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Stereocontrolled Synthesis of *Syn*- β -Hydroxy- α -Amino Acids by Direct Aldolization of Pseudoephedrine Glycinamide

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Abstract

β -Hydroxy- α -amino acids figure prominently as chiral building blocks in chemical synthesis, serving as precursors to numerous important medicines. We have developed and here report a method for the synthesis of β -hydroxy- α -amino acid derivatives by aldolization of pseudoephedrine glycinamide, which can be prepared from pseudoephedrine in a one-flask protocol. Enolization of (R,R)- or (S,S)-pseudoephedrine glycinamide with lithium hexamethyldisilazide in the presence of lithium chloride followed by addition of an aldehyde or ketone substrate affords aldol addition products that are stereochemically homologous with L- or D-threonine, respectively. These products, which are typically solids, can be obtained in stereoisomerically pure form in yields of 55–98%, and are readily transformed into β -hydroxy- α -amino acids by mild hydrolysis or into 2-amino-1,3-diols by reduction with sodium borohydride. This new chemistry greatly facilitates the construction of novel antibiotics of several different classes.

Keywords

pseudoephedrine; pseudoephedrine; asymmetric; synthesis; amino acids; glycine aldol

As part of a program to develop practical synthetic chemistry for the discovery of new antibiotics we investigated and here report a two-step method for the constructive assembly of enantiomerically pure *syn*- β -hydroxy- α -amino acids from simple starting materials. These products figure prominently as chemical precursors to a number of important medicines, most notably antibiotics, as evidenced by the fact that five of the compounds prepared in this study have been transformed into antibiotics from four different structural classes: amphenicols, monobactams, vancomycins, and macrolides. The chemistry we describe offers a number of practical advantages relative to existing methodology, which we discuss after presentation of our results.

The basis of the new methodology stems from the discovery that pseudoephedrine glycinamide (**1**) undergoes efficient and diastereoselective *syn*-aldolization with both aldehyde and (remarkably) ketone substrates.^[1] The key precursor in this transformation, pseudoephedrine glycinamide (**1**), is readily available in both enantiomeric forms on multi-gram scale from the appropriate enantiomer of pseudoephedrine^[2] and *N*-Boc glycine using either one- or two-step protocols (the yields are effectively the same, Scheme 1). Compound **1** is conveniently recrystallized from absolute ethanol and forms a free flowing, white crystalline solid (mp 168–170 °C, 78% overall yield employing the one-flask protocol followed by recrystallization, 30-g scale). X-ray crystallographic analysis reveals that the crystalline lattice is free of any solvent or water molecules. Furthermore, unlike pseudoephedrine glycinamide,^[3] in crystalline form **1** shows little or no propensity to hydrate upon exposure to the air and thus is easily weighed and transferred in the laboratory.

Enolization–*syn*-aldolization of **1** was readily achieved by the following general protocol. Freshly (flame) dried anhydrous lithium chloride (saturating, ~7.8 equiv)^[4] and **1** (1.3 equiv)^[5] were combined at 23 °C in anhydrous THF (~0.15 M in **1**) and the resulting suspension was stirred at 23 °C until **1** dissolved; a portion of the excess LiCl did not dissolve. The resulting suspension was cooled to –78 °C whereupon a freshly prepared solution of lithium hexamethyldisilazide in THF (1 M, 2.5 equiv) was added by syringe. After stirring at –78 °C for 5 min, the reaction flask was transferred to an ice–water bath for 25 min, then was re-cooled to –78 °C where a solution of an aldehyde or ketone substrate in THF (1 M, 1 equiv) was added. The progress of the aldol addition was conveniently monitored by TLC analysis; aldehyde reactants were typically completely consumed within 30 min at –78 °C, whereas reactions with ketone substrates proceeded more slowly and in certain cases required warming to 0 °C to achieve complete conversion (see Table 1 and Supporting Information). In all cases only one of the four possible diastereomeric aldol addition products predominated (Table 1), and this product was typically readily isolated in diastereomerically pure form by flash column chromatography (55–98% yield of purified product). The minor diastereomeric aldol addition product(s) typically constituted <15% of the product mixture.^{[6],[7]}

