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# A Concise Asymmetric Synthesis of A β-Lactam-Based Cholesterol Absorption Inhibitor

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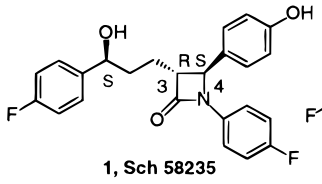
**Abstract:**

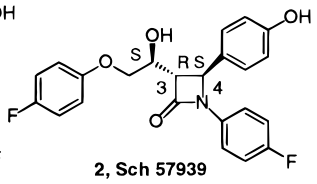
**A concise, four-step, asymmetric synthesis of a β-lactam-based cholesterol absorption inhibitor, Sch 57939, was developed. The discovery of a one-step enantio- and diastereoselective synthesis of a *trans*-β-lactam provided easy access to the desired three chiral centers. A novel zinc phenoxide-promoted ether synthesis was reported for the completion of the side chain.**

## Introduction

Recently, a class of β-lactam-based structures, represented by **1** and **2**, were found to be very potent cholesterol absorption inhibitors (CAI).[1] Since the discovery of lactam-based antibiotics, various methods have been developed for the synthesis of the *trans*-β-lactam ring.[2] The discovery of β-lactam-based CAIs further stimulated the interest in developing new procedures, and a number of them were reported recently.[3] These include a chiral auxiliary-based method,[3a] chiral pool-derived chemistry,[3b] and catalytic asymmetric synthesis.[3c] For the preparation of **2**, a racemic synthesis was reported.[1b] In addition to the loss of 50% enantiomer, the ether formation step provided product in very low yield. We now report a concise four-step asymmetric synthesis of **2** by taking advantage of our recently developed, one-step enantio- and diastereoselective formation of the *trans*-β-lactam ring.[3b] The newly discovered $ZnBr_2$-promoted ether synthesis more than doubled the yield for this step.



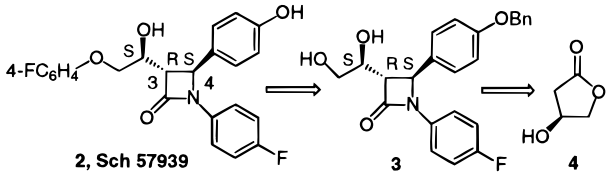

**1, Sch 58235**




**2, Sch 57939**

## Results and Discussion

Our synthetic strategy was to construct the side chain at the ether connection from metal phenoxide and a *trans*-β-lactam diol derivative. This diol derivative could be prepared from a regioselective conversion of the primary alcohol in **3** to a proper leaving group. The *trans*-β-lactam **3** could be obtained from the efficient one-step diastereo- and enantioselective procedure reported recently by our group.[3b]




**2, Sch 57939** **3** **4**

As shown in Scheme 1, the condensation of (*S*)-3-hydroxy-γ-lactone with an appropriately substituted imine provided easy access to a *trans*-β-lactam with three chiral centers in 64% isolated yield.[3b] A chiral HPLC assay indicated that all three of the chiral centers matched those in the desired intermediate **3**. A successful scale-up of this step provided a large quantity of *trans*-**3** for this study.

The regioselective conversion of primary alcohol in **3** to a leaving group was straightforward. Thus, treatment of **3** with TsCl in a 1:1 mixture of pyridine and THF at 5 °C gave monotosylate **5** in 73% isolated yield together with about 10% of the corresponding chloride. Neither the secondary monotosyslate nor the ditosylate was detected. The conversion of monotosylate **5** to ether **6**, however, turned out to be a challenging step. Displacement of monotosylate with sodium 4-fluorophenoxide gave a very slow reaction at 65 °C. The reaction mixture was complex with less than 10% of the desired ether. Several other metal phenoxides were examined, and the results are listed in Table 1. Use of calcium 4-fluorophenoxide gave only a trace of the desired product even at elevated temperature. In all of the reactions carried out, a common intermediate was isolated and found to be the corresponding epoxide. The opening of the this type of epoxide with sodium 4-fluorophenoxide was reported in very low yield (10−30%).[1b] Reaction with lithium 4-fluorophenoxide improved the yield to 43% but still with a long reaction time (95% conversion at 65 h). In addition, several impurities were observed probably due to the strong basicity of the reagent. The fact that sodium, calcium, and lithium gave different results suggested a cation effect. We

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***Scheme 1.*** **A four-step concise synthesis of 2**

