The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2018**, part iv, 195-214

An improved, gram-scale synthesis of protected 3-haloazetidines: rapid diversified synthesis of azetidine-3-carboxylic acids

Youngran Ji,[a] Lukasz Wojtas,[c] and Justin M. Lopchuk*[a,b,c]

[a] *Drug Discovery Department, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, Florida 33612, USA*

[b] *Department of Oncologic Sciences, College of Medicine, University of South Florida, Tampa, Florida 33612, USA*

[c] *Department of Chemistry, University of South Florida, Tampa, Florida 33620, USA*

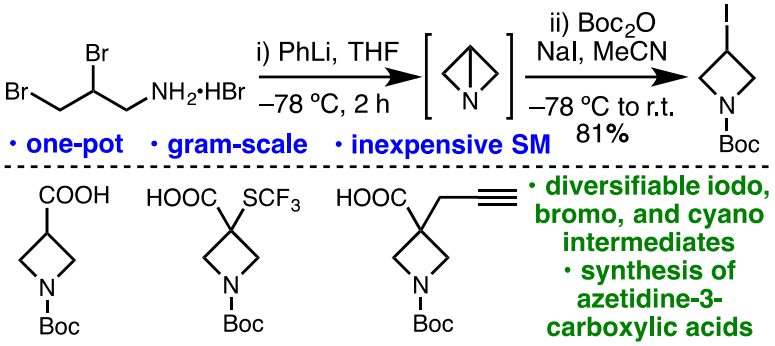
Email: justin.lopchuk@moffitt.org

Dedicated to Prof. Gordon W. Gribble on the occasion of his retirement from Dartmouth College

Received 02-27-2018 **Accepted** 04-05-2018 **Published on line** 04-21-2018

Abstract

Azetidines are increasingly important heterocycles found in a variety of natural products and pharmaceutical compounds. Protected 3-haloazetidines, widely used and versatile building blocks in medicinal chemistry, have been prepared in a one-pot, gram-scale strain-release reaction of 1-azabicyclo[1.1.0]butane from commercially available starting materials. These intermediates were subsequently used to prepare a series of high value azetidine-3-carboxylic acid derivatives including the first reported synthesis of 1-(*tert*-butoxy-carbonyl)-3-((trifluoromethyl)thio)azetidine-3-carboxylic acid.



Keywords: Azetidines, heterocycles, strain-release, 1-azabicyclo[1.1.0]butane, trifluoromethylthiolation

Introduction

Azetidines are four-membered nitrogen-containing heterocycles that appear in a variety of natural products and pharmaceutical agents.[1-3] 3-Substituted azetidines, in particular, are increasingly prevalent in medicinal chemistry as either linking fragments or rigidifying moieties.[4,5] Recently, azetidine-3-carboxylic acid has served as an integral part of a number of sphingosine-1-phosphate receptor (S1P) agonists as potential treatments for multiple sclerosis (Figure 1, **1**-**5**).[6-10] The S1P receptors regulate a wide variety of biological functions including cell proliferation, migration, and survival; as such, they present attractive targets for developing treatments of inflammatory diseases, autoimmunity, and cancer.[11,12] Despite the myriad uses for azetidines, methods for their synthesis and functionalization still lag behind their larger counterparts: pyrrolidine and piperidine.

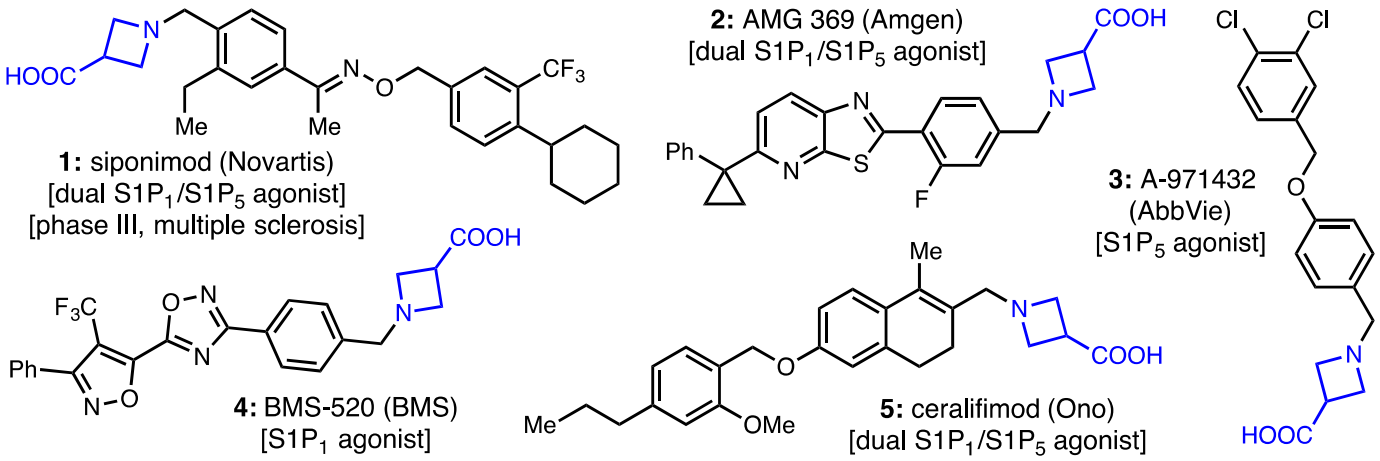
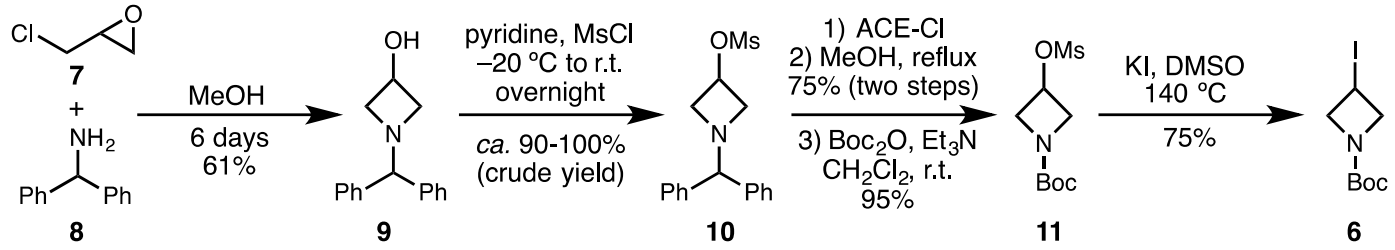


Figure 1. Drug candidates containing the azetidine-3-carboxylic acid fragment.

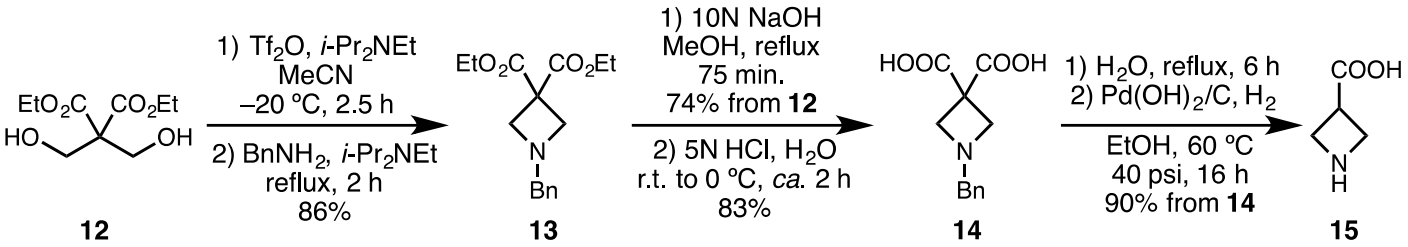
In general, azetidines are appended to lead molecules as pre-formed ring systems via a variety of coupling-type reactions (as opposed to forming the ring system in place with a cyclocondensation reaction).[1-3] This building block approach requires the ready availability of a diverse collection of azetidinyl fragments. One such moiety, *tert*-butyl 3-iodoazetidine-1-carboxylate (**6**), was first reported by Billotte in 1998.[13] When converted into the corresponding organozinc compound, it was shown to undergo facile palladium-catalyzed cross-coupling with (hetero)aryl halides. Since its initial report, the iodide **6** has proven to serve as a valuable intermediate in azetidine synthesis and functionalization through numerous published methodologies, including an iron- and cobalt-catalyzed arylation with Grignard reagents,[14] Suzuki couplings with arenes[15-17] or alkenes,[18] Minisci reactions with heteroarenes,[19,20] etherification with aryl boronic acids,[21] reductive couplings with 3-bromo-2,1-borazaronanaphthalenes[22] or chloroformates,[23] and a nickel-catalyzed enantioselective conjunctive coupling with vinyl boronates.[24] Furthermore, the iodide **6** has been used as a precursor to other small azetidine fragments including the corresponding hydrazine,[25] sulfone[26] or sulfinate salts,[27] and potassium tetrafluoroborate.[28]



Scheme 1. Literature synthesis of *tert*-butyl 3-iodoazetidine-1-carboxylate (**6**) from epichlorohydrin (**7**).

