

A Practical and Economical Route to (*S*)-Glycidyl Pivalate

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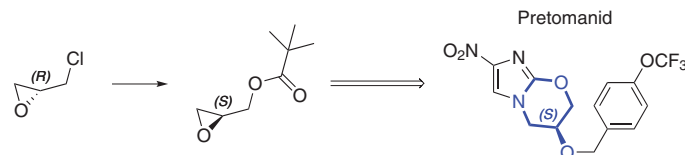
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Abstract An efficient method to prepare enantiopure (*S*)-glycidyl pivalate from (*R*)-epichlorohydrin and pivalic acid is reported. This work provides an alternative to the synthesis of this important building block from readily available and inexpensive materials.

Key words tuberculosis, API, pretomanid, epichlorohydrin, supply centered synthesis

Tuberculosis is one of the leading global causes of mortality, and it is believed that one third of the population has a latent case of the disease.¹ Pretomanid[®] is a therapy for treatment of tuberculosis that was recently approved by the US FDA under the Limited Population Pathway (LPAD Pathway) for treatment of pulmonary extensively drug resistant (XDR) tuberculosis in combination with Bedaquiline[®] and Linezolid[®]. It works as a respiratory poison against bacteria by releasing nitric oxide under anaerobic conditions.

Given the large quantities of drug substance that would be required to treat tuberculosis throughout the world, cost-effective syntheses are needed. A key structural feature of Pretomanid[®] is the dihydro-1,3-oxazine, containing an oxygen-substituted asymmetric center on the C₃ unit (Figure 1). One could foresee installation of this fragment from an (*S*)-glycidol derivative, and, not surprisingly, many of the current Pretomanid[®] routes make use of functionalized glycidols.²

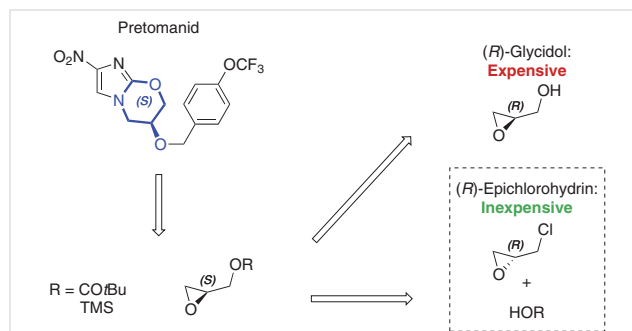
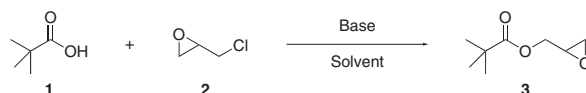


Figure 1 Pretomanid[®] retrosynthesis from glycidol and derivatives

Glycidyl pivalate appears to be a particularly important variant.³ However, optical enantiomers of glycidol are of considerable expense and construction from less expensive precursors would be desirable. Epichlorohydrin is a feed-stock chemical, and its pure enantiomers are more readily available in comparison to those of glycidol. As a result, (*R*)-epichlorohydrin is approximately 5–6% of the cost⁴ of (*S*)-glycidol and could thus form the basis of a more cost-effective route to this intermediate.

Numerous reports describe reaction of epichlorohydrin with carboxylates, particularly hindered carboxylates, as the ensuing glycidyl esters are used in alkyd resins, paints, coatings, and acrylate monomer compositions.⁵ Fewer reports detail the reaction of enantiopure epichlorohydrin with carboxylic acid derivatives.^{5i–k} This work describes the development of a practical route to (*S*)-glycidyl pivalate from low-cost and readily available (*R*)-epichlorohydrin and pivalic acid.

Our investigation began by screening typical conditions used to couple acids with racemic epichlorohydrin (Table 1). Variations in the numbers of equivalents of starting ma-

Table 1 An Initial Screen of Conditions for Glycidyl Pivalate **3** Synthesis using Racemic Epichlorohydrin **2**

Entry	2 (equiv.)	Base (equiv.)	Temp. (°C)	Time (h)	Solvent	Yield 3 (%) (LCAP)	Ref.
1	0.6	NaOH (0.25)	55	2	EtOH/H ₂ O (1:1)	ND	6
2 ^a	0.9	NaOH (1)	110	12	toluene	ND	5c
3 ^b	1.08	NaOH (1.5)	70	1–25	–	ND	5h
4	2	K ₂ CO ₃ (2)	80	12	MeCN	g ^d	7
5	5	K ₂ CO ₃ (0.02)	90	2	H ₂ O	ND	8
6 ^c	10	NaOH (1)	120	2	–	96	5d

^a 20 mol% tetrabutylammonium bromide (TBAB).

^b 8 mol% tetramethylammonium chloride (TMAC, 50% aq.).

