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Process Development and Scale-Up of the Potential Thiazolidinedione Antidiabetic Candidate PNU-91325

Donald E. Carpenter, Rick J. Imbordino, Mark T. Maloney, Jeffery A. Moeslein, Michael R. Reeder,* and Allen Scott

Early Process Research and Development, Pharmacia Corporation, Kalamazoo, Michigan 49001, U.S.A.

Abstract:

An efficient six-step synthesis has been developed for the preparation of the thiazolidinedione analogue PNU-91325 (3) from the commercially available olefin 12. This process involves a novel epoxide ring opening with a deactivated phenol under phase-transfer conditions. Significant improvements were made in the oxidation of a secondary alcohol to the ketone and the 1,4-reduction of an enone from a previous process. Overall, this route allows for the preparation of PNU-91325 in 25% yield.

Introduction

Pioglitazone analogue 5-{4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (**3**) was an antidiabetic thiazolidinedione candidate that was being evaluated for possible clinical development for the treatment of noninsulin-dependent diabetes mellitus (NIDDM).[1] Ketone **3**, although not identified as a metabolite of pioglitazone (**7**), has been added to a list of putative metabolites on the basis of analogy to alcohol **1** and known ketone metabolite **4** (Figure 1).

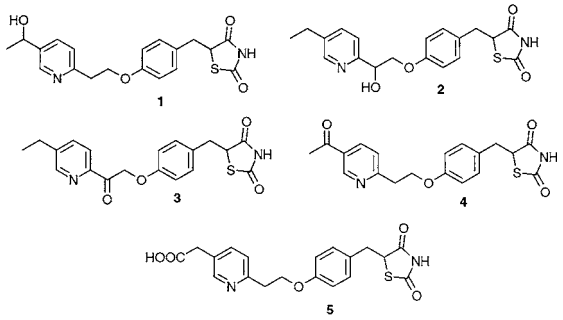

Figure 1.

The structure of **3** is similar to that of other thiazolidinonediones (Figure 2) that are or have been in clinical development such as pioglitazone (**7**)[2] (Takeda Chemical Industries, Inc./Upjohn), troglitazone (**8**)[3] (Sankyo and Parke-Davis), englitazone (**9**)[4] (Pfizer), and BRL-49653 (**10**)[5] (SmithKline Beecham).

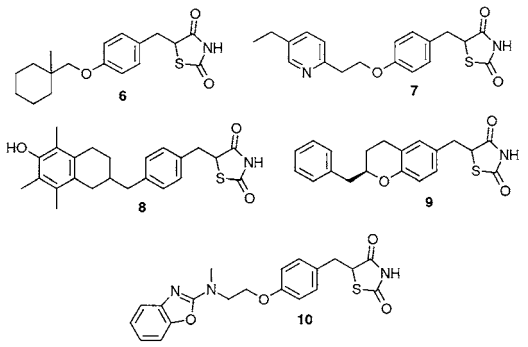

Figure 2.

Pharmacia wished to conduct studies that might serve to evaluate the biological properties of **3**; thus, bulk quantities were needed for this study. The former Upjohn Company has had experience with the synthesis of various pioglitazone analogues, and thus we had ample synthetic methodology to draw from as well as a significant amount of alcohol **11** which serves as a convenient starting material.

Results and Discussion

Our synthetic strategy for the synthesis of **3** (Scheme 1) began with dehydration of **11** with KOH to afford olefin **12**.[6] Epoxidation of **12** followed by subsequent ring opening of **13** with 4-hydroxybenzaldehyde provided aldehyde **14**. Knoevenagel condensation with 2,4-thiazolidinedione afforded olefin **15** which was reduced with $NaBH_4$ to provide diastereomeric alcohols **2**. Oxidation of the carbinol to the

* Author for correspondence: E-mail: michael.r.reeder@pharmacia.com.

(1) Tanis, S. P.; Parker, T. T.; Colca, J. R.; Fisher, R. M.; Kletzein, R. F. J. *Med. Chem.* **1996**, *39*, 5053 and references cited therein.

(2) Sohda, T.; Momose, Y.; Meguro, K.; Kawamasu, Y.; Sugiyama, Y.; Ikeda, H. *Arzeim-Forsch./Drug Res.* **1990**, *40*, 37.

(3) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421.

(4) (a) Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutler, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. F. *J. Med. Chem.* **1991**, *34*, 319. (b) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. *J. Med. Chem.* **1992**, *35*, 1853.

(5) Cantello. B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M., Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977.

(6) For our initial work, we contracted with a vendor to convert a large lot of alcohol **11** to olefin **12**. Additional **12** was subsequently purchased from Koei Chemical Company, Limited.

(7) Thurkauf, A.; Mattson, M. V.; Richardson, S.; Miradeghi, S.; Ornstein, P. L.; Harrison, E. A., Jr.; Rice, I. C. C.; Jacobson, A. E. Monn, J. A. *J. Med. Chem.* **1992**, *8*, 1323.

(8) The onset temperature of decomposition (56 °C) for the epoxide was determined from ARC and RC1 experiments and is representative of the neat oil. Further safety analysis for the PTC chemistry showed no exothermic decomposition of the epoxide at 80 °C while in solution.

