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Synthesis of key intermediate for (+)-tofacitinib through Co^{III}(salen)-catalyzed two stereocentered hydrolytic kinetic resolution of (±)-methyl-3-(oxiran-2-yl)butanoate

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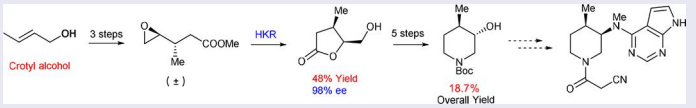
ABSTRACT

An enantiopure piperidine, a key intermediate for the synthesis of (+)-tofacitinib, has been achieved in high optical purity (98% ee) from readily available crotyl alcohol. The key steps involved is a Co^{III}(salen)-OAc-catalyzed two stereocentered hydrolytic kinetic resolution of (±)-methyl-3-(oxiran-2-yl)butanoate.

GRAPHICAL ABSTRACT



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KEYWORDS
γ-Butyralactone; enantioselective; hydrolytic kinetic resolution; iodolactonization

Introduction

Rheumatoid arthritis is a chronic autoimmune disease driven by immune system dysregulation which affects approximately 1% populations of the world. Till now the traditional disease-modifying antirheumatic drugs (DMARDs) or methotreaxate (MXT) are used for the treatment of rheumatic arthritis. Due to the acquired therapeutic resistance/adverse events of the MXT and DMARDs, the search for new molecules with a minimal risk is in progress. The Janus protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) act as a pacemaker in intracellular signaling of several cytokines, and they have been shown an important role in biological progressions like hematopoiesis and immune inflammatory responses.[1]

Tofacitinib 1 (Fig. 1) [CP-690550], a JAK 3 inhibitor designed by Pfizer and approved by Food and Drug Administration (FDA), turned to be effective for plenty applications and can be used toward rheumatoid arthritis, ulcerative colitis,[2] and prevention of organ transplant rejection as well. The immunosuppressive agents like cyclosporine A, tacrolimus, mycophenolate mofetil, and sirolimus have consequences like nephrotoxicity, neurotoxicity, hyperlipidemia, and hypertension. Tofacitinib is considered to be the best alternative to overcome such consequences.[3]

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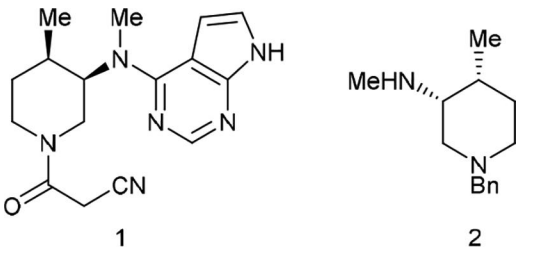


Figure 1. Structures of (+)-tofacitinib (1) and *cis-N*-benzyl-3-methylamino-4-methylpiperidine(2).

Due to pharmaceutical importance of tofacitnib, a variety of stereoselective synthetic approaches have been well documented in the literature.[4] Among the reported methods, asymmetric synthesis of tofacitinib is rarely explored.[5] Some complex routes are also known in the literature.[6] The efforts also devoted to the kinetic resolution.[7] The most important key synthetic intermediate *cis-N*-benzyl-3-methylamino-4-methylpiperidine **2** (Fig. 1) of tofacitinib has been synthesized by Pfizer in four steps through benzylation of 4-picoline followed by sodium borohydride reduction and hydroboration-oxidation sequence to offer 1-benzyl-4-methylpiperidin-3-one.[4] Jiang has used Garner's aldehyde as starting material and key step in their synthesis involves ring-closing metathesis reaction followed by catalytic hydrogenation using PtO_2 gives the *cis-anti* piperidine diastereomers in 1:1.5 dr, respectively.[5] Hao et al. have performed the asymmetric synthesis of key intermediate *cis*-(3*R*, 4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-3-(methylamino) piperidine from ethyl 1-benzyl-3-oxopiperidine-4-carboxylate.[6] Recently, Maricán et al. have synthesized the Tofacitinib from (*S*)-5-hydroxypiperidin-2-one which involves 1,4-Michael addition of Grignard methylcuprate as key step to offer tofacitinib in 9.5% overall yield.

