LITERATURE SURVEY ON SYNTHESIS OF SITAGLIPTIN

A MSc Dissertation report by
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LITERATURE SURVEY ON SYNTHESIS OF SITAGLIPTIN

A DISSERTATION REPORT

Submitted in Partial Fulfilment
Of
The Degree of MSc. (Organic Chemistry)

By
Ms. Jivita N. Parvatkar

To the
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Goa University
Goa 403206
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STATEMENT

I hereby declare that the dissertation report titled “LITERATURE SURVEY ON SYNTHESIS OF SITAGLIPTIN” submitted to the School of Chemical Sciences, Goa University is based on the original work done by me under the guidance of Dr. Bidhan A. Shinkre, Associate Professor in Chemistry. The information provided in the report is authentic to the best of my knowledge and the same has not been submitted to any other institution or university for the award of degree or diploma.

Jivita N. Parvatkar

CERTIFICATE

This is to certify that the dissertation entitled "***Literature survey on Synthesis of Sitagliptin"*** is bonafide work carried out by Ms. Jivita Narayan Parvatkar under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Prof. Dr. Bidhan A. Shinkre

Dissertation Guide

Associate Professor in Chemistry

Goa University

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Introduction

Type 2 diabetes has become very common over the past 25 years. It accounts for >90% cases of diabetes in adults. Type 2 diabetes1–4 mellitus is a commonly and rapidly growing disease, with millions of new cases reported annually worldwide. Diabetes has become a serious threat to human health and brings enormously high economic costs, not only to individuals and families, but also to the global health system. Dipeptidyl peptidase-4 (DPP-4) inhibitors, enzymes that act to degrade and inactivate glucagon-like peptide-1 (GLP-1) are the class of anti-hyperglycemic agents for the treatment of type-2 diabetes mellitus. GLP-1 is an incretin hormone that stimulates insulin secretion and biosynthesis, inhibits glucagon release in a glucose-dependent manner which also aids gastric emptying and reducing appetite.(Ye et al., 2021)

Sitagliptin is a chiral β-amino acid derivative that contains both a triflurophenyl moiety and a trifluromethylated triazole. Significance of sitagliptin as the active pharmaceutical ingredient in drugs like Januvia is the best-selling drugs since its first approval by the FDA in 2006. The best synthesis until today was developed by Merck, Sharp & Dohme (DSM) itself in cooperation with Codexis, which provided Sitaglaptin by a biocatalytic route utilizing an engineered transaminase enzyme. Sitagliptin is established as the benchmark target for chiral amine synthesis. There are many key methods to install chiral amine which include auxiliary controlled alkylation of amides followed by Arndt-Eistert homologation, intramolecular Pd-catalyzed [2,3]-sigmatropic rearrangement, asymmetric aza-Michael addition, auxiliary controlled amination of enolates, auxiliary controlled reduction or asymmetric hydrogenation and enantioselective or auxiliary controlled Mannich reaction. Also, biocatalyst is explored for consideration as green alternatives to alleviate the environmental issues encountered with the use of methods pertaining to traditional organic chemistry. Multi-enzyme cascade reactions have garnered attention owing to their elegance, comprehensiveness, and involvement in the synthesis of a considerable variety of pharmaceuticals, agrochemicals, and other industrially important chemicals.

Sitagliptin

Properties

Structure:

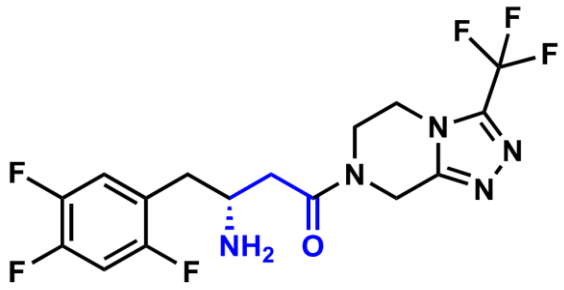


Figure 1: Sitagliptin

Molecular Formula: $C_{16}H_{15}F_6N_5O$

Molecular Weight: 407.31 g/mol

IUPAC name of (R)-Sitagliptin is (R)-4-oxo-4-[trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

Sitagliptin phosphate monohydrate is white to off-white crystalline solid. It is soluble in water and N,N-dimethyl formamide, slightly soluble in methanol, soluble in ethanol, acetone and acetonitrile and insoluble in isopropanol and isopropyl acetate. It is non-hygroscopic. It contains chiral centre and is used as single enantiomer (R). The active substance is susceptible to degradation under the influence of light. Structure elucidation was done using ultraviolet spectroscopy, infrared absorption spectroscopy, proton NMR spectroscopy, carbon NMR spectroscopy and molecular weight determined by mass spectroscopy.

Melting point of anhydrous Sitagliptin Phosphate: 214.92˚C

Melting point of Sitagliptin Phosphate Monohydrate: 206.37˚C (Stofella et al., 2019)

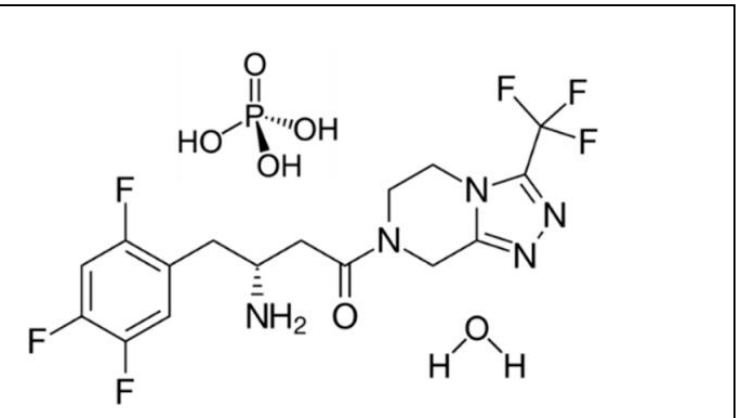
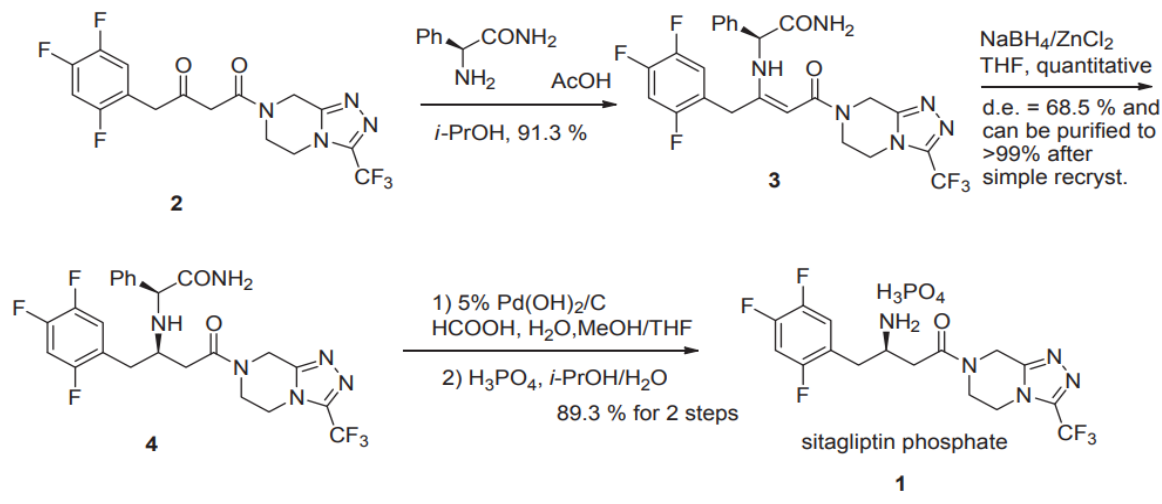


