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# Enantiocontrolled Synthesis of α-Methyl Amino Acids via $Bn_2N$-α-Methylserine-β-lactone†

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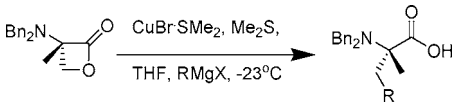
## ABSTRACT




**Enantiocontrolled synthesis of α-methyl amino acids proceeds via the regioselective organocuprate opening of $Bn_2N$-α-methylserine-β-lactone. From this chiral intermediate, a wide variety of α-methyl amino acids and building blocks were synthesized in excellent yields.**

Building blocks such as α-methyl amino acids have become important in bioorganic chemistry. Incorporation of these constrained building blocks into peptides results in conformational restrictions and increased constraints of the peptidomimetic structures.[1] These constrained building blocks have been used to force peptides into their biologically active conformations, often resulting in peptidomimetics with remarkable resistance to enzymatic degradation.[2] With the expanding role of α-methyl amino acids in bioorganic synthesis, a versatile route to optically pure α-methyl amino acids is desirable and has been the focus of many laboratories. The majority of synthetic routes involve the alkylation of a chiral alanine derivative. Among these are the bis-lactim ether of Schollkopf,[3] the imidazolidinones and oxazolidinones of Seebach,[4] the diphenyloxazolinones of Williams,[5] the chelation-controlled addition of acyclic alanine enolates of Ojima,[6] and the acyclic chiral alanine-derived dianion of Berkowitz.[7] While these methods are effective, many of them utilize a chiral auxiliary that is removed and often destroyed in the process of deprotection.

With the previous success in our laboratory of opening Boc-α-Me-Ser-β-lactone at the β-carbon with soft sulfur nucleophiles,[8] we were interested in opening this α-Me-Ser-β-lactone with various carbon nucleophiles to generate a wide variety of α-methyl amino acids from one common chiral intermediate. On the basis of previous studies, it was determined that Grignard-derived organocuprates are the best source of soft carbon nucleophiles for the opening of β-lactones. These studies showed that catalytic Cu(I) was successful in directing the Grignard reagents to 1,4-additions of enones and β-propiolactones.[9]

Inherent in the basic nature of the organocopper reagents, there were concerns about the removal of the acidic proton

† The authors would like to dedicate this paper to the memory of Dr. Murray Goodman for a lifetime of achievements in bioorganic chemistry.

‡ Deceased June 1, 2004.

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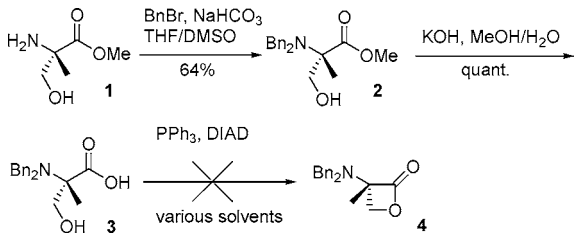
on the carbamate-protected nitrogen of Boc-α-Me-Ser-*β*-lactone. Vederas et al. showed that diprotected Ser-*β*-lactones could be opened in higher yields than monoprotected Ser-*β*-lactones due to the elimination of a base-catalyzed intramolecular rearrangement that produces an oxazoline and/or oxazolone, both of which are readily hydrolyzed to serine upon aqueous workup.[9a] An additional side reaction that was observed in their studies was the abstraction of the α-proton in an elimination reaction resulting in the formation of dehydroalanine.[9a]

Because of the absence of an α-proton in our α-methyl-Ser-*β*-lactone, we were only concerned with the formation of the oxazoline and/or oxazolone. We therefore sought an alternative protecting group for the amine that would eliminate the acidic proton and be stable to Grignard-derived organocuprates. There are only a few protecting groups that fit these requirements, including the stabase,[10] benzostabase,[11] pyrrole,[12] 2,5-dimethylpyrrole,[13] and dibenzyl.[14] Dibenzylation was chosen on the basis of the yield of protection compared to the others and because of its stability under aqueous workup conditions.

