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# Asymmetric synthesis of (−)-(*R*)-sitagliptin

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ABSTRACT

The asymmetric synthesis of (−)-(*R*)-sitagliptin was achieved in seven steps from commercially available starting materials using the highly diastereoselective conjugate additions of either lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide or lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl 4-(2′,4′,5′-trifluorophenyl)but-2-enoate to install the correct stereochemistry. Subsequent sequential acid-catalysed hydrolysis of the resultant β-amino esters, HOBt/EDC mediated coupling with the triazolopyrazine fragment, and hydrogenolysis gave (−)-(*R*)-sitagliptin in 43% and 42% overall yields, respectively.


Fluorinated β-amino acid motifs have appeared in a variety of medicinally valuable molecules over recent years.[1] For example, Taxol (paclitaxel) and Taxotere (docetaxel) have become the most widely used drugs in cancer chemotherapy.[2] Studies on fluorinated analogues, especially of the β-amino acid moieties within both Taxol and Taxotere, have been actively pursued and have revealed interesting biological activities.[3] Another important fluorinated β-amino acid derivative, (−)-(*R*)-sitagliptin (JANUVIA™) **1**,[4] has recently been developed by Merck and has been marketed as the first potent and selective orally active dipeptidyl peptidase IV (DPP-4) inhibitor for the treatment of type 2 diabetes (Fig. 1).[5]

Recently, Merck's three generations of syntheses for manufacturing (−)-(*R*)-sitagliptin **1** were highlighted[6] to showcase how process chemistry could overcome challenges such as reducing chemical waste by increasing atom efficiency, reducing cost by employing a recyclable biocatalyst instead of expensive transition metal catalysts, and achieving efficient target syntheses moving towards 'greener' chemical processes. In all three generations of syntheses, the key steps to install the correct configuration for (−)-(*R*)-sitagliptin **1** relied on asymmetric reductions: in the first generation synthesis a ruthenium-catalysed chemo- and stereoselective hydrogenation of a β-ketoester was followed by an EDC coupling/Mitsunobu reaction sequence; in the second generation synthesis a rhodium-catalysed asymmetric hydrogenation of an enamine was conducted under high pressure; and in the third generation synthesis a biocatalytic asymmetric reductive amination of a β-ketoamide was employed. On a laboratory scale, there have been a few other syntheses of (−)-(*R*)-sitagliptin **1** (or its ammonium salt derivatives) reported.[7,8] Among them, an elegant approach was demonstrated by the research groups from Merck and Takasago International Corporation, where they developed a ruthenium-catalysed direct asymmetric reductive amination protocol employing ammonium salicylate as a 'nitrogen' source.[9] In this synthesis the readily available β-ketoamide **2** was treated with ammonium salicylate under high pressure hydrogen in the presence of the chiral ruthenium complex $Ru(OAc)_2$[(*R*)-dm-segphos] to give enantiomerically pure (*R*)-sitagliptin salicylate **3** in 91% yield and 99.5% ee (Scheme 1).

We have previously established the highly diastereoselective conjugate addition of a variety of enantiopure secondary lithium amides (derived from α-methylbenzylamines) to a range of α,β-unsaturated esters and amides.[10] This methodology has been employed in numerous applications, including the total syntheses of natural products,[11] molecular recognition phenomena[12] and resolution protocols,[13] and has been reviewed.[14] As part of our ongoing research programme in this area we, as have others,[8] anticipated that (−)-(*R*)-sitagliptin **1** would be an ideal synthetic target to demonstrate the utility of this versatile and efficient methodology. Herein, the further application of this lithium amide conjugate addition protocol to facilitate an efficient and concise synthesis of (−)-(*R*)-sitagliptin **1** is delineated.

