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 peptidal 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 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 pD2 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.

Payne7 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
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.

Andrew Hughes was born in 1963 in Albany, Western Australia. He received his Ph.D. in 1989 under the supervision of Professor Melvyn Sargent at the University of Western Australia. He was a postdoctoral research associate at Cambridge University Chemical Laboratories (1989–1991) with Professor Andrew Holmes and then Shell Research Fellow at Robinson College, Cambridge, with Professor Holmes (1991–1992) and Professor Steven Ley (1993). He then returned to Australia to take up a position as Lecturer at La Trobe University, Melbourne. He became Senior Lecturer in 1999.

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 SN2 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, (2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt), has attracted the attention of this residue in the activity of cyclosporin A.

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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, who took a number of N-alkyl benzencesulfonamides 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.

The pioneering work of Emil Fischer and co-workers 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 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. 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. They describe the synthesis of N-methyl-D-tyrosine (D-surinamine) via nucleophilic substitution of intermediate α-bromo acids, and a separate paper concerns the synthesis of N-methylhydroxyamino acids in which a combination of Fischer’s methods was applied. The other publications 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). 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). The reaction proceeds with retention of configuration, and this outcome has been rationalized as a “Walden inversion.” The intermediate diazonium ion is attacked intramolecularly, in S2 fashion, by the neighboring carboxylate group to form the labile three-membered lactone. Nucleophilic addition, again in S2 mode, by bromide ion provides the optically active α-bromo acids with net retention of the original amino acid chirality.

Izumiya and Nagamatsu prepared N-methyl-D-tyrosine (D-surinamine) in this fashion by diazotization of O-methyl-D-tyrosine to give the optically active α-bromo acid (Scheme 2). Nucleophilic substitution with methylamine at 100 °C in a sealed tube provided N-methyl-D-tyrosine. Izumiya extended this methodology to other amino acids, such as methionine, arginine, and ornithine, in synthesizing their corresponding N-methyl derivatives.
As described, Izumiya made use of a combination of both of the above methods developed by Fischer to prepare NMAs. The focus was on the preparation of hydroxyamino acids. Thus, in the preparation 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 (6). 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

