Synthetic Preparation of *N*-Methyl-α-amino Acids

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1. Introduction

Amino acids are incorporated in proteins, peptides, enzymes, hormones, and an enormous array of secondary metabolites. Nature's exquisite creativity and precision in chemical modification generates the extraordinary diversity of structure and hence function in peptidal metabolites and materials. The "infinite" number of peptidic structures known to exist testifies to the importance of proteinaceous substances in biology.

Our interest in medicinal and synthetic organic chemistry has developed around a subset of peptidal compounds, namely the *N*-methylamino acid (NMA) containing peptides and depsipeptides. NMA containing peptide natural products have been isolated from a variety of sources, and their secondary metabolites (e.g. vancomycin, cyclosporin, actinomycin D) have found clinical use due in part to the physical properties and chemical stability conferred by the NMAs present in their structures.

Studies on NMA containing peptides reveal that *N*-methylamino acid residues increase proteolytic stability, increase membrane permeability (lipophilicity), and alter the conformational characteristics or properties of the amide bonds. A review by Fairlie et al.[1] discusses many aspects of the biological activity of peptides including numerous examples of *N*-methylation in natural products and therapeutic agents. The effects of *N*-methylamino acids mentioned above are important in actual and potential therapeutic compounds and the assay of biological activity of modified peptides.

Several groups have developed NMA containing peptides that have improved proteolytic resistance,[1−3] and an early report by Turker et al.[4] cites the substitution of sarcosine at the *N*-terminus of an angiotensin II analogue. The new octapeptide was a potent in vitro antagonist of angiotensin II, but it was even more potent in vivo. The improved activity was attributed to increased resistance to aminopeptidase activity resulting in a longer half-life, though this was not proven.

Haviv et al.[5] reported the site-specific substitution of certain peptides (e.g. the nonapeptide leuprolide), that are known luteinizing hormone−releasing hormone (LHRH) agonists, with the corresponding NMA. Three analogues were found that had significantly higher pD_2 values than the parent peptides. Other analogues were found to be completely resistant to the action of chymotrypsin. This was attributed to the interruption of key hydrogen bonds in the chymotrypsin active site by *N*-methylation of the peptide substrate.

Endothelin-1 is a peptidic constrictor of vascular smooth muscle cells. Cody et al.[6] developed hexapeptide antagonists of the receptor for Endothelin-1. One potent hexapeptide inhibitor was site-specifically *N*-methylated, and this significantly increased the proteolytic resistance of the compound, enhancing its antagonist activity.

Payne[7] also found proteolytic resistance in NMAs containing di- and tripeptides in research involving mutant strains of *E. coli*. The *N*-methylated peptides were actively transported to the intracellular space, where they accumulated in the absence of peptidase activity. This result introduces the increased lipophilicity conferred by *N*-methylation, which has consequences for membrane permeability and, hence, drug delivery.

A series of recent papers relating to Alzheimer's disease by Doig et al.[8−10] consider the use of small peptidic ligands bearing *N*-methyl amide bonds as a

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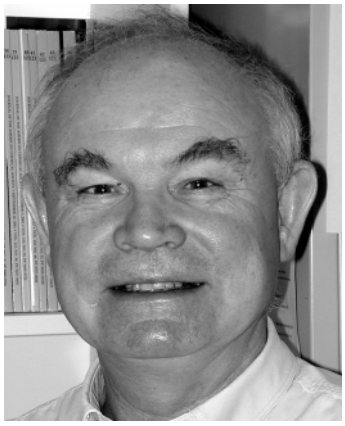
Luigi Aurelio was born in 1975 in Melbourne, Australia. He received his B.Sc. degree under the supervision of Dr. Andrew B. Hughes and Associate Professor Robert T. C. Brownlee at La Trobe University in 1998. He commenced his Ph.D. studies on the synthesis of *N*-methylamino acids in the same group in 1999. He is currently finalizing the writing and submission of his Ph.D. thesis. His current research interests are focused on the synthesis of modified peptides and peptide fragments with the aim to enhance in vivo stability via *N*-methylation and other related modifications. Luigi is a founding partner in Peptide Solutions Pty Ltd, a start-up company based on the research developed in his Ph.D. studies.



Robert Brownlee was born in 1943 in London. He studied for his B.A. in Cambridge and his Ph.D. with Professor Alan Katritzky at the then new University of East Anglia. He was a postdoctoral research fellow with Professor Bob Taft at the University of California at Irvine, and he was an Instructor in that Department from 1967 to 1970. In Australia he has been at the Department of Chemistry at La Trobe University, Melbourne, since 1970 and is now an Associate Professor and Head of Department. Bob Brownlee was awarded the Royal Australian Chemical Institute "Adrian Albert Award" for contributions to Medicinal Chemistry in 1999.

means of interrupting or reversing amyloid protein aggregation into toxic fibrils or lumps. In the first paper,[8] a Gly25 *N*-methyl analogue of β-amyloid prevented the formation of protein aggregates through interruption of hydrogen bonding. In the second paper,[9] an *N*-methyl-Gly33 analogue completely prevented fibril assembly. In the last paper of the series,[10] Doig cites studies that show these *N*-methylated peptide ligands have improved membrane permeability and can pass across the blood−brain barrier. Similar, related studies have been published by Gordon et al.[11] and Kapurniotu et al.[12]

Vitoux et al.[13] studied the effect of *N*-methylation on the conformation of amide bonds through the use of dipeptides with internal *N*-methylated amides. In particular, they found homo-dipeptides were the most severely affected, exhibiting a strong preference for

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the *cis*-amide form, which gave the dipeptides β-turn characteristics. Hetero-dipeptides were largely unaffected by *N*-methylation, and these materials preferred the *trans*-amide form. This was interpreted as meaning the chirality of the α-centers was a strong determinant of the presence of steric constraints around the amide bond. Comparison of these effects with dipeptides including a proline residue concluded that the effect of *N*-methylation giving a tertiary amide was less than the geometric constraints conferred by proline residues.

The discussion above of the physicochemical properties of *N*-methylated peptides shows that *N*-methylation can be used as a research tool and as a legitimate modification of lead therapeutic peptides. Most workers in this field focus on therapeutic development, and many authors comment on the inherently low toxicity of *N*-methylation of peptidic residues in their substrates. This further enhances the potential of *N*-methylated peptides in drug discovery and development. Consequently, researchers need access to a wide range of these derivatives for their studies.

One review of the chemistry of synthesis of the *N*-methyl-α-amino acid monomers has been published,[14] covering the period up until 1985. The present review commences discussion with reports of alkylation chemistry by Hinsberg in the late 1880s and includes contributions to the literature from then to the end of 2003.

This review describes methods for the synthesis of NMAs and addresses some of the synthetically challenging aspects of *N*-methylation including regiospecific methylation, mono-*N*-methylation, and development of racemization free chemistry. The synthetic methods reviewed reveal the difficulty that chemists have had in incorporating a single methyl group at the α-amino position and the problems encountered in applying these methods to the common 20 naturally occurring L-amino acids.

The review is divided into four main sections, and each section is subcategorized according to the par-

ticular method employed to achieve *N*-methylation. In the first section, *N*-methylation by alkylation is primarily based on S_N2 type reactions under basic conditions where nucleophiles are utilized as substrates. *N*-Methylation by alkylation is the main method for generating *N*-methylamino acids where sulfonamides, carbamates, and amides have been alkylated under various conditions. In the second section, *N*-methylation by reductive amination involves the reaction of amines with aldehydes to form Schiff base intermediates that are then reduced via borohydrides, transition metal hydrogenolysis, or formic acid to provide the NMAs. In the third section, *N*-methylation by a range of novel methods is described. In this section, chemists have approached the methylation of amino acids by use of chiral auxiliaries for asymmetric construction, ionic hydrogenation of 5-oxazolidinones, reduction of Diels−Alder adducts, and radical based methodology. Some of these novel approaches provide avenues for synthesizing *N*-methylamino acids with extreme variation in side chains (i.e. the chiral auxiliaries) and ameliorate some of the problems in the two prior sections encountered for various amino acids. In the final section, the synthesis of the cyclosporin A residue, (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt), has attracted the attention of many chemists, due to the demonstrable importance of this residue in the activity of cyclosporin A. The reader's attention is drawn to the excellent review of the syntheses of MeBmt by Durand and Genêt.[15] This section concentrates on those methods where the *N*-methylation of the MeBmt residue is novel compared with the literature in the preceding sections of this review.

Each section has concluding remarks about the utility of the methods with regard to physicochemical properties, reaction conditions, and application of the final *N*-methylamino acid products obtained. It is obvious to the peptide chemist that a number of the techniques employ *N*-protection that is not suitable in peptide synthesis and that some techniques reveal tendencies toward racemising the desired NMAs. The reader is encouraged to view the table within each section, which endeavors to compare methods according to expediency, chemical yields, and optical purity of the NMAs produced.

2. *N*-Methylation by Alkylation

See Table 1 for a summary of *N*-methylation by alkylation. The procedures first described were for direct *N*-methylation or *N*-alkylation and trace their origins to the seminal work of Hinsberg,[16] who took a number of *N*-alkyl benzenesulfonamides and treated them with alcoholic potassium hydroxide and an alkylating agent, usually ethyl or methyl iodide, to obtain di-*N*-alkyl sulfonamides. These compounds were intermediates in the synthesis of secondary amines. The extension to α-amino acids was obvious, and the concept was exploited by Fischer et al.[17]

The pioneering work of Emil Fischer and coworkers[17,18] provided a foundation for NMA synthesis involving *N*-methylation of intermediate *N*-tosyl amino acids extending Hinsberg's approach and also by nucleophilic substitution of α-bromo acids with methylamine. These two methods are discussed separately below.

Izumiya and co-workers[19,20] applied a combination of Fischer's methods to produce a broader range of NMAs and contributed most to the body of data available concerning NMAs at the time.[21b] Izumiya's work is described in the next section (Nucleophilic Substitution of α-Bromo Acids). Only two of the six articles cited in this review on Izumiya's work are written in English.[19,20a] They describe the synthesis of *N*-methyl-D-tyrosine (D-surinamine) via nucleophilic substitution of intermediate α-bromo acids,[19] and a separate paper concerns the synthesis of *N*-(methylhydroxy)amino acids in which a combination of Fischer's methods was applied. The other publications[20b−e] also describe NMA synthesis where the majority of products are made via α-bromo acids.

2.1. Nucleophilic Substitution of α-Bromo Acids

Fischer and Mechel prepared *N*-methylalanine, -leucine, and -phenylalanine by nucleophilic displacement of bromide from optically active (*R*)-α-bromo acids (Scheme 1).[18] The α-bromo acids were nucleophilically substituted with excess methylamine at 0 °C, providing NMAs with opposite configuration to the parent amino acids. In this mode, they prepared *N*-methylalanine, -leucine, and -phenylalanine, all of the L-configuration (Scheme 1).

A common route to obtaining the starting α-bromo acids is via diazotization of the parent amino acid in aqueous acidic media with sodium nitrite and potassium bromide (Figure 1).[19] The reaction proceeds with retention of configuration, and this outcome has been rationalized as a "Walden inversion".[23] The intermediate diazonium ion is attacked intramolecularly, in S_N2 fashion, by the neighboring carboxylate group to form the labile three-membered lactone **1**.[22] Nucleophilic addition, again in S_N2 mode, by bromide ion provides the optically active α-bromo acids **2** with net retention of the original amino acid chirality.

Izumiya and Nagamatsu[19] prepared *N*-methyl-D-tyrosine (D-surinamine) (**3**) in this fashion by diazotization of *O*-methyl-L-tyrosine (**5**) to give the optically active α-bromo acid **4** (Scheme 2). Nucleophilic substitution with methylamine at 100 °C in a sealed tube provided *N*-methyl-D-tyrosine (**3**). Izumiya extended this methodology to other amino acids, such as methionine,[20d] arginine,[20b] and ornithine,[20b] in synthesizing their corresponding *N*-methyl derivatives.

Scheme 1

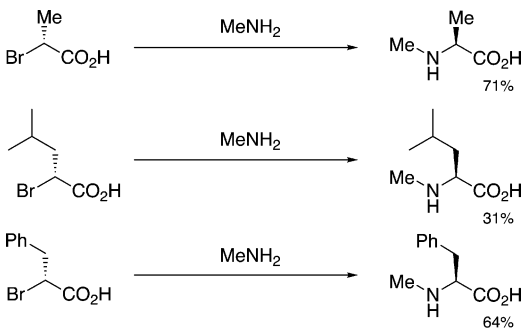


Table 1. Summary of *N*-Methylation by Alkylation

method	ref	amino acids employed	methylation step yield (%)	comments
nucleophilic substitution of α-bromo acids	18	Ala, Leu, Phe	31−71	rarely used technique; low yields and racemization
	19	Tyr	57	
	20a,c,e	Ser, Thr, β-OHVal	20−40	
(a) triflate displacement	24	Ala	96	racemization free S_N2 process; opposite enantiomer formed upon displacement
N-methylation of sulfonamides	17	Ala, Leu, Phe, Tyr	82−100	racemization occurs; vigorous techniques employed
(a) base mediated alkylation	25, 26	Ala, Val, Leu, Phe, Orn	near 100	racemization free process; utilizes detergent to improve phase mixing and removal of unreacted starting material
	27	Ser, Phe, Leu, Arg, Asn	≥ 95	excellent for small scale; excess reagents employed; particularly suited to SPS; no racemization observed
	28	Phe, Phg, Val	86−91	performed in solution phase using *N*-nosyl amino acid methyl esters
(b) diazomethylation	29	Ala, Val, Phe, Leu, Ile	100	excellent, neutral technique suitable for small scale due to diazomethane hazard; racemization free
(c) Mitsunobu protocol	35	Ala, Leu, Ile, Val, Lys	85−96	mild, racemization free solution phase technique; benzyl ester superior to methyl ester for removal without racemizing
	38	Ala, Phe, Lys	54−63	solution phase method; employs the *N*-Pmc sulfonamide protection that is more acid labile than *N*-tosyl
	39	Ala, Val, Phe, Trp, Lys, Ser, Asp	86−100	excess reagents employed; suited to SPS protocols on small scale
N-methylation of carbamates and amides (a) silver oxide/ methyl iodide	41, 42, 43	Ala, Ile, Leu, Phe, Val, Ser, Glu, Orn, Lys	52−99	very mild and racemization free process suited to small scale; imperative that fresh silver oxide is used and if the free acid is employed, *N*-methyl methyl esters result
(b) sodium hydride/ methyl iodide	30−33	Ala, Ile, Leu, Val, Phe, Ser, Met, Asp, Glu, Thr, Tyr	7−90	widely used technique for *N*-methylating amides not suitable for large scale, since most substrates suffer from incomplete methylation; 1−2% racemization observed in some substrates
	44	Gly, Ala, Leu, Ile, Met, Phe, Val	52−90	*N*-diphenylphosphinamides are utilized instead of carbamates; they provide morecrystalline NMA derivatives; optical rotation data reveal racemization occurs
	46	Ala, Ile, Leu, Tyr	68−72	using NaHMDS instead of sodium hydride improved the methylation step considerably; methyl ester formation also occurs
	48	proline dipeptides, amino acid amides, Val, Phe, Leu	90−98	catalytic amounts of water produced NaOH that has better solubility than NaH and improved the methylation step with dimethyl sulfate; reaction temp above RT encouraged racemization

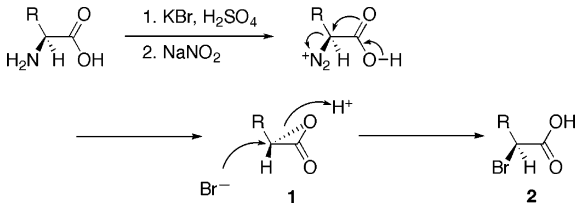
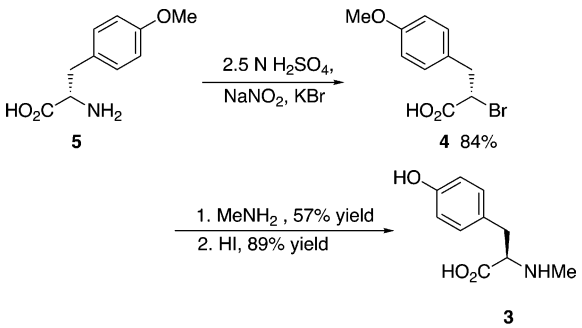


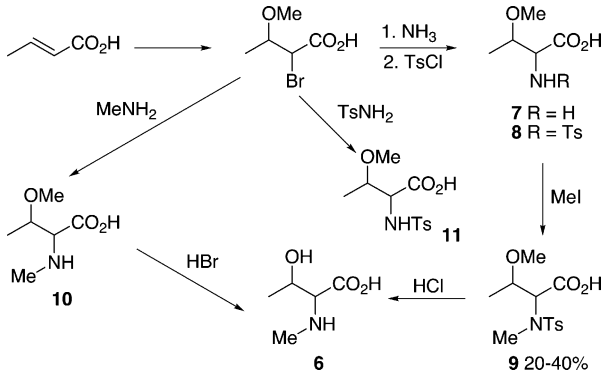
Figure 1. Mechanism of α-bromoacid formation via diazotization.

