Zinc Borohydride Reduction of α-Amino Ketones: A Highly Diastereoselective Synthetic Route to *anti*-γ-Hydroxy-β-amino Alcohols

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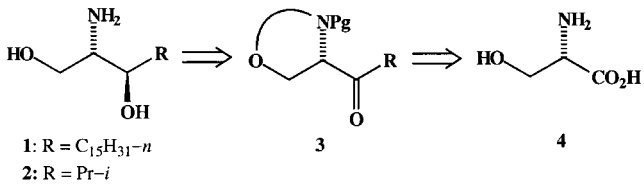
Abstract: A highly diastereoselective synthesis of *anti*-γ-hydroxy-β-amino alcohols via $Zn(BH_4)_2$ reductions of serine derived α-amino ketones is described. The latter were prepared from a serine derived γ-amino-β-ketosulfone via a α-alkylation-desulfonation sequence.

Key words: γ-hydroxy-β-amino alcohols, zinc borohydride, sphinganine, β-hydroxy leucinol, (+)-ephedrine

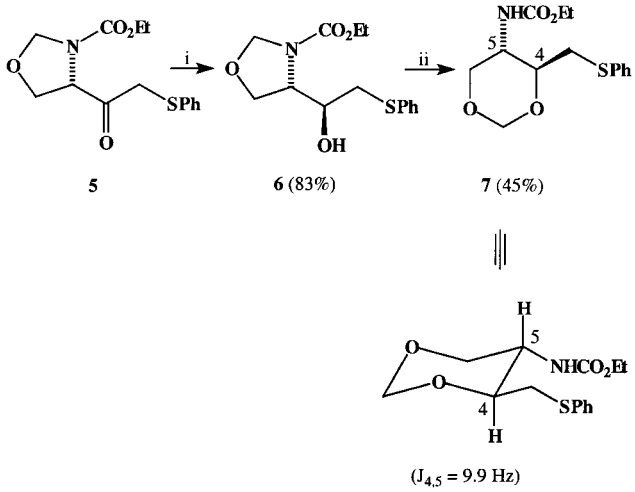
γ-Hydroxy-β-amino alcohols and their corresponding acids are the key structural units present in many bioactive natural products *viz*, sphingolipids, cyclopeptide antibiotics, amino sugars, etc.[1] The most widely used method for their synthesis involves organometallic addition reactions to serinal derivatives, in particular, to Garner's aldehyde.[2] However, the diastereoselectivities obtained in these reactions are often moderate, requiring tedious separation of the product mixtures. Moreover, the sense of diastereoselection (i.e. *syn vs. anti*) has been shown to be highly dependent on the nature of the organometallic reagent. For example, PhMgBr adds to Garner's aldehyde to give the *anti*-adduct as the major product, whereas *i*-PrMgCl reacts with the same aldehyde to give the *syn*-diastereomer in excess.[2a] In view of these, in recent years, diastereoselective synthesis of γ-hydroxy-β-amino alcohols via hydride reductions of serine derived α-amino ketones (serinyl ketones) is receiving increasing attention as an alternate pathway.[3] Based on this latter strategy, we now present here our results on the synthesis of two important γ-hydroxy-β-amino alcohol derivatives, namely *erythro*-sphinganine (**1**)[4] and *erythro*-β-hydroxyleucinol (**2**),[5] via a highly diastereoselective reduction of the corresponding serinyl ketones **3** (Scheme 1).



