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High *anti* Diastereoselectivity in a Tandem Oxyhomologation–Coupling Protocol for the Preparation of Amides and Peptides Incorporating α-Hydroxy β-Amino Acids

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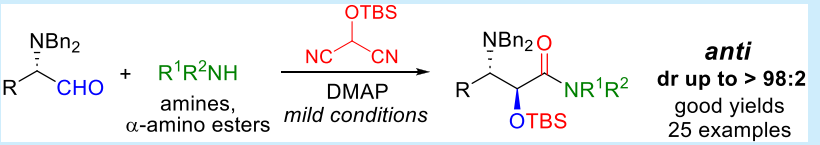

ABSTRACT: The one-pot MAC (Masked Acyl Cyanide) reaction is used to perform the tandem oxyhomologation reaction of *N*,*N*-dibenzyl-L-phenylalaninal and coupling with nitrogen nucleophiles to provide a wide selection of amide and peptide derivatives of (2*S*,3*S*)-allophenylnorstatin in generally good yields and with high *anti* selectivity, often with dr >98:2. The procedure works equally well with other selected *N*,*N*-dibenzyl α-amino aldehydes, and is used to achieve a very short synthesis of (2*S*,3*S*,*S*)-epibestatin.

α-Hydroxy β-amino acids are an important class of molecules in both natural products[1] and medicinal chemistry.[2] The two carbons bearing the vicinal amino alcohol moiety are often stereogenic, leading to the existence of two diastereoisomeric forms. Derivatives with an *anti* relative configuration appear in both linear and cyclic natural peptides (Figure 1), such as microginin 674[3] and perthamide C.[4] Small synthetic peptides incorporating *anti* α-hydroxy β-amino acids are important constituents of protease inhibitors, and particular attention has been given to (2*S*,3*S*)-allophenylnorstatin derivatives (Figure 1): AG-001859 was in preclinical development for anti-HIV activity,[5] and was recently considered as a SARS-CoV2 antiviral;[6] KMI-1027 acts as a BACE-1 inhibitor[7] and has potential for Alzheimer's disease treatment;[8] KNI-272 is an HIV-1 protease inhibitor,[9] and reduces HIV-related neurotoxicity.[10]

Given the widespread general interest in vicinal amino alcohols,[11] various diastereoselective synthetic methods have been established and are often applicable to α-hydroxy β-amino acids.[12] One arguably underdeveloped synthetic strategy is the three-component reaction between an α-amino aldehyde, a nucleophile, and a one-carbon reagent. The reaction is thought to proceed via a masked acyl cyanide (leading to the MAC reaction moniker), and the most common one-carbon reagent is *tert*-butyldimethylsilyloxymalononitrile (H-MAC-TBS).[13] This methodology was used by Nemoto (its progenitor) to perform a one-pot oxyhomologation–coupling reaction of Cbz-D-phenylalaninal with a L-leucine ester, with a preference for the *syn* diastereomer (dr 80:20).[14] This reaction led to a very short synthesis of the important therapeutic agent (2*S*,3*R*,*S*)-bestatin (Ubenimex),[15] (Scheme 1). Very few other MAC reactions

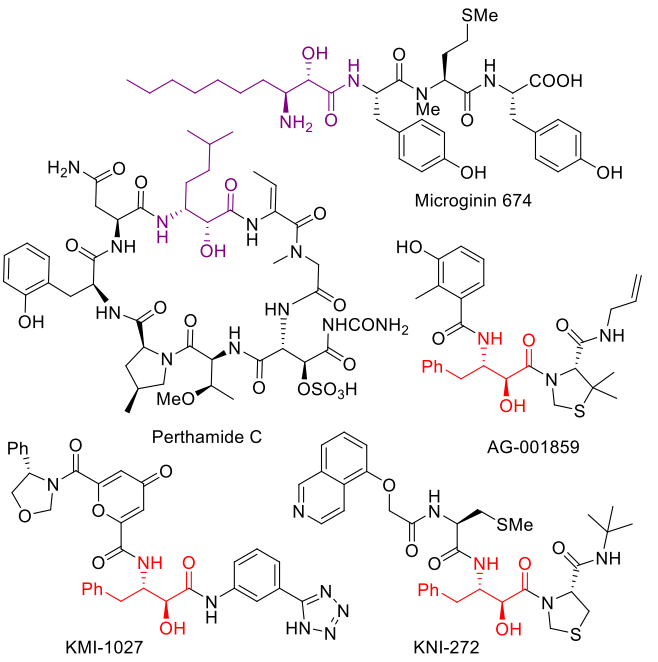

Figure 1. Examples of *anti* α-hydroxy β-amino acid residues in natural and synthetic peptides.

