Rearrangement of Epoxynitriles: A Convenient Homologation of Acyclic and Cyclic Ketones to Carboxylic Acids

Neil F. Badham,^{*a} Wilford L. Mendelson^a, Andrew Allen^b, Ann M. Diederich^a, Drake S. Eggleston^b,
John J. Filan^a, Alan J. Freyer^b, Lewis B. Killmer Jr.^b, Conrad J. Kowalski^a, Li Liu^a, Vance J. Novack^a,
Frederick Vogt^b, Kevin S. Webb^a, Jennifer Yang^a

GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, Pennsylvania 19406

Neil_F_Badham@gsk.com

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WARNING: Hydrogen cyanide will be released in the rearrangement of epoxynitriles **3**, and **7-12**. All appropriate safety precautions should be taken when working and handling cyanide.

Darzens Reaction

***Cis*-(±)-6-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxospiro[2.5]octane-2,6-dicarbonitrile (**3**):** To An 50% aqueous solution of potassium hydroxide (220 g) and THF (550 mL) was added benzyltriethylammonium chloride (8.1 g, 35 mmol) and the solution cooled to 0°C. A separate solution was made by dissolving the ketone **2** (230 g, 730 mmol) and chloroacetonitrile (59 g, 780 mmol) in THF (550 mL) at room temperature. While stirring the base solution at 0°C, the ketone solution was added in small portions over 15 mins. The temperature during the addition was maintained between 0-5°C and the reaction stirred for 1 h. The reaction was warmed to 25°C, and diluted with water:ethyl acetate 1:1. The layers were separated and the organic layer concentrated in vacuo to give an oil solid. Methanol (540 mL) was added and the residue heated to 40°C. While cooling to 20°C, hexanes (540 mL) was added. Cooling was continued and the product began to crystallize at 10°C. Cooling was continued to -5°C to 0°C and held at this temperature for 2 h. The product was filtered and washed with methanol:hexanes 1:1 at 0°C. The product was dried to afford *cis*-(±)-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxospiro[2.5]octane-2,6-dicarbonitrile **3** (190 g, 73%).

Figure S1: *Cis*-(±)-6-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxospiro[2.5]octane-2,6-dicarbonitrile (**3**)

IR (KBr pellet) cm^{-1} 2242, 2233, 1257, 942; ^1H (400 MHz, CDCl_3) δ 7.00 (1H, d, $J = 2.4$), 6.98 (1H, dd, $J = 2.4, 8.3$ Hz), 6.87 (1H, d, $J = 8.3$ Hz), 4.82 (1H, m), 3.85 (3H, s), 3.32 (1H, s), 2.54 (2H, m), 2.39 (2H, m); 2.07 (4H, m), 1.90 (4H, m), 1.62 (2H, m), 1.50 (2H, m); ^{13}C (100 MHz, CDCl_3) δ 150.21, 140.01, 130.96, 121.50, 117.49, 115.75, 113.05, 112.12, 80.88, 63.90, 56.10, 47.19, 42.33, 36.27, 35.88, 32.79, 30.25, 28.17, 24.03; m/z $[\text{M}+\text{C}_2\text{H}_5]^+$ 381 (8%), $[\text{M}+\text{H}]^+$ 353 (36%), $[\text{M}+\text{H}-\text{HCN}]^+$ 326 (83%)

2-3-Epoxy-3-(1-methylethyl)-heptanenitrile (8). To a solution of 2-methyl-3-heptanone (12.4 mL, 78.9 mmol) and ClCH_2CN (5.0 mL, 79.0 mmol) was added dropwise potassium *t*-butoxide (1M in *t*-BuOH, 80 mL, 80.0 mmol) while maintaining the temperature of the reaction between 20-25°C. The reaction was stirred overnight at ambient temperature, then filtered through a plug of silica. The silica was then washed with ether. The combined filtrates were concentrated in vacuo and the crude mixture chromatographed on silica gel (hexane:ether 95:5) to give as a colorless oil, 2-3-epoxy-3-(1-methylethyl)-heptanenitrile **8** (8.06g, 60.6%)

Several attempts were made to purify these compounds by column chromatography. However these samples failed C,H,N analysis. Small extra signals were observed in the NMR and the IR spectra.