Table 1. Summary of N-Methylation by Alkylation

<table>
<thead>
<tr>
<th>method</th>
<th>ref</th>
<th>amino acids employed</th>
<th>methylation step yield (%)</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>nucleophilic substitution of α-bromo acids</td>
<td>18</td>
<td>Ala, Leu, Phe</td>
<td>31–71</td>
<td>rarely used technique; low yields and racemization</td>
</tr>
<tr>
<td>(a) triflate displacement</td>
<td>19</td>
<td>Tyr</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>20a,c,e</td>
<td>Ser, Thr, β-OHVal</td>
<td>20–40</td>
<td></td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>24</td>
<td>Ala</td>
<td>96</td>
<td>racemization free S&lt;sub&gt;2&lt;/sub&gt;2 process; opposite enantiomer formed upon displacement</td>
</tr>
<tr>
<td>N-methylation of sulfonamides</td>
<td>17</td>
<td>Ala, Leu, Phe, Tyr</td>
<td>82–100</td>
<td>racemization occurs; vigorous techniques employed</td>
</tr>
<tr>
<td>(a) base mediated alkylation</td>
<td>25, 26</td>
<td>Ala, Val, Leu, Phe</td>
<td>near 100</td>
<td>racemization free process; utilizes detergent to improve phase mixing and removal of unreacted starting material</td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>27</td>
<td>Ser, Phe, Leu, Arg, Asn</td>
<td>≥ 95</td>
<td>excellent for small scale; excess reagents employed; particularly suited to SPS; no racemization observed</td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>28</td>
<td>Phe, Phe, Val</td>
<td>86–91</td>
<td>performed in solution phase using N-tosyl amino acid methyl esters</td>
</tr>
<tr>
<td>N-methylation of carbamates and amides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) silver oxide/ methyl iodide</td>
<td>29</td>
<td>Ala, Val, Phe, Leu, Ile</td>
<td>100</td>
<td>excellent, neutral technique suitable for small scale due to diazomethane hazard; racemization free</td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>30–33</td>
<td>Ala, Ile, Leu, Val, Phe, Ser, Met, Asp, Glu, Thr, Tyr</td>
<td>7–90</td>
<td>N-diphenylphosphinamides are utilized instead of carbamates; they provide more crystalline NMA derivatives; optical rotation data reveal racemization occurs</td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>34</td>
<td>Ala, Val, Leu</td>
<td>52–90</td>
<td>using NaHMDS instead of sodium hydride improved the methylation step considerably; methyl ester formation also occurs</td>
</tr>
<tr>
<td>N-methylation of carboxylic acids</td>
<td>35</td>
<td>Ala, Val, Phe, Trp, Lys, Ser, Asp</td>
<td>86–100</td>
<td>excess reagents employed; suited to SPS protocols on small scale</td>
</tr>
<tr>
<td>(a) triflate displacement</td>
<td>36</td>
<td>52–99</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>37</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>38</td>
<td>Gly, Ala, Leu, Ile, Met, Phe, Val</td>
<td>52–90</td>
<td>N-diphenylphosphinamides are utilized instead of carbamates; they provide more crystalline NMA derivatives; optical rotation data reveal racemization occurs</td>
</tr>
<tr>
<td>N-methylation of esters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) triflate displacement</td>
<td>39</td>
<td>7–90</td>
<td>excellent, neutral technique suitable for small scale due to diazomethane hazard; racemization free</td>
<td></td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>40</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>41, 42, 43</td>
<td>Ala, Ile, Leu, Phe, Val, Ser, Glu, Thr, Tyr</td>
<td>52–90</td>
<td>N-diphenylphosphinamides are utilized instead of carbamates; they provide more crystalline NMA derivatives; optical rotation data reveal racemization occurs</td>
</tr>
<tr>
<td>N-methylation of amides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) silver oxide/ methyl iodide</td>
<td>44</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>45</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(c) Mitsunobu protocol</td>
<td>46</td>
<td>7–90</td>
<td>N-diphenylphosphinamides are utilized instead of carbamates; they provide more crystalline NMA derivatives; optical rotation data reveal racemization occurs</td>
<td></td>
</tr>
<tr>
<td>N-methylation of amino acid amides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) triflate displacement</td>
<td>47</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(b) diazomethylation</td>
<td>48</td>
<td>7–90</td>
<td>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</td>
<td></td>
</tr>
<tr>
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<td>49</td>
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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, 3-hydroxyvaline, and also D-threonine and L-threonine. In a variation, the sulfonyl sequence could be made more efficient by amination with p-toluene-sulfonamide to give 11.

An alternative disconnection to â-bromo acids is to perform an S_N2 displacement on an activated â-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 trifluromethanesulfonate 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 revealed through comparison of optical rotation values. An obvious cause of the racemization is the methylation step, in which sodium hydride was used at elevated temperatures. The temperature is a major contributing factor to this racemization process, since the method of Hlaváček 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 Hlaváček 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-tosyl amino 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

### 2.2.1. Base Mediated Alkylation

The earliest report by Fischer and Lipschitz17 describes the preparation of N-tosyl-â-amino acids (Scheme 5), followed by base (NaOH) mediated N-tosylmethylation 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 hydride was used at elevated temperatures. The temperature is a major contributing factor to this racemization process, since the method of Hlaváček 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).

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methyl bicyclo[4.4.0]dec-5-ene (MTBD), and alkylated with nonionic guanidinium base, 7-methyl-1,5,7-triaza-
7-ene (DBU) via nucleophilic aromatic substitution. The sulfonamide was then deprotonated with the base depro-
tonation, and alkylation provided site-selective combination of sulfonamide protection, 


resulted in uncontrolled methylation of the amide in 87, 86, and 91% yields, respectively, for their respective N-methyl derivatives. The use of TEBA enabled the non-nucleophilic base potassium carbonate to be utilized whereas, in the absence of TEBA, N-alkyla-
tion was considerably reduced. Removal of the nitrobenzenesulfonamide group is affected by thiofenol/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. 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 mercaptaoacetic 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-acetylamino acid methyl esters gave almost no N-methylation. N-Noesy 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 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. 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. and Albanese et al. is unsuitable, since, commonly, ester removal is by base hydrolysis, which may have deleterious effects on the enantio-
meric 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. revealed the propensity of
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 protocol36 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 Kolodziejczyk38 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 workers38 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 Chiu39 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 from 86 to 100%. The difference between the two methods was that Yang and Chiu applied 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 thiofenoxime, 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-sulfonlamino 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 bond-
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 \(\alpha\)-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 \(\alpha\)-N-Boc, side chain N-phthaloyl protected ornithine, and lysine. By blocking the carboxyl group as a benzy1 ester, silver oxide/methyl iodide mediated N-methylation was achieved without trans-esterification to give the methyl ester. The benzyl ester was removed under hydrolytic 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 \(N^1\)-nitro-S-methylsiloxyurea on solid support.\(^{41, 45}\)