Figure 2: Sitagliptin Phosphate Monohydrate

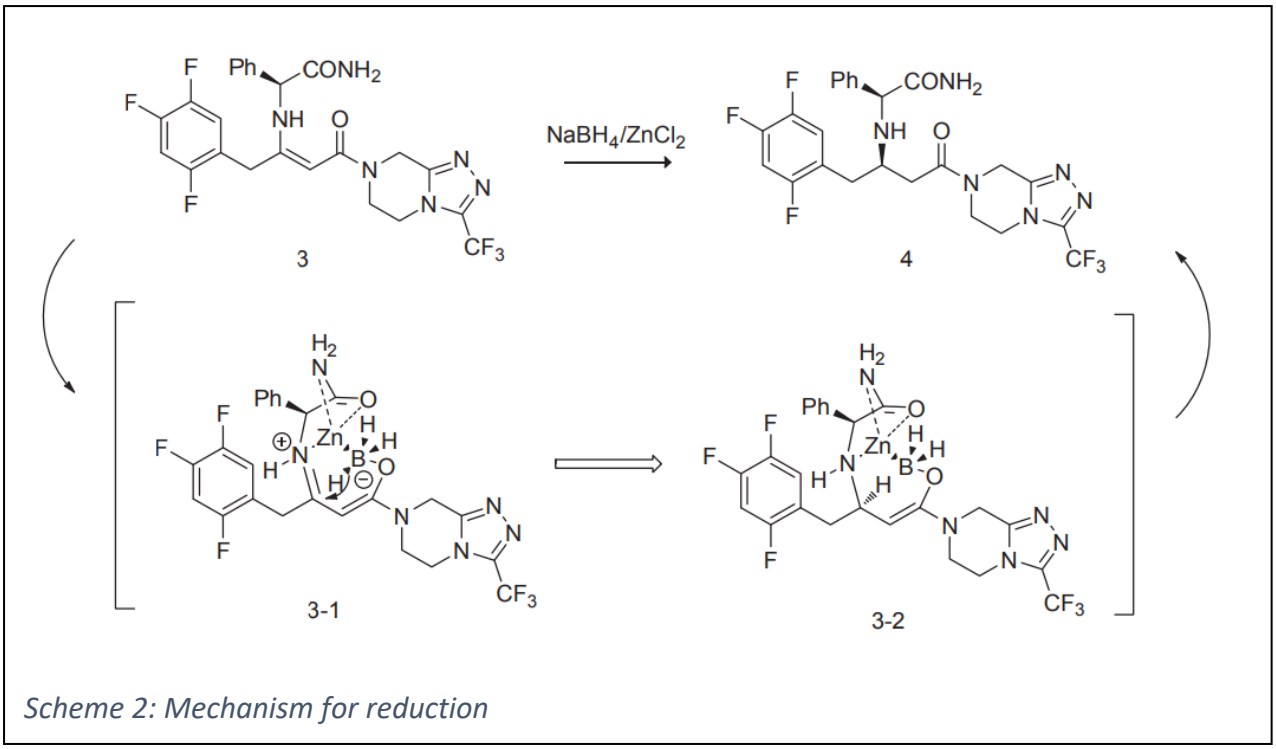
Synthesis

Synthesis of sitagliptin phosphate by a $NaBH_4/ZnCl_2$ – catalysed diastereoselective reduction

Asymmetric synthesis of sitagliptin was carried out via eneamination, diastereoselective reduction, amine-deprotection and phosphotization. Compound 2 after treating with (S)-phenylglycine amide in the presence of AcOH in IPA, compound 3 was obtained in good yield of 91%. Lewis acid-catalysed diastereoselective reduction using $NaBH_4$-$ZnCl_2$ was caried out for enamine intermediate (compound 3) in presence of THF. When the reaction was frozen at -60˚C chiral selectivity was enhanced, better yield and enantioselectivity was obtained. When the load of $ZnCl_2$ was reduced to 0.7 equiv, the diastereomeric pair of compound 4 was quantitatively obtained with good diastereoselectivity. This was may be due to balance between the temperature and the concentration of Zn^{2+}.In the reduction process, conjugated imine-enol intermediate (3-1) was formed in coordination to $NaBH_4$ and $ZnCl_2$, then imine was stereoselectively reduced to amine (3-2) by treatment with $NaBH_4$. Due to high temperature and high zinc ion concentration, chiral purity was reduced and if the concentration of zinc ion was low, the enamine was reduced by $NaBH_4$. Compound 4 was obtained with excellent yield of 57.1% after simple workup and recrystallisation with IPA/PE. This compound was treated with Pd $(OH)_2$/C and HCOOH aq. In MeOH/THF for 16hrs. Crude free base was recrystallised from toluene after workup and sitagliptin with 95% of yield was isolated. To get its phosphoric acid salt 85% of H_3PO_4 in IPA/H_2o was added, where 94% of this compound was obtained.(Pan et al., 2015)



