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Highly *anti*-selective dihydroxylation of 1,2-dialkyl substituted (*Z*)-allylic amines: stereoselective synthesis of a D-*ribo*-phytosphingosine derivative

Jongho Jeon, Moonyong Shin, Jae Won Yoo, Joon Seok Oh, Jae Gwang Bae, Seung Hwan Jung and Young Gyu Kim*

Department of Chemical and Biological Engineering, Seoul National University, Seoul 151-744, Republic of Korea

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Abstract—Protection of 1,2-dialkyl substituted (*Z*)-allylic amines with an *N*,*N*-diBoc group resulted in an opposite stereoselectivity in the OsO_4-catalyzed dihydroxylation reactions to that of *N*-Boc-(*Z*)-allylic amines. A higher *anti* selectivity (>10:1) was shown in CH_2Cl_2. An efficient stereoselective synthesis of a tetraacetyl derivative of D-*ribo*-phytosphingosine was reported using the *N*,*N*-diBoc-controlled dihydroxylation from Garner's aldehyde.

We have been interested in the stereoselective syntheses of some biologically active compounds with a vicinal amino dihydroxyl moiety (Fig. 1). In principle, they could be efficiently prepared from the stereo-controlled OsO_4-catalyzed dihydroxylations of chiral allylic amines that are readily derived from one of the chirality pools, α-amino acids.

We have recently reported the efficient stereoselective syntheses of the α-hydroxyisostatine[1a] and (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid (DADHA) derivatives[1b] by employing the *N*-diphenylmethylene-controlled osmylation of the corresponding chiral allylic amines.[1c] With the conjugated (*E*)-ester, the *anti* selectivity of about 12:1 was obtained, while the opposite syn selectivity of >13:1 was observed with the conjugated (*Z*)-ester without using any chiral auxiliaries. It is to be noted that the stereoselective dihydroxylation reactions of allylic amines have not been studied as much as those of allylic alcohols.[2] Often, the poor or inconsistent stereochemical results have been reported for acyclic allylic amino derivatives with flexible conformation.[2,3] In several cases, even the well-established Sharpless asymmetric dihydroxylation reactions resulted in mixed results.[2e,4]

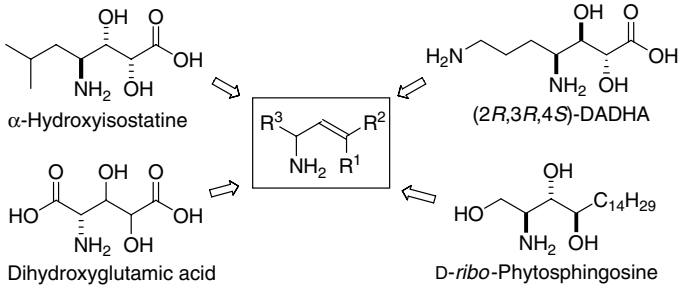

Figure 1. Compounds with an amino dihydroxyl unit.

* Corresponding author. Tel.: +82 2 880 8347; fax: +82 2 885 6989; e-mail: ygkim@snu.ac.kr

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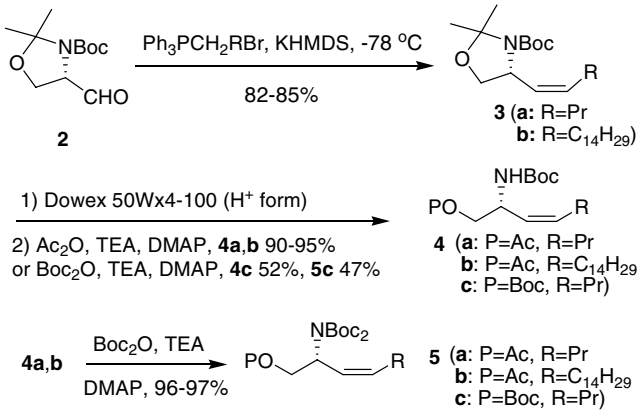
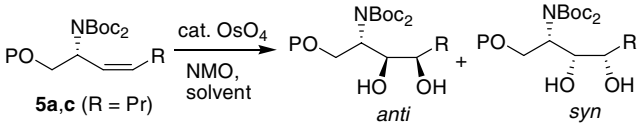
For an efficient stereoselective synthesis of D-*ribo*-phytosphingosine (Fig. 1), the *N*-diphenylmethylene-controlled dihydroxylation reactions were also applied to the corresponding allylic amino derivatives but showed much lower stereoselectivities of <3:1 for the undesired *syn* diastereomer. Through a model study, however, we have found that the highly *anti*-selective dihydroxylations of 1,2-dialkyl substituted (*Z*)-allylic amines are possible by simply changing the N-protecting group and the reaction conditions and wish to report the results as follows.

