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Synthesis of threo-β-aminoalcohols from aminoaldehydes via chelation-controlled additions. Total synthesis of L-threo sphingosine and safingol

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ABSTRACT

Chelation-controlled addition of organocuprates to *N*-carbamoyl aminoaldehydes, prepared from functionalized amino acids, generated predominately the threo-β-amino alcohol derivatives through chelation with the carbamoyl moiety. The carbamate group is a stronger chelating group than other potentially good chelators, for example ethers, esters, thioethers, and gives good diastereoselectivity with cuprates. Thus addition of lithium divinylcuprate to the aldehyde generated from the serine derivative **25** in the presence of extra copper for chelation afforded the threo compound **26** in 83% yield. Cross-metathesis and cleavage of the protecting groups furnished L-threo sphingosine **21**. In addition the lyso-sphingolipid protein kinase C inhibitor, safingol, **22**, was prepared from commercially available *O*-benzyl *N*-BOC serine **28** in six steps and 56% overall yield by this method.

Introduction

Vicinal amino alcohols are an important class of compounds having significant biological and chemical properties. In addition to peptides and sugars, a number of naturally occurring compounds that exhibit interesting biological properties, including ritonavir **1**, bestatin **2**, AI-77-B **3**, anisomycin **4**, and pseudo-ephedrine **5** (Fig. 1), all have a *syn*-vicinal amino alcohol moiety.[1,2] Moreover many compounds possessing a threo-amino alcohol moiety have been designed for a variety of scientific purposes.[3] Recently, numerous catalytic reactions have been developed using amino alcohols as catalysts or ligands for catalysis.[4] Therefore, finding a good stereospecific method to these amino alcohols would facilitate their preparation.[1] Among other approaches, strategies that utilize α-amino aldehydes might offer certain advantages,[5] namely many natural amino acids are commercially available and these starting materials already have one chiral center, which conceivably could be instrumental in directing the stereochemical outcome of subsequent transformations. Consequently, expensive chiral catalysts might not be required for these approaches. Figure 2 shows the two opposite approaches that follow different addition models. Pathway (a) would give the anti β-amino alcohols by the Felkin–Anh model[6] while pathway (b) would provide the *syn* β-amino alcohols by the chelation-controlled cyclic Cram model.[7] There have been some studies in which *N*,*N*-diprotected

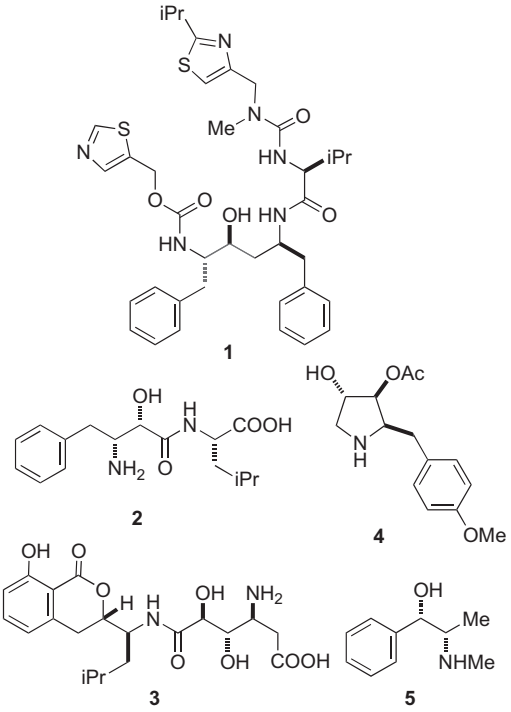

Figure 1. Threo vicinal amino alcohol containing compounds.

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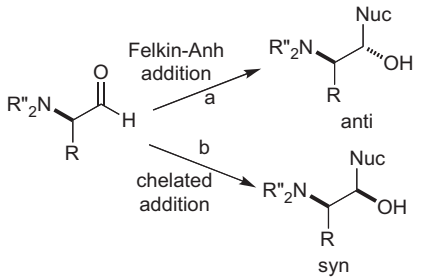


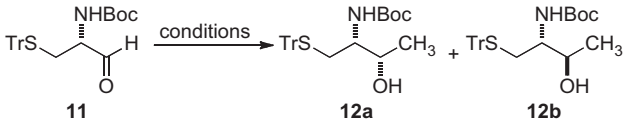
Figure 2. *Syn* and anti additions to α-aminoaldehyde derivatives.