Scheme 2



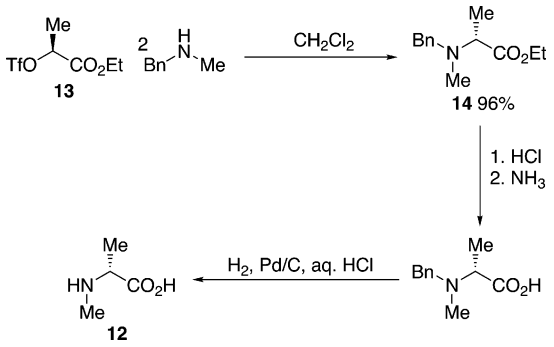
As described, Izumiya made use of a combination of both of the above methods developed by Fischer to prepare NMAs.[20a,c,e] The focus was on the preparation of hydroxyamino acids. Thus, in the preparation

Scheme 3



of NMAs, 3-methoxy-2-bromoalkanoic acids were prepared from alkenoic acids as precursors (Scheme 3). Izumiya describes two paths to NMAs exemplified by preparation of *N*-methylthreonine (**6**). The first involves amination with ammonia to generate *O*-methylthreonine (**7**). Sulfonylation with tosyl chloride gave **8**, and *N*-methylation with methyl iodide gave the protected threonine **9**. The sulfonyl and *O*-methyl groups were then removed with hydrochloric acid to give *N*-methylthreonine (**6**). The second path employed methylamine for the amination to make *N*,*O*-dimethylthreonine (**10**), thus obviating the steps to

Scheme 4



achieve *N*-methylation in the first sequence. *O*-Demethylation with hydrobromic acid gave *N*-methylthreonine (**6**). These sequences were applied to the synthesis of racemic serine, threonine, *allo*-threonine, *β*-hydroxyvaline, and also D-threonine and L-threonine. In a variation, the sulfonyl sequence could be made more efficient by amination with *p*-toluenesulfonamide to give **11**.

An alternative disconnection to α-bromo acids is to perform an S_N2 displacement on an activated α-hydroxy acid derivative. Effenberger et al.[24] applied this technique in the synthesis of *N*-methyl-D-alanine (**12**) (Scheme 4). Taking ethyl-L-lactate and converting it to the triflate **13**, and then treating **13** with *N*-methyl-*N*-benzylamine, provided the protected NMA **14** in good yields. The advantages of this technique are the excellent leaving group capability of the trifluoromethanesulfonate even with weak amine nucleophiles at room temperature and below[24] and the fact that excess amine and high temperatures in sealed vessels are eliminated, as in Izumiya's method (Scheme 2).

The synthesis of NMAs by nucleophilic substitution is generally a short sequence applying simple chemical techniques. However, it is also a low to moderate yielding method and racemization has not entirely been eliminated.[21b] It was not until 1963 that Quitt et al.[21] established a racemization free reductive amination of a range of NMAs and revealed by comparison of optical data that some racemization was occurring in the α-bromo acid nucleophilic substitution method employed by Fischer and Izumiya even with the addition of methylamine at 0 °C in the case of Fischer. This approach to NMA synthesis has essentially been abandoned, as Fischer and Izumiya are the sole contributors to the literature.

The alternative approach by Effenberger et al.[24] involving triflate displacement is considerably more mild though the carboxyl group needs to be suitably protected. Nonetheless, this technique was shown to provide optically pure derivatives and provides avenues to *N*-alkylamino acids.

2.2. *N*-Methylation of Sulfonamides

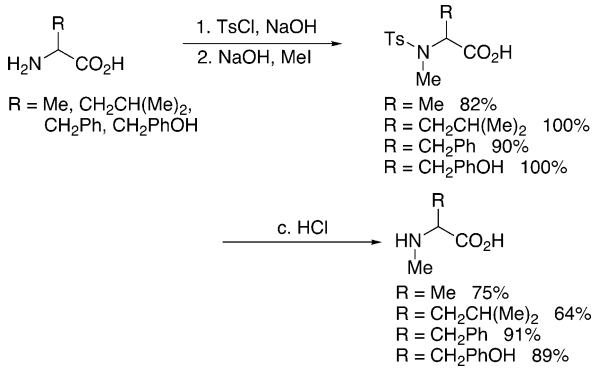
One of the common methods of *N*-methylation by alkylation under various conditions is to utilize *N*-sulfonamidoamino acids. Sulfonamide protection greatly enhances the acidity of the sulfonamido nitrogen, permitting deprotonation under basic conditions, and in the presence of an alkylating reagent furnishes the *N*-sulfonamide NMAs. Alternatively, the Mitsunobu protocol can be employed in the synthesis of NMAs with various sulfonamide groups (vide infra), again due to the acidity of the sulfonamide nitrogen. These two subjects are discussed separately below.

2.2.1. Base Mediated Alkylation

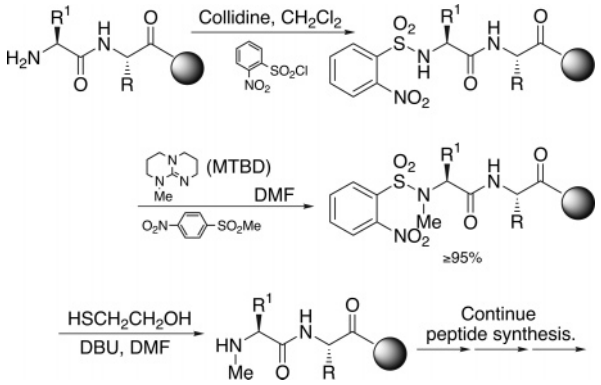
The earliest report by Fischer and Lipschitz[17] describes the preparation of *N*-tosyl-α-amino acids (Scheme 5), followed by base (NaOH) mediated *N*-methylation with methyl iodide at 65−70 °C. One of the advantages of *N*-tosyl protection is the high degree of crystallinity it confers on the products, as do other types of sulfonamide protection readily installed under standard conditions.[17] The only problem with the *N*-tosyl group is its removal, which requires vigorous conditions. The *N*-tosyl NMAs were subjected to acid hydrolysis with concentrated hydrochloric acid for up to 8 h at 100 °C to provide the free NMA. This base mediated method, of course, does not proceed without racemization, as the results of Quitt et al.[21] revealed through comparison of optical rotation values. An obvious cause of the racemization is the methylation step, in which sodium hydroxide was used at elevated temperatures. The temperature is a major contributing factor to this racemization process, since the method of Hlavácek et al.[25,26] reveals that treating *N*-tosyl amino acid esters at 0 °C with sodium hydroxide and dimethyl sulfate does not racemize *N*-tosyl substrates (vide infra).

N-Methylation of *N*-tosylamino acid isopropyl and *tert*-butyl esters of alanine and valine, using sodium hydroxide and dimethyl sulfate at 0 °C, was the method Hlavácek et al.[25,26] used in their preparation of active juvenoid analogues. Detergent was included to improve phase mixing and also helped in containing traces of unreacted starting materials. In this way, pure *N*-methylamino acid derivatives of leucine, valine, phenylalanine, alanine, and ornithine were isolated during workup in near quantitative yields for the methylation step.[26] The free acids were obtained by treating the *tert*-butyl esters with trifluoroacetic acid, and isopropyl esters were refluxed

Scheme 5



Scheme 6



in 4 M HCl solution in dioxane. Subsequent tosyl group removal was achieved either with calcium metal in liquid ammonia or with hydrobromic acid at reflux in the presence of phenol to provide optically active NMAs by comparison of optical data with that of Quitt et al.[21]

Miller and Scanlan extended the sulfonamide approach to site-selective *N*-methylation on solid support.[27] Exploiting the enhanced acidity of the sulfonamide NH over that of the amide NH allows for selective deprotonation of sulfonamides in the presence of amides, and consequently, selective methylation was achieved. The resin bound free amine was protected as the *o*-nitrobenzenesulfonamide (*o*-NBS), which can be removed selectively, with milder conditions when compared to *N*-tosyl protection, using β-mercaptoethanol/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) via nucleophilic aromatic substitution. The sulfonamide was then deprotonated with the nonionic guanidinium base, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and alkylated with methyl *p*-nitrobenzenesulfonate (Scheme 6). This combination of sulfonamide protection, base deprotonation, and alkylation provided site-selective *N*-methylation, without backbone methylation elsewhere in the growing peptide. It was found that the use of the guanidinium base MTBD was critical in achieving high yields and selectivity, since weaker bases gave poor or no yields and stronger bases resulted in uncontrolled methylation of the amide backbone. This method allows an "*N*-methyl scan" to be incorporated into the solid phase peptide synthesis (SPPS) protocol on a peptide chain. The less vigorous conditions of methylation and deprotection with this method provide a useful alternative approach to *N*-tosyl protection.

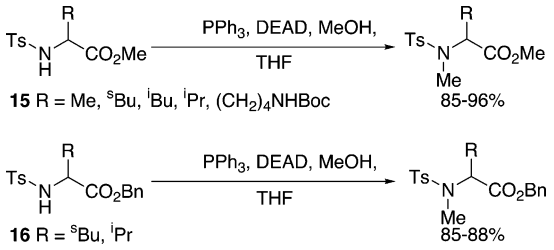
Albanese et al.[28] also used *o*-NBS protection of amino acid methyl esters and alkylated the intermediate *o*-NBS amides in solution phase. Treating the sulfonamide esters with solid potassium carbonate, triethylbenzylammonium chloride (TEBA) as phase transfer catalyst,[28] and alkyl halides furnished *N*-nitrobenzenesulfonamido-*N*-alkylamino acid esters at 25 or 80 °C. These transformations were accomplished with valine, phenylalanine, and phenylglycine in 87, 86, and 91% yields, respectively, for their *N*-methyl derivatives. The use of TEBA enabled the non-nucleophilic base potassium carbonate to be utilized whereas, in the absence of TEBA, *N*-alkylation was considerably reduced. Removal of the nitrobenzenesulfonamide group is affected by thiophenol/potassium carbonate/acetonitrile at 80 °C or potassium thiophenoxide/DMF at 25 °C, leaving the methyl ester intact.

An even milder approach to *N*-methylating amino acid sulfonamides is under the neutral conditions of diazomethylation. Di Gioia et al.[29] found that, by treating *N*-nosylamino acid methyl esters with a large excess of diazomethane, the corresponding NMA esters were obtained in quantitative yield for alanine, phenylalanine, valine, leucine, and isoleucine. The *N*-nosyl group was removed with 3 equiv of mercaptoacetic acid in the presence of 8 equiv of sodium methoxide at 50 °C, to provide the free amines in >84% yields. Initial attempts to *N*-methylate amino acid methyl ester hydrochlorides with excess diazomethane in the presence of aluminum trichloride provided intractable mixtures. In the case of the leucine methyl ester, the starting amino acid methyl esters and the di- and monoesters were isolated as a mixture in an approximate ratio of 4:2:4, respectively. Application of *N*-acetyl amino acid methyl esters gave almost no *N*-methylation. *N*-Nosyl protection presented optimal substrate properties for quantitative *N*-methylation with diazomethane without the need for including the Lewis acid aluminum trichloride.

N-Methylation by alkylating sulfonamides is advantageous in that the increased acidity of the sulfonamide nitrogen can allow for selective methylation in a peptide[27] on solid support or an orthogonally protected amino acid monomer. The Fischer method is undesirable, since some degree of racemization occurs under the vigorous conditions of *N*-methylation and tosyl group removal via acid hydrolysis is too vigorous for many sensitive amino acid residues. Therefore, *N*-tosyl protection is inappropriate for inclusion in peptide synthesis, since the conditions for removal also cleave peptide bonds by acid hydrolysis. The reductive method with sodium or calcium in liquid ammonia is a much milder process, yet when dealing with peptide chains, the workup is cumbersome and the reduction is not selective in protective group removal.

The *N*-*o*-NBS or *N*-nosyl protections are significant improvements, having the advantage of mild deprotection conditions while still allowing *N*-alkylation and easy workup in solution or solid phase. The method of Di Gioia et al.[29] involving diazomethane, while elaborate, is performed under neutral conditions, but it is to be used with great caution, especially if preparative scales are entertained, due to the *explosive* and *toxic* nature of diazomethane! Methyl ester protection as included in the work of Di Gioia et al.[29] and Albanese et al.[28] is unsuitable, since, commonly, ester removal is by base hydrolysis, which may have deleterious effects on the enantiomeric purity of the product. It is not recommended to include protecting groups that are removed by hydroxide or other strong bases, especially if there are no other ionizable sites in the amino acid other than the α-center where NMAs are concerned. Studies by Benoiton et al.[30−34] revealed the propensity of

Scheme 7



NMAs to racemize under basic, acidic, and coupling reaction conditions (vide infra).

2.2.2. Mitsunobu Protocol

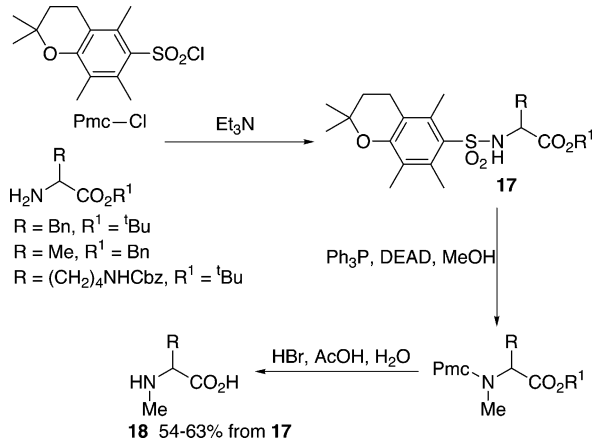
As mentioned, alkaline reagents can have an adverse effect on the optical purity of α-amino acids, particularly if the *N*- and *C*-termini are protected, making the α-center the most acidic site and prone to enolization. One variation on this approach was to exploit the inherent acidity of the *N*-tosyl nitrogen for inclusion in the Mitsunobu protocol.

Papaioannou et al.[35] used the Mitsunobu protocol[36] to effect the *N*-alkylation of *N*-tosyl protected amino acid methyl and benzyl esters **15** and **16** (Scheme 7) with retention of configuration and optical purity. Papaioannou et al. then performed a racemization study in the ester hydrolysis of *N*-methyl-*N*-tosyl-L-valine methyl ester. It was found that deprotection with methanolic sodium hydroxide at room temperature produced up to 44% of the D-enantiomer. Alternatively, deprotection with iodotrimethylsilane effectively removed the methyl ester without racemization. This reagent, however, is nonselective in that many other protecting groups are also removed.[37] It was found that benzyl esters, which can be removed by catalytic hydrogenation, did not racemize, and therefore, they are the preferred choice for carboxyl protection in this case. The *N*-tosyl protection was reductively cleaved with sodium in liquid ammonia, providing optically active NMAs.

