Synthetic Methods

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Straightforward Access to Protected *syn* α-Amino-β-hydroxy Acid Derivatives**

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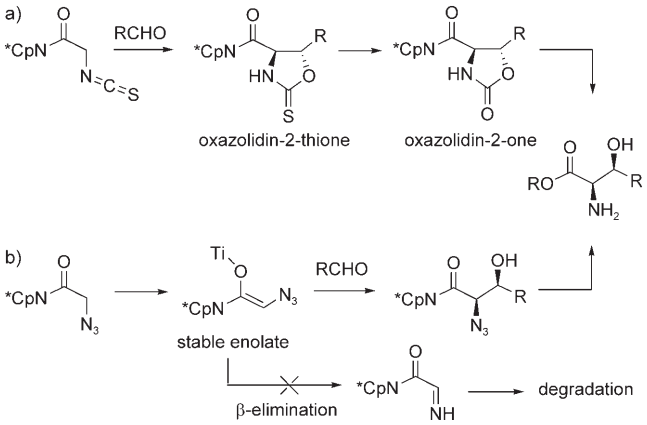
syn α-Amino-β-hydroxy acids are the key structures of many natural products exhibiting a wide range of biological activities. For example, *syn* α-amino-β-hydroxy acids are found in vancomycin[1] or polyoxins[2] (antibiotics), cyclomarins[3] (cytotoxic, anti-inflammatory), ustiloxins[4] (antibiotic, antimitotic), and exochelins[5] (iron chelator). Many studies have been devoted to the synthesis of this unit and most of them rely on an aldol reaction between a glycine equivalent[6] and an aldehyde. Among these glycine equivalents, the most effective are those bearing an isothiocyanate unit as a masked amino group, which proved to be very effective in either diastereoselective or enantioselective aldol reactions.[7] However, recovering the free amino alcohol requires hydrolysis of the resulting oxazolidin-2-thione; this is not a trivial step as prior transformation of the oxazolidin-2-thione into the more easily hydrolyzed oxazolidin-2-one is needed (Scheme 1).[7c,f] The need for a more straightforward and flexible approach to the *syn* α-amino-β-hydroxy acid moiety justifies the use of the azide goup as a masked amine.[8] This azide group is a convenient protecting group (Scheme 1) because it is readily converted into an amine. Nevertheless, it is well known that enolates of α-azido ketones or esters are not stable and that they spontaneously decompose into α-imino ketones or esters.[9] A few reports, however, show that these enolates can be trapped by electrophiles such as aldehydes when EtONa or DBU (DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene) is used as a base in substoichiometric amounts to give racemic aldol products in both moderate yields and diastereoselectivities.[9] To our knowledge, these are the only examples of using enolates of α-azido ketones or esters as aldol precursors. We believe that the potential of this reaction has long been underexploited because of the instability of the intermediate enolate. We have recently shown that titanium enolates derived from *N*-acyl-oxazolidin-2-thiones were stable and could be used in diastereoselective aldol reactions by forming the reputedly unstable α-CF_3 enolates.[10] Moreover, we have shown that *N*-acyl-thiazolidin-2-thiones[11] could be easily replaced by an ester or an amide by the simple addition of the corresponding alcohol or amine, respectively, in the presence of a slight excess of imidazole. The thiazolidin-2-thiones can act as a chiral auxiliary, as well as an activated ester.



Scheme 1. Isothiocyanate vs azide as a masked amino group. a) Isothiocyanate as a masked amino group; see reference [7]. b) Azide as a masked amino group; this work. *CpN = oxazolidin-2-one, oxazolidin-2-thione, or thiazolidin-2-thione.

Herein we report that the α-azido enolates (**2**) derived from *N*-acyl-thiazolidin-2-thione substrates (**1**) can also be used in diastereoselective aldol reactions, providing a convenient method to access protected *syn* α-amino-β-hydroxy acid derivatives (Table 1).