As shown in Table 1, many different aldehydes and ketones were found to be effective substrates. We observed that the majority of the purified primary aldol products were solids; in the case of product **4** (from isobutyraldehyde), crystals suitable for X-ray analysis were obtained. The solid state structure of **4** derived from (*R,R*)-**1** revealed it to be the *syn*-aldol product stereochemically homologous with L-threonine. In addition, the absolute and relative stereochemistries of *syn* aldol adducts **8** and **9** (from *para*-nitrobenzaldehyde and *para*-methanesulfonylbenzaldehyde, respectively) were rigorously established to form a homochiral series with **4** on the basis of their successful conversion to active antibiotics identical with chloramphenicol and thiamphenicol, respectively (*vide infra*). Stereochemical assignments of the remaining aldehyde addition products from Table 1 were made by analogy. The stereochemistry of these products conforms with the diastereofacial preferences for *alkylation* reactions of pseudoephedrine amide enolates, provided that a (*Z*)-enolate (with the α -amino group and enolate oxygen *cis*) is invoked, which seems to us

quite reasonable.^[2b] Syn stereochemistry presumably arises from conventional Zimmerman–Traxler-type arguments.^[8]

In addition to its general, efficient, and stereoselective reactions with aldehyde substrates (linear, branched, and α -tetrasubstituted aliphatic, aromatic, α -oxygenated, and α,β -unsaturated), pseudoephedrine glycinamide (**1**) also serves as an exceptional substrate for aldolization with ketone substrates, providing aldol adducts with fully substituted β -centres, as illustrated by the seven examples **13–19** in Table 1. The stereochemistry of aldol adduct **16** (from methyl isopropyl ketone) was established unambiguously by X-ray analysis of its crystalline hydrate; not surprisingly, it was found to be fully consistent with the stereochemistry of the aldehyde aldol adducts (the methyl group acts as the “small” group). We also rigorously established the stereochemistry of the aldol adduct **18** by X-ray analysis of a crystalline derivative (vide infra), and this also conformed to that of the other aldol products. This product appears to represent a case of stereochemical matching, where the diastereofacial preferences of the enolate and the chiral ketone substrate (the latter consistent with a Felkin–Ahn trajectory)^[9] are reinforcing, accounting for the extraordinarily high stereoselectivity and yield of this particular transformation. Product **19** (55% isolated yield), from methyl styryl ketone, was formed least efficiently, we believe as a consequence of competitive conjugate addition (est. ~15%).

As a seemingly minor point, we note that careful analysis of the ¹H NMR spectra of the majority of the purified aldol adducts from Table 1 reveals that in addition to the two rotameric forms of the expected *syn*-aldol diastereomers, trace (~5%) amounts of an “impurity” corresponding to the N→O-acyl transfer product, a β -amino ester, are present.^[10] This reveals that the latter constitutional isomer is only slightly higher in energy than the tertiary amide form, providing a rationale for the remarkable facility of the subsequent transformations of the direct aldol products discussed below, namely their hydrolysis and reduction.

In contrast to conditions typical for hydrolysis of tertiary amides, hydrolysis of the aldol adducts of Table 1 proceeds under remarkably mild conditions, more consistent with saponification of an ester than hydrolysis of a tertiary amide (Table 2). For example, hydrolysis of aldol adduct **4** was complete within 4 h at 23 °C in the presence of 1 equiv of sodium hydroxide in 1:1 THF:methanol. Once hydrolysis was complete, pseudoephedrine was recovered by extraction with dichloromethane in quantitative yield (~95% purity), and the alkaline aqueous solution was lyophilized to provide the β -hydroxy- α -amino sodium carboxylate **22** in 92% yield and ~98% ee (Table 2). The inclusion of methanol was critical to avoid retroaldol fragmentation during the hydrolysis, which was otherwise facile, especially with aromatic aldol addition products. In a noteworthy example, use of the THF-methanol-sodium hydroxide protocol with substrate **10** afforded the aromatic aldolate **25** in 94% yield and ~98% ee (auxiliary recovery: 97% yield). A protected form of the latter α -amino acid served as a key starting material in the synthesis of vancomycin reported by the Nicolaou group.^[11]