Scheme 1: Synthesis of Sitagliptin Phosphate

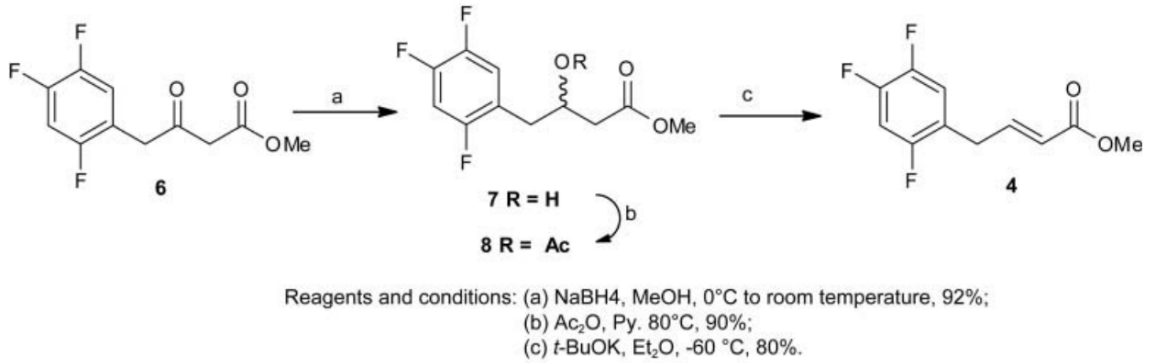


Scheme 2: Mechanism for reduction

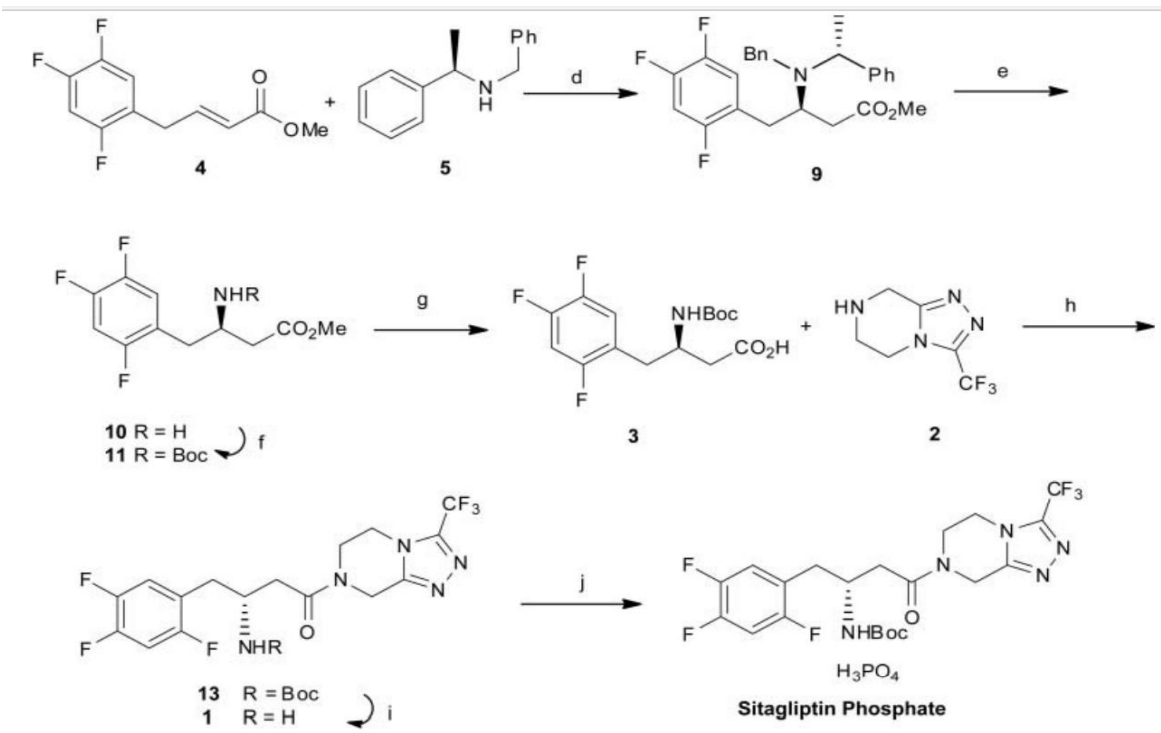
Asymmetric synthesis of sitagliptin

Asymmetric Michael addition of (E)-methyl 4-(2,4,5-trifluorophenyl)but-2-enoate and (R)-(α-methylbenzyl)benzylamine. B-keto ester was reduced to get β-amino acid. The reduction was done using 0.25 equiv. of $NaBH_4$ in methanol at 0˚C which gave compound 7 in 92% yield.

Acetylation of compound 7 was carried out by treating it with tert-BuOK in ethyl ether at low temperature yielded elimination compound 4. Conjugate addition of compound 5 to the α,β-unsaturated ester (compound4) was carried out in THF at -78˚C. β-amino acid ester(compound 9) was obtained in good yield. $Pd(OH)_2/C$ catalysed hydrogenation was carried out for deprotection of compound 9 and Boc_2O protection of the resultant amine lead to the β-amino ester (compound 11). Compound 11 was hydrolysed to the amino acid with NaOH in EtOH/water by stirring at 0˚C in 91% yield. Coupling of triazole with amino acid at 0˚C with HOBT-EDCl gave compound 13 in 95% yield. Compound 13 was stirred in presence of MeOH and conc. HCl at room temperature to remove Boc group. After this neutralisation was carried out with aq. Ammonia followed by workup and the crude product obtained was crystallised using toluene. Sitagliptin was isolated in 90% yield and its anhydrous phosphoric acid salt was obtained with 99.2% HPLC purity. Overall yield was 31%. (Liu et al., 2010)



Scheme 3: Synthesis for α, β-unsaturated ester.



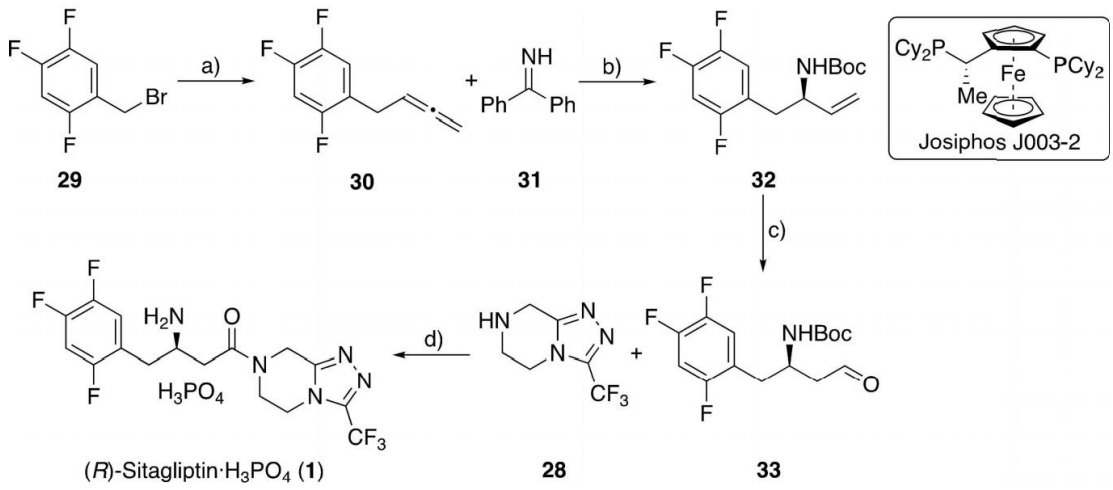
Scheme 3(a): Synthesis of Sitagliptin Phosphate.

Reagents and conditions: (d) 2.5M n-BuLi in hexane, THF, -78˚C, 76%; (e) $Pd(OH)_2$, 5atm H_2, MeOH, r.t (f) Boc_2O, Et_3N, CH_2Cl_2, r.t., 83% for 2 steps; (g) NaOH, EtOH-H_2O, 0˚C, 91%; (j) H_3PO_4, EtOH, 96%.

Synthesis of (-)-(R)-Sitagliptin by Rh'-catalysed asymmetric hydroamination

This method of Rh'/Josiphos J003-catalysed hydroamination of benzophenone imine of allenes provides an efficient access towards free or protected chiral primary allylic amines in a highly enantioselective fashion. This includes asymmetric installation of chiral amine.