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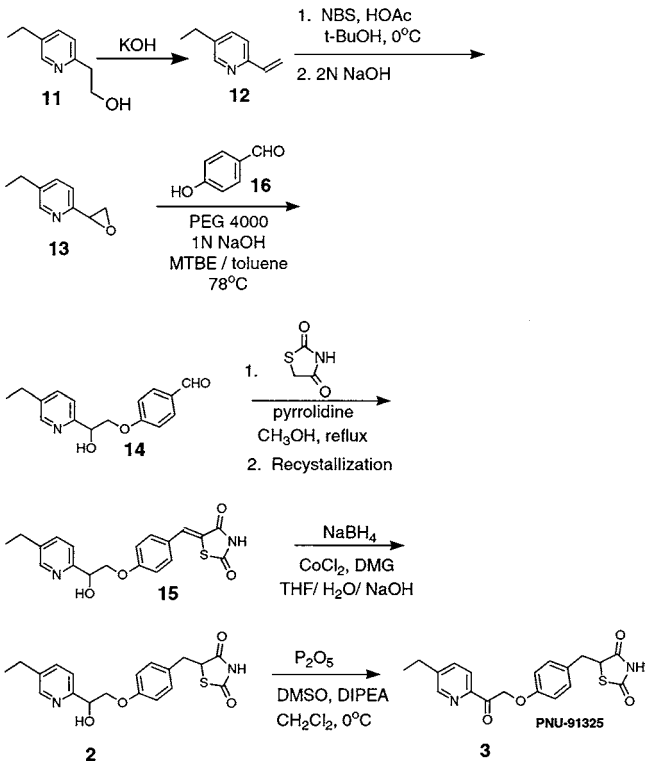
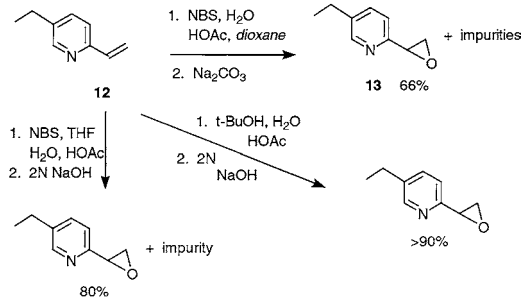
ketone afforded the target pioglitazone analogue **3**.

Scheme 1



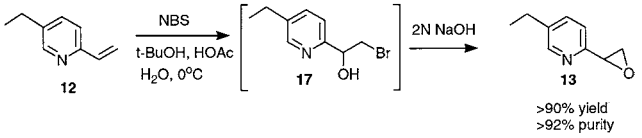
Epoxidation of Olefin 12. Our initial epoxidation conditions for **12** focused on work reported by Thurkauf et al.[7] Thurkauf's procedure called for treating 2-vinylpyridine with *N*-bromosuccinimide (NBS) in a solution of dioxane, water, and acetic acid. Subsequent treatment of the reaction mixture with Na_2CO_3 afforded the desired epoxide in 66% yield. Employing these conditions on **12**, epoxide **13** was obtained in ca. 66% (Scheme 2). While we were able to reproduce Thurkauf's yield, many other byproducts were formed during this reaction, and purification of **13** required column chromatography. In addition to the problematic chemistry, carcinogenic dioxane as a solvent was unattractive from a scale-up perspective. Substituting THF for dioxane in Tarkuaf's procedure did increase the yield to around 80% with the formation of one (major) unidentified impurity. Several modifications such as temperature, use of different bases, the rate and order of addition of reagents, and the solvent/water ratios failed to suppress this impurity.

Scheme 2



However, the use of *tert*-butyl alcohol/water (1:5) as the solvent afforded the epoxide **13** in 90% yield (>92% purity by GLC) without any significant impurities (Scheme 2). Optimization of this epoxidation of olefin **12** included a temperature-controlled addition of a *tert*-butyl alcohol solution of acetic acid (1 equiv) and **12** to a stirring aqueous slurry of NBS cooled to 0 °C. After 1 h, the resultant bromohydrin **17** was treated with an excess of 2 N NaOH and stirred at 0 °C until reaction was complete (Scheme 3). The crude epoxide product was extracted into MTBE and used without purification in step two.

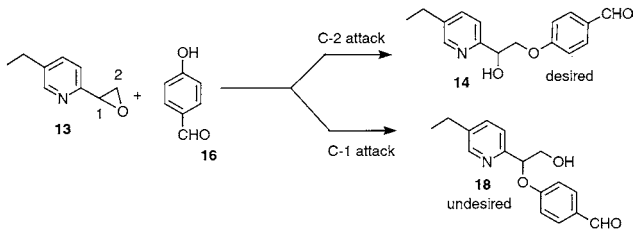
Scheme 3



Olefin **12** as a neat oil has been observed to polymerize upon standing even when stored cold with inhibitors, and it is recommended that it be used as quickly as possible. Little-to-no decomposition or polymerization has been observed for **13** stored in solution (MTBE) for up to 4 months; however, due to its low (56 °C) onset of thermal decomposition,[8] it is recommended that **13** be stored cold in solution and used as soon as possible after preparation.

Ring Opening of Epoxide 13: Nonmetal-Catalyzed. Ring opening of epoxide **13** remains problematic in this preparation. A significant amount of development has gone into this reaction trying to control the regiochemical ring opening of **13**. As seen in Scheme 4, there are two positions that can undergo nucleophilic ring opening. Most common is for the nucleophile to attack at the unhindered C-2 terminal position affording the desired ring-opened product **14**. Alternatively, attack at more hindered C-1 is considerably more likely to occur in **13** because of the resonance stabilization that can exist. Given our target, we wished to achieve a regioselective C-2 ring-opening of epoxide **13.** Three classes of reactions were tested to effect this ring opening: (1) nonmetal assisted, (2) metal-assisted, and (3) phase-transfer conditions (PTC).

