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Reversal of Diastereoselectivity in a Masked Acyl Cyanide (MAC) Reaction: Synthesis of Protected *erythro*-β-Hydroxyaspartate Derivatives

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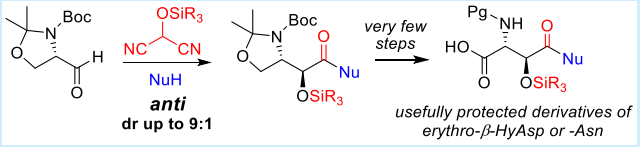
Supporting Information

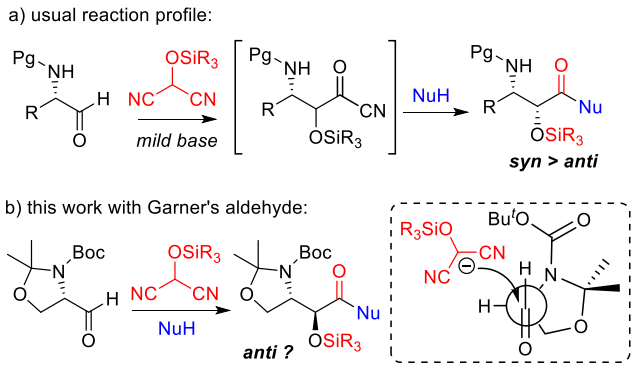
ABSTRACT: Using Garner's aldehyde as a substrate, one-pot MAC hydroxyhomologation reactions proceeded in good yields and with *anti* selectivity for the first time (dr up to 9:1). The products were used to prepare a panel of protected derivatives of *erythro*-β-hydroxyaspartic acid and *erythro*-β-hydroxyasparagine as single enantiomers in a few steps.



α-Hydroxy-β-amino acids are an important class of compounds found in many biologically active natural products.[1] A variety of approaches for their asymmetric synthesis have been considered, including aminohydroxylation,[2] Mannich reactions,[3] and chiral epoxide ring-opening,[4] among others.[5] Diastereoselective approaches include α-hydroxylation of a β-amino acid derivative,[6] addition of a hydroxyacetate equivalent to a chiral imine,[7] and addition of a carbon nucleophile to an α-amino aldehyde or α-amino acid derivative.[8]

In the latter context, the three-component MAC (Masked Acyl Cyanide) methodology can be used to combine an α-amino aldehyde, a one-carbon nucleophile in the form of a silyloxymalononitrile, and a nucleophile (alcohol or amine).[9] The α-hydroxy-β-amino acid moiety is thus constructed and derivatized (as an ester or an amide) in a one-pot procedure (Scheme 1a).[10] Since the nucleophile can be the free amine of an amino acid or a peptide, MAC reactions have been employed in the syntheses of the natural products bestatin[11] and cyclotheonamide C,[12] as well as α-ketoamide serine protease inhibitors[13] and heterocycles derived from 3-amino-2,4-dihydroxybutanoic acid.[14,15]

Scheme 1. MAC Reaction for Preparing α-Hydroxy-β-amino Acid Derivatives and Rationale for This Work



To date, MAC reactions have invariably shown a *syn* diastereoselectivity (*syn*:*anti* around 4:1); although the origin of this selectivity has not been probed, it may occur through a Cram-chelate model involving a hydrogen bond between the protected amine and the aldehyde during the first step of the reaction (Scheme 1a). For the further development of this methodology it would be advantageous if the diastereoselectivity could be reversed. To this end, we chose to study the reactivity of (*S*)-Garner's aldehyde.[16] Attack by the silyloxymalononitrile anion in nonchelating conditions might be expected to follow the Felkin–Anh model leading to an *anti* MAC product (Scheme 1b).[17]