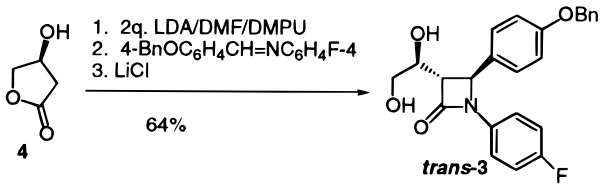
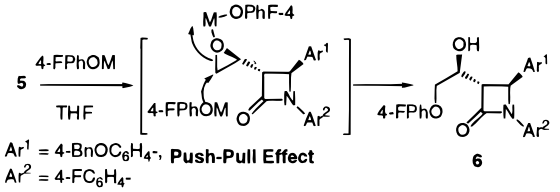



***Table 1.*** **Zn−Br-promoted ether formation**




| M | temp (°C) | time (h) | conversion (%) | isol. yield (%) |
|---|---|---|---|---|
| Na | 65 | 96 | 30 | 10 |
| $^1/_2$Ca | 65 | 96 | <5 | n/a |
| Li | 65 | 12 | 40 | n/a |
| Li | 65 | 65 | 95 | 43 |
| ZnBr | 55 | 12 | 95 | 67 |

thought that metal cations such as $Zn^{2+}$ with both Lewis-acid and -base properties would be best suited for this type of reaction. On the Lewis base side, 4-$FC_6H_4OZnX$ could act as a nucleophile, while on the Lewis acid side the $Zn^{2+}$ could activate the epoxide. This type of combined "push−pull" effect should speed up the epoxide opening and give a better yield. In fact, we have observed this type of "push−pull" effect in another synthesis, where an epoxide was effectively opened by an iminium−ZnX species.[4] Expoxide openings catalyzed by other Lewis acids such as $NiBr_2$, $CuCl_2$, and $TiCl_4$ were also reported.[5] As predicted, transmetalation of 4-$FC_6H_4ONa$ with $ZnBr_2$ to 4-$FC_6H_4OZnBr$ followed by reaction with monotosylate **5** completed the reaction in less than 12 h, which was 5 times faster than its lithium counterpart. Accordingly, the isolated yield of the desired ether **6** increased from 43% for lithium phenoxide to 67% for its zinc counterpart. Experimentally, the transmetalation of sodium phenoxide to zinc phenoxide was apparent. Thus, addition of a clear $ZnBr_2$/THF solution to a homogeneous THF solution of sodium 4-fluorophenoxide caused immediate precipitation of sodium chloride.

As shown in Scheme 2, the final debenzylation of **6** was achieved by using ammonium formate and 5% Pd−C to give **2** in 85% isolated yield.[6] The chiral purity was determined by chiral HPLC on a Chiralpak AS column and found to be >99%. This indicated that all three of the chiral centers were maintained through the whole reaction sequence. The 27% overall yield from this route is 6 times higher than that obtained from the racemic synthesis.[1b]

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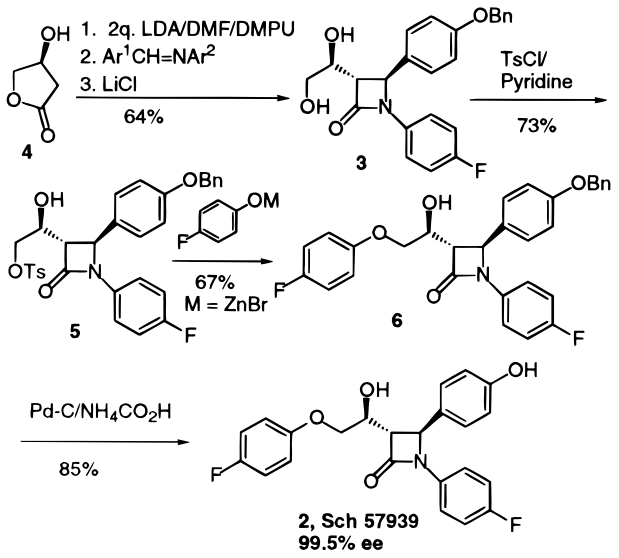
***Scheme 2.*** **One-step *trans*-$\beta$-lactam formation**




In summary, we have developed a concise four-step highly diastereo- and enantioselective synthesis of a $\beta$-lactam-based cholesterol absorption inhibitor with three consecutive chiral centers. We have also discovered an efficient $ZnBr_2$-promoted epoxide opening for ether synthesis.

## Experimental Section

All reactions were carried out under nitrogen. $^1$H and $^{13}$C NMR spectra (300 and 400 MHz) were recorded in $CDCl_3$ and referred to TMS unless otherwise noted. Melting points were not corrected.