The starting material for the synthesis of $Bn_2N$-α-Me-Ser-*β*-lactone was $H_2N$-α-Me-Ser-OMe, which was enantioselectively synthesized as previously described.[8] The $H_2N$-α-Me-Ser-OMe (**1**) was dibenzylated with BnBr in THF/DMSO with $NaHCO_3$ in a 64% yield (**2**, Scheme 1). The

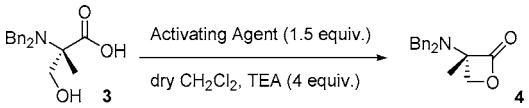
**Scheme 1.** Synthesis of $Bn_2N$-α-Me-Ser and Attempted Lactonization to $Bn_2N$-α-Me-Ser-*β*-Lactone




methyl ester was saponified with KOH in $MeOH/H_2O$ to give the carboxylic acid (**3**) required for lactonization. As previously described, we attempted the Mitsunobu lactonization utilizing $PPh_3$, as well as DIAD in THF.[8] This reaction was unsuccessful because of the insolubility of the starting material. In choosing the di-*N*-benzyl protecting group, we created a zwitterion that was completely insoluble in all solvents that are compatible with the Mitsunobu reaction, including THF, dioxane, DMF, and acetonitrile.

Therefore, we studied the formation of $Bn_2N$-α-Me-Ser-*β*-lactone via activation of the carboxylic acid with various coupling reagents. Previously, it was reported that BOP was an efficient reagent for lactonization.[15] In our study we chose, PyBroP, DEPBT, HBTU, DCC/DMAP, PyBoP, and BOP. The results are listed in Table 1.

**Table 1.** Lactonization Study of $Bn_2N$-α-Me-Ser




| activating agent | % yield of **4** |
|---|---|
| BOP | 36 |
| DEPBT | 0[a] |
| **HBTU** | **82** |
| PyBroP | 50 |
| PyBoP | 36 |
| DCC/DMAP (cat.) | 36 |

[a] DEPBT is known to be unreactive toward alcohols.

Three of the activating agents, BOP, PyBOP, and DCC/DMAP, produced the *β*-lactone in 36% yield, while PyBroP was slightly more effective, producing the *β*-lactone in 50% yield. The ineffectiveness of DEPBT as a lactonization reagent was not surprising since it was previously reported that DEPBT is unreactive toward alcohols.[16] By far, HBTU was the best activating reagent for the lactonization, resulting in $Bn_2N$-α-Me-Ser-*β*-lactone in 82% yield. Not only was this reagent superior to all other activating reagents, but it afforded yields over 15% higher than those achieved when utilizing Mitsunobu conditions for *β*-lactonization.[8,9a,17]

In examining the structure of the *β*-lactone, there are two possible mechanisms of attack. The first is *O*-acyl fission in which nucleophiles attack the lactone at the carbonyl carbon, leading to the undesired ketone intermediate. This ketone intermediate is then attacked with a second equivalent of the nucleophile, leading to the tertiary alcohol (Figure 1). The second mechanism of attack involves *O*-alkyl fission in which the nucleophile attacks at the methylene carbon, resulting in the desired α-methyl amino acids and building blocks (Figure 1). It is known that softer nucleophiles will preferentially attack at the methylene carbon, while harder nucleophiles attack at the carbonyl carbon.[9a]

We employed a variety of Grignard reagents for the ring opening of $Bn_2N$-α-Me-Ser-*β*-lactone under Cu(I) catalysis. The results of our study are listed in Table 2. The $Bn_2N$-α-Me-Ser-*β*-lactone was opened with primary alkyl Grignards in the presence of catalytic $CuBr{\cdot}SMe_2$ to afford $Bn_2N$-α-Me-norleucine (**5a**) and $Bn_2N$-α-Me-homoleucine (**6a**) in