Interestingly, the present hydrolysis conditions are much milder than those required for hydrolysis of pseudoephedrine^[10] and pseudoephedrine^[2b] amide alkylation products,

suggesting that the β -hydroxy group of the aldol adducts may facilitate N \rightarrow O-acyl transfer. In this regard, it is notable (though not surprising) that X-ray crystallographic analysis (structures **4** and **16**) reveals an internal hydrogen bond between the amide carbonyl groups and their β -hydroxy functions. We believe that facile hydrolysis (and reduction, *vide infra*) of pseudoephedrine amide aldol products occurs by rapid N \rightarrow O-acyl transfer followed by saponification (reduction) of the resulting β -amino ester, as we have previously proposed for alkaline hydrolyses of pseudoephedrine amides.^[10]

The α -amino sodium carboxylates obtained upon alkaline hydrolysis can be converted to α -amino acid methyl esters upon exposure to acidic methanol (e.g., **20** \rightarrow **26**, Scheme 2). Alternatively, treatment of the same substrates with di-*tert*-butyldicarbonate affords *N*-Boc-protected amino acids in high yield (e.g., **23** \rightarrow **27**, Scheme 2). The *N*-Boc α -amino acid **27** is noteworthy for it serves as precursor to the fully synthetic monobactam antibiotic BAL30072, which is currently in phase I clinical trials as an anticipated treatment for infections caused by Gram-negative bacteria.^[12]

Alkaline hydrolysis conditions were not uniformly successful with every substrate; in certain cases retroaldol fragmentation was faster than hydrolysis, even when employing our optimal protocol. For example, treatment of the ketone aldol adduct **17** with 1 equiv of sodium hydroxide in 1:1 methanol:water at 23 °C provided primarily three products: acetophenone, pseudoephedrine, and sodium glycinate (the latter two products presumably result from hydrolytic cleavage of **1**); none of the desired β -hydroxy- α -amino sodium carboxylate was observed.^[13] We envisioned that retroaldol fragmentation would be avoided if the β -hydroxy substituent were shielded, and for this purpose we chose a cyclic carbamate, which can easily be introduced and removed^[14] under very mild conditions and has the added benefit of protecting the α -amino function. Treatment of aldol adduct **17** with phosgene (1.1 equiv) and diisopropylethylamine (3 equiv) at -78 °C in dichloromethane formed within 30 min the cyclic carbamate **28**, isolated in pure form by simple aqueous extraction. Although carbamate **28** was resistant to alkaline hydrolysis (presumably due to the acidity of the carbamate function) we found that heating a solution of **28** in a 1:1 mixture of dioxane and pure water at reflux for 24 h effected clean hydrolysis of the auxiliary. Straightforward acid-base extraction then provided acid **29** in 85% yield (and, separately, pseudoephedrine in 97% yield). By an analogous sequence, treatment of aldol adduct **18** with phosgene provided carbamate **30**, (the stereochemistry of which was rigorously established by X-ray crystallography). This intermediate has been transformed into >100 novel macrolide antibiotics in ongoing research in our laboratory.^[15] Hydrolysis of **30** provided acid **31** in 94% yield (90% recovered pseudoephedrine).

To apply our new aldol methodology to synthesize chloramphenicol and thiamphenicol, antibiotics which are on the essential medicine list published by the World Health Organization^[16] and play critical roles in the treatment of infectious disease, especially in developing countries,^[17] we investigated reductive cleavage of the auxiliary to produce 2-amino-1,3-diols. Remarkably, treatment of aldol adduct **8** with the mild reducing agent sodium borohydride (5.0 equiv) in ethanol at 40 °C provided the 2-amino-1,3-diol **32** in 80% yield (Scheme 4); the auxiliary was recovered quantitatively in pure form. We are aware of only one previous report of the reduction of tertiary amides (α -hydroxy morpholinamides) to

the corresponding alcohols with sodium borohydride.^[18] Reduction of pseudoephedrine and pseudoephedrine amides to the corresponding primary alcohols has historically been achieved using lithium amidotrihydroborate (LAB),^[2b, 3b, 10] a much more reactive hydride donor that we introduced in 1996.^[19] Again, we believe that the facile reduction with sodium borohydride we observe is due to intramolecular N→O-acyl transfer followed by reduction of the resulting α -amino ester.^[20] The synthesis of chloramphenicol was completed by acylation of **32** with methyl dichloroacetate (Scheme 4), providing the antibiotic in excellent yield in just three steps from (*R,R*)-pseudoephedrine glycinamide (**1**) and *para*-nitrobenzaldehyde. Thiamphenicol was synthesized by an identical 2-step sequence from the aldol adduct **9**. In contrast to the 3-step routes to chloramphenicol and thiamphenicol reported here, the commercial routes to these substances require ~6 linear steps, including a resolution.^[21]

