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# A Concise and Convergent Synthesis of PA-824

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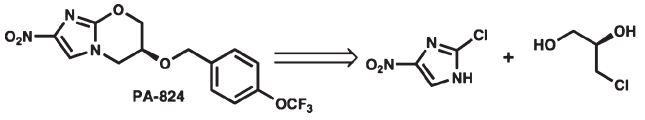


An efficient four-step synthesis of PA-824, a promising antituberculosis drug candidate, has been developed. This concise approach offers significant improvements over the synthetic route currently used for large-scale production.

Tuberculosis (TB) is a devastating bacterial infection that kills more than 1.8 million people each year worldwide.[1] Over 98% of TB fatalities result from one specific bacterial strain, *Mycobacterium tuberculosis* (Mtb), where the presence of a single bacterium can propagate a fatal infection. Although Mtb was identified nearly 130 years ago and antibiotics have been available to treat TB since the 1940s, this pathogen remains a persistent problem because of the emergence of multidrug resistant (MDR-TB) and extremely drug resistant (XDR-TB) strains, as well as the lack of resources available to provide drugs to endemic areas. As the FDA has not approved a new TB-specific drug in over 40 years, there exists a critical need for the development of new TB treatments that can be deployed on a large scale to developing areas of the world where the disease is most harmful.[2]

Currently, there are at least ten anti-TB drug candidates with varying biological mechanisms of action being evaluated in clinical trials.[3] These therapies fit into two general classes: (1) those already used in first- and second-line treatment of active TB, and (2) those with novel mechanisms of action against both replicating and nonreplicating TB. Among the second group, bicyclic nitroimidazoles have emerged as a promising structural class (Figure 1).[4] While metronidazole (**2**) is widely used as a general antibacterial treatment, PA-824 (**1**) stands out as an exciting experimental anti-TB drug candidate.[5] PA-824 was found to inhibit TB with minimum inhibitory concentration (MIC) values of 0.015−0.25 $\mu$g/mL.[6] Furthermore, several strains of MDR-TB exhibited comparable susceptibility to PA-824, indicating a lack of potential cross-resistance with current MDR-TB therapies.[7] PA-824 is being developed by the Global Alliance for TB Drug Development (GATB) and is now in advanced phase II clinical trials.[8]

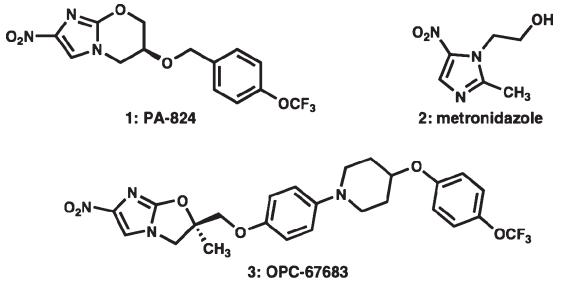


**FIGURE 1.** Nitroimidazole drug candidates for tuberculosis.

In replicating TB, compounds **1** and **3** are believed to inhibit Mtb cell wall formation by disrupting mycolic acid synthesis.[9] However, the primary mechanism of action in both replicating and nonreplicating TB is believed to involve reduction of the imidazole ring by Fgd1, an $F_{420}$-dependent glucose-6-phosphate dehydrogenase, and Rv3547, a deazaflavin-dependent nitroreductase, after passage through the bacterial cell membrane to afford the des-nitro compound and nitric oxide (NO).[10] Cyclic voltammetry studies[11] have since justified and guided the synthesis and biological investigation of several analogues of PA-824 (**1**) and OPC-67683 (**3**).[12]

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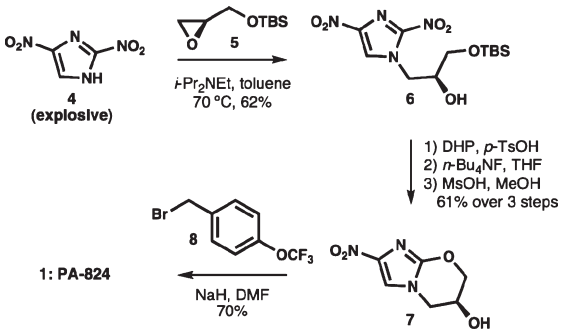
**SCHEME 1. Original Production Process for PA-824**[a]




[a]DHP = 3,4-dihydropyran; *p*-TsOH = *p*-toluenesulfonic acid; MsOH = methanesulfonic acid.