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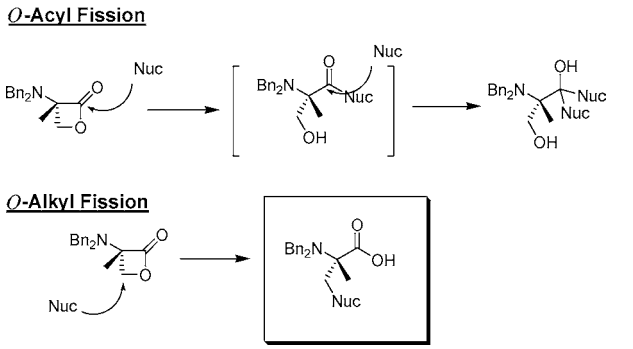
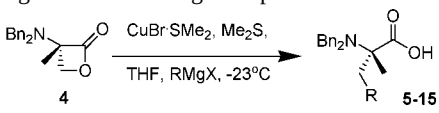


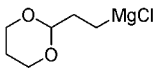
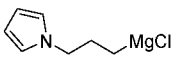
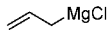
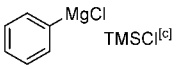
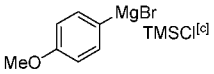
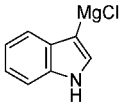

**Figure 1.** Two mechanistic pathways for $\beta$-lactone ring opening with nucleophiles.

excellent yields (98 and 94%, respectively). These reactions exhibited complete regioselectivity for *O*-alkyl fission over *O*-acyl fission. The compound $Bn_2N$-α-Me-leucine (**7a**) was also produced utilizing isopropylmagnesium chloride in 43% yield. The lower yield of this reaction was a result of an elimination reaction in which dibenzylamine acts as a leaving group, not from *O*-acyl fission.

Functionalized alkyl Grignard reagents were also utilized for the ring opening of $Bn_2N$-α-Me-Ser-$\beta$-lactone. To incorporate an oxygen functional group, (1,3-dioxan-2-ylethyl)magnesium bromide was utilized to give the protected aldehyde (**8a**, Table 2) in 94% yield with no formation of the *O*-acyl fission product. To demonstrate the versatility of this masked aldehyde intermediate, the carboxylic acid was esterified with $CH_3I$ and $K_2CO_3$ in DMF to form the methyl ester in 92% yield and the side chain acetal was cleaved in 83% yield under aqueous acidic conditions to unmask the aldehyde (**8c**, Scheme 2). This aldehyde was then reduced with sodium borohydride to the alcohol in 95% yield, representing an α-methylhomoserine derivative (**8d**). In addition, the aldehyde was oxidized with the Jones reagent to the carboxylic acid in 96% yield to give an α-methylglutamic acid derivative (**8e**, Scheme 2).

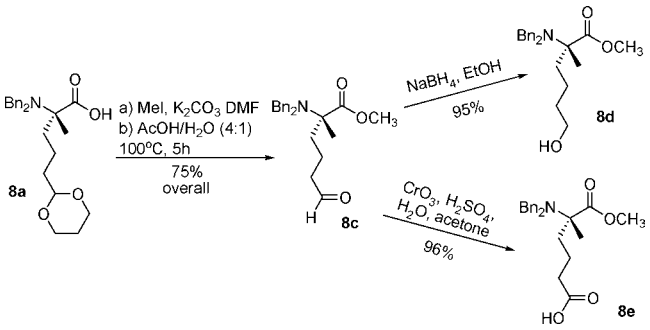
**Table 2.** Ring Opening of $Bn_2N$-α-Me-Ser-$\beta$-Lactone with Various Grignard-Derived Organocuprates




| entry | carbon nucleophile[a] | % yield (a) | % yield (b) |
|---|---|---|---|
| 5 |  | 98 | 0 |
| 6 |  | 94 | 0 |
| 7 |  | 43 | 0 |
| 8 |  | 94 | 0 |
| 9 |  | 91 | 0 |
| 10 |  | 0 | 87 |
| 11 |  | 51 | (0) 33[b] |
| 12 |  | 73<br>90 | 19<br>7 |
| 13 |  | 70<br>91 | 30<br>7 |
| 14 |  | 59 | 0 |
| 15 |  | 58 | 0 |

[a] Catalytic $CuBr{\cdot}SMe_2$ is used for *in situ* cuprate generation. [b] Ketone product (Scheme 3). [c] Addition of 1.6 equiv of TMSCl. [d] Tetrabutylammonium cyanide, $Cs_2CO_3$ in DMF.

