α-Aminoalkyl-α′-Halomethylketones: Preparation and Application to Pharmaceutically Interesting Compounds

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Contents

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1. Introduction and Scope of This Review

Optically active α-amino-α′-halomethylketones represent a biologically interesting class of compounds. These compounds have been reported to inhibit specific enzyme activity and have also been shown to possess potent antileukemic activity.[1] A large amount of work has been published on the synthetic utility of these α-aminoalkyl-α′-halomethylketones as precursors to chiral halohydrins (**3**) and epoxides such as **4** which are key intermediates in the synthesis of

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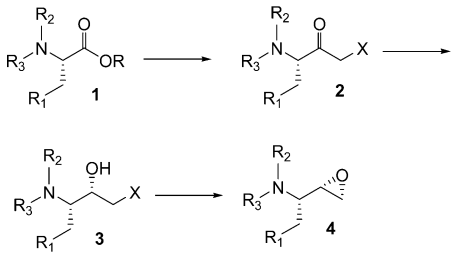
Scheme 1



many amino sugars, hydroxyethylene isosteres, and both renin and HIV protease inhibitors (Scheme 1).[2] These compounds can readily be prepared from the corresponding *N*-protected amino acids or amino acid esters, many of which are commercially available.

Given the interesting biological properties of compounds such as or derived from **2** and **4**, numerous synthetic methods for their preparation have been reported in the literature. While the small-scale preparation of these compounds can easily be achieved, the practical and safe synthesis of these materials on pilot plant or manufacturing scale remains a challenge. Scale-up challenges in the synthesis often include cryogenic temperatures (−60 °C or below) and the handling of dangerous reagents such diazomethane, methyllithium or *n*-BuLi, and gaseous HCl. Many of these methods also generate toxic byproducts or waste streams. Racemization of the starting material and/or product can also be problematic.

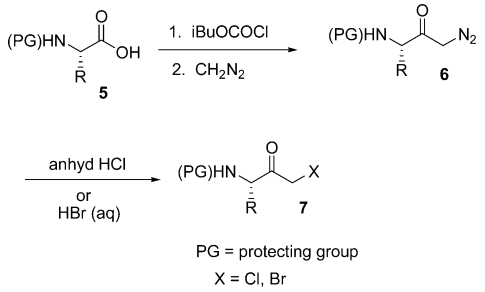
Given the synthetic utility of α-aminoalkyl-α′-halomethylketones, particularly regarding new "fast track" HIV protease inhibitors, industrial process chemists and engineers have been aggressively developing safe, scalable methodologies to prepare these compounds.

This report will concentrate on the most common methods of preparation that have been reported for the large-scale preparation of α-aminoalkyl-α′-halomethylketones, but some methods of preparation reported in the medicinal chemistry literature have been included to ensure a thorough review of the topic. The subsequent conversion of these halomethylketones to their corresponding halohydrins or epoxides will not be addressed here, nor will the preparation of halomethylketones derived from starting materials other than amino acids. A brief summary of key marketed pharmaceuticals derived from α-aminoalkyl-α′-halomethylketones will also be presented, and in this section, we will describe the large-scale development chemistry used to prepare kilogram quantities of key chloromethylketone intermediates used to synthesize various HIV protease inhibitors.

2. Preparation of α-Aminoalkyl-α′-halomethylketones via Diazomethane

Upon review of the literature, the most common method used to prepare these halomethylketones from an *N*-protected amino acid involves treatment of the activated acid with diazomethane, yielding a diazoketone intermediate. Subsequent treatment of this diazoketone with an acid such as anhydrous HCl or aqueous 48% HBr affords the halomethylketone product in high yield often with no loss of optical purity (Scheme 2). However, the vast number of examples reported in the literature that use diazomethane in these transformations have been primarily for small-scale preparation of halomethylketone products. The use of diazomethane

Scheme 2



on pilot plant or manufacturing scale becomes less attractive due to the well-known safety concerns associated with preparing, handling, transferring, reacting, and decomposing this reagent. Diazomethane is a highly toxic, low boiling (−23 °C), odorless gas and is known to be shock sensitive.[3] Despite these safety concerns, the use of diazomethane on a manufacturing scale is achievable and a limited number of contract chemical companies advertise this capability.[4] Archibald of Aerojet Fine Chemicals, a company that specializes in the use of diazomethane on a manufacturing scale, recently published a paper entitled Large-scale Use of Diazomethane in Pharmaceutical Production.[5a] In this paper, Archibald summarizes many of the historical misunderstandings with diazomethane and points out that diazomethane, "...when handled and used correctly, is a useful, safe and cost-effective reagent". Archibald also notes that Aerojet has run thousands of diazomethane reactions on a 750-gallon scale without an incident and currently produces in excess of seven metric tons of diazomethane per month. Archibald points out, however, that the large-scale manufacture and use of diazomethane is inappropriate for most locations due to the safety concerns and lack of process engineering controls.

Although the diazomethane methods summarized below primarily describe small laboratory scale procedures, they have had an enormous impact on the preclinical medicinal chemistry preparations of these compounds and, thus, were felt to be relevant to be reviewed within the context of this work.

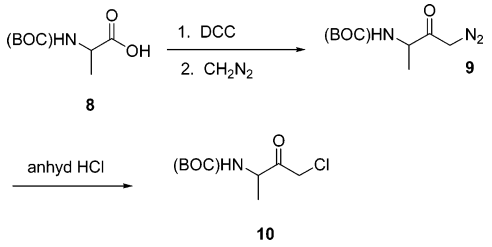
2.1. Preparation of α-Aminoalkyl-α′-chloromethylketones and α-Aminoalkyl-α′-bromomethylketones Using Diazomethane

α-Chloromethylketones and α-bromomethylketones are easily synthesized from their corresponding *N*-protected amino acids. In general, the acid **5** is first converted to its mixed anhydride or otherwise activated acid and then treated with an excess of diazomethane, affording the diazoketone **6**. Treatment of the diazoketone **6** with anhydrous HCl or HBr(aq) affords the halomethylketone **7** in good to excellent yields (Scheme 2). Loss of optical purity for the amino acid has not been reported for this reaction sequence. These reaction conditions are also quite tolerant for a variety of nitrogen protecting groups and heteroatom substituents.

The earliest reported example for the preparation of a halomethylketone derived from an amino acid was published in 1967 by Shaw.[6] In this work, a variety of amino acids as well as other acids were converted to the chloromethylketone product *via* treatment of the corresponding acid chloride with an excess of diazomethane followed by anhydrous HCl gas, affording the desired product in good yield. A few years later,

in 1972, Birch, El-Obeid, and Akhtar published work in which (±)-alanine was converted to the chloromethylketone **10** in a modest 22% yield (Scheme 3).[7] In this work, an

Scheme 3

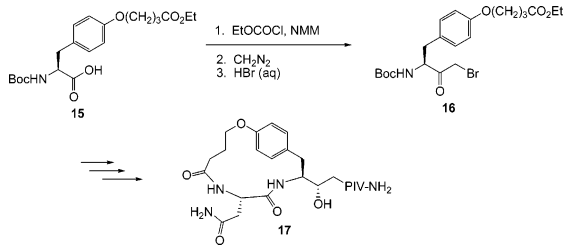


ethereal solution of *tert*-butyloxycarbonyl-DL-alanine (**8**) was first treated with dicyclohexylcarbodiimide (DCC) followed by the addition of an excess of diazomethane, affording the diazoketone **9**, which was isolated. Subsequent treatment of **9** with anhydrous HCl in diethyl ether afforded the chloromethylketone **10**. The corresponding bromomethylketone products were prepared in a similar fashion by treatment of **9** with 48% HBr(aq).

Because of the neutral conditions used in this transformation and the tolerability of a variety of functional groups toward diazomethane, this methodology has been quite popular for preparing more complex peptidyl halomethylketone products on a small scale, with numerous examples cited in the literature. Albeck and Perksy reported preparing the chloro- and bromomethylketones **12a**−**f**, respectively, in three steps starting from the *N*-Cbz-protected amino acid (Tables 1 and 2 in Scheme 4). The authors also report converting peptide **13** to its mixed anhydride and subsequent treatment with excess diazomethane followed by acidolysis with 48% HBr(aq) affording the bromomethylketone **14** in 67% yield (Scheme 4).[8]

Fairlie *et al*. have reported chemistry to prepare the bromomethylketone **16** in good yield *via* the three step process shown in Scheme 5. This material is a key

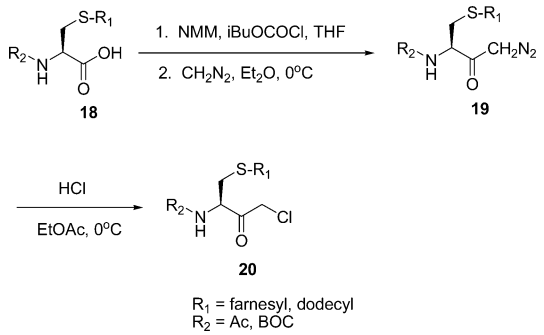
Scheme 5



intermediate used in the preparation of the potential HIV protease inhibitor **17**.[9]

Uckun and co-workers have reported preparing a variety of cysteine-derived chloromethylketone products *via* the diazoketone **19** (Scheme 6).[1] Treatment of **19** with HCl in

Scheme 6



EtOAc gave the desired product **20**. No yields were reported by the authors for this process.