Unfortunately, the currently available route to the iodide **6** is lengthy and time consuming (Scheme 1).[13,29] Over six days, epichlorohydrin (**7**) is allowed to condense with benzhydrylamine (**8**) to furnish alcohol **9**, which is then mesylated to afford **10**. A protecting group swap is accomplished over three steps to give Boc-protected azetidine **11** in good yield. Displacement of the mesylate with KI in DMSO produces the target compound **6**. More recently, Gandelman reported an iododecarboxylation reaction where iodide **6** was prepared in 75% yield by treating Boc-protected azetidine-3-carboxylic acid (**15**, the synthesis of which is detailed below) with 1,3-diiodo-5,5-dimethylhydantoin under irradiation conditions.[30]

As discussed above, azetidine-3-carboxylic acid (**15**) is another valuable azetidinyl fragment that has found repeated utility in medicinal chemistry.[31,32] For many years, the sole route to this compound required elaborating mesylate **10** (as prepared above in Scheme 1 from **7**) through a further sequence of cyanation, hydrolysis, and deprotection to yield **15**.[29] Researchers at Merck improved upon this as shown in Scheme 2.[33] Triflation of the commercially available diethyl bis(hydroxymethyl)malonate (**12**) followed by cyclization with benzylamine gave the diester **13**. A two-step hydrolysis afforded diacid **14** in high yield. Under carefully pH-controlled conditions, diacid **14** was monodecarboxylated to the benzyl-protected **15**; a final hydrogenolysis furnished the deprotected azetidine-3-carboxylic acid (**15**). This sequence, especially on large scale, represents a significant improvement on the route beginning with epichlorohydrin (**7**).



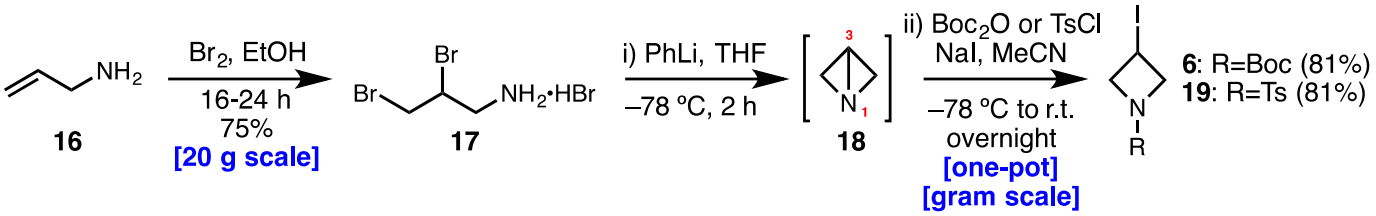
Scheme 2. Merck synthesis of azetidine-3-carboxylic acid (**15**).

Given the substantial utility of both 3-iodoazetidine **6** and azetidine-3-carboxylic acid (**15**), an opportunity existed to develop a more streamlined route to various protected 3-haloazetidines that would also serve as a diversity point to generate other azetidine fragments as well as a series of functionalized azetidine-3-carboxylic acid derivatives.

Results and Discussion

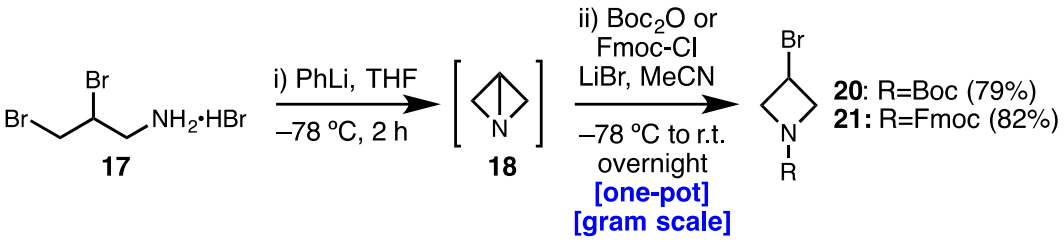
Synthesis of 3-haloazetidines

Contrasting with the syntheses of iodide **6** and carboxylic acid **15** above, which require the intermolecular reaction of an amine with a bis-electrophile, the underutilized 1-azabicyclo[1.1.0]butane (ABB, **18**) forms the azetidine ring system via two sequential intramolecular aminations.[34] This provides an opportunity for the rapid, one-pot synthesis of 1,3-disubstituted azetidines. First synthesized by Funke in 1969,[35] ABB (**18**) has been shown to react as a potent nucleophile with chloroformates, sulfonyl chlorides, and benzyl bromide, or as an electrophile with anilines, thiols, and turbo-amides.[36-38] The ABB precursor **17** was prepared as previously described[37-39] by the slow addition of allylamine (**16**) to an ice-cold solution of bromine in ethanol; the desired hydrobromide salt **17** was obtained in good yield after recrystallization on a 20 g scale (Scheme 3). Treatment of **17** with PhLi facilitated the formation of ABB (**18**) *in situ* over the course of 2 h. This was followed by the addition of MeCN, NaI and an electrophile (either Boc_2O or TsCl). Presumably, **18** engages first as a nucleophile generating a carbocation at C3 that is trapped by iodide.[40] After workup and purification, the Boc- and Ts-protected 3-iodoazetidines (**6** and **19**) were obtained in 81% yield on gram-scale (Scheme 3).



Scheme 3. Two-step, gram-scale synthesis of protected 3-iodoazetidines (**6** and **19**) from allylamine (**16**).

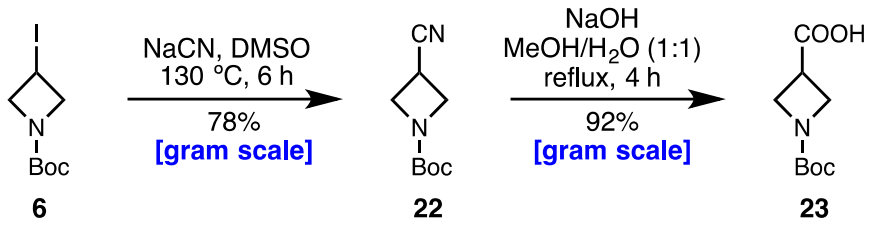
Over the last few years, the bromide **20** (an analog of iodide **6**) has been used in several new reactions, including a reductive cross-coupling with (hetero)aryl bromides,[41] an aqueous Lipshutz–Negishi cross-coupling with aryl electrophiles,[42] and a metallaphotoredox-catalyzed cross-coupling with (hetero)aryl halides.[43] Much like the other azetidines previously discussed, bromide **20** has traditionally been prepared from mesylate **11**.[14] However, by using a strain-release concept instead, bromide **20** was readily prepared in 79% yield on gram-scale by substituting LiBr for NaI (Scheme 4). Replacing Boc_2O with Fmoc-Cl allowed for the synthesis of bromoazetidine **21**, which could prove promising for peptide applications.[44] Taken as a whole, the strain-release methodology allows for a "mix-and-match" approach to the synthesis of protected 3-haloazetidines. Depending on the given downstream application, the protecting group (Boc, Ts, Fmoc) and halide (Br, I) can be interchanged as needed while still using the same one-pot sequence from hydrobromide salt **17**.



Scheme 4. Gram-scale synthesis of protected 3-bromoazetidines (**20-21**).

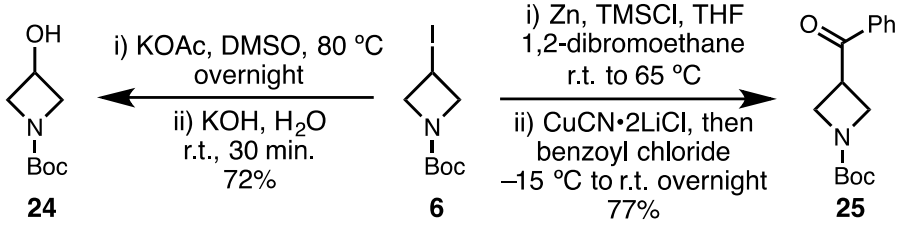
Applications of 3-haloazetidines

In order to demonstrate the utility of the expedited route to iodide **6**, azetidine-3-carboxylic acid **23** was targeted (Scheme 5). Treatment of **6** with NaCN in DMSO gave cyanoazetidine **22** in good yield on gram-scale. Basic hydrolysis of **22** afforded 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (**23**) in excellent yield. The final, three-step route to carboxylic acid **23** from hydrobromide salt **17** proceeds in 58% overall yield on gram-scale.



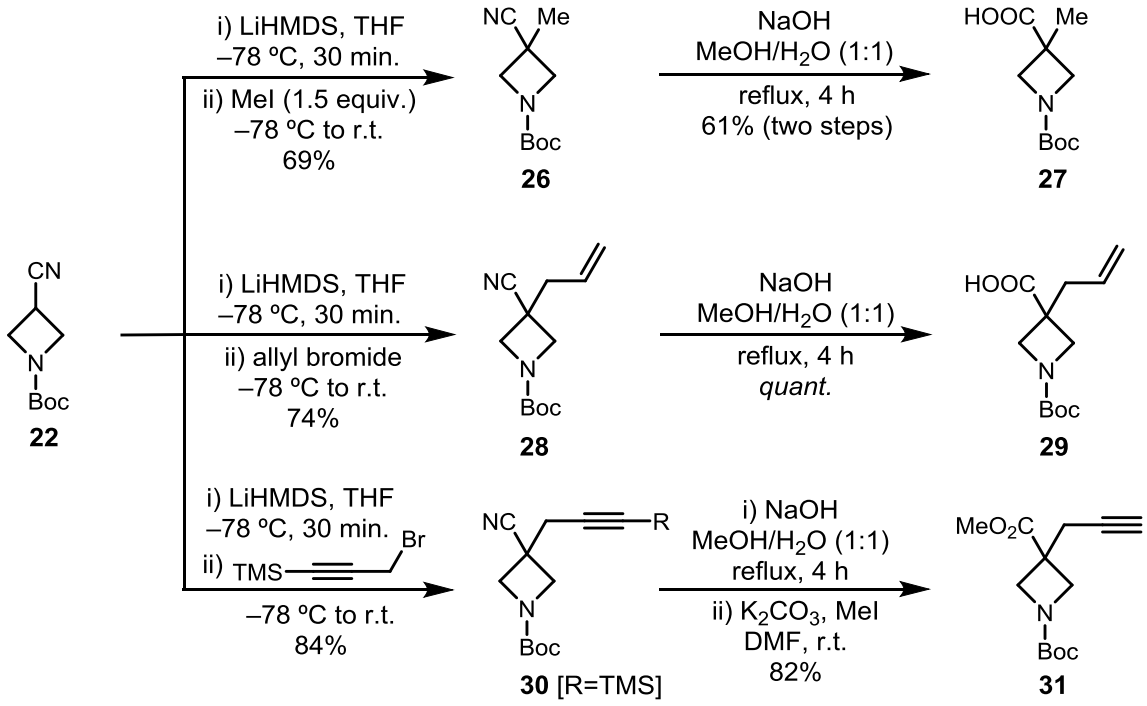
Scheme 5. Synthesis of azetidine-3-carboxylic acid **23**.