However, these reports suffer from some drawbacks such as production of dimethyl sulfide, use of costly chemicals and reagents, low yields, and long reaction sequences. Apart from this, the use of harsh reaction conditions, stoichiometric amount of resolution agent,

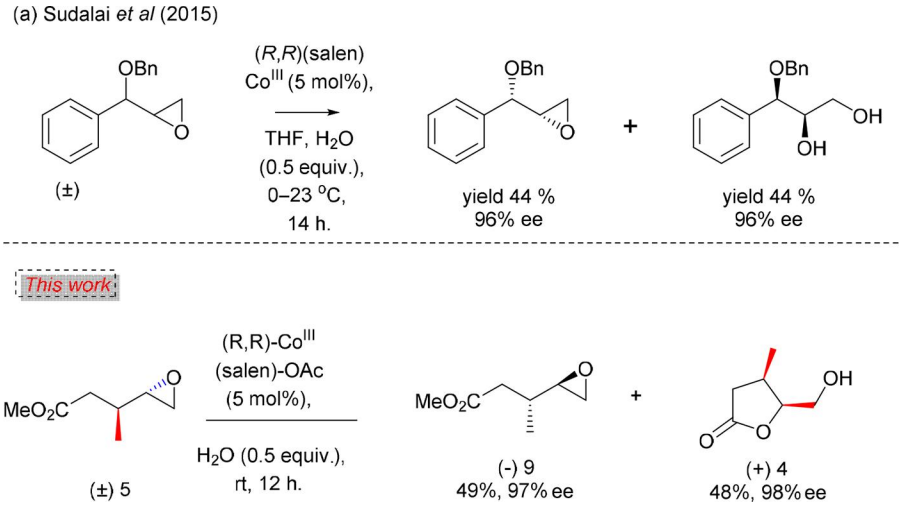


Figure 2. Two stereocentered HKR of α-functionalized epoxides.

and chiral pool approach affect the practicality of the synthesis. Therefore, there is a need for a practical route for the synthesis of tofacitinib **1**. Herein, we describe an alternative route for the synthesis of (+)-tofacitinib through Co^{III}(salen)-OAc-catalyzed two stereocentered hydrolytic kinetic resolution (HKR) as a key step (Fig. 2).

Two stereocentered HKR of α-functionalized epoxides have been extensively studied for the synthesis of biologically active intermediate.[8] Recently, Sudalai et al. reported that the HKR of racemic *anti*- or *syn*-3-substituted epoxy esters catalyzed by a $Co^{(III)}$salen complex provide corresponding enantioenriched 3,4-disubstituted γ-butyrolactones and 3-substituted epoxy esters as shown in Fig. 2.[8b] Hence, we envisioned that this method could be used for the synthesis of (+)-tofacitinib (1).

Results and discussion

According to our retrosynthetic approach as shown in Fig. 3, we envisioned that the key intermediate piperidine **2** could be obtained by hydrogenation of optically pure azidolactone **3**.

Further the azidolactone **3** could be obtained from enantiomerically pure γ-butyrolactone **4**. The enantiomerically pure γ-butyrolactone **4** can be synthesized from two stereocentered HKR of racemic *trans*-methyl-3-(oxiran-2-yl) butanoate **5**. The desired epoxide could be synthesized from the crotyl alcohol **6** by Claisen–Johnson rearrangement followed by iodolactonization.

Our approach toward the synthesis of racemic methyl-3-(oxiran-2-yl)butanoate **5** commences with Claisen–Johnson rearrangement of crotyl alcohol **6** using catalytic amount of hexanoic acid in trimethylorthoacetate at reflux conditions for 24 h to give the 3-methylpent-4-enoic acid **7** in 91% yield. The 3-methylpent-4-enoic acid **7** was then subjected to iodolactonization reaction using molecular iodine in CH_3CN at 0 °C to give racemic iodolactone in 1:9 (*cis:trans*) diasterteomeric ratio. The diastereomers were separated using flash chromatography to give the *trans* iodolactone **8**. Then *trans* iodolactone **8** was utilized for the base-catalyzed epoxide synthesis under reflux condition using methanol and Na_2CO_3 to yield racemic methyl 3-(oxiran-2-yl)butanoate **5** in 82% yield. Compound **5** was then subjected to HKR with (*R,R*)-salen Co^{III}(OAc) complex (5 mol %) and H_2O (0.5 equiv.) as shown in Scheme 1, which produced the corresponding