Wisniewski and Kolodziejczyk[38] addressed the problematic *N*-tosyl deprotection by employing the 2,2,5,7,8-pentamethylchroman-6-sulfonyl or Pmc group, which has increased lability to acid conditions, to protect the nitrogen. The *N*-Pmc group, when applied to an α-amino acid ester, yields a secondary sulfonamide **17** that is still sufficiently nucleophilic to participate in a Mitsunobu reaction. Thus, these workers[38] also avoided the strongly basic conditions (Fischer's approach) associated with the methylation of *N*-toluenesulfonamides to prepare three NMAs **18** (Scheme 8). Their approach included the use of *tert*-butyl and benzyl esters for carboxyl protection. Final deprotection of the *N*-methyl-*N*-Pmc-amino acid esters was performed with HBr/AcOH. The acidolytic cleavage contained 2% water to reduce the possibility of racemization using HBr/AcOH, which under anhydrous conditions is known to racemize NMAs, as discovered by Benoiton et al.[31−33]

Yang and Chiu[39] applied a strategy similar to that of Miller and Scanlan to synthesize Fmoc-*N*-methylamino acid forms of alanine, valine, phenylalanine, tryptophan, lysine, serine, and aspartic acid preloaded on 2-chlorotrityl resin with yields ranging

Scheme 8



from 86 to 100%. The difference between the two methods was that Yang and Chiu[39] *N*-methylated the corresponding 2-nitrobenzenesulfonamide under Mitsunobu conditions or with finely powdered potassium carbonate and methyl iodide. It was also noted that alcohols other than methanol could be used to provide the *N*-alkyl amino acids under Mitsunobu conditions.[39] The sulfonamide group was removed with sodium thiophenoxide, carbamoylated with Fmoc-Cl/diisopropylethylamine, and then cleaved from the resin with 0.5% TFA/dichloromethane to provide the Fmoc-*N*-methylamino acids, which were generally isolated in >90% yield. The methylated amino acids thus isolated were found to be racemization free.[39]

The Mitsunobu protocol for *N*-methylating *N*-sulfonylamino acids is an effective racemization free method for NMA synthesis. The use of *N*-nosyl protection over *N*-tosyl has provided a means for ready introduction and removal of sulfonamide type protection, and the neutral conditions of the Mitsunobu reaction permit a variety of protecting groups that can be included in an orthogonal protection scheme. This method, although mild and effective, can be expensive, and it would be preferable to limit this procedure to small scale and solid-phase synthetic schemes. The work of Papaioannou et al.[35] reveals the high degree of racemization that occurs when hydrolyzing alkyl esters with hydroxide ion and reinforces the fact that alkyl ester protection in NMA synthesis and NMA peptide synthesis can severely racemize the NMA substrates.

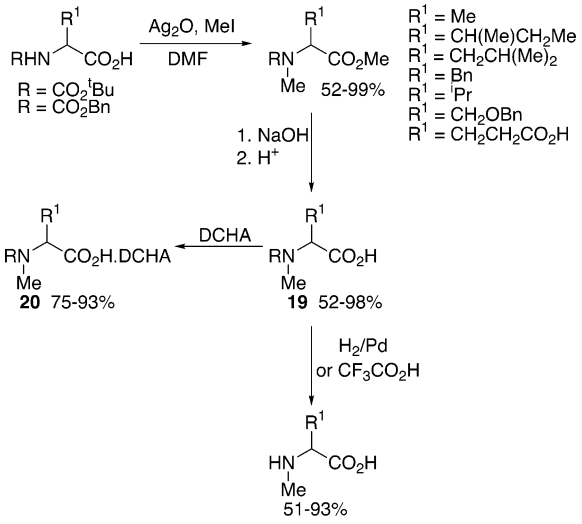
2.3. *N*-Methylation of Carbamates and Amides

The following section is devoted to the *N*-methylation of carbamates and amides and the seminal work of Benoiton et al., which provides crucial information concerning the tendencies of NMAs to racemize under various conditions.

2.3.1. Silver Oxide/Methyl Iodide

The *N*-methylation of carbamate, terminal amide, and internal amide bond amino acid residues was first described by Das et al.[40] when they permethylated peptides for use in mass spectrometry studies. Their intentions were purely based on the fact that oligopeptides are less volatile due to hydrogen bonding and therefore mass spectral analysis of such

Scheme 9



peptides for amino acid sequencing is difficult. *N*-Methylation of peptide bonds would alleviate the volatility problem by removing the possibility of hydrogen bonding. Their procedure involved treatment of substrate *N*-acyl peptides with excess methyl iodide and silver oxide in dimethyl formamide. The final methylated products showed higher volatility and allowed mass spectral analysis at lower temperatures in the ion source.

Olsen[41] developed the peptide methylation studies of Das et al.[40] to include α-amino acid *tert*-butyl (*N*-Boc) and benzyl (*N*-Cbz) carbamates. The yields of mono-*N*-methylamino acid methyl esters such as alanine and valine were routinely in the range 93−98% (Scheme 9). However, transformations of more reactive residues such as cysteine, arginine, methionine, aspartic acid, serine, and threonine were not successful.

Okamoto et al.[42] extended Olsen's procedure, and this time *N*-methyl analogues of glutamic acid and serine were synthesized with success (Scheme 9). Most of the *N*-methylamino acids **19** were isolated in crystalline form as their dicyclohexylamine (DCHA) salts **20** following ester saponification. However, it was found that the optical rotation data for *N*-methylserine and -glutamic acid were lower than reported values.

The silver oxide/methyl iodide method for *N*-methylation is a mild and racemization free process. However, the final NMAs are obtained as their methyl esters that are then saponified to give the corresponding free acids. This has been shown to compromise the chiral integrity of the NMAs. In addition, this method is not always reproducible due to the instability of silver oxide. It is imperative that fresh[42] silver oxide be used in anhydrous conditions in the absence of light. Alternatively, *N*-carbamoyl amino acid esters (suitable ester protection, i.e. *tert*-butyl or benzyl) should be employed in such a procedure to preclude methyl ester formation.[41] Tam et al.[43] did just that in the synthesis of *N*-methyl derivatives of α-*N*-Boc, side chain *N*-phthaloyl protected ornithine, and lysine. By blocking the carboxyl group as a benzyl ester, silver oxide/methyl iodide mediated *N*-methylation was achieved without transesterification to give the methyl ester. The benzyl ester was removed under hydrogenolytic conditions to afford the free acids that were used in the solid-phase synthesis of Arg-Ser-Arg-Lys tetrapeptide analogues in structure−function studies. The *N*-methylornithine derivatives were used as precursors for *N*-methylarginine by guanidination with N^{im}-nitro-*S*-methylisothiourea on solid support.[43]

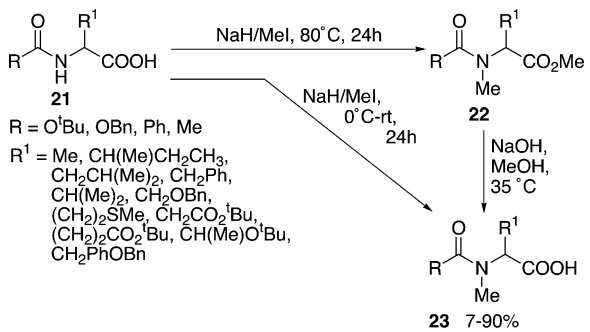
2.3.2. Sodium Hydride/Methyl Iodide

The most broadly applied method for NMA synthesis is *N*-methylating *N*-acyl- and *N*-carbamoyl-amino acids with sodium hydride and methyl iodide as developed by Benoiton et al.[30−33] It was reported that sodium hydride could remove the NH proton of secondary amides and urethanes.[30a] Benoiton exploited this in synthesizing a range of NMAs with different *N*-protection using excess sodium hydride and methyl iodide. Many others have since utilized this method and variations thereof in producing NMAs. Benoiton et al. subsequently established the propensity of NMAs to racemize in basic, acidic, and various coupling reaction conditions (vide infra).

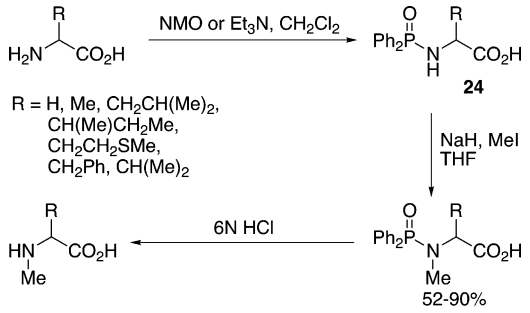
Benoiton et al.[30] initially attempted *N*-methylation employing *N*-acyl-, *N*-tosyl-, and *N*-carbamoyl-α-amino acids **21**. They treated these *N*-protected amino acids with sodium hydride and methyl iodide in THF/DMF at 80 °C for 24 h. Under these conditions, a large excess of methyl iodide (8 equiv) was required for optimal yields of the *N*-methyl methyl ester **22** (Scheme 10). The methyl ester was removed using warm sodium hydroxide in methanol/THF to give the corresponding *N*-Cbz/*N*-acyl-*N*-methylamino acids **23**, respectively.

The use of alkaline conditions in the formation of the *N*-methyl group and removal of the methyl ester causes varying degrees of undesired racemization at the α-carbon of the amino acids: the subject of several key papers by Benoiton et al.[31−33] A direct route to *N*-methylamino acids **23** was necessary so as to avoid hydrolysis of the ester **22** and therefore prevent racemization. McDermott and Benoiton[34] found that reaction temperature was an important factor in avoiding methyl ester formation (Scheme 10), identified acidic reaction conditions that caused α-amino acid racemization, and included in their studies the analysis of *N*-methylamino acid containing dipeptides. They found the anhydrous HBr/acetic acid used for *N*-Cbz removal caused racemization. Later, Benoiton et al. documented the increased and variable susceptibility of NMAs to racemization in

Scheme 10



Scheme 11

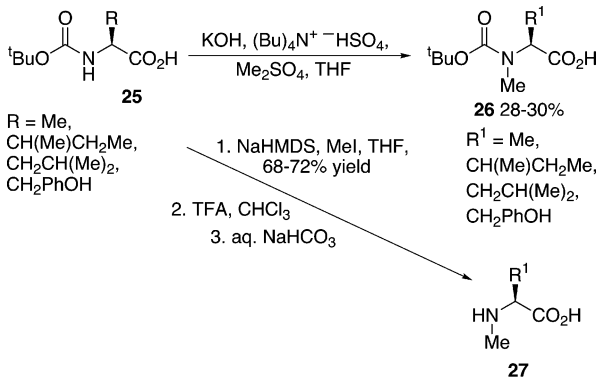


peptides during standard peptide coupling reactions.[33]

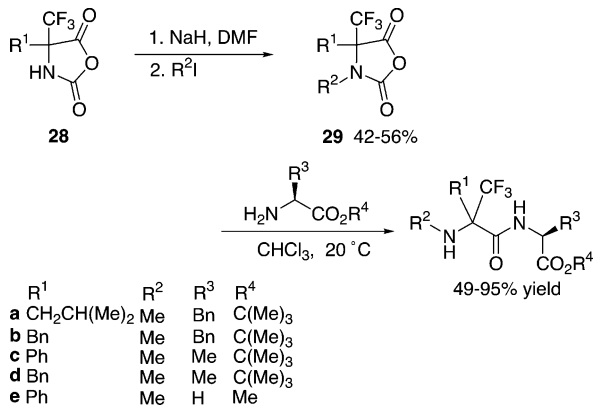
McDermott and Benoiton[32,33] undertook a systematic study of the extent of racemization of NMA residues in peptides during hydrolysis and peptide coupling reactions. It was concluded that appreciable racemization occurred with aqueous hydroxide due to the absence of ionizable groups other than the α-center. Analysis of the acid catalyzed racemization showed that anhydrous HBr/acetic acid caused racemization depending on acid strength, solvent polarity, and time. A decrease of each of these factors resulted in decreased racemization, and it was found that including water in the acidic mixtures suppressed racemization completely, as did hydrochloric acid mixtures in place of hydrobromic acid mixtures. The racemization studies were extended to include coupling reactions between NMA peptides via the mixed anhydride activation approach, and they identified factors such as ionic strength and solvent polarity as controlling racemization during peptide bond formation via the mixed anhydride activation/coupling procedure. They also found that polar solvents and increased ionic strength of the solvent medium due to tertiary amine salts of hydrochlorides or *p*-toluenesulfonates promoted racemization, and in the absence of these factors less racemization was observed. Only DCC/*N*-hydroxysuccinimide as an activating agent gave stereochemically pure coupled products. Furthermore, they found that an excess of base did not promote racemization.

The *N*-toluenesulfonamides, like those Fischer and Lipschitz[17] employed, are stable and often need quite vigorous conditions for deprotection. The use of *N*-Boc or *N*-Cbz protection causes difficulty in forming readily crystallizable NMA products. Coulton et al.[44] addressed these problems using diphenylphosphinamides **24**, which are acid labile (95% TFA). They demonstrated their approach through the preparation of seven NMAs (Scheme 11). The α-amino acid diphenylphosphinamides **24** were methylated using the conditions of Benoiton.[30,33,34,45] A further advantage of the α-amino acid diphenylphosphinamides was their increased crystallinity over the corresponding *N*-Boc and *N*-Cbz derivatives. A drawback of this procedure was that their experimental values for optical rotation did not agree well with those reported. This suggests that some racemization may have occurred, and the authors acknowledge this discrepancy, which reveals the need for further investigation of the stereochemical integrity of the product NMAs.

Scheme 12



Scheme 13



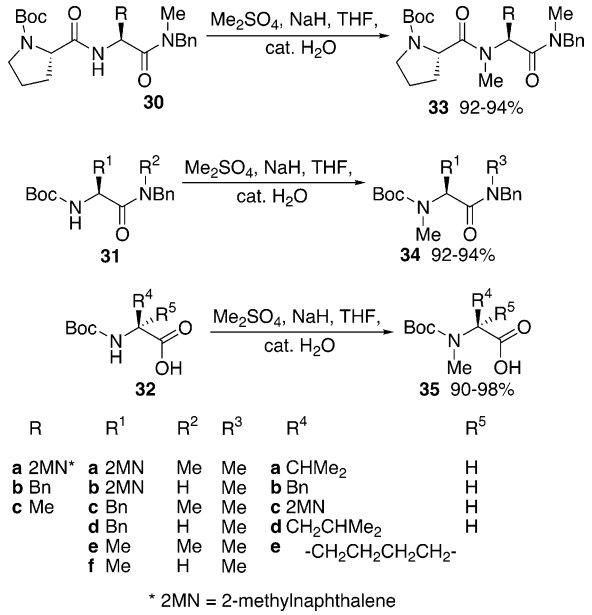
	R1	R2	R3	R4
a	$CH_2CH(Me)_2$	Me	Bn	$C(Me)_3$
b	Bn	Me	Bn	$C(Me)_3$
c	Ph	Me	Me	$C(Me)_3$
d	Bn	Me	Me	$C(Me)_3$
e	Ph	Me	H	Me

Belagali et al.[46] utilized a similar approach to that of Benoiton with *N*-Boc-L-amino acids (Scheme 12) but took the *N*-Boc-L-amino acids **25** and treated them with sodium hydride/methyl iodide under the Benoiton conditions;[30b] however, they found that the yields of the *N*-methyl derivatives **26** were in the range 30−40%. The harsher conditions depicted in Scheme 12, where the *N*-Boc-L-amino acids **25** were treated with finely powdered potassium hydroxide, tetrabutylammonium hydrogen sulfate (phase transfer catalyst), and dimethyl sulfate, also produced the *N*-methyl-*N*-Boc-L-amino acids **26** in low yields. However, by switching to sodium hexamethyldisilazide (NaHMDS), the yields of the *N*-methylation step improved 2-fold and the NMAs were isolated as their methyl esters **27** after cleavage of the *N*-Boc group with TFA.

Another variation on Benoiton's theme was that by Burger and Hollweck,[47] who alkylated 4-(trifluoromethyl)-1,3-oxazolidine-2,5-diones (TFM Leuchs anhydrides) **28** (Scheme 13) utilizing sodium hydride and alkyl iodides. The *N*-alkylated Leuchs anhydrides **29** were used in dipeptide syntheses, since peptide bond formation of α,α-dialkylated residues at the carboxyl terminus is generally difficult.[47] It was found that alkyl bromides were ineffective in the alkylation step and that alkyl iodides were superior.