Commercially available 2,4,5-trifluorobenzaldehyde **4** was homologated by Wittig reaction with the ylid derived from $[MeOCH_2PPh_3]^+[Cl]^-$ to give the corresponding enol ether **5** as a 55:45 [(*E*)/(*Z*)] mixture of geometric isomers. After treatment of **5** with 4.0 M HCl in 1,4-dioxane for 6 h, Wadsworth–Emmons reaction of the resultant aldehyde with *tert*-butyl diethylphosphonoacetate (promoted by MeMgBr)[15] gave α,β-unsaturated ester **6** as a single product in 74% isolated yield (from **4**) after purification. Two alternative N-protecting group strategies were next

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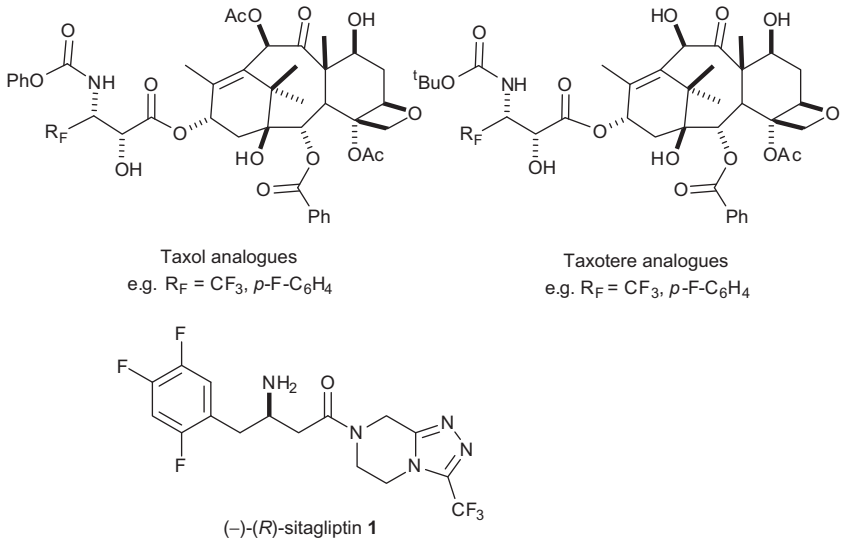
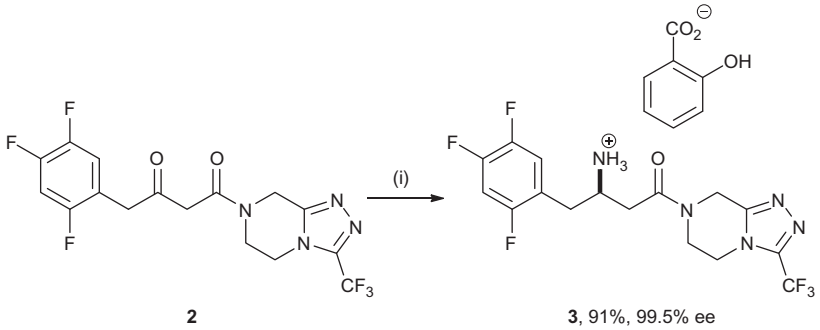



**Figure 1.** Fluorinated analogues of Taxol and Taxotere, and the structure of (−)-(*R*)-sitagliptin **1**.

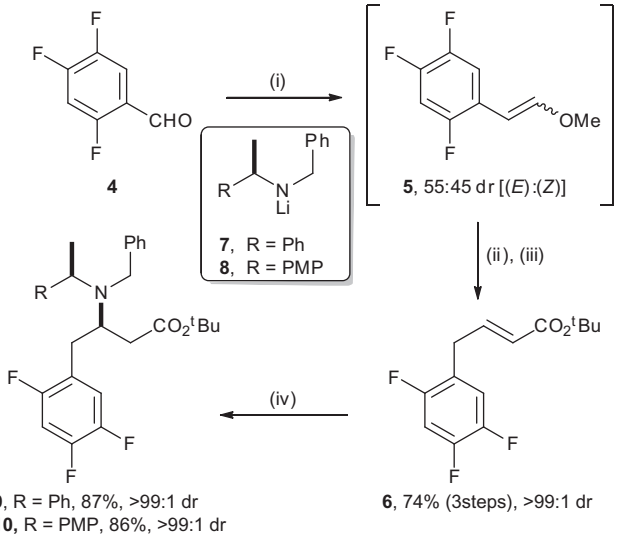



**Scheme 1.** Reagents and conditions: (i) Ru(OAc)$_2$[(*R*)-dm-segphos], ammonium salicylate, $H_2$ (435 psi), MeOH, 75 °C, 7 h.

envisaged: the conjugate additions of both lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **7** and lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **8** to α,β-unsaturated ester **6** were undertaken so that alternative N-deprotection step(s)[16] could be investigated for compatibility with the 2′,4′,5′-trifluorophenyl group. Thus, α,β-unsaturated ester **6** was treated with either (*R*)-**7** or (*R*)-**8** to give the corresponding β-amino esters **9** and **10** with excellent diastereoselectivity (>95:5 dr in each case), in 87% and 86% isolated yield, respectively, and >99:1 dr in each case after chromatographic purification (Scheme 2).