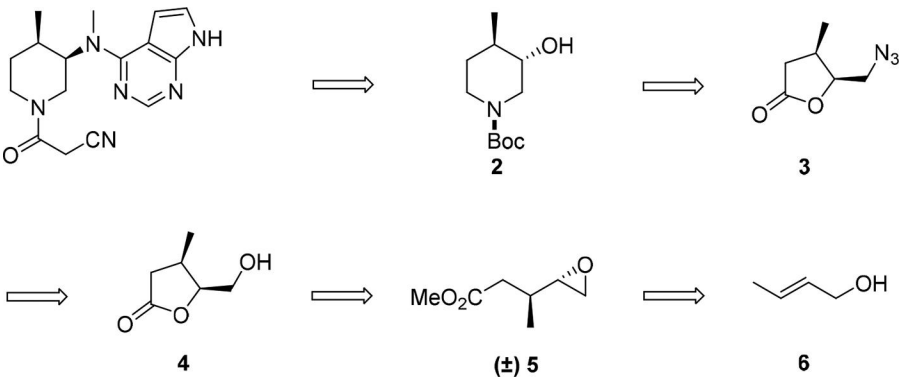
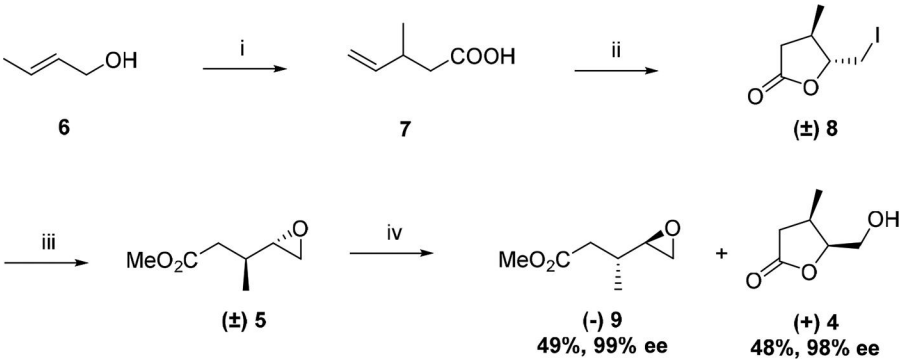
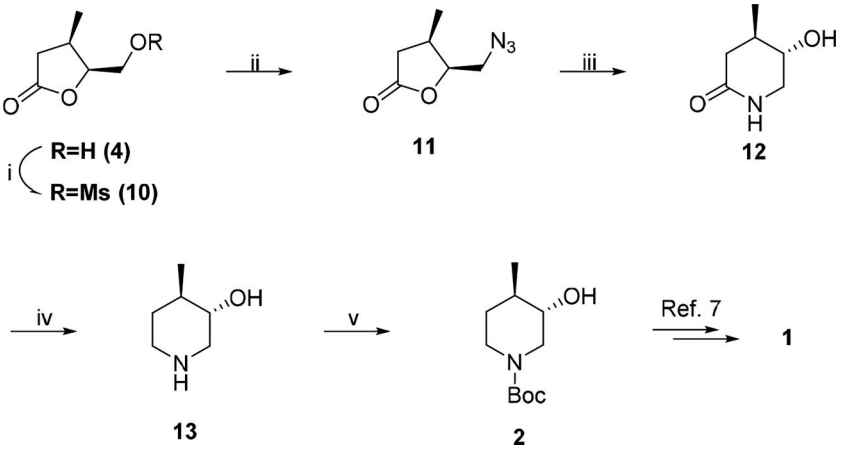


Figure 3. Retro synthetic approach of tofacitinib.



Scheme 1. Reaction conditions: (i) $MeC(OEt)_3$, hexanoic acid, 70–150 °C, 12 h, 91%; (ii) I_2, CH_3CN, 0 °C, 12 h, 82%; (iii) MeOH, K_2CO_3, Reflux, 3 h, 89%; (iv) (R,R)-CoIII(salen)-OAc (5 mol%), H_2O (0.5 equiv.), RT, 12 h.

