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Stereodivergent and Regioselective Synthesis of 3,4-*cis*- and 3,4-*trans*-Pyrrolidinediols from α-Amino Acids

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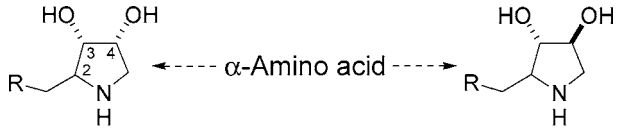
ABSTRACT



3,4-*cis*-diol 3,4-*trans*-diol

Highly stereodivergent Woodward–Prevost reaction applied to iodoacetates derived from homochiral α-amino acids afforded enantiopure 3,4-*cis*- and 3,4-*trans*-pyrrolidinediol derivatives, with control over the protecting group, allowing for differential protection.

Enantiopure 3,4-pyrrolidinediols have been extensively exploited both because of their wide-ranging pharmacological properties and also due to their serving as important functional units for further manipulation in organic synthesis. For example, many 1,4-dideoxy-1,4-iminopentositols,[1] swanisonine,[2] (−)-anisomycine,[3] lentiginosine,[4] and dihydroxyproline[5] are included in these series. Therefore, a number of synthetic strategies have been devoted to their stereoselective synthesis from both carbohydrate[6] and non-carbohydrate sources,[7] the latter mostly involve the use of aldolization, epoxidation, or dihydroxylation for selective hydroxylation. These methodologies are ideally suited to the preparation of a single stereoisomer of the target 3,4-pyrrolidinediol, but they all either have limited stereodivergent approach or require many tedious protection and deprotection steps. Obviously, homochiral α-amino acids are the most suitable starting material to synthesize an enantiopure 3,4-pyrrolidinediol, but only a few examples have been reported.[8] The main reason for the paucity of examples in this area is that although the stereoselective installation of 3-hydroxy group has been extensively studied, and highly

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effective methodologies now exist to generate such derivatives as single diastereoisomers from α-amino aldehydes,[9] the installation of the 4-hydroxy group has proved much more difficult and no general stereoselective methodology currently exists for this purpose (Figure 1). This report

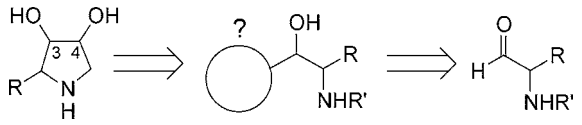
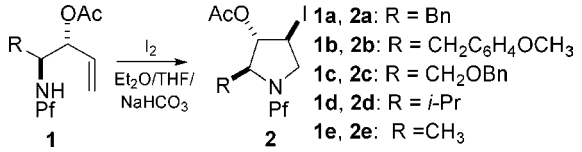


Figure 1.

describes the rational design of a chiral synthon for application of Woodward−Prevost reaction to 3,4-*cis*- and 3,4-*trans*-pyrrolidinediols stereodivergently.

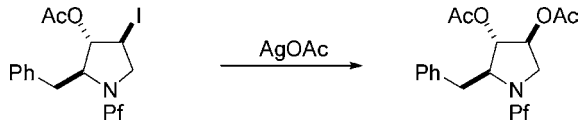
As first noted by Winstein,[10] α-haloacetates in the presence of metal carboxylates are easily transformed to the corresponding *cis* or *trans* diols by stereoselective nucleophilic displacement at the α-carbon.[11] This reaction refined by Woodward [12] and Prevost[13] involves the in situ generation of α-iodoacetate in a one-pot reaction. Although it has proved to be powerful methodology for stereoselective dihydroxylation, the vast majority of the examples suffer from a number of problems, such as poor facial selectivity of *epi*-iodination in cyclic substrates,[14] low reactivity of the haloacetate due to steric constraints,[15] and low yields.[16] However, many of the associated flaws can be circumvented by preforming the α-haloacetate and treating this species with the required Lewis acid. We previously reported that iodoamination of allyl acetate gives a novel iodoacetate precursor with high yield and stereoselectivity via endocyclization (Scheme 1).[17]

Scheme 1



The required starting materials were easily prepared from commercially available phenylalanine, tyrosine, serine, valine, and alanine, which were esterified with MeOH/TMSCl, protected with Pf, and then reduced to aldehyde ($LiAlH_4$, then Swern) in 73% overall yield.[18] Subsequent installation of the vinyl moiety could have been achieved stereoselectively,[9,19] but in this case a simple Grignard reaction was preferred because, fortunately, both of the allyl alcohols could be easily isolated as single diastereomers by chromatography on silica gel. The stereoselective iodoamination of allyl acetate (**1a**−**e**) afforded a minimum 25:1 ratio of *cis* and *trans* isomers of iodoacetates, and the single *trans* isomer (**2a**−**e**) was used for the subsequent Woodward−Prevost reaction (Table 1).