For the model study, the propyl substituted (*Z*)-allylic amines were prepared from Garner's aldehyde (**2**) using a commercially available phosphonium salt (Ph_3P^+-$BuBr^-$) according to the protocol shown in Scheme 1 ($R = C_3H_7$). The diBoc and dibenzyl groups were chosen as the N-protecting group because they are easily introduced and the monoBoc N-protecting group is known to give the *syn* selectivity with the similar (*Z*)-allylic amino derivatives.[5] In addition, the bulky diBoc or dibenzyl protecting group resulted in the high *anti* selectivity in the cyclic allylic amines.[3a] The diastereoselective osmylation results of the *N*,*N*-diBoc protected model compounds in some different solvents are shown in Table 1.[6] All entries show a consistent *anti* selectivity and the better results are obtained in less polar solvents (entries 3 and 4).[7] The best result is observed in CH_2Cl_2 when the alcohol is protected with an acetyl group (entry 5). We have also examined the dihydroxylations of the *N*,*N*-dibenzyl protected derivatives of the model olefin (not shown). They showed the good *anti* selectivity of about 8:1, but a significant amount of unknown byproducts were produced to cause low yields of the desired diol products. The dihydroxylation reaction rates of the *N*,*N*-dibenzyl derivatives were slow, too.[2e,8]



Scheme 1. Preparation of *N*,*N*-diBoc olefins **5**.

Table 1. Dihydroxylations of model compounds, **5a** and **5c** (R = Pr)



Entry	P	Solvent	*anti*:*syn*[a]	Yield (%)
1	Boc (**5c**)	THF–H_2O (2:1)	3.3:1	52
2	Boc (**5c**)	*i*-PrOH	4.0:1	82
3	Boc (**5c**)	Toluene	6.3:1	84
4	Boc (**5c**)	DCM	10:1	83
5	Ac (**5a**)	DCM	20:1	78[b]

[a] Determined by ^1H NMR.
[b] Isolated yield of diacetates after acetylation of the diols.

The observed *anti* selectivity of the *N*,*N*-diBoc protected (*Z*)-allylic amines can be explained by a transition state of an *H*-eclipsed conformation in Figure 2 as suggested by Kishi and co-workers in their monensin synthesis.[9a] It has been reported that the *N*-outside conformation is favored with the 1,2-dialkyl substituted *N*-Boc-(*Z*)-allylic amine to give the *syn* diol as a major product.[5] The *N*-outside conformation would reduce the 1,3-allylic ($A^{1,3}$) strain between the *N*-Boc group (P = H) and the alkyl (R) group although there is some increase in the 1,2-allylic ($A^{1,2}$) strain between the *N*-Boc group and the vinylic hydrogen atom. With the *N*,*N*-diBoc protected (*Z*)-allylic amines, however, the $A^{1,2}$ strain between the bulky *N*,*N*-diBoc group (P = Boc) and the vinylic hydrogen atom would be so severe that the *H*-eclipsed conformation is preferred to give *anti* diol as a major product.[9] The *H*-eclipsed conformation at the transition state can also explain the higher *anti* selectivity with the smaller acetyl group (Table 1, entries 4 and 5).

With the above results in hand, the *N*,*N*-diBoc controlled dihydroxylation reaction of (*Z*)-allylic amines was applied to an efficient stereoselective synthesis of D-*ribo*-phytosphingosine. D-*ribo*-Phytosphingosine is a key component of glycosphingolipids that are widely distributed in plants, fungi, marine organisms, and mammalian tissues. In addition to its structural role in membranes, it is shown to possess some important biological activities such as induction of apoptosis in some cancer cells[10a] and a heat stress response of the yeast cell.[10b] Because of its biological importance as well as its scarcity in nature, considerable efforts for the synthesis of phytosphingsine, its stereoisomers, and its homologues have been devoted to date.[11] Among them, there have been a few synthetic reports for D-*ribo*-phyto-