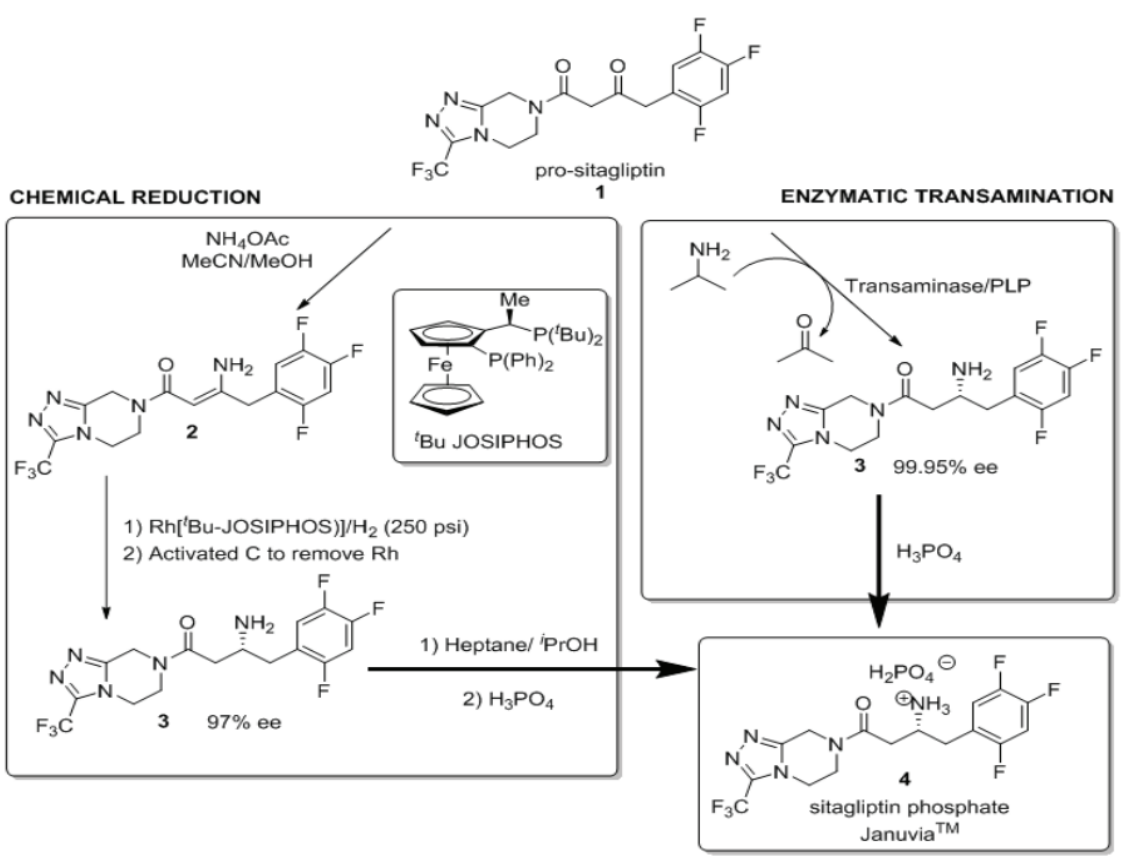
Fluorinated allene (compound 30) was prepared via a Cu'-catalysed Grignard addition of benzylic bromide (compound 29) to propargylic bromide. When this reaction was carried out on a 75 mmol scale, allene was obtained in 75% yield. Original conditions were optimized for asymmetric benzophenone imine addition to allenes to obtain satisfying yield. The reaction sequence involved a RhI /Josiphos-catalyzed hydroamination with benzophenone imine as an ammonia surrogate, cleaving of the imine and BOC-protection. The BOC-protected allylic amide (compound 32) was then obtained. Conditions for anti-Markovnikov selective Wacker oxidation were applied and compound 33 was obtained in 83% yield. Compound 33 was then converted in a three-step sequence via Pinnick oxidation and EDC-mediated amide coupling in (R)-Sitagliptin, which was isolated after the third step as the phosphate salt in 72% yield. Phosphate salt was obtained in an overall yield of 47%.(Berthold & Breit, 2021)



Scheme 4: Synthesis of (R)-Sitagliptin.

Enzymatic Synthesis of Sitagliptin

An enzymatic process for efficient manufacturing of sitagliptin was explored using an engineered transaminase, which is a biocatalyst with broad application for synthesis of chiral amines. (R) selective transaminase was used as the starting point and then was modified to accommodate non-naturally recognized bulk substrates as pro-sitagliptin 1. Enzyme was engineered to evolve its activity towards 1. Further, this enzyme was engineered to increase its activity and in-process stability. The best variant converted 200 g/L pro-sitagliptin ketone 1 to sitagliptin 3 with 92% yield and an enantiomeric excess higher than 99% by using 6g/L enzyme in 50% DMSO. The biocatalytic process provides sitagliptin with a 10-13% increase in overall yield compared to the chemical process, a 53% increase in productivity (kg/L per day), a 19% reduction in total waste, the elimination of all heavy metals, and a reduction in total manufacturing cost.(AR, 2018)



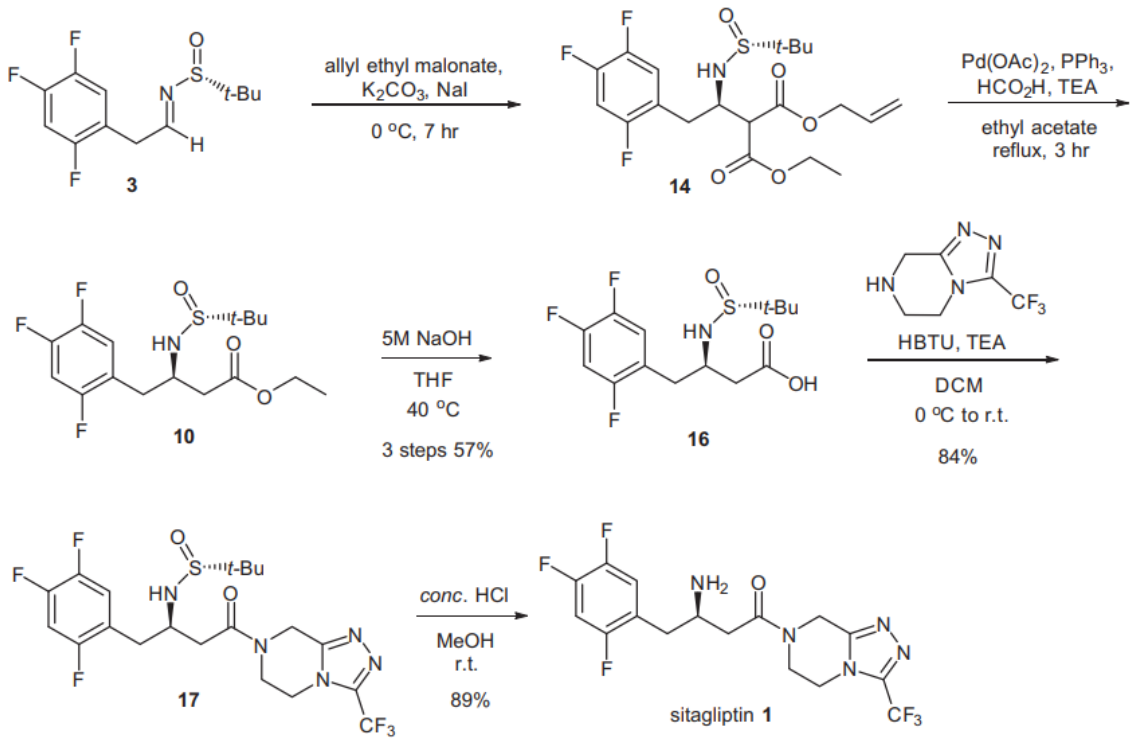
Scheme 5: Bio-catalysed synthesis of sitagliptin

Highly stereoselective and efficient synthesis of enantiomerically pure Sitagliptin

A very practical, economical and environment friendly approach for the preparation of optically pure sitagliptin. The main part of this approach is the strategy which involves highly stereoselective enolate addition of a malonate derivatives to sulfinyl imine to obtain the key amine intermediate. The reactivities of various esters for the enolate addition to sulfinyl imine was explored and it was found that Diethyl malonate provided the best yield. Different bases were explored, all gave high diastereoselectivities but for a long reaction time. Significantly diastereoselectivity was decreased due to high temperature. The rate of addition reaction was improved using a rate accelerating additive. Diastereoselectivity improved to 99.4% upon addition of NaI. The highly stereoselective enolate addition is seen through the transition state. Acid-catalysed hydrolysis of chiral sulfinamide was carried out followed by decarboxylation with 2M HCl to obtain β-amino ester.

