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

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

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

neil_f_badham@gsk.com

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Abstract: A convenient two-step homologation of both aliphatic and aromatic ketones to the corresponding carboxylic acid has been developed. First ketones were converted to epoxynitriles with the Darzens reaction. Second, a Lewis acid mediated rearrangement of these epoxynitriles with lithium bromide was achieved to give homologated secondary alkanoic acids (as well as aryl-alkanoic) in good yields. The mechanism and the scope of the rearrangement reaction were investigated. This strategy constitutes a two-step homologation of ketones to secondary carboxylic acids.

Secondary alkanoic acids are found in bile acids, as well as several important nonsteroidal antiinflammatory agents (e.g ibuprofen). We were interested in preparing quantities of SB-207499 by an efficient strategy. SB-207499 is in clinical trails for COPD (chronic obstructive pulmonary disease) and asthma. One approach to this secondary cyclohexane carboxylate (Figure 1) could be homologation of a cyclohexanone precursor.

There are various methodologies in the literature for the homologation of a ketone to a secondary carboxylic acid in two or three steps. Representative methodologies have involved intermediates such as enol ethers,[1] epoxides,[2] cyanohydrins,[3] α,β-unsaturated sulfones,[4] ketene thioacetals,[5] glycidic esters,[6] nitriles,[7] and α-acetoxyacrylonitriles[8] to add the one-carbon unit. These existing methodologies have been limited by their high cost or low efficiency and throughput for a scalable process. One underutilized strategy has been the formation of an epoxynitrile from a ketone by using the Darzens reaction[9] followed by rearrangement to give the secondary carboxylic acid. This methodology has been successfully demonstrated by White.[10]

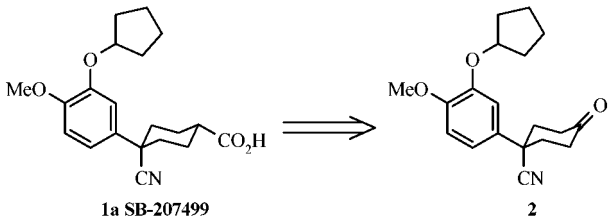
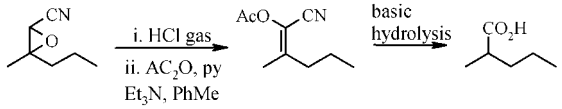
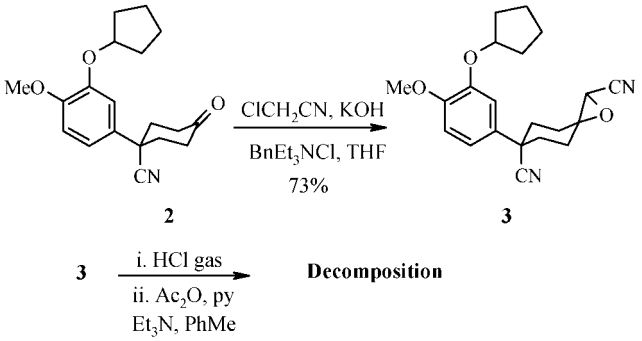


FIGURE 1. Retrosynthesis of SB-207499 from a ketone precursor.

SCHEME 1. White's Methodology for Alkyl-Substituted Epoxynitriles



SCHEME 2. Attempted Rearrangement of Epoxynitrile 3



Initially we focused our attention on White's conditions for alkyl-substituted epoxynitriles and their conversion to aliphatic secondary acids (Scheme 1). We successfully prepared epoxynitrile **3** in 73% yield (Scheme 2) under modified phase transfer conditions.[11] However, in attempting to use White's conditions (Scheme 1) to give the acid **1a**, exposure to anhydrous HCl resulted in decomposition of compound **3** without formation of White's disclosed intermediates.

Thus we tried other conditions for rearrangement of **3** which did not require strong acid. In the same publication, White had disclosed conditions specific for rearrangement of aryl-substituted epoxynitriles (Scheme 3).

White's synthetic approach for aryl-substituted epoxynitriles was very attractive, since it involved a one-pot rearrangement of the aryl precursors. However, application of this methodology failed with our dialkyl-substituted epoxynitrile **3**. For example, with White's Lewis acids, $LiClO_4$, $Li(OOCCF_3)$, and $KHSO_4$ in toluene or

* To whom correspondence should be addressed. Fax: 610 270 4829.
† Department of Synthetic Chemistry.
‡ Department of Analytical Chemistry.