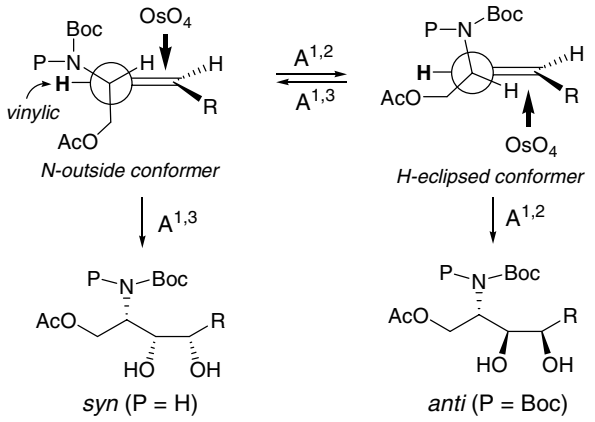
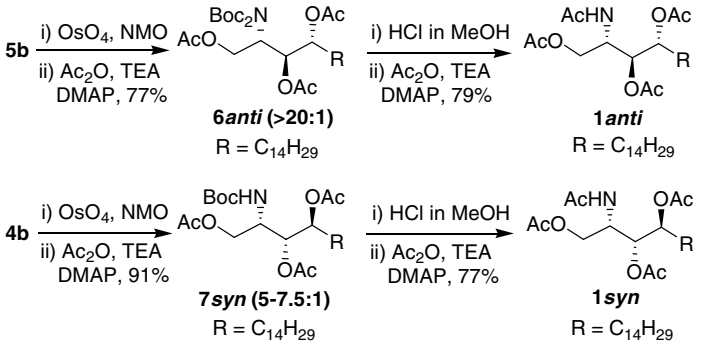


Figure 2. Probable transition states of the (*Z*)-allylic amines.



Scheme 2. Synthesis of the tetraacetyl derivatives of D-*ribo*- and L-*arabino*-phytosphingosine.

sphingosine employing the OsO_4-catalyzed dihydroxylations of the corresponding (*Z*)-allylic amines. However, the facial selectivities employing the osmylation reactions showed the mixed results ranging from 2.9:1 to 1:2.4 of an *anti*:*syn* ratio.[2c,4d,12] Even the asymmetric dihydroxylation reagent, AD-mix-β, gave the selectivity of less than 5:1 for the desired *anti* isomer.[4b]

In our synthetic effort for D-*ribo*-phytosphingosine, the required key intermediate **5b** ($R = C_{14}H_{29}$), *N*,*N*-diBoc (*Z*)-allylic amine, was obtained in an overall 73% yield from Garner's aldehyde (**2**) (Scheme 1). Here, the multi gram quantity of **2** was prepared from L-serine in a 78% yield over four steps according to the literature procedure.[13] The alkyl substituted (*Z*)-olefin **3b** ($R = C_{14}H_{29}$) was obtained as a major isomer in a 16:1 ratio [(*Z*)/(*E*)] under the salt-free conditions using the phosphonium salt, $Ph_3P^+C_{15}H_{31}Br^-$, which was prepared by heating $C_{15}H_{31}Br$ with Ph_3P under reflux of xylene. The acetonide group of **3b** was selectively removed under weakly acidic conditions[4b] and the following acetylation of the primary alcohol produced *N*-Boc-*O*-Ac (*Z*)-allylic amine **4b**. Further conversion of **4b** into *N*,*N*-diBoc protected **5b** required excess amount of Boc anhydride (ca. 10 equiv) because the reaction was sluggish. The minor *E*-olefin of **3b** was separable by column chromatography at the stage of either **3b** or **4b**.