Scheme 4

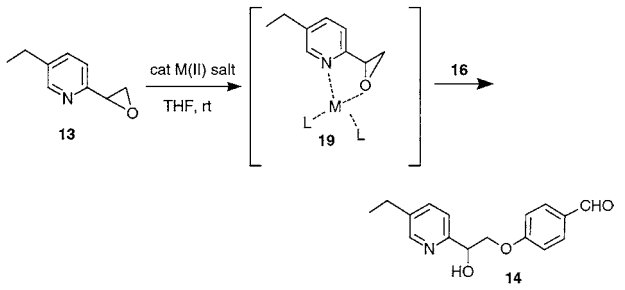


A preliminary literature search for epoxide ring opening with phenols revealed two recent reports in which sodium phenoxides opened the ring of 2-pyridyloxirane predominantly at C-2 at 60−90 °C in DMF in 50−68% yield.[9] Since a procedure was available for preparation of the potassium salt of 4-hydroxybenzaldehyde from our previous scale-up of other pioglitazones, we chose to substitute the potassium salt into our reaction. Using a 2:1 ratio of potassium salt to epoxide at 60−65 °C, we obtained a mixture of **14** and **18** in 65% yield. These products were purified by chromatog-

raphy on silica gel, providing a 43% yield of **14** as pale yellow crystals and a 5% yield of **18** as an oil. Variation of the molar ratios, dipolar aprotic solvent, temperature, time, and the use of 4-hydroxybenzaldehyde as proton donor, failed to produce a significant improvement in the outcome. A considerable amount of insoluble brown tar was produced in all cases, making workup of these reactions difficult.

Ring Opening of Epoxide 13: Metal-Assisted Ring Opening. In an effort to suppress the undesired ring opening at C-1, we explored using a Lewis acid to affect the regiochemistry. Evidence in the literature suggested that ring opening of 2-pyridyl epoxides with water, halides, phenols, amines, and alcohols catalyzed by Mg(II), Cu(II), Ni(II), and Zn(II) metal ions is highly regioselective for C-2 attack.[10] This regiochemical control can be rationalized by chelation of the bidentate metal to the oxygen lone pair on the oxirane as well as to the pyridine nitrogen via **19** favoring attack at C-2 (Scheme 5).

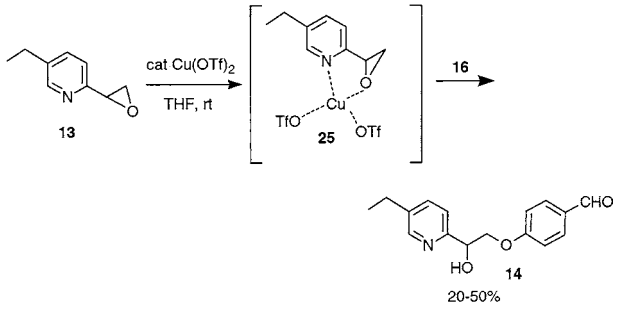
Scheme 5



Our first attempt at this chelation-controlled opening of **13** was done with the magnesium salt of 4-hydroxybenzaldehyde. This compound was easily prepared from commercially available magnesium methoxide and **16** in methanol at room temperature. The solvent was removed in vacuo, and the solid was dried under high vacuum with heat. Epoxide **13** was then treated with this magnesium salt (0.5 equiv) and 4-hydroxybenzaldehyde (1 equiv) as proton donor. After 2 days at 70 °C in DMF a 62% crude yield of product was obtained, consisting of **14** (80%) and **18** (1%). While the use of divalent magnesium uniformly reduced the amount of undesired isomer to < 2%, the use of monovalent potassium or sodium salts of 4-hydroxybenzaldehyde resulted in 15−20% undesired product. However, problematic with both sets of reaction conditions was the formation of a dark, insoluble tar that made workup difficult. Due to the low onset of thermal decomposition for **13** we hoped to avoid this tar formation by running this reaction at temperatures below 50 °C; however, these failed to suppress tar formation. While it was found that the small amount of wrong isomer **18** that was formed in these metal-catalyzed reactions could be removed in the next step by the usual crystallization from methanol (vide infra), more of a concern was developing an effective method to isolate the product from this tar.

Singh and Sekar recently reported that catalytic $Cu(OTf)_2$ catalyzes the ring opening of epoxides with a variety of amines to afford good yields of the resulting amino alcohols.[11] Initial results employing Singh's chemistry on **12** seemed promising. Epoxide **13** was treated with 4-hydroxybenzaldehyde (2 equiv) and $Cu(OTf)_2$ (10 mol %) in THF at room temperature (Scheme 6). HPLC analysis of the crude reaction mixture indicated a high selectivity for C-2 attack, and consumption of **13** was complete within 24 h. However, isolation of the crude product was problematic as the reaction produced a thick insoluble black tar isolating **14** in an unacceptable 20−50% yield.

Scheme 6



In an attempt to improve the isolated yield, several reaction parameters were investigated. The concentration was found to have a dramatic effect on the rate of reaction. Control experiments found that the optimal reaction rate was determined to be at a reaction concentration of 2.6 M based on phenol. Reactions run at lower concentration often did not go to completion coupled with compromised attack at the C-1 position. Decreasing the amount of catalyst to as low as 1 mol % did not reduce the amount of tar formation and required elevated temperatures to drive the reaction to completion. The stoichiometry of the phenol was investigated, and it was found that employing 2 equiv seemed to give the best yield and rate of reaction. Decreasing this amount to 1.5 equiv or lower led to incomplete reaction and increased impurity formation. It did appear that THF was the solvent of choice, however, mixtures of THF and MTBE were found to work as well. $Cu(OTf)_2$ was found to be insoluble in MTBE. Tar formation for reactions carried out at room temperature were found to be comparable to those reactions carried out at 45 °C, while heating the reactions above 45 °C often led to increased amounts of C-1 attack and other impurities. We did not investigate the origin for tar formation; however, a control reaction in which epoxide **13** was stirred with $Cu(OTf)_2$ (10 mol %) in THF at room temperature, resulted in decomposition of **13** with ensuing tar formation. Likewise, it is conceivable that epoxide **13** could potentially react with alcohol **14** to give a polymeric material. Other Lewis acids such as $Mg(OTf)_2$ or $CoCl_2$[12] gave consistent results similar to that for $Cu(OTf)_2$, whereas reactions carried out with $Ti(O\text{-}^iPr)_4$ stalled at 50% remaining **13**.