Preparation of (*R*)-*N*-2-azidoacetyl-4-phenylthiazolidin-2-thione (**1**) was achieved either by direct coupling of 2-azidoacetic acid[12] with (*R*)-4-phenylthiazolidin-2-thione (prepared from D-phenylglycine) in the presence of DCC (DCC = dicyclohexylcarbodiimide),[10,13] or by the preliminary formation of the corresponding acid chloride of 2-azidoacetic acid and subsequent coupling with (*R*)-4-phenyl-thiazolidin-2-thione in the presence of Et_3N (yields were usually slightly better than the first method, 70–80%). Aldol reactions were conducted by using reported procedures:[13,14] compound **1** in CH_2Cl_2 was cooled to −78 °C and treated with $TiCl_4$ (1.05 equiv), and stirred for 15 minutes. iPr_2NEt (1.1 equiv) was then added to the reaction mixture and stirred for 1 hour. NMP (2 equiv) was added and then the reaction mixture was stirred for 15 minutes, after which the aldehyde (1.5 equiv) was added.

Aldehydes **3a–g** readily afforded the *syn*-aldol products (**4**) as single diastereomers (as evaluated by ^1H NMR analysis of the crude reaction mixture) without noticeable degradation of the enolate (Table 1).[15]

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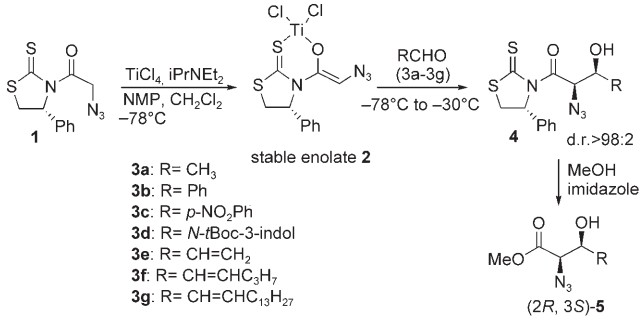
Table 1: Diastereoselective aldol reaction and transesterification.

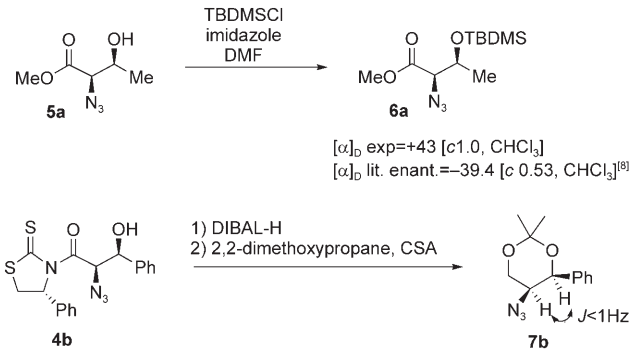


Entry	Aldehyde (**3a–g**)	**4** [%][a]	**5** [%][b]	d.r. **5**
1	CH_3CHO (**3a**)	n.a. (**4a**)	61 (**5a**)	>98:2
2	PhCHO (**3b**)	75 (**4b**)	64 (**5b**)	>98:2
3	*p*-NO_2PhCHO (**3c**)	76 (**4c**)	70 (**5c**)	>98:2
4	*N*-*t*Boc-indol-3-carboxaldehyde (**3d**)	70 (**4d**)	66 (**5d**)	>95:5[c]
5	CH_2=CHCHO (**3e**)	62 (**4e**)	68 (**5e**)	>98:2
6	(*E*)-C_3H_7CH=CHCHO (**3f**)	60 (**4f**)	68 (**5f**)	>95:5[c]
7	(*E*)-$C_{13}H_{27}$CH=CHCHO (**3g**)	n.a. (**4g**)	70 (**5g**)	>98:2

[a] Yield of aldol product after chromatography. [b] Yield of ester without prior purification of the aldol product. [c] Epimerization occurred during methanolysis (10 equiv imidazole for **5d** and 3 equiv imidazole for **5f**); measured by HPLC and ^{1}H NMR methods. n.a. = not applicable; product not isolated. NMP = *N*-methylpyrrolidinone.