**Regioselective Tosylation of 3**. To 4.1 g (10 mmol) of diol **3** in 10 mL of THF and 7 mL of pyridine at 5 °C was added 2.38 g (12 mmol) of TsCl. The resulting mixture was stirred at 5 °C for 16 h and poured into 30 mL of ice−water. The product was extracted with 2 × 25 mL of EtOAc. The combined organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on flash silica gel, eluting with hexanes:EtOAc (6:4), to give 4.1 g (73%) of the monotosylate **5** as a white solid; mp 52−54 °C. $^1$H NMR $\delta$ 7.71 (dd, $J$ = 6.6, 1.8 Hz, 2 H), 7.44−7.20 (m, 11 H), 6.98−6.90 (m, 4 H), 5.06 (s, 2 H), 5.05 (d, 1 H), 4.39−4.35 (m, 1 H), 4.23 (dd, $J$ = 10.6, 2.9 Hz, 1 H), 4.02 (dd, $J$ = 10.6, 6.2 Hz, 1 H), 3.13 (dd, $J$ = 5.6, 2.4 Hz, 1 H), 2.75 (d, $J$ = 5.1 Hz, 1 H), 2.44 (s, 3 H). $^{13}$C NMR $\delta$ 165.2, 161.2, 160.0, 158.8, 146.2, 137.6, 134.5, 133.1, 131.0, 129.9, 129.6, 129.1, 129.0, 128.6, 128.5, 119.7, 119.6, 117.0, 116.7, 116.5, 73.2, 71.2, 67.9, 63.3, 57.8, 22.9. Anal. Calcd for $C_{31}H_{28}FNO_6S\cdot{}^1/_2H_2O$: C, 65.25; H, 5.12; N, 2.45. Found: C, 65.69; H, 5.08; N, 2.41. IR (Nujol) 3420, 2920, 1740 cm$^{-1}$.

**Preparation of Epoxide Intermediate**. To a solution of 0.068 g (0.60 mmol) of 4-$FC_6H_4OH$ in 4 mL of THF at −35 °C was added 0.24 mL (0.60 mmol) of 2.5 M *n*-BuLi in hexanes. To this mixture at −35 °C was added a solution of 0.17 g of the tosylate **5** in 4 mL of THF. The resulting solution was stirred at −35 °C for 5 min and allowed to warm to rt for 30 min to give a white precipitation. TLC indicated that all starting material turned into epoxide. The

reaction mixture was poured into ice-cold 1.0 N NaOH, and the product was extracted with 2 × 20 mL of EtOAc. The combined organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on flash silica gel, eluting with hexanes:EtOAc (6:4), to give 0.10 g (85%) of the epoxide as a gel, which crystallized on standing; mp 36−38 °C. $^1$H NMR $\delta$ 7.42−7.33 (m, 5 H), 7.27−7.24 (m, 4 H), 6.99−6.92 (m, 4 H), 5.05 (s, 2 H), 4.79 (d, $J$ = 2.4 Hz, 1 H), 3.43−3.40 (m, 1 H), 3.25 (dd, $J$ = 4.8, 2.6 Hz, 1 H), 2.96 (t, $J$ = 4.2 Hz, 1 H), 2.71 (dd, $J$ = 4.8, 2.6 HZ, 1 H). $^{13}$C NMR $\delta$ 164.6, 161.2, 160.1, 158.8, 137.6, 134.6, 134.6, 129.8, 129.7, 129.1, 128.5, 128.3, 119.6, 119.6, 117.0, 116.8, 116.7, 71.2, 63.0, 57.6, 49.7, 46.9. Anal. Calcd for $C_{24}H_{20}FNO_3 \cdot {}^3/_4H_2O$): C, 71.54, H, 5.38, N, 3.48. Found: C, 71.49, H, 5.33, N, 3.99. IR (Nujol) 2920, 1760, 1620 cm$^{-1}$.

