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Total synthesis of *cis* and *trans*-hydroxyglimepiride: active metabolite of glimepiride

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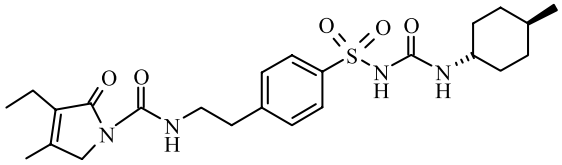
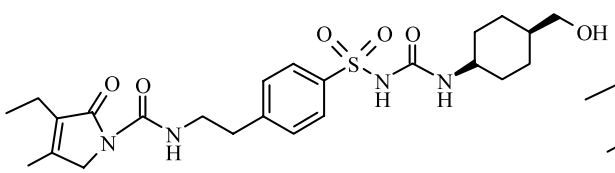
Abstract—Syntheses of *trans*-hydroxyglimepiride **2b**, a human metabolite of the blood glucose lowering agent glimepiride **1** and its corresponding *cis*-stereoisomer **2a**, are described.

Among the sulfonylurea[1] class of anti-diabetic drugs, glimepiride[2] **1** has many distinctive advantages and is by far the most superior blood glucose lowering agent.[3] Its biological activity initiates with binding to the 65 KD protein of the putative receptor. In addition, glimepiride shows a three-fold faster rate of association and a nine-fold faster rate of dissociation than glibenclamide,[1] which permitted its use as a once daily administration drug.[4] Glimepiride prevents post excessive insulin release thereby decreasing the risk of hypoglycemia.

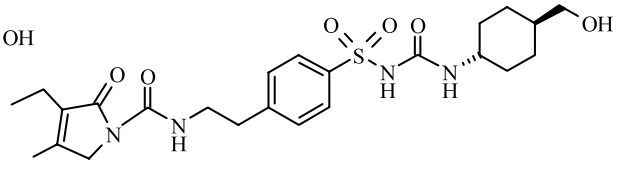
Studies on the metabolism of therapeutically active compounds are increasingly being carried out because metabolites provide superior safety and efficacy profiles, but more importantly offer opportunities to study the metabolic pathways. The metabolism of glimepiride has been observed in animals and humans via oxidative



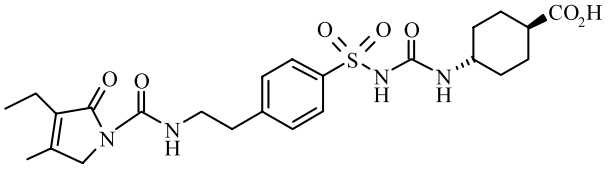
Glimepiride 1



***cis*-Hydroxyglimepiride 2a**



***trans*-Hydroxyglimepiride 2b**



Carboxyglimepiride 3

* Corresponding authors.

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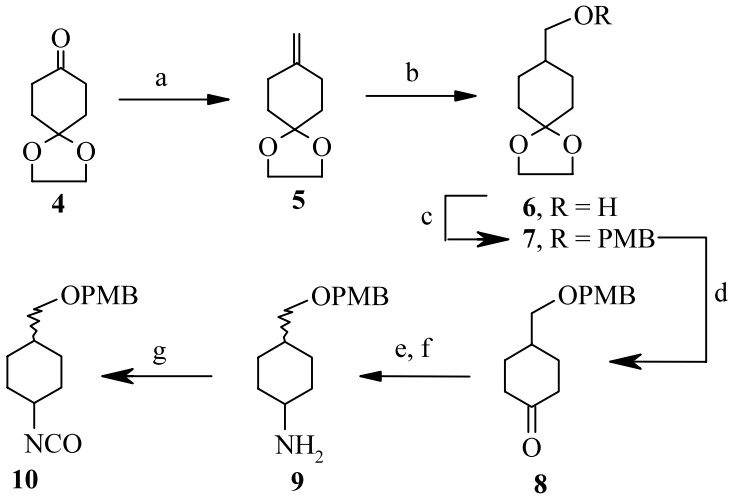


Scheme 1. *Reagents and conditions*: (a) CH_2=PPh_3, THF, −20°C–rt, 1.5 h (80%); (b) H_3B:SMe_2, THF, NaOAc, H_2O_2 (75%); (c) *p*-methoxybenzyl bromide, NaH, DMF, 0°C–rt (82%); (d) 0.8% H_2SO_4, MeOH, rt, 30 min (88%); (e) NH_2OH·HCl, EtOH, reflux, 2 h (80%); (f) LAH, THF, reflux, 2 h (70%); (g) $COCl_2$, $C_6H_5CH_3$, reflux, 7 h (93%).

