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A diastereoselective synthesis of boceprevir's *gem*-dimethyl bicyclic [3.1.0] proline intermediate from an insecticide ingredient *cis*-cypermethric acid

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ABSTRACT

An efficient multi-gram synthesis of (1*R*,2*S*,5*S*)-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate, a key chiral bicyclic proline fragment employed in the construction of the potent anti-HCV drug boceprevir, has been presented. The synthetic route commences with the readily available *cis*-cypermethric acid, a cheap source of the cyclopropane ring required in the targeted compound, and utilizes the *cis*-orientation of the 2,2-dichlorovinyl and carboxylic acid side arms, already present in the starting material, to effect a diastereoselective construction of the proline moiety.

1. Introduction

USFDA approval of the hepatitis C virus (HCV) NS3 protease inhibitor boceprevir (**1**, Victrelis®) in 2011 and its introduction as a direct-acting antiviral (DAA) component in hepatitis C treatment regimen was one of the key breakthroughs in combatting chronic HCV infection.[1,3b] Chronic HCV infection affects 130–150 million people worldwide, and eventually leads to liver cirrhosis or liver cancer in a significant number of cases.[2,3] Indeed, in 2012, it was estimated that almost 700000 people die each year from liver diseases resulting from HCV infection.[2] NS3 protease plays a critical role in HCV RNA replication and virion assembly so that the discovery and development of **1**, a peptidomimetic drug, represented a major landmark in the quest towards exploiting NS3 protease as a druggable target for hepatitis C treatment.[1b,4]

Our interest in **1** was piqued not only by its standing as one of the first DAAs approved for the treatment of hepatitis C, but also by the structurally appealing bicyclic [3.1.0] proline moiety that forms the core of **1** and is derived from the methyl ester **3**, one of the three key starting materials **2**–**4** employed for the synthesis of **1** (Fig. 1).[5] The bicyclic framework of **3** bears a 1,1-dimethyl cyclopropane *cis*-fused onto a proline ring and its construction, though well precedented in literature, is evidently more involved when compared to the L-*tert*-leucine derived urea **2** or the racemic cyclobutylalanine derived α-amino amide **4**.[5] Broadly speaking, most of the known syntheses of **3** involve either a cyclopropyl ring formation on an existing proline scaffold (general approach A) or an

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elaboration of a pre-existent cyclopropyl framework to **3** (general approach B) (Fig. 2).

The best known example of the first approach can be found in the original medicinal chemistry route to **3** delineated by the innovator (Schering-Plough).[6] The synthesis commenced with selenoxide elimination in the pyroglutamyl alcohol derivative **5** to obtain the unsaturated γ-lactam **6** that was subjected to diastereoselective cyclopropanation with *i*-propylphosphonium ylide to furnish the key intermediate **7**. Lactam reduction in **7**, followed by hydrogenolytic opening of the aminal ring, afforded **8**, which was then transformed to the desired bicyclic [3.1.0] proline intermediate **3**·**HCl** via sequential Jones oxidation, methyl ester formation and HCl mediated N–Boc deprotection (Scheme 1). Though initially followed for small scale generation of **1** and structurally related library molecules, this cyclopropanation strategy was later completely abandoned in favor of increasingly streamlined and efficient variants of the second approach (general approach B) as means to obtain **3** for large-scale synthesis of **1**.[7–9]