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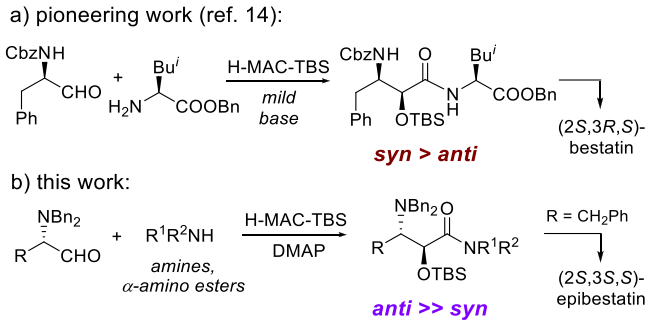
Scheme 1. MAC Reaction for Preparing α-Hydroxy β-Amino Acid Derivatives and Rationale for This Work (H-MAC-TBS = TBSOCH(CN)$_2$)

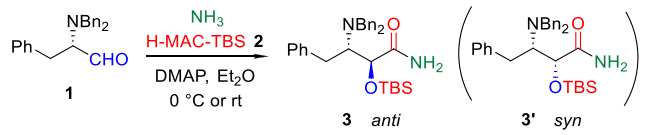


have been used to create an α-hydroxy β-amino acid and couple it with an amine or an amino acid derivative, and the diastereoselectivity was not considered, since the final target structures were oxidized at the C2 center.[16,17]

Recent studies suggested that control of the diastereoselectivity may be related to the protecting group of the α-amino aldehyde: Garner's aldehyde underwent *anti* diastereoselective MAC reactions with simple nucleophiles,[18] while *N,N*-dibenzyl-L-phenylalaninal reacted with simple alcohols and could be transformed into *anti* (2*S*,3*S*)-allophenylnorstatin.[19] Herein, we present MAC reactions of *N,N*-dibenzyl-L-phenylalaninal and other α-amino aldehydes with amines and α-amino acid derivatives that proceed with high *anti* diastereoselectivity (Scheme 1), illustrated by a very short synthesis of (2*S*,3*S*,*S*)-epibestatin.

N,N-Dibenzyl-L-phenylalaninal **1** was reacted with 2.4 equiv of H-MAC-TBS **2** on 0.5 mmol scale in a small series of experiments in which the reagent stoichiometry and the reaction temperature were varied (Table 1). In conditions that had been optimized previously for reactions employing alcohols as nucleophiles,[19] H-MAC-TBS (2.4 equiv), DMAP (2.0 equiv), and an excess of ammonia (3.0 equiv) were reacted for 16 h at 0 °C, to give the adduct **3** in 86% isolated yield (entry 1). Reducing the amount of the nucleophile to 1.2 equiv improved the yield marginally to 89% (entry 2). The reaction proceeded in 76% yield in the absence of DMAP, with ammonia presumably serving as the base (entry 3). The reaction was faster at room temperature, with TLC indicating that no aldehyde remained after 1.5 h, although the yield of **3** lowered to 71% (entry 4). With the conditions of entry 2 identified as being optimal, we carried out the reaction on a 2.2 mmol (near gram) scale to give **3** in 84% yield (entry 5).

Table 1. Optimization of MAC Reaction Conditions[a]



Entry	NH_3 (equiv)	DMAP (equiv)	Temp (°C)	Time (h)	Yield[b] (%)	dr[c] *anti:syn*
1	3.0	2.0	0	16	86	>98:2
2	1.2	2.0	0	16	89	>98:2
3	3.0	0	0	16	76	>98:2
4	1.2	2.0	rt	1.5	71	>98:2
5[d]	1.2	2.0	0	16	84	>98:2

[a]Reaction conditions: aldehyde **1** (0.5 mmol), H-MAC-TBS **2** (2.4 equiv), NH_3 (1 M in THF) and DMAP, reacted in Et_2O (5 mL). [b]Isolated yields are given. [c]Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude product. [d]Scale-up reaction using aldehyde **1** (2.2 mmol).

Only one set of signals was observed in the ^{1}H NMR spectrum of each of the crude product mixtures, suggesting a very high diastereoselectivity. Our expectation that this should be the *anti* form, with a (2*S*,3*S*) configuration, was confirmed by an X-ray diffraction study of a single crystal (Figure 2). We prepared an authentic sample of the *syn* form **3′** independently, using a three-step procedure that began with a minor adaptation of Nemoto's original protocol;[14] it showed distinct ^{1}H NMR spectral signals, and we were able to establish that the samples of **3** obtained in Table 1 had dr >98:2 (see Supporting Information (SI) for details). We also confirmed, by chiral hplc analysis, that the reaction conditions had not induced partial racemization of the amino aldehyde substrate (see SI for details).

