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A stereocontrolled route to the synthesis of (±)-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol

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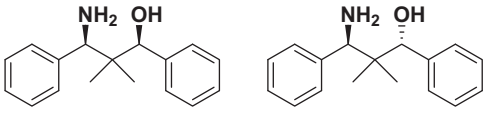
ABSTRACT

Both the diastereomers of (±)-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol were synthesized starting from a common intermediate, namely, β-hydroxy oxime **6**. Diastereoselective reduction with $NaBH_4/TiCl_4$ and H_2-Pd/C provided *syn*- and *anti*-isomers, respectively. Good overall yield and selectivity were realized using a simple protocol.

The design and synthesis of new chiral ligands for asymmetric synthesis is an important goal in organic synthesis.[1] 1,3-Aminoalcohols and their derivatives have proved to be excellent chiral auxiliaries as well as ligands for a variety of enantioselective reactions.[2] Various methodologies are described in the literature to prepare 1,3-aminoalcohols. Amongst these, the hydroxyl group-directed reduction of β-hydroxy oxime or β-hydroxy oximino ether has attracted much attention.[3] Narasaka et al.[3a] first reported the hydroxyl group-directed reduction of β-hydroxy oximino ether which results in the formation of *syn*-1,3-aminoalcohol as a major product. After this initial report, modifications were reported from various groups.[3b–h] In most cases *syn*-1,3-aminoalcohol was obtained as a major product. Reductive amination of β-hydroxy ketones was employed as an alternate approach by Menche et al.[4]

Diastereoselective reduction of β-hydroxy oxime or oximino ether would be an ideal approach for the synthesis of *syn*- and *anti*-isomers of 1,3-aminoalcohols. The only report describing such approach was that by Ellman and co-workers.[5] They reported the preparation of both *syn*- and *anti*-1,3-aminoalcohols starting from a β-hydroxy-*N*-sulfinyl ketimine. However this method requires extra steps for the preparation of the starting material.



1 2

We recently reported the synthesis and resolution of both *syn*- and *anti*-(±)-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, a new conformationally restricted 1,3-aminoalcohol **1** and **2**.[6] These aminoalcohols were synthesized from the corresponding *anti*- and *syn*-γ-hydroxybenzoate, respectively, employing nucleophilic substitution reactions followed by reduction of azidoalcohol. Though *anti*-γ-hydroxybenzoate can be prepared in a single step through Aldol–Tishchenko reaction, the synthesis of *syn*-γ-hydroxybenzoate is quite laborious. Also, the use of sodium azide needs to be avoided on large scale preparation. We now report herein a short route for the preparation of **1** and **2** starting from a common intermediate namely, β-hydroxy oxime **6**. The retrosynthetic analysis is shown as follows (Scheme 1).

The required β-hydroxy oxime **6** was prepared from γ-hydroxybenzoate **3** in three steps with excellent overall yield (Scheme 2).

The γ-hydroxybenzoate **3** was prepared employing Aldol–Tishchenko[6,7] reaction between isobutyrophenone and benzaldehyde in the presence of LiO^tBu. The resulting γ-hydroxybenzoate **3** was then oxidized to the corresponding keto benzoate **4** by chromic acid. We examined various conditions for the hydrolysis of compound **4** to the corresponding hydroxy ketone. In basic as well as in acidic conditions, retro aldol reaction took place. Therefore we first converted **4** into the corresponding oxime **5**, which upon hydrolysis with methanolic KOH gave the β-hydroxy oxime **6**.

For the preparation of *syn*-1,3-aminoalcohol, we attempted reduction of the oxime **6** with various hydride-reducing agents known in the literature. $LiAlH_4$[3c,f] in THF and $NaBH_3CN$[8] in aqueous $TiCl_3$ reduced the oxime **6** in moderate yield with low diastereoselectivity. The reduction did not proceed at all with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$.[3g] Finally we were successful in reducing