Commensurate with their importance in medicine, chemists have developed an extraordinarily diverse array of methods to synthesize enantiomerically enriched β -hydroxy- α -amino acids. These may be divided into two broad categories: constructive syntheses (as in the present work) and nonconstructive syntheses. The latter include the Sharpless asymmetric aminohydroxylation of certain alkenyl esters,^[22] multi-step transformations of Garner aldehyde-type intermediates,^[23] asymmetric hydrogenation of 2-amino- β -ketoesters,^[24] as well as other strategies.^[14f, 25]

Constructive syntheses are generally more powerfully simplifying, for they enable retrosynthetic targeting of the C–C bond linking the stereogenic, heteroatom-bearing centres. The pioneering advances of the Schöllkopf group employing bis-lactim ethers^[26] and the Seebach group employing masked glycine-derived heterocycles^[27] as substrates in diastereoselective aldol additions remain important enabling methodologies. To reveal the parent β -hydroxy- α -amino acids or esters, however, strongly acidic conditions are required and auxiliary-derived by-products can complicate isolation of the products.^[26e, 26f] Evans and Weber developed α -isothiocyanato acyl oxazolidinones as substrates in their diastereoselective tin-mediated aldol chemistry,^[28] and notable advances have been recorded by the Willis,^[29] Feng,^[30] and Seidel^[31] groups to transform this method into processes mediated by chiral catalysts. These α -isothiocyanate methodologies afford thiocarbamate heterocycles as products, which conveniently serve to protect the amine and alcohol functionalities of the aldol adducts, but require a 3-step procedure to reveal the embedded α -amino acids. Methods employing chiral glycine enolate equivalents have also been reported by the Bold,^[32] Iwanowicz,^[33] Caddick,^[34] and Franck^[35] groups. Hydroxymethylations of alanine equivalents to form α -alkyl serine derivatives have also been reported.^[36]

Another notable approach employs Schiff bases of glycine *tert*-butyl esters in aldol reactions with aldehyde substrates to provide aldol addition products that are then treated with acid to reveal the embedded β -hydroxy- α -amino esters. Advances in this area were reported by the Mukaiyama,^[37] Belokon,^[38] Miller,^[39] and Corey^[40] groups, and subsequently several modifications have emerged that provide both *syn*^[41] and *anti*^[42] products. While these methods are convenient due to the facile enolization of glycine Schiff bases and the direct conversion of the aldol products into β -hydroxy- α -amino esters, they often suffer from poor

diastereoselectivities, narrow substrate scope, and frequently require further functionalization to permit separation of syn and anti aldol addition products.

Ito, Hayashi, and coworkers employed α -isocyano esters and amides in aldol reactions catalyzed by chiral gold(I) complexes, providing oxazoline-4-carboxylate products that can be converted to β -hydroxy- α -amino acids upon treatment with strong acid.^[43] Oxazoline-4-carboxylates have also been constructed by the addition of 5-alkoxyoxazoles to aldehydes catalyzed by chiral aluminum catalysts, as demonstrated by Suga and Ibata^[44] and the Evans group.^[45] These systems were found to be highly effective only with aromatic aldehyde substrates, and conversion of the oxazoline products to β -hydroxy- α -amino acids requires three steps and harshly acidic conditions. Barbas, Tanaka, and coworkers reported a method for the aldolization of phthalimidoacetaldehyde catalyzed by proline that achieved high enantio- and diastereoselectivities, but only with α -branched aldehyde substrates.^[46] The Wong group has developed methodology for chemoenzymatic aldolization of glycine catalyzed by threonine aldolases that, while highly stereoselective for certain aldehyde substrates, is limited in scope.^[47]