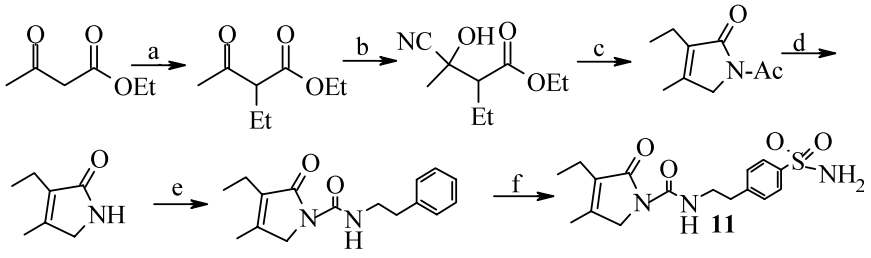
pathways giving rise to two active metabolites, *trans*-hydroxyglimepiride **2b** and carboxyglimepiride **3**.[5] In spite of their significance in metabolic studies, their syntheses are yet to be accomplished. However, we were confronted with the need to produce synthetically both *cis*-**2a** and *trans*-hydroxyglimepiride **2b**, for bio-equivalence studies and this communication describes the total synthesis.

The synthesis of hydroxyglimepiride was initiated from commercially available 1,4-cyclohexanedione *mono*-ethylene ketal **4**.[6] Subsequent Wittig reaction with PPh_3=CH_2 in THF at room temperature gave the *exo*-methylene product **5**. In the ^{1}H NMR spectrum of **5**, the characteristic signals due to olefinic protons were located at 4.66 ppm. Compound **5** was subjected to a hydroboration–oxidation reaction in the presence of 2M H_3B:SMe_2 solution in THF followed by treatment with H_2O_2–NaOAc. The product **6** showed a doublet (J=6.0 Hz) at 3.45 ppm in its ^{1}H NMR spectrum attributed to the hydroxymethyl protons. The rest of the spectrum was in conformity with the assigned structure. The free hydroxy group present in **6** was protected using PMB-bromide/NaH followed by acidic cleavage of ethylene ketal group to yield the ketone **8**.

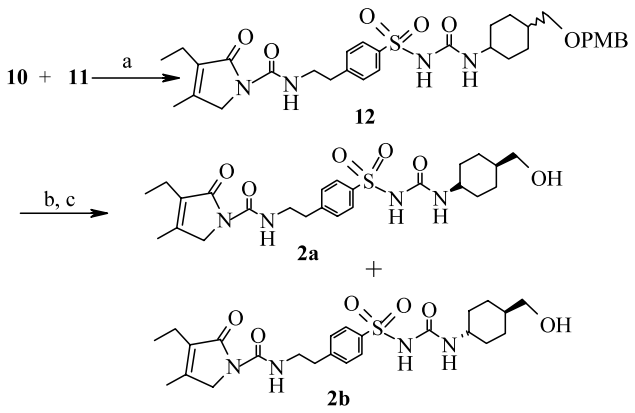
Our next concern was to convert **8** into the corresponding isocyanate **10**. For this endeavour **8** was first treated with NH_2OH·HCl in refluxing ethanol to produce the oxime whose structure was supported by spectroscopic data. Reduction of the oxime occurred smoothly in the presence of LAH in THF to provide a *cis* and *trans* mixture of cyclohexylamine derivatives **9**. An attempt to separate this *cis* and *trans* mixture at this juncture was not successful. Therefore, we decided to continue our synthetic strategy with the mixture and envisaged separation at a later stage of the synthetic sequence. Conversion of the amine **9** into the corresponding isocyanate derivative **10** was a straightforward exercise using phosgene in toluene at reflux (Scheme 1).

The synthesis[7] of sulfonamide intermediate **11** was completed by adopting the procedure shown in Scheme 2.

