A highly efficient and enantioselective synthesis of EEHP and EMHP: Intermediates of PPAR agonists

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Graphical Abstract

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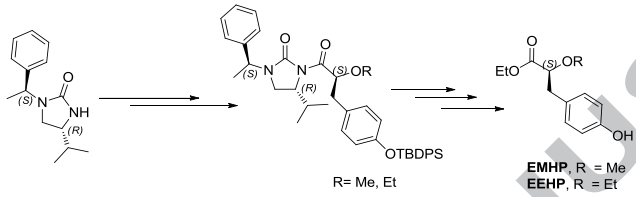

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A highly efficient and enantioselective synthesis of EEHP and EMHP: intermediates of PPAR agonists

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ABSTRACT

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Glycolate alkyation reactions of (*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one auxiliary has been optimized with high yields and diastereoselectivity on substituted benzyl and allyl bromides. The standardised reaction condition was employed for the stereoselective synthesis of EEHP and EMHP intermediates of PPAR agonists.

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(*S*)-Ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (EEHP), (*S*)-ethyl 2-methoxy-3-(4-hydroxyphenyl)propanoate (EMHP), isopropyl (*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (IEHP) and their corresponding acids are pharmaceutically active compounds as they form the core of a series of anti-diabetic drugs such as ragaglitazar, saroglitazar, tesaglitazar, navaglitazar, broadly named as glitazars, and other peroxisome proliferator activated receptor (PPAR) agonists (Fig. 1).[1] The potential of these intermediates to provide biologically active compounds and drug molecules is of immense importance, and so is their synthesis. Many viable strategies have been developed over the years for their synthesis in enantiomerically pure form.[2] However most of the reported methods are based on chiral resolution of racemic mixtures using enzymatic and chemical methods.[2d-e,3] Chiral resolution is substrate selective and is difficult to employ when synthesising a library of molecules due to significant loss of yield. The other strategies employed make use of metal catalyzed asymmetric hydrogenation of α-ethoxy cinnamic acid derivatives.[2h,2i] Even then the optical purity is not satisfactory and often expensive catalysts are used. Organocatalyzed asymmetric glycolate alkylation reactions suffer from poor enantioselectivity, require stoichiometric excess of substrate, harsh conditions, low overall yield and tedious purification steps making it unfavourable.[4] All these factors necessitate a cost effective and stereoselective strategy for accessing this class of molecules.

Literature survey led us to the conclusion that a major problem associated with many of the reported strategies are ineffective protocols for the installation of chiral center and alkylation of the secondary hydroxyl group which leads to partial racemisation.[5] Based on our interests in stereoselective C-C bond forming reactions we decided to explore a chiral auxiliary mediated alkylation for the synthesis of the EEHP and EMHP.

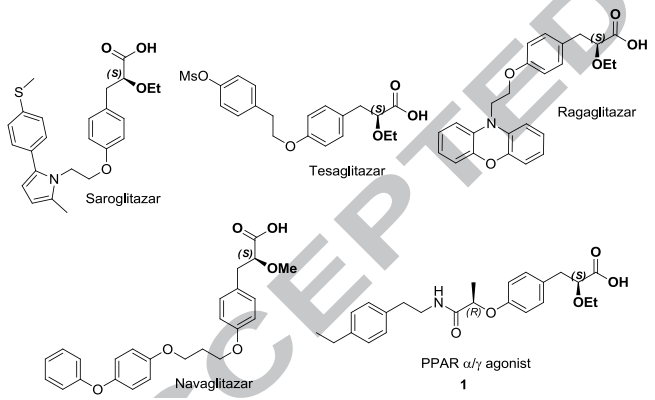
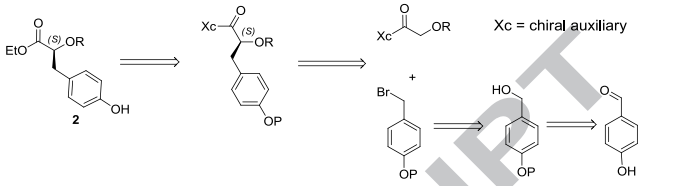