The titanium enolate of **1** reacts with either aliphatic, aromatic, or α,β-unsaturated aldehydes to give the *syn*-aldol products (**4**) in good yields and diastereoselectivities. The products proved to be quite sensitive to hydrolysis during the workup, upon standing, and during column chromatography (particularly for those derived from acetaldehyde or hexadec-2-en-1-al; Table 1, entries 1 and 7, respectively).[15] Therefore, we found it beneficial to directly submit the crude mixture to methanolysis (MeOH/imidazole, 3 equiv of imidazole) to afford the methyl esters (**5**) in good yields. Some degree of epimerization occurred during methanolysis (5% with **5f** and 15% with **5d**). Notably, **4** undergoes epimerization, whereas **5** does not or less; the transesterification of **4d** with 10 equivalents of imidazole decreased the epimerization to only 5% (instead of 15% with 3 equiv). Thus, epimerization can be minimized by using additional amounts of imidazole. The relative and absolute stereochemistry of the aldol products were secured by chemical correlation and shown to correspond to that of the Evans aldol product as expected.[13,14] Indeed, ester **5a** was silylated with TBDMSCl (TBDMS = *tert*-butyldimethylsilyl) to give **6a**, the optical rotation of which compared well with the literature data.[8] As additional proof, **4b** was directly reduced with diisobutylaluminum hydride (DIBAL-H) to the diol, which was then protected as the acetonide (**7b**) and assigned a *cis* configuration based on the measurement of the coupling constants: the measured value ($J < 1$ Hz) is typical for $H_{ax.}$–$H_{eq.}$ coupling constants in an acetonide (Scheme 2).

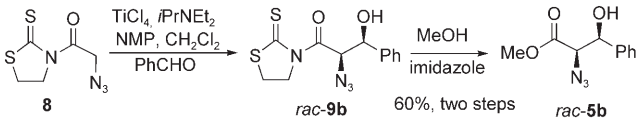
Enantiomeric purity was additionally checked by chiral HPLC analysis. *rac*-**9b** was prepared by using achiral thiazolidi-2-thione **8** and transesterified to *rac*-**5b**. Chiral HPLC (Daicel, Chiralcel OD-H, 250 × 4.6 mm, 5 μm) analysis performed on *rac*-**5b** and (*2R*, *3S*)-**5b**, obtained with the chiral auxiliary **1**, showed >99% *ee* for (*2R*, *3S*)-**5b** (Scheme 3).



Scheme 2. Determination of absolute and relative configurations of aldol products. CSA = camphorsulfonic acid.

As a proof of concept for the efficacy of our methodology, we synthesized two simple natural products and advanced intermediates for drug or complex natural product targets. Indeed, the aldol reaction with aromatic aldehydes provides entries to aryl-β-hydroxy-α-amino acids that can be found in numerous biologically active compounds.

For example, the long chain aliphatic aldehyde hexadec-2en-1-al (**3g**) provided an attractive route to the *threo*-sphingosine skeleton (Scheme 4). Indeed, (2*S*,3*S*)-azido-sphingosine (**10g**) can be obtained efficiently (58% yield)

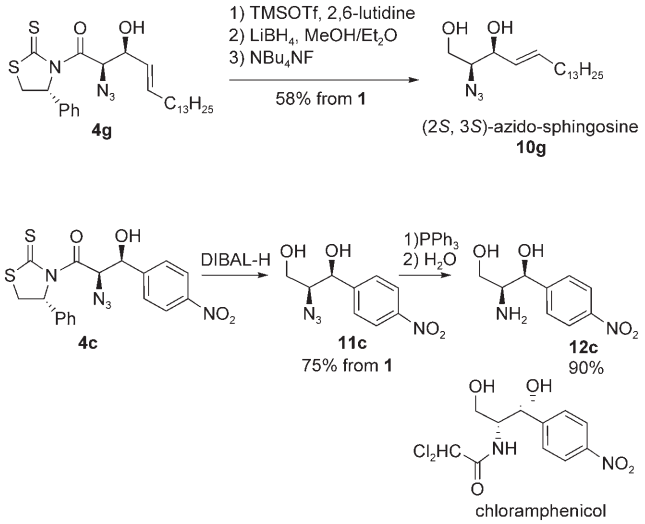


Scheme 3. Preparation of *rac*-**5b**.