From the experimental evidence obtained thus far, employing divalent metal catalysts appeared to favor attack at

(9) (a) Maoleon, D.; Pujol, M. D.; Rosell, G. *J. Med. Chem.* **1988**, *31*, 2122. (b) Hanzlik, R. P.; Edelman, M.; Michaely, W. J.; Scott, G. J. *J. Am. Chem. Soc.* **1976**, *98*, 1952.

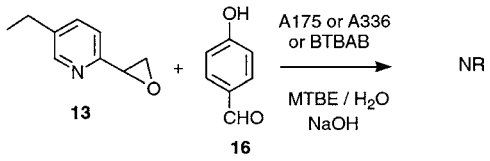
(10) (a) Hanzlik, R. P.; Hamburg, A. *J. Am. Chem. Soc.* **1978**, *100*, 1745. (b) Hanzlik, R. P.; Michaely, W. J. *J. Chem. Soc., Chem. Comm*. **1975**, *113*.

(11) Singh, V. K.; Sekar, G. *J. Org. Chem*. **1999**, *64*, 287.

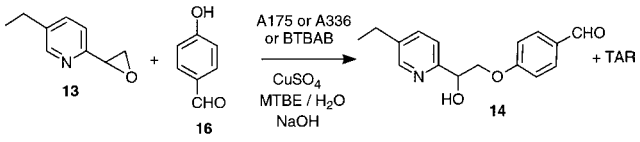
(12) Iqbal, J.; Pandey, A. *Tetrahedron Lett*. **1990**, *31*, 575.

the C-2 position; however, the ensuing tar formation coupled with problematic workup and isolation of crude product made this approach unattractive from a scale-up perspective. Further development on this approach was abandoned at this time.

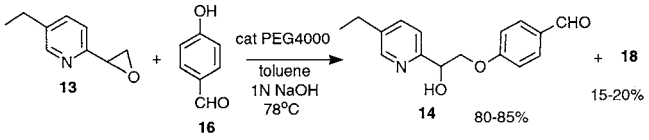
Ring Opening of Epoxide 13: Phase-Transfer Conditions (PTC). We were hopeful that we could achieve a regioselective ring opening of **13** and suppress tar formation using phase-transfer conditions. There are few examples in the literature for the preparation of phenolic ethers using PTC[13] and we were concerned at the outset for this chemistry due to the poor nucleophilicity of **16**. Initially, we screened three readily available PT catalysts we had in-house, A175 (methyl-tribuylammonium chloride), A336 (tricaprylylmethylammonium chloride) and BTBAB (benzyl(tributyl)-ammonium bromide). To test this reaction, 1 N NaOH (0.5 equiv), the PT catalyst, and epoxide **13** were added to a solution of 4-hydroxybenzaldehyde (1.5 equiv) in MTBE/H_2O (1:1), and the reaction was vigorously stirred for 12 h (eq 1).



Unfortunately, only recovered **13** was observed for all PT catalysts tested. We felt that adding a Lewis acid to this reaction might overcome the lack of reactivity; we thus hoped that we could introduce inexpensive $CuSO_4$ to aid in both reactivity and regioselectivity. Repeating these reactions with $CuSO_4$ (100 mol %) we observed complete consumption of **13** in the HPLC assay; however disappointingly, a significant amount of tar was formed, and a low isolated yield of **14** resulted (eq 2). Decreasing the amount of $CuSO_4$ decreased the amount of tar, but also decreased the yield and eroded the regioselectivity.



Disappointed in our preliminary PTC results, we subsequently performed a literature search which revealed a report by Bhattacharyya and Maiti who report the ring opening of oxiranes with sulfides and sulfones catalyzed by poly(ethylene glycol) 4000 (PEG 4000).[14] An important aspect of this paper was the authors' claim that these conditions were highly regiospecific, giving ring opening from the less hindered site in the absence of a Lewis acid. Therefore, to test this claim, epoxide **13** was added to the preformed sodium phenoxide in toluene/H_2O with a catalytic amount of PEG 4000 and heated to 80 °C (eq 3).[8]



After stirring for 24 h, the reaction was cooled to room temperature, and HPLC analysis indicated no **13**. To our pleasure, we found that little to no tar resulted from these conditions and that workup proved much easier, providing a crude dark brown/black solid in 50−70% mass recovery. Unfortunately, the authors' high regiochemical claim could not be applied to this reaction, and between 10 and 20 area % of **18** resulted. Products **14** and **18** could not be easily separated at this stage; however, these regioisomers could be separated during the purification of the Knoevenagel products (vide infra). Although these conditions resulted in up to as much as 20% of **18**, the lack of tar formation made this attractive for scale-up.