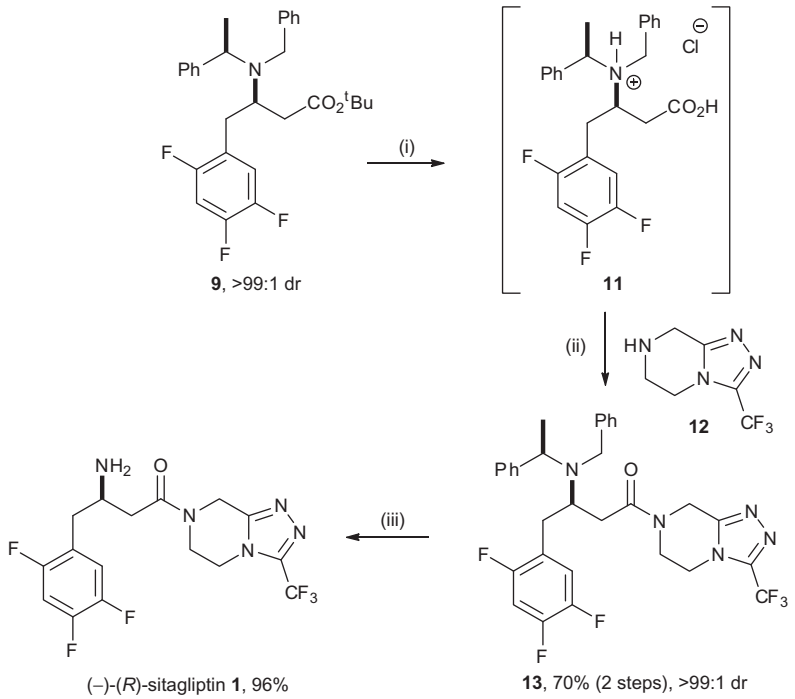
*N*-Benzyl-*N*-α-methylbenzyl protected β-amino ester **9** was treated with 2.0 M aq HCl at reflux to give the corresponding carboxylic acid hydrochloride salt **11**. Subsequent HOBt/EDC mediated amide coupling of **11** with triazolopyrazine **12**[17] gave amide **13** in 70% yield over two steps. Finally, removal of the N-protecting groups by hydrogenolysis in the presence of Pearlman's catalyst [Pd(OH)$_2$/C] gave (−)-(*R*)-sitagliptin **1** in 96% yield. Interestingly, it was noted that defluorination was not observed under these conditions (Scheme 3). The spectroscopic data obtained for this sample of (−)-(*R*)-sitagliptin **1** were in excellent agreement with those for the sample previously reported in the literature {$[\alpha]_D^{25}$ −23.3 (*c* 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{26}$ −22.8 (*c* 1.0, $CHCl_3$)}.

Similarly, *N*-benzyl-*N*-α-methyl-*p*-methoxybenzyl protected β-amino ester **10** was hydrolysed by treatment with 2.0 M aq HCl to give the corresponding carboxylic acid hydrochloride salt **14**, during which the acid-labile α-methyl-*p*-methoxybenzyl group was also removed. Subsequent HOBt/EDC mediated coupling of