To ensure we obtain pure sitagliptin, complete separation of by-products was done. To overcome this problem Pd-catalysed decarboxylation of 1,3-diester consisting of an allyl ester was investigated, which was successful. Reactivity and selectivity of enolate addition for allyl malonates was examined. Allyl ethyl malonate afforded the best results in terms of selectivity and reactivity.

Hydrolysis of the terminal ester afforded pure β-amino acid. Coupling of β-amino acid with the piperazine unit with the assistance of HBTU produced amide. To complete the synthesis, the sulfinyl chiral auxiliary was removed by HCl to produce sitagliptin with perfect enantioselectivity (>99.9%ee).(Bae et al., 2016; Kang et al., 2017)



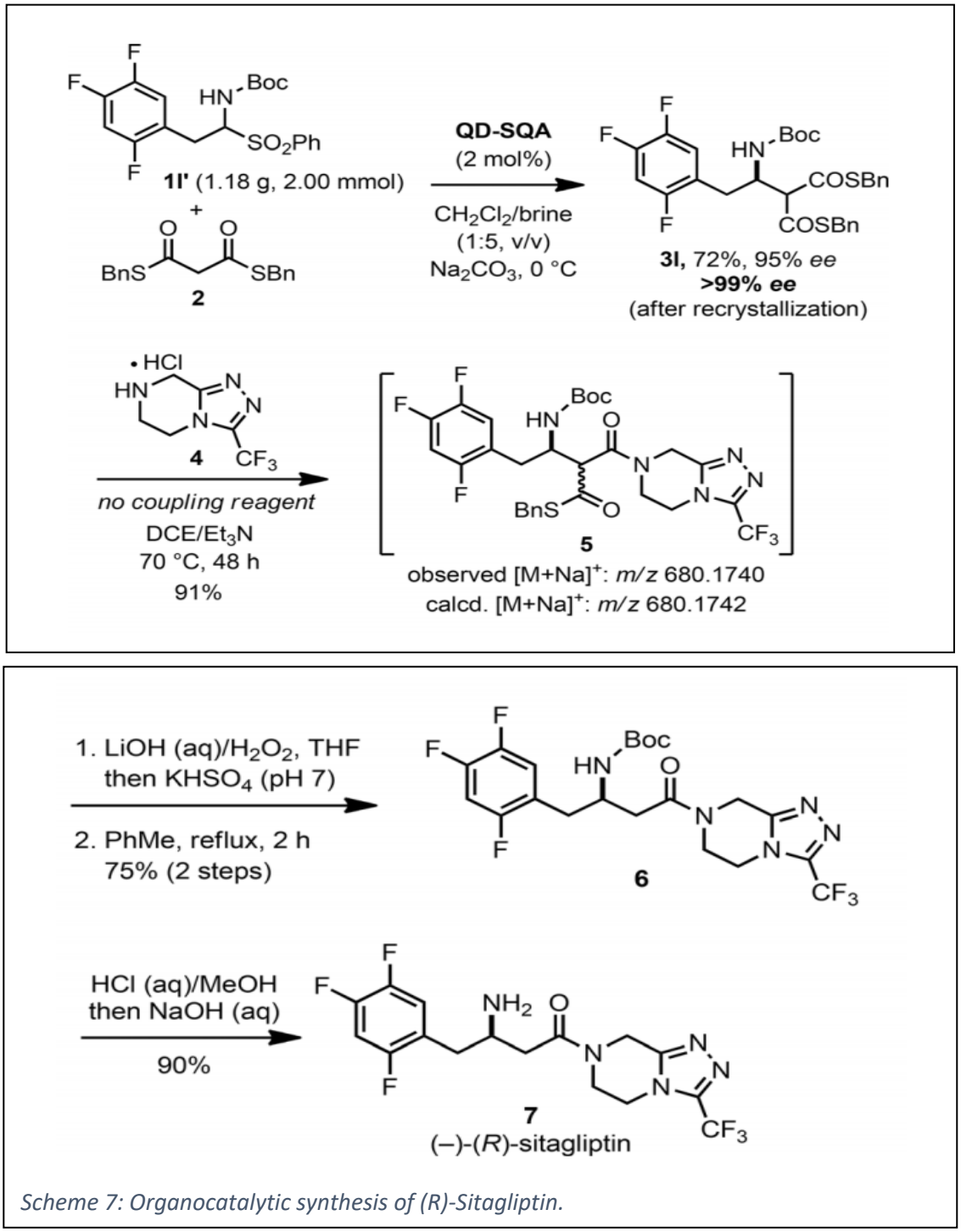
Scheme 6: Complete synthesis of sitagliptin.

Direct Catalytic Asymmetric Mannich Reaction with Dithiomalonates as an excellent mannich donors: Organocatalytic Synthesis of (R)-Sitagliptin

Dithiomalonates were demonstrated to be exceptionally efficient Mannich donors in terms of reactivity and stereoselectivity in cinchona-based-squar-amide-catalysed enantioselective Mannich reactions of diverse imines or α-amidosulphones as imine surrogates. In this reaction, reduction of catalyst loadings to 0.1 mol % without the erosion of enantioselectivity (up to 99%) was seen. The synthetic utility of chiral Mannich adducts which was obtained from primary alkyl substrates was highlighted by the first organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (-)-(R)-Sitagliptin.

The one-pot Mannich reaction of 1l' with DTM 2 in the presence of QD-SQA (2 mol%) afforded the desired product (R)-3l (72%, 95% ee). The obtained product was recrystallized from CH2Cl2/hexane to afford enantiomerically pure (R)-3l (> 99% ee). Next, 3l was coupled with the commercially available triazole salt 4 without the use of any coupling reagent to give