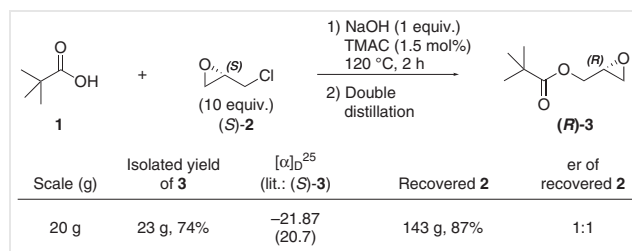
^c 1.5 mol% tetramethylammonium chloride.

^d Yield (%) determined by qNMR using 1,3,5-trimethoxybenzene as internal standard.

terial, preformation of the carboxylate, solvent, temperature, and time were explored. Introducing an excess of epichlorohydrin was advantageous (entries 4–6). Furthermore, removal of exogenous solvent led to the best results, giving glycidyl ester **3** in greater than 95% yield by NMR assay. While a high stoichiometry of epichlorohydrin was employed, we were encouraged that these conditions could be rendered economical if excess starting material were to be recovered.

We subsequently shifted our focus to isolation of the desired compound from the reaction mixture, and the reaction scale was increased to 20 g of pivalic acid and 182 g (10 equiv) of (*S*)-epichlorohydrin (Scheme 1). The reaction of sodium pivalate with epichlorohydrin produced one equivalent of sodium chloride that was easily removed by filtration because of its low solubility. Next, the epichlorohydrin (bp 118 °C) was evaporated and collected and a high proportion of the excess epichlorohydrin was recovered, an important consideration in rendering an economically viable synthesis (143 g, 87%). The residual crude glycidyl pivalate (33 g, contaminated with ca. 6% epichlorohydrin) was distilled twice at 50–70 °C under high vacuum (ca. 6–10 Torr), resulting in 74% isolated yield of the pure glycidyl pivalate. The compound appeared to be temperature sensitive at high concentration, and thus short distillation times were optimal. The product showed good specific activity (–21.9, CHCl₃, 25 °C), as compared to literature values for (*S*)-glycidyl pivalate (+20.7);⁹ however, the sign of rotation was inverse, indicating that the undesired (*R*)-enantiomer had been made. Therefore, starting from (*R*)-epichlorohydrin led to (*S*)-glycidyl pivalate samples with [α]_D values of 18.8 and 18.9. Attack of the pivalate anion on the epoxide rather than the primary chloride rationalizes this observation. De-

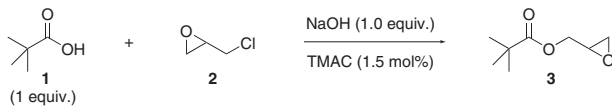
spite these highly encouraging results, analysis of the recovered epichlorohydrin revealed that the epichlorohydrin racemized over the course of the reaction.

**Scheme 1** 20 g scale-up transposed from initial conditions with isolation of optically pure glycidol pivalate

Further reaction screening was required to identify a cost-effective system. Our approach was that either epichlorohydrin epimerization would need to be fully suppressed or that consumption of epichlorohydrin would need to be decreased in order to negate the requirement of starting material recycling. We first explored suppression of epimerization with the thought that, at lower temperatures, the rate of substrate racemization might be significantly slower. The esterification was carried out at 60 °C, which gave 98% yield of product by NMR analysis. At this temperature, the enantiomeric ratio increased from 50:50 to 90:10 (Table 2, entries 1–2). While this was a positive development, further improvements were still required. The high assay yield (AY) was maintained at 50 °C, and the enantiomeric ratio was increased to 95:5 (entry 3). This moved the conditions toward economic viability; however, even the slight erosion of optical activity limits the ability to recycle epichlorohydrin.

Removing the need to recycle the epichlorohydrin would be preferable as it would simplify the procedure. If the epichlorohydrin equivalence could be reduced, the economic driver to recycle the starting material would be eliminated. However, simply reducing the equivalents of epichlorohydrin led to much lower yields, and a large amount of decomposition was observed (Table 2, entries 4 and 5). The root cause was believed to be heat sensitivity, where bimolecular degradation of the product was most likely accelerated at elevated concentrations. To evaluate this hypothesis, the reaction was investigated with 3 and 6 equivalents of epichlorohydrin, but diluted with inert chlorobenzene to a volume equivalent to that of 10 equivalents of epichlorohydrin. This did indeed provide a significant increase in yield up to and above 80% (entries 6 and 7). Decreasing temperature to 60 °C was found to be the best solution as it further increased yield, avoided the need for exogenous solvent, greatly increased throughput of material, and rendered the system highly economical as compared to glycidol.