We believe aldolization of pseudoephedrine glycinamide offers a number of advantages. Enolization of **1** proceeds under very mild conditions (LiHMDS, LiCl) without metal additives, and the syn aldol products are readily obtained in stereoisomerically pure form by column chromatography. A broad selection of electrophiles, including alkyl and aryl aldehydes and ketones, undergo efficient aldolization with **1**, whereas many other glycine equivalents react efficiently only with aryl or alkyl aldehydes, and very few are reported to react efficiently with ketones.^[48] With the exception of chemoenzymatic approaches,^[47] the aforementioned glycine equivalents all require shielding of the α -amino group, but this is not necessary with our method. Hydrolysis of the aldol adducts of **1** proceeds under unusually mild conditions compared to other glycine equivalents, and both the product and the auxiliary can be isolated by straightforward biphasic extraction. Additionally, reduction of pseudoephedrine glycinamide aldol adducts to the corresponding primary alcohols can be accomplished with the mild reducing agent sodium borohydride. We believe pseudoephedrine glycinamide (**1**) is an exceedingly practical reagent for the synthesis of β -hydroxy- α -amino acids and chiral 2-amino-1,3-diols, and anticipate the methods reported herein will have broad applicability in chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

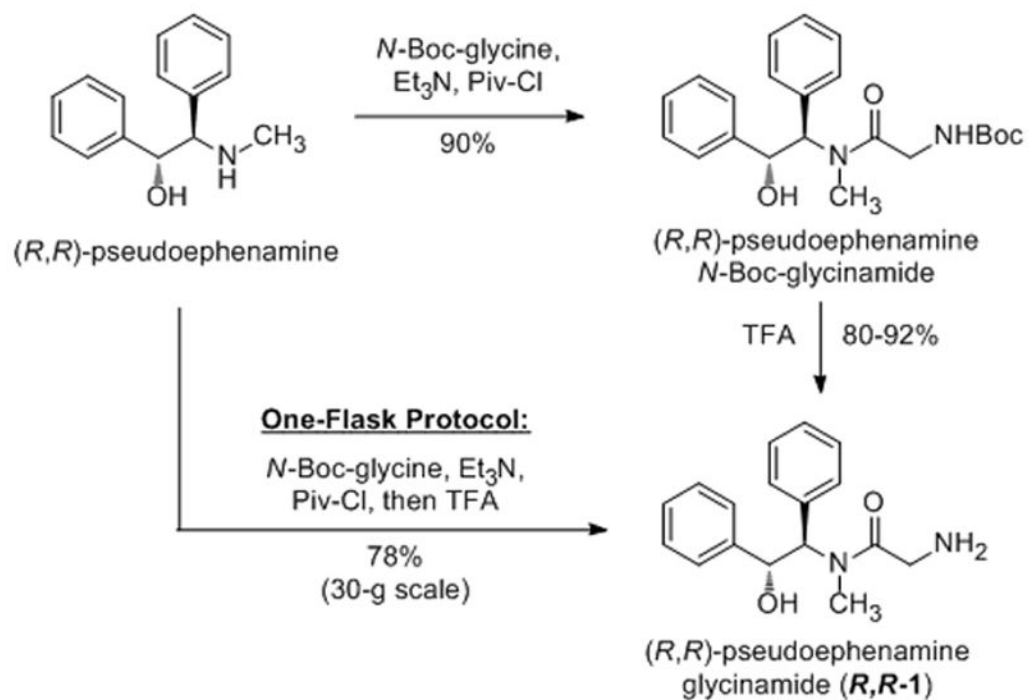
We express our gratitude to Dr. Shao-Liang Zheng for his exceptional work in conducting X-Ray crystallographic analyses. J.A.M.M. acknowledges Pfizer for financial support through the ACS SURF program. I.B.S. acknowledges postdoctoral fellowship support from the National Institutes of Health (F32GM099233). Z. Z. is a Howard Hughes Medical Institute International Student Research fellow.