Table 1. [a]



entry	conditions	time (h)	yield[b] (%)	de[c] (%)
1	toluene, rt	>100	75	>95
2	toluene, 60 °C	76	85	>95
3	toluene, reflux	4	94	>95
4	CH_2Cl_2, reflux	24	68	>95
5	THF, 60 °C	12	trace	*d*

[a] The reactions were all run at 0.2 M concentration. [b] Isolated yield. [c] Determined by ^1H NMR integration. [d] Not determined.

Initially, precursor **2a** was chosen as a substrate on which to test the utility, both with respect to the diversity and selectivity, of the Woodward−Prevost reaction in this system. Compound **2a** was treated with silver(I) salts under a range of reaction conditions, while varying the solvent and temperature (Scheme 2). It was found that low polarity solvent and vigorous conditions gave optimal results in this reaction. Thus iodoacetate was treated with AgOAc at reflux for 4 h in dry toluene to give the expected 3,4-*trans*-diacetate **5** as the sole product in 94% yield via intermolecular substitution at the C4-position (vida infra). Both yield and selectivity were very sensitive to the water content of reaction mixture. Diacetate **5** could subsequently be converted to the *trans*-3,4-diol **3a**, as proved by NOESY data, in >95% de by treatment with $LiAlH_4$ in 98% yield. Synthesis of the C4 epimer **4a** was attempted using Woodward-type conditions on the same starting material **2a**. Hence, treatment of **2a** with $AgBF_4$ in wet toluene at room temperature for 12 h yielded two isomeric hydroxy acyl compounds **6** and **7**, which were separable by chromatography on silica in a 1:1 ratio in 72% yield. Treatment of these monoacyl derivatives with $LiAlH_4$

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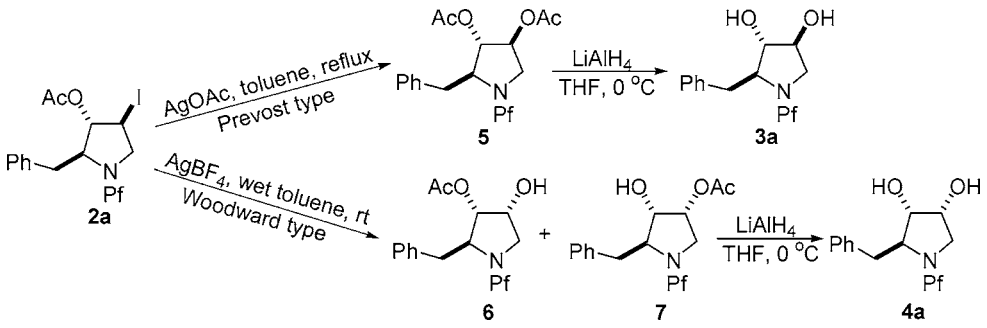
Scheme 2



yielded the same product C3, C4 *cis*-pyrolidinediol **4a**, as proved by NOESY data, demonstrating that the two monoacyl species, derived from collapse of the ortho ester type intermediate, differed only in the position of the acyl group, not in the stereochemistry of the diol framework. Accordingly, both diastereoisomers of a homochiral pyrrolidinediol (**3a** and **4a**) were synthesized using a remarkably stereodivegent strategy from α-amino acids. To test the versitility of this methodology with respect to its steric and electronic demands, a range of C2 position substituted precursors **2b**−**e** were screened. The compounds (**2b**−**e**) were all subjected to the optimized Prevost reaction conditions, used in the model substrate, and rewardingly the results were all similar: in all cases the all-*trans* derivatives were isolated as the sole product in excellent yield. Table 2 shows that methyl (entry 9), the smallest group, was big enough to afford high regio- and stereoselectivity. These imply that many chiral α-amino acids will be able to generate either diastereomer of 3,4-pyrrolidine-diol in a stereoselective manner. Furthermore, as previously shown, the *cis*-diols (**4b**−**e**) were simply obtained by treatment of $AgBF_4$ and H_2O in toluene and reaction of the diesters with $LiAlH_4$. The relative stereochemistry of each product was determined using ^1H NMR data based on both coupling constant values and NOESY experiments.

Mechanistically, the observations broadly agree with the overall scheme of the Woodward−Prevost-type reaction (Figure 2). The stereoselectivity in the case of the formation of 3,4-*cis* systems arises from the trapping of the cyclic cation

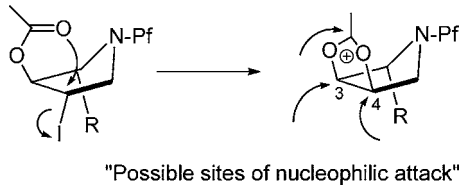


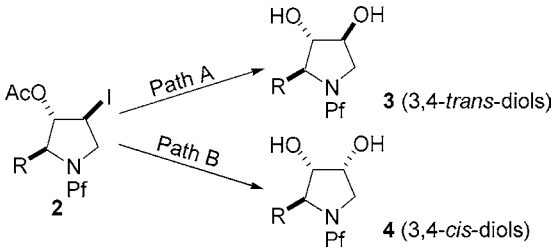
Figure 2.

derived from neighboring group participation of the acetate group, by water. This process is irreversible, and the intermediate is hydrolyzed to hydroxyacetate. As shown in the data above, this process can give either 3- or 4-acetoxy species with equal probability. In the case of the 3,4-*trans* compounds, the initial mechanism of the reaction is the same.