The dihydroxylation reaction of **5b** was conducted using catalytic amount of OsO_4 and 2.5 equiv of *N*-methylmorpholine *N*-oxide (NMO) in DCM at room temperature (Scheme 2). After quenching the reaction with aq Na_2SO_3, the crude diol products were acetylated to give a diastereomeric mixture of triacetates **6** that was separable on ^1H NMR and whose ratio was more than 20:1 for the desired *anti* isomer, ***6anti***. The relative stereochemistry at the new stereogenic centers of ***6anti*** was confirmed by converting **6** to the known tetraacetyl derivative ***1anti***. The ^1H and ^{13}C NMR spectra of the major isomer (***1anti***) were in excellent agreement with those reported in the literature.[2c,14] Thus, the major isomer of **6**, ***6anti***, should have the same relative stereochemistry as that of D-*ribo*-phytosphingosine. Meanwhile, it was expected, as discussed in Figure 2, that the other diastereomer with the L-arabino configuration, ***1syn***, could be obtained when *N*-Boc-(*Z*)-allylic amine **4b** was subjected to the same dihydroxylation conditions. Although the *syn* selectivity of the dihydroxylation reactions of **4b** was lower ($5 \sim 7.5$:1), the major isomer obtained after derivatization to the tetraacetyl derivative, ***1syn***, matched the minor isomer derived from **5b** in every aspect.[2c]

In summary, we have found through a model study that the *anti*-selective OsO_4-catalyzed dihydroxylations of 1,2-dialkyl substituted (*Z*)-allylic amines could be achieved consistently via their *N*,*N*-diBoc derivatives. The best selectivity of 20:1 for the *anti* isomer was obtained with the *O*-acetyl group in CH_2Cl_2 as a reaction solvent. It is a great improvement over the previously reported results that showed inconsistent selectivities, and better than the well-known asymmetric dihydroxylation reactions employing AD-mix-β. The selectivity observed in the present study was rationalized with the *H*-eclipsed conformation at the transition state. These results are interesting in that the opposite *syn* selectivity has been known with 1,2-dialkyl substituted *N*-Boc-(*Z*)-allylic amines. The addition of one more Boc group to the allylic nitrogen atom shifted the favored transition state from the *N*-outside conformation to the *H*-eclipsed conformation. Thus, the dihydroxylation results in the present study are complementary to the *syn* selectivity shown with the *N*-Boc protected (*Z*)-allylic amines, but is better in terms of the degree of asymmetric induction.

As an application of the *N*,*N*-diBoc-controlled dihydroxylation reactions, an efficient stereoselective synthesis of the tetraacetyl derivative of D-*ribo*-phytosphingosine was realized in eight steps over a 45% overall yield from Garner's aldehyde with more than a 20:1 ratio. The consistent *anti* selectivity reported here should be useful in predicting the stereochemical outcome of the dihydroxylation products of 1,2-dialkyl substituted (*Z*)-allylic amines, in particular, phytosphingosine homologues, both natural and unnatural.

Acknowledgements

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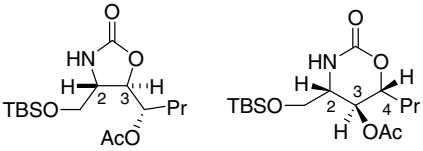
7. The relative configuration of each diastereomer obtained from the dihydroxylation products after the SiO_2 column separation was determined by converting separately into the following cyclic compounds and comparing their coupling constants. The small coupling constants of 4–5 Hz as in **8*syn*** are generally assigned to the *trans* oxazolidinones [(a) Ref. 1a and references cited therein. (b) Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles*, **1992**, *33*, 1051 and references cited therein. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439]. The large coupling constants of 8–10 Hz as in **8*anti*** are typically due to the diaxial relationship between the two adjacent protons in six-membered rings [Pretsch, E.; Bühlmann, P.; Affolter, C.; *Structure Determination of Organic Compounds*, 3rd ed.; Springer: Berlin, 2000; pp 161–198]. The sense of asymmetric induction caused by the *N*,*N*-diBoc group was confirmed further by stereoselective syntheses of the known derivatives of both diastereomers, D-*ribo*- and L-*arabino*–phytosphingosine, from each dihydroxylation product as described in the text.



8*syn* $J_{2,3}$ = 4.0 Hz

8*anti* $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 8.4 Hz

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14. **1*anti***: $[\alpha]_D^{27} + 26.5$ (*c* 0.84, $CHCl_3$) [lit.[2c] $[\alpha]_D^{23} + 26.2$ (*c* 2.0, $CHCl_3$)]; **1*syn***: $[\alpha]_D^{28} - 22.1$ (*c* 0.74, $CHCl_3$) [lit.[2c] $[\alpha]_D^{25} - 25.1$ (*c* 1.5, $CHCl_3$)].