3-Hydroxyazetidines (as well as azetidin-3-ones) are frequently used building blocks in medicinal chemistry since they are suitable as oxygen nucleophiles and reductive amination partners.[1-3] They are typically prepared from epichlorohydrin (**7**) as outlined in Scheme 1.[29] As an alternative one-pot approach, 3-hydroxyazetidine **24** was synthesized in good yield by sequentially treating 3-iodoazetidine **6** with KOAc and KOH (Scheme 6).[45] A modification of Billotte's procedure was used to improve the reported yield of the acylation of iodide **6** (38% → 77%).[13] The reaction proceeds in one-pot via zinc insertion into the C–I bond, conversion to a zinc-copper species, and trapping with benzoyl chloride to afford azetidine **25**.



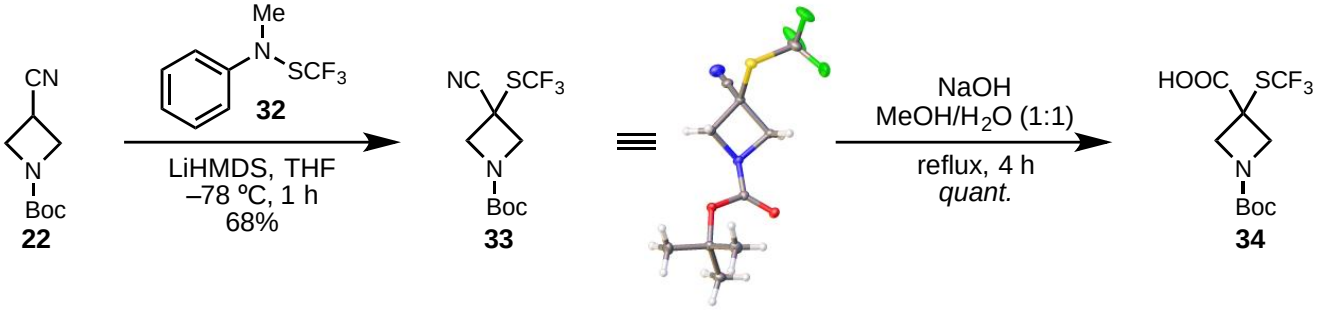
Scheme 6. Diversification of 3-iodoazetidine **6** to 3-hydroxyazetidine **24** and 3-acylazetidine **25**.

Cyanoazetidine **22** also has significant potential as a diversifiable intermediate for the synthesis of 3-substituted azetidine-3-carboxylic acids (Scheme 7). The treatment of cyanoazetidine **22** with LiHMDS in THF at –78 °C for 30 minutes proved the optimal conditions for deprotonation. Trapping of the resulting anion with methyl iodide, allyl bromide, or 3-(trimethylsilyl)propargyl bromide gave good yields of the corresponding 3,3-disubstituted azetidines **26**, **28**, and **30**. Hydrolysis as previously described furnished 3-substituted azetidine-3-carboxylic acid derivatives **27**, **29**, and **31**. If desired, the cyanoazetidine **30** could be obtained directly as the unprotected acetylene by treatment with TBAF in the same pot as the propargylation (see experimental section for details). Propargyl azetidine **31**, in particular, may find utility as a click-based reagent in the synthesis of unnatural peptidomimetics or other bioactive lead compounds.[46]



Scheme 7. Diversification of 3-cyanoazetidine **22**.

Notwithstanding the popularity of fluorinated compounds in medicinal chemistry,[47] no known examples have been reported of fully saturated 3-(trifluoromethylthiolated)azetidines. After deprotonation, azetidine **22** was treated with *N*-methyl-*N*-(trifluoromethylthio)aniline (**32**)[48] to give the trifluoromethylthiolated azetidine **33** whose structure was confirmed by X-ray crystallography. Standard hydrolysis conditions completed the first synthesis of 1-(*tert*-butoxycarbonyl)-3-[(trifluoromethyl)thio]azetidine-3-carboxylic acid (**34**, Scheme 8).



Scheme 8. Synthesis of trifluoromethylthiolated azetidine **34**.

Conclusions

In summary, a short, gram-scale synthesis of protected 3-haloazetidines **6**, **19**, **20**, and **21** via 1-azabicyclo-[1.1.0]butane (**18**) has been reported. By using this method, the halide and protecting group can be "mixed-and-matched" as desired in order to tailor the azetidine fragment to its intended downstream application. The concise synthesis, along with readily available starting materials, should enable the widespread use of this

method. This route allows for the rapid preparation of numerous protected azetidines including 3-hydroxyazetidine **24**, 3-acylazetidine **25**, azetidine-3-carboxylic acid **23** and a series of 3-substituted azetidine-3-carboxylic acid derivatives **27**, **29**, **31**, and **34**. Other applications exploring the utility of 1-azabicyclo[1.1.0]butane (**18**) in the preparation and functionalization of azetidines and their implications in the synthesis of anticancer compounds are currently in progress and will be reported in due course.

Experimental Section

General. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF), acetonitrile (MeCN), and dimethylformamide (DMF) were obtained by passing the previously degassed solvent through an activated alumina column (PPT Glass Contour Solvent Purification System). Anhydrous dimethylsulfoxide (DMSO) was purchased from Acros (Extra Dry over Molecular Sieves) and used as received. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Room temperature (rt) refers to ambient temperature in the laboratory (*ca.* 22–24 ^{o}C). Reactions were monitored by LC-MS or thin layer chromatography (TLC) carried out on 250 µm SiliCycle SiliaPlates (TLC Glass-Backed Extra Hard Layer, 60 Å), using shortwave UV light as the visualizing agent and iodine or $KMnO_4$ and heat as developing agents. Flash column chromatography was performed with a Biotage Isolera One (ZIP or SNAP Ultra cartridges) or with traditional glass flash columns using SiliCycle SiliaFlash® P60 (particle size 40 – 63 µm). NMR spectra were recorded on a Bruker Ascend™ 500 MHz spectrometer and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; DMSO-d_6: 2.50 ppm ^{1}H NMR, 39.5 ppm ^{13}C NMR; MeOD: 3.31 ppm ^{1}H NMR, 49.0 ppm ^{13}C NMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, tt = triplet of triplets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC-MS TOF mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. Melting points were recorded on a Chemglass DMP 100 melting point apparatus.

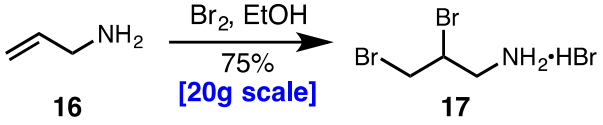


Figure 1

1-Amino-2,3-dibromopropane hydrobromide (**17**). Br_2 (10 mL, 0.196 mol, 2.1 equiv.) was added slowly to ice-cold ethanol (25 mL) in a 125 mL round bottom flask at 0 ^{o}C and stirred vigorously (the flask was covered with ice up to the neck to prevent fuming). Allylamine (7.0 mL, 0.0936 mol, 1 equiv.) was added very slowly to the Br_2/EtOH solution. After allowing the reaction mixture to warm to rt, stirring was continued at the same temperature overnight. Small portions of ice-cold diethyl ether (5 x 10 mL) were added to the red-brown colored reaction mixture which was then filtered to obtain the crude compound **17**. The crude material was recrystallized using methanol to give the pure hydrobromide salt **17** (20.9 g, 75%). Physical State: white solid (mp 174–175 ^{o}C); ^{1}H NMR (500 MHz, D_2O): δ 4.64 – 4.55 (m, 1H), 4.04 (dd, *J* 11.0, 4.6 Hz, 1H), 3.90 – 3.77 (m, 1H), 3.90 – 3.77 (m, 1H), 3.46 (dd, *J* 14.1, 9.6 Hz, 1H); ^{13}C NMR (126 MHz, D_2O): δ 46.4, 44.2, 33.0; ^{1}H NMR (500

MHz, MeOD): δ 4.62 – 4.52 (m, 1H), 4.04 (dd, *J* 11.0, 4.7 Hz, 1H), 3.90 (dd, *J* 11.0, 8.5 Hz, 1H), 3.74 (dd, *J* 14.0, 3.2 Hz, 1H), 3.38 (dd, *J* 14.0, 9.6 Hz, 1H); ^{13}C NMR (126 MHz, MeOD): δ 48.0, 45.6, 34.1; HRMS (ESI-TOF): calc'd for $C_3H_8Br_2N$ [M+H] 215.9023; found 215.9015.