Kaldor and co-workers have reported converting the *N*-CBz-protected *S*-phenyl cysteine to chloromethylketone **22** by reaction of **21** with isobutylchloroformate and an excess of diazomethane followed by treatment with HCl (Scheme 7).[10] This is one of many examples in which diazomethane was used to prepare preclinical supplies of nelfinavir (Viracept) (**23**), an FDA-approved HIV protease inhibitor.

Scheme 4

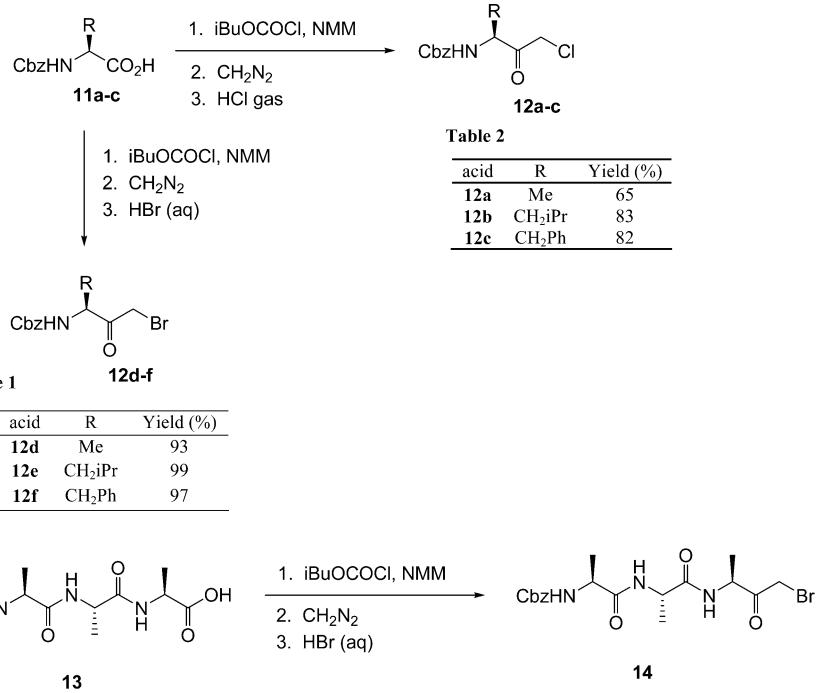


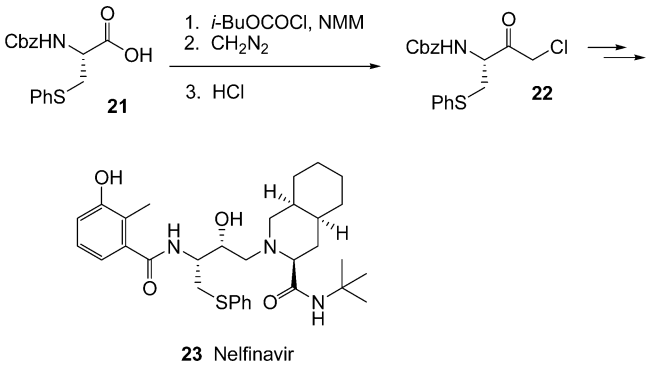
Table 2

acid	R	Yield (%)
12a	Me	65
12b	CH_2iPr	83
12c	CH_2Ph	82

Table 1

acid	R	Yield (%)
12d	Me	93
12e	CH_2iPr	99
12f	CH_2Ph	97

Scheme 7



Despite its touted high efficiency and low cost to prepare halomethylketones, we were successful at finding only one literature example that used diazomethane to prepare these intermediates on a manufacturing scale.[5] Also, despite Archibald's claim that diazomethane can have its place in large-scale organic synthesis and would be an excellent method to prepare these amino acid isosteres, his paper fails to reference any such large-scale processes.

2.2. Preparation of α-Aminoalkyl-α′-iodomethylketones

Relatively few examples of iodomethylketones derived from amino acids have been reported in the literature. Of these literature examples, the most common method of preparation involved conversion of an amino acid to the α-chloromethylketone or α-bromomethylketone using diazomethane and HCl or HBr. Subsequent treatment with NaI afforded the target iodomethylketone in good yield. This methodology seems to be confined to small laboratory syntheses of these intermediates, and no literature examples for the preparation of iodomethylketones on pilot plant or manufacturing scale could be found. The main synthetic utility for these iodomethylketones seems to be directed at nucleophilic displacement of the iodine, giving various α-substituted ketones. One such example of their preparation has been reported by Chambers and co-workers, who describe the preparation of a variety of amino acid- and peptidyl-derived iodomethylketones (Table 3 in Scheme 8).[11] The appropriate amino acid **24** was treated with isobutylchloroformate followed by an excess of diazomethane (3 equiv), affording the diazoketone, which was isolated. Treatment of this diazoketone with HCl in dioxane gave the chloromethylketone **25**, which was then converted to the iodomethylketone by dissolving **25** in acetone and adding excess NaI (3 equiv), affording the desired iodoketone **26** product in 80−90% yield (Scheme 8).

Scientists at Shionogi in Japan have reported using this protocol to prepare chloromethylketone **28**.[12] The authors began by first treating acid **27** with isobutylchloroformate followed by diazomethane and then HCl in EtOAc to give the chloromethylketone **28**, which, due to its stability, was used immediately in the next step (Scheme 9). Subsequent treatment of **28** with NaI and morpholine in acetonitrile affords **29** in 29% overall yield starting from **27**. The mild conditions allowed for the preparation of these intermediates without protection of the carbinol and resulted in no loss in optical purity.

Scheme 8

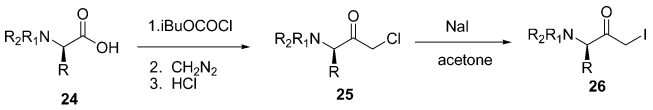
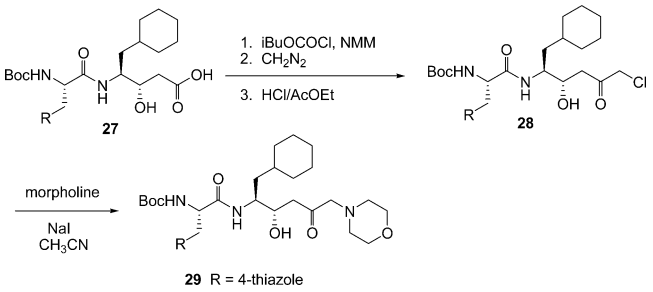


Table 3

Entry	Compound	Yield (%)
1	Boc-ValCHN$_2$	86.5
2	Boc-ValCH$_2$Cl	83
3	Boc-ValCH$_2$I	92.6
4	TriCbz-Arg-CHN$_2$	83
5	TriCbz-Arg-CH$_2$Cl	90
6	TriCbz-Arg-CH$_2$I	82.7
7	Boc(tBu)-Asp-CHN$_2$	108
8	Boc(tBu)-Asp-CH$_2$Cl	56
9	Boc(tBu)-Asp-CH$_2$I	80

Scheme 9

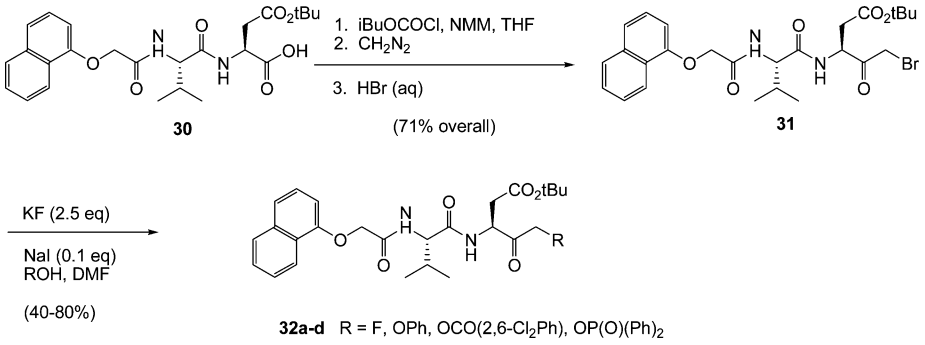


2.3. Preparation of α-Aminoalkyl-α′-fluoromethylketones

2.3.1. Preparation of α-Aminoalkyl-α′-fluoromethylketones Using Diazomethane

Fluorinated molecules continue to be an important class of biologically interesting compounds; thus, a convenient synthesis of such compounds is highly desirable. Analogous to the methodology to prepare chloro-, bromo-, and iodomethylketones that has already been discussed, the synthesis of fluoromethylketones derived from amino acids and diazomethane can be accomplished through a multistep process. The most common method of preparation involves the three-step conversion of the amino acid to the α-chloro- or bromomethylketone. Subsequently, the fluoromethylketone is then prepared *via* the *in situ* formation of the more reactive α-iodomethylketone using catalytic NaI in a polar solvent such as DMF and using KF as the fluoride source. As is the case for iodomethylketones, the synthetic utility of fluoromethylketones has only been reported for small laboratory preparations. No large-scale or commercial synthesis for a fluoromethylketone could be found in the chemical or patent literature. Ullman and co-workers report using this synthetic sequence to prepare a variety of potential caspase inhibitors on small scale.[13] Dipeptide **30** was first converted to the α-bromomethylketone **31** in three steps using diazomethane. Bromide **31** was then treated with a catalytic amount of NaI