**Scheme 2.** Synthesis of an α-Methylhomoserine Derivative (**8d**) and an α-Methylglutamic Acid Derivative (**8e**) from the Masked Aldehyde (**8a**)



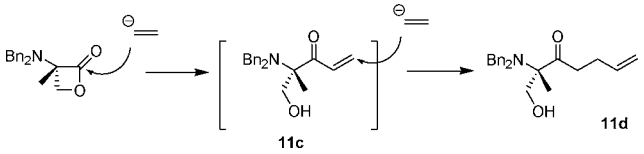

Functionalized alkyl Grignard reagents were also utilized for the ring opening of $Bn_2N$-α-Me-Ser-$\beta$-lactone. To incorporate a nitrogen functional group, the Grignard reagent of 1-(3-bromopropyl)pyrrole was synthesized and the corresponding cuprate reacted with $Bn_2N$-α-Me-Ser-$\beta$-lactone to yield the pyrrole-protected α-methyllysine derivative (**9a**, Table 2) in 91% yield with no formation of the *O*-acyl fission product.

The $Bn_2N$-α-Me-Ser-$\beta$-lactone was allowed to react with allyl and vinylmagnesium chloride in order to install an alkene group onto the side chain of the α-methyl amino acid. The reaction with allylmagnesium chloride in the presence of catalytic $CuBr{\cdot}SMe_2$ resulted in exclusively *O*-acyl fission, affording the tertiary alcohol (**10b**) in 87% yield. This reaction was repeated with stoichiometric $CuBr{\cdot}SMe_2$, and the same result was observed. The preference of allylmagnesium chloride to react at the carbonyl carbon of $\beta$-propiolactones was also reported by Kawashima *et al.*[18] Vinylmagnesium chloride provided a mixture of the desired *O*-alkyl fission product and *O*-acyl fission product. The

(18) Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403−412.

α-methyl amino acid (**11a**) was isolated in 51% yield. Interestingly, the tertiary alcohol (**11b**) was not isolated. Instead, the ketone (**11d**, Scheme 3) resulting from a Michael addition to the α,*β*-unsaturated ketone intermediate (**11c**) of the initial *O*-acyl opening was the only side product observed (Scheme 3). This side reaction was also noted by Kawashima et al. in their studies with *β*-propiolactones.[18]

**Scheme 3.** Formation of the Ketone Side Product via Conjugate Addition of a Presumed Vinylcuprate




The $Bn_2N$-α-Me-Ser-*β*-lactone was opened with aryl Grignard reagents to give $Bn_2N$-α-Me-Phe, $Bn_2N$-α-Me- Tyr, and $Bn_2N$-α-Me-Trp building blocks. The opening of $Bn_2N$-α-Me-Ser-*β*-lactone with phenylmagnesium chloride in the presence of catalytic CuBr·$SMe_2$ resulted in 73% yield of the desired $Bn_2N$-α-Me-Phe (**12a**) and 19% yield of the tertiary alcohol (**12b**). The results were very similar with 4-methoxyphenylmagnesium bromide, producing 70% yield of $Bn_2N$-α-Me-Tyr (**13a**) and 30% yield of the tertiary alcohol (**13b**). The opening of $Bn_2N$-α-Me-Ser-*β*-lactone with indole Grignard was less successful, producing $Bn_2N$-α-Me-Trp (**14a**) in 59% yield.