The practical convenience that approach B offered stemmed from the built-in framework of 1,1-dimethylcyclopropane ring present in ethyl chrysanthemate **9**, an inexpensive pyrethroid, which offered a facile access to the bicyclic [3.1.0] proline moiety, present in **3**. All synthetic routes, described under the ambit of this second approach, involved transformation of the non-symmetric **9** to the symmetrical caronic anhydride **10** that served as a template for the synthesis of **3**. Typically, elaboration of **9** to **3** necessarily required: (a) an oxidative degradation of the isobutylene side arm in **9** to obtain **10**, and (b) late-stage use of cyanide to introduce the carbomethoxy group present in **3** (Scheme 2a–c). Indeed, all known improvements for bulk production of **3** have largely centered on reducing of the number of synthetic stages from **10** to the cyanation step, and more importantly, streamlining the process for introduction of chirality in **3**. For example, the first demonstration[7] of approach B, as reported by Schering-Plough, involved desymmetrization of achiral **10** with allyl alcohol and subsequent chiral resolution of ***rac*-11** with (*R*)-(+)-α-methylbenzylamine. The (1*S*,3*R*) allyl ester **11** was converted via the intermediacy of **12** into the protected aminal **13**, which was then subjected to Lewis acid mediated cyanation with TMSCN to afford **14**. Sodium methoxide mediated methanolysis of **14**, followed by hydrolysis of the imido methyl ether intermediate and subsequent N–Cbz deprotection in the methyl ester obtained, afforded **3** (Scheme 2a).

A considerably shortened second-generation synthesis[8] of **3** from **10** employed the achiral bicyclic pyrrolidine **15**, which was desymmetrized to the racemic imine ***rac*-16** in presence of $K_2S_2O_8$ and $AgNO_3$. Cyanation of ***rac*-16** and subsequent methanolysis of the nitrile ***rac*-17** under acidic conditions afforded ***rac*-3**, from which the desired (1*R*,2*S*,5*S*) enantiomer **3** was isolated by diastereomeric salt formation with D-DTTA (Scheme 2b). Constraints imposed on material generation by this late stage chiral resolution was later ameliorated through application of biocatalysis in securing an enantioselective transformation of **15** to **17** (Scheme 2c).[9] The key step in this route, *i.e.* **15** → **16**, stands out till date as one of the finest examples of monoamine oxidase mediated chiral desymmetrization of a pyrrolidine and owes its success to the extensive enzyme optimization studies that were carried out to custom-make a monoamine oxidase for the specific substrate in question. Despite its highlights, the downstream chemistry in this chemoenzymatic process is definitely undesirable from industrial safety perspective, since it still depended on a late stage cyanation with an inorganic cyanide, followed by nitrile hydrolysis under strongly acidic conditions, to convert **16** to **3**. Against this background, we decided to devise a new synthetic route to **3**, based on the general approach B, which will not only be bereft of any exotic reagents and customized biocatalytic transformations, but also address the safety concerns associated with the use of cyanide for introduction of the carbomethoxy group present in **3**.[10]

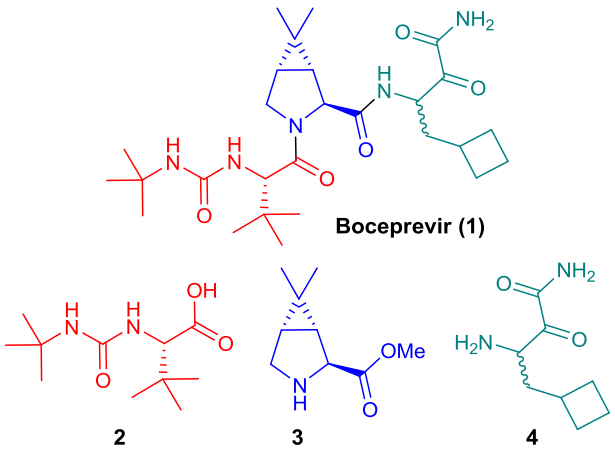


Fig. 1. Boceprevir and its key starting materials.