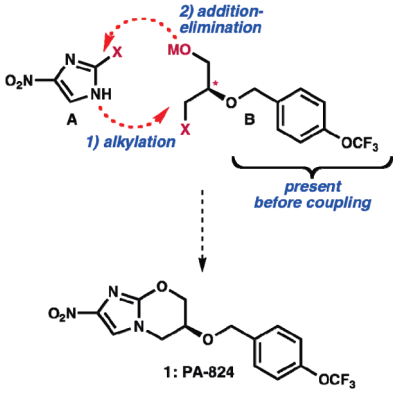
The original synthesis used to obtain material for clinical trials provides PA-824 in five linear steps from 2,4-dinitroimidazole **4** (Scheme 1).[13] Unfortunately, dinitroimidazole **4** is explosive, and both **4** and the starting epoxide **5** are expensive for use on large scale. Furthermore, the synthesis requires four chromatographic separations and an inefficient protection−deprotection sequence in order to selectively construct the oxazine core that are not suitable for use in a kilogram-scale process. A solventless modification of this pathway has also been developed.[14]

Since the overall cost of any anti-TB drug is a major factor in future production and necessitates a safe, efficient, and economic synthesis of this active compound, we set out to develop a synthesis of PA-824 that would address these concerns and be amenable to large-scale process development (Scheme 2).

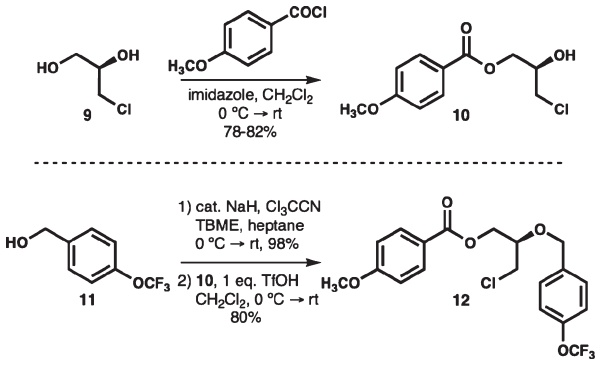
Our key tactical consideration hinges upon the direct, convergent coupling of a suitably safe alternative to 2,4-dinitroimidazole (**A**) and an appropriately functionalized pseudosymmetrical glycidol derivative (**B**). Ideally, glycidol **B** would contain the essential *p*-(trifluoromethoxy)benzyl ether moiety with the correct stereochemical configuration as well as functional groups to enable either a direct or stepwise construction of the central six-membered oxazine ring.

Our studies began with the synthesis of a suitable glycidol derivative (Scheme 3). (*R*)-3-Chloro-1,2-propanediol (**9**), which is commercially available and easily obtainable from the hydrolytic kinetic resolution (HKR)[15] of racemic epichlorohydrin on ton-scale, is selectively benzoylated to afford chlorohydrin **10** in 78−82% yield and >99% ee without the need for further purification. We chose the *p*-methoxybenzoyl group as

**SCHEME 2. General Synthetic Strategy**




**SCHEME 3. Synthesis of a Functionalized Glycidol Derivative**[a]




[a]$Cl_3CCN$ = trichloroacetonitrile; TBME = *tert*-butylmethyl ether; TfOH = trifluoromethanesulfonic acid.

a removable trigger for our proposed oxazine construction because of its stability and migratory resistance.[16] To circumvent epoxide formation, benzylation of **10** was accomplished under acidic conditions utilizing the benzyltrichloroacetimidate derived from *p*-(trifluoromethoxy)benzyl alcohol **11** and stoichiometric trifluoromethanesulfonic acid in $CH_2Cl_2$ at 0 °C in 80% yield. This sequence assembles the desired chloride **12** in two linear steps from chloride **9** and 60% overall yield.

