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A Convenient Synthesis of the Novel Hypoglycemic Agent SDZ PGU 693

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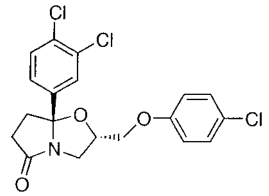
Noninsulin-dependent diabetes mellitus (NIDDM, type 2) is a chronic, multifactorial metabolic disease, typically characterized by insulin resistance in the liver and peripheral tissues.[1] The resulting hyperglycemia and hyperlipidemia in type 2 diabetes patients may also contribute to long-term organ complications such as neuropathy, retinopathy, nephropathy, and atherosclerosis.[2] Thus, in diabetic patients, maintaining tight control of blood glucose would be desirable to lessen the risk of the above-mentioned complications.[3] Recently, researchers at Novartis laboratories published a report describing a novel class of tetrahydropyrrolo[2,1-*b*]oxazol-5(*6H*)-one based hypoglycemic agents.[4] In this class, SDZ PGU 693 (**1**) was reported to significantly improve glucose metabolism in diabetic and insulin-resistant animals. Though the mechanism of this novel class of insulin-sensitizing agents as represented by **1** is not known at present, it provides a novel approach to improving glucose lowering in type 2 diabetic patients.



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In connection with an ongoing project in these laboratories, multigram quantities of **1** were required. We found the published patent procedure[5] for the synthesis of this compound to be less than optimal for various reasons. First, it involves a tedious resolution procedure for the synthesis of the key intermediate **3,** and second, unlike the reported procedure, in our hands, the reaction of the chiral epoxide **2** with ammonia in the sealed tube was accompanied with varying amounts of the bis-alkylated product **5**, thus necessitating the cumbersome chromatographic purification of the highly basic amino alcohol intermediate **4**. We wish to report herein a facile synthesis of **1**.

4-Chlorophenyl-*S*-glycidyl ether **2** was conveniently prepared on a large scale using the Sharpless procedure[6] (Scheme 1). Thus, reaction of 4-chlorophenol and (2*S*)-glycidyl 3-nitrobenzenesulfonate in the presence of sodium hydride afforded the desired ether derivative **2** in 80% yield.

Initially, we subjected this epoxide to react with liquid ammonia in a sealed tube. Unfortunately, this epoxide opening reaction with ammonia also gave the bis-alkylated product **5**, requiring the tedious chromatographic purification of the highly basic amino alcohol intermediate **4**. To address this problem, we employed various ammonia equivalents such as dibenzylamine and benzhydrylamine in the epoxide-opening reaction. While these reactions provided the desired protected amino alcohol derivatives in good yields, efforts to unmask the latent amino functionality using either phase-transfer hydrogenation conditions or Pd/C catalysts were also accompanied, to varying degrees, by the reduction of the chloro substituent on the phenyl ring.

Faced with this difficulty, we explored the use of tritylamine as a masked ammonia surrogate in the reaction with the epoxide **2**. While the use of tritylamine as an ammonia equivalent in the electrophilic reactions with halides is precedented,[7] to the best of our knowledge, the corresponding reaction with epoxides as electrophile has not been described. Thus, reaction of **2** with tritylamine gave the protected amino alcohol **3** ($R = C(C_6H_5)_3$) in 75% yield. Treatment of this compound with either TFA in methylene chloride or HCl in methanol furnished intermediate **4.** Alternatively, we also employed successfully dibenzosuberylamine ($DBS\text{-}NH_2$)[8,9] as an ammonia equivalent in the reaction with **2**. Elaboration of the intermediate **4** to **1**[5] was straightforward as shown in Scheme 1.

In conclusion, we have developed a convenient synthesis of SDZ PGU 693. The unprecedented use of tritylamine as well as dibenzosuberylamine as ammonia equivalents in the reaction with epoxide to provide 1,2-amino alcohols should be quite useful in the synthesis of other analogues of this pharmacologically important class of compounds.

Experimental Section

3-(4-Chlorophenoxy)-2*S*-hydroxypropylamine (4). To a solution of 4-cholrophenyl-*S*-(+)-glycidyl ether **2** (50 g, 0.27 mol) in ^{i}PrOH (60 mL) was added tritylamine (76.6 g, 0.29 mol), and the resulting mixture was heated under reflux for 24 h.

The solution was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a column of silica gel, eluting with CH_2Cl_2 to give 90 g of **3** ($R = C(C_6H_5)_3$) as a gum: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.22 (m, 18H), 6.83 (d, 1H), 4.1 (m, 1H), 4.01 (m, 2H), 2.45 (m, 2H).

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(9) To the best of our knowledge, there is only one instance of epoxide opening reaction with $DBS\text{-}NH_2$. However, in this case, $DBS\text{-}NH_2$ was not used as an ammonia surrogate. Vejdelek, Z.; Protiva, M. Collect. *Czech. Chem. Commun.* **1990**, *55*, 1290−129.

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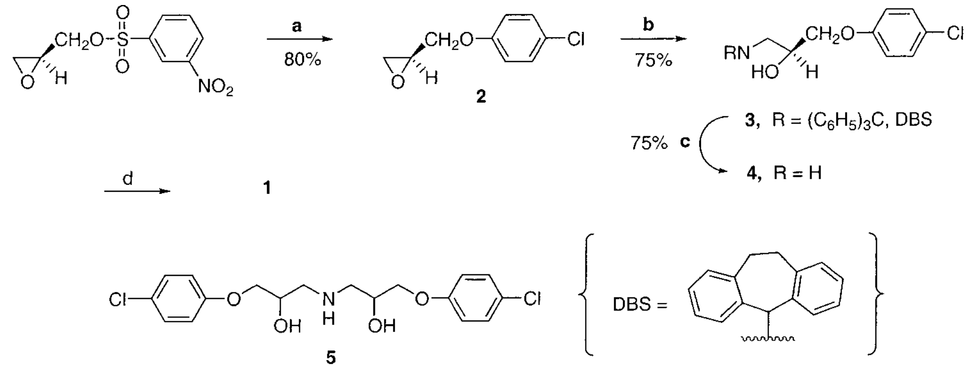
Scheme 1[a]



[a] Reagents: (a) 4-ClC_6H_4OH, NaH, DMF; (b) RNH_2, ^iPrOH, reflux; (c) TFA, CH_2Cl_2; (d) 3,4-$Cl_2C_6H_3COCH_2CH_2COOH$, PTSA, toluene, reflux.

Compound **3** (88 g) was dissolved in a mixture of CH_2Cl_2 and methanol (1:1, 500 mL), and the resulting solution was cooled to 0 °C. TFA (500 mL) was added gradually, and the mixture was stirred at room temperature until the reaction was complete by TLC. The solution was concentrated in vacuo, and the residue was partitioned between ether and water. The aqueous phase was made alkaline using aqueous NaOH and extracted with ether. The combined extracts were washed with water, dried and concentrated in vacuo to furnish 30 g (75%) of **4**: mp 109−111 °C; $[\alpha]^{25}_{D}$ −4.86 ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H), 6.86 (d, 2H), 3.96 (m, 3H), 2.99 (m, 1H), 2.86 (m, 1H). Alternatively, this deprotection reaction may also be carried out using 2 N HCl in methanol.[10]

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