We began by evaluating the three-component MAC reaction between Garner's aldehyde **1**, the *tert*-butyldimethylsilyl ether of hydroxymalononitrile (H-MAC-TBS, the most common MAC reagent) **2**, and methanol, using different bases and reaction conditions in ether (Table 1). Using 1 equiv of 4-pyrrolidinopyridine (4-PP) as the base and 2 equiv of **2** at 0 °C, conditions which were employed previously,[10,11] we obtained a separable mixture of the diastereomeric adducts **3** (major) and **3′** (minor) in 79% yield (entry 1). DMAP performed equally well as the base, while imidazole was less efficient and pyridine failed completely (entries 2–4). Raising or lowering the temperature of the reaction using DMAP led to lower yields (entries 5–6). In reactions employing only a slight excess of **2** (1.2 equiv), the yield was effectively maintained (77%) with 4-PP and improved slightly to 91% with DMAP (entries 7–8). No improvement was observed when 2 equiv of DMAP were used (entry 9).

^{1}H NMR spectroscopy in DMSO-d_6 solution at 80 °C was used to establish the **3**/**3′** diastereomeric ratios (dr). Rapid interconversion of rotamers occurred at the elevated temper-

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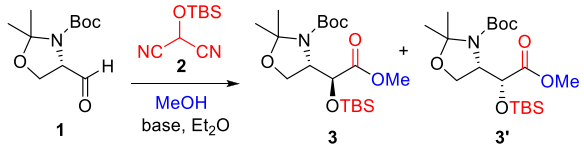
Table 1. Optimization of MAC Reaction Conditions[a]



entry	2 (equiv)	base	T (°C)	dr[b] 3/3′	yield[c] (%)
1	2	4-PP	0	80:20	79
2	2	DMAP	0	80:20	80
3	2	imidazole	0	75:25	46
4	2	pyridine	0	–	0
5	2	DMAP	20[d]	80:20	72
6	2	DMAP	−25	80:20	58
7	1.2	4-PP	0	80:20	77
8	1.2	DMAP	0	80:20	91
9	1.2	DMAP[e]	0	80:20	71

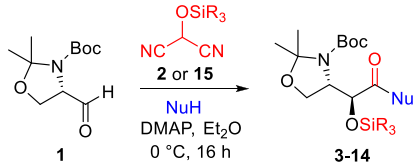
[a]Reaction conditions (unless otherwise indicated): Garner's aldehyde **1** (*c.* 0.5 mmol), H-MAC-TBS **2**, base (1 equiv), and MeOH (3 equiv) in Et_2O (12 mL/mmol of **1**) for 16 h. [b]Diastereomeric ratio (dr) was determined by ^1H NMR analysis (DMSO-d_6 at 80 °C) on the crude product. [c]Isolated yield of diastereomeric mixture. [d]Reaction time 5 h. [e]2 equiv of DMAP were used.

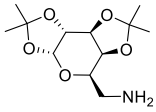
ature, which simplified the spectra and facilitated the analyses. In all the reactions shown in Table 1, the dr was close to 4:1; gratifyingly, the major isomer **3** had the desired *anti* relative configuration. Tentative assignment was made at this point by comparison with published NMR data for **3** and **3′**, previously prepared from Garner's aldehyde by a longer route,[17d] and subsequently confirmed by chemical transformations and X-ray data (*vide infra*).