(1) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.
(2) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867.
(3) (a) Eliel, E. L.; Freeman, J. P. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 58. (b) Ruzicka, L.; Plattner, P. A.; Heusser, H.; Meier, K. *Helv. Chim. Acta* **1947**, *30*, 1342.
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(5) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; DeWolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborn, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; O'Leary Bartus, J.; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. *J. Med. Chem.* **1998**, *41*, 821.
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(9) Rosen, T. *Compr. Org. Synth.* **1991**, *2*, 409.
(10) (a) White, D. R.; Wu, D. K. *J. Chem. Soc., Chem. Commun.* **1974**, 988. (b) White, D. R. U.S. Patents 3994964, 397431, and 4021478.
(11) Jonczyk, A.; Fedorynski, M.; Makosza, M. *Tetrahedron Lett.* **1972**, 2395.

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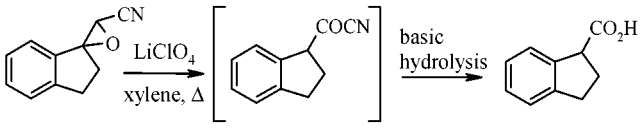
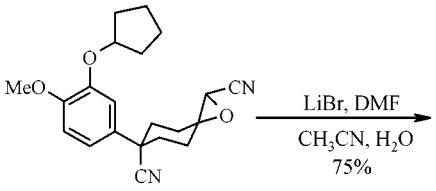
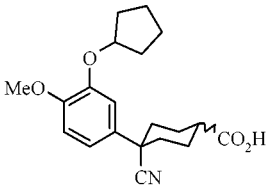
SCHEME 3. White's Methodology for Aryl-Substituted Epoxynitriles



SCHEME 4. Rearrangement of Epoxynitrile 3



3



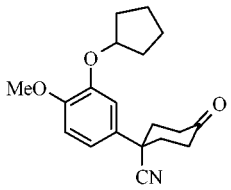
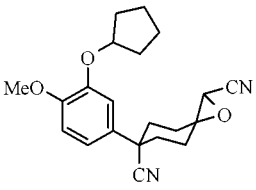
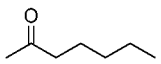
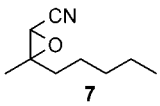
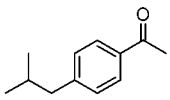
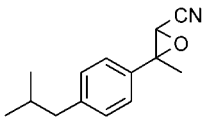
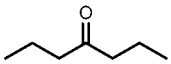
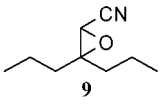
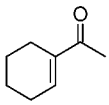
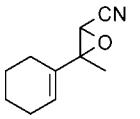
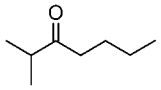
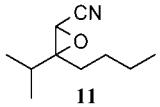
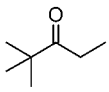
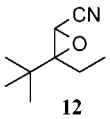
1a: equatorial COOH, SB-207499 (cis isomer)
1b: axial COOH (trans isomer)

xylene at reflux resulted in recovery of starting material. We therefore extended our studies to other Lewis acids and solvents with the hope that they could be applied to substrate **3**.

Ultimately we found a set of conditions that did work for this pivotal transformation. The combination of lithium bromide (or magnesium bromide) in DMF, acetonitrile, and a small amount of water efficiently transformed the cyclohexyl-epoxynitrile **3** into acids **1**[12] in 75% yield (Scheme 4). Moreover, we were successful in carrying out the above conversion of precursor **3** to SB-207499 in the pilot plant.

Intrigued by this result, we wanted to see how general this new rearrangement methodology was for other alkyl-, alkenyl-, or aryl-substituted epoxynitriles. A selection of epoxynitriles **7**−**12** were synthesized (Table 1) according to the methods of Stork,[13] Svoboda,[14] or Mongelli.[15] In the case of epoxynitrile **10** the reported method (solid NaOH) was too slow in our hands to be practical,[16] therefore the method implemented by Stork was used. In all of these examples the epoxynitriles **7**−**12** could be isolated in good yield. Epoxynitriles **7**−**12** were formed as mixtures of cis and trans isomers. The mixtures were treated under our rearrangement conditions (LiBr, DMF, CH_3CN, H_2O, 90−95 °C, 24 h); we were pleased to find that in most cases good yields of the secondary carboxylic acids were obtained (Table 2).