Scheme 10



Scheme 11

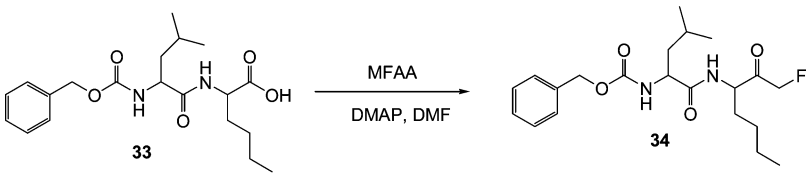
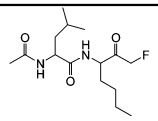
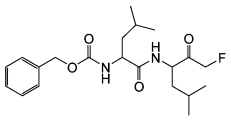
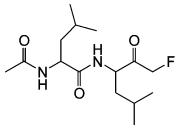
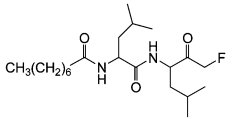
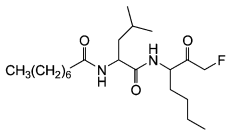


Table 4

entry	Fluoro product[a]	Yield (%)
1		60
2		50
3		22
4		52
5		42

[a]Product stereochemistry not given

in the presence of KF and an alcohol, affording the target ketones **32a**−**d** (Scheme 10).

2.3.2. Preparation of α-Aminoalkyl-α′-fluoromethylketones Using Monofluoroacetic Anhydride

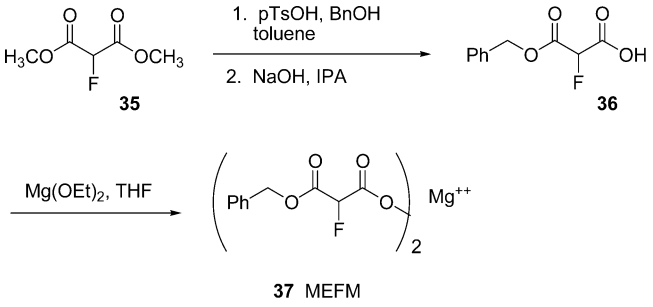
Other methods to prepare α-fluoromethylketones from amino acids have also been reported in the literature. Higuchi and co-workers have published the conversion of amino acids and peptides such as **33** to their α-fluoromethylketones such as **34** using monofluoroacetic anhydride (MFAA) and DMAP in DMF in modest yields (22−60%) (Scheme 11).[14] Other fluoromethylketone products that were prepared *via* this method are shown in Table 4 in Scheme 11.

While this method would appear to be a process that could be scaled-up into a pilot plant, MFAA could not be identified as a commercially available reagent nor could references to its bulk preparation be found.

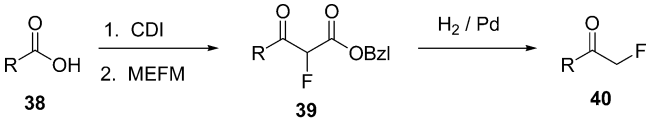
2.3.3. Preparation of α-Aminoalkyl-α′-fluoromethylketones Using Magnesium Benzyl Fluoromalonate

Palmer has reported using the magnesium benzyl fluoromalonate (MEFM) (**37**) to prepare α-fluoromethylketones derived from amino acids and peptides (Scheme 12).[15] In this procedure, the corresponding acid **38** was treated with CDI followed by MEFM, giving the β-keto-α-fluoroester **39**, which was then converted to the α-fluoromethylketone **40**

Scheme 12



Scheme 13



Entry	Amino acid	Yield	Product	yield
1	Boc-Ala-OH	93	Boc-Ala-CH_2F	80
2	Boc-Phe-OH	93	Boc-Phe-CH_2F	73
3	Boc-Val-OH	69	Boc-Val- CH_2F	87
4	Fmoc-(Boc)-Lys-OH	82	Fmoc-(Boc)-Lys-OH CH_2F	18
5	Boc-(Mtr)-Arg-OH	53	Boc-(Mtr)-Arg- CH_2F	33
6	Boc-Pro-OH	52	Boc-Pro-OH CH_2F	90
7	Boc-(OBzl)-Aso-OH	85	Boc-(OBzl)-Aso- CH_2F	36
8	Boc-(OBzyl)-Tyr-OH	93	Boc-(OBzyl)-Tyr- CH_2F	69
9	Boc-Leu-OH	86	Boc-Leu- CH_2F	66

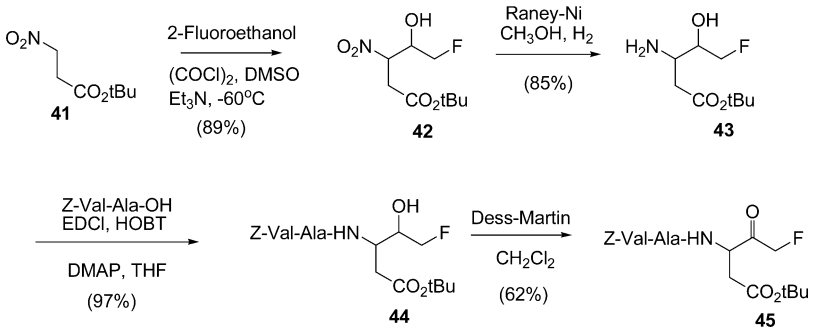
via decarboxylation of **39** using hydrogenation (Scheme 13). The yields for this process range from 53 to 93%. While this approach would seem like an attractive procedure to prepare these substrates on large scale, the author also reports a difficult synthesis for **37**, which would make large-scale implementation of this methodology unlikely (Scheme 12). Other amino acids were converted to their fluoromethylketones using this methodology (Table 5 in Scheme 13).

Revesz *et al*. have published a multistep sequence to prepare a racemic α-fluoromethylketone starting from the nitro ester **41** (Scheme 14).[16] Swern oxidation of 2-fluoroethanol to the fluoroaldehyde (which was not isolated) and then treatment with **41** afforded the fluoroalcohol **42** in 89% yield. Subsequent reduction of the nitro group and then coupling to the peptide followed by oxidation of the carbinol gave racemic α-fluoromethylketone **45** in 62% yield. Cai *et al*. have reported using Revesz's methodology to prepare a variety of dipeptide α-fluoromethylketones.[17] Preparation of carbinol **46** was done according to Revesz's protocol, was then coupled to *Z*-Val, and was then oxidized with Dess−Martin reagent to afford the α-fluoromethylketone **49** (Scheme 15).

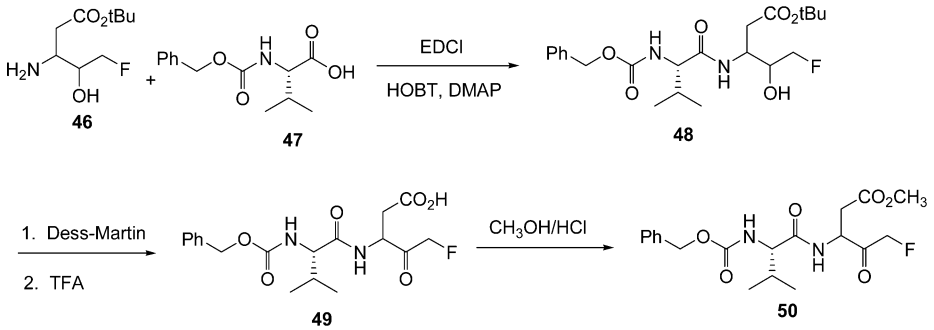
3. Preparation of α-Aminoalkyl-α′-halomethylketones via $LiCH_2X$

The predominant method reported in the literature to prepare α-aminoalkyl-α′-halomethylketones on a pilot plant or manufacturing scale was by treating the corresponding amino ester (or activated acid) with a monohalolithium reagent (X = Br, Cl) at low temperature to afford the desired halomethylketone directly. This methodology has clear advantages for preparing these compounds with respect to the safety challenges associated with using diazomethane, but it is not without its own disadvantages. Preparation of the monohalolithium reagent requires cryogenic temperatures, often below −60 °C, and also employs hazardous reagents such methyllithium or butyllithium. Racemization of the product (or starting material) can also be problematic with this chemistry, and these reactions often produce toxic and difficult to remove side products. Due to the interesting biological properties of α-halomethylketones and their

Scheme 14

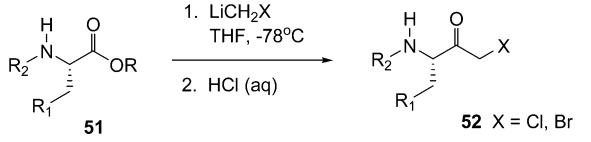


Scheme 15



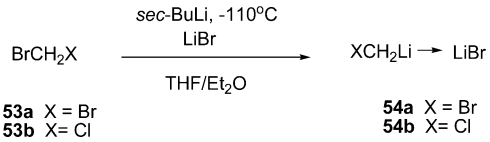
usefulness as intermediates in preparing more complex molecules, intense synthetic and engineering activity has been focused on developing a practical and scalable synthesis of these compounds using halomethyllithium reagents. The general protocol for preparing α-halomethylketones from *N*-protected amino esters is treatment of the ester with an excess of halomethyllithium reagent generated *in situ* below −60 °C followed by acid hydrolysis, which affords the corresponding halomethylketones **52** in modest to good yields (Scheme 16).