Retaining the best conditions from the above survey, we confirmed the scope of the *anti*-selective MAC reaction of Garner's aldehyde **1** using other reaction partners (Table 2). Four other primary alcohols (ethyl, benzyl, allyl, isobutyl) performed satisfactorily, giving adducts **4**–**7** in moderate to good yields (55–73%), while isopropyl alcohol gave **8** less efficiently (27%). In all cases, the *anti*/*syn* dr was 4:1. Use of ammonia as the nucleophile furnished the primary carboxamide **9** rapidly, again with a 4:1 dr. With *N*,*O*-dimethylhydroxylamine, Weinreb amide **10** was obtained more slowly but in excellent yield (90%) and with an improved dr (9:1). The reaction of a more highly functionalized chiral amine, 6-amino-6-deoxy-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose, gave **11** in good yield and with a dr of 4:1, suggesting the diastereoselectivity to be largely independent of chiral information embedded in the nucleophilic partner. Compound **11** bears the protected core of an advanced intermediate in the synthesis of a sialyl Lewis^x mimetic designed as a selectin antagonist.[18] A MAC reagent with a more robust silyl group, the *tert*-butyldiphenylsilyl ether of hydroxymalononitrile (H-MAC-TBDPS, **15**), was also investigated. Its reactions with methanol and benzyl alcohol (entries 10–11) gave the *anti* products **12** and **13** in good yields and with a rewarding dr of 9:1, probably the result of the increased steric bulk of the reagent. The MAC reaction of **15** with ammonia furnished carboxamide **14** in 75% yield and a dr of 5.7:1. The *anti* diastereomer was isolated pure by chromatography, and its structure was confirmed by X-ray crystallography (CCDC 1888027; Figure 1).

Compound **3** was subjected to acidic conditions to effect the hydrolysis of the *N*,*O*-acetonide. This resulted in spontaneous

Table 2. Scope of the *anti*-Selective MAC Reaction[a]



entry	SiR_3	NuH	product	dr[b]	yield[c] (%)
1	TBS	MeOH	**3**	80:20	91
2		EtOH	**4**	80:20	63
3		BnOH	**5**	80:20	64
4		allyl-OH	**6**	80:20	73
5		*i*-BuOH	**7**	80:20	55
6		*i*-PrOH	**8**	80:20	27
7		NH_3[d]	**9**	80:20	63
8		MeONHMe[e]	**10**	90:10	90
9			**11**	80:20	79
10	TBDPS	MeOH	**12**	90:10	67
11		BnOH[f,g]	**13**	90:10	87
12		NH_3[d,g]	**14**	85:15	75

[a]Reaction conditions (unless otherwise indicated): Garner's aldehyde **1** (*c.* 0.5 mmol), H-MAC-TBS **2** or H-MAC-TBDPS **15** (1.2 equiv), DMAP (1 equiv), and nucleophile (3 equiv) in Et_2O (12 mL/mmol of **1**). [b]Diastereomeric ratio (dr) was determined by ^1H NMR analysis (DMSO-d_6 at 80 °C) on the crude product. [c]Isolated yield of diastereomeric mixture. [d]Reaction time 30 min. [e]Reaction time 72 h. [f]2 equiv of **15** were used; reaction carried out at rt. [g]2 equiv of DMAP were used.

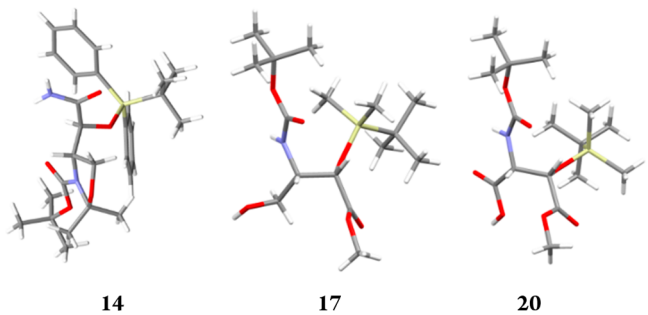


Figure 1. X-ray crystallographic structures of **14**, **17**, and **20**.

lactonization, providing γ-lactone **16** in 61% yield (Scheme 2). Efficient conversion of this latter compound to **17** was facilitated by mild methanolysis, and the reverse reaction could be performed in acidic conditions. The *anti* geometry of **17** was confirmed by X-ray crystallography (CCDC 1888028; Figure 1). Both **16** and **17** were observed previously as side products in the studies of the *syn*-selective MAC reaction conducted on *N*-Boc-*O*-benzylserinal.[14] In those studies, the *syn* diastereomer of **17** was transformed into a *syn* α-hydroxy-β-aziridino ester.[14] To complement that work, **17** was tosylated in excellent yield to give **18**, which was cyclized upon