However, reversible addition to the cyclic intermediate allows for the thermodynamic product to be formed in an S_N2 reaction at either the C3 or C4 position, but in this system the R group is set up optimally to shield attack at the 3-position, due to 1, 2 steric strain. The ability to synthesize a differentilly protected 3,4-pyrrolidinediol is one of the most attractive aspects of this was attempted using AgOBz. As shown in Scheme 3, treatment of iodoacetate **2b** with silver benzonate in toluene at reflux for 5 h gave 3-*O*-acetyl-4-*O*-benzoyl diol **8** in 94% yield. The positions of C3 and C4 protons were supported by HMBC correlation.

With this result proving the principle of differential protection, a short route to anisomycine derivative **11** was

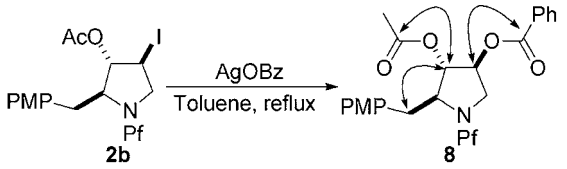
Table 2. Preparation of 3,4-*trans*- and *cis*-Pyrrolidinediols[a]



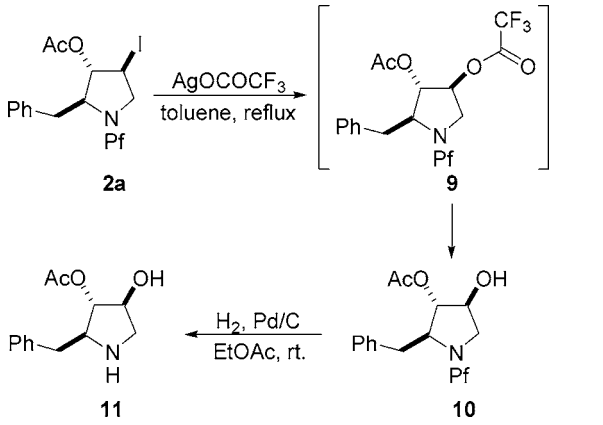
entry	R group	product	yield[b] (%)	de[c] (%)
1	**2a** (Bn)	**3a**	94	>95
2	**2a** (Bn)	**4a**	72	>95
3	**2b** (*p*-methoxybenzyl)	**3b**	92	>95
4	**2b** (*p*-methoxybenzyl)	**4b**	68	>95
5	**2c** (CH_2OBn)	**3c**	87	>95
6	**2c** (CH_2OBn)	**4c**	64	>95
7	**2d** (*i*-Pr)	**3d**	95	>95
8	**2d** (*i*-Pr)	**4d**	75	>95
9	**2e** (CH_3)	**3e**	97	>95
10	**2e** (CH_3)	**4e**	73	>95

[a] The reactions were all run at 0.2 M concentration. Path A: AgOAc, toluene, reflux; LAH, THF, 0 °C. Path B: $AgBF_4$, toluene/water (10/1), rt; LAH, THF, 0 °C. [b] Two-step yield. [c] Determined by ^1H NMR integration.

Scheme 3



Scheme 4



attempted. Iodoacetate **2a** was refluxed with silver trifluoroacetate to give monoacetate **10** in 83% yield directly (Scheme 4). The trifluoroacetyl group in intermediate **9** was completely removed in the course of silica chromatography. The *N*-Pf groups in compound **10** was removed by hydrogenation with 10% Pd/C in ethyl acetate at room temperature for 3 h to give target compound **11** in 89% yield. Hence, application of Woodward conditions to iodoacetate **2a** allowed the synthesis of compound **11** using straightforward steps in excellent yield, thus removing the protection/deprotection and chiral induction step previously required. In conclusion, we have successfully developed an excellent highly stereodivergent method for approaching 3,4-pyrrolidinediols.

This representative example demonstrates the inherent synthetic potential of this methodology: after simple deprotection of Pf group in **3c** and **4c**, 1,4-dideoxy-1,4-imino-L-arabinitol and 1,4-dideoxy-1,4-imino-L-ribitol will be generated, respectively. Both efforts to prepare other biologically important 3,4-pyrrolidinediols and also research into the utility of the 2,3-*cis* isomers previously synthesized by the group are currently underway.

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Supporting Information Available: Experimental procedures, product characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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