Scheme 16



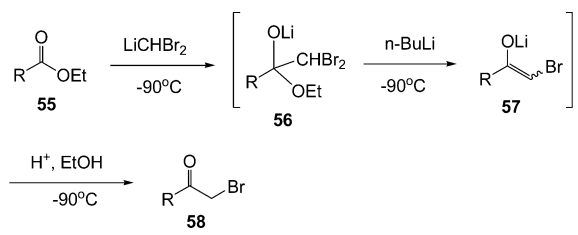
The first successful preparation of a bromomethyllithium reagent and its use to prepare bromomethylketones from esters was reported in 1984 by Villieras and co-workers.[18] This reagent was prepared by treating dibromomethane with *sec*-BuLi in THF/Et_2O at temperatures below −110 °C in the presence of 1 equiv of LiBr (Scheme 17). The ester was

Scheme 17



then added and the contents were warmed to room temperature and then stirred until the reation was complete, giving a modest yield of the desired bromomethylketone products (55−62%). The authors claim that LiBr serves to stabilize the $BrCH_2Li$ carbenoid and that attempts to prepare this reagent in the absence of LiBr lead to immediate decomposition of the reagent. For the dual purpose of preparing α-halomethylketones and avoiding potential decomposition, these monohalomethyllithium reagents must be prepared *in situ* in the presence of the amino acid ester. Several groups have reported on the mechanism for this reaction. In 1985, Kowalski and Haque published work that studied the mechanism for converting a variety of substituted esters to their bromomethylketone products.[19] The authors propose that, upon treating the ester **55** with the dibromomethyllithium (produced *in situ* from dibromomethane and lithium tetramethylpiperidide) at −90 °C, the very stable tetrahedral intermediate **56** was produced (Scheme 18). Subsequent

Scheme 18

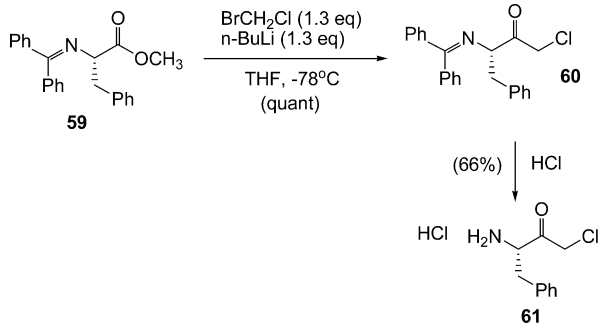


treatment of **56** with *n*-BuLi resulted in rapid metal−halogen exchange with loss of ethoxide, giving enolate **57**, which, after acid hydrolysis, afforded the bromomethylketone **58**. This mechanistic hypothesis has been extended to other reactions in which the chloromethylketone is prepared by treating the ester with chloroiodomethane and LDA, affording the presumed tetrahedral intermediate that upon hydrolysis gave the desired product (*vide infra*).

An abundant number of literature examples have been published that describe the conversion of esters and amino acid esters into α-chloromethylketones using halomethyllithium; however, we have chosen to only highlight those examples that have been applied to pilot plant or manufacturing syntheses.

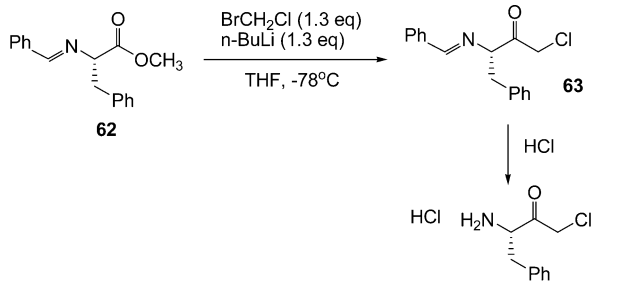
Scientists at Ajinomoto Co. have published several papers that describe the conversion of *N*-imine-protected amino acid esters into their α-aminoalkyl-α′-chloromethylketones in good yield without racemization.[20] The *N*-diphenylmethylene-protected amino acid ester **59** and bromochloromethane were treated with *n*-BuLi in THF at −78 °C, affording the chloromethylketone product **60** in quantitative yield followed by acid hydrolysis to give **61** (Scheme 19).

Scheme 19



The authors claim that this process proceeds with no racemization of the starting material or product, which seems to contradict claims made by Rapoport and co-workers, who suggest that substrates lacking an available proton on the amino group have been shown to undergo racemization when treated with nucleophiles.[21] Rapoport suggests that the dianion resulting from first deprotonation of the N−H of the amino protecting group followed by the addition of the nucleophile to the substrate prevents abstraction of the proton α to the carbonyl and hence suppresses racemization. Although the Ajinomoto procedure gives a high yield of the chloromethylketone product, acid hydrolysis of **60** to remove the diphenyl protecting group occurred in a modest 66% yield. In an effort to find a more easily removed *N*-protecting group, the authors replaced the *N*,*N*-diphenyl protecting group with a *N*-benzylidene protecting group, giving **61** in 75% overall yield without racemization of the starting material or product (Scheme 20).

Scheme 20



Chemists at Bristol-Myers Squibb (BMS) have published work describing a large-scale methodology for the conversion

Scheme 21

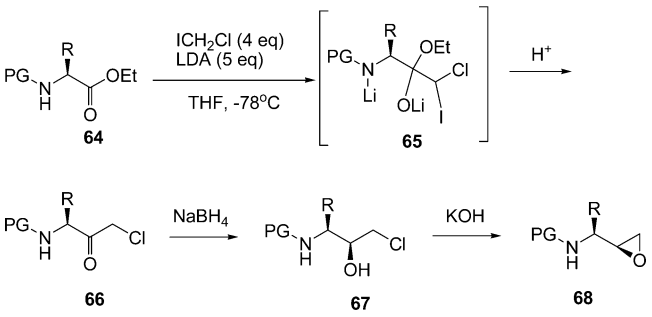
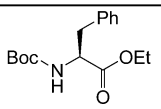
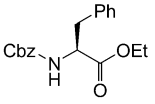
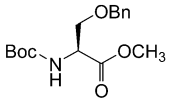
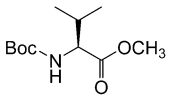
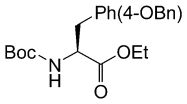
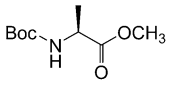
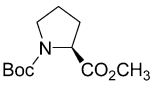


Table 6

Entry	Ester	Chloroketone Yield (%)
1		86
2		77
3		83
4		50
5		82
6		81
7		79

of a variety of protected amino acid esters to their α-chloromethylketones in good yield.[22] In this procedure, the *N*-protected amino acid ester **64** was treated with an excess of chloroiodomethane (4 equiv) and lithium diisopropylamide (LDA) in THF at −78 °C, generating LiCHICl *in situ*, which can then react with the starting ester again, yielding the presumed stable tetrahedral intermediate **65** (Scheme 21). *In situ* reaction of **65** with another equivalent of LiCHICl reduces the iodide, causing loss of LiOEt, and subsequent acid hydrolysis of the resultant enolate affords the desired chloromethylketone product **66** in good to excellent yield. The authors have prepared a variety of chloromethylketone products using this methodology (Table 6 in Scheme 21). A significant limitation for pilot plant or manufacturing scale-up is the formation of chlorodiiodomethane: a toxic, high boiling, and difficult to remove byproduct. In an effort to circumvent isolation of **66** and in turn remove the chlorodiiodomethane, the authors developed a multistep synthesis for epoxide **68** that avoided isolation of the chloromethylketone product. After formation of the chloromethylketone, the crude reaction mixture was treated with excess sodium borohydride, reducing **66** to the chlorohydrin **67,** as well as *in-situ* reduction of I_2CHCl. Subsequent treatment of **67** with potassium hydroxide in ethanol then gave the desired epoxide **68**. The authors report carrying out this "one-pot" procedure to prepare multiple kilograms of epoxide **68** in a 39% overall yield starting from the protected amino acid ester.