Figure 1. PPAR α/γ agonists

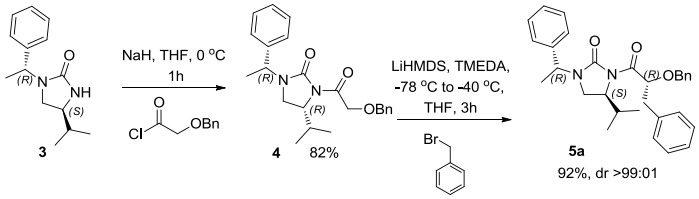
A retrosynthetic analysis (Scheme 1) of the intermediate **2** indicates asymmetric glycolate alkylation as the key step. To obtain the enantiomerically pure alkylated adduct, the acetylated auxiliary was treated with benzyl bromides. The reported chiral auxiliaries for the glycolate alkylation reaction suffer from various disadvantages like low yield, longer reaction time, costly reagents and also endocyclic cleavage.[6] Asymmetric glycolate alkylation reactions of an imidazolidinone based chiral auxiliary in solid phase resulted in only moderate enantiomeric excess. Also the use of large excess of electrophiles, long reaction time, costly solid resins and low yields makes this procedure less appealing.[6a] Glycolate alkylation had been attempted for the synthesis of various natural products but the procedure relies mainly on the use of allylic iodides.[6b] Pseudoephedrine has been used as a chiral auxiliary for the glycolate alkylation reactions with protected and unprotected hydroxyl group, however low diastereoselectivity and longer reaction time were major drawbacks.[6d] We had recently investigated some of the crucial factors which govern the stereoselectivity of C-C bond formation in aldol reactions on various substrates.[7] This led us to further explore an imidazolidinone based chiral auxiliary for the glycolate alkylation reaction.



Scheme 1. Retrosynthetic analysis of **2**

Result and discussion:

The *N*-acylation reaction was carried out by the deprotonation of the chiral auxiliary (*S*)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one **3** with NaH in freshly dried THF followed by the treatment with benzyloxyacetyl chloride to afford the acylated chiral auxiliary (**4**). The efficacy of benzyloxy acylated chiral auxiliary was examined in the glycolate alkylation reaction using benzyl bromide as electrophile. A preliminary experiment involving the formation of lithium enolate of **4** generated using LiHMDS at -78 °C and its subsequent alkylation with benzyl bromide either at -78 °C or 0 °C did not afford the product (Table 1). Furthermore, the corresponding sodium and potassium enolates were also not successful. The use of the Lewis acid $TiCl_4$ along with DIPEA also failed to give the product.



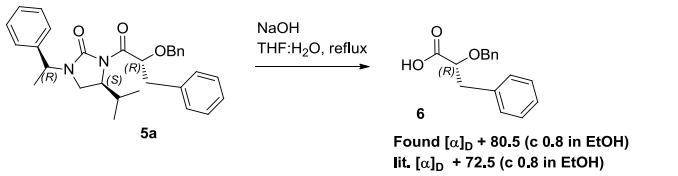
Scheme 2. Synthesis of (*S*)-3-((*R*)-2-(benzyloxy)-3-phenylpropanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one **5a**

Later attempts were to enhance the deprotonation by chelating the lithium cation using TMEDA so that the hexamethyldisilylamide anion is sufficiently basic for the proton abstraction. To our delight, the addition of equimolar amount of LiHMDS and TMEDA to a solution of **4** in THF at -78 °C followed by the addition of benzyl bromide and thereafter increasing the temperature to -40 °C resulted in a dramatic improvement in the reaction (Scheme 2). The reaction mixture was purified using column chromatography to give the product **5a** in high yield. A diastereomeric ratio of >99:01 was determined from the ^{1}H NMR spectrum of the reaction mixture. The absolute configuration was confirmed by cleaving the auxiliary using NaOH in THF:water under reflux condition to give the (*R*)-2-(benzyloxy)-3-phenylpropanoic acid **6** (Scheme 3). Based on the correlation of the optical rotation value with the literature [observed $[\alpha]_D$ +80.5 (c 0.8 in EtOH), reported $[\alpha]_D$ +72.5 (c 0.8 in EtOH)], an *R* configuration was unambiguously assigned.[8] The chiral auxiliary was recovered in 88% yield after the hydrolysis.