Cis and trans

IR (neat) cm^{-1} 3000-2800, 2243, 1257

Figure S2: *Cis*-2-3-Epoxy-3-(1-methylethyl)-heptanenitrile (8a)

^1H (400 MHz, CDCl_3) δ 3.36 (1H, s), 2.05 (1H, m), 1.86 (2H, m), 1.75 (2H, m), 1.29 (2H, m), 1.16 (2H, m); 1.13 (3H, d, $J = 6.9$), 1.11 (3H, d, $J = 6.9$), 0.89 (3H, t, $J = 7.2$); ^{13}C (100 MHz, CDCl_3) δ 116.55, 68.91, 45.65, 33.84, 26.49, 25.45, 22.67, 18.33, 17.63, 13.83.

Figure S3: *Trans*-2,3-Epoxy-3-(1-methylethyl)-heptanenitrile (8b)

^1H (400 MHz, CDCl_3) δ 3.31 (1H, s), 2.02 (1H, m), 1.81 (2H, m), 1.50 (2H, m), 1.40 (2H, m), 0.96 (2H, d, $J = 6.9$); 0.95 (3H, t, $J = 7.2$), 0.90 (3H, d, $J = 6.9$), 0.89 (3H, t, $J = 7.2$); ^{13}C (100 MHz, CDCl_3) δ 116.66, 68.88, 44.78, 30.99, 29.96, 27.00, 22.82, 18.19, 17.01, 13.84.

2,3-Epoxy-3-(1,1-dimethylethyl)-pentanenitrile (9). To a solution of 2,2-dimethyl-3-pentanone (5.0 g, 43.8 mmol) and ClCH_2CN (2.8 mL, 44.2 mmol) was added potassium *t*-butoxide (1M in *t*-BuOH, 44.0 mL, 44.0 mmol) dropwise over 30 minutes, maintaining the temperature between 15-20°C. The reaction was then allowed to stir overnight at ambient temperature. The reaction was then filtered through a plug of silica and the silica washed with ether. The resulting solution was concentrated in vacuo and the crude mixture chromatographed on silica gel (ether:hexane 5:95) to give the product 2,3-epoxy-3-(1,1-dimethylethyl)-pentanenitrile (**9**) as a colorless oil, (3.054 g, 46%). The *cis* and *trans* isomers could not be separated, but the ^1H and ^{13}C spectra could be assigned to each compound in the mixture.

Cis and trans

IR (neat) cm^{-1} 3000-2800, 2243, 921

Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NO}$: C, 70.55; H, 9.87; N, 9.14; Found C, 70.43; H, 9.69; N, 9.12.

Figure S4: *Cis*-2,3-Epoxy-3-(1,1-dimethylethyl)-pentanenitrile (9a)

^1H (400 MHz, CDCl_3) δ 3.28 (1H, s), 1.99, 1.88 (2H, m), 1.17 (9H, s), 0.84 (3H, t); ^{13}C (100 MHz, CDCl_3) δ 117.20, 71.28, 42.47, 34.56, 26.80, 23.64, 8.69.

Figure S5: *Trans*-2,3-Epoxy-3-(1,1-dimethylethyl)-pentanenitrile (9b)

^1H (400 MHz, CDCl_3) δ 3.44 (1H, s, $J = 0.72$ Hz), 2.05, 1.95 (2H, dm), 1.11 (3H, t, $J = 7.7$), 0.98 (9H, s); ^{13}C (100 MHz, CDCl_3) δ 116.79, 70.47, 44.37, 34.88, 25.86, 22.57, 10.18.

2-3-Epoxy-3-[4-(2-methylpropyl)phenyl]-butanenitrile (10). A solution of 4-isobutylacetophenone (5.086 g, 28.4 mmol) and ClCH_2CN (1.8 mL, 28.4 mmol) in CH_2Cl_2 (22 mL), was treated dropwise with potassium *t*-butoxide (1M in *t*-BuOH, 29 mL, 29.0 mmol) over 15 minutes keeping the temperature between 5-10°C. After 1 hour, ice-cold water (140 mL) was added and the product extracted with ether (3×45 mL) and dried over magnesium sulfate. The reaction was filtered and concentrated in vacuo. The crude mixture was chromatographed on silica gel (5-12% EtOAc in hexane) to give as colorless oil, 2-3-epoxy-3-[4-(2-methylpropyl)phenyl]-butanenitrile (**10**) (4.532 g, 73.0%). The accompanying data are consistent with the literature.¹