Prashad et al.[48] *N*-methylated *N*-Boc-dipeptides **30**, amino acid amides **31**, and amino acids **32**, using a modified version of the Benoiton method (Scheme 14). They treated the substrates with sodium hydride in THF and methylated the resulting anion with dimethyl sulfate. It was found that methylation under anhydrous conditions did not provide the correspond-

Scheme 14



ing *N*-methylated derivatives, but catalytic amounts of water added to the reaction mixture gave excellent yields of products **33**, **34**, and **35**. The authors postulate that the addition of water produces dry sodium hydroxide that has better solubility in THF compared to sodium hydride. It was also noted that approximately 10% epimerization occurred at 30 °C for substrate **30a**, but this could be ameliorated by ensuring that the reaction was conducted at a temperature in the range 17−20 °C.

A number of NMA derivatives have been synthesized by the method of Benoiton, and NMAs manufactured by this method have been employed in a number of natural product syntheses. This method has generally been accepted as a mild procedure that enables the *N*-methylation of a number of *N*-acyl- and *N*-carbamoylamino acids. In the case of Fmoc amino acids, this method is not applicable due to the base lability of this protecting group. Low temperature in the methylation step is crucial for suppressing esterification, and racemization is not entirely avoided.[30−34] As described by Prashad et al.,[48] sodium hydride does not have high solubility in organic solvents, and the anion formed by treating the substrate amino acid with sodium hydride has low solubility in some cases (Boc-Ala-OH requires twice the volume of organic solvent; otherwise, the reaction is incomplete due to precipitation during the reaction).[30] The addition of phase transfer catalysts and equimolar amounts of water to increase the solubility of reagents and intermediates has been a successful strategy to overcome this problem. It was also found by Boger et al.[49] (section 4. *N*-Methylation by Novel Methods) that potassium hydride was a much better reagent than sodium hydride in methylating α-amino-*β*-hydroxyamino acids in THF solvent.

3. N-Methylation by Reductive Amination

See Table 2 for a summary of *N*-methylation by reductive amination.

3.1. Transition Metal Catalyzed Reduction

A promising method for installing the *N*-methyl function is reductive amination, which offers the possibility of placing alkyl groups other than methyl, simply by varying the carbonyl source. Methods devised for reducing the intermediate Schiff bases involve transition metal catalyzed hydrogenation, borohydride reduction, and Leuckart type reactions. Borane reduction has also been extended to *N*-formylamino acids with success. The simplicity of Schiff base reduction is extremely appealing, since the Schiff base formation is generally a mild, straightforward process performed by adding equivalent amounts of aldehyde and amine in an appropriate solvent and then reducing the intermediate. *N*-Alkylation of amino acids by the Schiff base approach works well for aldehydes other than formaldehyde.[50−53] The steric hindrance conferred by the alkyl group and amino acid side chains helps to minimize or prevent dialkylation, but not in the case of formaldehyde. In all cases reported, attempted mono-*N*-methylation of amino acids with formaldehyde results in a combination of *N,N*-dimethylation, *N*-monomethylation, and no reaction (starting material).[51,54] This is readily explained by the fact that the Schiff base intermediate when reduced to the *N*-methyl species is then a secondary amine that has greater nucleophilicity than the parent primary amino acid. Given that the methyl group is the smallest alkyl group, Schiff base formation with the secondary amine is favorable and occurs readily. This was the case for Keller-Schierlein et al.,[54] who synthesized N^{α}-methyl-N^{δ}-benzyloxycarbonyl-L-ornithine from N^{δ}-benzyloxycarbonyl-L-ornithine. N^{δ}-Benzyloxycarbonyl-L-ornithine was treated with formaldehyde solution and reduced with sodium borohydride to give a mixture of di- and mono-*N*-methylamino acids and starting material. However, after chromatography of the mixture on Sephadex LH-20, N^{α}-methyl-N^{δ}-benzyloxycarbonyl-L-ornithine was obtained in only 35% yield.

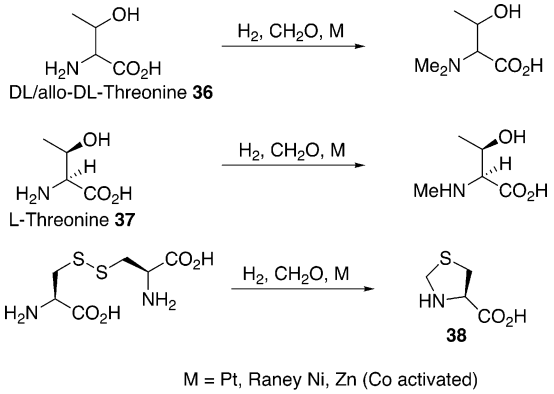
In a series of three papers, Bowman[55−57] describes the *N,N*-dimethylation of amino acid residues through the use of aqueous formaldehyde over palladized charcoal in a hydrogen atmosphere. The work in this paper was primarily concerned with dimethylation and not monomethylation. This method provided quantitative yields of the *N,N*-dimethylamino acids of alanine, valine, leucine, phenylalanine, tyrosine, cystine, aspartic acid, and glutamic acid. It was noted that the *N,N*-dimethyl derivative of aspartic acid was racemized in aqueous solution at 100 °C.[55]

The second paper in the series extends the methodology to the mono-*N*-alkylation of valine, leucine, and phenylglycine with various alkanals in ethanol or aqueous ethanol. In this case, *N,N*-dialkylglycine can also be produced.[56] The last paper in this series describes the reductive alkylation of di- and tripeptides as a means for the identification of the *N*-terminal amino acid, utilizing the same protocols as the two previous papers.[57] Ikutani[58] applied the Bowman method to synthesize *N,N*-dimethylamino acids of glycine, alanine, leucine, phenylalanine, and tyrosine and converted them to *N*-oxides by peroxide

Table 2. Summary of *N*-Methylation by Reductive Amination

method	ref	amino acids employed	methylation step yield (%)	comments
(a) transition metal catalyzed reduction	55	Ala, Leu, Phe, Val, Tyr, Cys, Asp, Glu	100	*N*,*N*-dimethylation of amino acids possible; selective monomethylation is rarely achieved[60]
(b) Leuckart reaction	21	Ala, Val, Leu, Ser, Phe, Lys, Arg	70−94	racemization free process that is cheap and effective; has also been extended to other amino acids but lower yielding[61]
(c) quaternization of imino species	64	Trp	85	racemization free route to *N*-methyltryptophan on a multigram scale
	65, 66	Val, Phe, ClPhe, α-Me-ClPhe	41−75	a racemization free process only when amino acid esters are involved
(d) borohydride reduction	67	proteins	100	regiospecific *N*,*N*-dimethylation of proteins at *N*-termini and lysyl side chains
	50	Ala, Ser, Thr, Leu, Trp	71−91	very mild technique, providing optically pure NMAs; excess reagents limit these techniques to solid phase
	69	most amino acids	56−99	as with ref 69 and small scale solution phase as in ref 50
(e) borane reduction	74	D-Trp	56	mild racemization free technique in solution phase; limited to amino acids not bearing amides or amide protection
	75	Ala, Phe, Val, Ser	≤72	a solid-phase method that also has the same limitations as above

Scheme 15



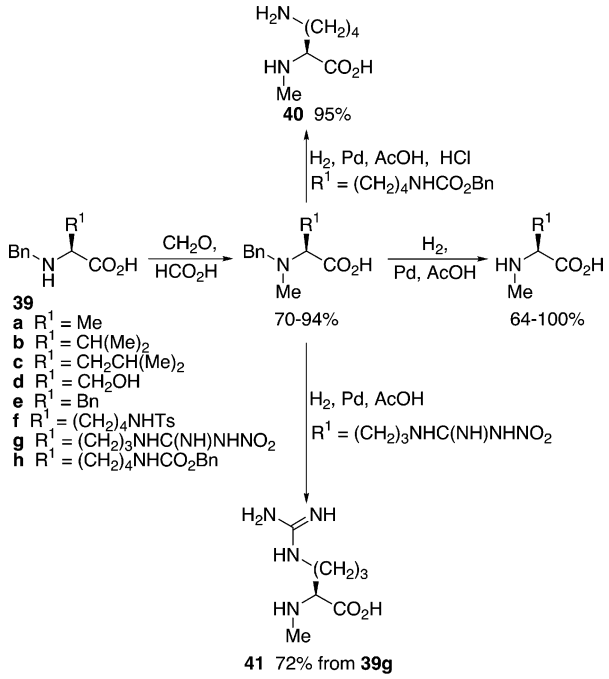
treatment. This was also the approach Poduska[59] used in dimethylating lysine derivatives.

The reductive amination of amino acids via palladium catalysis is a cheap, effective, and racemization free route to *N*,*N*-dimethylamino acids and mono-*N*-alkylamino acids. Monomethylation is impractical with this method, as dimethylamino acids and starting material are byproducts that require tedious chromatography for their removal. However, a case in which selective monomethylation was possible via transition metal catalyzed reduction has been reported by Suyama et al.[60] They catalytically reduced amino acids in the presence of formaldehyde with platinum, Raney nickel, and zinc activated with cobalt. They found that DL- and *allo*-DL-threonine (**36**) were easily dimethylated, but L- (**37**) and *threo*-D-threonine were mainly monomethylated. Under the same conditions, cystine provided the thiazolidine carboxylic acid **38** (Scheme 15).

3.2. Leuckart Reaction

The Leuckart reaction is a standard method for the reductive amination of a ketone or aldehyde with an amine in the presence of formic acid. The procedure involves heating *N*-benzylamino acids in formic acid solution in the presence of formaldehyde until effervescence due to carbon dioxide ceases. This is the only type of reductive amination with formic acid/formaldehyde to produce NMAs; no other variations have been described in the literature. Quitt et al.[21] reveal the functional group tolerance of this strategy

Scheme 16

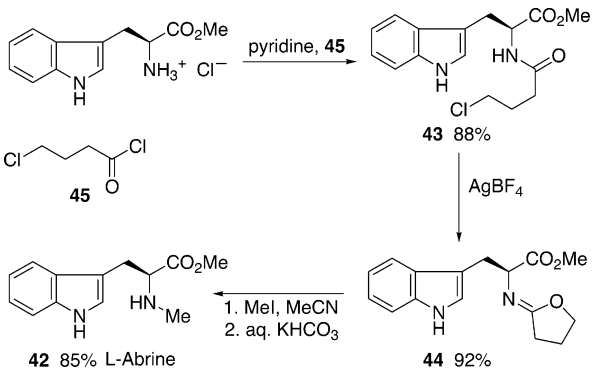


for *N*-methylating *N*-benzylamino acids (Scheme 16). Two substrates that present difficulties for some other methods, lysine **39f** and **39h** and arginine **39g**, were successfully *N*-methylated via reductive amination with formaldehyde and formic acid to give structures **40** and **41**, respectively. To date, the physical data obtained from these derivatives have provided a benchmark for comparison of NMAs due to the mildness of this racemization free method. In 1966, Ebata et al.[61] extended the methodology to other amino acids such as aspartic and glutamic acid, isoleucine, threonine, tyrosine, and glycine with success; albeit, the reactions were low yielding. Brockmann and Lackner employed this sequence to prepare *N*-methylvaline and isoleucine as components in their synthesis of actinomycin C3,[62] and Eloff[63] prepared *N*-methyl-L-^{14}C-alanine on a microscale for metabolism studies.

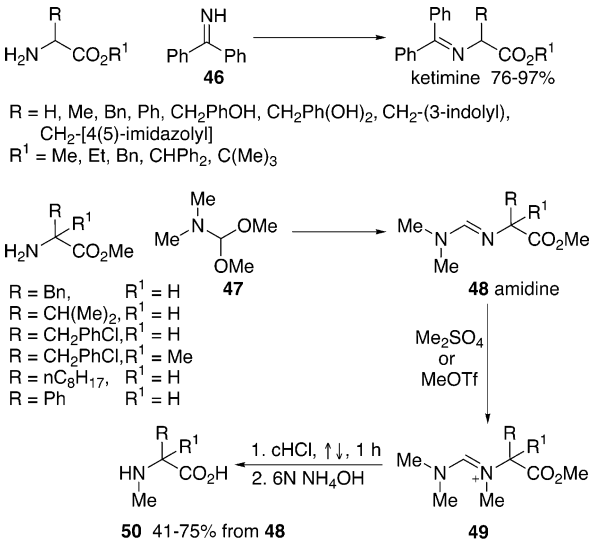
3.3. Quaternization of Imino Species

A method rarely adopted for NMA preparation is quaternization of imino species. However, this is an

Scheme 17



Scheme 18



attractive approach for monomethylation of amino acids given that the imino group can only be alkylated once and this precludes possible dialkylation. Eschenmoser et al.[64] applied this novel procedure to the formation of *N*-methyltryptophan (L-abrine) (**42**), in which *N*-chlorobutyroyltryptophan methyl ester (**43**) was treated with silver tetrafluoroborate, resulting in a cyclization to the iminolactone **44** limiting the valences of the nitrogen available for alkylation (Scheme 17). Quaternization of the imino species with methyl iodide was followed by hydrolysis with aqueous potassium carbonate to give *N*-methyltryptophan (L-abrine) (**42**). The conversions of **43** to **44** to **42** can be done in one pot in 85% yield, and notably, the process was free of racemization.

O'Donnell and Polt[65] described the efficient preparation of Schiff base derivatives (ketimines) of amino acids (Scheme 18) by transimination from the reactive benzophenone Schiff base **46**. Subsequently, the corresponding reaction with dimethylformamide dimethyl acetal (**47**) that generated the amidine was communicated.[66] Quaternization of the resulting amidine **48** with methyl sulfate or methyl triflate gives an iminium salt **49**, which was then hydrolyzed to give the *N*-methylamino acid **50**. Several operational points were identified; first, the amidines were more reactive than the simple alkyl Schiff bases; second, amidines prepared directly from the free amino acid and dimethylformamide dimethyl acetal in refluxing toluene were racemized; and, third, the reaction of the amidine of phenylglycine methyl ester with methyl triflate in dichloromethane at room temperature gave, after hydrolysis, optically active *N*-methylphenylglycine. This last point demonstrates that less vigorous transformations are particularly mild, as phenylglycine is prone to racemization.

3.4. Borohydride Reduction

Borohydride reductions are alternative approaches to transition metal catalyzed reduction of Schiff base intermediates; however, they are seldom used to reduce Schiff bases, since chemical yields are compromised by competing side reactions.[67] Milder borohydrides such as sodium cyanoborohydride are more suited to this application, especially in the *N*-alkylation of amino acid esters with aldehydes.[51,54,68] Alternatively, triacetoxyborohydride has been recommended as a replacement reducing agent to sodium cyanoborohydride in that less toxic side products are formed and better yields and reproducibility of results can be obtained.[52,53]

Jentoft and Dearborn[67] have described the reductive amination of proteins with formaldehyde in the presence of sodium cyanoborohydride, to produce *N*,*N*-dimethylated proteins. The reaction was described as regiospecific, with methylation occurring only at the *N*-terminus and at lysyl side chains. They also discuss the superiority of sodium cyanoborohydride over sodium borohydride in its mildness and specificity in the reductive amination.

Polt et al.[50] expanded on the utility of the ketimines by reducing them with sodium cyanoborohydride to give secondary amines. Condensation of a secondary amine with excess formaldehyde or other aldehydes in the presence of excess sodium cyanoborohydride gave *N*-(diphenylmethyl)-*N*-methylamino esters that were hydrogenolyzed over palladium catalyst to afford the *N*-methylamino acid esters. In this way, tryptophan was monoalkylated without competing Pictet−Spengler cyclization, nor was there any mention of methylation occurring at the indole nitrogen.[50] This procedure was applied to alanine, serine, threonine, leucine, and tryptophan and is closely related to the approach of Quitt et al.[21] Kaljuste and Undén[69] reported a novel small-scale approach to *N*-methylation via reductive alkylation on solid phase, effecting the mono-*N*-methylation of resin bound terminal amino acid residues. The authors describe the need for a readily removed *N*-protecting group as a means to prevent dialkylation, and to achieve this, the acid labile 4,4′-dimethoxydiphenylmethyl (4,4′-dimethoxydityl or Dod) group was employed.[70] *N*-Methylation of terminal solid-phase bound amines was performed with formaldehyde, acetic acid, and sodium cyanoborohydride in DMF. This reaction proceeded in yields in the range 56−99% for most common amino acids. Up to three methylation cycles for some amino acids were needed for complete reaction. It was noted that trifunctional amino acids required longer reaction times that could lead to undesirable side reactions. This could be avoided by decreasing reaction time, but consequently, incomplete methylation occurred.