α-amino aldehydes,[8] Garner's aldehydes,[9] and monoprotected α-amino aldehydes[10] are used as electrophiles to synthesize either anti-amino alcohols or *syn*-amino alcohols. However, these studies were limited to only simple amino aldehydes and often suffered from poor selectivities and low yields. To the best of our knowledge, amino aldehydes derived from cysteine, glutamic acid, aspartic acid, threonine, and tyrosine have never been studied for the chelation-controlled addition to produce β amino alcohols stereospecifically. Herein, we report the highly stereoselective chelation-controlled addition of nucleophiles to amino aldehydes that provide *syn*-β-amino alcohols with synthetically useful functionalized alkyl side chains.

Results and discussion

For one of our medicinal chemistry projects, we designed the peptidomimetic compound **6** (Cbz-LPAT∗) that mimics the sorting signal of Sortase A from *Staphylococcus aureus* (Fig. 3). Previously[3] we reported the synthesis of the protected thiol-containing threonine analogue **8** from L-threonine **7**. Because of the demand for larger quantities of **6** for use in other sorting signal mimics, we designed a new synthetic route that could improve the synthesis but required the addition of a methyl group to a protected aldehyde derived from cysteine **9** in a stereospecific manner to afford the desired *syn*-configuration **10**. Although we could find no precedent for clean addition of alkyl groups to a protected cysteine aldehyde, we envisioned a bulky thio-protecting group enhancing the diastereoselectivity of the reaction while shielding the sulfur from any undesired chelation. Therefore, we chose the acid-labile *tert*-butoxycarbonyl (Boc) and triphenylmethyl (trityl, Tr) groups as the *N*- and *S*-protecting groups, respectively, for the protected cysteine aldehyde in our study of the alkylation. The *N*-Boc, *S*-Tr protected cysteine aldehydes were prepared from the corresponding readily available protected acid by borane reduction followed by oxidation using freshly prepared Dess–Martin periodinane. The sequence was chosen over other possible routes, for example, DIBAL reduction of the Weinreb amide, because of its practicality and mild conditions, which are known to give minimal

Table 1
Optimization of the chelation controlled addition



Entry	Nucleophiles	Solvents	Temp	h	**12a**:**12b**
1	MeLi	Et_2O	−78 °C	1	1:1
2	MeMgBr	Et_2O/tol	0 °C	2	2:1
3	$Me_2CuMgBr$	Et_2O/tol	−40 °C	5	7:3
4	Me_2CuLi	THF	−40 °C	3	N.R.
5	Me_2CuLi	Et_2O	−40 °C	3	**12a** only
6	MeCu	Et_2O	−40 °C	3	N.R.

epimerization.[10,11] As shown in Table 1, although addition of methyllithium gave no selectivity (entry 1), we were able to obtain the two, diastereomeric products[12] that were easily separable by flash column chromatography. Addition of methylmagnesium bromide (entry 2) gave a slight excess (2:1) of the desired *syn* compound, and the addition of bromomagnesium dimethylcuprate improved the selectivity (7:3) but was not satisfactory. Lithium dimethylcuprate in THF (entry 4) gave no reaction. Therefore the result of alkylation using lithium dimethylcuprate in diethyl ether (entry 5) was somewhat unexpected. We observed complete diastereoselectivity and did not see any of the other diastereomer in this case. We believe that the bulky nature of the trityl protected thiol blocks the other side of the aldehyde and at the low reaction temperature, the reaction gives only the desired *syn*-amino alcohol product. Methyl copper (I) was not reactive at all under the same conditions (entry 6). With the optimal conditions for the chelation-controlled alkylation established, we applied this method to the synthesis of **17**, the intermediate for the threonine modifier **6**, from D-*N*-Boc *S*-trityl cysteine **13** (Scheme 1). Borane reduction of the carboxylic acid of **13** afforded the primary alcohol **14** in 96% yield. The alcohol **14** was then oxidized with Dess–Martin periodinane in the presence of sodium bicarbonate to give the aldehyde **15**. In order to avoid any epimerization, the crude aldehyde **15** was subjected to the crucial alkylation using the optimized conditions of Table 1. The secondary alcohol **16** was isolated in 92% yield for the two steps. Deprotection of the *N*-Boc group of **16** was effected by treating **16** with 50% TFA solution in dichloromethane to yield the threonine modifier **17** in 85% yield. Therefore, the new modifier **17** was prepared in four steps from the protected amino acid in 75% overall yield. This improved procedure provided a sufficient amount of **17** for preparing **6** as well as other sorting signal mimics.