While the glycidol-derived alkyl chloride **12** was anticipated to be relatively unreactive as an alkylating agent, we observed that the desired *N*-alkylation of 2-chloro-4-nitroimidazole **13** (CNI)[17] could be achieved by the action of sodium iodide and potassium carbonate on a mixture of **12** and **13** in DMF at 120 °C (Scheme 4). This union was completely regioselective, most likely due to the bulkiness of the alkylating agent and higher reaction temperature, and afforded the desired product **14** in yields ranging from 40% to 50% after recrystallization of the crude reaction mixture. This alkylation step offers a significant advantage to the existing route by circumventing the need for an excess of expensive reagents to obtain the desired regioselectivity.

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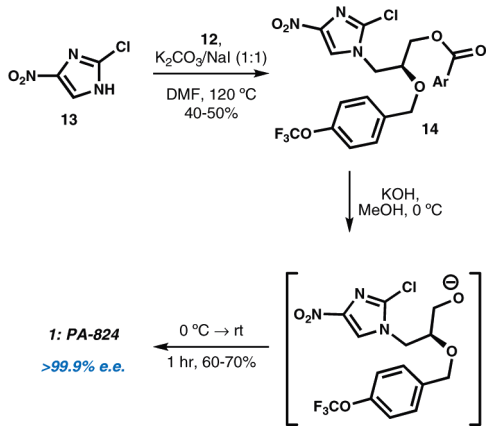
(17) (a) 2-Chloro-4-nitroimidazole **13** (CNI) is a non-explosive, crystalline compound that is commercially available from Asahi Kasei. For information concerning the preparation of 2-halo-4-nitroimidazoles and intermediates thereof, see: Wuellner, G.; Herkenrath, F.-W.; Juelich, A.; Yamada, Y.; Kawabe, S. PCT Int. Appl. WO 2010021409, August 21, 2009. (b) For an example of the use of this reagent in the synthesis of PA-824 analogues, please see: Kim, P.; Zhang, L.; Manjunatha, R. S.; Patel, S.; Jiricek, J.; Barry, C. E.; Dowd, C. S. *J. Med. Chem.* **2009**, *12*, 1317–1328.

**SCHEME 4. Synthesis of PA-824**




The key annulation of the oxazine ring could then be achieved by exposing compound **14** to 3 equiv of potassium hydroxide in methanol at 0 °C; this simple procedure effected saponification of the benzoate ester and, after warming to room temperature, anionic cyclization−elimination to produce PA-824 (**1**) in 60−70% yield and >99.9% ee after recrystallization.

The hallmarks of this efficient, concise synthesis of PA-824 include the convergent design, simplicity of reagents and experimental procedures, the utilization of the safe imidazole derivative **13**, and easy accessible chiral building block **12**. The suitability of this process for the kilogram-scale production of Pa-824 is being investigated.

## Experimental Section

**(*R*)-3-Chloro-2-hydroxypropyl-4-methoxybenzoate 10.** To a stirred solution of (*R*)-3-chloro-1,2-propanediol (6.61 g, 59.8 mmol) in $CH_2Cl_2$ (120 mL) was added imidazole (4.07 g, 59.8 mmol). After the reaction mixture had cooled to 0 °C, *p*-methoxybenzoyl chloride (10.2 g, 59.8 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise via addition funnel. The resulting solution was allowed to warm to room temperature and stirred until complete consumption of starting material by thin layer chromatography (TLC). The mixture was poured into saturated aq $NH_4Cl$ (150 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to provide chlorohydrin **10** as a clear, viscous oil (11.43 g, 78%) that was used without further purification. $R_f$ 0.3 (20% EtOAc/hexanes); ee >99% as determined by chiral SFC (see the Supporting Information); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.07−7.94 (m, 2H), 7.00−6.88 (m, 2H), 4.46 (d, $J$ = 5.1 Hz, 2H), 4.22 (dd, $J$ = 10.6, 5.3 Hz, 1H), 3.88 (s, 3H), 3.78−3.64 (m, 2H), 2.73 (d, $J$ = 5.6 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 166.7, 163.9, 132.1, 121.9, 114.0, 70.1, 65.7, 55.7, 46.3; IR [$CH_2Cl_2$ solution] $\nu_{max}$ ($cm^{-1}$) 3454, 2959, 2889, 1713, 1606, 1512, 1259, 1170, 1104, 1028, 848, 770, 697, 614; HRMS (ESI-TOF) calcd for $C_{11}H_{13}ClO_4$ $(M)^+$ 244.0573, found 244.0501.