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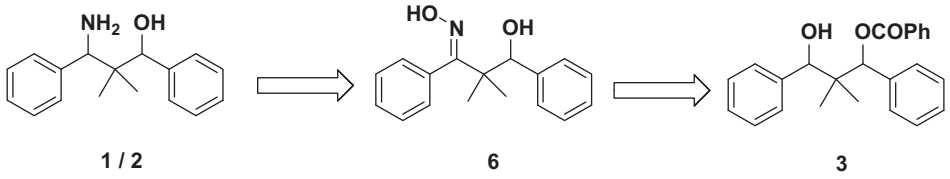
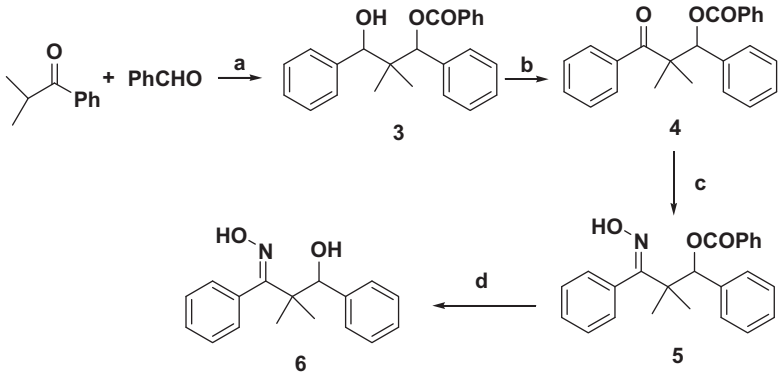


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of compound **6**. Reagents and conditions: (a) LiO^{t}Bu, THF, 0 °C to rt, 73%; (b) $K_2Cr_2O_7$, dil H_2SO_4, Et_2O, rt, 95%; (c) $NH_2OH{\cdot}HCl$, CH_3COONa, ethanol, reflux, 90%; (d) KOH, MeOH, rt, 90%.

the oxime **6** with $NaBH_4$ in the presence of $TiCl_4$.[9] The reduction proceeded smoothly with 2 equiv of $TiCl_4$ and excess of $NaBH_4$ at room temperature. The *syn*-1,3-aminoalcohol **1** was formed in high yield (80%) exclusively (Scheme 3).[10]

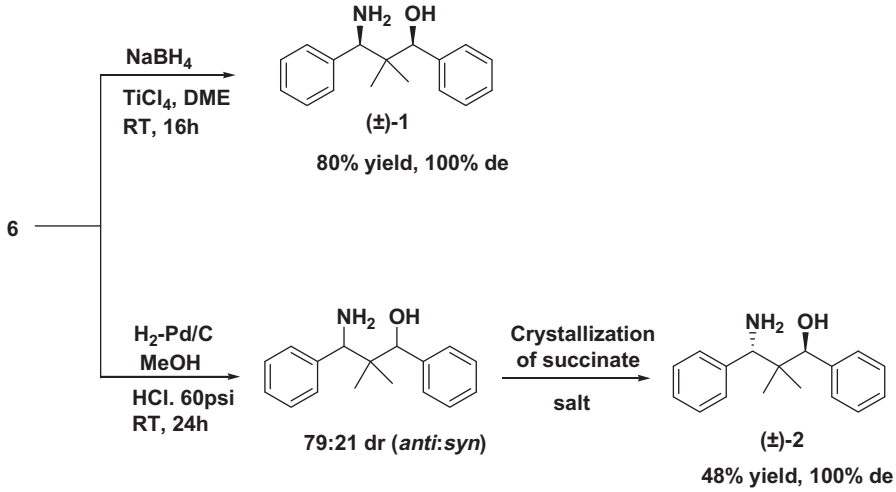
Hydrogenation of **6** proved a little tricky. The reduction did not take place with hydrogen in the presence of Pd/C in methanol. Hydrogenation with Raney Ni and $HCOONH_4$-Pd/C in methanol also failed to yield the reduced product. Hydrogenation in the presence of 1 equiv acetic acid did give the product, but the reaction was incomplete. Finally we observed that hydrogenation in the presence of 1 equiv of hydrochloric acid efficiently reduced the oxime **6** to 1,3-aminoalcohol in 80% yield with good distereoselectivity (*anti*:*syn* = 79:21). The desired *anti*-isomer **2** was isolated as its succinate salt by recrystallization (48% yield, >99 de).[11]