Inspired by the excellent selectivity and yields of this cysteine case, we decided to screen other amino aldehydes that are derived from functionalized amino acids such as serine, threonine, aspartic

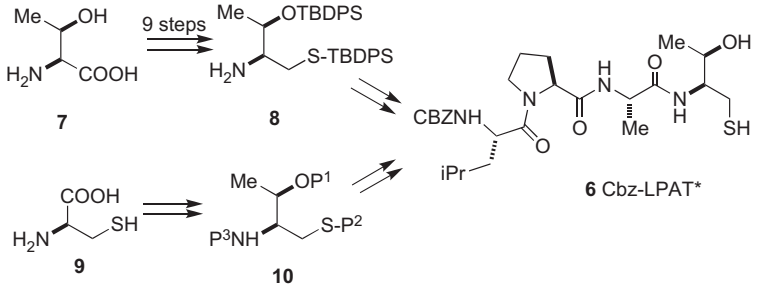
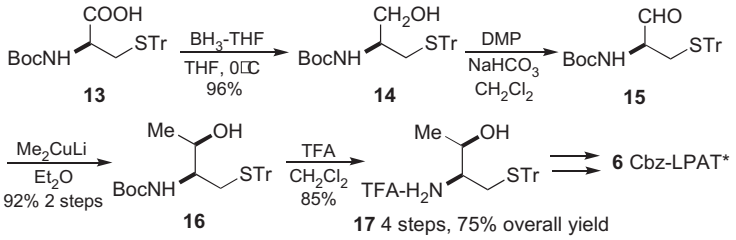


Figure 3. Proposed preparation of the new threonine modifier **10**.



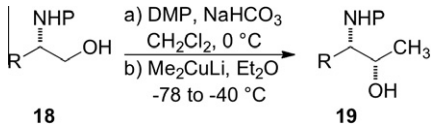
Scheme 1. Improved method for synthesis of **6**.

acid, glutamic acid, and tyrosine. Although chelation-controlled addition of metallated nucleophiles to protected α-aminoaldehydes derived from less functionalized amino acids or cyclic derivatives such as Garner's aldehyde is well known,[10,13] analogous additions to functionalized systems where additional chelating groups are present has not been reported. The results of the initial screening studies were quite good as shown in Table 2.

All of the primary alcohols were prepared by reduction of the corresponding acids with the borane-THF complex. As shown, both Boc and Cbz groups were suitable for the N-protecting groups. For the alcohol protection, a *tert*-butyl ether (entries 2, 3, 6, and 7) proved to be an excellent choice for increasing the *syn*-selectivity of the addition. The large TIPS ether also gave the desired *syn*-compound with excellent selectivity (entry 4). A benzyl ether was a good protecting group for the aldehydes derived from serine (entry 5), threonine (entry 8), and tyrosine (entry 11). The *tert*-butyl esters of aspartate and glutamate (entries 9 and 10) were also shown to improve selectivity. It is noteworthy that the *tert*-butyl ethers of the aldehydes derived from homoserine (entry 6) and even bis-homoserine (entry 7) both gave excellent selectivity.

After the good results obtained with lithium dimethylcuprate, we wanted to see if other nucleophiles could be utilized. As shown in Table 3, adding longer alkyl groups, butyl and hexyl, to the protected cysteine (entries 1 and 3) and serine (entries 2 and 4) aldehydes presented no problems for the selectivity. We wanted to extend our methodology to unsaturated nucleophiles, since alkenyl groups are synthetically quite useful and versatile. However, our initial attempts at adding alkenyl nucleophiles to the protected aldehydes were problematic. The addition of vinyl-magnesium bromide (entry 5) to the Boc and benzyl protected serine aldehyde gave only a 60:40 mixture of the *syn*- and anti-compounds. Addition of bromomagnesium divinylcuprate (entry 6) had essentially no effect on the selectivity. Addition of vinylmagnesium chloride (entry 7) and chloromagnesium divinylcuprate (entry 8) improved the selectivity slightly. We believed that the poor selectivity came from weaker chelation and therefore decided to add a chelating agent before adding the nucleophiles. Since we postulated that the lithium dialkylcuprates chelated the aldehydes well (Tables 2 and 3, entries 1–4), we decided to add one equiv of lithium dialkylcuprate to chelate the aldehydes before the addition of the alkenyl nucleophiles. One equivalent of lithium dimethylcuprate followed by the addition of excess chloromagnesium divinylcuprate (entry 9) gave a much better selectivity and allowed us to isolate 62% of the desired *syn*-product. Since transferring the