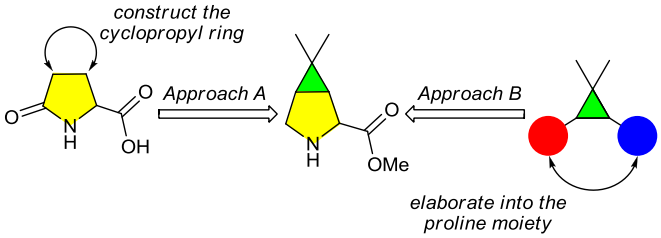
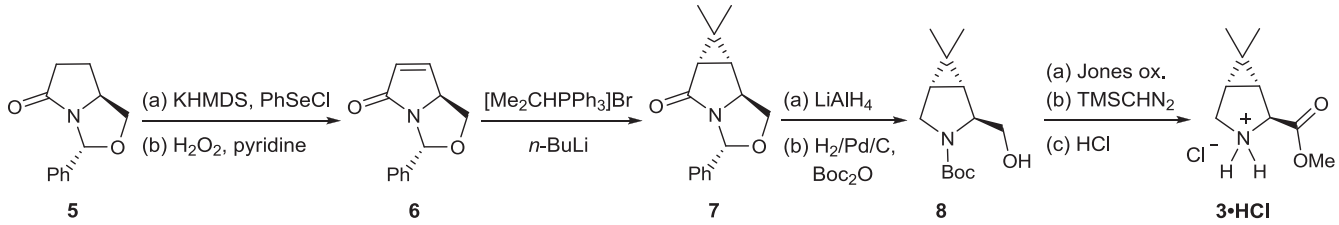


Fig. 2. Schematic representation of the two general approaches to **3**.

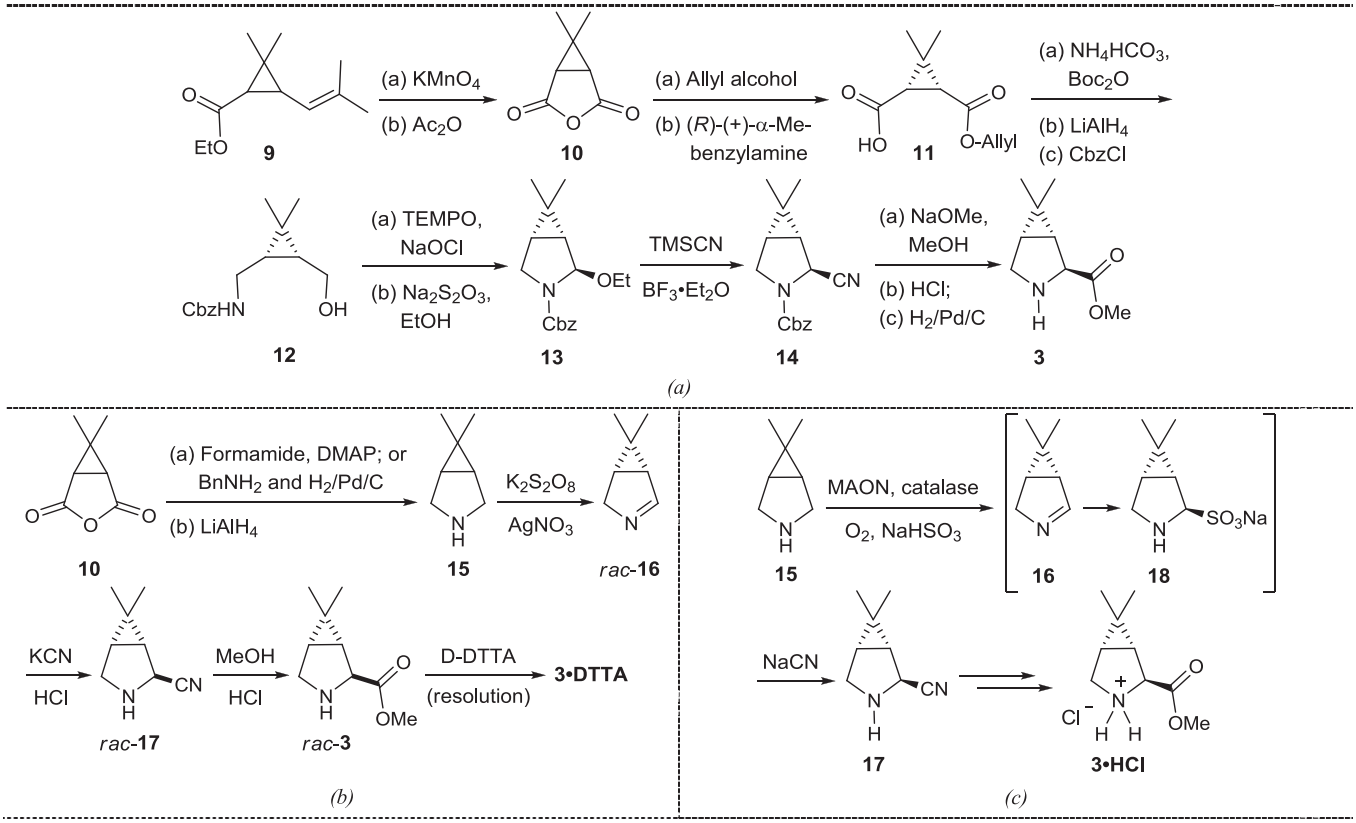
In keeping with this intent, (1*S*)-*cis*-cypermethric acid **19** was chosen as a readily available chiral pool for the synthesis of **3**.[11] As illustrated in Scheme 3, the pyrethroid **19** was particularly appealing as a starting material since, unlike the structurally related **9**, it presented us with an opportunity to utilize its entire carbon framework and delineate an enantiospecific 'carbon conservative approach' to accessing the bicyclic [3.1.0] proline moiety of **3**. More specifically, we desired to employ the built-in *cis*-orientation of the 2,2-dichlorovinyl and carboxylic acid side arms in **19** to construct a bicyclic pyrrolidone, such as **20**, and subsequently capitalize on the topological bias, inherent in **20**, to diastereoselectively transform the vinyl chloride moiety into the β-oriented carbomethoxy group present in **3**. In order to assess the feasibility of this proposed synthesis of **3** from **19**, we decided to be prudent and establish the proof-of-concept for chemistry viability with the inexpensive *rac*-cypermethric acid chloride (***rac*-21**) first.