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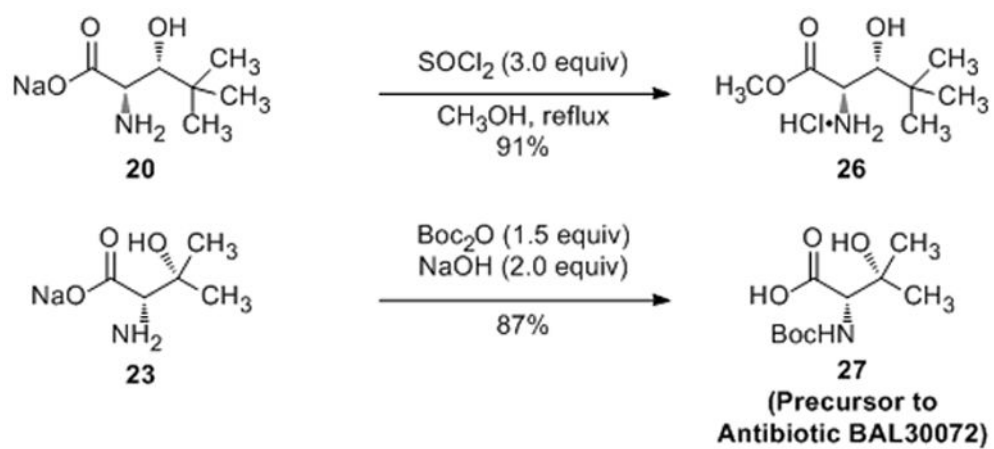
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4. Lithium chloride was essential to achieve high diastereoselectivities in aldol addition reactions. For example, addition of the lithium enolate derived from 1 (in absence of LiCl) to benzaldehyde afforded a much reduced dr (53% desired: 47% sum of minor isomers).
5. Pseudoephedrine glycinamide (1) can also be used as the limiting reagent, with a moderate decrease in yield: aldolization of 1 (1.0 equiv) with benzaldehyde (1.2 equiv) provided pure 7 in 65% yield (standard conditions provided the product in 80% yield).
6. These minor products were not readily separated and therefore were not carefully studied, with the exception of the minor adducts from symmetric ketone substrates (13–15). See Supporting Information for further details.
7. Interestingly, we observed that aldol addition reactions of pseudoephedrine glycinamide (ref. [3]) were inferior to those of pseudoephedrine glycinamide (1). For example, the isolated yield of the major *syn*-aldol adduct of pseudoephedrine glycinamide and benzaldehyde was just 57% (dr 72% desired: 28% sum of minor isomers) whereas the parallel transformation with 1 gave an 80% yield of pure *syn*-aldol product (dr 85% desired: 15% sum of minor isomers).
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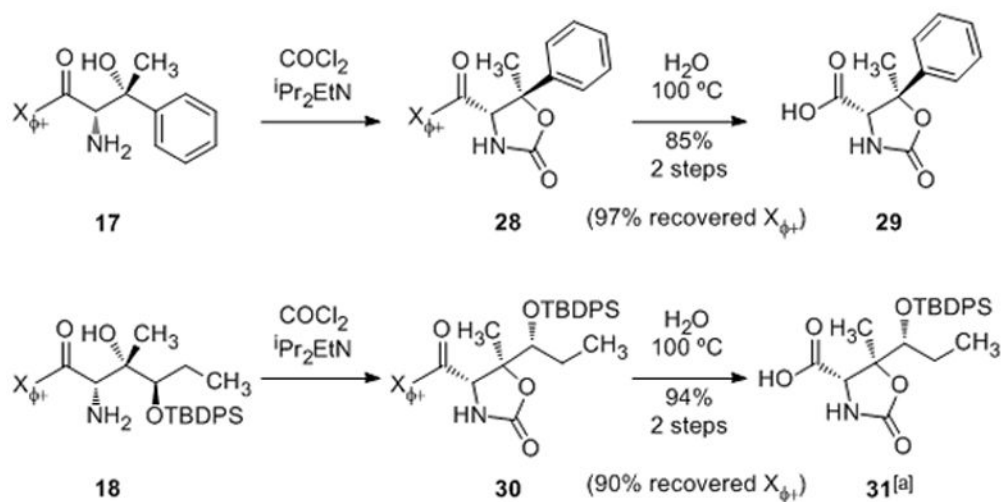
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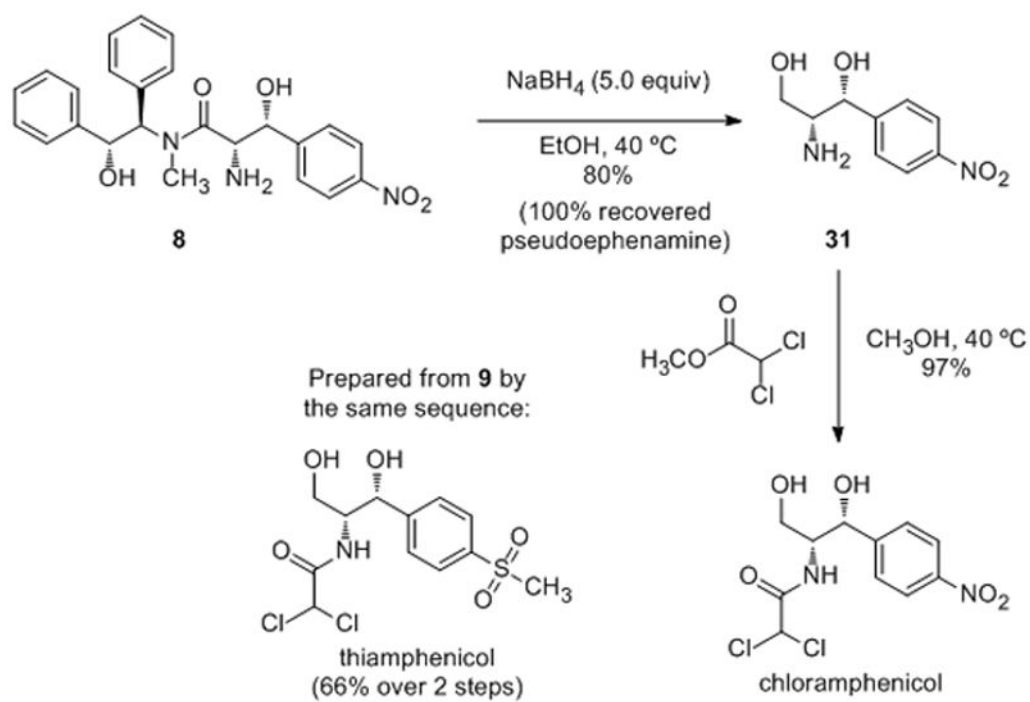