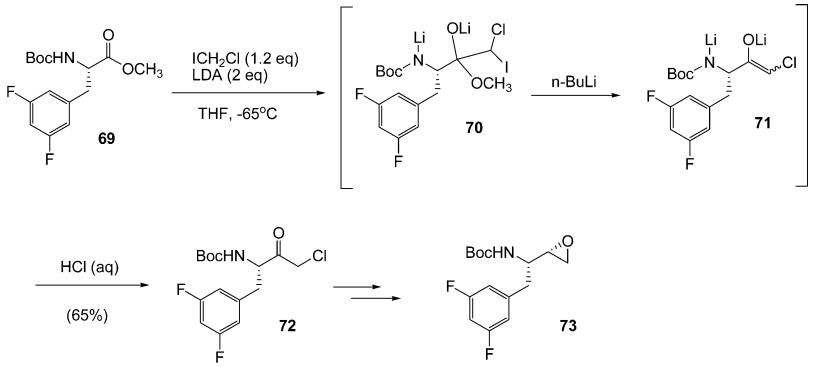
Reeder and co-workers at Pfizer have published a modification of the BMS procedure that eliminated the formation of the toxic CHI_2Cl from this chemistry (Scheme 22).[23] Reeder described the conversion of the *N*-BOC-difluorophenylalanine **69** to the α-chloromethylketone **72** by treating **69** and chloroiodomethane (1.1 equiv) with LDA (2.0 equiv) in THF below −65 °C, giving the presumed tetrahedral intermediate **70**. Treatment of **70** with *n*-BuLi (2.0 equiv) resulted in rapid metal−halogen exchange, generating the more volatile butyl iodide (rather than CHI_2Cl), followed by acid hydrolysis to afford **72** in 65% yield.

This procedure significantly reduced the LDA and chloroiodomethane stoichiometry relative to the BMS procedure and also was reported to give an improved overall yield of the epoxide product **73** with no reported loss of stereochemistry for either the chloromethylketone or epoxide products.

4. Preparation of α-Aminoalkyl-α′-halomethylketones via Dimethylsulfoxonium Methylide

While developing chemistry for implementation into a pilot plant or manufacturing site, process chemists and engineers must balance the advantages and disadvantages when considering a particular route for scale-up. With respect to

Scheme 22



the large-scale preparation of α-halomethylketones derived from amino acids, the quest to find a safe and scalable methodology has been difficult. Despite the synthetic utility of diazomethane or halomethyllithium reagents to prepare these compounds, their safety concerns cannot be ignored when considering their use on a large scale. Chemists, both process and academic alike, continue their efforts to find a safer process to these intermediates.

Nugent and co-workers at BMS have published work to prepare α-aminoalkyl-α′-chloromethylketone products derived from amino acid esters using the dimethylsulfoxonium methylide **75**.[24,25] The authors describe this methodology as a "safer alternative to using diazomethane or halomethyllithium reagents".

Conversion to the chloromethylketone begins by first preparing the sulfur ylide **75** *in situ* from trimethylsulfoxonium chloride and potassium *tert*-butoxide in refluxing THF for 2 h. Three equivalents of **75** are used in this procedure. After the contents were cooled to 0 °C, a THF solution of the ester **74a**−**c** was added, and the resulting solution was stirred until the reaction was complete, to afford the *β*-ketosulfur ylide **76a**−**c** in good to excellent yield (85−95%) (Scheme 23). The authors noted that little or no

Scheme 23

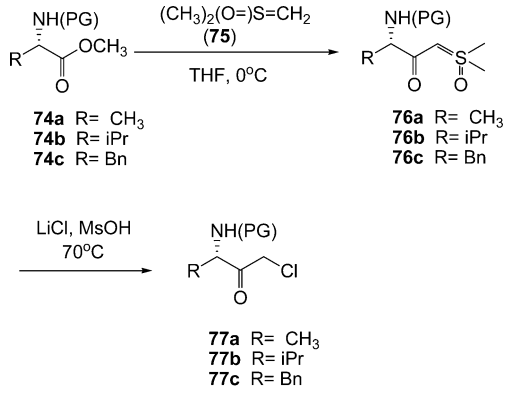


Table 7

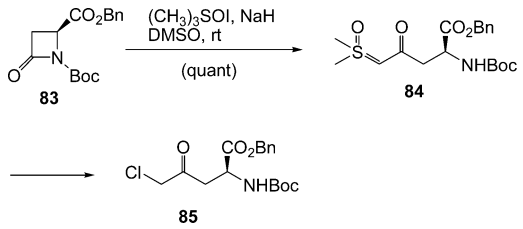
Ylide	PG	product	yield (%)	ee (%)
76a	Cbz	**77a**	70	>99
76b	Cbz	**77b**	75	>99
76c	BOC	**77c**	81	>99

racemization of the ylide products was observed in this process except for in the case of converting **74c** to **76c**, in which complete racemization of the product was observed. Racemization could be avoided, however, by replacing the methyl ester in **74c** with a 4-nitrophenyl ester (Np). Subsequent treatment of this ylide at 70 °C with HCl, prepared from lithium chloride and methanesulfonic acid (MsOH), provided the chloromethylketone products **77a**−**c** in 70−80% yield (Table 7 in Scheme 23). The authors also noted that ylide **75** prepared from trimethylsulfoxonium iodide gave 10−15% lower yield for the ylide products **76a**−**c** and the reactions were less clean. The source of HCl proved important for converting the sulfur ylides to their chloromethylketone products. Other sources of HCl, such as concentrated HCl or tetrabutylammonium chloride/MsOH, resulted in competitive cleavage of the methyl C−S bond.

An interesting use of Nugent's methodology has been published by scientists at Shionogi for the preparation of a variety of dipeptides (Scheme 24).[11] The authors reported that treating the *N*-BOC-protected aspartic acid **78** derivative with isobutylchloroformate gave anhydride **79**. Subsequent treatment of **79** with ylide **75** in toluene/DMSO (9:1) gave ester **80** in 85% yield. Acid hydrolysis of **80** with HCl in ethyl acetate afforded the chloromethylketone **81** in 84% yield.

Another application of this ylide methodology has been published by Baldwin and co-workers, who reported preparing *δ*-chloromethyl-*γ*-keto-α-amino acid products from *β*-lactams (Scheme 25).[26] The authors described the nucleo-

Scheme 25

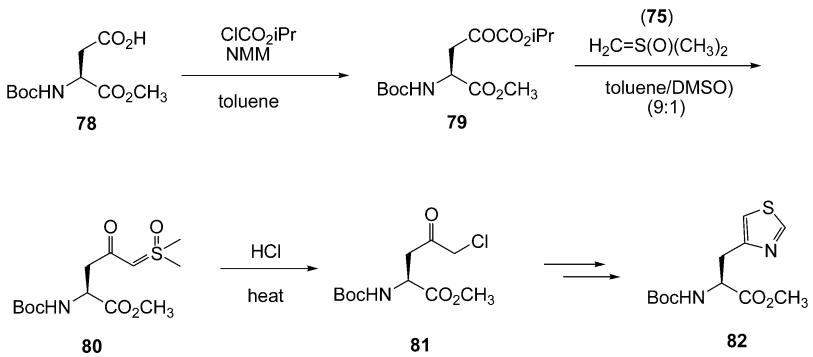


philic ring opening of the *β*-lactam **83** with the trimethylsulfoxonium ylide, giving the α-ketosulfoxonium species **84** in quantitative yield. Treatment of **84** with HCl in acetic acid/DMF afforded the chloromethylketone product **85** in 74% yield. The bromomethylketone analogue was prepared in 62% yield by treating **84** with 48% HBr in acetic acid and DMF.