Figure S6: *Cis*-2-3-Epoxy-3-[4-(2-methylpropyl)phenyl]-butanenitrile (10a)

IR (neat) cm^{-1} 3000-2800, 2247, 1615, 1249; ^1H (400 MHz, CDCl_3) δ 7.34 (2H, dm, $J = 8.4$) 7.19 (2H, dm, $J = 8.4$) 3.59 (1H, s) 2.49 (2H, d, $J = 7.2$) 1.88 (1H, m) 1.78 (3H, s) 0.91 (6H, d, $J = 6.6$); ^{13}C (100MHz, CDCl_3) δ 142.66, 132.95, 129.30, 125.68, 115.49, 63.95, 49.73, 45.09, 30.10, 22.34, 22.30; Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$: C, 78.10; H, 7.96; N, 6.51. Found C, 77.99; H, 7.88; N, 6.50.

Figure S7: *Trans*-2-3-Epoxy-3-[4-(2-methylpropyl)phenyl]-butanenitrile (10b)

IR (neat, cm^{-1}) 3000-2800, 2245, 1614, 1287; ^1H (400 MHz, CDCl_3) δ 7.24 (2H, dm, $J = 8.2$) 7.15 (2H, dm, $J = 8.2$) 3.37 (1H, s) 2.48 (2H, d, $J = 7.2$) 1.95 (3H, s) 1.86 (1H, m) 0.89 (6H, d, $J = 6.6$); ^{13}C (100MHz, CDCl_3) δ 142.67, 134.65, 129.49, 124.95, 115.83, 62.62, 49.66, 44.99, 30.14, 22.28, 19.62; Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$: C, 78.10; H, 7.96; N, 6.51; Found C, 78.21; H, 7.94; N, 6.49.

2,3-Epoxy-3-[cyclohex-1-enyl]-butanenitrile (11). To a solution of 1-acetyl-1-cyclohexene (20.8 mL, 162 mmol) and ClCH_2CN (13.6 mL, 215 mmol) in CH_2Cl_2 (125 mL) was added dropwise potassium *t*-butoxide (1M in *t*-BuOH, 216 mL, 216 mmol) under nitrogen over 1.75 h maintaining the reaction temperature between 5-10°C. It was then stirred overnight at ambient temperature. The solution was filtered through a plug of silica, and the silica washed with ether. The organics were concentrated in vacuo and the crude reaction mixture chromatographed on silica gel (ether:hexane 1:9) to give as a colorless oil, 2,3-epoxy-3-[cyclohex-1-enyl]-butanenitrile (21.078 g, 79.8%).

Figure S8: *Cis*-2,3-Epoxy-3-[cyclohex-1-enyl]-butanenitrile (11a)

IR (neat) cm^{-1} 3000-2800, 2245, 1660, 1268; ^1H (400 MHz, CDCl_3) δ 5.93 (1H, m), 3.31 (1H, s), 2.09 (4H, m), 1.67 (4H, m), 1.47 (3H, s); ^{13}C (100 MHz, CDCl_3) 132.55, 125.95, 115.92, 65.07, 48.45, 25.40, 24.54, 22.28, 21.90, 20.49; Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}$: C, 73.59; H, 8.03; N, 8.58; Found C, 73.53, H, 8.14, N, 8.63

Figure S9: *Trans*-2,3-Epoxy-3-[cyclohex-1-enyl]-butanenitrile (11b)

IR (neat) cm^{-1} 3100-3000, 2243, 1659, 1280; ^1H (400 MHz, CDCl_3) δ 5.86 (1H, m), 3.33 (1H, s), 2.04 (4H, m), 1.94 (4H, m), 1.65 (3H, s), 1.58 (6H, m); ^{13}C (100 MHz, CDCl_3) 134.02, 126.40, 116.31, 64.11, 47.23, 24.84, 24.07, 22.16, 21.78, 18.73; Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}$: C, 73.59; H, 8.03; N, 8.58; Found C, 73.31, H, 8.12, N, 8.59

2-3-Epoxy-3-(1-propyl)-hexanenitrile (12). To a solution of 4-heptanone (9.97 g, 12.2 mL, 87.6 mmol), and ClCH_2CN (6.68 g, 5.6 mL, 88.5 mmol) was added dropwise potassium *t*-butoxide (1M in *t*-BuOH, 88.0 mL, 88.0 mmol) over 45 minutes maintaining the reaction between 20-25°C. The reaction was stirred overnight at ambient temperature, then filtered through a plug of silica gel. The silica gel was then washed with ether. The solution was concentrated in vacuo and the crude mixture

chromatographed on silica gel (ether:hexane 5:95) to give as a colorless oil, 2-3-epoxy-3-(1-propyl)-hexanenitrile (**12**) (8.130 g, 60.8%).