Scheme 1.
Synthesis of pseudoephedrine glycinamide (**1**).

**Scheme 2.**Esterification and *N*-Boc protection of amino carboxylates.

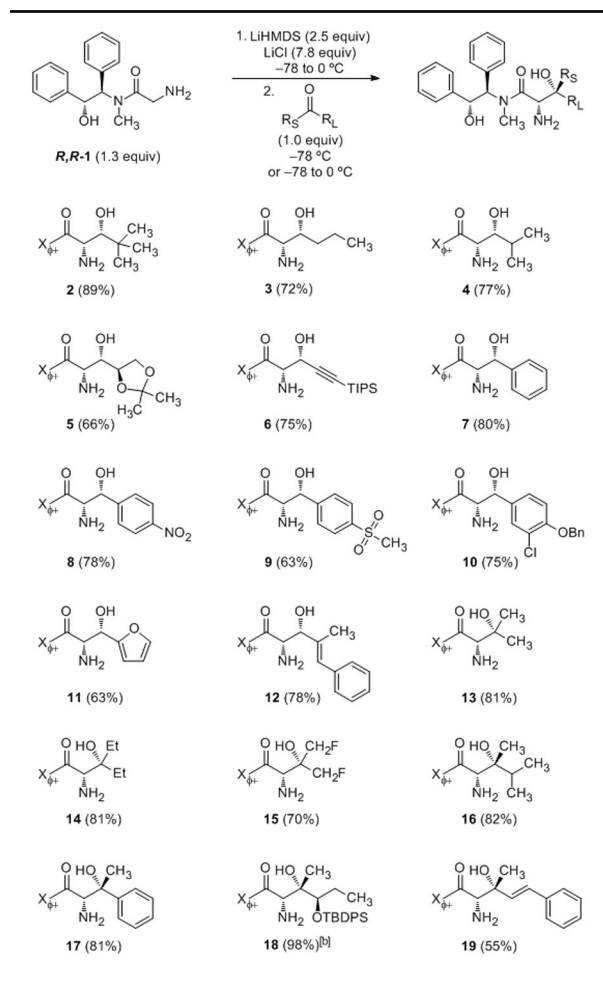
**Scheme 3.**

Cyclic carbamate formation followed by hydrolysis under neutral conditions affords protected α -amino acid derivatives. $X_{3^+} = (R,R)$ -pseudoephedrine. [a] Product contained 8% TBDPS-OH after aqueous extraction.

**Scheme 4.**

Mild reductive cleavage of aldol adducts applied to the syntheses of chloramphenicol and tiamphenicol.