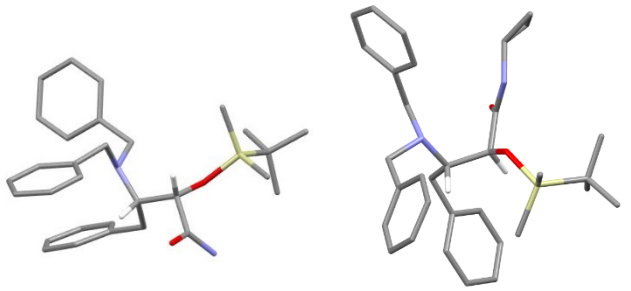
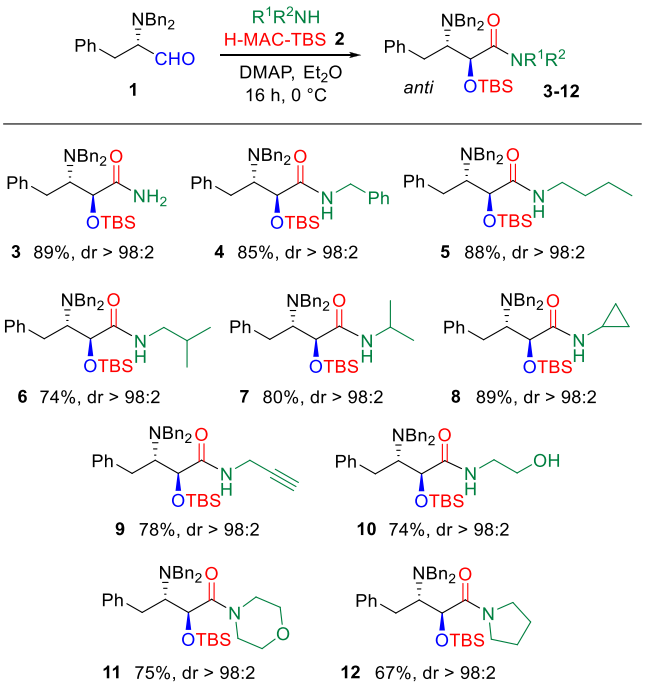


Figure 2. X-ray crystallographic structures of compounds **3** (left) and **8** (right). For clarity, only the hydrogen atoms on C2 and C3 are shown, confirming the *anti* configuration.

We examined the MAC reaction with a panel of amines as nucleophiles (1.2 equiv). Results are presented in Scheme 2,

Scheme 2. Preparation of Amides



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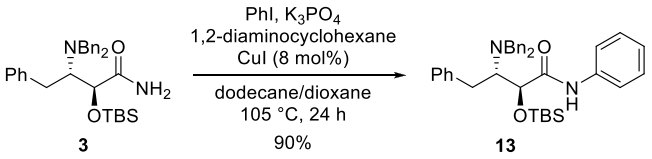
wherein diastereomeric ratios (dr) were calculated from the ^{1}H NMR spectrum of the crude product mixture after workup (by integrating the Me_2Si signals) and yields are given for isolated material after column chromatography. Akin to ammonia, five primary amines (benzyl, butyl, isobutyl, isopropyl, and cyclopropyl) all performed well, giving adducts **4**–**8** in high yields (74–89%), as did the two functionalized amines propargylamine and ethanolamine providing **9** and **10** (78% and 74% yields, respectively). In reactions with the secondary amines morpholine and pyrrolidine, the yields of adducts **11** and **12** were still satisfying (75% and 67% respectively). The standout feature for all of these reactions was the uniformly high diastereoselectivity with dr >98:2; only the *anti* stereoisomer was observed in the ^{1}H NMR spectrum in each case. Compound **8** provided single crystals amenable to X-ray diffraction, allowing further confirmation of the *anti* form and the (2*S*,3*S*) configuration (Figure 2).

When the above reaction was repeated using aniline as the nucleophile, no identifiable products were obtained. We prepared the target anilide **13** autoschediastically by Buchwald amination of **3** in 90% yield (Scheme 3). This indirect approach may provide a means to circumvent limitations of the MAC reaction with anilines, although we did not pursue this further.