2. Results and discussion

Thus, the commercially available *cis*-cypermethric acid chloride ***rac*-21** was treated with ammonia gas at low temperature to furnish the amide ***rac*-22** in 82% yield (Scheme 4). Cyclization of the 2,2-dichlorovinyl and amide side arms in ***rac*-22** with NaH in DMAc afforded the *cis*-fused bicyclic pyrrolidone ***rac*-20**, presumably *via* a base mediated 5-*exo*-*dig* cyclization,[12] involving a *Z*-selective nucleophilic addition of the amide side arm to a chloroalkyne[13] derived from the 2,2-dichlorovinyl moiety[14] present in ***rac*-22**. We then decided to explore whether an epoxidation of the vinyl chloride moiety in ***rac*-20** would afford an oxirane that would hydrolyze under acidic conditions to afford an aldehyde (***rac*-29** or ***rac*-30**). However, attempted epoxidation of ***rac*-20**, employing *in-*



Scheme 1. An example of a synthetic route to **3**, based on the general approach A.



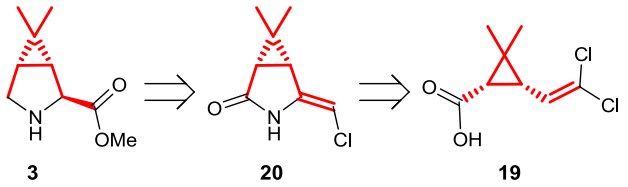
Scheme 2. Salient examples of synthetic routes to **3**, based on the general approach B.

situ generated peracids (such as acetic acid/30% aq. H_2O_2 or trifluoroacetic acid/30% aq.