A direct comparison of the ring opening of **13** under PTC or with the magnesium salt of **16** revealed that both methods gave comparable yields. The PTC process proved operationally superior with respect to lack of tar formation, whereas the magnesium process resulted in significant tar formation that required a tedious and difficult workup and was thus abandoned at this time. Because epoxide **13** would be used as a solution in MTBE in this reaction, we examined if any problems would arise by having this solvent in our phase-transfer chemistry. We were pleased to find that introducing **13** dissolved in MTBE (1 kg epoxide/L MTBE) caused no adverse effects on the reaction, yield, tar formation, or regiochemical outcome.

In our first scale-up run of step 3, we allowed this reaction to proceed until less than 1% of **13** remained. While we were able to reach this limit, impurities generated during this prolonged reaction (28 h at 80 °C) resulted in a 67% yield of **14** and **18**. Knowing that we could upgrade in the next step, we decided to raise the level of **13** that remained to 3%, thus decreasing the reaction time to about 17 h. While use tests in the laboratory showed that running this reaction until 3% of **13** remained caused a decrease in the yield of up to 10%, the amount of impurities generated were significantly less.

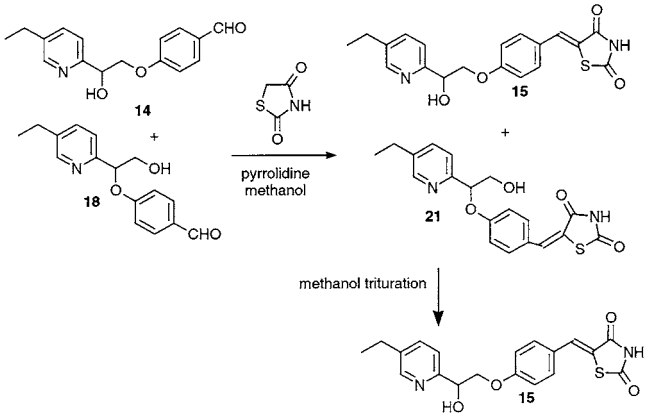
Knoevenagel Condensation Following previous pioglitazone methodology,[2,15] only minor modifications were made to include removal of half the solvent (methanol) prior to crystallization and the addition of water washes to remove residual pyrrolidine from the product. Although we did not study this, we were concerned that small amounts of pyrrolidine could interfere with the cobalt-catalyzed reduction of **15** to **2**. Additional water washes of the product reduced the pyrrolidine level to below 3% which was an acceptable level giving a good yield in the methanol trituration.[16]

Treating a mixture **14** and **18** (4:1) with 2,4-thiazolidinedione and pyrrolidine in CH_3OH (35−45 °C) after

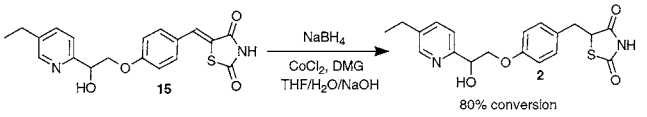
(13) McKillop, A.; Fiaud, J.-C.; Hug, R. P. *Tetrahedron* **1974**, *30*, 1379 and references cited therein.
(14) Bhattacharyya, P.; Maiti, A. K. *Tetrahedron* **1994**, *50*, 10483.
(15) Sohda, T.; Ikeda, H.; Megura, K. *Chem. Pharm. Bull*. **1995**, *43*, 2168.
(16) As determined by ^{1}H 400 MHz NMR.

workup gave a mixture of the olefin products **15** and **21** (97:3) (Scheme 7). The crude product mixture was purified by triturating the solids at reflux in methanol (20 mL/g) which reduced the level of **21** to below 0.5% with a ~90% recovery. Solids purified in this manner were isolated as a solvate and contained about 7% methanol.

Scheme 7



Reduction of Olefin 15. At this point in the synthesis we hoped to apply the chemistry developed in-house for previous pioglitazone syntheses for the reduction **15** to **2**.[17] The initial reduction of **15** using these conditions proved-problematic in that the reaction would stall after 80% conversion (eq 4).

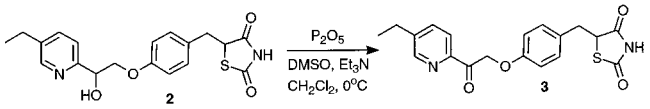


Attempts to restart this reduction by adding either more $NaBH_4$ or $CoCl_2$/DMG (dimethylglyoxime) catalyst did not consume the remaining **15**. In addition to this reduction stalling, we saw the need to develop a less cumbersome workup.

We quickly identified conditions to prevent this reduction from stalling by adjusting the reaction stoichiometry.[17,18] Optimal conditions for reduction were found to be: to a stirring solution of **13** (1 equiv), $CoCl_2$ (0.0006 equiv), and DMG (0.029 equiv) in H_2O, THF, and 1 N NaOH (1.6:1:1.1) was added dropwise a solution of $NaBH_4$ (1.44 equiv) dissolved in 0.2 N NaOH, maintaining the internal temperature between 15 and 20 °C. The observed blue/purple reaction mixture gives a visual indication that reduction is taking place, and consequently, when the reaction becomes yellow, no reduction is occurring. The ideal pH range for this reduction was determined to be between 9 and 11. We found that if the reaction pH becomes greater than 11, it can be restarted by lowering the pH with acetic acid. Once the reduction was complete, excess acetone was added to consume any remaining $NaBH_4$, and the crude product **2** was extracted into EtOAc. The complex workup procedure described in the earlier syntheses was avoided, and simple extraction into EtOAc was effective. A near quantitative yield for this reduction has been observed, providing **2** in greater than 95 area% purity.