1: R = $C_{15}H_{31}$–*n*
2: R = Pr–*i*
3
4

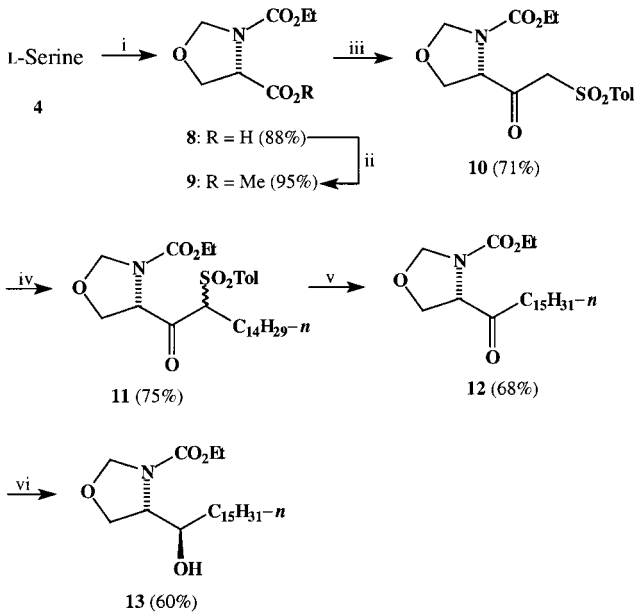
Scheme 1

The *erythro*-stereochemistry present in **1** and **2** called for an efficient *anti*-selective reduction of the serinyl ketones **3**. Model studies on the serinyl ketone **5**[6] revealed that $Zn(BH_4)_2$ is an excellent reagent for this purpose producing the *anti*-amino diol **6** (83%) in ≥90% de (Scheme 2). $NaBH_4$ reduction of **5** (MeOH, 0 °C), on the other hand, gave a modest diastereoselectivity (60/40) and that too, in favour of the *syn*-product. The *anti*-stereochemistry in **6** was established via isomerization (MeOH, dry HCl)[7] to the dioxane derivative **7**[8] which showed a large coupling constant between the H-4 and H-5 protons ($J_{4,5}$ = 9.9 Hz), indicative of a *trans*-diaxial relationship. This, in turn, proved the *anti*-relationship in **6**.



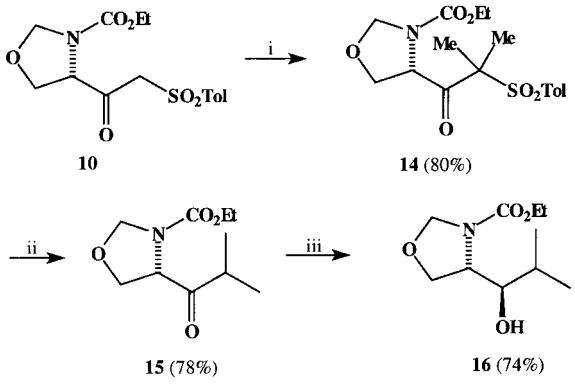
Scheme 2 (i) $Zn(BH_4)_2$, benzene-THF (8:2), 0 °C; (ii) MeOH, dry HCl (g), reflux

Having established the conditions for *anti*-selective reduction of serinyl ketones, we then set out for the synthesis of **1** and **2**. L-Serine (**4**) was first N,O-diprotected with formaldehyde and further N-protected with ethyl chloroformate to give the oxazolidine carboxylic acid **8** (88%) (Scheme 3). Esterification with excess CH_2N_2 gave the methyl ester **9** (95%) which upon reaction with α,α-dilithio methyltolyl sulfone (THF, –78 °C) produced the γ-amino-β-ketosulfone **10** in 71% yield. α-Alkylation of **10** with myristyl iodide according to Lygo-protocol (K_2CO_3, DMF, r.t.)[9] gave **11** (52%; 75% based on recovered **10**) as a diastereomeric mixture.The yield of this alkylation step was somewhat moderate, perhaps due to steric crowding around the α-carbon in **10**. However, unreacted **10** could be easily recovered and recycled. Subsequent desulfonation of **11** with Al(Hg) produced the key 3-ketosphinganine derivative **12** in 68% yield.[10] $Zn(BH_4)_2$ reduction of **12** in benzene-THF (8:2) at 0 °C then led to the protected *erythro*-sphinganine **13** (60%) with high *anti*-selectivity (>90% de).[10]



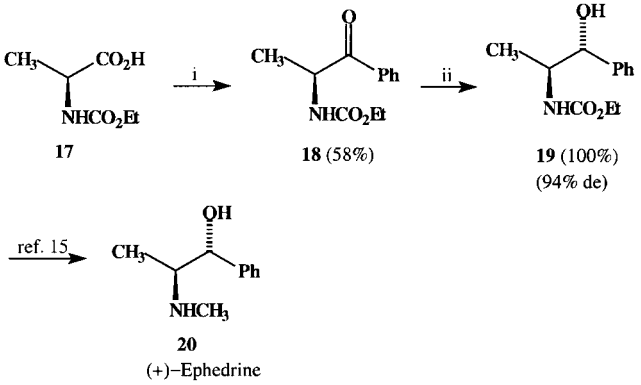
Scheme 3 (i) 40% formalin, 2N NaOH, 0 °C then $ClCO_2Et$, $NaHCO_3$, acetone, rt; (ii) excess CH_2N_2, ether, 0 °C; (iii) $MeSO_2Tol$, 2.2 equiv n-BuLi, THF, –78 °C; (iv) n-$C_{14}H_{29}I$, K_2CO_3, DMF, rt; (v) Al(Hg), THF-H_2O (9:1), reflux; (vi) $Zn(BH_4)_2$, benzene-THF (8:2), 0 °C.