Figure S10: 2-3-Epoxy-3-(1-propyl)-hexanenitrile (12)

IR (neat) cm^{-1} 3000-2800, 2244, 1266; ^1H (400 MHz, CDCl_3) δ 3.23 (1H, s), 1.79 (2H, m), 1.66 (2H, m), 1.52 (2H, m), 1.39 (2H, m), 1.11 (3H, t, $J = 7.3$), 0.93 (3H, t, $J = 7.3$); ^{13}C (100 MHz, CDCl_3) δ 116.45, 65.76, 46.47, 34.87, 34.21, 18.30, 17.73, 13.99, 13.88; Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NO}$: C, 70.55; H, 9.87; N, 9.15; Found C, 70.23; H, 9.73; N, 9.01.

Rearrangement Reaction

4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid (1): A solution of DMF (580 g), acetonitrile (480 g), lithium bromide (72 g, 830 mmol) and water (20 g, 1.1 mol) was stirred at 25-30°C followed by addition of compound **3** (180 g, 510 mmol). The reaction was heated to 90-95°C for 16 h. The reaction was cooled to 20°C, followed by addition of sodium hydroxide solution (92 g NaOH, 2.3 mol dissolved in 200 mL water). The suspension was stirred at 20°C for 30 mins and treated with sodium hypochlorite (600 mL, 460 mmol). The contents were stirred for an additional 90 mins, followed by addition of TBME and 6N HCl (644 mL, 3.86 mol). The bottom aqueous layer was separated and back extracted with TBME; the combined organic layers washed four times with water. The organics were concentrated to a residue, EtOAc was added and the organics heated to reflux. The solution was cooled to 50°C, hexanes were added and continued to be cooled to 0°C. The suspension was held at this temperature for 1 h. The solid was collected, washed with hexanes:EtOAc 9:1 and dried to afford *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid (**1a**) as an off-white powder (125 g, 69%). A small portion of the solid was recrystallized for characterization purposes. The other product *trans*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexane carboxylic acid (**1b**) remained in the crystallization mother liquors. A small portion of the

crude solid from the mother liquors was recrystallized for characterization purposes. The analytical data are consistent with the literature.²

Figure S11: *Cis*-4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid (1a)

***Cis*-4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid (1a)** IR (KBr pellet) cm^{-1} 3300-2400, 2231, 1707, 1694; ^1H (400 MHz, CDCl_3) δ 11.75 (1H, br. s), 7.02 (1H, d, $J = 2.3$), 6.98 (1H, dd, $J = 2.3, 8.4$ Hz), 6.87 (1H, d, $J = 8.4$ Hz), 4.82 (1H, m), 3.86 (3H, s), 2.43 (1H, tt, $J = 3.7, 12.2$ Hz), 2.29 (2H, br. d, $J = 15.6$ Hz); 2.25 (2H, br. d, $J = 16.4$ Hz), 2.05 (2H, m), 1.94 (4H, m), 1.86 (2H, m), 1.82 (2H, m), 1.64 (2H, m); ^{13}C (100 MHz, CDCl_3) δ 180.5, 149.8, 147.8, 132.8, 122.2, 117.3, 112.9, 111.9, 80.7, 56.1, 43.0, 41.7, 36.4, 32.8, 25.9, 24.0; m/z $[\text{M}+\text{C}_2\text{H}_5]^+$ 372 (1%), $[\text{M}+\text{H}]^+$ 344 (6%), $[\text{M}+\text{H}-\text{HCN}]^+$ 317 (100%)

Figure S12: *Trans*-4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid (1b)