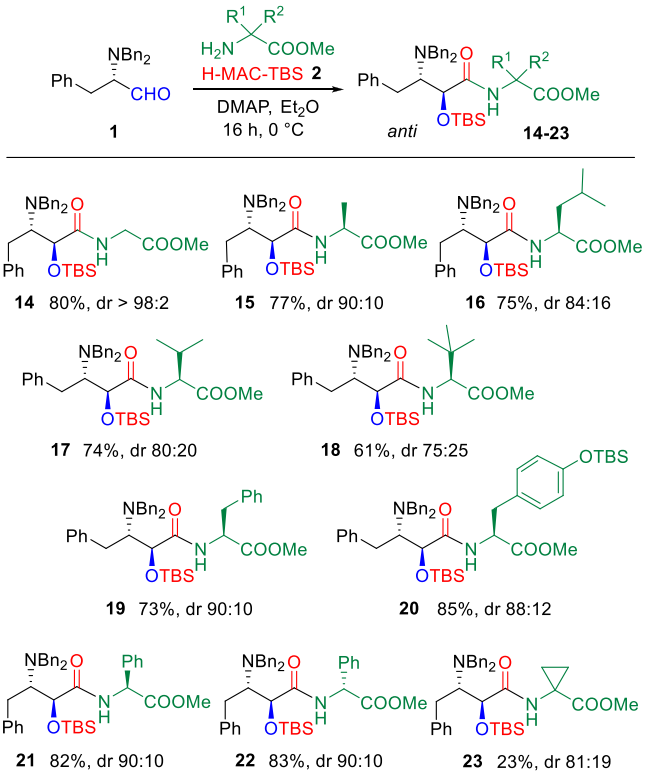
Scheme 3. Indirect Preparation of Anilide 13



With the success of the MAC reaction using aliphatic amines in hand, we turned to the use of α-amino acid derivatives as nucleophiles. Each nucleophile was employed in C-terminal methyl ester protected form, either as a free amine or as a hydrochloride; in the latter case, an extra equivalent of DMAP was used to liberate the free base. Results are listed in Scheme 4. Dr values are given for crude reaction products and yields are given for isolated materials, as before. With glycine, the reaction was as rewarding as those employing primary amines, providing **14** in 80% yield with dr >98:2. Amino esters with a single alkyl α-substituent of increasing size (methyl, isobutyl, isopropyl, and *tert*-butyl) reacted to give the corresponding *anti* adducts **15**–**18** in yields (from 77% to 61%) and dr values (from 90:10 to 75:25) that both diminished with increasing substituent size. Phenylalanine and protected tyrosine derivatives gave reasonable yields of **19** and **20** (73% and 85%, respectively) with dr values around the 9:1 mark. With phenylglycine, which has a higher susceptibility to epimerization at the α-carbon, we examined both the D and the L enantiomers; the diastereomeric derivatives **21** and **22** were obtained in almost identical yields and dr values, testifying to the lack of epimerization under the MAC reaction conditions and the absence of a stereochemical match-mismatch phenomenon. In contrast, the reactions of more sterically hindered amino acid derivatives were less successful: the methyl ester of 1-aminocyclopropanecarboxylic acid gave product **23** in only 23% yield with a dr of 81:19, while those of Aib (aminoisobutyric acid) and proline did not react.

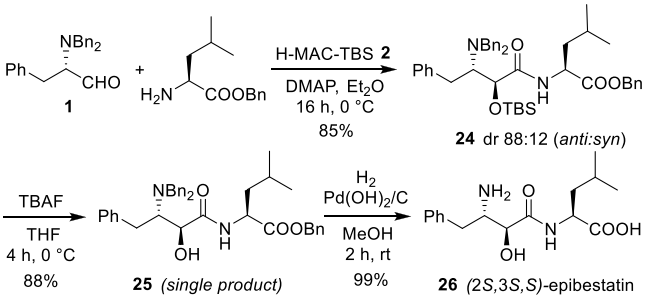
The results leading to dipeptides were sufficiently successful to envisage an application of this reaction for the synthesis of a

Scheme 4. Preparation of Dipeptides



selected target peptide. (2*S*,3*S*,*S*)-Epibestatin is a diastereoisomer of bestatin, acting as a strong inhibitor of aminopeptidases[20] and of LTA4 hydrolase.[21] *N*,*N*-Dibenzyl-L-phenylalaninal **1** was reacted with H-MAC-TBS **2** and the benzyl ester of L-leucine to give the expected *anti* derivative **24** in 85% yield with a dr of 88:12. This mixture was treated with TBAF (1.5 equiv) at 0 °C to give pure *anti* alcohol **25** in 88% yield after chromatography, which represents a near-quantitative yield of this diastereomer from the substrate mixture. Complete debenzylation was achieved in a single step by hydrogenolysis in the presence of Pearlman's catalyst, to provide (2*S*,3*S*,*S*)-epibestatin **26** in 99% yield. This 3-step synthesis from *N*,*N*-dibenzyl-L-phenylalaninal was achieved in 74% overall yield (Scheme 5), making it considerably more

Scheme 5. Preparation of (2*S*,3*S*,*S*)-Epibestatin



efficient than the previous literature preparations,[20,21] that implicated a nondiastereoselective several-step oxyhomologation of Boc- or Cbz-protected L-phenylalaninal followed by diastereomeric separation to obtain protected (2*S*,3*S*)-allophenylnorstatin before classical coupling of the latter with L-leucine.