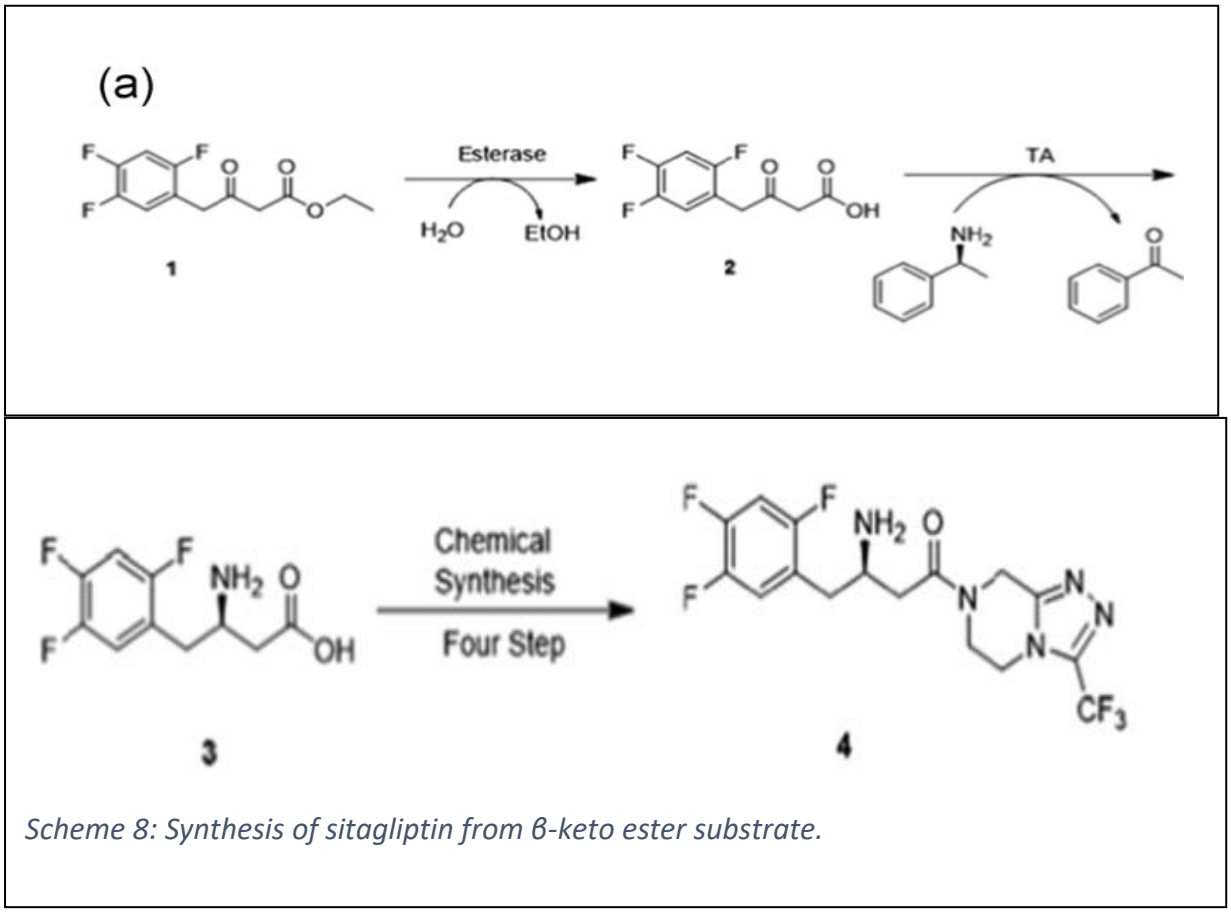
amide 5 (91%). The diastereomeric mixture of amide 5 was then transformed into N-Boc-protected sitagliptin 6 through hydrolysis and subsequent decarboxylation (75%). Finally, Boc deprotection under acidic conditions gave the target compound ()-(R)-sitagliptin. (Bae et al., 2016)



Scheme 7: Organocatalytic synthesis of (R)-Sitagliptin.

Promoter engineering-mediated Tuning of esterase and transaminase expression for the chemoenzymatic synthesis of sitagliptin phosphate

In this synthesis, esterase enzyme was screened for hydrolysis of β-keto ester. Whole-cell bio-tranformation was carried out using recombinant Escherichia coli co-expressing an esterase and transaminase for the synthesis of (R)-3-amino-4-(2,4,5-triflurophenyl) butanoic acid. This was done by promoter engineering (coordinating multiple enzymes in biosynthetic pathway). Small scale reactions were performed at various amounts of substrates which resulted in excellent conversions of 82-92% for the desired product. Then a kilogram scale enzymatic reaction was carried out to produce desired intermediate β-amino acid, which was isolated and purified. Sitagliptin phosphate was chemically synthesized from β-amino acids with 82% yield and > 99% purity.(Khobragade, Yu, et al., 2021)

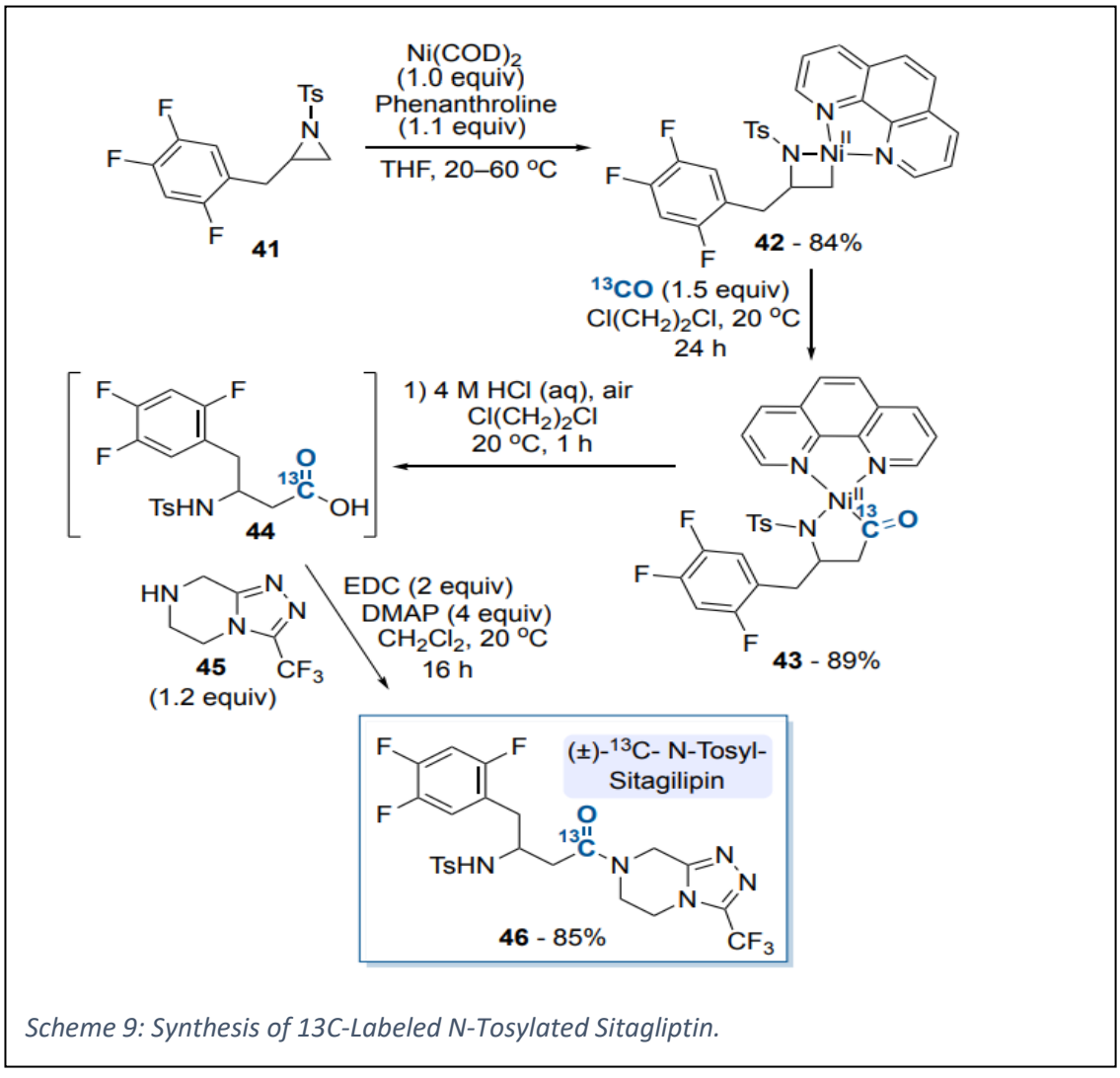


Scheme 8: Synthesis of sitagliptin from β-keto ester substrate.