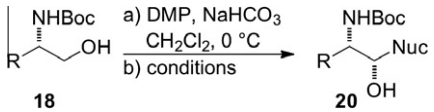
Table 2
Reaction of lithium dimethylcuprate with amino aldehydes



18 19

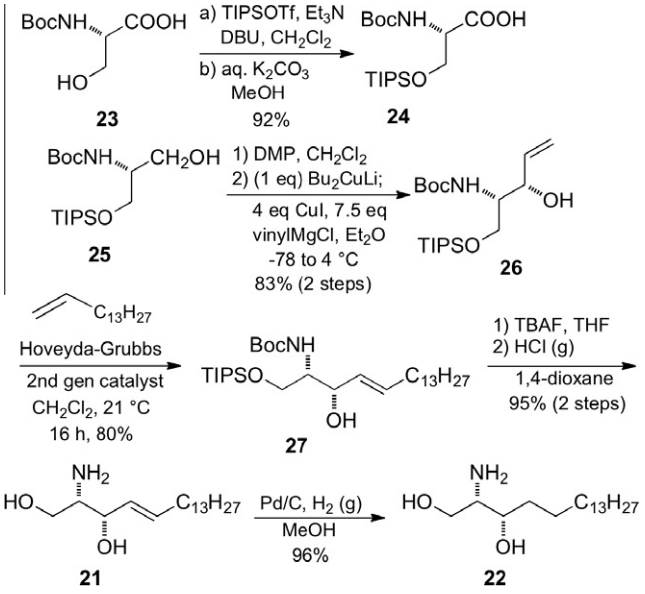
Entry	P	R	Yield (%)	(% de)
1	Boc	CH_2STr	92	⩾99
2	Cbz	CH_2OtBu	87	⩾95
3	Boc	CH_2OtBu	88	⩾95
4	Boc	CH_2OTIPS	91	⩾95
5	Boc	CH_2OBn	88	⩾95
6	Cbz	$(CH_2)_2OtBu$	82	⩾95
7	Cbz	$(CH_2)_3OtBu$	85	⩾95
8	Boc	(*R*) MeCHOBn	90	⩾95
9	Cbz	CH_2CO_2tBu	83	⩾90
10	Cbz	$(CH_2)_2CO_2tBu$	90	⩾95
11	Boc	CH_2-4-$(OBn)C_6H_4$	85	⩾95