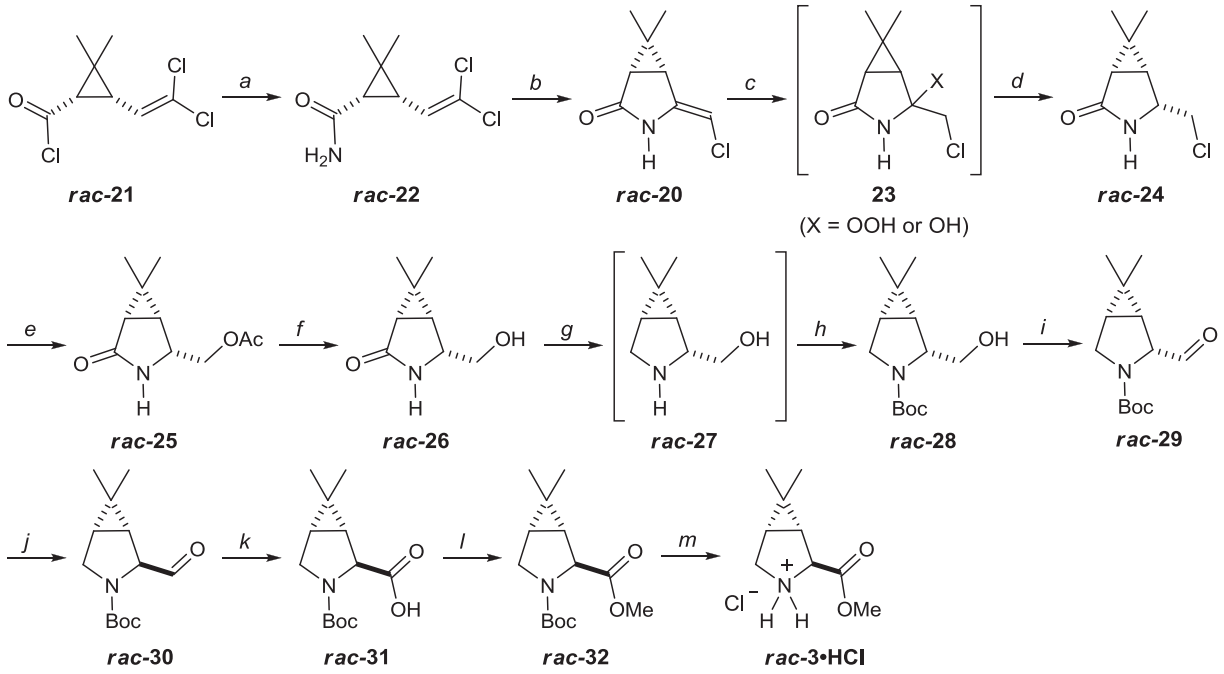
H_2O_2), failed to show any product formation. Surprisingly, when ***rac*-20** was reacted with hydrogen peroxide in presence of Amberlite® IR120, a product, exhibiting key NMR spectral signatures of the hydroperoxide[15] (or alcohol) **23**, could be isolated in its crude form as a pale yellow solid.

Without attempting any further purification, this solid was subjected to classical silyl hydride reduction, using triethylsilane and trifluoroacetic acid in dichloromethane. To our pleasant surprise, the chloromethyl derivative ***rac*-24** was obtained as a single diastereomer. Displacement of chloride in ***rac*-24** with acetate was carried out in a facile manner using NaOAc under phase transfer conditions to obtain ***rac*-25**. Hydrolysis of the acetate group using K_2CO_3 gave the alcohol ***rac*-26**, which was further reduced using LAH to access the desired bicyclic [3.1.0] pyrrolidine (***rac*-27**) followed by protection with Boc_2O to furnish ***rac*-28**. The stereochemistry of hydroxy-methyl group in ***rac*-28** *syn* to the *gem*-dimethyl cyclopropyl ring was needed to be inverted. We decided to perform an oxidation of the hydroxy-methyl moiety to an acid or an aldehdye, thereby creating a handle for an epimerization to the thermodynamically favored and desired product.

