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Diastereoselective reduction of *N*-phthaloyl α-amino ketones: synthesis of *syn*-3-amino-1,2-diol derivatives†

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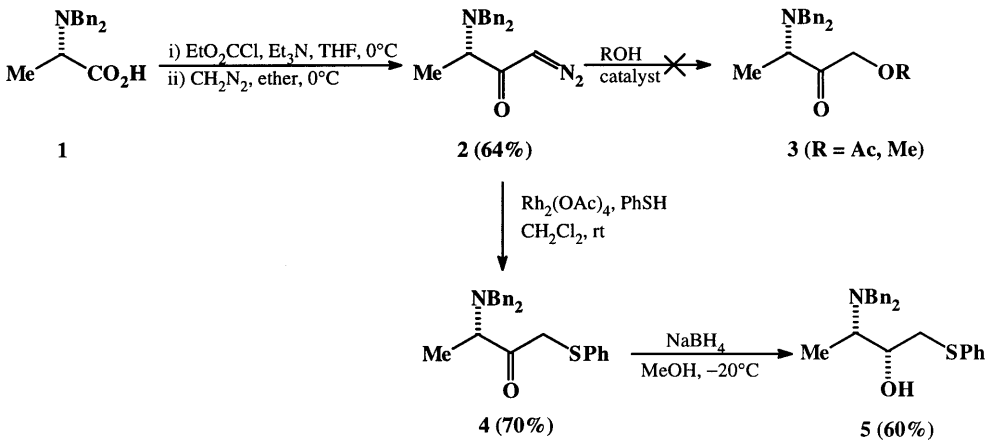
Abstract—$LiAlH(OBu\text{-}t)_3$ reduction of the chiral-pool derived *N*-phthaloyl α-amino-α′-acetoxy ketones has led to a facile diastereoselective synthesis of *syn*-3-amino-1,2-diols (>75% de).

In a study directed towards Ni-catalyzed enantioselective conjugate additions of diorganozincs to enones, we required both the *syn*- and *anti*-isomers of 3-amino-1,2-diols as stereocomplementary chiral auxiliaries. Several methods are available for the synthesis of *anti*-3-amino-1,2-diols, notably among which are the ring-opening of *trans*-glycidols with amines,[1] organometallic addition reactions to glyceraldehyde imines and nitrones,[2] reductive amination of α-epoxy or glyceryl ketones,[3] etc. However, synthetic routes to *syn*-3-amino-1,2-diols are severely limited and currently confined to the chiral auxiliary controlled Grignard additions to 2-*O*-benzyl-glyceraldehyde *N*-(1-phenylethyl)imines[2b,c] and $ZnBr_2$ mediated Grignard additions to glyceraldehyde nitrones.[2e] In view of their specialized nature, we looked for new synthetic avenues to *syn*-3-amino-1,2-diols and towards this end, report here a facile synthesis of some of these derivatives via a highly diastereoselective *syn*-reduction of *N*,*N*-diprotected α-amino-α′-hydroxy-ketones. Since *anti*-3-amino-1,2-diols have already been used in the synthesis of various bioactive compounds viz. nor-statines, dipeptide isosteres, α-amino epoxides, β-amino acids and amino sugars,[1] we believe that our new synthesis of the *syn*-isomers will provide opportunities for the preparation of the opposite enantiomers of these important targets.



Scheme 1.

Keywords: α-amino diazoketones; lithium tri-*t*-butoxyaluminium hydride; *syn*-reduction; *syn*-amino diols.

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† In memory of Professor Amalendu Das.

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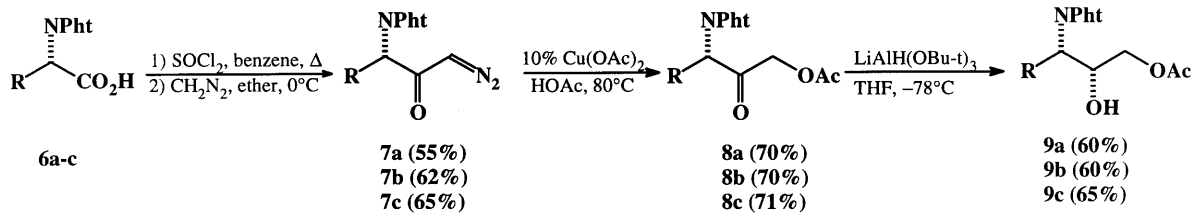

a : R = Me; b : R = *i*-Bu; c: R = CH_2Ph

Scheme 2.