Towards β-hydroxyleucinol, α,α-dialkylation of **10** with excess MeI (K_2CO_3, DMF, r.t.)[9d] gave **14** (80%) which upon desulfonation with Al(Hg) produced the isopropyl ketone **15** in 78% yield (Scheme 4). In view of the fact that nucleophilic acylation reactions[11] with isopropyl organometallics usually fail due to rapid hydride elimination from the organometallic reagent, the above synthetic route to isopropyl ketones can be an useful alternative. $Zn(BH_4)_2$ reduction of **15**, as before, then produced the *erythro*-β-hydroxy leucinol derivative **16** (74%) in 80% de. A small amount of the *syn*-isomer produced in this reaction was easily separated by chromatography and shown (^1H and ^{13}C NMR) to be entirely different from the *erythro*-isomer.[10]



Scheme 4 (i) MeI (excess), K_2CO_3, DMF, rt; (ii) Al(Hg), THF-H_2O (9:1), reflux; (iii) $Zn(BH_4)_2$, benzene-THF (8:2), 0 °C.

$Zn(BH_4)_2$ has been widely used for the chelation-controlled *anti*-reduction of α-hydroxy ketones.[12] However, its use in the stereoselective reduction of enantiopure α-amino ketones is very much limited.[3h,13] Our success with the *anti*-reduction of serinyl ketones **5**, **12** and **15** with $Zn(BH_4)_2$, presumably via chelation-controlled transition states, led us to investigate its utility in the diastereoselective reduction of other α-amino ketones. With an eye to synthesize (+)-ephedrine (**20**), the readily prepared enantiopure α-amino phenyl ketone **18**[14] was chosen as the test substrate (Scheme 5).



Scheme 5 (i) $(COCl)_2$, CH_2Cl_2, rt then benzene, $AlCl_3$, rt; (ii) $Zn(BH_4)_2$, benzene-THF (8:2), 0 °C.

In the event, $Zn(BH_4)_2$ reduction of **18** at 0 °C gave rise to a quantitative formation of the *anti*-amino alcohol **19** in >90% de. It may be noted that $NaBH_4$ reduction of **18** also leads to **19**, but only in 60% de.[14] The *erythro*-stereochemistry in **19** was clearly evident from the ^1H NMR spectrum of the corresponding acetate which showed a small coupling constant between the H-2 and H-3 protons ($J_{2,3}$ = 3 Hz).[15] A comparison between the rotation value of **19** ($[\alpha]_D^{20}$ -39.6, *c* 0.3, $CHCl_3$) with that reported in the literature ($[\alpha]_D^{20}$ -41.0, *c* 0.2, $CHCl_3$)[16] indicated that **19** was produced in, at least, 94% diastereomeric excess. $LiAlH_4$ reduction of **19** to (+)-ephedrine (**20**) has already been described by other workers.[14,16]

In conclusion, we have shown that α-amino ketones can be reduced with $Zn(BH_4)_2$ with high *anti*-selectivity (≥90% de). New synthetic routes to two important γ-hydroxy-β-amino alcohols viz. *erythro*-sphinganine and *erythro*-β-hydroxyleucinol has been developed via $Zn(BH_4)_2$ reductions of serine derived oxazolidinyl ketones. In addition, $Zn(BH_4)_2$ reduction of a N-monoprotected alanyl phenyl ketone have led to a formal synthesis of (+)-ephedrine with high diastereoselectivity.

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(8) **7**: $[\alpha]_D^{20}$ -17.21 (*c* 2.0, $CHCl_3$); IR (CH_2Cl_2): 3200, 3050, 2980, 1710, 1450, 1420 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.27 (t, 3H, *J* 7.1), 2.17 (s, 1H), 3.16-3.26 (pair of dd, 2H, *J* 6.1, 13.8), 3.72-3.77 (m, 2H), 3.89 ((dd, 1H, *J* 5.7, 9.9), 4.18 ((q, 2H, *J* 7.1), 4.74 (d, 1H, *J* 4.4), 5.15 (s, 1H), 7.24-7.41 (m, 5H); δ_C (75 MHz, $CDCl_3$): 14.5, 32.9, 36.0, 60.3, 61.8, 62.0, 63.7, 76.6, 78.8, 79.3, 126.7, 126.9, 129.1, 129.9, 130.2, 135.1, 157.2.