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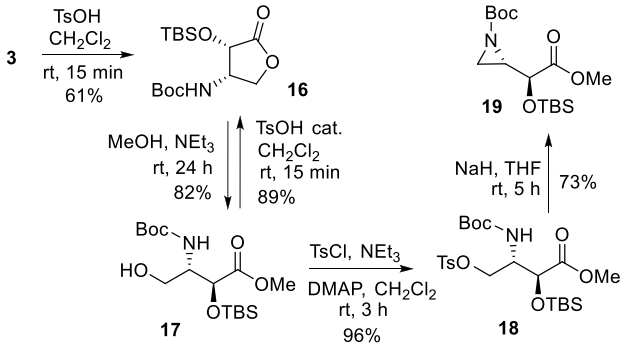
Scheme 2. Transformations of Compound 3

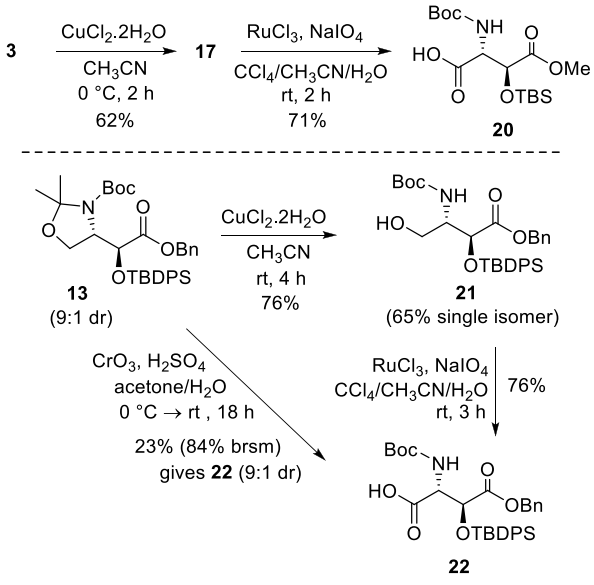


treatment with sodium hydride, giving the corresponding *anti* α-hydroxy-β-aziridino ester **19** (Scheme 2). This latter derivative is an example of a 2-(carboxymethyl)aziridine, a class of compounds which represent strained β-amino acids.[19]

Pertinent synthetic targets for this new development of MAC methodology came in the form of the special-case α-hydroxy-β-amino acids *erythro*-β-hydroxyaspartic acid (*e*HyAsp) and *erythro*-β-hydroxyasparagine (*e*HyAsn). These residues appear in a range of complex peptide or depsipeptide natural products,[20] many of which display cytotoxic, antibacterial, and/or siderophore activities. Nonetheless, access to protected nonracemic *e*HyAsp and/or *e*HyAsn derivatives amenable to peptide synthesis is limited: syntheses are generally inefficient and require multistep sequences, implicating ammonolysis of (2*R*,3*R*)-epoxysuccinic acid,[21] desymmetrization of (2*R*,3*R*)-tartaric acid,[22] or strong-base mediated hydroxylation of an aspartate diester.[23] More expedient access to orthogonally protected *e*HyAsp and *e*HyAsn derivatives was now forthcoming from the *anti*-selective MAC reaction.

