A novel protocol for *N*-methyl-γ-amino-β-hydroxy acids from oxazolidinones

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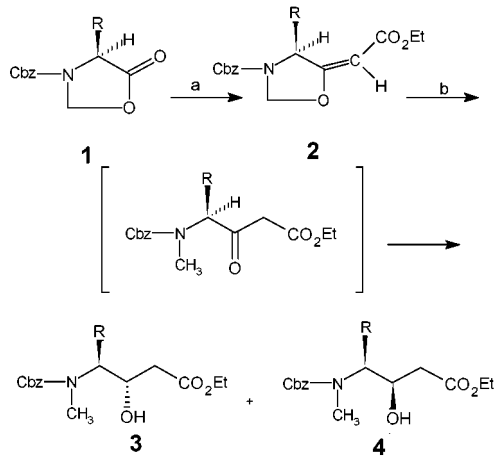
A new two step methodology for *N*-methyl-γ-amino-β-hydroxy acids from oxazolidinones is described

Optically active *N*-methyl-γ-amino-β-hydroxy acids are a class of nonproteinogenic amino acids present in a variety of biologically active compounds, *e.g.* Hapalosin,[1] a multidrug resistance active compound containing 3-hydroxy-4-*N*-methylamino-5-phenylpentanoic acid, and Dolastatine 10,[2] an anticancer compound containing 3-hydroxy-4-*N*-methylamino-5-methylheptanoic acid. Due to their promising biological activity, they have become an interesting class of compounds in the pharmaceutical industry. Although there are methods[3] available for preparation of *syn* and *anti* isomers of γ-amino-β-hydroxy acids, there is no effective method available to make their *N*-methylated analogues. The literature methods[4] of their preparation involves the treatment of *N*-protected-γ-amino-β-hydroxy acid with NaH followed by MeI. However, this method suffers due to competitive reactions such as the β-elimination resulting in the formation of α,β-unsaturated acid derivatives, and pyrrolidinone ring formation. The other problems associated with this method are *O*-methylation and *N*-deprotection, resulting in a complex mixture of products. In view of this, alternative methods have been developed.[5] Herein, we report an elegant, entirely novel, short and efficient protocol for the title compounds involving two new reactions, *viz*. (a) Wittig reaction of oxazolidinones (**1**→**2**) and (b) a reductive process of their corresponding α,β-unsaturated esters (**2**→**3**) (Scheme 1).

N-Cbz-oxazolidinones[6] (**1**) obtained from *N*-Cbz-α-amino acids by the reaction of paraformaldehyde in the presence of catalytic TsOH, were subjected to the Wittig reaction with Ph_3PCHCO_2Et to give α,β-unsaturated esters (**2**) in excellent yields. Since there was no enhancement of the signal in the NOE experiment between the olefinic proton and the methine proton in the ring, the olefin geometry was assumed to be '*E*'.

The reaction of α,β-unsaturated ester **2a** with $NaCNBH_3$–TMSCl under N_2 atmosphere afforded an easily separable mixture of *syn* and *anti* *N*-Cbz-*N*-methyl-γ-amino-β-hydroxy acids **3a** (syrup; $[\alpha]_D^{24}$ −29.4 (*c* 1, MeOH)) and **4a** (syrup; $[\alpha]_D^{25}$ −26.6, (*c* 1, MeOH)) in a ratio of 4:1 in 94% combined yield (Scheme 1).

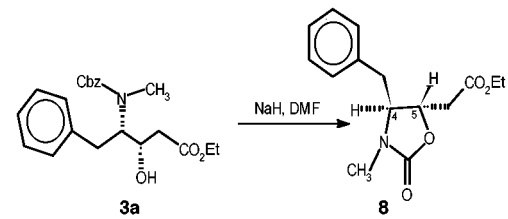


Scheme 1 *Reagents and conditions:* a, Ph_3P=CHCOOEt, toluene, reflux, 3 h; b, $NaCNBH_3$, TMSCl, CH_3CN, N_2, rt, 30 min.

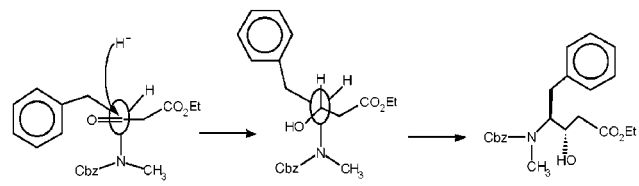
As expected the major isomer **3a** was found to be *syn* from the ^{1}H-NMR of the corresponding oxazolidinone[7] **8** obtained by the treatment of **3a** with NaH in DMF (J = 4.5 Hz for ring protons 4-H and 5-H, Scheme 2), which may be explained by the Felkin–Anh model[8] (Fig. 1). This was further confirmed by converting the minor *anti* isomer **4a** into the known compound **7** (oil; $[\alpha]_D^{25}$ −43.7 (*c* 1, MeOH); lit.[4c] $[\alpha]_D^{25}$ −41.2, (*c* 1, MeOH)) and by comparing specific rotations and spectral data with those of reported values which are found to be in good agreement (Scheme 3).