3.5. Borane Reduction

Although the reduction of amides to *N*-alkylamines and amino acids[71−73] diverges from the parent topic title of reductive amination, its inclusion in this section is warranted due to its similarity with borohydride reduction of Schiff base intermediates. Krishnamurthy[72] achieved selective reduction of aniline formamide intermediates with a borane dimethyl sulfide complex (BH_3·SMe_2). A minimum of 2 equiv is required for the reduction, where 1 equiv is involved in the reduction and the other equivalent is involved in complexation with the *N*-methylamine derivative formed. The two-step process provided high purity *N*-methylanilides in 80−100% yield.

Chu and co-workers[74] exploited the strategy of Krishnamurthy[72] in the reduction of *N*-formyl-D-tryptophan methyl ester with a borane dimethyl sulfide complex. The reduction provided, after workup, *N*-methyl-D-tryptophan methyl ester in 56% yield.

Hall et al.[75] reduced amides in solution and on solid support with diborane. Iodine was employed in the reduction to promote oxidative cleavage of the borane−amine adducts. In this fashion, amino acid formates coupled to Wang resin were reduced with diborane in >72% yield and >75% purity for alanine, valine, serine, and phenylalanine.

Reductive amination is a very mild and racemization free process. Quitt's method[21] of reductive amination involving *N*-benzylamino acids is, to date, one of the recommended methods for the synthesis of NMAs and has been used frequently for comparison of physicochemical data. Amino acids such as lysine, serine, and arginine are readily *N*-methylated by this method. A similar approach, adopting sodium cyanoborohydride reduction of *N*-(diphenylmethyl)-amino acid ester Schiff base intermediates in solution and solid phase as described by Polt et al.[50] and Kaljuste and Undén,[69] respectively, has revealed the efficacy of this approach as applied to a wide variety of amino acids, albeit on a small scale. Although, in principle, this technique is similar to Quitt's method, there are more manipulations involved and the carboxyl terminus must be blocked. Another drawback is the excessive amounts of formaldehyde and sodium cyanoborohydride required for complete reaction that further limit this procedure to small-scale synthesis.

Reductive amination involving transition metal hydrogenolysis is somewhat limited to dimethylation with formaldehyde, but monoalkylation with aldehydes other than formaldehyde is possible.[55−57] Even though there has been a case of selective monoalkylation of *threo* type threonines,[60] this selectivity is not conferred on other amino acids.

One seldom reported technique is the reduction of *N*-formylamino acids. This approach is an obvious one, since formylation of amino acids is readily achieved and, therefore, concerns of dialkylation and the need for multistep syntheses are eradicated. The only problem is the carboxyl group needs to be protected, since the use of borane can reduce acids to alcohols, and other amide groups present may also be reduced.

4. N-Methylation by Novel Methods

The following section is a collection of novel and sometimes-elaborate methods for *N*-methylamino acid synthesis. See Table 3 for a summary of these methods. Although some of the methods employ aspects of previous sections for installing the *N*-methyl moiety, techniques were devised to prepare especially unusual NMAs required for natural product synthesis and other studies. The techniques devised for unusual NMA syntheses in most cases catered for particular NMA derivatives and are often not applicable to all or even some other amino acids.

4.1. 5-Oxazolidinones

Ben-Ishai[76] noted that, when combining *N*-Cbz-amino acids with paraformaldehyde under acid catalysis, the reaction assumes an intramolecular mode and so 5-oxazolidinones **51** are prepared (Scheme 19). The 5-oxazolidinone intermediates are often solid derivatives that resemble *N*-hydroxymethyl amides and display distinct carbonyl stretches in the IR region between 1790 and 1810 cm^{-1}. The 5-oxazolidinone ring is susceptible to nucleophilic attack and is easily opened by amines to form amides.[76,77] Ben-Ishai demonstrated this in the treatment of the 5-oxazolidinone **51c** with 1 equiv of benzylamine to afford the *N*-hydroxymethyl amide **52c**. Hydrogenation then gave an *N*-methylglycine (sarcosine) derivative **53c**. It was noted that the *N*-hydroxymethyl amide **52c** could be treated with 1 equiv of benzylamine that removed the *N*-hydroxymethyl moiety to provide *N*-Cbz-glycine benzylamide. The reduction of 5-oxazolidinones to NMAs was not realized until later with the work of Freidinger et al.[78] (vide infra).

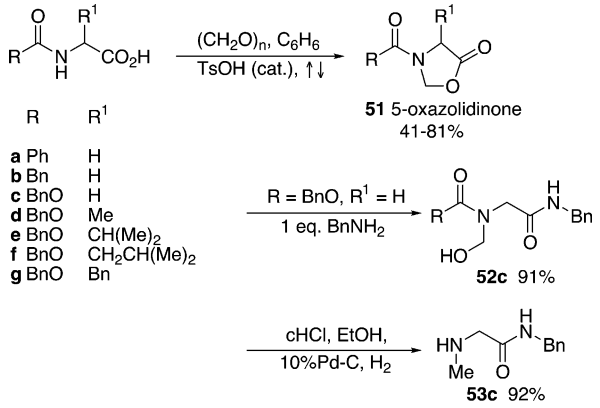
Auerbach et al.[79] set the scene for later contributions when they synthesized *N*-hydroxymethyl (or *N*-methylol) amides analogous to structure **52** from primary and secondary amides. They then demonstrated that the *N*-methyl amide could be generated by treatment with triethylsilane/trifluoroacetic acid in chloroform. They inferred the reduction proceeds by hydride transfer from the silane to an acyliminium ion derived from the *N*-hydroxymethyl amide. Auerbach et al. also describe the palladium catalyzed hydrogenation of *N*-hydroxymethyl amides to *N*-methyl amides in the presence of trifluoroacetic acid.

Several chemists have recognized the efficacy of 5-oxazolidinones, and so improvements have been made to their preparation and utility in conversion to other synthetically useful intermediates. Freidinger et al.[78] extended the range of substrates that can be converted to 5-oxazolidinones through the use of 9-fluorenylmethoxycarbonyl (Fmoc) protected amino acids and alkanals including paraformaldehyde. Using the conditions of Auerbach et al., triethylsilane/trifluoroacetic acid reductive cleavage gave the expected *N*-Fmoc-*N*-methylamino acids and the *N*-alkyl derivatives. This sequence was applied to Fmoc-alanine, valine, methionine, phenylalanine, lysine, serine, and histidine. The lack of racemization in the method was established through NMR analysis of the ^{13}C satellites of the methoxyl signal as internal reference peaks of D- and L-methyl-*N*-Fmoc-*N*-meth-

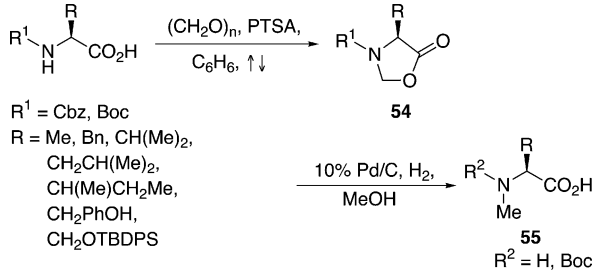
Table 3. Summary of *N*-Methylation by Novel Methods

method	ref	amino acids employed	methylation step yield (%)	comments
(a) 5-oxazolidinones	76, 78, 81, 82, 84	most amino acids	60−100	racemization free technique; utilizes carbamate protection but limited to acid stable protecting groups, as they are removed in the reduction process
(b) asymmetric syntheses	89	Phe	67	an inventive, cheap, and effective synthesis that provided 90% ee after a simple hydrogenolysis
	90	Phe, Ala, Val, Phg		utilizes *N*-benzylsarcosine and L-prolinol to form a chiral auxiliary (de = 93%); side chain installed by treatment with a Grignard reagent
	91, 92	variety of α-alkyl, vinyl, and allyl amino acids		*N*-methylphenylglycinol provides the *N*-methyl group and asymmetric center; the chiral auxiliary thus obtained from condensation with glyoxal and thiophenol provides excellent stereocontrol of the newly formed α-center (>98%) upon treatment with nucleophiles
	93	Ala, Val, Leu, Phe, Asp	64−86	this method, to date, is the only asymmetric synthesis that allows for very unusual and common NMAs to be made with >99% ee
	94	pseudoephedrine dimers		pseudoephedrine-sarcosine dimer is alkylated in >94% de
	95	Leu, Phe, Val, Tyr, Phg, Lys, Ser, di- and tripeptide esters	67−92	regiospecific *N*-methylation using cyclopentadiene and formaldehyde
	96	tertLeu, Tyr, Phg	63−98	optically active azides required; racemization is temp dependent
	98	Val, Phe, Leu, Tyr, Asp	74−95	solid supported *N*-methylation with pinacol chloromethylboronic ester.; peroxide workup required; oxidizable amino acids are incompatible
(c) racemic syntheses	100	N-Me-Dopa		azalactone intermediate in which the *N*-methyl group is provided by creatinine; moderate yields
	101	γ,δ-unsaturated NMAs		palladium catalyzed allylation of an *N*-methylsulfone; completely selective for *E*-stereoisomers
	99	diamino- and guanidino-amino NMAs		*N*-methyl group introduced via *N*-methyl-*N*-benzylamine through an intermediate aldehyde
	102	Ala, Abu, norVal, norLeu, Val, Leu	79−89	racemates were resolved via *N*-acyl-L-proline acylase; enzyme has high substrate specificity
(d) synthesis of natural product	105	*N*-methyl-γ-amino-β-hydroxy acids	69	*N*-methyl group installed with NaH/MeI
derived NMAs	49	*N*-methyl-α-amino-β-hydroxy acids	55−98	regioselective epoxide opening with $MeNH_2$ or MeNCO; also KH/MeI treatment of Boc carbamate

Scheme 19



Scheme 20

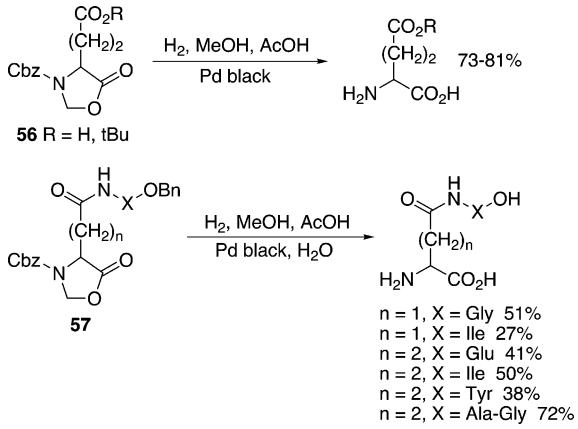


yl-*O*-benzylserinate. Chipens et al.[80] applied the same methodology to the *N*-Cbz-5-oxazolidinones of glycine and phenylalanine and reduced them with triethylsilane/trifluoroacetic acid to the corresponding *N*-methyl derivatives, as did Aurelio et al.[81] (vide infra).

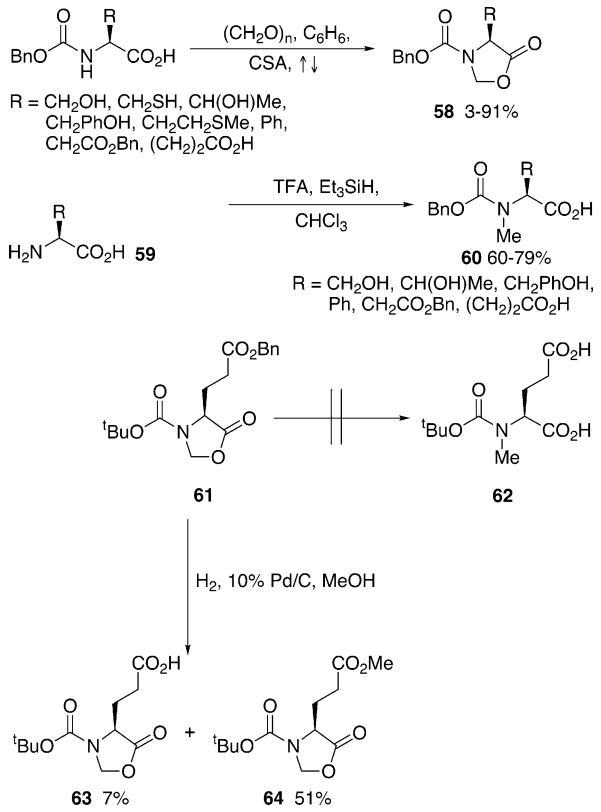
Reddy et al.[82] further extended the technique by preparing 5-oxazolidinones **54** with *N*-Cbz and *N*-Boc protection (Scheme 20) and then converted the *N*-Cbz compounds to NMAs with concomitant removal of the benzyl carbamate by hydrogenation over palladium catalyst. This was the first report of success in the use of hydrogenation of 5-oxazolidinones as a means of producing the *N*-methyl group directly. Reddy et al. also report reducing *N*-Boc-5-oxazolidinones over palladium catalyst to generate *N*-Boc-*N*-methylamino acids **55**. This result, however, seems doubtful given Itoh's theory[77] that the oxazolidinone ring becomes labile by removal of the *N*-protection and the experience of Aurelio et al.[81] In 1969, Itoh[77] studied the chemical conversions of 5-oxazolidinones, in particular, the hydrogenolyses of *N*-Cbz-5-oxazolidinones **56** and **57** (Scheme 21). Interestingly, *N*-methylamino acids were not isolated from these conversions. Instead, the formyl carbon was cleaved entirely from the substrate. Williams and Yuan[83] also observed this result.

Aurelio et al.[81] used the conditions described by Reddy et al.[82] to prepare the *N*-Cbz-5-oxazolidinones **58** of numerous α-amino acids (Scheme 22). Several substrates with reactive side chains were attempted, with varying degrees of success. Threonine and serine, in particular, were prone to oxazolidinine formation by reaction with the side chain hydroxyl, and side chain protection was necessary for 5-oxazolidinone syntheses of α-amino acids with basic side chains in order for the intermediates to form. Other

Scheme 21



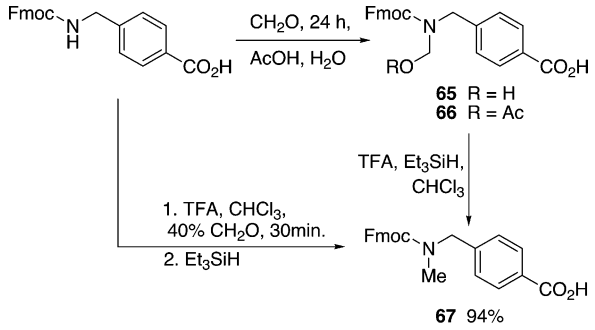
Scheme 22



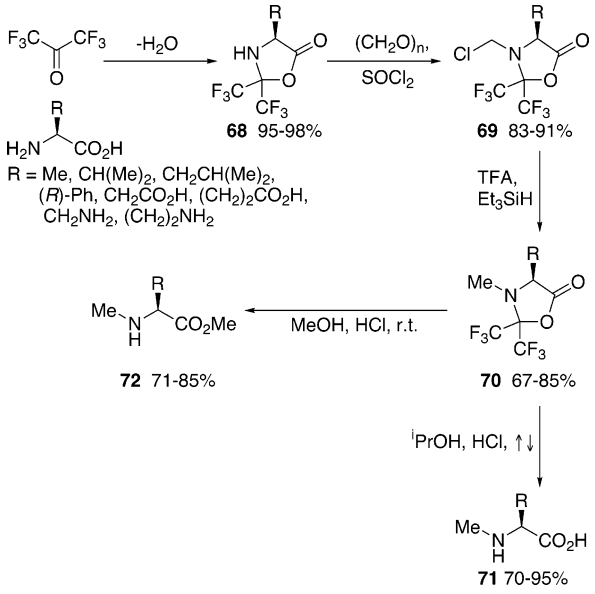
α-amino acids such as tyrosine, glutamic acid, and methionine were converted to the corresponding 5-oxazolidinone. Reduction of several of these substrates by catalytic hydrogenation gave varying amounts of the free α-amino acid **59** in accord with Itoh.[77] The authors resorted to the triethylsilane/trifluoroacetic acid reductive cleavage applied by Freidinger et al.[78] to effect formation of NMAs **60**. Aurelio et al.[81] also attempted the hydrogenolysis of the *N*-Boc-5-oxazolidinone **61** but did not isolate any of the expected NMA **62**. Instead, two products **63** and **64** from reaction of the side chain were recovered.