Table 2 Optimization of the Synthesis of Glycidyl Pivalate^a



Entry	2 (equiv.)	Temp. (°C)	Time (h)	AY 3 (%) ^b	2 ^{er} (R/S)
1	10	120	3	96	50:50
2	10	60	3	98	90:10
3	10	50	17	96	95:5
4	6	120	3	62	–
5	3	120	3	13	–
6 ^c	6	120	3	88	–
7 ^c	3	120	3	80	–
8	6	60	3	76	–
9	6	60	24	98	–
10	3	60	3	61	–
11	3	60	24	93	–

^a Reaction conditions: Pivalic acid (1 g) combined with epichlorohydrin, NaOH (0.39 g, 1.0 equiv.) and TMAC (0.021 g, 1.5 mol%) added. 1,3,5-trimethoxybenzene (0.165 g, 1.0 equiv.) added as an internal standard. Reaction heated and monitored by quantitative NMR.

^b Assay yield.

^c Chlorobenzene added as solvent to reach volume equivalent to reaction volume at 10 equiv. of epichlorohydrin.

With the optimized preparative procedure, we then investigated glycidyl pivalate isolation methods. Two feasible solutions were identified as (1) *in situ* solution of glycidyl pivalate, or (2) distillation to access a higher purity of product.

Each approach has benefits and drawbacks. The first option is desirable, in that it avoids distillation of epoxide **3**. Some temperature sensitivity was noted for epoxide **3**, and production of a reactive solution could maximize yield by limiting the heat history and concentration of the epoxide. However, this approach does not provide a means of purifying the glycidyl pivalate, and the excess epichlorohydrin must still be removed. If successful, the second option provides a means of removing byproducts from the glycidyl pivalate to obtain a more highly controlled and pure product.

Production of an *in situ* solution was explored first (Figure 2). Changing the reaction solvent to toluene was considered desirable as toluene could be used in the subsequent steps. In first attempts toward this goal, epichlorohydrin was directly distilled from the reaction mixture under vacuum, and then toluene was added intermittently to compensate for the volume lost from epichlorohydrin evaporation. Volatiles were then fully removed to give a glycidyl pivalate residue. The process was repeated three times. This led to a loss of active glycidyl pivalate in solution, as observed by decrease in the NMR assay (10–15%) and the observation of unidentified by-products (Figure 2).

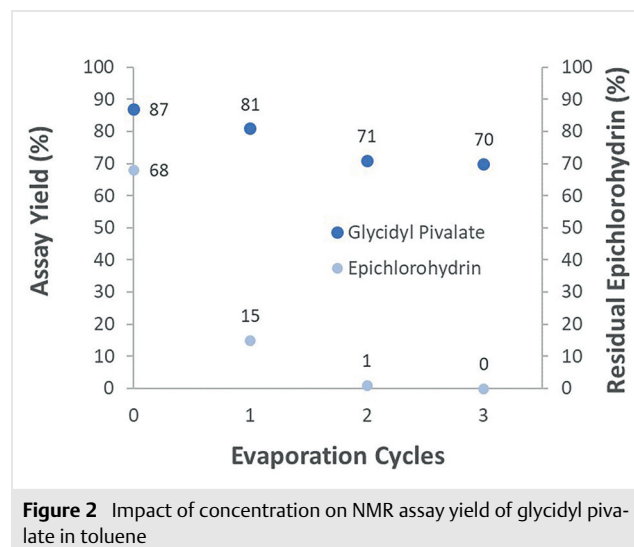


Figure 2 Impact of concentration on NMR assay yield of glycidyl pivalate in toluene

Again, heat and concentration sensitivities were suspected to cause the loss in yield. If the solvent replacement could be conducted while maintaining constant volume, the decomposition would be expected to be mitigated by the maintained concentration and less direct heat application. This was accomplished by adding toluene continuously to a stirred solution of the glycidyl pivalate reaction mixture whilst under vacuum (Figure 3). Performing the solvent exchange in this manner largely prevented the loss of active glycidyl pivalate to decomposition products. The reaction mixture had a 94% NMR yield at the end of reaction and a

90% NMR yield after removal of epichlorohydrin after toluene solvent exchange. This yielded a solution of epoxide **3** that could be used for the subsequent alkylation step.^{2b}

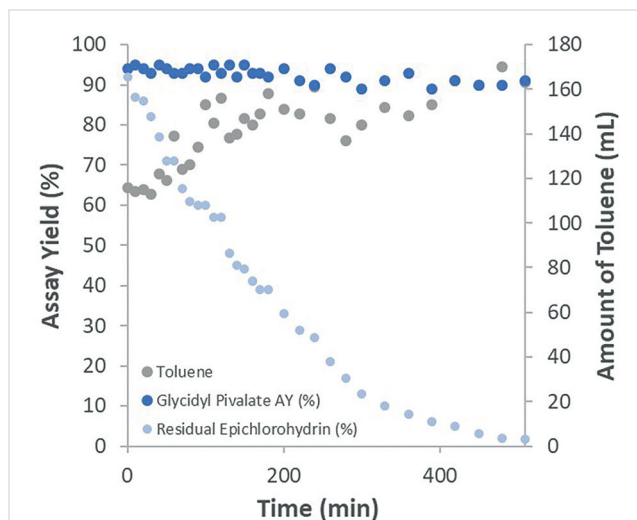
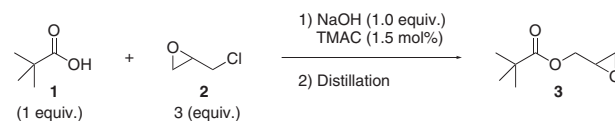