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(10) **12**: $[\alpha]_D^{20}$ -0.48 (*c* 5, $CHCl_3$); IR (CH_2Cl_2): 3000, 2840, 1710, 1690, 1410 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.88 (t, 3H, *J* 6.8), 1.25-2.31 (m, 29H), 2.50 (br s, 2H), 4.01-4.20 (m, 3H), 4.37-4.42 (m, 2H), 5.00 (br m, 2H); δ_C (75 MHz, $CDCl_3$): 14.0, 14.5, 21.5, 22.6, 22.9, 25.6, 28.2, 29.3, 29.4, 29.5, 29.6, 31.8, 39.6, 54.5, 61.8, 63.2, 69.5, 70.4, 79.4, 80.2, 152.5, 208.3. **13**: $[\alpha]_D^{20}$ -0.15 (*c* 1.9, $CHCl_3$); IR (CH_2Cl_2): 3150, 2980, 1710, 1580 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.88 (t, 3H, *J* 6.8), 1.14-1.37 (m, 32H), 3.82 (br s, 1H), 3.92-4.07 (m, 3H), 4.13-4.22 (m, 2H), 4.71 (dd, 1H, *J* 4.3, 9.0), 5.02-5.07 (m, 1H); δ_C (75 MHz, $CDCl_3$): 14.0, 14.5, 22.6, 25.3, 25.9, 29.3, 29.6, 31.8, 32.7, 33.4, 60.5, 61.8, 62.0, 69.0, 71.4, 73.1, 79.3, 79.6, 152.1. *anti*-**16**: $[\alpha]_D^{20}$ -3.18 (*c* 5.4, $CHCl_3$); IR (CH_2Cl_2): 3200, 3050, 2960, 1710, 1420, cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.95 (d, 3H, *J* 6.8), 1.01 (d, 3H, *J* 6.6), 1.27 (t, 3H, *J* 7.2), 1.65 (m, 1H), 2.55 (br s, 1H), 3.68 (br s, 1H), 3.97-4.21 (m, 5H), 4.69 (d, 1H, *J* 4.4), 5.05 (s, 1H); δ_C (75 MHz, $CDCl_3$): 14.4, 18.0, 19.3, 30.6, 58.1, 61.5, 67.2, 75.5, 79.3, 154.5. *syn*-**16**: $[\alpha]_D^{20}$ -2.43 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2): 3150, 3050, 2980, 1710, 1420, cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.94 (d, 3H, *J* 6.9), 1.03 (d, 3H, *J* 6.6), 1.28 (t, 3H, *J* 7.2), 1.58-1.64 (m, 1H), 3.40-3.42 (m, 1H), 3.72 (dd, 1H, *J* 4.8, 7.9), 3.99-4.11 (m, 2H), 4.19 (q, 2H, *J* 7.2), 4.67 (d, 1H, *J* 4.8), 5.12 (d, 1H, *J* 4.5); δ_C (75 MHz, $CDCl_3$): 14.5, 15.2, 20.1, 30.6, 59.3, 62.3, 69.4, 76.6, 77.9, 79.3, 156.5.

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(15) **19**: mp 71-72 °C (EtOAc-petroleum ether); lit.[16] mp 71 °C; $[\alpha]_D^{20}$ -39.6 (*c* 0.3, $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ -41 (*c* 0.2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 0.98 (d, 3H, *J* 7), 1.26 (t, 3H, *J* 7), 3.09 (br s, 1H), 3.90-4.15 (m, 1H), 4.09 (q, 2H, *J* 7), 4.80-4.90 (m, 2H), 7.20-7.40 (m, 5H); δ_H (300 MHz, $CDCl_3$) of **19**-OAc (Ac_2O, Et_3N, CH_2Cl_2, 81%, oil): 1.16 (d, 3H, *J* 7), 1.23 (t, 3H, *J* 7), 2.14 (s, 3H), 4.10 (m, 3H), 4.66 (d, 1H, *J* 6.6), 5.84 (d, 1H, *J* 3), 7.16-7.40 (m, 5H).

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