Luke et al.[84] applied a similar protocol to that of Freidinger for their non-α-amino acid substrates. Isolating the methylol derivatives **65** and **66** resulted in varying degrees of decomposition back to starting material upon workup. For instance, they found treatment of Fmoc *p*-aminomethylbenzoic acid with formaldehyde in acetic acid gave a mixture of compounds **65** and **66** (Scheme 23) which underwent reduction to give the corresponding *N*-Fmoc-*N*-methylamino acids **67**. Yields were in the range 27−100% for various substrates. However, a one-pot process was developed for these non-α-amino acids, which involved exposing the *N*-Fmoc substrate to TFA and 40% formaldehyde solution for 30 min and then treating the intermediate methylol with triethylsilane. This one-pot process eliminated isolation of the methylol intermediate, which causes reversion to the starting material during workup.

Scheme 23



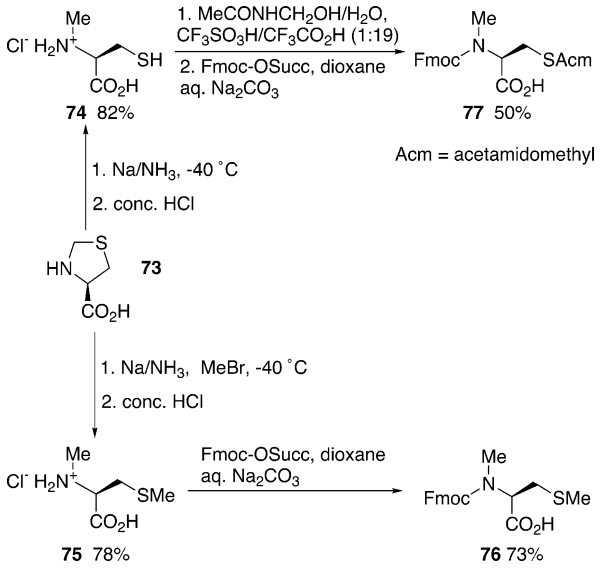
Scheme 24



A variation on the theme was described by Spengler and Burger[85] employing 5-oxazolidinones not as the source of the *N*-methyl carbon but as a means of forming a cyclic aminal **68** (Scheme 24). The 2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-ones were formed by reaction of the α-amino acids with hexafluoroacetone. The product aminals have the carboxylic function removed from the possibility of reaction and have only one nitrogen valence left for reaction, ensuring the mono-*N*-methylamino acid forms. The aminal **68** was chloromethylated, and then the chloromethylaminal **69** was converted to the *N*-methyl-5-oxazolidinone **70** with triethylsilane and trifluoroacetic acid. Finally, acidolysis with 2-propanol or methanol allows for the isolation of either the NMA **71** or the NMA methyl ester **72**, respectively.

Another variation was described by Yamashiro et al.,[86] who utilized the thiazolidine intermediate **73**

Scheme 25



(Scheme 25) in the synthesis of [1-(*N*-methylhemi-L-cystine)]oxytocin by treating cysteine with formaldehyde solution. Sodium in liquid ammonia reduction of the thiazolidine intermediate thus obtained with an equivalent amount of water provides the *N*-methylcysteine, which was treated in the same pot with an equivalent amount of benzyl chloride, providing the *N*-methyl-*S*-benzyl-L-cysteine in 90% yield (the addition of water is crucial in suppressing dimerization).[86] Carbamoylation with CbzCl furnished *N*-Cbz-*S*-benzyl-L-cysteine in 84% yield. Liu et al.[87] employed the same reductive protocol as Yamashiro et al.[86] in synthesizing Fmoc derivatives of *N*-methyl-L-cysteine (Scheme 25). The thiazolidine **73**[88] was reduced in the usual manner to provide *N*-methyl-L-cysteine **74**. In situ treatment with methyl bromide provides the *S*-methyl derivative **75**, which was treated with Fmoc-succinimide to afford *N*-Fmoc-*N*,*S*-dimethyl-L-cysteine **76**. Alternatively, treatment of **74** with *N*-hydroxymethylacetamide and an organic acid provided an *S*-acetamidomethyl intermediate that was converted to the Fmoc derivative **77**.

5-Oxazolidinones, as prepared by Ben-Ishai, offer an advantage over the direct alkylation procedures in that the new N−C bond also ties up the carboxyl group in one step under mildly acidic conditions. This offers simultaneous *N*- and *C*-terminal protection, and thus, side chain manipulations are possible. Further, these stable derivatives are analogous to protected *N*-hydroxymethyl amides that are smoothly converted to their *N*-methyl analogues by reduction under acidic conditions. Although the triethylsilane/trifluoroacetic acid combination is the recommended choice for reduction,[81] the expense of these reagents and problems of removing trace amounts of TFA make catalytic hydrogenation a more enticing approach. Even so, this process requires more experimentation, and selective catalysts are required in order to retain the Cbz group.

Reduction of the thiazolidine intermediate in the synthesis of *N*-methylcysteine is probably the most cost-effective and scalable procedure for synthesizing this derivative. The chemical manipulations involved are trivial, and the added advantage is the fact that regioselective alkylation of the thiol group enables a variety of cysteine derivatives to be synthesized.

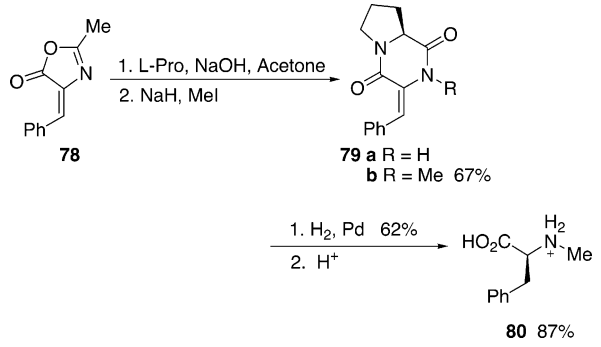
4.2. Asymmetric Syntheses

Few authors have built NMAs in a way that requires the α-center be created. The following section involves diverse methodologies that incorporate chiral auxiliaries that confer the required asymmetry on the α-carbon under construction.

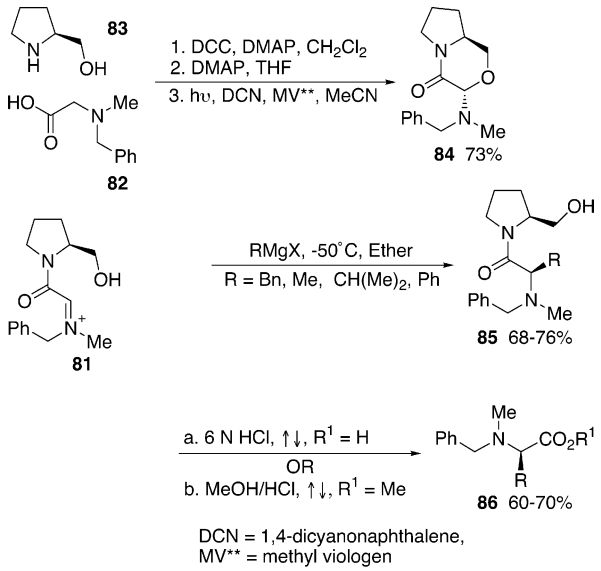
One of the earliest reports of an asymmetric synthesis of NMAs was reported by Poisel and Schmidt.[89] They exploited proline as an auxiliary in the asymmetric synthesis of amino acid derivatives (Scheme 26). The azlactone **78** prepared from *N*-acetylglycine and benzaldehyde was treated with L-proline under basic conditions to form an arylidenedioxopiperazine **79a**. Methylation with sodium hydride/methyl iodide provided the chiral piperazine **79b**. Simple hydrogenation conditions using palladium metal provided *N*-methyl-L-phenylalanine-L-proline diketopiperazine in 90% ee, which was cleaved under acidic hydrolysis, affording the free *N*-methylphenylalanine **80**.

Pandey et al.[90] utilized a sarcosine derived chiral precursor based on a recyclable L-prolinol auxiliary as a masked iminium ion equivalent **81** (Scheme 27). *N*-Benzylsarcosine **82** and L-prolinol **83** were con-

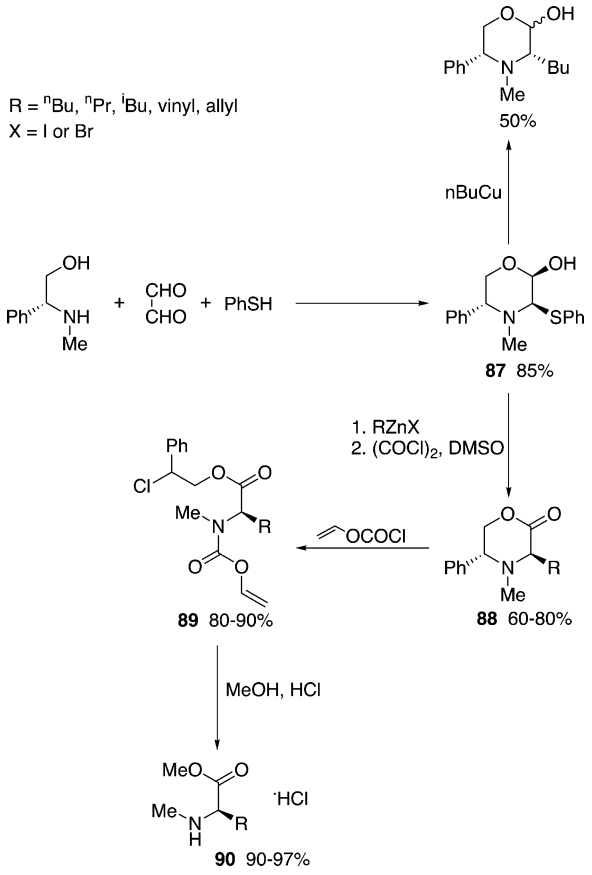
Scheme 26



Scheme 27



Scheme 28

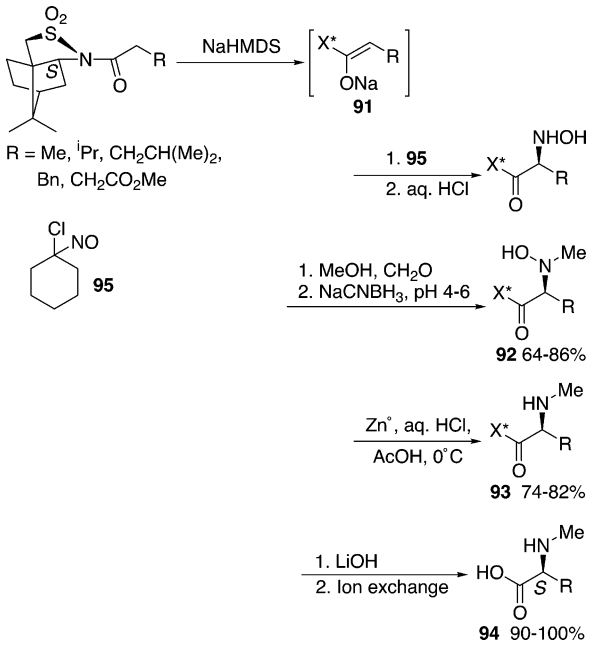


densed to form the chiral auxiliary **84** (de = 93%), and this was then treated with Grignard reagents to yield *N*-methylamino acid-L-prolinol dipeptides **85** with good stereoselectivity. Hydrolysis of the dipeptides **85** with either aqueous HCl or methanolic HCl provided the corresponding *N*-benzyl-*N*-methylamino acids or esters **86**, respectively, and L-prolinol **83**, which was recycled (96% recovery).

Agami et al.[91,92] have devised an elaborate method for construction of NMAs using the "*asymmetric derivatization of glycine cation equivalents*" to construct various NMAs (Scheme 28). The first step involves a three-component condensation between *N*-methyl-D-phenylglycinol, glyoxal, and thiophenol to make the chiral morpholine **87**.[91] This intermediate can then be treated with an organozinc reagent (giving retention of configuration) or cuprate reagent (giving inversion of configuration) in a stereocomplementary fashion to generate the required α-center with excellent control (>98% in most cases). The hemiacetal was oxidized with activated DMSO to afford the lactone **88** (60−80%), which can be completely epimerized at the newly created stereocenter with potassium *tert*-butoxide at 40 °C to give the more stable cis epimer. Release of the target NMA was achieved by treatment with vinyl chloroformate to give the acyclic carbamate **89** (80−90%). Methanolic hydrochloric acid then cleaves the carbamate from the nitrogen, and acid catalyzed methanolysis converts the chlorophenethyl ester to the corresponding methyl ester **90** (90%).

Oppolzer and co-workers[93] have a long and distinguished record of stereoselective transformations

Scheme 29

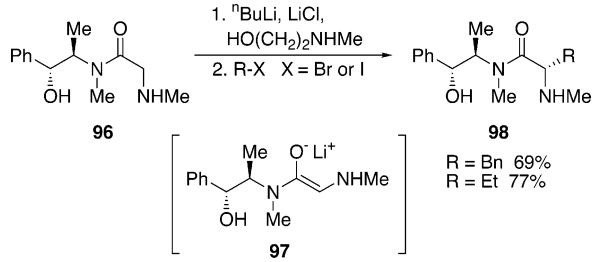


with camphorsultams and have used the π-face selective hydroxyamination of the camphorsultam enolate **91** to construct the α-amino acid skeleton as a hydroxylamine **92** (Scheme 29). The hydroxyamination was highly stereoselective, and the crystalline hydroxyamino products had enantiomeric excesses > 99%. Reductive alkylation of the hydroxylamine in methanolic formaldehyde with sodium cyanoborohydride followed by *N*,*O*-hydrogenolysis with zinc dust afforded the (*N*-alkylamino)acylsultam **93**. The chiral sultam auxiliary was then cleaved by base hydrolysis to give the NMA **94**. The advantages of this multistep sequence are twofold: First, by the simple expedient of changing the camphorsultam auxiliary to the other enantiomer, preparation of the *R*-configured *N*-alkyl-α-amino acid is allowed equally efficiently. And second, the acyl function that was first appended to the auxiliary comprises the side chain of the final α-amino acid, and so modified α-amino acids can be constructed with extreme structural variation. This last point demonstrates the versatility of the camphorsultam auxiliary, which has the potential to be applied in the development of *N*-methylamino acid libraries with high structural diversity.

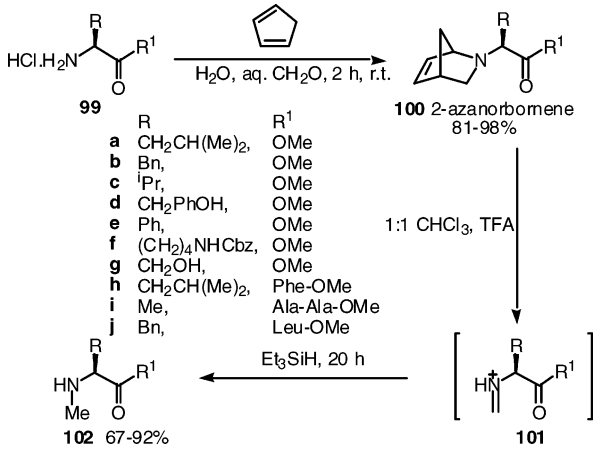
Myers et al.[94] have made use of pseudoephedrine as a chiral auxiliary in the asymmetric synthesis of amino acids and *N*-methylamino acids. (*R*,*R*)-Pseudoephedrine was coupled to sarcosine to provide pseudoephedrine sarcosinamide **96** (Scheme 30). Treatment with *n*-butyllithium produced the enolate **97,** which was quenched with an alkyl halide to provide the *N*-methylamino acid pseudoephedrine dimer **98**, with excellent stereocontrol. Where R = Bn, the alkylation product **98** (*N*-methylphenylalanine) was isolated in 93% yield and 88% de in the crude state. Recrystallization afforded product **98** in 69% yield and 99% de. Where R = Et, **98** was isolated in 77% yield and 94% de after purification.