TABLE 1. Preparation of Epoxynitriles[a]

Ketone	Darzens Product	Yield (%)
		73
2	**3**	
		68
	7	
		73
	8	
		61
	9	
		80
	10	
		61
	11	
		46
	12	

[a] All yields are isolated.

In the case of compound **7** the *cis*- and *trans*-epoxynitriles were separated. Rearrangement of both isomers separately gave identical results (products/reaction times). This result suggested a mechanism that involved a common intermediate for the rearrangement of both *cis*- and *trans*-epoxynitriles. Most substrates showed complete reaction within 12−24 h, with very few impurities observed. Hydrogen cyanide was liberated as a byproduct of the rearrangement and care was taken when handling the reaction and subsequent workup and disposal of waste.

Increasing the steric bulk α to the epoxynitrile proved deleterious and no reaction was observed for either the isopropyl epoxynitrile **11** or the *tert*-butyl epoxynitrile **12**. Starting material was recovered in either case. These results suggested that steric factors are critical. It was

(12) Allen, A.; Diederich, A. M.; Mendelson, W.; Liu, L. PCT Int. Appl. 1998, 9834584.
(13) Stork, G.; Worrall, W. S.; Pappas, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 4315.
(14) Svoboda, J.; Kocfeldova, Z.; Palecek, J. *Collect. Czech. Chem. Commun.* **1988**, *53*, 822.
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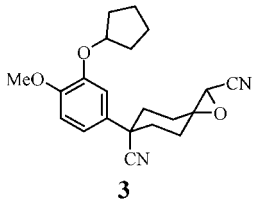
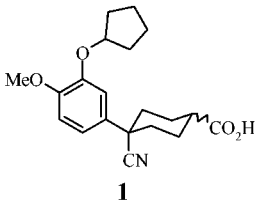
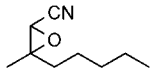
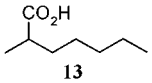
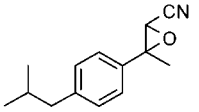
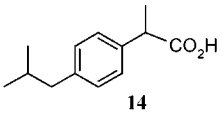
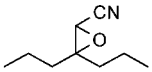
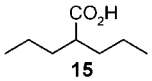
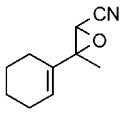
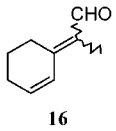
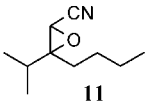
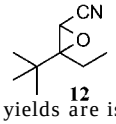
(16) Zakharova, N. I.; Gutnikova, N. P.; Bekker, A. R.; Filippova, T. M.; Miropol'skaya, M. A.; Samokhvalov, G. I. *J. Org. Chem. USSR (Engl. Trans.)* **1986**, *21*, 1870.

TABLE 2. Rearrangement Products from the Epoxynitriles[a]

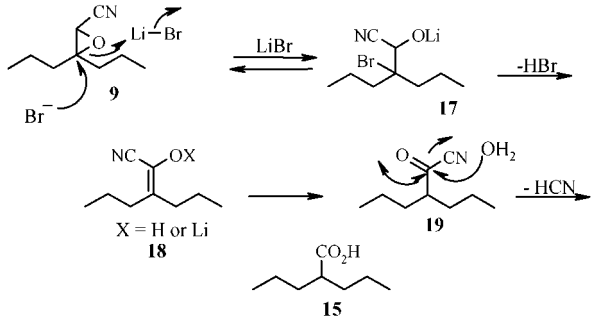
Darzens Product	Rearrangement Product	Yield (%)
 **3**	 **1**	75
 **7**	 **13**	63
 **8**	 **14**	54
 **9**	 **15**	49
 **10**	 **16**	19
 **11**	**No reaction**	
 **12**	**No reaction**	

[a] All yields are isolated.