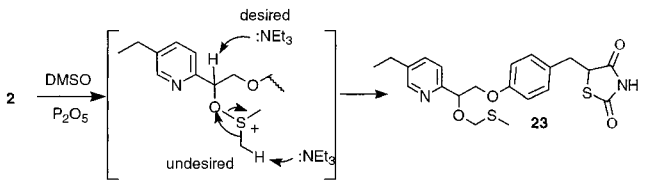
Although **2** could be isolated and purified, this added an additional purification step to our synthesis, and it was desirable, given the excellent yield and high purity of **2**, to not isolate this material but to use it crude in the subsequent oxidation. This idea presented a few challenges to include extraction of **2** into CH_2Cl_2 in which **2** was not significantly soluble, as well as determining if having THF (from the reduction) in the subsequent oxidation reaction would be problematic. The former was easily tested, and it was found that after reduction of **15**, extraction of crude **2** into CH_2Cl_2 proved quite facile (probably due to the THF present); however, **2** was found to precipitate from this solution if left standing at 20−25 °C. The next question that needed attention was the impending THF that was present in the CH_2Cl_2 from the reduction step. Control reactions conducted employing up to as much as 20 vol % THF in the oxidation found that this did not compromise reactivity or product quality. Because repeated distillation of the THF from CH_2Cl_2 would prove cumbersome upon scale-up, it was decided to add the appropriate amount of DMSO which was to be used for the oxidation and subsequently distill the THF and CH_2Cl_2 under vacuum, leaving the product as a solution in DMSO. This method proved successful at removing all or most of the THF from the DMSO, and oxidation of **2** using this solution has been carried out without incident (vide infra).

Oxidation of 2. Prior unoptimized efforts for the oxidation of **2** to **3** in our group on small kilogram scale proved problematic with respect to isolation of the final product.[19] Purification of **3** required silica gel chromatography followed by several upgrade recystallizations giving **3** in 40−45% yield. While many oxidation conditions were tested, only conditions reported by Taber were successful.[1,20] Following a modified Taber procedure, oxidation of **2** was carried out by treatment of a slurry of P_2O_5 (2.5 equiv) in CH_2Cl_2 cooled to 0 °C with a solution of **2** dissolved in DMSO (8 equiv)/CH_2Cl_2 followed by the addition excess Et_3N (eq 5).



While oxidation of **2** to **3** occurred without incident, 10−25% of an impurity was formed under these reaction conditions. Although not identified prior to our efforts, the known Swern oxidation pathway would expect to yield **23** as a potential byproduct (Scheme 8).[21]

Scheme 8



(17) Huber, J.; Hewitt, B. Pharmacia Corp., Early Process Research & Development, Kalamazoo, MI. Unpublished results.
(18) Leutenegger, U.; Madin, A.; Pflatz, A. *Angew Chem., Int. Ed. Engl*. **1989**, *28*, 60.

Disappointingly, the use of the more bulky base diisopropylethylamine (DIPEA) did not suppress it's formation; thus, this impurity was isolated and characterized and found to be consistent with ketone **24** and not the initial hypothesis of **23** (Figure 3).

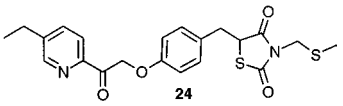
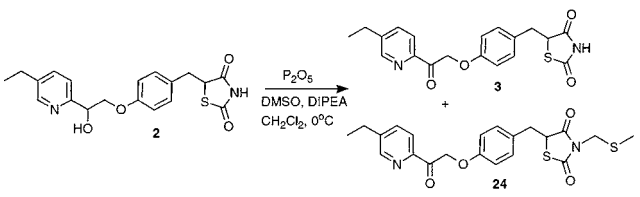


Figure 3.

Formation of **24** can be rationalized by the fact that as oxidation of **2** to **3** slows, **3** could react with any activated DMSO complex providing **24**. To test this hypothesis, **3** was submitted to the oxidation conditions and after stirring at room temperature for 24 h provided **24** in quantitative yield. After reexamination of the current oxidation conditions using 2.5 equiv of P_2O_5 and 8 equiv of DMSO, it seemed reasonable that if the amount of activated DMSO complex was decreased, less alkylation on the imide would result. Therefore, oxidation of **2** to **3** was carried out using 2.5 equiv of P_2O_5 and 5 equiv of DMSO stirring at 0 °C, and the reaction progress was monitored by HPLC analysis. Normally, **2** is dissolved in DMSO prior to addition; however, by employing less DMSO in this reaction we encountered solubility problems and had to add **2** as a DMSO slurry. After stirring for 50 h, oxidation stalled at 75% conversion, however, only 7% of **24** was detected by HPLC. In an effort to understand the relative rate of oxidation, we carried out an experiment in which we removed reaction samples over a 50-h period and recorded the relative amounts of **3** and **24**. We were surprised to find that almost all of the oxidation was complete within 45 min, and that as reaction time continued, both **2** and **3** decreased. This analysis was key to understanding that to obtain the highest yield for this oxidation, we needed to allow **2** to react with an excess of activated DMSO complex at low temperature for about 1 h and then quench the reaction. To test this hypothesis, oxidation of **2** now employed 5 equiv P_2O_5 and 10 equiv of DMSO in CH_2Cl_2 at −30 °C followed by the addition of 3 equiv of DIPEA; HPLC analysis showed that 15% of **2** remained after 45 min and that very little (approximately 4%) of **24** was produced. Alternatively, running this reaction at 0 °C gave complete consumption of **2** and between 3 and 7% of **24** which could be removed in the recrystallization step (eq 6).