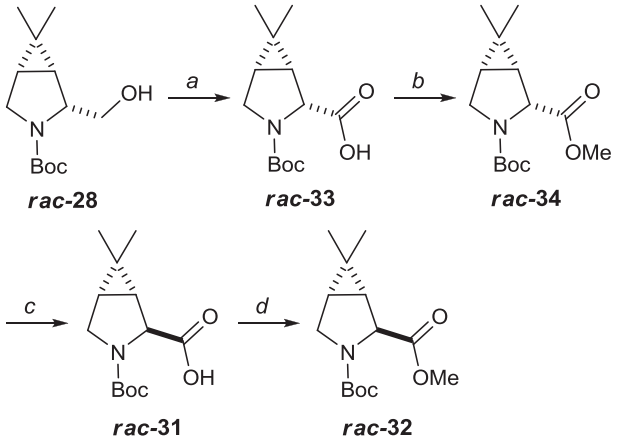
Initial efforts towards epimerization strategy involved direct oxidation of alcohol ***rac*-28** to the corresponding *cis*-acid (***rac*-33**) using Jones oxidation, followed by transformation to the methyl ester ***rac*-34** (Scheme 5). A one-pot NaOMe mediated epimerization-ester hydrolysis on ***rac*-34** afforded the epimerized acid ***rac*-31**, which was transformed to the methyl ester using methyl iodide in the presence of potassium carbonate to access ***rac*-32**. One of the drawbacks in the above route was the noticeably



Scheme 3. Retrosynthetic analysis of **3** from (1*S*)-*cis*-cypermethric acid **19**.



Scheme 4. *Reagents and conditions*: (a) NH_3, CH_2Cl_2, −10 °C, 2–3 h, 82%; (b) NaH, DMAc, 0 → 35 °C, 6 h, 62%; (c) H_2O_2, Amberlite® IR120, rt, 5 h; (d) TES, TFA, CH_2Cl_2, 5 °C → rt, 16 h, 60%; (e) CH_3COONa, TBAB, toluene, 110–115 °C, 18 h, 64%; (f) K_2CO_3, MeOH, rt, 2 h, 86%; (g) LAH, THF, 65 °C, 16 h; (h) $(Boc)_2O$, CH_2Cl_2, rt, 2 h, 55% (from ***rac*-26**); (i) $(COCl)_2$, DMSO, Et_3N,CH_2Cl_2, −78 °C → rt, 45 min, 94%; (j) DBU, CH_2Cl_2, rt, 3 h; (k) CrO_3-H_2SO_4 (1:1.6), acetone, −30 → 0 °C, 3 h, 58% (from ***rac*-28**); (l) K_2CO_3, MeI, acetone, rt, 16 h, 84%; (m) 1 M HCl in EtOAc, 1,4-Dioxane, 25 °C, 2 h, 94%.



Scheme 5. *Reagents and Conditions*: (a) CrO_3:H_2SO_4 (1: 1.6), Acetone, −5 °C→rt, 16 h, 47%; (b) Cs_2CO_3, MeI, DMF, rt, 4 h, 33%; (c) NaOMe, MeOH, rt, 16 h, 84%; (d) K_2CO_3, MeI, Acetone, rt, 16 h, 85%.