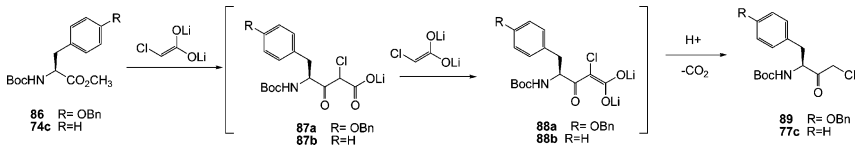
5. Preparation of α-Aminoalkyl-α′-chloromethylketones via Claisen Condensation Chemistry

In 2000, process chemists at BMS reported a large-scale procedure using a Claisen condensation to prepare chloro-

Scheme 24



Scheme 26



Scheme 27

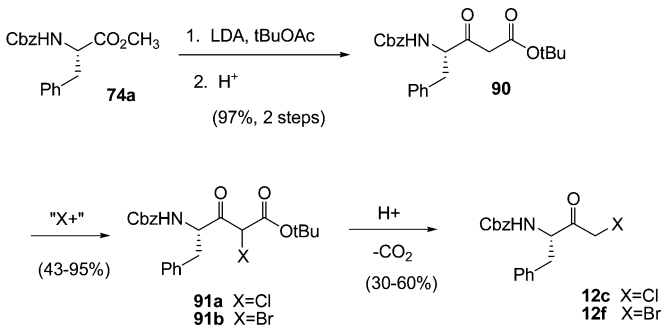


Table 8

Product	Reagent	Conditions	Yield (%)[a]
91a	NCS (1 eq)	$CHCl_3$	43
91a	SO_2Cl_2 (1.2 eq)	CH_2Cl_2	95
91b	NBS (1 eq)	CH_2Cl_2	40
91b	NBS (1 eq)/DMAP	CH_2Cl_2	56
91b	Br_2 (1 eq)/$CaCO_3$	CH_2Cl_2	93

[a]Yield determined by HPLC

Table 9

Reactant	Product	Reagent	Conditions	Yield (%)
91a	**12c**	HCO_2H	80°C, 20 min	60[a], 74
91a	**12c**	4M HCl (30 eq)	25°C, 15 h	30[a]
91b	**12f**	TFA (30 eq)	60°C, 17 h	42[a]
91b	**12f**	HCO_2H	25°C, 15 h	53[a]

[a]Isolated yield purified on preparative TLC

methylketones. Polniaszek, Thottathil, and Wang report that the Claisen condensation of the lithium dianion of chloroacetic acid with *N*-Boc-protected amino acid esters gives chloromethylketone products in good yields.[27a] The reaction was carried out by first preparing an excess (3.5 equiv) of the dianion of chloroacetic acid with LDA in THF at −78 °C (Scheme 26). The anion was then slowly added to a precooled THF solution of the amino acid ester and then again cooled to −78 °C, at which time acetic acid was added, resulting in decarboxylation. The contents were then stirred for 12 h at −45 °C, affording the α-chloromethylketone product in 60−81% yield. The authors report no racemization of the products under these reaction conditions. One limitation to this chemistry is the fact that only the corresponding methyl esters can be used in this reaction. Under similar conditions, the ethyl esters gave incomplete reaction.

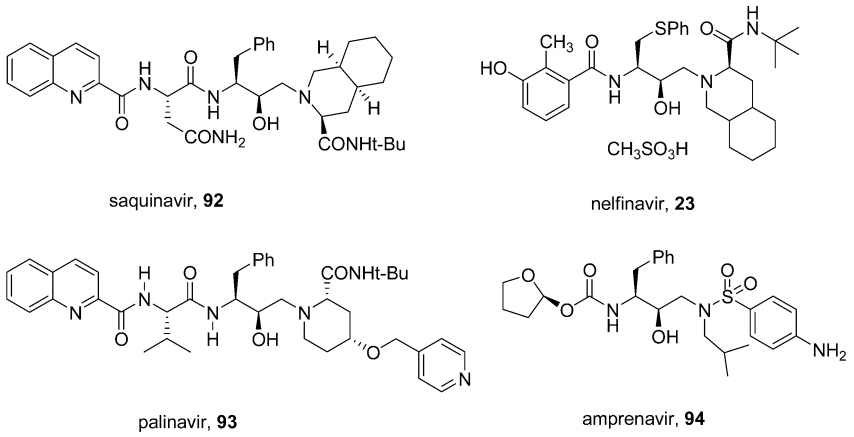
Although initially reported in the patent literature in 1998 and 1999, three years later in 2002, Izawa and co-workers at Ajinomoto published a manuscript to disclose their full results for a three step cross-Claisen condensation approach to prepare α-aminoalkyl-α′-halomethylketones (Scheme 27).[28] This methodology is similar to the chemistry reported by chemists at BMS;[27a] however, the Izawa procedure isolated the *β*-ketoester **90**. The authors reported that their procedure was developed as a result of needing an industrial procedure that avoided the safety concerns associated with diazomethane. This procedure begins with Claisen condensation of the amino acid ester **74a** and an excess of *tert*-butyl acetate and LDA in THF at −50 °C, affording the *β*-ketoester **90** in quantitative yield without racemization. Halogenation at the α-position with SO_2Cl_2 gave the chloro-*β*-ketoester **91a** in 95% yield (Table 8 in Scheme 27). The bromo analogue was prepared by treating **90** with Br_2, affording the bromo-*β*-ketoester **91b** in 93% yield. Unfortunately, acid hydrolysis and subsequent decarboxylation of **91a**,**b** was reported to occur in low yields (Table 9 in Scheme 27).

6. Industrial Applications of α-Aminoalkyl-α′-chloromethylketones toward the Synthesis of Pharmaceutically Interesting Compounds

Halomethylketones, in particular, chloromethylketones, serve as key building blocks for many pharmaceutically interesting compounds. Although a large number of marketed pharmaceutical products contain or have a halomethylketone intermediate in their synthesis, only those halomethylketone products derived from α-amino acids are summarized in this section. Despite their synthetic usefulness, only a small number of examples have been reported in the patent or chemical literature in which α-aminoalkyl-α′-halomethylketones have been prepared on a pilot plant or manufacturing scale. These examples have been primarily confined to the preparation of HIV protease inhibitors such as saquinavir (**92**), nelfinavir (**23**), palinavir (**93**), and amprenavir (**94**) (Scheme 28).

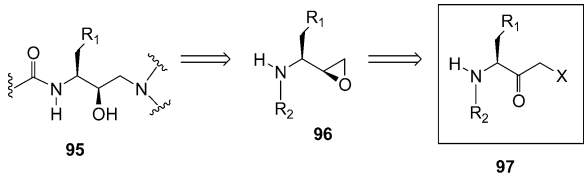
Not surprisingly, much of the early medicinal chemistry as well as preclinical supplies of **23** and **92**−**94** were synthesized *via* the diazomethane procedure. As previously alluded to in this review, despite the efficiency and cost-effectiveness of using diazomethane, the potential scale-up hazards with this reagent make it an unattractive option to prepare bulk quantities of these intermediates; thus, process chemists and engineers have aggressively been trying to develop a safe, cost-effective, and environmentally friendly process to create these compounds. A common synthetic strategy to prepare the compounds in Scheme 28 is *via* the nucelophilic ring opening of a chiral epoxide **96**, which is

Scheme 28



in turn derived from the α-aminoalkyl-α′-chloromethylketone **97** (Scheme 29).

Scheme 29

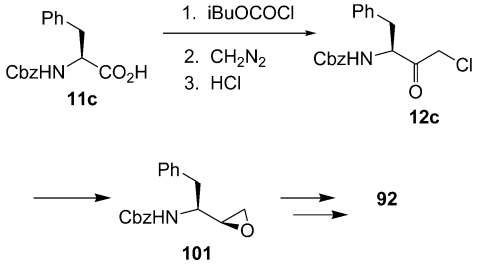


As a result of the fact that many pharmaceutical companies do not often publish their exact manufacturing route for a key marketed product, we have attempted to summarize the most relevant manufacturing process and development work to prepare the α-alkylamino-α′-chloromethylketone intermediate for each of these products. The synthesis of other key intermediates along with the total synthesis for each of these products is not reviewed.

7. Saquinavir (Invirase)

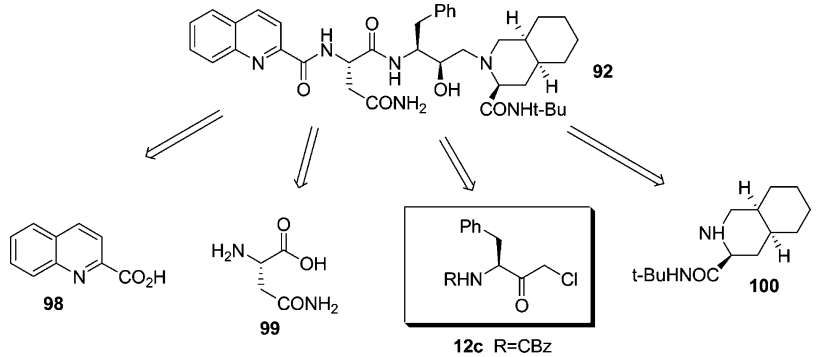
In 1996, saquinavir (**92**) was the first HIV protease inhibitor to reach the market, and because of the urgent medical need for HIV patients, this product was introduced into the market in only 6 years. The retrosynthetic analysis for **92** is given in Scheme 30. In the initial SAR (structure activity relationship) synthesis of **92** developed at Hoffmann La Roche (Scheme 31), the *N*-Cbz chloromethylketone **12c** was prepared by first treating the amino acid **11c** with isobutylchloroformate and then reacting the resulting mixed anhydride with diazomethane followed by acidolysis.[29] Diastereoselective reduction of the ketone afforded the chlorohydrin, which was then converted to the desired epoxide **101**. No yield was reported for these initial transformations.