During our development of this oxidation, we noticed that the quench method seemed to affect the amount of **24** observed. It was found that if water (pH = 7) was added *to* the crude reaction mixture, the amount of **24** observed after the workup was significantly higher than it was prior to workup. Alternatively, if the crude oxidation mixture was quenched *into* water (pH = 7), the amount of **24** before and after workup remained the same. Current conditions now call for this oxidation to be quenched into water (pH = 7). Unfortunately, after extraction with methylene chloride, the resultant product did not crystallize, presumably due to residual DMSO present after the extractions. Subsequent aqueous washes of the combined CH_2Cl_2 layers were not successful at removing this DMSO. Alternatively, the crude oil could be dissolved in EtOAc and washed with water (pH = 7) which after removal of the solvent, provided **3** as an off-white to light-yellow/orange solid. Recrystallization of this material from absolute ethanol (25 mL/g) provided **3** as a colorless solid.

Conclusions

Herein we have described a six-step synthesis of the antidiabetic candidate **3** in an overall 25% yield from olefin **12**. The regiochemical ring opening of epoxide **13** with 4-hydroxybenzaldehyde proved difficult; thus, we chose a nonselective phase-transfer reaction on the basis of ease of workup, giving up to as much as 20% of the undesired ring-opened product. This mixture was carried on crude into the Knoevenagel condensation at which time the undesired product could be removed. The reduction conditions in step 5 were greatly improved from past analogue syntheses with a simplified extractive workup. Controlling the stoichiometry, temperature, and reaction time proved vital to obtaining a high yield in the final oxidation reaction.

Experimental Section

General Procedures. ^1H and ^{13}C spectra were obtained using a Bruker Avance 400 in dilute d_6-DMSO or $CDCl_3$ solution. Chemical shifts are reported as δ (ppm) values from Me_4Si as an internal standard.

5-Ethyl-2-oxiran-2-ylpyridine (13). To a dry, nitrogen-purged 4000-L glass-lined reactor was added NBS (133 kg, 747.4 mol, 1.22 equiv) and water (815 L), and the resultant slurry was cooled to 0 °C. To a separate dry nitrogen-purged 4000-L glass-lined reactor (add reactor) was added *tert*-butyl alcohol (122 kg) followed by ethyl vinyl pryidine **12** (81.6 kg, 612.6 mol, 1 equiv) and this homogeneous dark solution was cooled to 0 °C at which time glacial acetic acid (40.5 kg, 674.4 mol, 1.1 equiv) was added, resulting in a 4 °C exotherm. This *tert*-butyl alcohol/**12**/HOAc solution was then added to the NBS slurry at rate to maintain the internal temperature below 10 °C. Once this addition was complete, the reaction was allowed to stir at ca. 10 °C. After 1 h, the dark-yellow reaction slurry was assayed by TLC and GLC, indicating that no **12** remained. The reaction was then quenched with excess 2 N NaOH (1200 L) at a rate to maintain the internal temperature below 25 °C. During this addition the reaction color changed from a bright yellow to a very dark brown. After the addition of the 2 N NaOH, the reaction stirred for 30−60 min and was judged complete by GLC analysis. The crude epoxide was then extraced into

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(21) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651.

MTBE (305 kg, 412 L) followed by the addition of DW water (496 L) and sodium chloride (158 kg). The aqueous layer was separated and subsequently extracted twice with MTBE (147 kg, 193 L), and the combined organic layers were then distilled under vacuum to an approximate 1:1 volume of product to MTBE and then transferred into drums. The crude isolated yield for this reaction was found to be 95% (87.1 kg of epoxide **13**), and the purity for this material was 92.7 area % (GLC). This epoxide was used without further purification, and these drums where stored cold until needed for step 2. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 7.36 (m, 1H), 7.17 (m, 1H), 3.61 (s, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.80 (q, $J = 7.6$ Hz, 2H), 1.90 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.31, 148.96, 138.67, 135.94, 119.28, 52.59, 50.01, 28.33, 25.67, 15.15.

4-[2-(5-Ethylpyridin-2-yl)-2-hydroxyethoxy]benzaldehyde (14). To a dry, nitrogen-purged 4000-L glass-lined reactor was added 4-hydroxybenzaldehyde (108.8 kg, 890. mol, 1.5 equiv), poly(ethylene glycol) 4000 (PEG4000) (14.6 kg) and 1 N NaOH (843 L), resulting in a dark homogeneous solution. To this mixture was added toluene (896 L) followed by the crude epoxide **13**/MTBE solution (87.1 kg, 583.8 mol, 1 equiv), and the contents were heated to ca. 78 °C for approximately 13−17 h at which time the reaction was assayed by HPLC. Once complete (<3% starting **13**), the reaction was cooled to room temperature, and the layers were allowed to separate. The aqueous layer was separated and extracted with toluene (3 × 405 L), and the combined organic layers were washed twice with 1 N NaOH (594 L) and once with DW water (405 L). The organic layer was distilled under vacuum to about 300 L at which time the crude reaction was transferred into drums to determine yield. *Note: It has been observed that concentration of this material to low volume can cause the product to precipitate from solution*. The crude yield for this reaction was determined to be 57.3% (92.3 kg product **14**) whose HPLC assay indicated a 18.5/81.5 product ration of **18** to **14**. The crude product was then charged back into the reactor, the drums were rinsed with toluene, and the mixture was vacuum-distilled to dryness, affording a black solid. **14:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.86 (s, 1H), 8.41 (s, 1H), 7.78 (m, 2 H), 7.57 (m, 2 H), 7.40 (m, 2 H), 7.02 (m, 2 H); 5.14 (t, $J = 5.6$ Hz, 1 H), 4.67 (s, 1 H), 4.27 (m, 2 H), 2.65 (q, $J = 5.2$ Hz, 2 H), 1.23 (t, $J = 5.2$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.69, 163.6, 155.63, 148.09, 138.74, 136.28, 131.86, 130.11, 120.76, 114.87, 72.58, 71.20, 25.71, 15.20. (**18**) ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 8.36 (s, 1 H), 7.67 (m, 2 H), 7.41 (m, 1 H), 7.20 (m, 1 H), 6.94 (m, 2 H), 5.41 (t, $J = 5.6$ Hz, 1 H), 4.00 (d, $J = 5.6$ Hz, 2 H), 2.56 (q, $J = 7.6$ Hz, 2 H), 1.16 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.66, 161.77, 153.60, 148.07, 138.02, 135.55, 130.92, 129.35, 119.74, 114.94, 80.30, 64.64, 24.76, 14.06.