Table 1: Standardisation of reaction condition for the glycolate alkylation reaction

No.	Condition	Time (h)	Temp. (^{0}C)	Yield (%)	dr[a]
1	*n*-BuLi	4	-78 to 0	NA	-
2	LiHMDS	4	-78 to 0	Trace	-
3	NaHMDS	4	-78 to 0	10	-
4	KHMDS	4	-78 to 0	NA	-
5	$TiCl_4$, DIPEA	4	-78 to 0	NA	-
6	LiHMDS, TMEDA	3	-78 to -40	92	>99:01

a: diastereomeric ratio was determined from the ^{1}H NMR spectrum of the reaction mixture



Scheme 3. Hydrolysis of the alkylated adduct **5a**

A plausible mechanism for the stereoselectivity in glycolate alkylation is proposed in fig. 2. The generation of the enolates with lithium base at –78 °C occurs with high stereoselectivity. The (*Z*) selectivity can be understood by the sterically controlled six membered transition state formed from the imidazolidinone based chiral auxiliary and the lithium base. In transition state B the imidazolidine ring would face a 1,2 diequatorial steric interaction with the benzyloxy group, which is prohibitively high. Therefore, a deprotonation via transition state A occures inspite of the repulsive1,3-interaction. The alkylation reaction is thought to proceed through the chelation enforced transition state of the (Z) enolate as depicted in fig. 2. Herein the *Re* face attack is favored over the *Si* face by the enolate due to the steric hindrance imparted by the resident endocyclic isopropyl group.

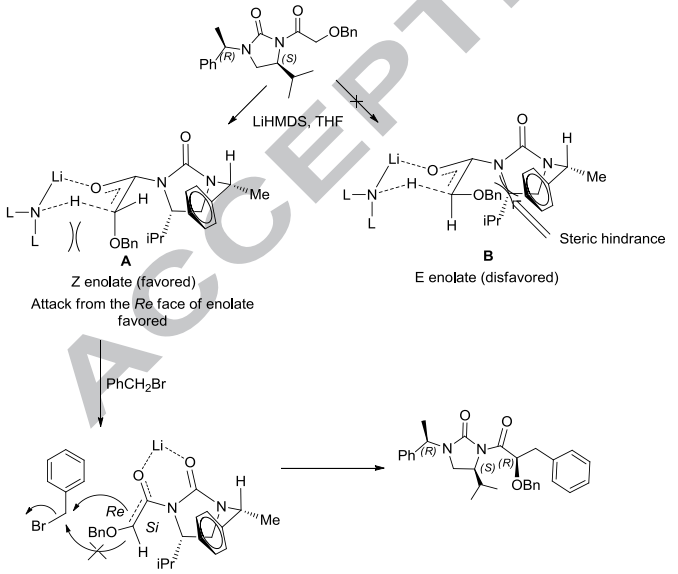
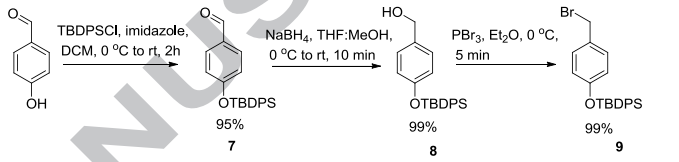


Figure 2. Plausible transition state for the glycolate alkylation reaction

Table 2. Glycolate alkylation reactions of (*S*)-4-isopropyl-1-(*R*)-1-phenylethyl]imidazolid- in-2-one (**4**)

No.	Starting material	Product	Yield[a] (%)	dr (*R*:*S*)[b]
1	$C_6H_5CH_2Br$	5a	92	>99:01
2	4-F-$C_6H_4CH_2Br$	5b	86	99:01
3	4-Cl-C_6H_4 CH_2Br	5c	88	99:01
4	4-Br-C_6H_4 CH_2Br	5d	88	99:01
5	4-Me-C_6H_4 CH_2Br	5f	82	99:01
6	2-Br-C_6H_4 CH_2Br	5g	75	99:01
7	3-Bromoprop-1-ene	5h	92	99:01
8	1-Bromo-3-methyl but-2-ene	5i	90	99:01