### 2.3.2. Sodium Hydride/Methyl Iodide

The most broadly applied method for NMA synthesis is N-methylating N-acyl- and N-carbamoylamino 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-\(\alpha\)-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 \(\alpha\)-carbon of the amino acids: the subject of several key papers by Benoiton et al.\(^{31–35}\) 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 \(\alpha\)-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 9

![Scheme 9](image)

### Scheme 10

![Scheme 10](image)
peptides during standard peptide coupling reactions.\textsuperscript{33} McDermott and Benoiton\textsuperscript{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\textsuperscript{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.\textsuperscript{44} addressed these problems using diphenylphosphinamidates 24, which are acid labile (95% TFA). They demonstrated their approach through the preparation of seven NMAs (Scheme 11). The \( \alpha \)-amino acid diphenylphosphinamidates 24 were methylated using the conditions of Benoiton\textsuperscript{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.

Belagali et al.\textsuperscript{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;\textsuperscript{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,\textsuperscript{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 \( \alpha \),\( \alpha \)-dialkylated residues at the carboxyl terminus is generally difficult.\textsuperscript{47} It was found that alkyl bromides were ineffective in the alkylation step and that alkyl iodides were superior.

Prashad et al.\textsuperscript{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-
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 compared to sodium hydride. It was also noted that sodium hydroxide that has better solubility in THF postulate that the addition of water produces dry 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 lability of this protecting group. Low temperature in acids, this method is not applicable due to the base lability of this protecting group. Low 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. 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). 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 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.,55 who synthesized N,N,N-trimethyl-N,N-benzamidocarboxyl-L-ornithine from N,N,N-trimethylcarboxyl-L-ornithine. N,N-Benzamidocarboxyl-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,N,N-trimethyl-N,N-benzamidocarboxyl-L-ornithine was obtained in only 35% yield.

In a series of three papers, Bowman55–57 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-dimethylation of carbamoyl-L-ornithine from arginine and 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 alklylation 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 Ikutani58 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.
treatment. This was also the approach Poduska 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. 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. reveal the functional group tolerance of this strategy 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. 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, and Eloff prepared \( N \)-methyl-\( L \)-\( \textsuperscript{14} \)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 approach Poduska used in dimethylating lysine derivatives.

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### Table 2. Summary of \( N \)-Methylation by Reductive Amination

<table>
<thead>
<tr>
<th>method</th>
<th>ref</th>
<th>amino acids employed</th>
<th>methylation step yield (%)</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) transition metal catalyzed reduction</td>
<td>55</td>
<td>Ala, Leu, Phe, Val, Tyr, Cys, Asp, Glu</td>
<td>100</td>
<td>( N,N )-dimethylation of amino acids possible; selective monomethylation is rarely achieved(^ {60} )</td>
</tr>
<tr>
<td>(b) Leuckart reaction</td>
<td>21</td>
<td>Ala, Val, Leu, Ser, Phe, Lys, Arg</td>
<td>70–94</td>
<td>racemization free process that is cheap and effective; has also been extended to other amino acids but lower yielding(^ {61} )</td>
</tr>
<tr>
<td>(c) quaternization of imino species</td>
<td>64</td>
<td>Trp</td>
<td>85</td>
<td>racemization free route to ( N )-methyltryptophan on a multigram scale</td>
</tr>
<tr>
<td>(d) borohydride reduction</td>
<td>67</td>
<td>Val, Phe, ClPhe, α-Me-ClPhe</td>
<td>41–75</td>
<td>a racemization free process only when amino acid esters are involved</td>
</tr>
<tr>
<td>(e) borane reduction</td>
<td>65</td>
<td>Ala, Ser, Thr, Leu, Trp</td>
<td>71–91</td>
<td>regioselective ( N,N )-dimethylation of proteins at ( N )-termini and lysyl side chains</td>
</tr>
</tbody>
</table>