**Lithium Phenoxide to 6**. To 0.34 g (3.0 mmol) of 4-$FC_6H_4OH$ in 3 mL of THF at −35 °C was added dropwise 1.21 mL (3.0 mmol) of 2.5 M *n*-BuLi/hexane. Some white precipitation occurred after stirring at −35 °C for 10 min. To this mixture at −35 °C was added a 3 mL THF solution of 0.34 g (0.6 mmol) of tosylate **5**. The reaction mixture was allowed to warm to room temperature and then heated at 65 °C for 65 h as monitored by TLC. After completion, the reaction was cooled to room temperature and poured slowly into 20 mL of 1.0 N HCl solution. The product was extracted with 2 × 20 mL of EtOAc. The combined organic layer was washed sequentially with 1.0 N NaOH solution and water. After concentration, the residue was chromatographed on silica gel, eluting with hexanes:EtOAc (6:4), to give 0.13 g (43%) of ether **6** as a gel which crystallized on standing; mp 47−49 °C. $^1$H NMR $\delta$ 7.43−7.25 (m, 9 H), 6.98−6.92 (m, 6 H), 6.85−6.81 (m, 2 H), 5.11 (d, $J$ = 2.4 Hz, 1 H), 5.05 (s, 2 H), 4.51−4.49 (m, 1 H), 4.13 (dd, $J$ = 9.5, 3.5 Hz, 1 H), 4.02 (dd, $J$ = 9.5, 6.4 Hz, 1 H), 3.34 (dd, $J$ = 6.4, 2.4 Hz, 1 H), 2.68 (d, $J$ = 5.1 Hz, 1 H). $^{13}$C NMR $\delta$ 165.6, 161.2, 159.9, 159.7, 158.8, 157.4, 155.2, 137.6, 134.6, 130.3, 129.6, 129.1, 128.5, 128.4, 119.6, 119.5, 117.1, 116.9, 116.8, 116.7, 116.5, 72.1, 71.2, 69.1, 63.8, 58.2. Anal. Calcd for $C_{30}H_{25}F_2NO_4 \cdot {}^1/_2H_2O$: C, 70.58; H, 5.13; N, 2.74. Found: C, 70.71; H, 5.34; N, 2.70. IR (Nujol) 3400, 2920, 1730 cm$^{-1}$.

**$ZnBr_2$-Promoted Ether Formation to 6**. To 1.43 g (35 mmol) of NaH in 10 mL of THF at 5 °C was added dropwise a solution of 4.0 g (36 mmol) of 4-$FC_6H_4OH$. To the mixture was added dropwise 63 mL of 0.57 M dry $ZnBr_2$ solution in THF. The mixture was stirred at 5 °C for 10 min to give white precipitation of NaCl and a clear solution. To this reaction mixture was added a 2 mL THF solution of 2.0 g (3.6 mmol) of the monotosylate **5**. The reaction mixture was heated to 65 °C for about 12 h as followed by TLC and cooled to rt. Most of the THF was removed under vacuum, the residue was diluted with 150 mL of water, and the product was extracted with 3 × 50 mL of EtOAc. The combined organic layers were first washed with 1.0 N NaOH and then with water, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on flash silica gel, eluting with hexaznes:EtOAc (6:4), to give 1.2 g (67%) ether of **6**.

**Debenzylation to 2**. To a 25 mL flask were sequentially added 0.50 (1.0 mmol) of ether **6**, 0.32 g (5.0 mmol) of ammonium formate, 0.05 g of 5% Pd/C, and 7 mL of MeOH. The pH was adjusted to between 3 and 5 with HOAc. The mixture was heated to 40 °C for about 10 h, cooled to rt, and poured into a mixture of 30 mL of water and 30 mL of EtOAc. The layer was separated, and the aqueous layer was extracted with another 15 mL of EtOAc. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on flash silica gel, eluting with hexanes:EtOAc (6:4), to give 0.35 g (85%) of **2** as a white solid; mp 128−130 °C. $^1$H NMR $\delta$ 7.27−7.23 (m, 4 H), 6.98−6.91 (m, 4 H), 6.83−6.80 (m, 4 H), 5.29 (s, 1 H), 5.10 (d, $J$ = 2.4 Hz, 1H), 4.55−4.45 (m, 1H), 4.12 (dd, $J$ = 9.4, 3.3 Hz, 1 H), 4.02 (dd, $J$ = 9.4, 6.5 Hz, 1 H), 3.32 (dd, $J$ = 6.4, 2.4 Hz, 1 H), 2.70 (d, $J$ = 5.1 Hz, 1 H). $^{13}$C NMR $\delta$ 164.7, 160.9, 159.3, 157.6, 156.0, 154.3, 154.2, 133.7, 133.6, 129.2, 127.6, 118.7, 118.6, 116.2, 116.1, 116.0, 115.9, 115.8, 70.9, 68.2, 62.6, 57.3. Anal. Calcd for $C_{23}H_{19}F_2NO_4 \cdot H_2O$: C, 64.33; H, 4.93; N, 3.26. Found: C, 64.03; H, 5.06; N, 3.40. IR (Nujol) 3410, 3220, 2920, 1730 cm$^{-1}$.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