(4*R*, 5*S*)-5-(hydroxymethyl)-4-methyldihydrofuran-2(3H)-one **4** (48% yield and 98% ee) and the chiral (2*R*, 3*R*)-methyl-3-(oxiran-2-yl)butanoate **9** (49% yield and 99% ee) in high optical purity. Surprisingly, we get the *cis* isomer of (4*R*, 5*S*)-5-(hydroxymethyl)-4-methyldihydrofuran-2(3*H*)-one 4 instead of *trans*, whereas Sudalai et al. reported the *trans* γ-butyrolactone. The *cis*-stereochemistry of protons was confirmed by the NOESY technique. The spectral data and optical rotation of enantiomerically pure γ-butyrolactone **4** well match with the previous literature.[9] The enantiomeric excess of epoxide 9 and γ-butyrolactone 4 was determined by conversion to their corresponding Mosher esters (see SI). The enantiomerically pure γ-butyrolactone **4** was further used for the synthesis of tofacitinib. The γ-butyrolactone **4** was then subjected to mesylation reaction using methanesulfonylchloride in CH_2Cl_2 and TEA as a base at 0 °C to give mesylate product **10** in 92% yield.



Scheme 2. Reaction conditions: (i) MsCl, TEA, CH_2Cl_2, 0 °C,1 h 92%; (ii) NaN_3, DMF, 80 °C; 8 h, 88%; (iii) Pd/C, H_2, MeOH, 24 h, 91%; (iv) $BH_3 \cdot DMS$, THF, reflux, 6 h; (v) $(Boc)_2O$, Na_2CO_3, 8 h, 80% over the two step.

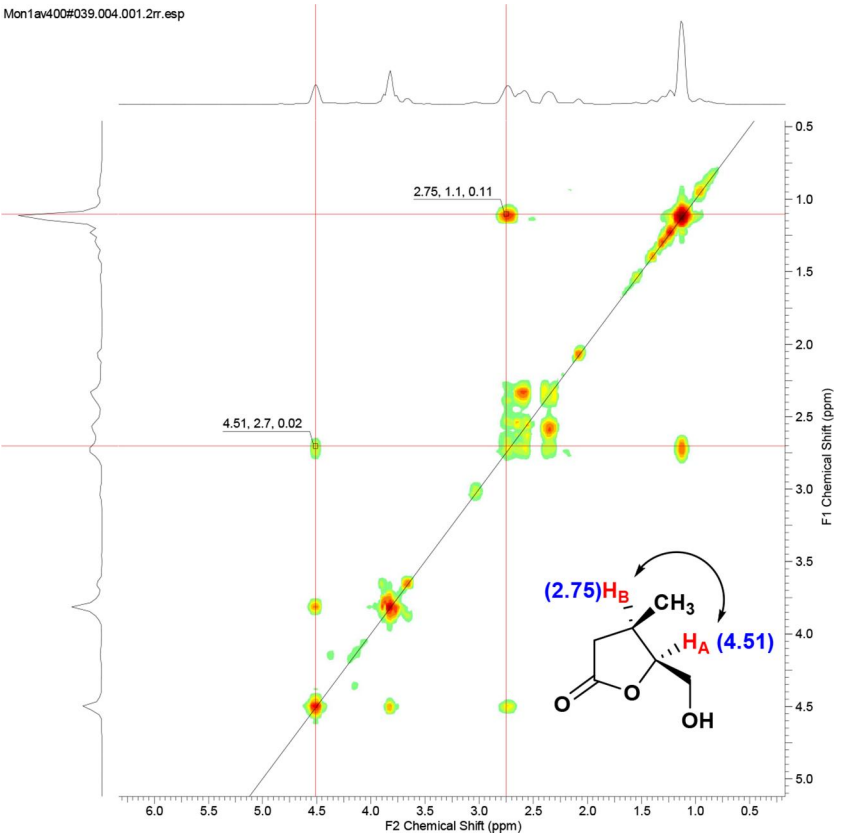


Figure 4. NOESY of (4*R*, 5*S*)-5-(hydroxymethyl)-4-ethyldihydrofuran-2(3H)-one.