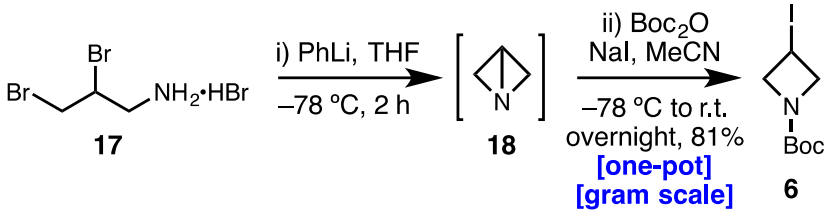


Figure 2

***tert*-Butyl 3-iodoazetidine-1-carboxylate** (**6**). To a flame-dried 500 mL round bottom flask was added 1-amino-2,3-dibromopropane hydrobromide (**17**) (7.5 g, 0.025 mol, 1 equiv.) and stirred without solvent to obtain **17** as a fine powder under argon (alternatively, crystals of **17** could be ground to a fine powder by hand before use). Dry THF (75 mL) was added to the flask and cooled to –78 °C. PhLi solution (1.8M in dibutyl ether, 39.8 mL, 0.075 mol, 3 equiv.) was slowly added via syringe and the reaction mixture stirred at –78 °C for 2 h. To the resulting mixture was added MeCN (240 mL), NaI (11.4 g, 0.075 mol, 3 equiv.) and Boc_2O (11.2 mL, 0.050 mol, 2 equiv.) at –78 °C and warmed at rt overnight. The resulting mixture was poured into water (200 mL), washed with sat. aq. $Na_2S_2O_3$ (100 mL) and then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **6** (5.8 g, 81%). Physical State: light yellow oil; R_f = 0.55 (2:8 EtOAc/hexanes, vis. UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 – 4.60 (m, 2H), 4.50 – 4.43 (m, 1H), 4.33 – 4.24 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 80.3, 61.7 (br, 2C), 28.4 (3C), 2.7; HRMS (ESI-TOF): calc'd for $C_8H_{14}INNaO_2$ [M+Na^+] 305.9967; found 305.9950.

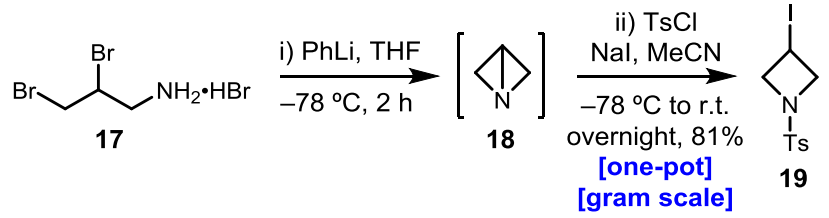


Figure 3

3-Iodo-1-tosylazetidine (**19**). To a flame-dried 500 mL round bottom flask was added 1-amino-2,3-dibromopropane hydrobromide (**17**) (2.80 g, 9.46 mmol, 1 equiv.) and stirred without solvent to obtain **17** as a fine powder under argon (alternatively, crystals of **17** could be ground to a fine powder by hand before use). Dry THF (28 mL) was added to the flask and cooled to –78 °C. PhLi solution (1.8M in dibutyl ether, 14.9 mL, 28.4 mmol, 3 equiv.) was slowly added via syringe and the reaction mixture stirred at –78 °C for 2 h. To the resulting mixture was added MeCN (89 mL), NaI (21.3 g, 141.9 mmol, 15 equiv.) and tosyl chloride (3.6 g, 18.8 mmol, 2 equiv.) at –78 °C and warmed at rt overnight. The resulting mixture was poured into water (150 mL), washed with sat. aq. $Na_2S_2O_3$ (150 mL) and then extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude material was

purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **19** (2.43 g, 81%). Physical State: white solid (mp 125–126 °C); R_f = 0.38 (2:8 EtOAc/hexanes, vis. UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 – 7.72 (m, 2H), 7.42 – 7.38 (m, 2H), 4.47 – 4.44 (m, 2H), 4.37 – 4.28 (m, 1H), 4.10 – 4.07 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.8, 131.3, 130.1 (2C), 128.5 (2C), 62.0 (br, 2C), 21.8, 0.5; HRMS (ESI-TOF)**:** calc'd for $C_{10}H_{12}INNaO_2S$ [M+Na$^+$] 359.9531; found 359.9522.

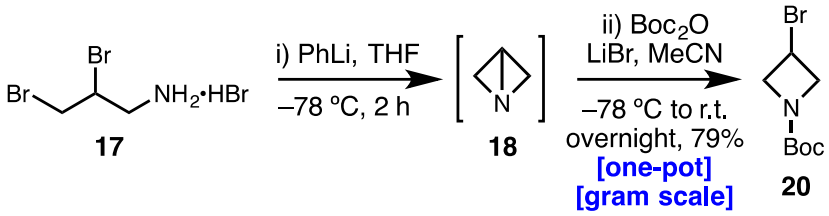


Figure 4

***tert*-Butyl 3-bromoazetidine-1-carboxylate** (**20**). To a flame-dried 500 mL round bottom flask was added 1-amino-2,3-dibromopropane hydrobromide (**17**) (3.5 g, 11.8 mmol, 1 equiv.) and stirred without solvent to obtain **17** as a fine powder under argon (alternatively, crystals of **17** could be ground to a fine powder by hand before use). Dry THF (35 mL) was added to the flask and cooled to –78 °C. PhLi solution (1.8M in dibutyl ether, 18.5 mL, 35.3 mmol, 3 equiv.) was slowly added via syringe and the reaction mixture stirred at –78 °C for 2 h. To the resulting mixture was added MeCN (112 mL), LiBr (4.2 g, 35.3 mmol, 3 equiv.) and Boc_2O (5.4 mL, 23.6 mmol, 2 equiv.) at –78 °C and warmed to rt overnight. The resulting mixture was poured into water (200 mL), washed with sat. aq. $Na_2S_2O_3$ (50 mL) and then extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–20% EtOAc in hexanes) to give the desired product **20** (2.21 g, 79%). Physical State: clear liquid; R_f = 0.38 (1:9 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 – 4.46 (m, 3H), 4.22 – 4.14 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 80.2, 60.3 (br, 2C), 33.0, 28.4 (3C); All spectral data are in accordance with the previously reported literature values.[14]

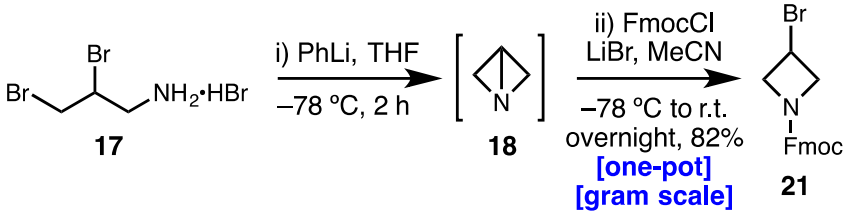


Figure 5

(9*H*-Fluoren-9-yl)methyl 3-bromoazetidine-1-carboxylate (**21**). To a flame-dried 500 mL round bottom flask was added 1-amino-2,3-dibromopropane hydrobromide (**17**) (3.00 g, 10.1 mmol, 1 equiv.) and stirred without solvent to obtain **17** as a fine powder under argon (alternatively, crystals of **17** could be ground to a fine powder by hand before use). Dry THF (30 mL) was added to the flask and cooled to –78 °C. PhLi solution (1.8M in dibutyl ether, 15.9 mL, 30.2 mmol, 3 equiv.) was slowly added via syringe and the reaction mixture stirred at –78 °C for 2 h. To the resulting mixture was added MeCN (96 mL), LiBr (3.6 g, 30.2 mmol, 3 equiv.) and Fmoc-Cl (5.23 g, 20.2 mmol, 2 equiv.) at –78 °C and warmed to rt overnight. The resulting mixture was poured into water (200 mL), washed with sat. aq. $Na_2S_2O_3$ (50 mL) and then extracted with EtOAc (3 x 150 mL). The

combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 20–100% CH_2Cl_2 in hexanes) to give the desired product **21** (2.95 g, 82%). Physical State: clear liquid; R_f = 0.42 (2:8 hexanes/CH_2Cl_2, vis. UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* 7.6 Hz, 2H), 7.57 (d, *J* 7.5 Hz, 2H), 7.41 (t, *J* 7.5 Hz, 2H), 7.32 (td, *J* 7.5, 1.2 Hz, 2H), 4.64 – 4.55 (m, 2H), 4.58 – 4.52 (m, 1H), 4.39 (d, *J* 7.1 Hz, 2H), 4.31 – 4.23 (m, 2H), 4.22 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.1, 143.9 (2C), 141.5 (2C), 127.9 (2C), 127.2 (2C), 125.2 (2C), 120.1 (2C), 67.4, 60.4 (2C), 47.3, 32.9; HRMS (ESI-TOF)**:** calc'd for $C_{18}H_{16}BrNNaO_2$ [M+Na$^+$] 380.0262 (^{79}Br), 382.0242 (^{81}Br); found 380.0245 (^{79}Br), 382.0222 (^{81}Br).

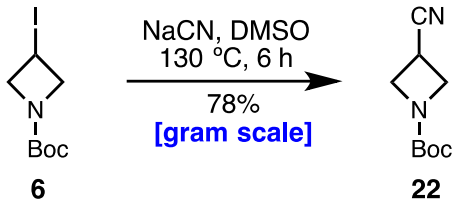


Figure 6

***tert*-Butyl 3-cyanoazetidine-1-carboxylate** (**22**). To a 100 mL round bottom flask was added *tert*-butyl 3-iodoazetidine-1-carboxylate (**6**) (6.54 g, 0.0231 mol, 1 equiv.) and DMSO (25 mL). NaCN (2.3 g, 0.0462 mol, 2 equiv.) was added to the solution in one portion and stirred at 130 °C for 6 h. The resulting mixture was cooled to rt, poured into water (200 mL), and extracted with diethyl ether (5 x 200 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The crude compound was purified by flash chromatography (silica gel, 5–50% EtOAc in hexanes) to give the desired product **22** (3.27 g, 78%). Physical State: off-white solid (mp 78–80 °C); R_f = 0.40 (2:8 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 – 4.11 (m, 4H), 3.38 (tt, *J* 8.9, 6.3 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.6, 119.6, 80.8, 52.6 (br, 2C), 28.4 (3C), 17.2.