A Carbon Isotope Labeling Strategy for b-Amino Acid Derivatives via Carbonylation of Azanickellacycles

A series of ^{13}C-labelled acyl nickellacycles were prepared by oxidative addition of Ni(0) with aziridines. ^{13}C labelled carbon monoxide was incorporated via Ni-C bond insertion to generate air stable and isolable cyclic Ni-acyl complexes. When these were subjected to various nucleophiles, β-amino acids, its derivatives and β-amino ketones were isolated. This methodology was applied for the synthesis of N-tosyl protected ^{13}C-labelled Sitagliptin.(Ravn et al., 2019)

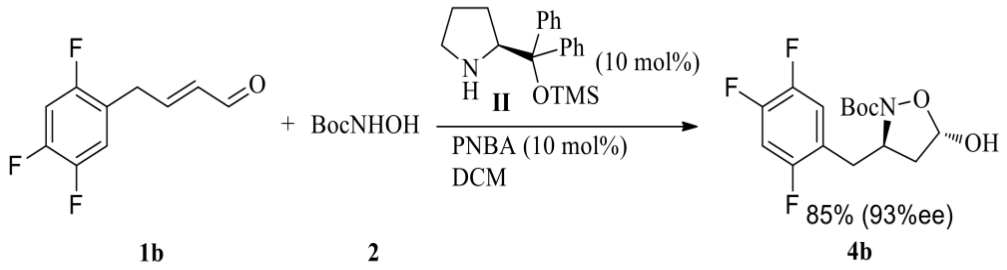
*Since reaction process involved many steps, this synthesis is not discussed in detail.



Scheme 9: Synthesis of 13C-Labeled N-Tosylated Sitagliptin.

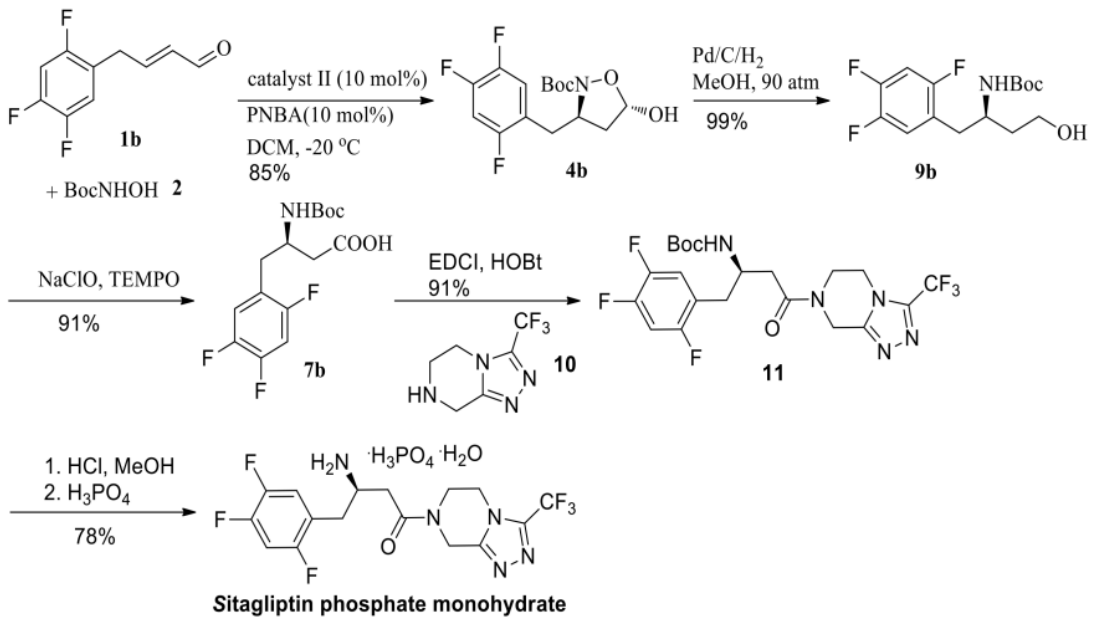
Practical Asymmetric Synthesis of Sitagliptin Phosphate Monohydrate

Optically pure sitagliptin phosphate monohydrate was efficiently and practically synthesized through a chiral hemiacetal as the key intermediate. (E)-4-(2,4,5-Trifluorophenyl)but-2-enal 1b was obtained by cross-metathesis reaction between 1-allyl-2,4,5-trifluorobenzene and crotonaldehyde. (3R,5S)-N-Boc-5-hydroxy-3-(2,4,5-trifluorobenzyl)isoxazolidine 4b was obtained in 85% yield and 93% ee when Tandem aza-Michael/hemiacetal reaction between (E)-4-(2,4,5-trifluorophenyl)but-2-enal 1b and N-Boc-hydroxylaminecatalyzed by 10 mol % (S)-diphenylprolinol-TMS II and 10 mol % p-nitrobenzoic acid was carried out.



Scheme 10: Tandem aza-Michael/hemiacetal reaction.

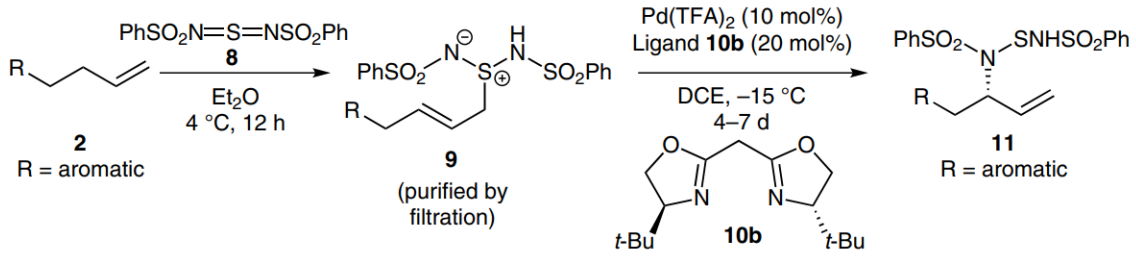
(R)-N-Boc-β-(2,4,5-trifluorobenzyl)-β-amino acid 7b was synthesized from (E)-4-(2,4,5-trifluorophenyl)but-2-enal in 76% total yield. (R)-tert-butyl4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-tri-fluorophenyl)butan-2-ylcarbamate 11 was obtained in 91% yield via the coupling reaction between triazole (10) and (R)-N-Boc-β-(2,4,5-trifluorobenzyl)-β-aminoacid 7b,using HOBt-EDCI as the coupling agent. Finally, sitagliptin phosphate monohydrate was obtained in 78% yield and >99.9% ee. Overall yield was 54% yield.(Gao et al., 2018)



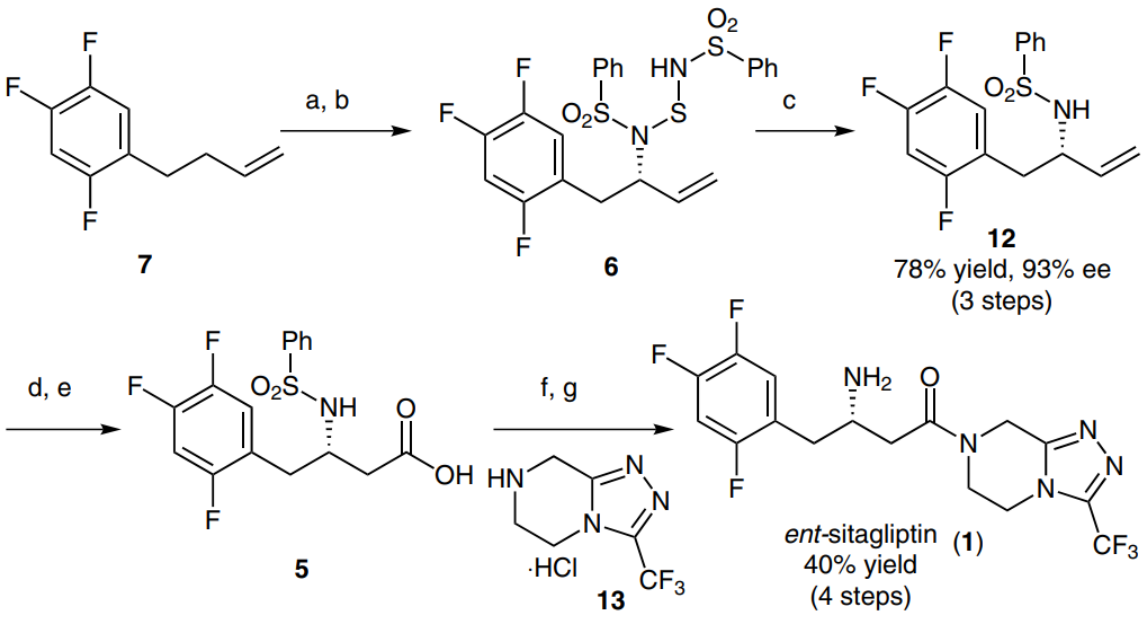
Scheme 11: Synthesis of Sitagliptin phosphate monohydrate.

