rate: 1.5 mL/min; r_t = 8.6 min ((*R*)-*p*TMSO); r_t = 9.6 min ((*S*)-*p*TMSO).

Synthesis of 3 from (*R*)-*p*TMSO and 2. A solution of (*R*)-*p*TMSO (10.0 g, 35.9 mmol) in THF (75 mL) was cooled to −65 to −70 °C, and LDA (25.2 mL, 37.74 mmol, mono-THF 1.5 M in cyclohexane) was added over 15 min and the reaction stirred for 20 min. Then a solution of **2** (10.0 g, 35.9 mmol, 1.0 equiv) in THF (25 mL) was added dropwise. At the completion of the reaction as monitored by TLC analysis, saturated aqueous NH_4Cl (50 mL) and ethyl acetate (100 mL) were added. The aqueous layer was removed, and the organic phase was washed once with brine (50 mL). The organic phase was concentrated, and the residue was subjected to chromatographic purification eluting with EtOAc/hexanes (3:7) to afford the desired isomer (9.2 g) in 59.3% yield and >99% de and the undesired isomer (5.1 g) in 32.7% yield. Major isomer ^{1}H NMR (DMSO-d_6) δ 7.35−7.32 (m, 4 H), 6.98 (dd, 1 H, J = 10.9, 3.0 Hz), 6.89−6.87 (m, 1 H), 6.80 (dd, 1 H, J = 9.0, 5.0 Hz), 6.24 (s, 1 H), 3.68 (s, 3 H), 2.84 (d, 1 H, J = 15.1 Hz), 2.71 (d, 1 H, J = 14.4 Hz), 2.47 (d, 1 H, J = 14.3 Hz), 2.38 (s, 3 H), 2.10 (d, 1 H, J = 15.1 Hz), 1.51 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 157.6, 155.7, 154.4, 142.1, 141.7, 137.6, 137.5, 130.2, 126.2 (q, J = 287 Hz), 123.9, 114.8, 114.6, 113.5, 113.3, 113.2, 76.0 (q, J = 26.6 Hz), 61.1, 55.9, 41.7, 37.6, 30.9, 29.3, 21.2; $[\alpha]^{25}_{365}$ +18.3 (*c* 0.508 g/100 mL, MeOH); LC−MS (ES): 433.43 $[M + H]^+$. Minor isomer ^{1}H NMR ($CDCl_3$) δ 7.27(m, 4H), 7.04−7.01 (m, 1H), 6.90−6.85 (m, 1H), 6.77−6.74 (m, 1H), 3.79 (s, 3H), 2.95−2.71 (m, 3), 2.40 (s, 3H), 2.4−2.36 (m, 1H), 1.57 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.3, 155.93, 154.1, 142.2, 140.3, 137.04, 136.9, 130.2, 126.5 (q, J = 286 Hz), 123.9, 115.5, 115.3, 113.5, 113.3, 112.2, 112.1, 61.0, 55.4, 42.0, 37.7, 31.6, 31.0, 21.4. Chiral HPLC method: column: Super-ODS column, 4.6 mm × 10 cm, particle size 2 μ; wavelength 220 nm, at 25 °C; mobile phases: A: water with 0.05% TFA, B: MeCN with 0.05% TFA; gradient conditions are 90% A to 10% A in 15 min, hold 5 min, back to 90% A, followed by a 3-min post-run; flow rate: 1 mL/min. r_t = 11.45 min for minor isomer, r_t = 13.22 min for major isomer.

One-Pot Synthesis of 3 from 5. To a solution of **5** (220 g, 626 mmol) in THF (2000 mL) at −65 to −70 °C was added *p*-tolyl magnesium bromide (626 mL, 1.0 M in THF) over 1.5−2 h. After addition, the reaction mixture was stirred for 0.5 h, and the reaction was monitored by TLC analysis. Methyl magnesium chloride (209 mL, 3.0 M in THF) was added at −55 to −70 °C over 15 min, and the reaction mixture was warmed up to ∼0 °C. At the completion of the reaction as monitored by TLC, the reaction mixture was cooled to −65 to −70 °C, and LDA (438 mL, 1.5 M in cyclohexane) was added over 15 min. The orange reaction mixture that formed was stirred for 20 min, and **2** (132 g, 455 mmol, 96% purity) was added dropwise over 30 min. The reaction mixture was stirred for 0.5 h, and the reaction was monitored by HPLC analysis. At the completion of the reaction, saturated aqueous NH_4Cl (800 mL) and ethyl acetate (1000 mL) were added. The aqueous phase was removed, and the organic phase was washed with brine (800 mL). The organic solvents were removed, and the residue was diluted with heptane (100 mL) and EtOAc (20 mL) and loaded onto a silica pad prepared by slurrying 700 g of silica in heptane. The pad was flushed with heptane first (500 mL) and then

(10) When ethyl acetate/hexane (4:6) was used as eluting solvent, the R_f values are as follows: desired alcohol (major isomer): 0.56; minor isomer: 0.37; *N*-tosyl norephedrine: 0.32; sulfoxide: 0.08.

(11) See Experimental Section for details.

with 15% EtOAc/heptane, and the fractions containing the major isomer were collected (~3 L). The solvents were concentrated and solvent-switched to *n*-PrOH (131 mL) with residual EtOAc (solvent weight ratio was *n*-PrOH/EtOAc = 4.5:1). The mixture was heated to reflux to get a clear solution and cooled to rt over 1 h. Crystallization occurred at this temperature, and heptane (26 mL) was added. The mixture was further cooled to −20 °C and held for 1 h. The mixture was filtered and rinsed once with 50 mL of cold *n*-PrOH (−20 °C). The crystals were air dried followed by oven drying at 60 °C under vacuum for 15 h to give **3** (98.5 g) in 48% yield, >99% de, and 99.5% chemical purity.

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