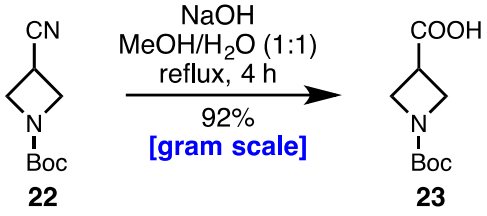


Figure 7

1-(*tert*-Butoxycarbonyl)azetidine-3-carboxylic acid (**23**). To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate **22** (3.7 g, 0.0202 mol, 1 equiv.) in MeOH (35 mL) was added a solution of NaOH (4.03 g, 0.101 mol, 5 equiv.) in H_2O (35 mL) and refluxed until the reaction was complete by TLC (*ca.* 4 h). The resulting reaction mixture was cooled to rt and concentrated to remove the MeOH. The mixture was neutralized with 10 % aq. citric acid (200 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the desired product **23** (3.72 g, 92%). Physical State: white solid (mp 106–107 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.13 (d, *J* 7.5 Hz, 4H), 3.41 – 3.35 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.4, 155.3, 80.3, 51.8 (br, 2C), 32.0, 28.5 (3C); HRMS (ESI-TOF)**:** calc'd for $C_9H_{14}NO_4$ [M-H] 200.0928; found 200.0923.

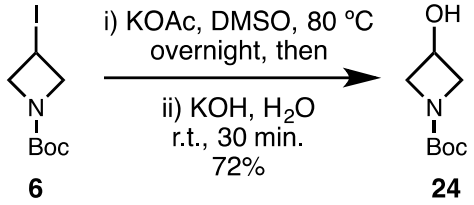


Figure 8

***tert*-Butyl 3-hydroxyazetidine-1-carboxylate** (**24**). To a flame-dried reaction tube under argon was added *tert*-butyl 3-iodoazetidine-1-carboxylate (**6**) (83.8 mg, 0.249 mmol, 1 equiv.), potassium acetate (36.6 mg, 0.375 mmol, 1.5 equiv.) and dry DMSO (2.5 mL). The mixture was heated at 80 ^{o}C and stirred overnight. Completion of the acetoxylation step was monitored by TLC and ^{1}H NMR of the crude reaction mixture. A solution of potassium hydroxide (21.0 mg, 0.374 mmol, 1.5 equiv. in 0.8 mL of H_2O) was slowly added and the mixture stirred at rt for 30 min. The resulting mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 10–60% EtOAc in hexanes) to give the desired product **24** (31.2 mg, 72%). Physical State: white solid (mp 51–52 ^{o}C); R_f = 0.13 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): [mixture of rotamers] δ 4.58 – 4.53 (m, 1H), 4.12 (dd, *J* 10.6, 6.7 Hz, 2H, major), 4.12 (dd, *J* 8.3, 6.7 Hz, 2H, minor), 3.79 (dd, *J* 10.6, 4.4 Hz, 2H, major), 3.79 (dd, *J* 8.4, 4.4 Hz, 2H, minor), 3.12 (br s, 1H, major), 3.10 (br s, 1H, minor), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.6, 79.9, 61.6, 59.1 (br, 2C), 28.5 (3C). All spectral data are in accordance with the previously reported literature values.[49]

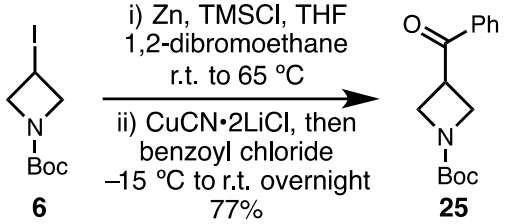


Figure 9

***tert*-Butyl 3-benzoylazetidine-1-carboxylate** (**25**). To a flame-dried reaction tube was added Zn dust (35.3 mg, 0.540 mmol, 1.3 equiv.) and dry THF (0.3 mL) under argon. 1,2-Dibromoethane (4.3 µL, 0.050 mmol, 0.12 equiv.) was added at rt and stirred at 65 ^{o}C for 5 min. The resulting mixture was cooled to rt, TMSCl (5.8 µL, 0.0457 mmol, 0.11 equiv.) was added, and the reaction mixture stirred at rt for 30 min. A solution of *tert*-butyl 3-iodoazetidine-1-carboxylate (**6**) (117.5 mg, 0.415 mmol, 1 equiv.) in THF (0.3 mL) was added and the resulting mixture stirred at 65 ^{o}C for *ca.* 30 min. (zinc insertion was monitored by TLC). When the zinc insertion was complete, the reaction mixture was cooled to –15 ^{o}C and a freshly made solution of 1M CuCN•2LiCl[50] (0.415 mL, 0.415 mmol, 1 equiv.) was added and stirring continued for another 1 h at the same temperature. Benzoyl chloride (58 µL, 0.498 mmol, 1.2 equiv.) was added via syringe and the mixture stirred overnight at rt. The reaction was filtered through a short pad of celite and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product

25 (83.8 mg, 77%). Physical State: colorless liquid; R_f = 0.27 (2:8 EtOAc/hexanes, vis. UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 – 7.79 (m, 2H), 7.60 – 7.54 (m, 1H), 7.49 – 7.43 (m, 2H), 4.29 – 4.07 (m, 5H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.3, 156.3, 134.9, 133.8, 129.0 (2C), 128.3 (2C), 79.8, 51.0 (br, 2C), 35.7, 28.5 (3C); HRMS (ESI-TOF): calc'd for $C_{15}H_{19}NNaO_3$ [M+Na$^+$] 284.1263; found 284.1250.

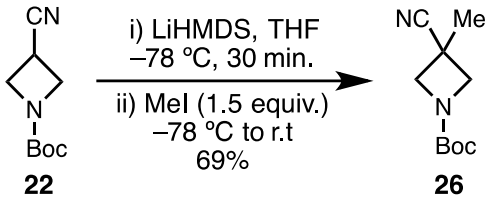


Figure 10

***tert*-Butyl 3-cyano-3-methylazetidine-1-carboxylate** (**26**). To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (**22**) (50 mg, 0.275 mmol, 1 equiv.) in THF (1.0 mL) was added LiHMDS (1M in THF, 0.302 mL, 0.302 mmol, 1.1 equiv.) at –78 °C and stirred for 30 min. at the same temperature. Methyl iodide (25.7 µL, 0.411 mmol, 1.5 equiv.) was added via syringe and stirred at –78 °C for 45 min. followed by stirring at rt for 1 h. The resulting mixture was quenched with NH_4Cl (1 mL) and extracted with ethyl acetate (3 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **26** (37.4 mg, 69%, *caution:* product can be lost through sublimation under high vacuum.). Physical State: yellow crystalline solid (mp 57 °C); R_f = 0.53 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.29 (d, *J* 8.6 Hz, 2H), 3.80 (d, *J* 8.6 Hz, 2H), 1.67 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 122.2, 80.7, 59.3 (br, 2C), 28.3 (3C), 26.0, 23.5; HRMS (ESI-TOF): calc'd for $C_{10}H_{16}N_2NaO_2$ [M+Na$^+$] 219.1109; found 219.1087.

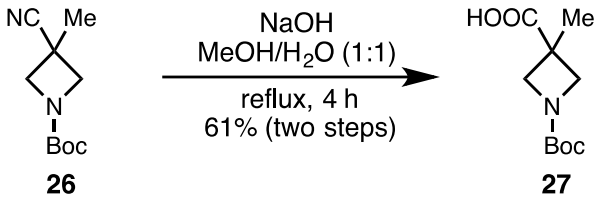


Figure 11

1-(*tert*-Butoxycarbonyl)-3-methylazetidine-3-carboxylic acid (**27**). [Note: Since cyanoazetidine **26** is volatile, a combined procedure designed to maximize the yield is provided here. However, if azetidine **26** is already in hand, follow just the NaOH hydrolysis step.] To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (**22**) (150 mg, 0.823 mmol, 1 equiv.) in dry THF (3 mL) was added LiHMDS (1M in THF, 0.905 mL, 0.905 mmol, 1.1 equiv.) at –78 °C and stirred for 30 min. at the same temperature. Methyl iodide (77 µL, 1.23 mmol, 1.5 equiv.) was added via syringe and stirred at –78 °C for 45 min. followed by stirring at rt for 1 h. The resulting mixture was quenched with NH_4Cl (2 mL) and extracted with ethyl acetate (3 x 2 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. Compound **26** was used in the next step without further purification. A solution of NaOH (115 mg, 4.12 mmol, 5 equiv.) in H_2O (3 mL) was slowly added to a solution of *tert*-butyl 3-cyano-3-methylazetidine-1-carboxylate (**26**) in MeOH (3 mL) and then refluxed until judged complete by TLC (*ca.* 4 h). The reaction mixture was cooled to rt and the MeOH was removed *in*

vacuo. The mixture was neutralized with 10 % aq. citric acid (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the desired product **27** (107.5 mg, 61% for 2 steps). Physical State: white crystalline solid (mp 135–136 °C); ^{1}H NMR (500 MHz, $CDCl_3$): [mixture of rotamers] δ 6.71 (br s, 1H, COOH minor rotamer), 5.91 (br s, 1H, COOH major rotamer), 4.25 (d, *J* 8.5 Hz, 2H, major), 4.19 (d, *J* 8.4 Hz, 2H, minor), 3.69 (d, *J* 8.5 Hz, 2H, minor), 3.68 (d, *J* 8.6 Hz, 2H, major), 1.55 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): [mixture of rotamers] δ 179.3 (major), 178.5 (minor), 156.6 (minor), 156.5 (major), 80.3 (minor), 80.1 (major), 58.5 (br, major + minor, 2 x 2C), 39.1 (minor), 38.7 (major), 28.5 (major, 3C), 28.5 (minor, 3C), 23.1 (minor), 22.6 (major); HRMS (ESI-TOF): calc'd for $C_{10}H_{16}NO_4$ [M-H] 214.1079; found 214.1080.