Catalytic Enantioselective Allylic Amination of Olefins for the synthesis of ent-sitagliptin

In this synthesis, a palladium-catalysed enantioselective allylic amination of nonactivated terminal olefins through an ene reaction/ [2,3]-rearrangement was reported for the enantioselective synthesis of ent-sitagliptin. From retrosynthetic approach it was found 1-but-3-en-1-yl-2,4,5-trifluorobenzene as suitable starting material. After trying various approaches with different reaction conditions and unsatisfactory results, reaction conditions were reoptimized. This was done by exploring different ligands and palladium sources. Temperature conditions and loading of ligand was also optimized. 1-but-3-en-1-yl-2,4,5-trifluorobenzene 7 was converted to allylic amine derivative 6 by hetero-ene reaction followed by a palladium-catalysed enantioselective [2,3]-rearrangement. Then, allylic amination product 6 was treated with methanolic potassium carbonate to give allylic sulfonamide 12 in 78% yield and 93% ee. Further, hydroboration and extensive oxidation of olefin 12 gave β-amino acid 5. Then, coupling of this β-amino acid with amine 13 and subsequent deprotection of the sulfonamide gave ent-sitagliptin.(Bao et al., 2013)



Scheme 12: Substrate scope of Enantioselective Allylic Amination.



Scheme 12(a): Enantioselective synthesis of ent-sitagliptin.

Reaction conditions: (a) 8, Et2O, 4 °C, 12 h; (b) Pd(TFA)2 (10 mol%), ligand 10b (20 mol%), DCE, –15°C, 7 d; (c) K2CO3, MeOH, H2O, 16 h; (d) 9-BBN, THF, then aq NaOH, H2O2; (e) CrO3, H5IO6, MeCN, 0 °C; (f) 13, 1H-1,2,3-benzotriazol-1-ol, EDC, DIPEA, DMF; (g) MsOH, TFA, PhSMe, 40 °C.

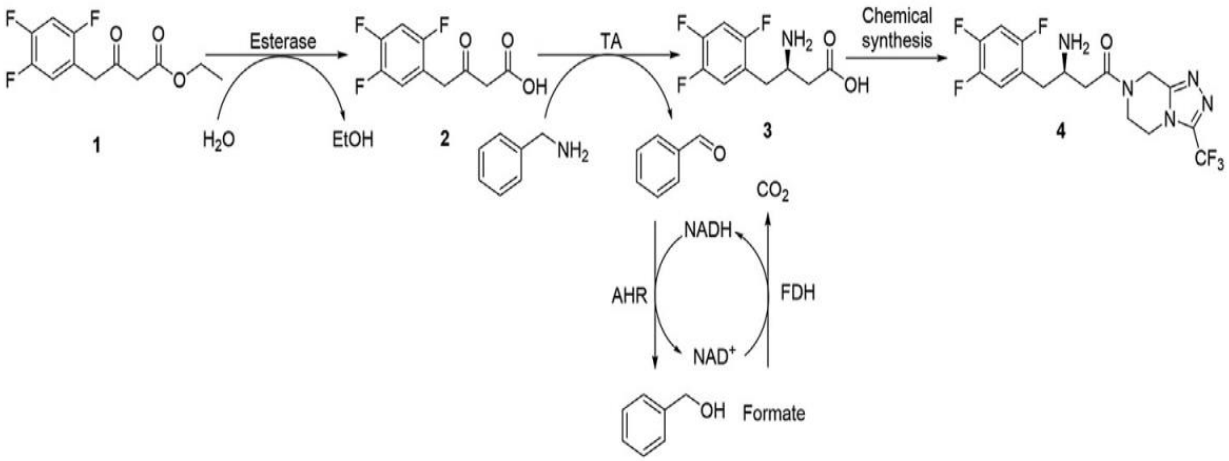
Synthesis of key intermediate for synthesizing Sitagliptin

For synthesizing Sitagliptin, preparation of intermediate in good yield is the key step.

Synthesis of Sitagliptin Intermediate by a Multi-Enzymatic Cascade System Using Lipase and Transaminase with Benzylamine as an Amino Donor

In this synthesis development of multi-enzyme cascade using transaminase (TA), esterase, aldehyde reductase (AHR), and formate dehydrogenase (FDH), using benzylamine as an amino donor to synthesize Sitagliptin intermediate, was discussed.

Screening of TAs with specificity for benzylamine was done and optimisation of reaction parameters such as pH, buffer system, and amine donor concentration was carried out. Inhibition of TAs or lipase by benzaldehyde was resolved by the application of an AHR/FDH system. AHR catalysed the conversion of benzaldehyde into benzyl alcohol at the expense of NAD(P)H cofactor and FDH supplied the depleted NAD(P)H by recycling the corresponding NAD(P)+ cofactor. A single whole-cell system was developed for TA and esterase. In this system, promoter engineering strategy was adopted to control the expression level of each biocatalyst. Whole-cell bio-transformations using various substrate concentrations (10-100mM) led to the achievement of excellent conversion rates (72-91%) to yield Sitagliptin intermediate. pH-stat system was used to control the pH of the system to improve the yield by ~50% at substrate concentration of 100mM. This optimized cascade with 100mM substrate resulted in the achievement of 61% yield. This was determined by spectroscopic and chromatographic methods.(Khobragade, Sarak, et al., 2021)



Scheme 13: Synthesis of sitagliptin phosphate from β-keto ester substrate.

Conclusion

It was found that there are many inexpensive as well as economical friendly methods for synthesizing Sitagliptin. There were many approaches reviewed for the synthesis of sitagliptin like, diastereoselective reduction, asymmetric Michael addition, asymmetric hydroamination, asymmetric Mannich reaction, Tandem aza-Michael/ hemiacetal reaction, ene reaction/ [2,3]-rearrangement of terminal olefins. 13C-labeled variant of the anti-diabetic drug sitagliptin was also reported where the air stable Ni-acyl complexes might provide new opportunities for selective incorporation of carbon isotopes into bioactive molecules. Biocatalyst being environment friendly and having comprehensive nature were also used as an alternative for chemical processes for synthesis of Sitagliptin. These included multi-enzyme cascade reactions which used promoter engineering strategy for sitagliptin synthesis. This has increased the interest in exploring more economical and environmentally methods in future.

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