from **1** after the aldol reaction and subsequent reduction (temporary protection of the hydroxy group is required to obtain good yields).[16] Reduction of the azido group by classical Staudinger reaction conditions should lead to known L-*threo*-sphingosine,[17] thereby illustrating that this aldol reaction represents one of the simplest and most efficient methods, reported so far, for the synthesis of a sphingosine core.[18]

As another example, we used **4c** (R = *p*-NO_2Ph) for the synthesis of amino alcohol **12c**, the enantiomer of a known precursor of the antibiotic chloramphenicol (Scheme 4). **12c** was prepared in 67% yield over three steps from **1** with excellent enantiomeric purity (99% *ee*). Aldol product **4c** was reduced to **11c** by using DIBAL-H and the the reduction of the azido group was accomplished by using a Staudinger reaction. This is one of the most efficient methods to access chloramphenicol.[18a,19]

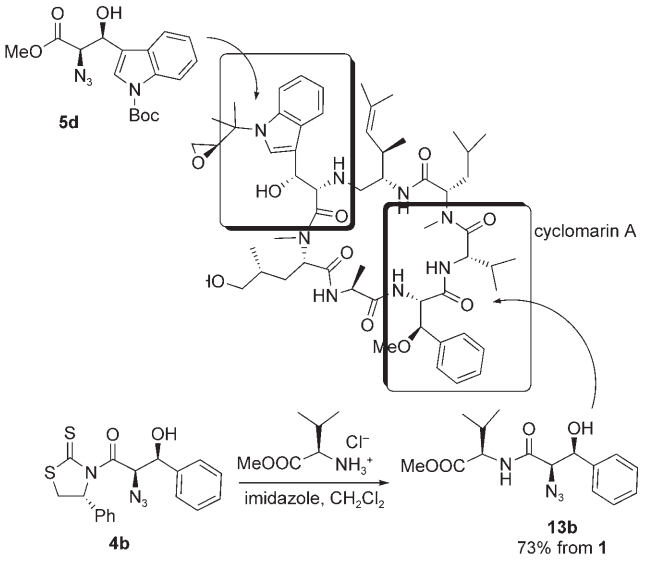
A last example is provided by derivative **5d**, the enantiomer of which can be found in the cyclomarins, and



Scheme 4. Preparation of L-*threo*-azido-sphingosine (**10g**) and chloramphenicol precursor **12c**.

has been prepared in 66% yield from *N*-*t*Boc-indol-3-carboxaldehyde (**3d**) (Scheme 5).[3] Furthermore, **4b**, when treated with D-valine methyl ester yields dipeptide **13b** with high enantiomeric purity in two steps; the enantiomer of **13b** is also present in the cyclomarins. Aldol products **4** can therefore be directly incorporated into a peptidic sequence without the requirement of an additional activating agent because the thiazolidin-2-thione moiety is a good leaving group. Again, our methodology competes favorably for the efficient synthesis of such amino acid derivatives.[20]

We have thus developed an easy and efficient aldol reaction procedure to generate *syn* α-amino-β-hydroxy acids. This is the first report of stable titanium enolates of α-azidoacetyl derivatives being efficiently used in an aldol reaction. The products obtained can be directly incorporated into a peptidic sequence or reduced to the diols as precursors to numerous biologically active compounds.



Scheme 5. **5d** and **13b** derivatives in cyclomarins. Boc = *tert*-butyloxycarbonyl.

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[15] To ensure high yields, caution should be taken: all solvents and reagents must be distilled prior to use. HCl free $TiCl_4$ bottle should be used as traces of HCl gave rise to deacylation of the *N*-acyl-thiazolidin-2-thione (**1**) during enolization. Caution should also be taken during hydrolysis and extraction which should be realized quickly with cold solutions to avoid partial hydrolysis of the aldol products. Products should also be used as soon as possible in subsequent reactions, preferably without purifications, and should not be kept on the bench at room temperature (see the supporting information).

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