\( \textit{Scheme 15} \)

\( \textit{Scheme 16} \)
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.\textsuperscript{64} applied this novel procedure to the formation of N-methyltryptophan (L-abraine) (42), in which N-chlorobutyrolytryptophan 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-abraine) (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\textsuperscript{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.\textsuperscript{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 rigorous 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.\textsuperscript{67} Milder borohydrides such as sodium cyanoborohydride are more suited to this application, especially in the N-alkylation of amino acid esters with aldehydes.\textsuperscript{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.\textsuperscript{52,53}

Jentoft and Dearborn\textsuperscript{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.\textsuperscript{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.\textsuperscript{50} This procedure was applied to alanine, serine, threonine, leucine, and tryptophan and is closely related to the approach of Quitt et al.\textsuperscript{21} Kaljuste and Undén\textsuperscript{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 Dd) group was employed.\textsuperscript{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\(^1\) 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\(^2\) achieved selective reduction of aniline formamide intermediates with a borane dimethyl sulfide complex (BH\(_3\)·SM\(_2\)). 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-methylamides in 80–100% yield.

Chu and co-workers\(^3\) exploited the strategy of Krishnamurthy\(^2\) in the reduction of N-formyl-D-tryptophan methyl ester with a borane dimethyl sulfide complex. The reduction provided, after work-up, N-methyl-D-tryptophan methyl ester in 56% yield.

Hall et al.\(^4\) 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\(^5\) of reductive amidation of valine, serine, and phenylalanine, though there has been a case of selective monoalkylation of tryptophan methyl ester with a borane dimethyl diborane in formates coupled to Wang resin were reduced with 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.

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### 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\(^6\) 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.\(^7\) Ben-Ishai demonstrated this in the treatment of the 5-oxazolidinone \(51\) with 1 equiv of benzylamine to afford the \(N\)-hydroxymethyl amide \(52\). Hydrogenation then gave an \(N\)-methylglycine (sarcosine) derivative \(53\). It was noted that the \(N\)-hydroxymethyl amide \(52\) 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.\(^7\) (vide infra).

Auerbach et al.\(^8\) set the scene for later contributions when they synthesized \(N\)-hydroxymethyl (or \(N\)-methyl) amides analogous to structure \(52\) from primary and secondary amides. They then demonstrated that the \(N\)-methyl amide could be generated by treatment with triethyloxysilane/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.\(^7\) 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., triethyloxysilane/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-
methyl derivatives, as did Aurelio et al. 81 (vide infra). Methodology to the silane/trifluoroacetic acid to the corresponding and phenylalanine and reduced them with triethyl-

protection (Scheme 20) and then converted 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.

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 NMAEs 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 oxazolidinone 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
R-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 R-amino acid 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-R-amino acid substrates. Isolating the methylol derivatives 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.

A variation on the theme was described by Spengler and Burger85 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...
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). Carbamoylation with CbzCl furnished N-Cbz-S-benzyl-L-cysteine in 84% yield. Liu et al. employed the same reductive protocol as Yamashiro et al. in synthesizing Fmoc derivatives of N-methyl-L-cysteine (Scheme 25). The thiazolidine was reduced in the usual manner to provide N-methyl-L-cysteine. In situ treatment with methyl bromide provides the S-methyl derivative, which was treated with Fmoc-succinimide to afford N-Fmoc-N,S-dimethyl-L-cysteine. Alternatively, treatment of with N-hydroxymethylacetamide and an organic acid provided an S-acetamidomethyl intermediate that was converted to the Fmoc derivative.