Table 3
Reactions of various amino aldehydes with other nucleophiles

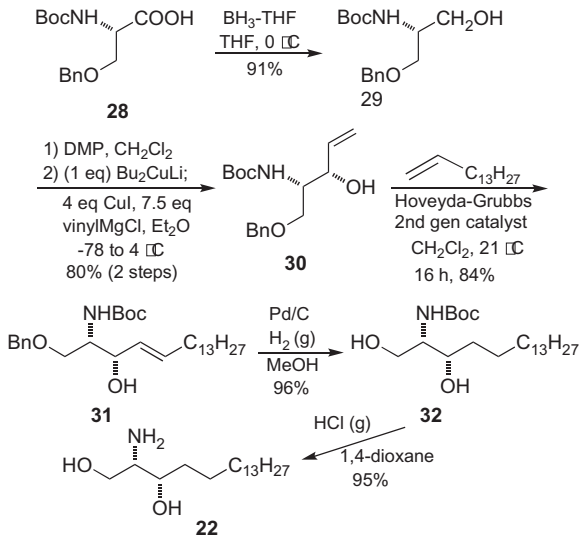


18 20

Entry	Nucleophiles	R	Solvent	Temp/hours	Yield (%)	*syn*/anti
1	nBu_2CuLi	CH_2STr	Et_2O/hexanes	−78 °C to −40 °C/ 4 h	88	⩾98/2
2	nBu_2CuLi	CH_2OBn	Et_2O/hexanes	−78 °C to −40 °C/ 4 h	83	⩾95/5
3	$nHex_2CuLi$	CH_2STr	Et_2O/hexanes	−78 °C to −40 °C/ 5 h	91	⩾95/5
4	$nHex_2CuLi$	CH_2OBn	Et_2O/hexanes	−40 °C/ 5 h	86	⩾95/5
5	VinylMgBr	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	n/c	60/40
6	$(Vinyl)_2MgBr$	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	n/c	63/37
7	VinylMgCl	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	n/c	65/35
8	$(Vinyl)_2MgCl$	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	n/c	67/33
9	Me_2CuLi (1 equiv)/ $(Vinyl)_2MgCl$	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	62	76/24
10	Me_2CuLi(1 equiv)/ CuI+VinylMgCl	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	69	78/22
11	Bu_2CuLi (1 equiv)/ CuI+VinylMgCl	CH_2OBn	Et_2O/THF	−78 °C to 0 °C/ 1 h	80	85:15
12	Me_2CuLi (1 equiv)/ CuI+VinylMgCl	CH_2OTIPS	Et_2O/THF	−78 °C to 0 °C/ 1 h	72	80:20
13	Bu_2CuLi (1 equiv)/ CuI+VinylMgCl	CH_2OTIPS	Et_2O/THF	−78 °C to 0 °C/ 2 h	83	89:11



Scheme 2. Synthesis of threo-sphingosine **21** and safingol **22**.



Scheme 3. Alternative synthesis of Safingol **22**.

suspension of the pregenerated halomagnesium divinylcuprate was cumbersome, we attempted to generate the divinylcuprate species in the reaction mixture after the initial chelation by the lithium dialkylcuprate (entries 10–13) by adding copper iodide and vinylmagnesium chloride sequentially. This improved the selectivity and convenience of the procedure. Moreover, substituting lithium dibutylcuprate for lithium dimethylcuprate enhanced the selectivity in favor of *syn*-products, presumably due to its larger steric bulk (entries 12 and 13).

The good selectivity for the addition of alkenyl organometallics to the protected serine aldehydes prompted us to design syntheses of L-threo-sphingosine and safingol. Both molecules possess a *syn*-β amino alcohol unit and have shown interesting biological activities.[14] Although many other synthetic approaches to these molecules have been described,[14a,15] we believed that straightforward routes from protected serine aldehydes could offer new alternatives for the syntheses of these molecules. Commercially available L-*N*-Boc-serine **23** was converted in three steps via acid **24** to the silyl protected serinol **25** (Scheme 2). Oxidation to the aldehyde followed by the chelation-controlled vinylation gave the desired threo amino alcohol **26** in 83% yield. Cross-metathesis reaction with 1-pentadecene using the Hoveyda–Grubbs second generation catalyst[16] afforded the *E*-alkene **27** in 80% yield. Final two-step removal of the protecting groups provided L-threo-sphingosine **21** in only 8 steps and in 44% overall yield. Additionally, safingol, **22**, a lysosphingolipid protein kinase C inhibitor,[14b,17] was obtained by palladium-catalyzed hydrogenation of L-threo-sphingosine **21** in 96% yield.

Furthermore, a shorter synthesis of safingol **22** was also accomplished. Commercial *N*-BOC serine benzyl ether **28** was converted in three steps, via alcohol **29**, to the amino alcohol **30** (Scheme 3). Cross-metathesis of **30** with 1-pentadecene, hydrogenation, and *N*-BOC deprotection afforded safingol **22** in only six steps and 56% overall yield.

Conclusion

In summary, the chelation-controlled addition of an organocuprate species to various protected α-amino aldehydes was shown to afford highly functional *syn*-β-amino alcohols diastereoselectively. The bulky protecting groups on the α-amino aldehydes directed the addition to give the corresponding β-amino alcohols with very high *syn*-selectivity. Using this new protocol, we synthesized three targets: the new threonine modifier for a structural study of Sortase A, L-threo-sphingosine, and safingol. Further applications of this protocol in synthetic organic chemistry are underway and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (proton and carbon NMR data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.153.

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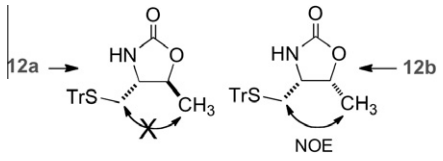
12. The relative stereochemistry of compounds **12a** and **12b** was confirmed by NOESY experiments on oxazolidinones that were prepared from those diastereomers by Boc-deprotection followed by cyclization with carbonyl diimidazole (CDI).



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