Finally the condensation reaction between **10** and **11** was performed in the presence of potassium carbonate in acetone at reflux to give the coupled product **12**. The ^{1}H NMR spectrum of **12** clearly indicated that the coupling had indeed taken place because characteristic signals of both the coupling partners were distinctly visible (Scheme 3).



Scheme 2. *Reagents and conditions:* (a) $HNMe_2$, Et_2SO_4, 10–15°C (70%); (b) NaCN, DMF, 0–5°C (80%); (c) H_2, Ra–Ni, Ac_2O, 40°C, 5 Kg/cm^2 (15%); (d) Na_2CO_3, H_2O, reflux (90%); (e) $PhCH_2CH_2NCO$, $C_6H_5CH_3$, reflux (65%); (f) *i*. $ClSO_3H$, 10°C; *ii*. NH_3, H_2O, 60°C, 4 h (80%, 2 steps).



Scheme 3. *Reagents and conditions*: (a) K_2CO_3, CH_3COCH_3, reflux, 8 h (80%); (b) BF_3:OEt_3, CH_2Cl_2, rt (65%); (c) preparative HPLC.

Deprotection of the PMB group turned out to be difficult. We observed that the deprotection of PMB with DDQ in aqueous acetonitrile produced a number of compounds which were difficult to separate. The best result for the deprotection was when compound **12** was exposed to a catalytic amount of BF_3:Et_2O in CH_2Cl_2 at 0°C giving a mixture of *cis*/*trans* hydroxyglimepirides **2**. The ^{1}H NMR spectrum and elemental analysis supported the assigned structure. It is pertinent to mention that to the best of our knowledge deprotection of a PMB group with BF_3:Et_2O is being reported for the first time.

Separation of the *cis* and *trans* mixture was accomplished by preparative HPLC (mobile phase, 40:60 acetonitrile:pH3 buffer) using an ODS column. Based on the comparision of their ^{1}H and ^{13}C NMR spectroscopic data with that of authentic glimepiride **1**, the structures for the *cis*-isomer **2a** and the *trans*-isomer **2b** of hydroxyglimepiride were assigned.[8]

In summary, we have successfully synthesized *cis* and *trans*-hydroxyglimepiride using a very straightforward method.

Acknowledgements

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8. NMR spectroscopic data for hydroxyglimepiride-**2a** (*cis*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (t, 3 H, J=6.4 Hz), 1.5–1.65 (m, 7 H), 1.68–1.77 (m, 2 H), 2.05 (s, 3 H), 2.27 (q, 2 H, J=6.4 Hz), 2.97 (t, 2 H, J=6.3 Hz), 3.51 (d, 2 H, J=6.3 Hz), 3.62 (dd, 2 H, J=7.8, 14.1 Hz), 3.90 (m, 1 H), 4.19 (s, 2 H), 6.71 (d, 1 H, J=8.5 Hz), 7.41 (d, 2 H, J=8.3 Hz), 7.87 (d, 2 H, J=8.3 Hz), 8.52 (t, 1 H, J=6.9 Hz); ^{13}C (125 MHz): δ 12.7, 13.1, 16.6, 24.0 (2C), 29.3 (2C), 36.1, 38.8, 40.5, 46.2, 52.2, 67.2, 127.3, 129.7, 133.9, 138.0, 145.6, 150.5, 152.6, 172.6. **2b** (*trans*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, 3 H, J=6.5 Hz), 1.1 (m, 4 H), 1.5–2.0 (m, 5 H), 2.04 (s, 3 H), 2.28 (q, 2 H, J=6.5 Hz), 2.94 (t, 2 H, J=6.7 Hz), 3.42 (d, 2 H, J=6.7 Hz), 3.58 (m, 3 H), 4.18 (s, 2 H), 6.43 (d, 1 H, J=7.6 Hz), 7.39 (d, 2 H, J=8.3 Hz), 7.83 (d, 2 H, J=8.3 Hz), 8.52 (t, 1 H, J=6.4 Hz); ^{13}C (125 MHz): 12.8 (2C), 13.1, 16.7 (2C), 28.1, 32.5, 36.2, 39.5, 41.0, 49.7, 52.3, 67.8, 127.4, 129.6, 133.9, 138.1, 145.5, 150.8, 152.7, 172.5. FAB-MS m/z 529 (M^++Na), 507 (M^++1).