An inventive approach to *N*-methylation of α-amino acids involves the trapping of an iminium intermediate as a cycloadduct. Cycloreversion in the presence

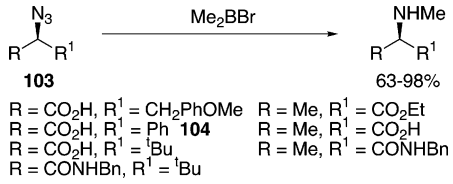
Scheme 30



Scheme 31



Scheme 32

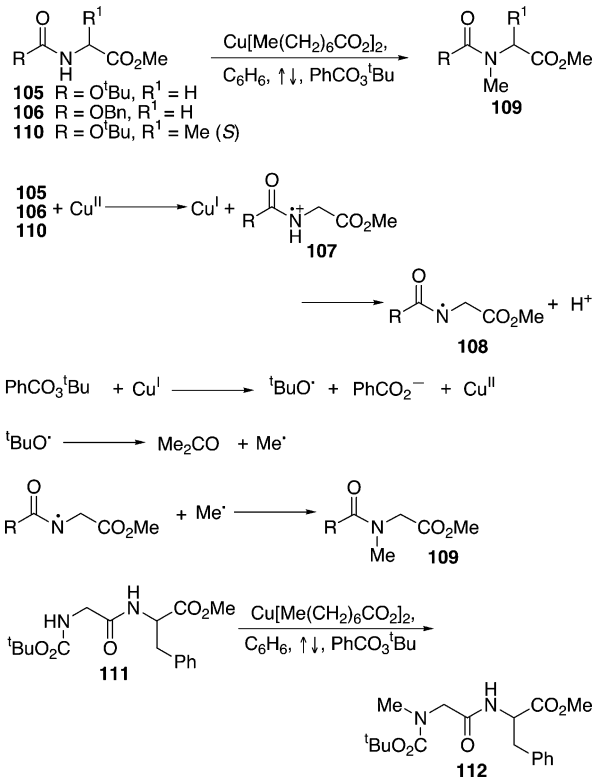


of a reducing agent then furnishes the NMA. Thus, Grieco and Bahsas[95] treated various methyl ester hydrochlorides **99** with aqueous formaldehyde in the presence of excess cyclopentadiene to give 2-azanorbornenes **100** via aza-Diels–Alder reaction (Scheme 31). Trifluoroacetic acid catalyzed the retro-aza-Diels–Alder reaction to generate the iminium ion **101** that first participated in formation of the 2-azanorbornene. In the presence of triethylsilane, the iminium ion was reduced to the NMA methyl ester **102**.

Dorow and Gingrich[96] sought to solve several problems associated with the production of *N*-methyl-α-amino acids via the reductive alkylation of optically active scalemic azides **103** (Scheme 32). The susceptibility of the sequence to epimerization was tested through application to 2-azidophenylacetic acid **104** (99% ee), which was prone to racemization. Treatment of **104** with dimethylbromoborane at 40 °C gave the product in 68% yield and 38% ee. When the same conditions were applied to **104** at 20 °C, (*S*)-*N*-methylphenylglycine was obtained in 99% yield, yet the enantiomeric excess was not divulged. This temperature dependence was attributed to the possibility of enolization of the α-center at higher temperature, and therefore, the lower temperatures excluded the enolization pathway providing optically active NMAs.

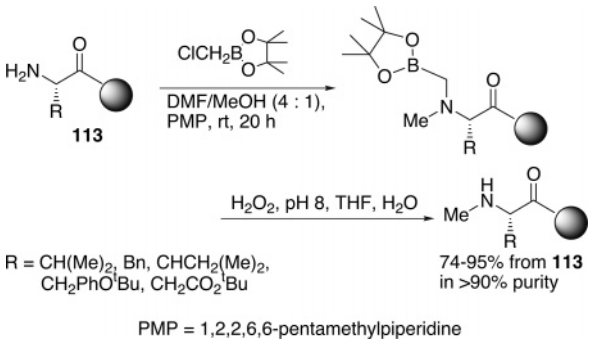
Radical based chemistry is one approach that has found limited use in NMA synthesis. The inapplicability of radicals for synthesizing a range of NMA intermediates was described by Easton et al.[97] They noted that "*copper-catalyzed reactions of peresters with organic substrates are often used for introduction of the acyloxy functional group*". When this reaction was conducted with *tert*-butyl **105** and benzyl carbamates **106** of glycine, the only product isolated was the corresponding *N*-methyl compound in moderate yield (Scheme 33). The authors rationalize this result as shown in Scheme 33. Copper(II) reacts with the substrate carbamate to form a radical cation **107** that loses a proton to give a carbamate radical **108** and Cu(I). Reaction of *tert*-butyl perbenzoate with copper(I) generates copper(II) and a *tert*-butoxy radical. The *tert*-butoxy radical undergoes β-scission to generate a methyl radical that is responsible for *N*-methylation. The methyl and carbamate radicals then combine to give the NMA **109**. The process was shown to be free of racemization by conducting the reaction of copper(II) octanoate and *tert*-butyl perbenzoate with (*S*)-*N*-Boc-alanine **110**. NMR spectroscopy with a chiral shift reagent and comparison with an authentic sample revealed that no racemization had occurred. The reaction, however, had limitations. Use of a valine carbamate resulted in no reaction. The preference for the substrate carbamate functions to participate in this electron-transfer reaction was demonstrated by the conversion of the dipeptide **111** to the *N*-methyl dipeptide **112**, in which the internal acyl nitrogen did not undergo any *N*-methylation.

Scheme 33



Laplante and Hall[98] have devised an ingenious solid supported *N*-methylation with pinacol chloromethylboronic ester (Scheme 34). The process is based on Matteson's 1,2-carbon-to-nitrogen migration of boron in α-aminoalkylboronic esters. This is basically the only procedure in which monomethylation

Scheme 34



of an *N*-unprotected amino acid is achieved in high yields with relative ease. The free amine **113** was bound to either Wang resin or the highly acid sensitive SASRIN (4-hydroxymethyl-3-methoxyphenoxybutyric acid benzhydrylamide) resin and was treated with an excess of boronic ester (5 equiv) to achieve dialkylation followed by cleavage with hydrogen peroxide in pH 8 buffered solution. The peroxide treatment was designated as a "*repair mechanism*" that removes overalkylated sites. The dialkylation/peroxide process revealed, after analysis of the crude cleaved products of *N*-methyl derivatives, >90% purity for valine, phenylalanine, leucine, tyrosine, and aspartic acid, whereas use of the boronic ester as a limiting reagent always resulted in varying degrees of alkylation. The procedure has limitations in that amino acids that are sensitive to oxidation are not suitable candidates. Methionine was found to be incompatible with the *N*-methylation conditions.

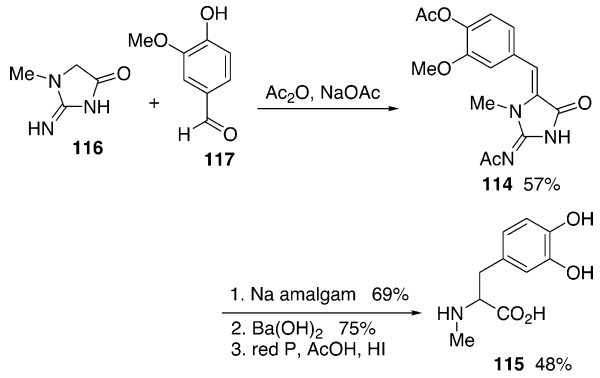
4.3. Racemic Syntheses

The focus of the review until now has been the application of "chirally friendly" methodology that reduces or eliminates racemization when synthesizing NMAs. It is obvious that the majority of authors realized the propensity of NMAs to racemize and therefore developed conditions to eradicate the effect. Racemic amino acids are rarely employed in natural product synthesis but have been evaluated as potential therapeutics.[99] The disadvantage of racemic mixtures is the resolution process that follows if single enantiomers are required. Yet one advantage of racemic substrates is that conditions which usually racemize amino acids and, in particular, NMAs are compatible with racemic syntheses.

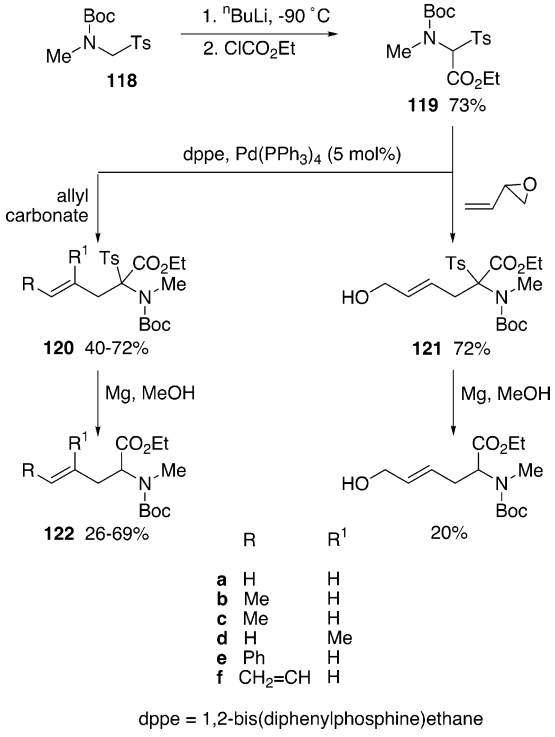
Guerrero et al.[100] employed the azlactone intermediate **114** in the synthesis of *N*-methyl-Dopa **115** (Scheme 35). Creatinine **116** and vanillin **117** were condensed in acetic anhydride and fused sodium acetate to provide the azlactone **114** with the *N*-methyl group made available from creatinine. The double bond was reduced in symmetrical fashion with sodium amalgam with concomitant removal of the *O*-acetyl group. Base hydrolysis removed the formamidine moiety, and red phosphorus reduction provided racemic *N*-methyl-Dopa **115**.

Alonso et al.[101] applied the sulfone **118** in the synthesis of racemic unsaturated *N*-methylamino acids (Scheme 36). Lithiation of the sulfone **118** followed by reaction with ethyl chloroformate pro-

Scheme 35



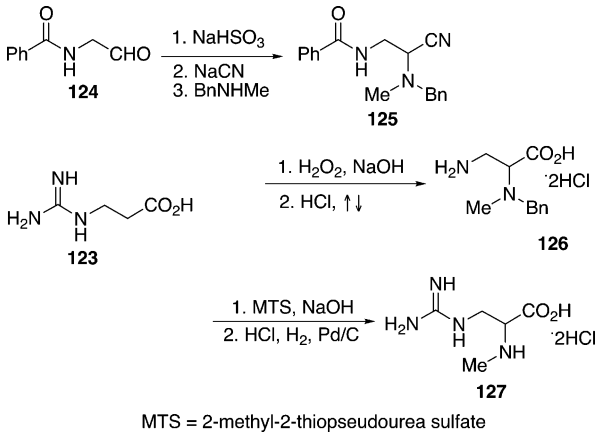
Scheme 36



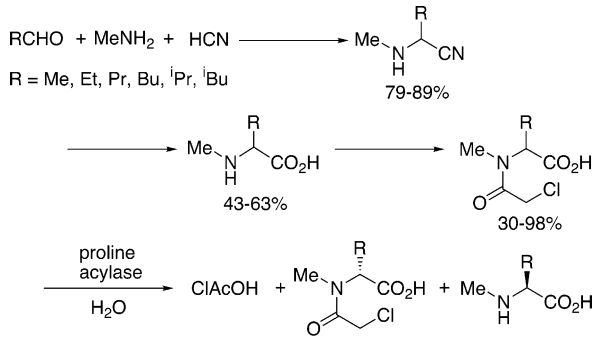
vides α-tosyl-*N*-Boc-sarcosine ethyl ester **119**. Nucleophilic substitution via palladium catalyzed allylation with allyl carbonates or epoxide affords α-tosyl-γ,δ-unsaturated-*N*-methylamino acids **120** and **121**, under neutral conditions. The sulfone derivatives **120** and **121** were found to be very unstable and were immediately treated with magnesium powder in methanol to effect desulfonylation at room temperature. The nucleophilic substitution was highly regioselective and completely stereoselective for compounds **122b**, **c**, **e**, and **f**, affording only the *E*-stereoisomers.

Larsen et al.[99] have synthesized novel aminoguanidinoacetic acids based on analogues of the antidiabetic/antiobesity agent, 3-guanidinopropionic acid **123** (Scheme 37). The aldehyde **124** was converted to the aminonitrile **125** in three steps and was then hydrolyzed to the carboxylic acid **126**. The carboxylic acid **126** was amidinated with 2-methyl-2-thiopseudourea sulfate (MTS) and debenzylated under hydrogenating conditions to provide the *N*-methyl analogue **127** as a racemate.

Scheme 37



Scheme 38



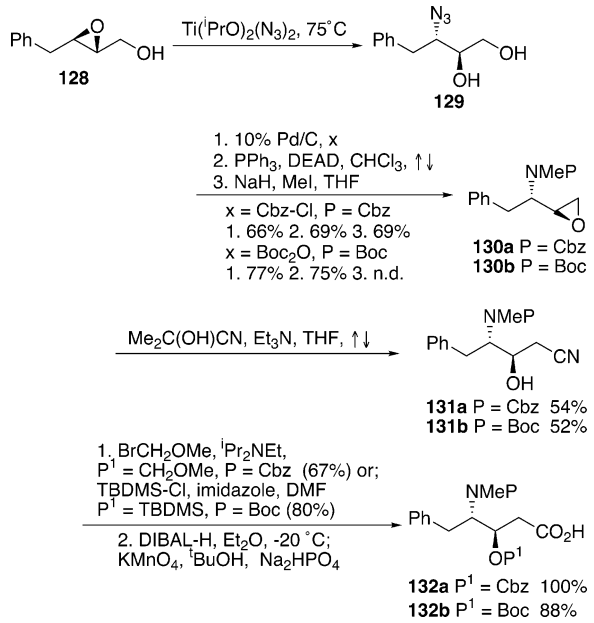
Given the propensity for NMAs to racemize, as proven by Benoiton et al.,[31−33] the application by Groeger et al.[102] of an acylase to the resolution of racemic *N*-acyl NMAs was particularly useful. Synthesis of the racemic NMAs was performed in a combinatorial fashion (Scheme 38), and the NMAs were then chloroacetylated. The new *N*-acyl-L-proline-acylase was then used in reactions to release the *S*-configured NMA. The enzyme suffers from a high level of substrate specificity in that α-substituents greater than two carbons long or branched caused a complete loss of activity.

4.4. Synthesis of Natural Product Derived *N*-Methylamino Acids

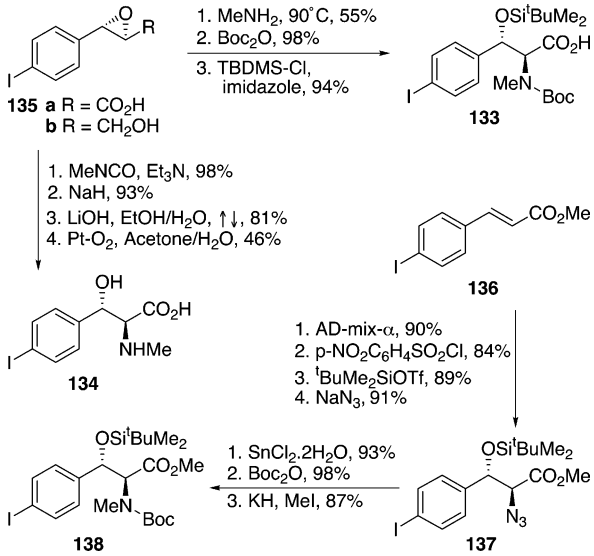
This section entails custom synthesis of NMAs that are found in natural products. *N*-Methylated α- and γ-amino-β-hydroxy amino acids are constituents of larger peptidic molecules, and as with the MeBmt residue (vide infra), devoted syntheses of these important molecules have been devised.[103,104]

N-Methyl-γ-amino-β-hydroxy acids are found in some biologically active depsipeptides such as Hapolosin[103] and Dolastatin 10,[104] and Catass et al.[105] have developed a stereo- and regioselective nucleophilic opening of the oxirane ring of the chiral epoxy alcohol **128** (Scheme 39) as a starting point for these compounds. The resultant azido diol **129** was reduced to the amine and carbamoylated. Sodium hydride/methyl iodide served to install the *N*-methyl group, and Mitsunobu conditions gave the epoxide **130**. Cyanide ion then effected ring opening to afford the hydroxy nitrile derivative **131**, and protection of the

Scheme 39



Scheme 40



hydroxyl functionality followed by oxidative hydrolysis of the nitrile provides the *N*-methyl-γ-amino-β-hydroxy acid **132**, ready for coupling via the carboxyl terminus.