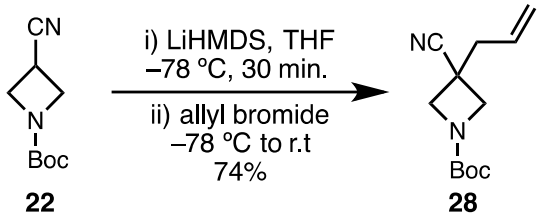


Figure 12

***tert*-Butyl 3-allyl-3-cyanoazetidine-1-carboxylate** (**28**). To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (**22**) (100 mg, 0.549 mmol, 1 equiv.) in dry THF (2 mL) was added LiHMDS (1M in THF, 0.549 mmol, 0.549 mL, 1 equiv.) at –78 °C and stirred for 30 min. at the same temperature. Allyl bromide (57 µL, 0.659 mmol, 1.2 equiv.) was added via syringe and stirred at –78 °C for 45 min. followed by stirring at rt for 1 h. The resulting mixture was quenched with NH_4Cl (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **28** (90.5 mg, 74%). Physical State: colorless liquid; R_f = 0.63 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 – 5.73 (m, 1H), 5.41 – 5.19 (m, 2H), 4.22 (d, *J* 8.8 Hz, 2H), 3.85 (d, *J* 8.8 Hz, 2H), 2.62 (dt, *J* 7.0, 1.2 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 130.3, 121.2, 121.1, 80.8, 57.3 (br, 2C), 40.6, 30.1, 28.4 (3C).

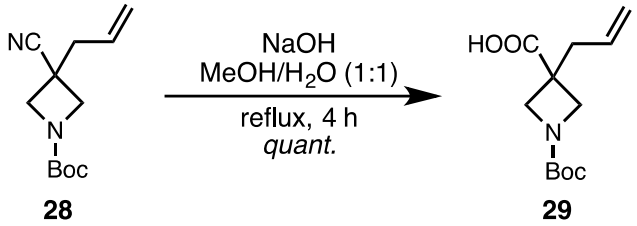


Figure 13

3-Allyl-1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (**29**). To a solution of *tert*-butyl 3-allyl-3-cyano-azetidine-1-carboxylate (**28**) (35 mg, 0.166 mmol, 1 equiv.) in MeOH (0.5 mL) was added a solution of NaOH (33 mg, 0.83 mmol, 5 equiv.) in H_2O (0.5 mL). The reaction was heated to reflux and monitored until completion by TLC (*ca.* 4 h). The reaction mixture was cooled to rt and the MeOH removed *in vacuo*. The mixture was neutralized with 10 % aq. citric acid (2 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the desired

product **29** (39.8 mg, *quant*.). Physical State: colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$): [mixture of rotamers] δ 6.81 (br s, 1H, COOH rotamer 1), 6.03 (br s, 1H, COOH rotamer 2), 5.86 – 5.77 (m, 1H), 5.25 – 5.07 (m, 2H), 4.17 (d, *J* 8.7 Hz, 1H), 4.12 (d, *J* 8.7 Hz, 1H), 3.75 (dd, *J* 8.7, 6.0 Hz, 2H), 2.62 (t, *J* 7.2 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): [mixture of rotamers] δ 177.8 (minor), 177.5 (major), 156.6 (minor), 156.5 (major), 132.2 (minor), 132.0 (major), 119.8 (minor), 119.3 (major), 80.3 (minor), 80.1 (major), 56.4 (br, major + minor, 2 x 2C), 42.7 (minor), 42.2 (major), 40.8 (major), 40.1 (minor), 28.5 (major, 3C), 28.5 (minor, 3C); HRMS (ESI-TOF): calc'd for $C_{12}H_{18}NO_4$ [M-H] 240.1236; found 240.1234.

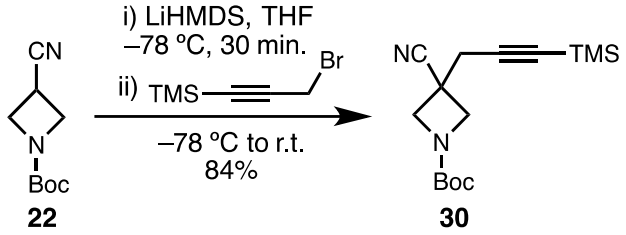


Figure 14

***tert*-Butyl 3-cyano-3-[3-(trimethylsilyl)prop-2-yn-1-yl]azetidine-1-carboxylate** (**30**). To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (**22**) (100 mg, 0.549 mmol, 1 equiv.) in dry THF (2 mL) was added LiHMDS (1M in THF, 0.549 mL, 0.549 mmol, 1 equiv.) at –78 °C and stirred for 30 min. at the same temperature. 3-Bromo-1-(trimethylsilyl)propyne (0.107 mL, 0.659 mmol, 1.2 equiv.) was added via syringe and stirred at –78 °C for 30 min. followed by stirring at rt overnight. The resulting mixture was quenched with NH_4Cl (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **30** (126.4 mg, 84%). Physical State: white solid (mp 83–84 °C); R_f = 0.7 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (d, *J* 8.8 Hz, 2H), 4.00 (d, *J* 8.8 Hz, 2H), 2.79 (s, 2H), 1.45 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.5, 120.7, 98.3, 90.2, 80.9, 56.9 (br, 2C), 29.8, 28.4 (3C), 27.8, –0.1 (9C).

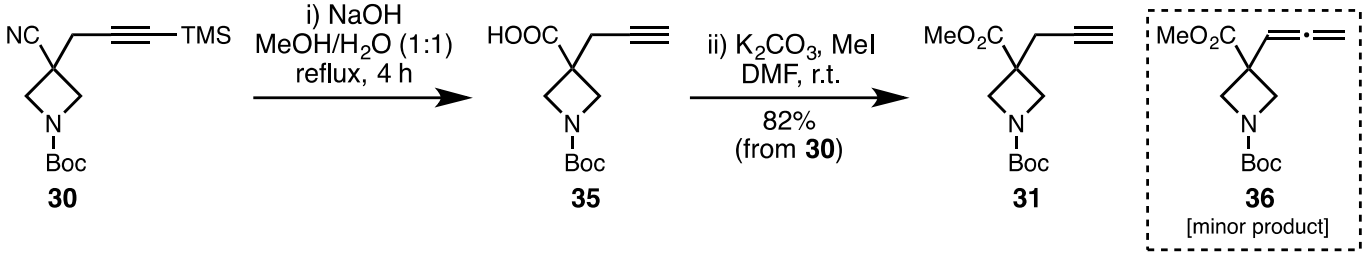


Figure 15

1-(*tert*-Butoxycarbonyl)-3-(prop-2-yn-1-yl)azetidine-3-carboxylic acid (**35**). To a solution of *tert*-butyl 3-cyano-3-[3-(trimethylsilyl)prop-2-yn-1-yl]azetidine-1-carboxylate (**30**) (100 mg, 0.359 mmol, 1 equiv.) in MeOH (2 mL) was added a solution of NaOH (72 mg, 1.80 mmol, 5 equiv.) in H_2O (2 mL). The reaction was heated to reflux and monitored until completion by TLC (*ca.* 4 h). The reaction mixture was cooled to rt and the MeOH removed *in vacuo*. The mixture was neutralized with 10 % aq. citric acid (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to

give crude 1-(*tert*-butoxycarbonyl)-3-(prop-2-yn-1-yl)azetidine-3-carboxylic acid (**35**) as a clear liquid (85 mg, *ca.* 90%). Note: Due to the presence of an inseparable minor byproduct (*ca.* 10%, characterized as methyl ester **36** below), the carboxylic acid **35** was converted to the corresponding methyl ester **31** (see below). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (d, 8.9 Hz, 2H), 3.93 (d, *J* 8.9 Hz, 2H), 2.76 (d, *J* 2.7 Hz, 2H), 2.06 (t, *J* 2.6 Hz, 1H), 1.44 (d, *J* 1.3 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.6, 156.5, 80.5, 78.7, 71.3, 55.9 (br, 2C), 41.6, 28.5 (3C), 25.1; HRMS (ESI-TOF)**:** calc'd for $C_{12}H_{17}NNaO_4$ [M+Na^+] 262.1055; found 262.1046.

***tert*-Butyl 3-methoxycarbonyl-3-(prop-2-yn-1-yl)azetidine-1-carboxylate** (**31**). The crude carboxylic acid **35** was dissolved in dry DMF (3 mL) at rt and K_2CO_3 (59.5 mg, 0.43 mmol, 1.2 equiv.) was added and stirred for 30 min. at rt. Methyl iodide (0.025 mL, 0.394 mmol, 1.1 equiv.) was added to the reaction mixture and stirred overnight at rt. The resulting mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–30% EtOAc in hexanes) to give the desired product **31** (74.3 mg, 82% from **30**). Physical State: clear liquid; R_f = 0.33 (2:8 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): 4.16 (d, *J* 8.8 Hz, 2H), 3.89 – 3.84 (m, 2H), 3.76 (s, 3H), 2.72 (d, *J* 2.6 Hz, 2H), 2.01 (t, *J* 2.6 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 156.2, 80.0, 78.8, 71.0, 55.9 (br, 2C), 52.8, 41.6, 28.4 (3C), 25.3; HRMS (ESI-TOF): calc'd for $C_{13}H_{19}NNaO_4$ [M+Na^+] 276.1212; found 276.1205.