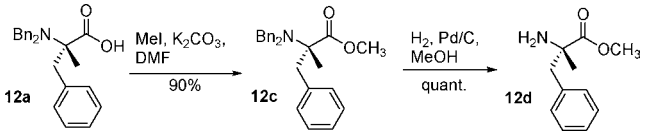
In an attempt to improve the regioselectivity of the phenyl and 4-methoxyphenyl Grignard-derived organocuprate additions, TMSCl was added to the reaction mixture. The beneficial effects of adding TMSCl to organocopper-mediated addition reactions are well documented,[19] and Nelson *et al*. have reported an improved regioselectivity for the $S_N2$ addition of methylmagnesium bromide to *β*-lactones.[20] The exact role of TMSCl in these addition reactions remains unclear. It is possible that the TMS group coordinates to the carbonyl oxygen, increasing the steric hindrance about the carbonyl carbon and therefore directing the nucleophile to the less hindered methylene carbon, resulting in *O*-alkyl fission of the *β*-lactone.

When TMSCl was added to the reaction mixture of phenylmagnesium chloride, the regioselectivity for *O*-alkyl fission was improved, resulting in a 90% yield of $Bn_2N$-α-Me-Phe as compared to 73% without TMSCl (**12**, Table 2). There was still 9% formation of the *O*-acyl fission side product. Similar results were observed when TMSCl was added to the organocuprate derived from 4-methoxyphenylmagnesium bromide. The yield of $Bn_2N$-α-Me-Tyr was improved from 70 to 91% by the addition of TMSCl (**13**, Table 2) with 9% yield of the *O*-acyl fission side product. The effects of TMSCl were limited to the addition of organocuprates derived from aryl Grignard reagents. There was no change in regioselectivity for the additions of organocuprates derived from allyl or vinylmagnesium chloride.

In addition to Grignard-derived organocuprates, $Bn_2N$-α-Me-Ser-*β*-lactone was opened with tetrabutylammonium cyanide to install a nitrile on the side chain of the dibenzyl-protected α-methyl amino acid. This reaction was carried out in DMF in the presence of $Cs_2CO_3$ to give (**15a**) in 58% yield (Table 2).[21] Once again, despite the reduced yield of **15a**, the reaction was regioselective for *O*-alkyl fission, resulting in the α-methyl amino acid derivative.

To prove the versatility of this synthetic strategy for the synthesis of α-methyl amino acid derivatives, a representative example was chosen for deprotection (Scheme 4). The carboxylic acid of $Bn_2N$-α-Me-Phe (**12a**) was esterified utilizing MeI and $K_2CO_3$ in DMF to give methyl ester (**12c**) in 90% yield. The dibenzyl group was then removed under hydrogenation conditions utilizing 5% Pd/C to give the free amine (**12d**) in a quantitative yield. The ease of dibenzyl deprotection makes these amino acid building blocks valuable tools for peptidomimetic synthesis.

**Scheme 4.** Dibenzyl Deprotection of $Bn_2N$-α-Me-Phe-$OCH_3$




In conclusion, we have developed a novel, versatile, enantioselective route to α-methyl amino acids and building blocks utilizing $Bn_2N$-α-Me-Ser-*β*-lactone. This *β*-lactone can be synthesized in high yield from $Bn_2N$-α-Me-Ser utilizing HBTU and TEA in $CH_2Cl_2$. With HBTU, the lactonization proceeded in 82% yield, which is remarkably higher than the yields achieved with other activating reagents and under Mitsunobu conditions. The $Bn_2N$-α-Me-Ser-*β*-lactone was regioselectively opened at the methylene carbon with alkyl, functionalized alkyl, alkene, and aryl Grignard-derived organocuprates, resulting in α-methyl amino acid building blocks in excellent yields.

**Acknowledgment.** We thank the NIH (DA05539) for financial support and fellowship support (N.D.S.) (DA07315) and Joseph Taulane for helpful discussions on purification and characterization.

**Supporting Information Available:** Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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