(5*Z*)-5-{4-[2-(5-Ethylpyridin-2-yl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (15). To a dry, nitrogen-purged 4000-L glass-lined reactor (add reactor) was added thiazolidine-2,4-dione (41.4 kg, 353 mol, 1.1 equiv) followed by methanol (1150 L) and then stirred at ca. 25 °C until dissolved. This solution was then transferred into a 4000-L reactor that contained crude **14** (87 kg, 320 mol, 1 equiv) and was stirred at ca. 25 °C until all the solids were dissolved at which time pyrrolidine (22.9 kg, 320 mol, 1 equiv) was added. This reaction mixture was then heated to ca. 38 °C to 42 °C for at least 1 h and then assayed. Once complete, the contents were cooled to ca. 25 °C, and the pH was adjusted to less than 7 with acetic acid (21.1 kg). The reaction was then distilled to about 100 L and then cooled to ca. 20 °C to effect crystallization of the desired product. These solids were collected by filtration and washed twice with cold (−5 °C) methanol (110 L) followed by washing with 20 °C water (3 × 160 L) and then blown dry with heated single-pass nitrogen (35−40 °C), affording 70.4 kg (59%) of **15** as a dark solid. **Recrystallization of crude 15:** To a dry, nitrogen-purged 4000-L glass lined reactor was added crude PNU-276559 (**15**) (70.4 kg, 190 mol) followed by methanol (1050 L). The resultant slurry was then heated to reflux for at least 60 min. *Note: Not all solids are dissolved after this time*. The reaction was then cooled to ca. 25 °C over at least 30 min at which time the reaction was further cooled to ca. 0 °C over a 30-min period and stirred for at least 30 min at this temperature. The resulting solids were collected by filtration and washed with cold (0 °C) methanol (3 × 115 L). The solids were dried with single-pass nitrogen heated to ca. 35−40 °C until the residual methanol content was between 6 and 8 wt %, affording 66.8 kg (95%) of **15** as a slightly colored solid. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.40 (s, 1H), 7.44 (s, 1H), 7.66 (m, 1H), 7.52 (m, 2H), 7.11 (d, 2H), 5.83 (bs, 1H), 4.98 (bs, 1H), 4.39 (m, 1H), 4.19 (m, 1H), 2.61 (q, $J = 7.6$ Hz, 2H), 1.19 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 168.29, 167.80, 160.74, 158.70, 148.32, 138.00, 136.23, 132.39, 132.14, 135.85, 120.97, 120.64, 115.81, 72.83, 72.18, 25.37, 15.70.

5-{4-[2-(5-Ethylpyridin-2-yl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione (2). To a clean dry 5-L round-bottom flask was added alcohol **15** (100 g, 0.29 mol), $CoCl_2$ (0.045 g, 0.0002 mol), DMG (0.91 g, 0.0078 mol) followed by water (295 mL), THF (175 mL), and 1 N NaOH (185 mL). To this resulting solution was added at room temperature, $NaBH_4$ (15.7 g, 0.42 mol) dissolved in 0.2 N NaOH (240 mL) over 30 min, resulting in a deep-purple solution. The reaction was adjusted to pH ≈ 10 with acetic acid and monitored by HPLC until complete (less than 3% **15** remaining). Once judged complete, the reaction was quenched by slow addition of acetone (150 mL). After stirring for 15 min, the reaction was was adjusted to pH ≈ 3 with 6 N HCl and then to pH = 7 with 2 N NaOH. The product was extracted into CH_2Cl_2 (3 × 500 mL) and then concentrated to dryness to afford 103 g (>100%) of alcohol **2** as a solid. This material could be used without purification. Spectral data were consistent with literature values.[1]

5-{4-[2-(5-Ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (3). To a dry 250-mL round-bottom flask was added P_2O_5 (9.52 g, 67.1 mmol) followed by CH_2Cl_2 (40 mL) giving a stirrable slurry. Once the reaction cooled to 0 °C, **2** (5.0 g, 13.42 mmol) dissolved in DMSO

(9.5 mL, 10 equiv) was added dropwise, maintaining an internal temperature of about 0 °C, causing the contents to become orange. After stirring for 15 min, DIPEA (7 mL, 40.26 mmol) was added dropwise, maintaining an internal temperature of about 0 °C, causing the contents to become homogeneous. After stirring for 45 min, the reaction mixture was poured into water (pH = 7). The product was extracted into EtOAc (3 × 50 mL), the combined organic layers were washed with water (pH = 7) (3 × 50 mL), and the solvent was removed in vacuo. The resultant solid was then recrystallized from ethanol (25 mL/g) to afford 3.72 g (75%) of **3** as a white solid. Spectral data were consistent with literature values.[1]

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