As depicted in Table 1, the observed *syn* diastereoselectivity in the present case is similar to that reported by other groups.[3,4] However the reduction with $NaBH_4/TiCl_4$ is not easy to explain because the combination can involve several reactive species which would vary with stoichiometry of the reactants.[12] Our preliminary

Table 1
Reduction of the β-hydroxy oxime **6**

Entry	Reagent	% Yield[a]	dr (*syn*:*anti*)[b]
1	$LiAlH_4$	71	47:53
2	$Na(BH_3)CN$/aq $TiCl_3$	68	55:45
3	$NaBH_4/NiCl_2{\cdot}6H_2O$	[c]	—
4	$NaBH_4/TiCl_4$	80	>99:1
5	H_2, Raney-Ni	[c]	—
6	$HCOONH_4$, Pd/C	[c]	—
7	H_2, HCl (1 equiv), Pd/C	78	21:79

[a] Isolated combined yield.
[b] Determined by ^{1}H NMR.
[c] Very slow or no reaction.



Scheme 3. Reduction of β-hydroxy oxime **6**.

experiments[13] rule out Ti (IV)-mediated reduction with $NaBH_4$ as is the case with reductive amination.[4] The anti-selectivity of the hydrogenation reaction can be explained based on the mechanism proposed for α-hydroxy ketone.[14]

In conclusion, we have described a short and efficient synthetic route for the synthesis of both diastereomers of 1,3-aminoalcohol through the stereoselective reduction of β-hydroxy oxime. The required β-hydroxy oxime was prepared in excellent yield using easily accessible materials. The present work will facilitate the synthetic applications of the homochiral aminoalcohols **1** and **2**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.011.

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10. Preparation of *syn*-(±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (**1**). A solution of **6** (2.69 g, 10 mmol) in anhydrous 1,2-dimethoxyethane (30 mL) was added dropwise to an ice-cooled, stirred mixture of $TiCl_4$ (2.2 mL, 20 mmol) and $NaBH_4$ (1.51 g, 40 mmol) in anhydrous 1,2-dimethoxyethane (30 mL). After the addition, the ice-bath was removed and stirring was continued at room temperature for 48 h. The reaction mixture was then quenched by the addition of ice-cold water, followed by 10% aqueous NaOH. The resulting suspension was filtered and the solid was washed with dichloromethane. Combined filtrate was transferred to a separating funnel,; dichloromethane layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by crystallization from ethanol to obtain **1** as a white solid (2.04 g, 80%), >99% de (by ^{1}H NMR). mp 168–170 °C; R_f (40% MeOH/EtOAc) 0.45; IR ($CHCl_3$): 3388, 3018, 1215 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.39 (s, 3H), 0.94 (s, 3H), 4.02 (s, 1H), 4.84 (s, 1H), 7.23–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 11.8, 24.8, 41.1, 66.2, 84.9, 127.0, 127.2, 127.3, 127.5, 128.0, 128.4, 141.6, 143.5. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.95; H, 8.28; N, 5.27.
11. Preparation of *anti*-(±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (**2**). To a solution of **6** (2.69 g, 10 mmol) in methanol (35 mL) was added concentrated HCl (1 mL) and the resulting mixture was hydrogenated (60 psi) at room temperature in the presence of 10% Pd/C (350 mg) for 10 h. The catalyst was removed by filtration and methanol was evaporated under rotavapour. The crude salt obtained was dissolved in water, washed with diethyl ether to remove neutral impurities, and the aqueous solution was basified with ammonia to obtain the aminoalcohol (2.05 g, 80% yield) as a 79:21 mixture of *anti*:*syn*. This mixture was converted into the corresponding succinate salt, which was crystallized using ethanol/ethyl acetate (1:9). The salt was treated as described earlier[6] to obtain the desired *anti* aminoalcohol **2** as a white solid (1.22 g, 48%), >99% de (by ^{1}H NMR), mp 137–139 °C. R_f (40% MeOH/EtOAc) 0.45; IR ($CHCl_3$): 3388, 3018, 1215 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.67 (s, 3H), 1.00 (s, 3H), 4.04 (s, 1H), 4.65 (s, 1H), 7.24–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.7, 23.6, 40.0, 65.9, 79.5, 126.8, 127.2, 127.6, 128.1, 128.2, 141.1, 141.7. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.84; H, 8.18; N, 5.33.
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