**4-(Trifluoromethoxy)benzyl Trichloroacetimidate.** To a stirred suspension of NaH (60%, 127 mg, 3.45 mmol) in *t*-BuOMe (100 mL) was added 4-(trifluoromethoxy)benzyl alcohol **11** (5 mL, 34.5 mmol) dropwise by syringe at room temperature. After $H_2$ evolution had ceased (about 5 min), the clear mixture was cooled to 0 °C. $Cl_3CCN$ (3.46 mL, 34.5 mmol) was added dropwise by syringe, and the resulting solution was stirred for 1 h. After warming to room temperature, the solution was concentrated in vacuo, and the residue was resuspended in heptane (100 mL) containing MeOH (0.14 mL, 3.45 mmol). After 10 min of stirring, the suspension was filtered through a thin bed of silica and washed with heptane. Concentration in vacuo affords the title compound as a yellow-orange liquid (11.4 g, 98%) that was used directly without further purification. $R_f$ 0.3 (5% EtOAc/hexanes); $^1$H NMR (501 MHz, $CDCl_3$) $\delta$ 8.43 (s, 1H), 7.48 (d, $J$ = 8.2 Hz, 2H), 7.24 (d, $J$ = 8.2 Hz, 2H), 5.35 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 162.6, 149.3, 134.3, 129.4, 121.6, 121.3, 119.6, 69.9; IR [$CH_2Cl_2$ solution] $\nu_{max}$ ($cm^{-1}$) 3345, 2954, 1667, 1511, 1261, 1221, 1166, 1077, 998, 828, 797, 649; HRMS (ESI-TOF) calcd for $C_{10}H_7Cl_3F_3NO_2$ 334.95, found $C_8H_6F_3O$ 174.03.

**(*R*)-3-Chloro-2-(4-(trifluoromethoxy)benzyloxy)propyl 4-Methoxybenzoate 12.** To a stirred solution of chlorohydrin **10** (7.15 g, 29 mmol) and 4-(trifluoromethoxy)benzyl trichloroacetimidate (9.76 g, 29 mmol) in $CH_2Cl_2$ (58 mL) at 0 °C was added TfOH (1.95 mL, 29 mmol) dropwise via glass syringe. The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. After completion, the mixture was quenched slowly with saturated aq $NaHCO_3$ until gas evolution ceased. The layers were separated, and the aqueous layer was extracted once with $CH_2Cl_2$ (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (5% EtOAc/hexanes) affords chloride **12** (9.7 g, 80%) as a clear, light yellow oil. $R_f$ 0.2 (5% EtOAc/hexanes); $^1$H NMR (501 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 8.9 Hz, 2H), 7.42 (d, $J$ = 8.5 Hz, 2H), 7.19 (d, $J$ = 8.2 Hz, 2H), 6.95 (d, $J$ = 8.9 Hz, 2H), 4.72 (d, $J$ = 13.6 Hz, 2H), 4.63−4.40 (m, 2H), 3.99 (t, $J$ = 5.1 Hz, 1H), 3.90 (s, 3H), 3.79−3.65 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 166.1, 163.8, 136.5, 131.9, 129.4, 122.1, 121.7, 121.2, 113.9, 110.2, 77.0, 71.7, 63.5, 55.7, 43.6; IR [$CH_2Cl_2$ solution] $\nu_{max}$ ($cm^{-1}$) 2959, 2872, 2843, 1904, 1715, 1607, 1511, 1450, 1258, 1030, 921, 823, 770; HRMS (ESI-TOF) calcd for $C_{19}H_{18}ClF_3O_5$ 418.0795, found 418.0791.