***tert*-Butyl 3-methoxycarbonyl-3-(propa-1,2-dien-1-yl)azetidine-1-carboxylate** (**36**). Formed as an inseparable minor byproduct during the hydrolysis of cyanoazetidines **30** and **37**. Separated and characterized as the methyl ester during the synthesis of **31** (above). Physical State: clear liquid; R_f = 0.37 (2:8 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51 (t, *J* = 6.6 Hz, 1H), 5.01 (d, *J* = 6.7 Hz, 2H), 4.25 (d, *J* = 8.6 Hz, 2H), 3.94 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.5, 173.2, 156.3, 91.9, 80.1, 79.9, 57.1 (br, 2C), 52.9, 41.4, 28.5 (3C); HRMS (ESI-TOF): calc'd for $C_{13}H_{19}NNaO_4$ [M+Na^+] 276.1212; found 276.1207.

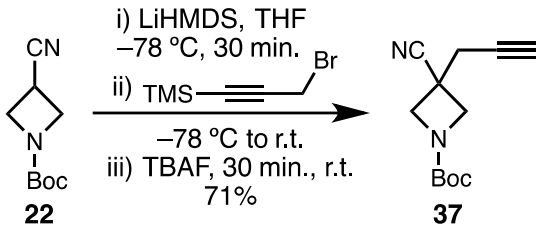


Figure 16

***tert*-Butyl 3-cyano-3-(prop-2-yn-1-yl)azetidine-1-carboxylate** (**37**). To a solution of *tert*-butyl 3-cyano-azetidine-1-carboxylate (**22**) (30 mg, 0.165 mmol, 1 equiv.) in dry THF (1 mL) was added LiHMDS (1M in THF, 0.165 mL, 0.165 mmol, 1 equiv.) at –78 °C and stirred for 30 min. at the same temperature. 3-Bromo-1-(trimethylsilyl)propyne (32 µL, 0.198 mmol, 1.2 equiv.) was added via syringe and stirred at –78 °C for 30 min. followed by stirring at rt overnight. A solution of tetrabutylammonium fluoride (TBAF, 1M in THF, 0.165 mL, 0.165 mmol, 1 equiv.) was added to the reaction mixture at rt and stirred for 30 min. The resulting mixture was quenched with NH_4Cl (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **37** (25.8 mg, 71%). Physical State: white solid (mp 119–120 °C); R_f = 0.53 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ

4.26 (d, *J* 8.9 Hz, 2H), 3.98 (d, *J* 8.9 Hz, 2H), 2.78 (d, *J* 2.7 Hz, 2H), 2.18 (t, *J* 2.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.6, 120.5, 81.0, 76.6, 72.8, 57.1 (br, 2C), 29.9, 28.4 (3C), 26.6.

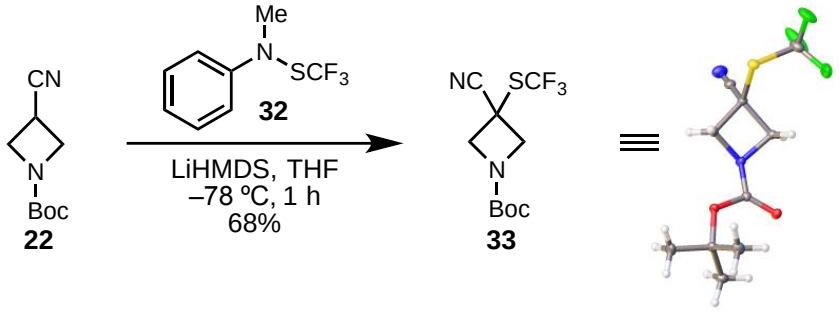


Figure 17

***tert*-Butyl 3-cyano-3-[(trifluoromethyl)thio]azetidine-1-carboxylate** (**33**). To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (**22**) (25 mg, 0.137 mmol, 1 equiv.) and *N*-methyl *N*-trifluoromethylthioaniline (**32**)[48] (34.1 mg, 0.165 mmol, 1.2 equiv.) in dry THF (1 mL) was added LiHMDS (1M in THF, 0.151 mL, 0.151 mmol, 1.1 equiv.) at –78 ^{o}C and stirred for 1 h at the same temperature. The resulting mixture was quenched with NH_4Cl (1 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (silica gel, 5–40% EtOAc in hexanes) to give the desired product **33** (26.3 mg, 68%). Physical State: colorless crystalline solid (mp 122–123 ^{o}C); R_f = 0.7 (3:7 EtOAc/hexanes, vis. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 (d, *J* 9.5 Hz, 2H), 4.20 (d, *J* 9.5 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.0, 128.6 (q, *J* 311.0 Hz), 117.5, 81.9, 60.5 (br, 2C), 31.6 (q, *J* 2.3 Hz), 28.3 (3C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –38.86 (s, 3F). X-ray quality single crystals were obtained by slow evaporation from CH_2Cl_2:hexanes. The CIF file was deposited in the Cambridge Crystallographic Data Centre (CCDC 1826005).

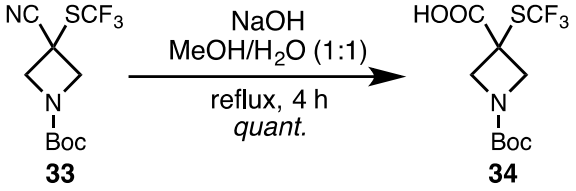


Figure 18

1-(*tert*-Butoxycarbonyl)-3-[(trifluoromethyl)thio]azetidine-3-carboxylic acid (**34**). To a solution of *tert*-butyl 3-cyano-3-[(trifluoromethyl)thio]azetidine-1-carboxylate (**33**) (10 mg, 0.035 mmol, 1 equiv.) in MeOH (0.2 mL) was added a solution of NaOH (7.1 mg, 0.175 mmol, 5 equiv.) in H_2O (0.2 mL). The reaction was heated to reflux and monitored until completion by TLC (*ca.* 4 h). The reaction mixture was cooled to rt and the MeOH removed *in vacuo*. The mixture was neutralized with 10 % aq. citric acid (0.5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give the desired product **34** (10.5 mg, *quant*.). Physical State: white solid, mp 139–140 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 (d, *J* 9.8 Hz, 2H), 4.14 (d, *J* 9.7 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 156.1, 129.3 (q, *J* 309.7 Hz), 81.6, 58.7 (br, 2C), 44.9, 28.4 (3C); ^{19}F NMR (471 MHz, $CDCl_3$): δ –39.15 (s, 3F); HRMS (ESI-TOF): calc'd for $C_{10}H_{14}F_3NNaO_4S$ [M+Na^+] 324.0493; found 324.0475.

Acknowledgements

We gratefully acknowledge the H. Lee Moffitt Cancer Center & Research Institute for financial support. This work has also been supported in part by the Chemical Biology Core Facility (NMR, LC-MS, HRMS) at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292).

Supplementary Material

Copies of ^{1}H, ^{13}C, and ^{19}F NMR are available in the supplementary material. X-Ray crystallographic data for compound **33** (CCDC 1826005) are included.

References

1. Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331–358. https://pubs.acs.org/doi/abs/10.1021/cr60320a003
2. Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev*. **2008**, *108*, 3988–4035. https://pubs.acs.org/doi/abs/10.1021/cr800325e
3. Antermite, D; Degennaro, L.; Luisi, R. *Org. Biomol. Chem*. **2017**, *15*, 34–50. http://pubs.rsc.org/en/content/articlehtml/2017/OB/C6OB01665K
4. Han, Y.; Han, M.; Shin, D.; Song, C.; Hahn, H.-G. *J. Med. Chem.* **2012**, *55*, 8188–8192. https://pubs.acs.org/doi/10.1021/jm3008294
5. Han, M.; Song, C.; Jeong, N.; Hahn, H.-G. *ACS Med. Chem. Lett.* **2014**, *5*, 999–1004. https://pubs.acs.org/doi/abs/10.1021/ml500187a
6. Pan, S.; Gray, N. S.; Gao, W.; Mi, Y.; Fan, Y.; Wang, X.; Tuntland, T.; Che, J.; Lefebvre, S.; Chen, Y.; Chu, A.; Hinterding, K.; Gardin, A.; End, P.; Heining, P.; Bruns, C.; Cooke, N. G.; Nuesslein-Hildesheim, B. *ACS Med. Chem. Lett*. **2013**, *4*, 333–337. https://pubs.acs.org/doi/abs/10.1021/ml300396r
7. Cee, V. J.; Frohn, M.; Lanman, B. A.; Golden, J.; Muller, K.; Neira, S.; Pickrell, A.; Arnett, H.; Buys, J.; Gore, A.; Fiorino, M.; Horner, M.; Itano, A.; Lee, M. R.; McElvain, M.; Middleton, S.; Schrag, M.; Rivenzon-Segal, D.; Vargas, H. M.; Xu, H.; Xu, Y.; Zhang, X.; Siu, J.; Wong, M.; Bürli, R. W. *ACS Med. Chem. Lett*. **2011**, *2*, 107–112. https://pubs.acs.org/doi/abs/10.1021/ml100306h
8. Hobson, A. D.; Harris, C. M.; van der Kam, E. L.; Turner, S. C.; Abibi, A.; Aguirre, A. L.; Bousquet, P.; Kebede, T.; Konopacki, D. B.; Gintant, G.; Kim, Y.; Larson, K.; Maull, J. W.; Moore, N. S.; Shi, D.; Shrestha, A.; Tang, X.; Zhang, P.; Sarris, K. K. *J. Med. Chem*. **2015**, *58*, 9154–9170. https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.5b00928
9. Watterson, S. H.; Guo, J.; Spergel, S. H.; Langevine, C. M.; Moquin, R. V.; Shen, D. R.; Yarde, M.; Cvijic, M. E.; Banas, D.; Liu, R.; Suchard, S. J.; Gillooly, K.; Taylor, T.; Rex-Rabe, S.; Shuster, D. J.; McIntyre, K. W.; Cornelius, G.; D'Arienzo, K.; Marino, A.; Balimane, P.; Warrack, B.; Salter-Cid, L.; McKinnon, M.; Barrish, J. C.; Carter, P. H.; Pitts, W. J.; Xie, J.; Dyckman, A. J. *J. Med. Chem*. **2016**, *59*, 2820–2840. https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.6b00089