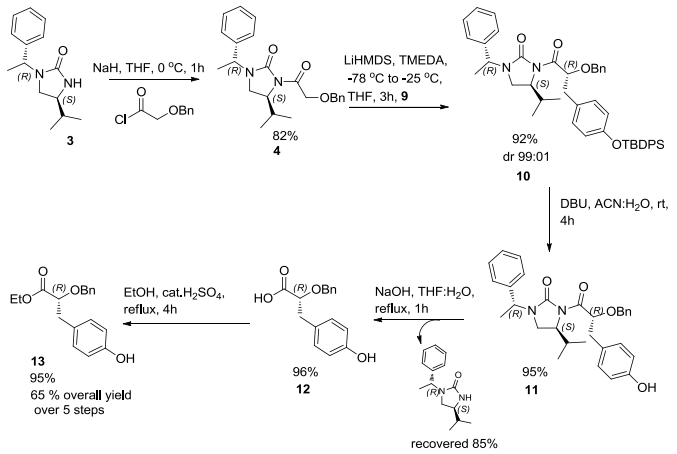
a: isolated yields; b: diastereomeric ratios were determined from the ^{1}H NMR spectra of the reaction mixtures.



Scheme 4. Synthesis of (4-(bromomethyl)phenoxy)(*tert*-butyl)diphenylsilane **9**

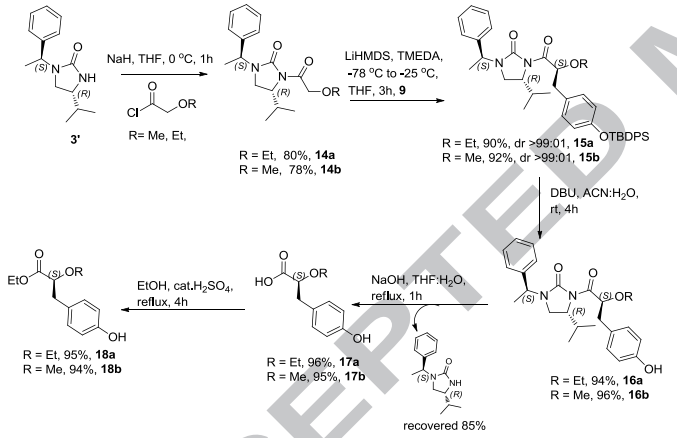
The reaction conditions were then generalized with substituted benzyl bromides bearing electron donating and -withdrawing groups and also with allyl bromides (Table 2, entries 1-8). The scope of the glycolate alkylation reaction was further illustrated in the synthesis of EEHP and MEHP. The synthesis of the TBDPS protected benzyl bromide commenced with the protection of 4-hydroxy benzaldehyde using TBDPSCl in the presence of imidazole in DCM giving **7** (Scheme 4). It was then reduced using $NaBH_4$ and taken to the next step without purification. The primary hydroxyl group was converted to bromide quantitatively using PBr_3 in Et_2O.[9] The alkylation reaction was performed on the benzyloxy acetylated chiral auxiliary with *p*-OTBDPS protected benzyl bromide (**9**) giving the alkylated product **10** with a diastereoselectivity of >99:01 (Scheme 5). This product, without further purification, was further subjected to deprotection using DBU in acetonitrile-water medium. The desired product **11** was isolated and then hydrolysed using the NaOH and the corresponding acid **12** was obtained after acid-base work up. It was then esterified to give the essential synthetic intermediate **13**. An enantiopurity of 99.7% was recorded by HPLC.