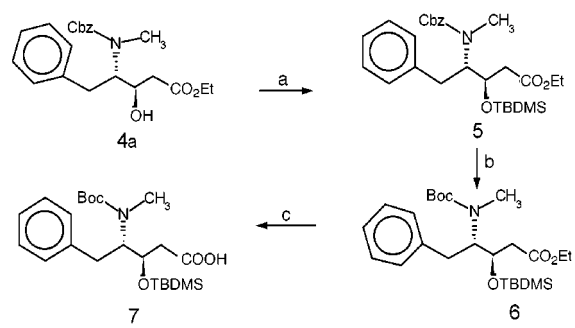
In order to probe the generality of the reaction, the process was further applied to **2b**–**2c.** *N*-Cbz-*N*-methyl-γ-amino-β-hydroxy acids (**3b**,**c**, **4b**,**c**) obtained using this methodology are shown in Scheme 1 (Table 1). All the compounds obtained were fully characterized by spectral data.[9] Important characteristic NMR signals of **3a** [δ_H 2.80 (s, 3H, N-CH_3), 1.30 (t, 3H, J 6.4, CH_3), 4.20 (q, 2H, J 6.4, CH_2)] clearly indicate the *N*-methyl group and ethyl esters. The spectroscopic data and optical rotations are in accordance to those of reported values.

In summary, we report an entirely novel, straightforward and practical methodology for *N*-methyl-γ-amino-β-hydroxy acids,



Scheme 2





Scheme 3 *Reagents and conditions :* a, TBDMSCl, imidazole, DMF, rt, 10 h, 95%; b, 10% Pd–C/H_2, Boc_2O, MeOH, rt, 12 h, 98%; c, 2M NaOH, THF, rt, 4 h, 92%.

Table 1 Preparation of *N*-Cbz-*N*-methyl-γ-amino-β-hydroxy acids from oxazolidinones

		2		**3** and **4**
S. No	R	Yield (%)	$[\alpha]_D^{25}$ [a]	Yield (ratio)[b]
A	$PhCH_2$	96	−13.8	94 (4 : 1)[c]
B	Me_2CHCH_2	94	45.2	92 (3:1)[d]
C	$MeCH_2CHMe$	96	25.6	96 (3:1)[d]

[a] Specific rotations were measured with c = 1 in MeOH. [b] Yield (%) are combined yields. Ratio is [c] based on isolated yield, [d] based on crude ^{1}H-NMR.

key precursors of the potential bioactive molecules and enzyme inhibitors, for the first time. The present methodology enables the synthesis of a variety of *N*-methyl-γ-amino-β-hydroxy acids with ease, and hence offers a practical alternative to the earlier methodologies. Further work is in progress and will be reported in due course.