Figure 3 Solvent exchange of epichlorohydrin for toluene with continuous addition of toluene to maintain constant volume

Next, we attempted to isolate glycidyl pivalate in good purity by direct distillation¹⁰ (Table 3). Firstly, the sodium chloride was removed from the reaction mixture by filtration, and then the excess epichlorohydrin was removed from the filtrate by evaporation under reduced pressure. Care was taken to remove the epichlorohydrin at low temperature (<60 °C) under high vacuum (<10 torr). After evaporation, the NMR assay yield of the crude glycidyl pivalate residue was 87%. The product was then distilled. Again, it was important to carry this out under reduced pressure so that the temperature of the glycidyl pivalate did not exceed 70 °C. At higher temperature, lower yields were observed as a result of product decomposition. Optimal conditions used in this work were to distil at 50 °C and 6 Torr. This is likely a function of system configuration, which can be further optimized upon subsequent implementation, and might benefit from a continuous distillation system such as a thin-film evaporator so as to minimize thermal exposure of the heat-sensitive compound. In this way, the isolated yield of **3** reached 76% with material of 95% purity.

The optical purity of the epoxide samples was confirmed through derivatization with 4-nitro-2-bromimidazole. The derivatives synthesized from optically active epichlorohydrin were compared against those of racemic epichlorohydrin by HPLC. Supercritical fluid chromatography traces indicated an enantiomeric ratio of 97:3,¹¹ which was consistent with the high optical purity observed from the specific rotation (see the Supporting Information for the derivatization procedure).

Table 3 Scale-Up for the Synthesis of Glycidyl Pivalate



Entry	Scale (g)	AY 3 , EOR (%) ^a	AY 3 , Epi. Removal (%)	IY 3 (%) ^b	Assay (wt%)	Residual 2 (%)
1	10	98	81	40	99	1.0
2	20	90	83	66	96	0.0
3	40	92	87	76	95	0.2

^a End of Reaction (determined by qNMR with an internal standard of tri-methoxybenzene)

^b Isolated yield.

In conclusion, we have developed an efficient method to prepare enantiopure (*S*)-glycidyl pivalate from (*R*)-epichlorohydrin and pivalic acid. We believe this work provides an alternative to the synthesis of this important building block from readily available and inexpensive materials.

Starting materials, reagents, and solvents were purchased from commercial sources and were used as received unless otherwise noted. The reactions were monitored with a Bruker Avance III 600 MHz NMR spectrometer, using 1,3,5-trimethoxybenzene as internal standard. Solvents were removed under reduced pressure using a rotary evaporator. Purification was performed using vacuum distillation (see the Supporting Information for more information).

Synthesis of Glycidyl Pivalate (*S*-**3**)

To a solution of pivalic acid **1** (20 g, 196 mmol, 1 equiv) in (*R*)-epichlorohydrin **2** (54.4 g, 587 mmol, 46.1 mL, 3 equiv) were added NaOH (7.8 g, 196 mmol, 1 equiv, pellets) and TMAC (430 mg, 4 mmol, 0.02 equiv) at r.t. in one portion. The suspension was then stirred at 50 °C until the reaction was complete as monitored by NMR analysis, with 1,3,5-trimethoxybenzene being used as an internal standard. Once complete, the reaction suspension was filtered and washed with DCM (30 mL). The DCM was then removed by rotary evaporation and the reaction mixture was purified by vacuum distillation. (*S*)-Glycidyl pivalate was obtained in high purity (>95%) and 63% yield.

$[\alpha]_D^{25} +19.1$ (c 1.8, CHCl₃, 25 °C).

¹H NMR (600 MHz, DMSO-*d*₆): δ = 4.38 (dd, *J* = 2.26, 12.46 Hz, 1 H), 3.85 (dd, *J* = 5.92, 12.50 Hz, 1 H), 3.17 (m, 1 H), 2.77 (t, *J* = 4.42 Hz, 1 H), 2.62 (dd, *J* = 2.38, 4.86, 1 H), 1.17 (s, 9 H).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 177.11, 64.41, 48.94, 43.54, 38.22, 26.79.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0042-1751375>.

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