Employing the standardised conditions, the synthesis of EEHP and EMHP was initiated. (*R*)-4-isopropyl-1-((*S*)-1-phenylethyl)imidazolidin-2-one **3'** was employed for acetylation using two different alkyloxyacetyl chlorides giving the corresponding acylated auxiliaries (**14a, 14b**) in high yields (Scheme 6). Alkylation was carried out using LiHMDS as base and TMEDA as additive at -78 °C and to our delight excellent yields of **15a, 15b** were obtained in diastereomeric ratios of >99:01. The TBDPS group in the alkylated product was then cleaved using DBU in acetonitrile-water medium at room temperature to obtain the free phenolic group. The absolute stereochemistry was ascertained by single crystal X-ray analysis (Fig. **3**).[10]



Scheme 5. Synthesis of (*R*)-ethyl 2-(benzyloxy)-3-(4-hydroxyphenyl)propanoate **13**

Cleavage of the chiral auxiliary was done with NaOH as base in THF-H_2O medium under reflux conditions. The corresponding acids (**17a, 17b**) were purified by acid-base workup, and without the necessity for column chromatography. Alternatively the cleavage of the auxiliary can be carried out at room temperature in the presence of H_2O_2-LiOH.H_2O in THF-H_2O medium also. After cleavage, the carboxylic acid was converted to ester in the presence of catalytic amount of H_2SO_4 in ethanol with excellent enantioselectivity.



Scheme 6. Synthesis of EEHP **18a** and EMHP **18b**

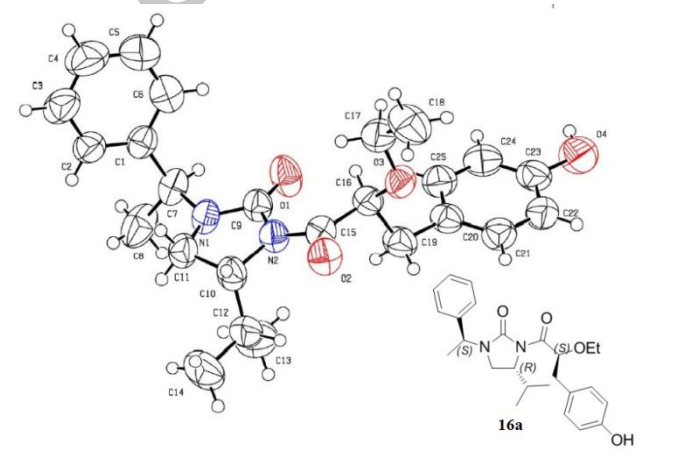


Figure 3. Ortep diagram of **16a**

Conclusion

The synthesis of PPAR agonist intermediates, EEHP and EMHP, was standardised in 5 steps employing an imidazolidinone based chiral auxiliary in high yields and excellent stereoselectivity. The nature of the procedure being general, can be applied to the synthesis of various molecules involving these intermediates.

Acknowledgement

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Supporting Information

Crystallographic data for the compound **16a** has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. **1452339**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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9 PBr_3 when used in stoichiometric equivalents resulted in partial degradation of the substrate. However using PBr_3 in excess of stoichiometric equivalents resulted in a fast and clean reaction.

10 Crystals were developed in Ethanol-Hexane (1:1) medium.

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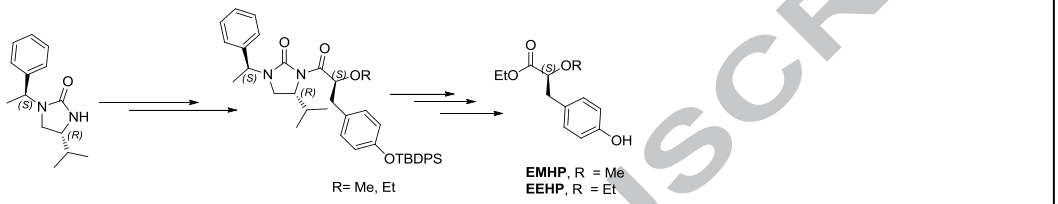

Highlights

- Chiral auxiliary mediated glycolate alkyation reactions.
- High yields and diastereoselectivities compared to the reported strategies.
- Efficient enantioselective synthesis of the intermediates of PPARα/γ agonists.
- Transition state model for the glycolate alkylation reaction.
- Wide scope of the synthetic protocol for accessing similar intermediates.