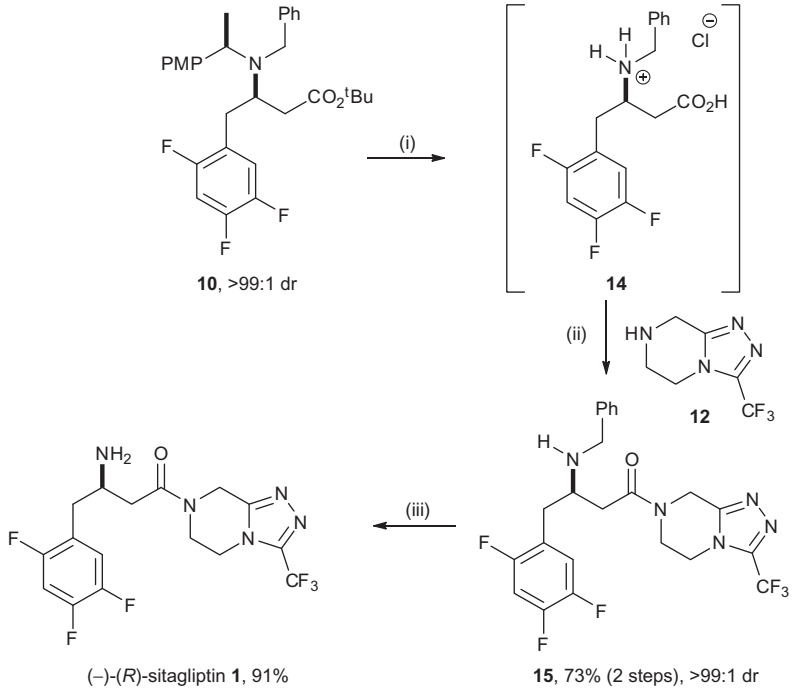



**Scheme 2.** Reagents and conditions: (i) $[MeOCH_2PPh_3]^+[Cl]^-$, $^t$BuOK, THF, rt, 48 h; (ii) 4.0 M HCl in 1,4-dioxane, rt, 6 h; (iii) MeMgBr, *tert*-butyl diethylphosphonoacetate, THF, reflux, 15 h; (iv) (*R*)-**7** or (*R*)-**8**, THF, −78 °C, 2 h. [PMP = *p*-methoxyphenyl].

**14** with triazolopyrazine **12** afforded amide **15** in 73% yield over two steps, and N-debenzylation of **15** under high pressure




**Scheme 3.** Reagents and conditions: (i) HCl (2.0 M, aq), reflux, 6 h; (ii) HOBt, EDC·HCl, DIPEA, $CHCl_3$, rt, 16 h; (iii) $H_2$ (5 atm), $Pd(OH)_2/C$ (30% w/w), MeOH, rt, 24 h.




**Scheme 4.** Reagents and conditions: (i) HCl (2.0 M, aq), reflux, 6 h; (ii) HOBt, EDC·HCl, DIPEA, $CHCl_3$, rt, 16 h; (iii) $H_2$ (5 atm), $Pd(OH)_2/C$ (20% w/w), MeOH, rt, 24 h. [PMP = *p*-methoxyphenyl].

hydrogen in the presence of Pearlman's catalyst gave (−)-(*R*)-sitagliptin **1** in 91% isolated yield (Scheme 4). The spectroscopic data obtained for this sample of (−)-(*R*)-sitagliptin **1** were also found to be in excellent agreement with those for the sample originally reported in the literature {$[\alpha]_D^{25}$ −22.0 (*c* 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{26}$ −22.8 (*c* 1.0, $CHCl_3$)}. Finally, this sample of (−)-(*R*)-sitagliptin **1** was converted into its phosphate salt **1**·$H_3PO_4$ and recrystallised from $^i$PrOH. The spectroscopic data for this sample were also found to be in excellent agreement with those for the sample originally reported in the literature {$[\alpha]_D^{25}$ −75.8 (*c* 1.0, $H_2O$); lit.[8] $[\alpha]_D^{20}$ −72.9 (*c* 1.0, $H_2O$); lit.[7c] $[\alpha]_D$ −74.4 (*c* 1.0, $H_2O$)}.

In conclusion, two efficient and concise asymmetric syntheses of (−)-(*R*)-sitagliptin **1** were accomplished in seven steps from commercially available starting materials. Two alternative protecting group strategies were evaluated which gave comparable overall yields of (−)-(*R*)-sitagliptin **1** (43% overall yield employing

*N*-α-methylbenzyl protection and 42% overall yield using *N*-α-methyl-*p*-methoxybenzyl protection). In the latter case, elaboration of the mono-*N*-protected amine intermediate **15** should allow access to libraries of analogues.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.025.

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