Since Reetz et al. have shown that *N*,*N*-diprotected α-aminoketones, particularly the *N*,*N*-Bn_2 α-amino ketones, can be reduced via the Felkin-mode with high *syn*-selectivity,[4] we first decided to study the diastereoselective reductions of some *N*,*N*-Bn_2 α-amino-α′-hydroxyketones. Towards this end, a catalyzed intermolecular O–H insertion reaction of the *N*,*N*-Bn_2 α-aminodiazoketone **2** (readily prepared from *N*,*N*-Bn_2 alanine (**1**)[5] in 64% yield) was explored as a route to the key hydroxyketone **3** (Scheme 1). However, all attempts at insertion reactions of **2** to HOAc or MeOH in the presence of various catalysts ($Rh_2(OAc)_4$, $Cu(OAc)_2$, $BF_3{\cdot}Et_2O$) failed to deliver **3**, perhaps due to interference from the α-*N*,*N*-Bn_2 group via intramolecular nitrogen–ylide formation. Intermolecular S–H insertion reactions of **2** to PhSH, however, proceeded smoothly to give **4** (70%) indicating that formation of sulfonium ylides (believed to be the initial step in S–H insertion reactions) are favored over that of nitrogen–ylides. The α-thiophenylketone **4** could be easily reduced with $NaBH_4$ to give **5** (60%) with high *syn*-selectivity ($J_{2,3} = 9.4$ Hz). The latter promises to be a new amino alcohol based chiral auxiliary having an additional chalcogenide chelating arm and is under active investigation.

The failure to synthesize **3** led us to search for other *N*,*N*-diprotecting groups that would not interfere in the O–H insertion step. The *N*-phthaloyl (NPht) protecting group appeared to be quite promising in this regard, especially since we have previously shown that catalyzed O–H insertion reactions to NPht α-amino diazoketones can be carried out in good yields.[6] In the event, the NPht α-amino acids **6a**–**c** were first converted to the respective α-diazoketones **7a**–**c** by conventional methods (Scheme 2). $Cu(OAc)_2$ catalyzed O–H insertion reactions of the latter with HOAc then smoothly produced the key NPht α-amino acetoxy ketones **8a**–**c** in ca. 70% yields. The latter were then reduced via the Felkin-mode ($LiAlH(OBu\text{-}t)_3$, THF, −78°C) to give the *syn*-amino diol monoacetates **9a**–**c** in >75% de's, as judged by the ^1H NMR (300 MHz) spectra of the crude reduction products. The minor *anti*-isomers were easily separated by chromatography or recrystallization (for **9c**) to give the pure *syn*-products **9a**–**c** in 60–65% isolated yields.[7] The *syn*-stereochemistry in **9** were clearly evident from the relatively large coupling constants shown by their H-2 protons (δ 4.51–4.70, $J_{2,3} = 5$–7 Hz).[7,8] $LiAlH(OBu\text{-}t)_3$, a bulky and chemoselective reducing agent[9] was found to be absolutely essential for these reductions. $NaBH_4$, $NaB(CN)H_3$ or L-Selectride led to extensive hydride attack on the phthaloyl and acetate moieties of **8** resulting in complex product mixtures. Moreover, two equivalents of $LiAlH(OBu\text{-}t)_3$ were found to be necessary for complete reductions of **8**. The best de's were obtained at −78°C, whereas reductions carried out at 0°C to −20°C led to only a 60/40 ratio of the products.

It may also be mentioned here that NHBoc α-aminoacetoxyketones, prepared from NHBoc α-amino acids via the above O–H insertion route, can be reduced with $NaBH_4$[8b,c,10] in THF–MeOH at −78°C to give the *anti*-3-amino-1,2-diol products in ≥80% de's.[11] Therefore, via appropriate *N*-protecting group tuning, the present methodology, i.e. O–H insertion reactions of α-amino diazoketones followed by stereoselective reduction, provides a stereo-complementary strategy for the synthesis of both the *syn*- and *anti*-3-amino-1,2-diol derivatives.

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7. All new compounds gave satisfactory IR, NMR and microanalytical (C, H, N) data. **9a**: oil; $[\alpha]_D^{25}$ +3.75 (*c* 0.8); IR (neat): 3400, 1780, 1740, 1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.50 (d, 3H, *J* 7.2), 2.03 (s, 3H), 3.63 (br d, 1H), 4.07–4.13 (m, 2H), 4.20–4.23 (m, 1H), 4.55 (qnt, 1H, *J* 7.2), 7.73–7.76 (m, 2H), 7.84–7.86 (m, 2H). **9b**: oil; $[\alpha]_D^{25}$ +8.40 (*c* 0.5); IR (neat): 3400, 1775, 1740, 1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.91 (d, 3H, *J* 6.3), 0.94 (d, 3H, *J* 6.3), 1.33–1.58 (m, 1H), 2.00 (s, 3H), 2.04–2.21 (m, 2H), 3.70 (br d, 1H), 3.99–4.14 (m, 2H), 4.15–4.22 (m, 1H), 4.51 (ddd, 1H, *J* 5.1, 5.1, 10.3), 7.71–7.77 (m, 2H), 7.82–7.86 (m, 2H). **9c**: mp 84–85°C (EtOAc/hexane); $[\alpha]_D^{25}$ −57.9 (*c* 2.0); IR (KBr): 3400, 1770, 1740, 1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.98 (s, 3H), 3.25 (d, 2H, *J* 8.2), 4.02–4.12 (m, 2H), 4.11 (br d, 1H), 4.17–4.24 (m, 1H), 4.70 (dt, 1H, *J* 4.6, 8.0), 7.14–7.21 (m, 5H), 7.70–7.74 (m, 4H).
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