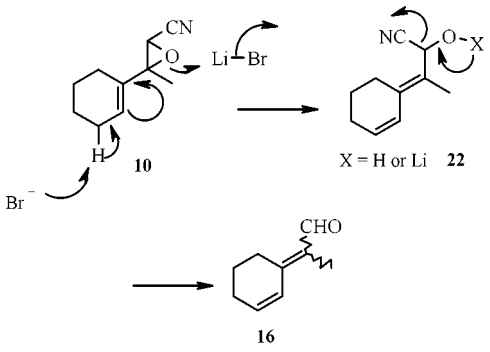
also found that aryl-substituted epoxynitriles rearrange to give acids. Thus, compound **8** rearranged to give ibuprofen (**14**).[17] A proposed mechanism for the rearrangement is given for the bisalkyl-substituted epoxynitriles in Scheme 5.

In our proposed mechanism, bromide attacks the epoxide at the quaternary position either in a S_N1 or S_N2 fashion to give intermediate **17**, which then undergoes loss of elements of HBr to give the enol or enolate **18**. This enol or enolate may be protonated to give compound **19**, which undergoes hydrolysis in situ to give compound **15**. In support of the mechanism, in the case of compound **3**, intermediates were isolated and identified in which bromide had added to the dialkyl portion of the epoxide.[18] Also if the lithium bromide was acting only as a Lewis

SCHEME 5. Proposed Mechanism for the Rearrangement of Bisalkyl-Substituted Epoxynitriles



SCHEME 6. Proposed Mechanism for Formation of Compound 16



acid (Lewis acid promoted ring opening/hydride shift) it would be expected that epoxynitriles **11** and **12** would rearrange readily to give acid products. This was not observed, thus this alternative mechanism is considered unlikely.

Water was found to be essential for the rearrangement reaction. We believe it is required to hydrolyze the proposed intermediate acyl-nitriles, e.g. compound **19** (Scheme 5). In the absence of water, acyl-nitrile dimer products were formed almost exclusively instead of the acid product. Such dimers are known to be formed from acyl-nitriles in the presence of HCN.[19] To ensure acid product formation, water (1.5−3.0% w/w) was added at the start of the reaction, leading to the desired transformation of epoxynitrile to acid rather than producing unwanted dimer products.

When the rearrangement was extended to an α,β-unsaturated epoxynitrile **10**, the desired acid product was not formed. Instead, a rather unstable $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **16** was isolated (1:1 mixture of cis and trans isomers) (Scheme 6). Isolation of the unsaturated aldehydes indicated that the double bond in epoxynitrile **10** had participated in the rearrangement.

Our proposed mechanism for formation of compound **16** (Scheme 6) is consistent with the results found with Ph_3SiClO_4 for selective isomerization of glycidates.[20]

We have developed a strategy for the two-step homologation of ketones to secondary carboxylic acids. This

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(18) This compound gave satisfactory analysis by NMR and mass spectroscopy.

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efficient protocol produces secondary carboxylic acids in good to high yield. The rearrangement reaction is unfavorable for alkyl-ketones with hindered aliphatic substituents α to the epoxynitrile. The course of the rearrangement was found to be different in the case of an α,*β*,*γ*,*δ*-unsaturated epoxynitrile. Finally, water was found to be essential for the rearrangement reaction. In its absence, the secondary carboxylates are not produced.

Experimental Section

Warning: Hydrogen cyanide will be released in the rearrangement of epoxynitriles **3** and **7**−**12**. All cyanide safety precautions should be taken during handling of reaction solutions, purification, and waste disposal of contaminated materials.

Representative Darzens Reaction. 2,3-Epoxy-3-methyloctanenitrile (7): To a solution of 2-heptanone (5.74 g, 7.0 mL, 50.3 mmol) and $ClCH_2CN$ (3.82 g, 3.2 mL, 50.6 mmol) was added dropwise potassium *tert*-butoxide (1 M in *t*-BuOH, 50.3 mL, 50.3 mmol) over 45 min. The reaction was stirred overnight under nitrogen at ambient temperature. The reaction solution was then filtered through a plug of silica gel, which was then washed with ether. The crude mixture was concentrated in vacuo and chromatographed on silica gel (ether:hexane 1:9) to give 2,3-epoxy-3-methyloctanenitrile (**7**) (5.217 g, 68.2%) as a colorless oil. These data are consistent with published data.[21]

***cis*-2,3-Epoxy-3-methyloctanenitrile:** IR (neat) 2245, 1250 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 3.23 (1H, s), 1.76 (2H, m), 1.54 (2H, m), 1.38 (3H, s), 1.36 (4H, m), 0.93 (3H, t, $J = 9.9$ Hz); ^{13}C (100 MHz, $CDCl_3$) δ 116.29, 63.55, 47.62, 34.53, 31.53, 24.84, 22.42, 19.96, 13.86. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.44; H, 9.87; N, 9.14.