Scheme 31

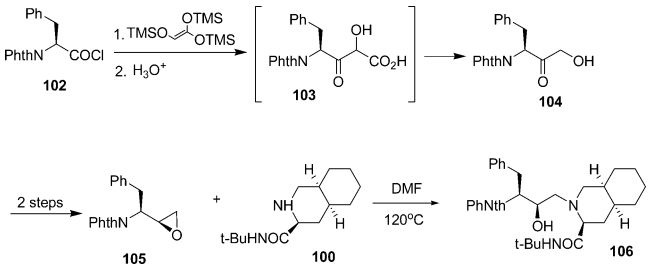


In an effort to support requests for kilogram quantities, five alternative syntheses were developed that avoided the use of diazomethane.[29] Three of the syntheses required a significant amount of process development prior to scale-up, while the remaining two syntheses—a hydroxyl ester route and the tris(trimethylsilyloxy)ethene route—were seen as more amenable to kilogram synthesis. The trimethylsilyl route, which avoided the preparation of a chloromethylketone intermediate altogether, was directed at preparing α-hydroxyketone **104** with subsequent conversion to the epoxide **105** (Scheme 32). Synthesis of this α-hydroxyketone began by treating the acid chloride **102** with neat tris(trimethylsilyloxy)ethene (2.1 equiv) at 90 °C, affording the hydroxyacid **103**, which then was acidified and decarboxylated *in situ*, affording the α-hydroxymethylketone **104** in 63% yield. After protection of the carbinol as its THP ether, diastereoselective reduction of the ketone with $NaBH_4$ afforded the (*S*,*R*)-diol as the major diastereomer. After conversion of this carbinol to the mesylate, the desired epoxide was prepared

Scheme 30



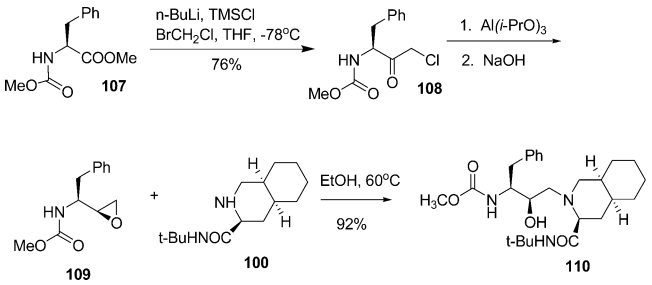
Scheme 32



by removal of the THP group with TsOH and subsequent treatment with KOtBu, affording **105** in 15−22% overall yield for this 10-step sequence. Epoxide **105** was then converted to **92** in 10−13% overall yield in an amazing 26 steps overall, starting from **102**. Early development supplies were prepared using this synthetic strategy.

Although this route was successfully used to prepare almost 300 kg of saquinavir over two and a half years, the high demand for **92** necessitated the development of a safer, shorter, more efficient route. The process research group at Hoffmann-La Roche later developed a more convergent 11-step synthesis of **92** with an impressive overall yield of 50% (Scheme 33).[30] Interestingly, they returned to the chloromethylketone intermediate used in the initial SAR route in order to prepare the phenylalanine-derived epoxide. The chloromethylketone intermediate **108** was prepared by treating ester **107** with *n*-BuLi, TMSCl, and chlorobromomethane at −78 °C, resulting in *in situ* carbamate protection as well as the formation of chloromethyllithium, which added to the ester. Deprotection of the carbamate occurred upon workup to give the chloromethylketone **108** in 76% yield with no reported loss in stereochemistry. The authors noted, however, that when the carbamate group was not protected, only modest yields for **108** (35−51%) were achieved, presumably due to deactivation of the ester. This interpretation of a lower yield as a result of not protecting the carbamate seems somewhat skeptical based on the numerous examples for similar transformations using chloromethyllithium and various unprotected carbamates. Although not explicitly stated in any publication, the chemistry outlined in Scheme 33 to prepare the chloromethylketone **108** appeared to be used to support clinical trials and the manufacture of saquinavir.

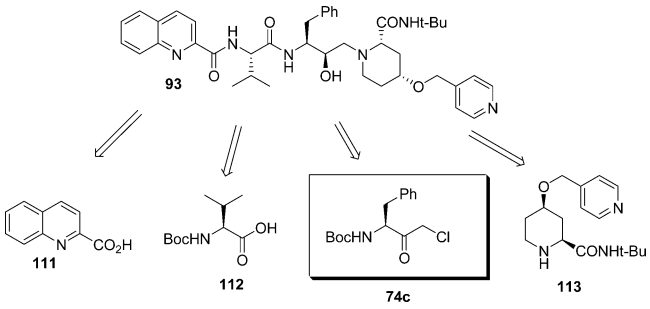
Scheme 33



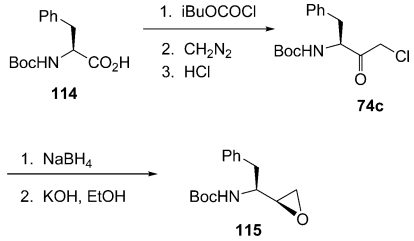
8. Palinavir

Retrosynthetic analysis of palinavir (Scheme 34), a potent HIV protease inhibitor developed at Boehringer Ingleheim, employed standard diazomethane chemistry to prepare the key chloromethylketone intermediate **74**, which was subsequently converted to the epoxide **115** in a 36% yield over four steps (Scheme 35).[31]

Scheme 34

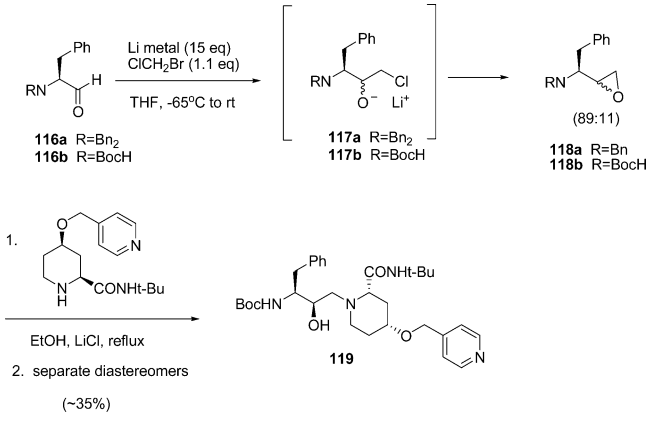


Scheme 35



The obvious safety concerns for using diazomethane on a manufacturing scale prompted these development chemists to consider alternative syntheses to support bulk quantities of **93** for preclinical studies.[32] The authors noted that although several suitable large-scale approaches to these key epoxides have been reported in the literature, none of these published procedures were applicable to their needs. Therefore, the authors report developing a novel process for the large-scale preparation of the requisite epoxide based on the diastereoselective addition of chloromethyllithium (which was generated *in situ* by treating bromochloromethane with lithium metal) to *N*,*N*-dibenzylphenylalaninal **116a** (Scheme 36). The authors claim that this four-step procedure afforded epoxide **118a** in 28−35% yield overall on kilogram scale and with >99.5% isomeric purity. In this approach, the authors' goal was to generate the chloromethyllithium *in situ* using lithium metal rather than using a metal−halogen exchange with an alkyllithium such as *n*-BuLi or MeLi, citing that these reagents are quite hazardous to handle on large scale. Using lithium metal would also be much less hazardous and considerably cheaper. Furthermore, the byproduct from this chemistry would be a lithium halide. The authors report

Scheme 36

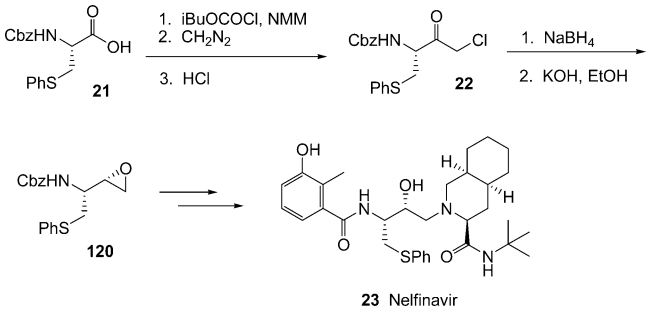


developing two procedures for preparing the requisite epoxide on a 2.2 kg scale: one using a vigorous stirring method and the other using a specially designed reactor fitted with two ultrasonic probes (Scheme 36). Both procedures required using a large excess of lithium shot (15 equiv) but claim that the excess metal could be recovered and recycled. Both procedures typically gave an 89:11 ratio with the (2*S*,3*R*) epoxide being the major diastereomeric product formed. Epoxide **118b** was then treated with racemic amine **113**, giving a 1:1 mixture of diastereomeric carbinol products. The two diastereomeric products were separated by chromatography, affording **119** in 35% yield. The authors point out that while ultrasound-mediated reactions can be used for large-scale organic synthesis, implementation of such a methodology on a manufacturing scale does not appear practical. Development activities toward palinavir were discontinued in 1996.[33]

9. Nelfinavir (Viracept)

In an early synthesis of nelfinavir, an FDA-approved HIV protease inhibitor developed at Agouron, Kaldor *et al*. reported preparation of a chloromethylketone intermediate by treating the *N*-Cbz-protected amino acid **21** with isobutylchloroformate, triethylamine, and diazomethane to give the diazoketone intermediate in an isolated 73% yield.[10,34] Treatment of this diazoketone with HCl gas gave the corresponding chloromethylketone **22**, which was then converted to the epoxide **120** (Scheme 37).