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, 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. They exploited proline as an auxiliary in the asymmetric synthesis of amino acid derivatives (Scheme 26). The azlactone prepared from N-acetylglycine and benzaldehyde was treated with L-proline under basic conditions to form an arylidene-dioxopiperazine. Methylation with sodium hydride/methyl iodide provided the chiral piperazine. Simple hydrogenation conditions using palladium metal provided N-methyl-L-phenylalanine-L-proline diketopiperazine. Pandey et al. utilized a sarcosine derived chiral precursor based on a recyclable L-prolinol auxiliary as a masked iminium ion equivalent (Scheme 27). N-Benzylsarcosine and L-prolinol were converted to the Fmoc derivative.
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) to generate the required R-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-workers93 have a long and distinguished record of stereoselective transformations 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 hydroxylamino 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 of...
of a reducing agent then furnishes the NMA. Thus, Grieco and Bahsas treated various methyl ester hydrochlorides with aqueous formaldehyde in the presence of excess cyclopentadiene to give 2-azanorbornenes via aza-Diels-Alder reaction (Scheme 31). Trifluoroacetic acid catalyzed the retro-aza-Diels-Alder reaction to generate the iminium ion that first participated in formation of the 2-azanorbornene. In the presence of triethylsilane, the iminium ion was reduced to the NMA methyl ester.

Dorow and Gingrich sought to solve several problems associated with the production of N-methyl-R-amino acids via the reductive alkylation of optically active scalemic azides (Scheme 32). The susceptibility of the sequence to epimerization was tested through application to 2-azidophenylacetic acid (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-methylglycine 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. 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 and benzyl carbamates 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 that loses a proton to give a carbamate radical 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. 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. 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 to the N-methyl dipeptide, in which the internal acyl nitrogen did not undergo any N-methylation.

Laplante and Hall 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
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. 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 formamide 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-methy lamino acids (Scheme 36). Lithiation of the sulfone 118 followed by reaction with ethyl chloroformate provided 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-methy lamino 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 anti-diabetic/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.
Given the propensity for NMAs to racemize, as proven by Benoiton et al.,\textsuperscript{31-33} the application by Groeger et al.\textsuperscript{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 R-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.\textsuperscript{103,104} N-Methyl-γ-amino-β-hydroxy acids are found in some biologically active depsipeptides such as Haplosin\textsuperscript{103} and Dolastatin 10,\textsuperscript{104} and Catass et al.\textsuperscript{105} have developed a stereo- and regioselective nucleophilic opening of the oxirane ring of the chiral epoxy alcohol\textsuperscript{128} (Scheme 39) as a starting point for these compounds. The resultant azido diol\textsuperscript{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\textsuperscript{130}. Cyanide ion then effected ring opening to afford the hydroxy nitrile derivative\textsuperscript{131}, and protection of the hydroxyl functionality followed by oxidative hydrolysis of the nitrile provides the N-methyl-γ-amino-β-hydroxy acid\textsuperscript{132}, ready for coupling via the carboxyl terminus.

Boger et al.\textsuperscript{49} used a similar approach to that of Catass in synthesizing N-methyl-α-amino-β-hydroxy acids\textsuperscript{133 and 134} (Scheme 40) as intermediates in the synthesis of the antitumor, antibiotic Bouvardin. The epoxide\textsuperscript{135} was employed in two different pathways: First, treating\textsuperscript{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\textsuperscript{133} ready for coupling. A second approach utilized the epoxy alcohol\textsuperscript{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 R,α-unsaturated ester 136. The ester 136 was converted to a diol by the Sharpless asymmetric dihydroxylation with AD-mix-α to provide the (2R,3S)-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 SN2 fashion to provide the azide 137 with appropriate 2S,3S 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 Genêt15 and covers the literature up to 1994. Some of the reactions summarized in the following schemes have been reviewed by Durand and Genêt15 and are included here to emphasize preparations that exploit novel methods or reagents for incorporating the N-methyl functionality.

Wenger106 in the original preparation of MeBmt 139 from diethyl tartrate took the aldehyde 140 (Scheme 41) and performed an aminocyanation using methylvamine, 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 methylvamine in S_N2 fashion provided the N-methyl moiety with the correct configuration 144.

Schmidt and Siegel110 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-methyloxazolidinone 147. These conversions were very efficient, giving the oxazolidinone 147 in 91% yield from 145. 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
source of the $N$-methyl group. Seebach et al.\textsuperscript{114} achieved $N$-methylation of an oxazolidinone intermediate like structure 150 with excess methyl iodide/silver oxide in DMF.

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

Genêt et al.\textsuperscript{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.\textsuperscript{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

<table>
<thead>
<tr>
<th>NMA</th>
<th>ref no.</th>
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<td>MeIle</td>
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<td>MeLeu</td>
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</tr>
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</table>
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 6Z-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

(23) Mizuno, O. Synthesis 1981, 1.