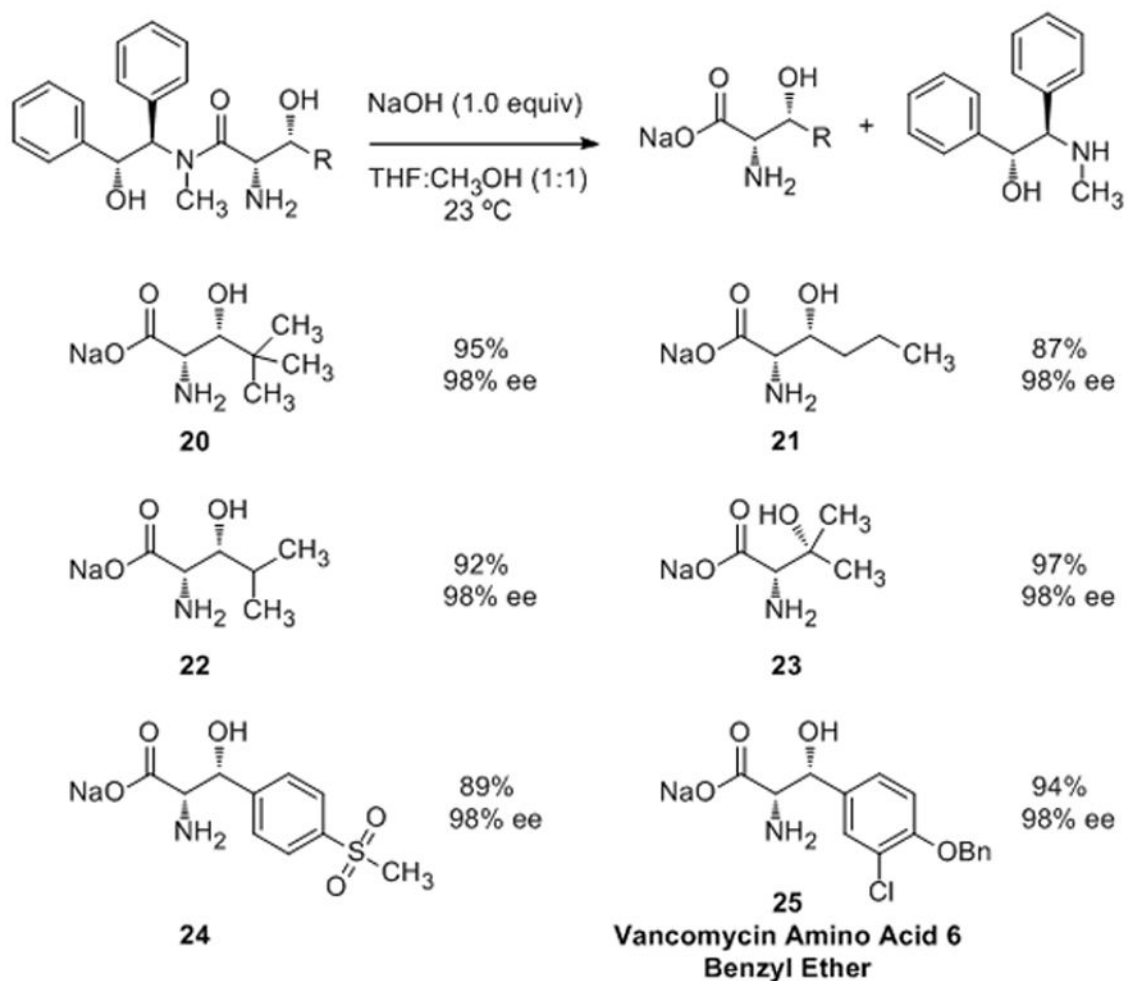
Table 1

Aldolization of pseudoephedrine glycinamide (**1**) with aldehyde and ketone substrates.

[a] X_{2+} = (*R,R*)-pseudoephedrine. Reactions were run at a final concentration of 0.1 M (aldolate) and were performed on at least a 1-mmol scale. Isolated yields of major diastereomers are reported; diastereomeric ratios can be found in the Supporting Information.

[b] Reaction was run on a 20-g scale. Enolization was conducted at 0 °C, and the final concentration of aldolate was 0.05 M.

Table 2

Mild alkaline hydrolysis of aldol adducts.^[a]

^[a] (R,R)-Pseudoephedrine was recovered in 90% yield in each case in high purity. Enantiomeric purity was determined by ¹H-NMR analysis of the (R)- and (S)-MTPA amides. For experimental details, see Supporting Information.