10. Kurata, H.; Kusumi, K.; Otsuki, K.; Suzuki, R.; Kurono, M.; Komiya, T.; Hagiya, H.; Mizuno, H.; Shioya, H.; Ono, T.; Takada, Y.; Maeda, T.; Matsunaga, N.; Kondo, T.; Tominaga, S.; Nunoya, K.-I.; Kiyoshi, H.; Komeno, M.; Nakade, S.; Habashita, H. *J. Med. Chem*. **2017**, *60*, 9508–9530. https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.7b00785
11. Blaho, V. A.; Hla, T. *J. Lipid Res.* **2014**, *55*, 1596–1608. http://www.jlr.org/content/55/8/1596.full.pdf+html
12. Pyne, N. J.; Pyne, S. *Nature Reviews Cancer* **2010**, *10*, 489–503. https://www.nature.com/articles/nrc2875
13. Billotte, S. *Synlett* **1998**, 379–380. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-1998-37503
14. Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett.* **2014**, *16*, 6160–6163. https://pubs.acs.org/doi/abs/10.1021/ol503043r
15. Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259–3262. https://pubs.acs.org/doi/abs/10.1021/ol8011327
16. Zhang, X.; Yang, C. *Adv. Synth. Catal.* **2015**, *357*, 2721–2727. http://onlinelibrary.wiley.com/doi/10.1002/adsc.201500346/abstract
17. Zhang, Y.; Geng, Z.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Adv. Synth. Catal*. **2017**, *359*, 390–394. http://onlinelibrary.wiley.com/doi/10.1002/adsc.201600470/abstract
18. Di Franco, T.; Epenoy, A.; Hu, X. *Org. Lett.* **2015**, *17*, 4910–4913. https://pubs.acs.org/doi/10.1021/acs.orglett.5b02482
19. Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A.; Gangé, Y.; Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309–15313. http://onlinelibrary.wiley.com/doi/10.1002/anie.201707958/abstract
20. Duncton, M. A. J.; Estiarte, M. A.; Johnson, R. J.; Cox, M.; O'Mahony, D. J. R.; Edwards, W. T.; Kelly, M. G. *J. Org. Chem.* **2009**, *74*, 6354–6357. https://pubs.acs.org/doi/abs/10.1021/jo9010624
21. Song, J.; Li, X.; Liang, A.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett*. **2014**, *55*, 2369–2372. https://www.sciencedirect.com/science/article/pii/S0040403914003505
22. Molander, G. A.; Wisniewski, S. R.; Traister, K. M. *Org. Lett.* **2014**, *16*, 3692–3695. https://pubs.acs.org/doi/10.1021/ol501495d
23. Zheng, M.; Xue, W.; Xue, T.; Gong, H. *Org. Lett.* **2016**, *18*, 6152–6155. https://pubs.acs.org/doi/10.1021/acs.orglett.6b03158
24. Lovinger, G. J.; Morken, J. P. *J. Am. Chem. Soc*. **2017**, *139*, 17293–17296. https://pubs.acs.org/doi/abs/10.1021/jacs.7b10519
25. Swain, N. A.; Batchelor, D.; Beaudoin, S.; Bechle, B. M.; Bradley, P. A.; Brown, A. D.; Brown, B.; Butcher, K. J.; Butt, R. P.; Chapman, M. L.; Denton, S.; Ellis, D.; Galan, S. R. G.; Gaulier, S. M.; Greener, B. S.; de Groot, M. J.; Glossop, M. S.; Gurrell, I. K.; Hannam, J.; Johnson, M. S.; Lin, Z.; Markworth, C. J.; Marron, B. E.; Millan, D. S.; Nakagawa, S.; Pike, A.; Printzenhoff, D.; Rawson, D. J.; Ransley, S. J.; Reister, S. M.; Sasaki, K.; Storer, R. I.; Stupple, P. A.; West, C. W. *J. Med. Chem*. **2017**, *60*, 7029–7042. https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00598

26. Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett*. **2014**, *16*, 154–157. https://pubs.acs.org/doi/10.1021/ol4031233
27. Nassoy, A.-C. M. A.; Raubo, P.; Harrity, J. P. A. *Chem. Commun.* **2015**, *51*, 5914–5916. http://pubs.rsc.org/en/Content/ArticleLanding/2015/CC/C5CC00975H
28. Presset, M.; Fleury-Brégeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615–4619. https://pubs.acs.org/doi/10.1021/jo4005519
29. Anderson Jr., A. G.; Lok, R. *J. Org. Chem*. **1972**, *37*, 3953–3955. https://pubs.acs.org/doi/abs/10.1021/jo00797a046
30. Kulbitski, K.; Nisnevich, G.; Gandelman, M. *Adv. Synth. Catal.* **2011**, *353*, 1438–1442. http://onlinelibrary.wiley.com/doi/10.1002/adsc.201100145/abstract
31. Van Hende, E.; Verniest, G.; Deroose, F.; Thuring, J.-W.; Macdonald, G.; De Kimpe, N. *J. Org. Chem*. **2009**, *74*, 2250–2253. https://pubs.acs.org/doi/abs/10.1021/jo802791r
32. Žukauskaitė, A.; Mangelinckx, S.; Buinauskaitė, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541 – 558. https://link.springer.com/article/10.1007/s00726-011-0879-1
33. Miller, R. A.; Lang, F.; Marcune, B.; Zewge, D.; Song, Z. J.; Karady, S. *Synth. Commun.* **2003**, *33*, 3347–3353. http://www.tandfonline.com/doi/abs/10.1081/SCC-120023992
34. Bartnik, R.; Marchand, A. P. *Synlett* **1997**, 1029–1039. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-1997-1520
35. Funke, W. *Angew. Chem. Int. Ed.* **1969**, *8*, 70–71. http://onlinelibrary.wiley.com/doi/10.1002/anie.196900701/full
36. Lopchuk, J. M.; Baran, P. S. **2017**. 1-Azabicyclo[1.1.0]butane. *E-EROS Encyclopedia of Reagents for Organic Synthesis*. 1–3. http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rn02056/abstract
37. Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science* **2016**, *351*, 241–246. http://science.sciencemag.org/content/351/6270/241
38. Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *J. Am. Chem. Soc*. **2017**, *139*, 3209–3226. https://pubs.acs.org/doi/abs/10.1021/jacs.6b13229
39. Hayashi, K.; Kumagai, T.; Nagao, Y. *Heterocycles* **2000**, *53*, 447–452. https://heterocycles.jp/newlibrary/payments/form/07618/PDF
40. Hayashi, K.; Hiki, S.; Kumagai, T.; Nagao, Y. *Heterocycles* **2002**, *56*, 433–442. https://www.heterocycles.jp/newlibrary/payments/form/00667/PDF
41. Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem*. **2014**, *79*, 5771–5780. https://pubs.acs.org/doi/10.1021/jo500905m
42. Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1849–1853. http://onlinelibrary.wiley.com/doi/10.1002/anie.201509341/abstract

43. Zhang, P.; Le, C.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2016**, *138*, 8084–8087. https://pubs.acs.org/doi/10.1021/jacs.6b04818
44. Behrendt, R.; White, P.; Offer, J. *J. Pept. Sci*. **2016**, *22*, 4–27. http://onlinelibrary.wiley.com/doi/10.1002/psc.2836/abstract
45. Lee, J. K.; Sirion, U.; Jang, K. S.; Lee, B. S.; Chi, D. Y. *Bull. Korean Chem. Soc*. **2008**, *29*, 2491–2495. http://journal.kcsnet.or.kr/main/j_search/j_download.htm?code=B081237
46. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2001**, *40*, 2004–2021. http://onlinelibrary.wiley.com/doi/10.1002/1521-3773(20010601)40:11%3C2004::AID-ANIE2004%3E3.0.CO;2-5/abstract
47. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem*. **2015**, *58*, 8315–8359. https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.5b00258
48. Baert, F.; Colomb, J.; Billard, T. *Angew. Chem. Int. Ed*. **2012**, *51*, 10382–10385. http://onlinelibrary.wiley.com/doi/10.1002/anie.201205156/abstract
49. Karlsson, S.; Bergman, R.; Löfberg, C.; Moore, P. R.; Pontén, F.; Tholander, J.; Sörensen, H. *Org. Process Res. Dev*. **2015**, *19*, 2067–2074. https://pubs.acs.org/doi/10.1021/acs.oprd.5b00319
50. Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 6802–6806. http://onlinelibrary.wiley.com/doi/10.1002/anie.200801968/abstract