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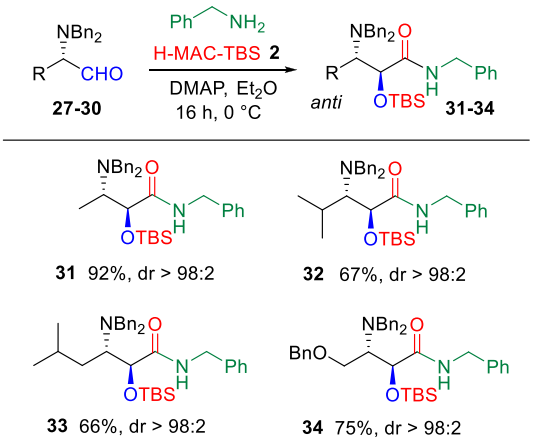
Finally, we assessed a small panel of other *N,N*-dibenzyl α-amino aldehydes as the electrophilic partners using benzylamine as the representative nucleophile. Results are listed in Scheme 6. The derivatives of L-alaninal, L-valinal, L-leucinal,

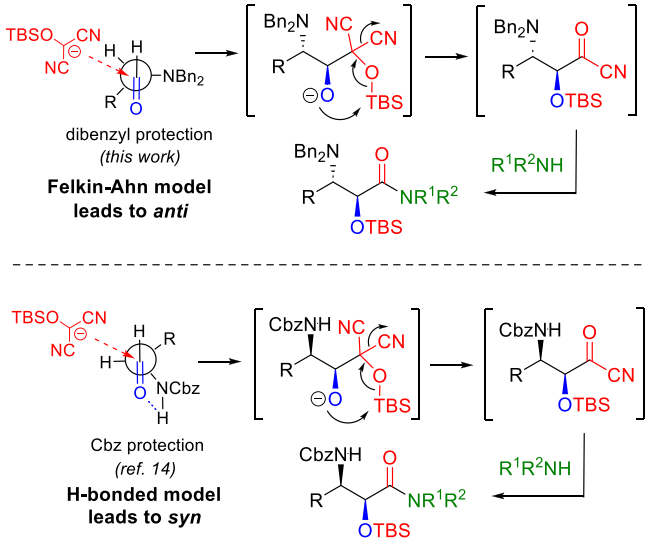
Scheme 6. MAC Reactions Using Selected *N,N*-Dibenzyl α-Amino Aldehydes



and *O*-benzyl-L-serinal (**27**−**30**) each gave the corresponding amide (**31**−**34**, respectively) in satisfactory isolated yields (66−92%). For these compounds, only one set of ^{1}H NMR spectral signals was observed in the crude product mixture, pointing to a dr >98:2 in each case.

On the basis of the above experimental observations and our previous studies on MAC reactions, we suggest that the *anti* diastereoselectivity can be rationalized by the Bürgi−Dunitz approach of the deprotonated H-TBS-MAC reagent on the preferred conformation of the α-amino aldehyde substrate, following the Felkin−Ahn model (Scheme 7). In contrast, the *syn* diastereoselectivity, observed previously by Nemoto in MAC reactions using Cbz-D-phenylalaninal,[14] can be explained by an H-bonded conformation of the electrophilic substrate (Scheme 7).

Scheme 7. Proposed Mechanism Accounting for the *anti* Diastereoselectivity in This Work and the *syn* Diastereoselectivity in Previous Work



In summary, the one-pot MAC reaction protocol facilitates the tandem oxyhomologation of *N,N*-dibenzyl α-amino aldehydes and then coupling with nitrogen nucleophiles, with high *anti* diastereoselectivity and without compromise of the enantiomeric purity of the electrophilic substrate. The reactions proceed in mild conditions and lead to a small library of orthogonally protected amide and peptide derivatives. This technique provides an expedient access to derivatives of *anti* α-hydroxy β-amino acids, bypassing the classical approaches that commence with (and thus require procuration of) these compounds themselves.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00370.

Synthetic procedures, NMR spectra, stereochemical analyses, and crystallographic data (PDF)

Accession Codes

CCDC 2093596 and 2311576 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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