Boger et al.[49] used a similar approach to that of Catass in synthesizing *N*-methyl-α-amino-β-hydroxy acids **133** and **134** (Scheme 40) as intermediates in the synthesis of the antitumor, antibiotic Bouvardin. The epoxide **135** was employed in two different pathways: First, treating **135a** with methylamine caused a regioselective nucleophilic ring opening of the epoxide. Global protection of the intermediate, *N*-methyl-α-amino-β-hydroxy acid, and base hydrolysis with potassium carbonate of the preformed silyl ester provided the free acid **133** ready for coupling. A second approach utilized the epoxy alcohol **135b** that was treated with methyl isocyanate to provide an intermediate *N*-methylamino carbamate that was treated with sodium hydride. The sodium hydride effects cyclization to a mixture of two isomeric oxazolidinones that both contain appropriate stereo-

chemistry for synthesizing **134**. These oxazolidinones were not separated but were subjected to base hydrolysis, followed by oxidation with platinum catalyst to afford the *N*-methyl-α-amino-*β*-hydroxy acid **134**.

The last method by Boger et al.[49] exploited the α,*β*-unsaturated ester **136**. The ester **136** was converted to a diol by the Sharpless asymmetric dihydroxylation with AD-mix-α to provide the (2*R*,3*S*)-derivative in >95% ee. Selective sulfonylation provided an α-sulfonate, and silylation of the *β*-hydroxyl provided a globally protected intermediate that was treated with sodium azide. Azide anion displaced the sulfonate in S_N2 fashion to provide the azide **137** with appropriate 2*S*,3*S* stereochemistry. Reduction of the azide to the amine and protection with Boc anhydride furnished the amino acid carbamate that was treated with potassium hydride/methyl iodide to provide the fully protected *N*-methyl-α-amino-*β*-hydroxy acid **138**. The authors noted that if sodium hydride was used in the methylation step, only starting material was recovered upon workup and that switching to potassium hydride provided the required *N*-methyl moiety in 87% yield.

5. Synthesis of the Cyclosporin Residue, MeBmt 139

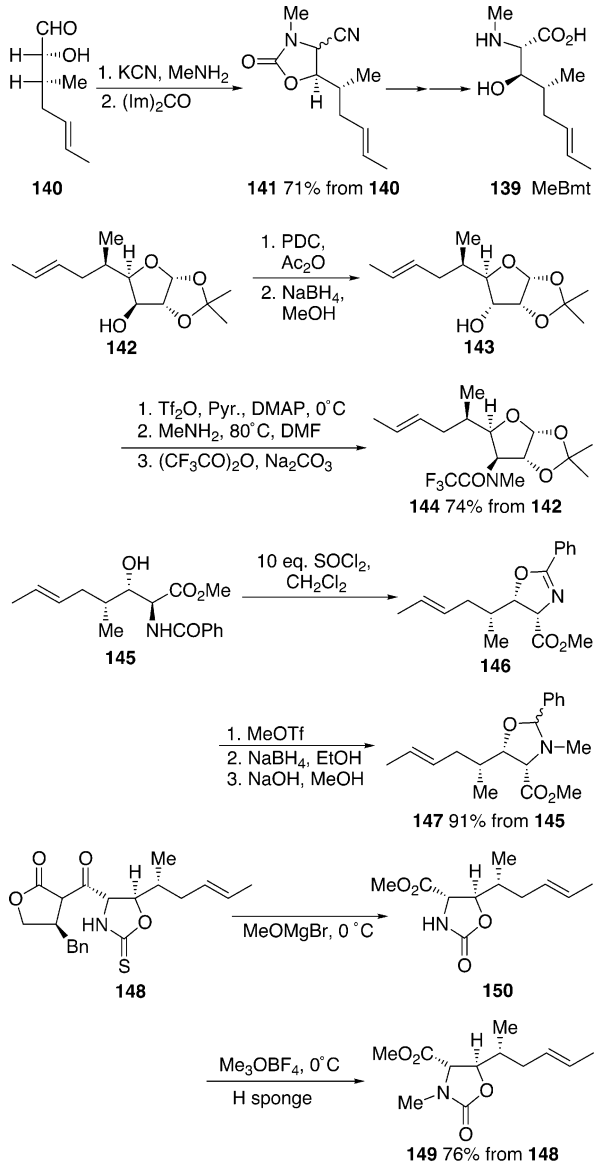
Though the C9 MeBmt residue **139** of cyclosporin constitutes a single, albeit modified NMA, its critical importance to the bioactivity of cyclosporin has meant a body of synthetic literature has grown around its synthesis. In the course of these syntheses, several methods for achieving *N*-methylation not seen in other NMA preparations have been devised. Thus, a section devoted to this residue is of consequence to a discussion of the synthesis of NMAs.

A review of the synthesis of this important NMA has been published by Durand and Genêt[15] and covers the literature up to 1994. Some of the reactions summarized in the following schemes have been reviewed by Durand and Genêt[15] and are included here to emphasize preparations that exploit novel methods or reagents for incorporating the *N*-methyl functionality.

Wenger[106] in the original preparation of MeBmt **139** from diethyl tartrate took the aldehyde **140** (Scheme 41) and performed an aminocyanation using methylamine, which served to install the *N*-methyl group. Subsequent treatment of the products with carbonyldiimidazole gave the diastereomeric oxazolidinones **141**. Other authors have also performed aminocyanation of aldehydes based on Wenger's approach. Ogorodniichuk et al.[107] used a similar aminocyanation on an aldehyde derived from a dithiane in their carbohydrate based approach to MeBmt. Lee et al.[108] sought to improve the carbohydrate based approach to MeBmt by commencing their synthesis with 2-deoxy-D-ribose.

Rao et al.[109] engaged the glucose-derived chiral precursor **142** in the synthesis of MeBmt. First oxidizing the alcohol **142** and then stereoselectively reducing the oxidized product provided the inverted alcohol **143**. Nucleophilic displacement of a triflate formed from the alcohol with methylamine in S_N2 fashion provided the *N*-methyl moiety with the correct configuration **144**.

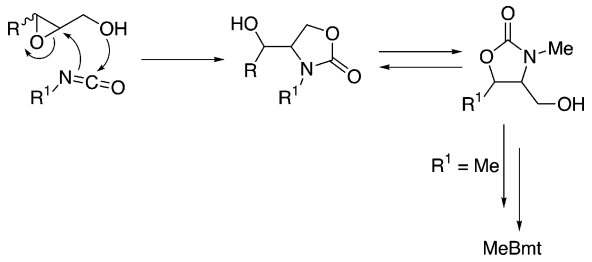
Scheme 41



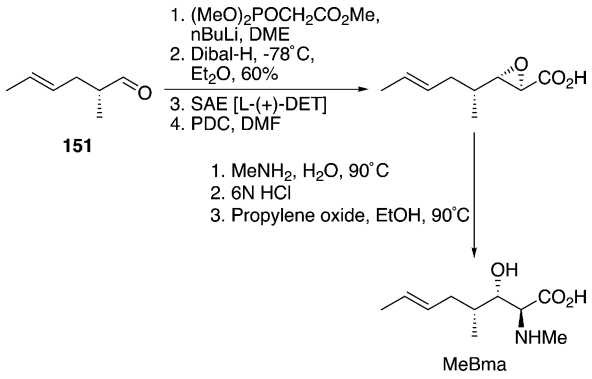
Schmidt and Siegel[110] treated the benzamide **145** with excess thionyl chloride to obtain the cyclic imine **146** (Scheme 41). The imino nitrogen was then quaternized with methyl triflate to give the *N*-methyliminium species, which was non-stereoselectively reduced with borohydride to give the *N*-methyloxazolidinine **147**. These conversions were very efficient, giving the oxazolidinine **147** in 91% yield from the benzamide **145**. Similarly, Ito et al.[111] used trimethyloxonium tetrafluoroborate to *N*-methylate an oxazoline-like compound **147**.

A number of syntheses have employed Evan's auxiliaries in approaches to MeBmt. Evans and Weber[112] used a chiral aldolization to prepare the adduct **148**. Transesterification of adduct **148** with methoxymagnesium bromide was followed by *N*-methylation with trimethyloxonium tetrafluoroborate to give the *N*-methyloxazolidinone **149** in 76% yield from **148**. A further variation on this chemistry by Evans et al.[113] that allows the synthesis of a MeBmt analogue (MeBma **151**) uses methyl isocyanate as the

Scheme 42



Scheme 43

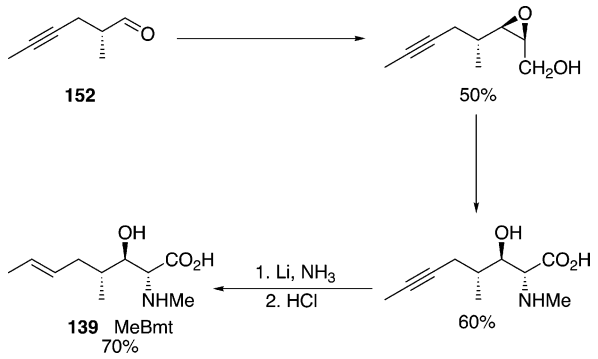


source of the *N*-methyl group. Seebach et al.[114] achieved *N*-methylation of an oxazolidinone intermediate like structure **150** with excess methyl iodide/silver oxide in DMF.

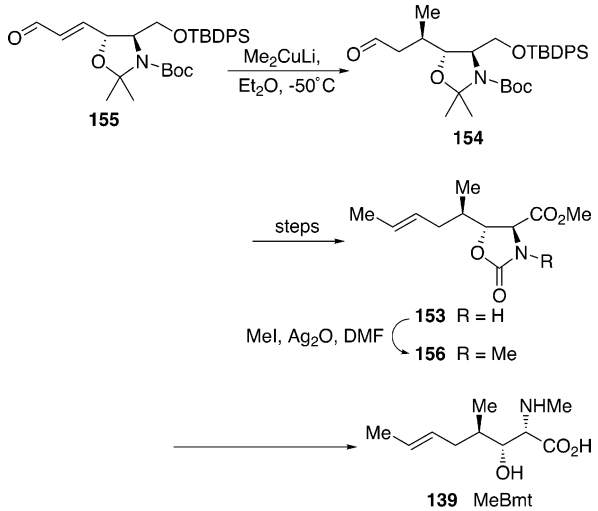
Roush and Adam[115] described the epoxyurethane rearrangement of epoxyalcohols and isocyanates to construct oxazolidinones (Scheme 42), and Rich et al.[116] and Rama-Rao et al.[117] applied this reaction employing methyl isocyanate to MeBmt syntheses.

Genêt[118,119a] installed the *N*-methyl function of MeBmt by the regiospecific nucleophilic opening of an epoxide with methylamine (Scheme 43). Thus, the aldehyde **151** underwent a Horner−Emmons chain extension. The ester was reduced to the allylic alcohol, which was a substrate for a Sharpless asymmetric epoxidation (SAE). The alcohol was oxidized to the epoxy acid, and finally, methylamine provided the *N*-methyl group via nucleophilic epoxide opening.

Scheme 44



Scheme 45



Genêt et al.[119b] also cite a *Z*-selective variation of the Horner−Emmons reaction of the aldehyde **152**, which allowed the synthesis of MeBmt **139** according to the previous scheme. The MeBmt synthesis was accompanied by some synthetic variations to prepare the *Z*-allylic alcohol for the SAE and to deal with the alkyne (Scheme 44).

Tuch et al.[120] prepared *E*-**153** and the *Z*-isomer of the oxazolidinine **154** derived from the enal **155** by an asymmetric 1,4-addition (Scheme 45) which generated the last of the three chiral centers for MeBmt.

Table 4. Reference List of Papers Dealing with Specific Aspects of Certain NMAs

NMA	ref no.
MeAla	17, 18, 21, 24−26, 30, 35, 38, 39, 41, 44, 46, 50, 55, 58, 60, 61, 63, 69, 75, 78, 81, 82, 85, 90, 93, 94, 102
MeArg	20, 21, 61, 69, 81
MeAsn	69, 81
MeAsp	34, 39, 55, 61, 69, 81, 85
MeCys	69, 81, 86, 87
MeGln	69, 81
MeGlu	34, 42, 55, 61, 69, 81, 85
MeGly	44, 58, 76, 80, 81, 85
MeHis	69, 78, 81
MeIle	30, 34, 35, 41, 44, 46, 60−62, 69, 81, 82
MeLeu	17, 18, 21, 26, 30, 34, 35, 42, 44, 46, 47, 55, 58, 61, 69, 81, 82, 85, 93−95, 102
MeLys	21, 35, 38, 39, 59−61, 69, 78, 81, 95
MeMet	20, 44, 60, 69, 78, 81
MePhe	17, 18, 21, 28, 30, 38, 39, 41, 42, 44, 47, 48, 55, 58, 61, 66, 69, 75, 78, 80−82, 89, 90, 93−95
MePro	60, 81
MeSer	20, 21, 30, 39, 42, 50, 60, 61, 69, 75, 78, 81, 82, 93, 95
MeThr	20, 30, 50, 60, 61, 69, 81
MeTrp	39, 50, 60, 64, 69, 74, 81
MeTyr	17, 19, 30, 46, 55, 58, 61, 69, 81, 82, 96
MeVal	20, 21, 25, 26, 28, 30, 34, 35, 39, 41, 42, 44, 48, 55, 56, 58, 60−62, 66, 69, 75, 78, 81, 82, 85, 90, 93, 95, 98, 102

Further transformations formed the oxazolidinone **156**. *N*-Methylation was achieved in 86% yield using the methyl iodide/silver oxide method. Deprotection of the oxazolidinone and the methyl ester allowed formation of MeBmt **139** or 6*Z*-MeBmt if the *Z*-isomer of **153** was used.

6. Future Directions

It is obvious from the material reviewed that the methods for installing the *N*-methyl moiety in the full range of amino acids are challenging. Generally, in the more simple methods only aliphatic amino acids were employed. The seminal work of Benoiton et al.[30−33] revealed the propensity of *N*-methylamino acids to racemize under basic and acidic conditions, and this has set the standard for synthetic chemists to devise mild reaction conditions when producing these intermediates. The development of 5-oxazolidinones (Ben-Ishai) and their reductive cleavage to the corresponding *N*-methyl derivatives (Freidinger et al.) have provided a mild and racemization free route to optically pure *N*-methylamino acids. This methodology has been extended to the 20 naturally occurring amino acids.[81] The utilization of carbamate protection with these sequences offers the advantage that the *N*-methyl derivatives are ready for coupling via solid or solution phase synthesis, chiefly for peptide applications.

For those readers seeking direct access to discussion on specific *N*-methylamino acids, Table 4 tabulates selected references in this review according, primarily, to the specific NMAs.

At the present time synthetic routes to all natural NMAs have been described; however, extensive use of NMAs as building blocks for modified peptides has not been developed because a range of protected NMAs are not available. If such building blocks were more widely commercially available, there would be an exponential growth in the use of these compounds in peptide synthesis as well as in development of associated technologies including coupling reactions, ring formation, and side-chain manipulation.

7. References

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