The mesylate **10** was then used for the nucleophilic displacement reaction with sodium azide in DMF at 80 °C to give the azidolactone **11** in 88% yield. The structure of compound **11** was confirmed by its characteristic IR frequencies (2100 and 1781 cm^{-1}) arise due to azide and lactone functions, respectively. Azide **11** was then subjected to intramolecular reductive cyclization over 10% Pd/C and H_2 (1 atm) to afford *trans*-3,4-disubstituted piperidinone core **12** in 91% yield. Reduction of **12** with $BH_3 \cdot SMe_2$ followed by *in situ* *N*-Boc protection gave the known key intermediate *trans*-piperidine derivative **2** in 80% yield (Scheme 2). The spectral data and optical rotation of the synthesized key intermediate piperidine **2** are in good agreement with the reported values.[7] The relative stereochemistry of γ-butyrolactone **4** was confirmed by NOESY studies. A significant NOESY correlation was observed between H_A–H_B which confirms the *syn* relationship between H_A and H_B as shown in Figure 4.

Conclusion

In conclusion, we have described an efficient enantioselective synthesis of key intermediate for the synthesis of (+)-tofacitinib (1). The key intermediate (2) has been synthesized in a good overall yield (18.7%) and high optical purity (98% ee). The key reaction used was iodolactonization, two stereocentered HKR with minimal catalyst loading in key step.

The synthetic strategy described herein has significant potential for the synthesis of a variety of other biologically important piperidine alkaloids. Further application of HKR and iodolactonization strategy is undergoing in our laboratory for the synthesis of piperidine alkaloids.

Experimental section

General information

Solvents were purified and dried by standard procedures before use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on a PerkinElmer model 683 B and absorption is expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was performed on a Carlo Erba CHNS-O analyzer. Purification was done using column chromatography (60–120 mesh). Enantiomeric excesses were determined by Moshers ester derivative using ^{19}F NMR spectrum. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

Hydrolytic kinetic resolution

To a solution of (*R*, *R*)-Co(II)complex (0.024 mmol, 5 mol%) in toluene (1 mL), acetic acid (0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown and it was then concentrated under reduced pressure to get the $Co^{(III)}$-salen complex-**1** as brown-colored solid. To this, racemic methyl-3-oxiran-2-yl) butanoate (±)-**5** (4.85 mmol) and H_2O (0.043 g, 2.42 mmol) were added at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 12 h. After completion of the reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral epoxy esters 9 [solvent system; petroleum ether: ethyl acetate (9:1)] and chiral γ-butyrolactones 4 [solvent system; petroleum ether: ethyl acetate (1:1)] in pure form.

Methyl (S)-3-((S)-oxiran-2-yl)butanoate (9)

Yield: 49% (0.380 g), Colorless oil; $[\alpha]_D^{25} - 23.4$ (c 1, $CHCl_3$); The NMR values are same as compound **5**. ^{1}H NMR (200 MHz, CHLOROFORM-d) δ 3.67 (3H, s), 2.74–2.83 (1H, m), 2.71 (1H, t, $J = 4.4$ Hz), 2.54 (1H, dd, $J = 4.9$ Hz, $J = 2.7$ Hz), 2.30 (2H, qd, $J = 15.3$ Hz, $J = 7.2$ Hz), 1.83–2.06 (1H, m), 1.06 (3H, d, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, CHLOROFORM-d) δ 172.2, 55.5, 51.4, 45.9, 37.6, 32.6, 16.6; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_7H_{12}O_3Na$: 167.0676, found: 167.0679.

(4R, 5S)-5-(hydroxymethyl)-4-methyldihydrofuran-2(3H)-one (4)

Yield: 48% (0.40 g), Colorless oil; $[\alpha]_D^{25} - 43.87$ (c 1, $CHCl_3$); {($[\alpha]_D^{20} - 53.6$ (c 2.1,CH_2Cl_2)}[9]; ^{1}H NMR (500 MHz, CHLOROFORM-d) δ 4.48–4.62 (1H, m), 3.79–3.97 (2H, m), 2.68–2.88 (2H, m), 2.62 (1H, dd, $J = 17.4$ Hz, $J = 8.5$ Hz), 2.38 (1H, dd, $J = 17.2$ Hz, $J = 8.4$ Hz), 2.07 (1H, br.s), 1.15 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (126 MHz, CHLOROFORM-d) δ 177.5, 83.1, 61.6, 36.7, 32.0, 13.8; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_6H_{10}O_3Na$: 153.0522, found: 153.0519.

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