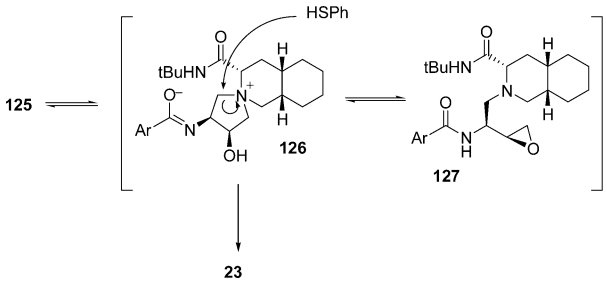
Scheme 37



Upon careful review of the patent and chemical literature, a manufacturing process for nelfinavir could not clearly be identified; however, several literature references suggest that numerous other routes were explored which did not rely on the formation of a chloromethylketone intermediate.[35] Given the scale-up challenges associated with using diazomethane, coupled with the fact that nelfinavir required a large dosing (ca. 2.5 g/day), process chemists at Agouron began efforts to develop an efficient and cost-effective synthesis of **22**. The authors report the development of a synthesis that circumvented the formation of both the chloromethylketone and epoxide products and have developed a process on kilogram scale where a nucleophilic ring-opening of oxazoline **125** with thiophenol directly afforded **23** (Scheme 38).

This concise synthesis takes advantage of chemistry reported by Inaba and co-workers in their synthesis of **23**.[35] A possible mechanism by which **23** is prepared from thiophenol is given in Scheme 39. The authors state that this

Scheme 39

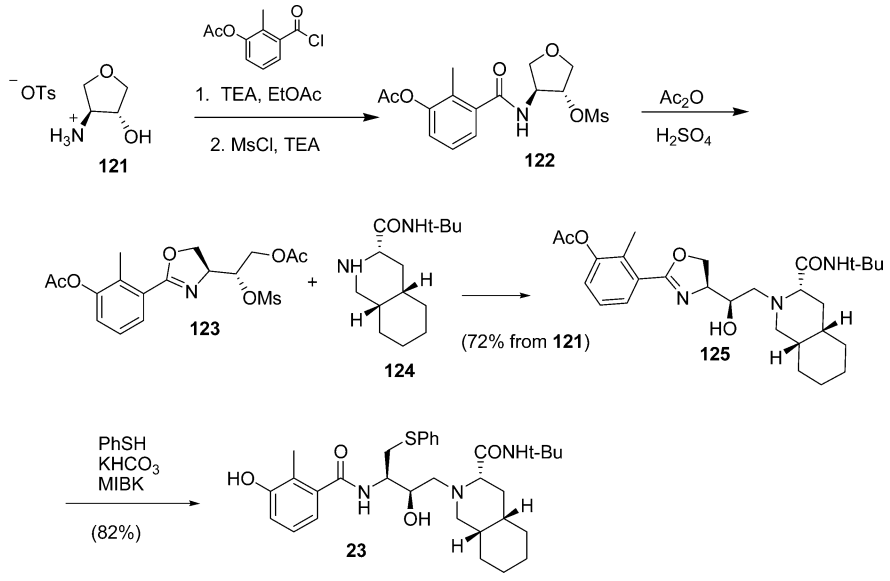


synthesis utilizes three reactors and two reslurries for purification with only one aqueous workup (59% over 5 steps). No additional information could be found supporting that this chemistry was used as the manufacturing route for **23**.

10. Amprenavir (Agenerase)

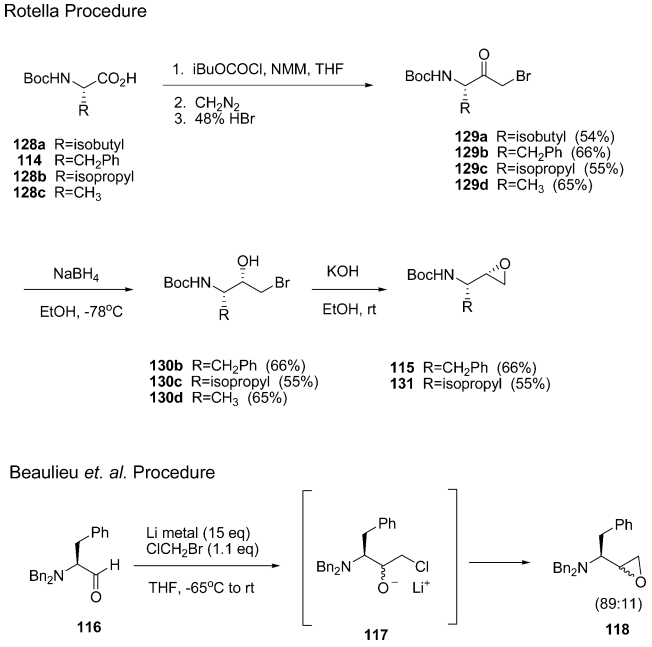
Similar to the cases of saquinavir and nelfinvir, the initial synthetic strategy to prepare amprenavir, another HIV protease inhibitor, involved the preparation of an α-chloromethylketone intermediate and subsequent conversion to the key chiral epoxide. Despite an extensive review of the literature, no synthetic reports were found that described how preclinical supplies of **94** had initially been prepared.

Scheme 38



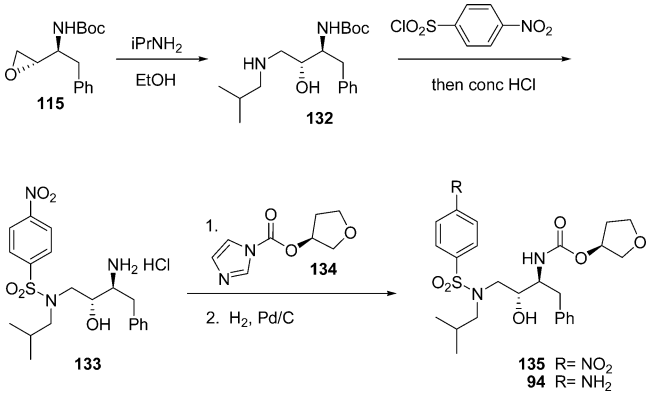
Scientists at Vertex, however, have published a process that claims the ability to prepare large quantities of **94** in four steps from epoxide **115**.[36] This patent application, however, is quite vague at indicating how the halomethylketone or epoxide products were prepared, citing that "protected amino epoxides are known in the art and can be prepared by methods described in the literature". The two methods referenced in this work are chemistry published by Rotella,[37] in which a bromomethylketone is prepared *via* diazomethane and HBr, and by Beaulieu[32] *et al*., who reported the preparation of **118a** *via* the chloromethyllithium reagent already described in the synthesis of **93** (Scheme 40).[15]

Scheme 40



Based on this patent application, it would seem reasonable that the authors used the Rotella procedure to prepare the bromomethylketone **129b** and then converted this to epoxide **115**, given that the *N*-Boc protecting group is referenced in amino alcohol **132**. The large-scale synthesis of **94** is outlined in Scheme 41. Conversion of the presumed epoxide **115** to

Scheme 41



the amino alcohol **132** was accomplished by heating **115** with isopropylamine in EtOH. Treating **132** with *p*-nitrobenzenesulfonyl chloride in toluene then gave the *N*-Boc-protected sulfonamide, which was then deprotected *in situ* with concentrated HCl, giving the carbinol **133** in 73% yield overall. This sulfonamide hydrochloride was then added to 3-(*S*)-tetrahydrofuryl imidazole-1-carboxylate (**134**) and heated to reflux for 22 h, affording carbamate **135** in 82% yield. Reduction of the nitro group in **135** to the amine was accomplished using palladium on carbon to give the target compound **94** in 80% yield.

11. Conclusion

Owing to the intense pressure on the pharmaceutical industry to develop new and novel medicines, medicinal chemists are continually challenged to find highly active compounds to treat today's indications. Recent advances in technology have allowed these chemists to develop site specific compounds, often prepared *via* a complex multistep synthesis frequently containing multiple stereogenic centers. Scale-up of these new compounds has in turn placed intense pressure on process chemists and engineers to develop safe, robust, efficient, and, in recent years, "green" processes.

The syntheses of α-aminoalkyl-α′-halomethylketones and the products derived from these intermediates reflect these challenges. While small-scale syntheses of these intermediates can easily be accomplished from the desired amino acid and diazomethane to support preclinical needs, identifying a pilot plant or manufacturing process to create these highly synthetically useful intermediates that avoids diazomethane remains a significant challenge. This review makes it clear that, at the present time, while process chemists and engineers have developed some very elegant methods to synthesize these compounds that circumvent the use of diazomethane, these processes often use hazardous reagents and involve very reactive intermediates. With the custom chemical industry growing at an unprecedented rate fueled by the high demand for new drugs such as HIV protease inhibitors, many of which contain an α-aminoalkyl-α′-chloromethylketone intermediate, the synthesis of such intermediates on a manufacuting scale using diazomethane may soon be realized.

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