Trans-4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-r-cyclohexanecarboxylic acid (1b) IR (KBr pellet) cm^{-1} 3427, 2229, 1701, 1262; ^1H (400 MHz, CDCl_3) δ 11.24 (1H, br. s), 7.00 (1H, d, $J = 2.3$), 6.95 (1H, dd, $J = 2.3, 8.4$ Hz), 6.85 (1H, d, $J = 8.4$ Hz), 4.80 (1H, m), 3.85 (3H, s), 2.87 (1H, m), 2.28 (2H, m); 2.08 (6H, m), 1.90 (4H, m), 1.85 (2H, m), 1.61 (2H, m); ^{13}C (100 MHz, CDCl_3) δ 180.67, 149.76, 147.80, 132.80, 122.61, 117.51, 113.19, 111.88, 80.78, 56.07, 42.73, 37.66, 33.59, 32.78, 24.34, 24.05; m/z $[\text{M}+\text{Na}]^+$ 366 (100%), $[\text{M}+\text{H}]^+$ 344 (6%)

2-[4-(2-Methylpropyl)phenyl]-propanoic acid (14, ibuprofen). A solution of 2,3-epoxy-3-[4-(2-methylpropyl)-phenyl]-butanenitrile (**10**) (0.550 g, 2.32 mmol), LiBr (0.333 g, 3.83 mmol), DMF (2.7 mL), CH_3CN (2.7 mL), and H_2O (115 μL , 6.39 mmol) was stirred overnight at 90°C . The reaction was cooled, diluted with EtOAc (20 mL) and washed with H_2O (3 $\times$ 5 mL). The aqueous layer was extracted with EtOAc (2 $\times$ 5 mL), and then the combined organics dried over Na_2SO_4 . The solution was filtered and concentrated in vacuo. The crude mixture was chromatographed on silica gel (ether:hexane 2:3) to give the product 2-[4-(2-methylpropyl)phenyl]-propanoic acid (**14**) as a white powder (0.325 g, 54.3%). The analytical data are consistent with the literature.³

Figure S13: 2-[4-(2-Methylpropyl)phenyl]-propanoic acid (14)

IR (KBr disc) cm^{-1} 3100-2500, 3100-3000, 1720, 1507, 1462, 1231, 1067, 936; ^1H (400 MHz, CDCl_3) δ 7.22 (2H, dm, $J = 8.1$), 7.11 (2H, dm, $J = 8.1$), 3.72 (1H, q, $J = 7.1$), 2.45 (2H, d, $J = 7.2$), 1.85 (1H, m), 1.51 (3H, d, $J = 7.2$), 0.90 (6H, d, $J = 6.6$); ^{13}C (100 MHz, CDCl_3) δ 180.30, 140.84, 136.96, 129.38, 127.25, 45.02, 44.86, 30.13, 22.37, 18.09; Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.79; Found C, 75.81; H, 8.78.

4-Heptanoic acid (15). 2-3-Epoxy-3-(1-propyl)-hexanenitrile (0.5 g, 3.26 mmol), LiBr (0.426g, 4.91 mmol), CH_3CN (2.5 mL), DMF (2.5 mL), and H_2O (110 μL , 6.11 mmol) was stirred at 91°C for two days. The reaction was cooled, diluted with ether (20 mL) and washed with water (3 $\times$ 5 mL). The

solution was then dried over Na₂SO₄. The solution was filtered and concentrated in vacuo. The crude mixture was chromatographed on silica gel (hexane:ether 7:3) to give as a colorless oil, 4-heptanoic acid (**16**) (0.230 g, 49%). The analytical data are consistent with the literature.⁴

Figure S14: 4-Heptanoic acid (15)

IR (neat) cm⁻¹ 3000-2800, 1707, 1467, 1253; ¹H (400 MHz, CDCl₃) δ 10.7 (1H, br s), 2.39 (1H, m), 1.63 (2H, m), 1.48 (2H, m), 1.35 (4H, m), 0.92 (6H, t, *J* = 6.8); ¹³C (100 MHz, CDCl₃) δ 183.12, 45.08, 34.30, 20.52, 13.94; Anal. Calcd for C₈H₁₆O₂: C, 66.63; H, 11.18; Found C, 66.90; H, 11.11

* To whom correspondence should be addressed. Fax: 610 270 4829

^a Department of Synthetic Chemistry; ^b Department of Analytical Chemistry

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