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Notes and references

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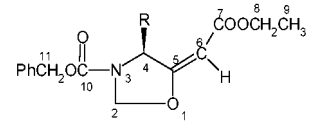
9 *Selected data* for **2a**: Colorless syrup; δ_H 1.30 (3H, t, J 6.4, CH_2CH_3), 3.00–3.40 (2H, m, $PhCH_2$), 4.20 (2H, q, J 6.4, CH_2CH_3), 4.80–4.90 (1H, m, *CH*Bn), 5.05 (2H, s, $PhCH_2O$), 5.20–5.32 (1H, br s, N-CH_2), 5.35 (1H, s, olefin), 5.60 (1H, br s, N-CH_2), 7.00–7.40 (10H, m, Ar) ; δ_C 14.3 (C-9), 38.7 (CH_2Ph), 59.5 (C-8), 59.8 (C-4), 67.7 (C-11), 91.0 (C-2), 126.7 (Ar), 128.0 (Ar), 128.2 (Ar), 128.3 (Ar), 128.6 (Ar), 129.7 (Ar), 130.5 (Ar), 132.5 (Ar), 136.3 (C-6), 154.2 (C-10), 167.1 (C-5), 171.5 (C-7); *m*/*z* 382 (M^+ + H). For **2b**: Colorless syrup; δ_H 0.82 (3H, d, J 6.7, CH_3), 1.00 (3H, d, J 6.7, CH_3), 1.22 (3H, t, J 6.2, CH_2CH_3), 1.30–1.80 (3H, m), 4.10 (2H, q, J 6.2, CH_2CH_3), 4.90 (1H, d, J 4.5), 5.12 (2H, ABq, J_{gem} 13.5, CH_2Ph), 5.22 (1-H, s, olefin), 5.50 (1H, br s, N-CH_2), 5.65 (1H, br s, N-CH_2), 7.30 (5H, m, Ar); δ_C 14.2 (C-9), 20.8 (CH_3), 23.5 (CH_3), 24.9 (CH_2), 39.9 (*C*H), 57.6 (C-8), 59.4 (C-4), 67.9 (C-11), 89.9 (C-2), 128.2 (Ar), 128.4 (Ar), 135.4 (C-6), 154.0 (C-10), 166.6 (C-5), 172.1 (C-7); *m*/*z* 348(M^+ + H). For **2c**: Colorless syrup; δ_H 0.88 (3H, t, J 6.2, CH_3CH_2), 1.20 (3H, d, J 6.8, CH_3), 1.28 (3H, t, J 6.2, CH_2CH_3), 1.30–1.50 (2H, m, CH_2CH_3), 2.00–2.20 (1H, m, $CH(CH_3)CH_2CH_3$), 4.10 (2H, q, J 6.2, CH_2CH_3), 4.92 (1H, d, J 4.6, N-CH), 5.15 (2H, ABq, J_{gem} 14.0, OCH_2Ph), 5.30 (1H, s, olefin), 5.40 (1H, br s, N-CH_2), 5.62 (1H, br s, N-CH_2), 7.30 (5H, m, Ar); δ_C 11.7 (CH_3), 14.0 (C-9), 16.2 (CH_3), 23.6 (CH_2), 39.1 (*C*H), 59.3 (C-8), 63.9 (C-4), 67.7 (C-11), 90.6 (C-2), 128.0 (Ar), 128.1 (Ar), 128.2 (Ar), 135.4 (C-6), 154.2 (C-10), 166.6 (C-5), 171.4 (C-7); *m*/*z* 348 (M^+ + H). For **3a**: Colorless syrup; $[\alpha]_D^{25}$ −29.4, (*c* 1, MeOH); δ_H 1.25 (t, 3H, CH_3), 2.40–2.55 (m, 2H, CH_2Ph), 2.80 (s, 3H, N-CH_3), 2.95–3.10 (m, 2H, CH_2CO_2), 4.00–4.18 (quartet overlapped with multiplet, 4H, CH_2CH_3 and *CH*NH and *CH*OH), 4.90–5.20 (m, 2H, $PhCH_2O$), 7.05–7.35 (m, 10H, Ar); δ_C 14.1, 30.6, 39.4, 58.6, 59.2, 59.9, 69.8, 79.2, 126.2, 128.2, 128.5, 128.7, 129.5, 130.2, 132.3, 154.4, 171.4; *m*/*z* 386 (M^+ + H). For **4a**: Colorless syrup; $[\alpha]_D^{25}$ −26.6 (*c* 1, MeOH); δ_H 1.20 (t, 3H, CH_3), 2.30–2.45 (m, 2H, CH_2Ph), 2.75 (s, 3H, N-CH_3), 3.00–3.20 (m, 2H, CH_2CO_2), 4.00–4.20 (quartet overlapped with multiplet, 4H, CH_2CH_3 and *CH*NH and *CH*OH), 5.00–5.15 (m, 2H, $PhCH_2O$), 7.10–7.35 (m, 10H, Ar); *m*/*z* 386 (M^+ + H). For **7**: Colorless oil; $[\alpha]_D^{25}$ −43.7 (*c* 1, $CHCl_3$); lit.[4c] $[\alpha]_D^{25}$ −41.2 (*c* 1, $CHCl_3$); δ_H 0.09 (s, 3H, Si-CH_3), 0.20 (s, 3H, CH_3-Si), 0.95 (s, 9H, $(CH_3)_3C$-Si), 1.35 (s, 9H, $(CH_3)_3C$), 2.35–2.50 (m, 2H, CH_2Ph), 2.75 (s, 3H, N-CH_3), 2.90–3.05 (m, 2H, CH_2CO_2), 4.25–4.40 (m, 2H, *CH*-NH and *CH*-OH), 7.10–7.35 (m, 5H, Ph); δ_C −4.7, −4.6, 14.2, 18.3, 25.6, 30.5, 35.7, 39.9, 56.2, 60.9, 71.1, 76.9, 79.2, 126.3, 128.0, 129.2, 138.7, 155.0, 171.5; *m*/*z* 324 (M^+ + H).



2a R = $PhCH_2$
2b R = Me_2CHCH_2
2c R = $MeCH_2CHMe$

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