***trans*-2,3-Epoxy-3-methyloctanenitrile:** IR (neat) 2245, 1250 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 3.23 (1H, s), 1.61 (2H, m), 1.54 (3H, s), 1.39 (6H, m), 0.90 (3H, t, $J = 6.9$ Hz); ^{13}C (100 MHz, $CDCl_3$) δ 116.43, 63.55, 46.87, 36.12, 31.46, 24.44, 22.42, 18.49, 13.86. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.26; H, 9.74; N, 9.21.

Representative Rearrangement Reaction. 2-Methylheptanoic acid (13): 2,3-Epoxy-3-methyloctanenitrile (**7**) (0.500 g; 3.26 mmol), LiBr (0.426 g, 4.90 mmol), CH_3CN (2.5 mL), DMF (2.5 mL), and H_2O (110 μL, 6.11 mmol) were heated and stirred overnight at 91 °C. The reaction was then cooled and diluted with EtOAc and washed with H_2O. The aqueous layer was separated and the pH of the aqueous layer was adjusted to 2 with 3 N HCl. This was then extracted with ether. The organic layers were combined and dried with 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 2-methyl-heptanoic acid (**13**) (0.296 g, 62.8%) as a colorless oil. These data are consistent with published data.[22]

2-Methylheptanoic acid (13): IR (neat) 3100−2500, 1708, 1243 cm^{-1} ; ^1H (400 MHz, $CDCl_3$) δ 2.48 (1H, m), 1.69 (1H, m), 1.46 (1H, m), 1.30 (6H, m), 1.18 (3H, d, $J = 7.0$ Hz), 0.90 (3H, t, $J = 6.8$ Hz); ^{13}C (100 MHz, $CDCl_3$) δ 183.62, 39.39, 33.46, 31.65, 26.76, 22.44, 16.76, 13.95, 13.92. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.76; H, 10.89.

Rearrangement of an α,*β*-Unsaturated Epoxynitrile. 2-[Cyclohex-2-enyl]idenepropanal (16): A solution of 2,3-epoxy-3-[cyclohex-1-enyl]butanenitrile (**11**) (2.00 g, 12.3 mmol), LiBr (2.10 g, 24.18 mol), DMF (10 mL), CH_3CN (10 mL), and H_2O (0.45 mL, 25.0 mmol) was stirred overnight at 91 °C. The reaction was cooled, diluted with Et_2O, and washed with H_2O and then dried over Na_2SO_4. The solution was filtered and concentrated in vacuo. The crude reaction mixture was chromatographed on silica gel (ether:pentane 1:9) to give an unstable, colorless oil, 2-[cyclohex-2-enyl]idene-propanal (**16**) (0.320 g, 19.2%). IR (neat) 1664, 1648, 1612, 1582 cm^{-1}.

***cis*-2-[Cyclohex-2-enyl]idenepropanal:** ^1H (400 MHz, $CDCl_3$) δ 10.26 (1H, s), 7.16 (1H, dt, $J = 2.1$, 10.4 Hz), 6.17 (1H, m), 2.47 (2H, m), 2.18 (2H, m), 1.76 (2H, m), 1.72 (3H, d, $J = 0.8$ Hz); ^{13}C (100 MHz, $CDCl_3$) δ 189.82, 151.90, 136.80, 129.72, 122.25, 28.35, 25.71, 21.73, 10.47.

***trans*-2-[Cyclohex-2-enyl]idenepropanal:** ^1H (400 MHz, $CDCl_3$) δ 10.16 (1H, s), 6.54 (1H, dt, $J = 2.1$, 10.1 Hz), 6.27 (1H, m), 2.84 (2H, m), 2.22 (2H, m), 1.76 (2H, m), 1.74 (3H, s); ^{13}C (100 MHz, $CDCl_3$) δ 191.14, 150.30, 139.11, 129.35, 126.65, 26.27, 24.68, 22.37, 9.82. Due to the compound's instability, CHN analysis was not possible.

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Supporting Information Available: Procedures for the preparation and full characterization of compounds **1**, **3**, **8**−**12**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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