To prepare derivatives of *e*HyAsp, a milder *N*,*O*-acetonide hydrolysis was required (Scheme 3). Treatment of **3** with copper(II) chloride dihydrate[24] allowed its direct transformation into **17** in 62% yield. Oxidation of **17** using ruthenium chloride/sodium periodate in a ternary solvent system[25] was achieved smoothly to furnish **20** in 71% yield; the

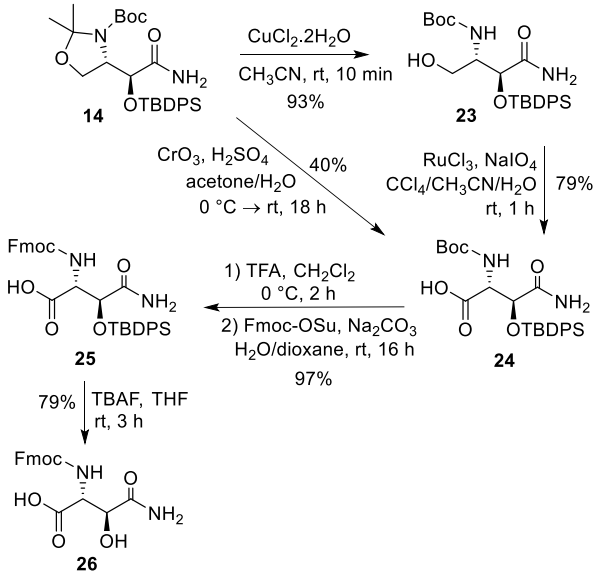
Scheme 3. Preparation of *e*HyAsp Derivatives 20 and 22



structure of this compound was confirmed by X-ray crystallography (CCDC 1888026; Figure 1). Previously, the enantiomer of **20** was prepared by a more onerous route and used as an intermediate in the total synthesis of mugenic acid, a phytosiderophore.[26] To prepare a complementary derivative, the diastereomeric mixture **13**/**13′** was hydrolyzed as above and the minor *syn* isomer was removed by chromatography to leave **21** as a single compound (65% yield); it was oxidized uneventfully to provide **22** (76% yield). Although this *e*HyAsp derivative has not been described before, its protecting group suite was considered propitious for the *threo* stereoisomer, prepared in 11 steps, and employed in a total synthesis of alterobacin A, a siderophore natural product from an ocean bacterium.[27] We also found that the diastereomeric mixture **13**/**13′** (9:1 dr) could be transformed directly into the diastereomeric mixture **22**/**22′** (9:1 dr) using Jones reagent, although the reaction was sluggish, as had been noted in previous studies on related systems.[17a,b]

The *anti*-selective MAC methodology also provided rapid access to *e*HyAsn derivatives (Scheme 4). Mild hydrolysis of

Scheme 4. Preparation of *e*HyAsn Derivatives 24, 25, and 26



14 gave **23** in 93% yield, and then oxidation led to **24** in 79% yield. The direct transformation **14** → **24** was also achieved in 40% yield using Jones reagent. Derivative **24** was the preferred protected form of *e*HyAsn in the multistep synthesis of the southern hemisphere of theonellamide F, a cytotoxic bicyclic dodecapeptide isolated from a marine sponge;[21a] previously, its synthesis required at least five chemical steps.[21a,28] Solid phase peptide synthesis (SPPS) techniques usually employ an Fmoc coupling strategy, and there is a paucity of Fmoc-protected *e*HyAsn derivatives in the literature. Compound **24** was transformed into **25** in two steps in near-quantitative yield. Fluoride-mediated selective removal of the silyl group gave the derivative **26** in 79% yield. While full details were not disclosed, 6 or 7 steps appear to have been used to prepare this singular Fmoc-protected *e*HyAsn, employed in a total synthesis of stellatolide A, a cytotoxic cyclodepsipeptide.[20d]

In summary, we have used Garner's aldehyde to demonstrate the first examples of the MAC hydroxyhomologation reaction with an *anti* diastereoselectivity; the products serve as polyfunctionalized nonracemic building blocks. The

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modularity of the nucleophile component in the reaction lends itself to very short syntheses of a selection of orthogonally protected derivatives of *e*HyAsp and *e*HyAsn, which can be expected to be of use in multistep syntheses of complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00664.

Experimental procedures; spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds; X-ray crystallographic data for **14**, **17**, and **20** (PDF)

Accession Codes

CCDC 1888026−1888028 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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