**(*S*)-3-(2-Chloro-4-nitro-1*H*-imidazol-1-yl)-2-(4-(trifluoro-methoxy)benzyloxy)propyl 4-Methoxybenzoate 14.** To a stirred solution of chloride **12** (17.4 g, 41.4 mmol) in DMF (42 mL) was added 2-chloro-4-nitroimidazole (CNI, **13**, from Asahi Kasei, 6.11 g, 41.4 mmol), $K_2CO_3$ (7.53 g, 53.9 mmol), and NaI (7.80 g, 53.9 mmol). The resulting suspension was then heated to 120 °C (oil bath) and stirred at this temperature for 16 h. After completion, the reaction mixture was allowed to cool to room temperature and poured into ice/$H_2O$. The mixture was extracted with EtOAc (3 × 300 mL), and the combined organic extracts were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The resulting residue was directly recrystallized from *i*-PrOH/hexanes to afford compound **14** (8.6 g, 41%) as a white solid. Mp 109−112 °C; $R_f$ 0.2 (1:2 EtOAc/hexanes); $^1$H NMR (501 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 8.9 Hz, 2H), 7.82 (s, 1H), 7.19 (dd, $J$ = 24.3, 8.2 Hz, 2H), 6.96 (d, $J$ = 8.8 Hz, 2H), 4.73 (d, $J$ = 11.8 Hz, 2H), 4.47 (d, $J$ = 4.8 Hz, 2H), 4.32 (d, $J$ = 14.5 Hz, 2H), 4.17 (dd, $J$ = 14.6, 8.5 Hz, 2H), 3.99 (s, 2H), 3.89 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 165.9, 164.2, 147.9, 135.2, 132.7, 132.0, 130.2, 129.7, 126.9, 122.0, 121.4, 114.2, 110.3, 74.8, 71.9, 62.1, 55.8, 49.7; IR [$CH_2Cl_2$ solution] $\nu_{max}$ ($cm^{-1}$) 2955, 1715, 1606, 1547, 1510, 1472, 1388, 134, 1258, 1221, 1168, 1029, 848; HRMS (ESI-TOF) calcd for $C_{22}H_{19}ClF_3N_3O_7$ 529.0864, found 529.0859.

**PA-824 (1).** To a stirred suspension of compound **14** (6.0 g, 11.32 mmol) in anhydrous MeOH (18 mL) at 0 °C was added ground KOH (1.91 g, 34 mmol). The mixture was pulled from the bath and stirred at room temperature for 1 h. The resulting suspension was poured into $H_2O$ and extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated. Chromatography (75% EtOAc/hexanes) followed by recrystallization (*i*-PrOH/hexanes) affords PA-824 (**1**) (2.41 g, 62%) as a crystalline solid. Mp 150−151 °C (lit.[11a] mp 149−150); $R_f$ 0.2 (75% EtOAc/

hexanes); ee >99.9% as determined by chiral SFC (see the Supporting Information); $^1$H NMR (500 MHz, $d_6$-DMSO) $\delta$ 8.09 (s, 1H), 7.48 (d, $J$ = 8.6 Hz, 2H), 7.39 (d, $J$ = 8.2 Hz, 2H), 4.81−4.62 (m, 3H), 4.51 (d, $J$ = 11.9 Hz, 1H), 4.39−4.19 (m, 3H); $^{13}$C NMR (126 MHz, $d_6$-DMSO) $\delta$ 148.7, 148.1, 143.0, 138.3, 130.4, 122.0, 120.0, 119.8, 69.7, 68.8, 67.51, 47.73; IR [$CH_2Cl_2$ solution] $\nu_{max}$ ($cm^{-1}$) 2877, 1580, 1543, 1509, 1475, 1404, 1380, 1342, 1281, 1221, 1162, 1116, 1053, 991, 904, 831, 740; HRMS (ESI-TOF) calcd for $C_{14}H_{12}F_3N_3O_5$ 359.0729, found 359.0728.

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**Supporting Information Available:** $^1$H NMR and $^{13}$C NMR spectra of **1** and **9**−**14** and chiral SFC data for **10** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.