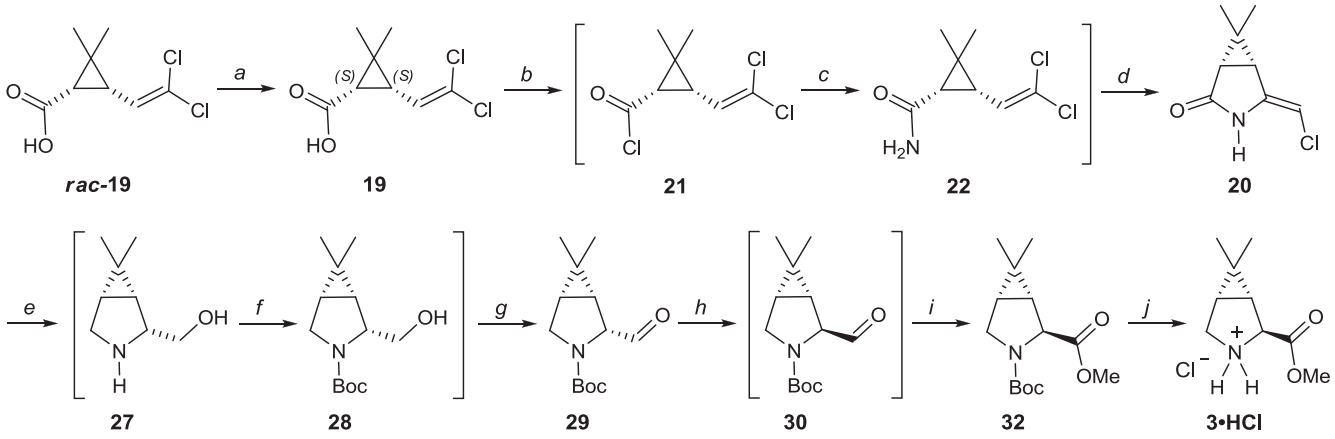
sluggish epimerization for ***rac*-34**, and this prompted us to look for an alternative epimerization approach.

Oxidation to ***rac*-28** under Swern conditions afforded ***rac*-29** with good yield (Scheme 4). Epimerization of ***rac*-29** in the presence of DBU furnished ***rac*-30**, wherein the disposition of the aldehyde was *anti* to gem-dimethyl cyclopropyl ring. Further oxidation of the aldehyde (***rac*-30**) under Jones conditions afforded the desired acid ***rac*-31**, which was then transformed to the methyl ester ***rac*-32**. Treatment of ***rac*-32** with 1*M* HCl in EtOAc led to the removal of Boc-group to afford boceprevir intermediate ***rac*-3** as a hydrochloride salt.

Having established the chemistry proof-of-concept, we decided to focus on areas of improvement to render the overall route shorter by using transformations that avoided multiple functional group manipulations and choosing reaction conditions amenable for scale-up. We contemplated a one-pot reduction of the amide and vinyl chloride present in the intermediate (***rac*-20**) using borane to directly access the alkyl chloride in order to avoid a peroxy intermediate due to safety considerations. Based on the aforementioned thoughts, a scale-up amenable route was developed as shown in Scheme 6.

This time we embarked on the synthesis starting with the originally envisaged chirally pure (1*S*)-*cis*-cypermethric acid **19**. Diastereomeric salt based resolution on ***rac*-19** was studied using various resolution agents, namely, (*S*)-1-(1-napthyl)ethylamine, (*R*)-2-amino butanol, D-ephedrine, quinine, cinchonidine, *S*-prolinol and (*R*)-phenylethyl amine. Amongst the chiral bases studied, best results were obtained with (*R*)-phenylethyl amine which afford the desired acid **19** with ≥99% ee, *albeit* with a moderate yield of 40%. As a complementary approach to the chiral resolution of ***rac*-19** by diastereomeric salt formation, we also explored the possibility of accessing the desired enantiomer **19** via enzymatic resolution of the ethyl ester of ***rac*-19**. In an initial screening of reaction conditions with commercially available enzymes (PLE, CALB-L and BC-esterase), BC-esterase fared best and catalysed the hydrolysis of *rac-cis*-cypermethric acid ethyl ester to furnish the acid **19** with good enantioselectivity (>98%), *albeit* at extremely high enzyme loadings and low substrate concentrations. Esterase V was subsequently tested on account of our observations that it is able to promote hydrolysis of substrates deemed refractory with other enzymes. Exhibiting a substrate selectivity opposite to BC-esterase, esterase V afforded the desired enantiomer **19** as the unreacted ethyl ester with high enantioselectivity (97%) and was indeed able to bring about excellent conversion (49%) even at substrate concentrations of 60 g/l.[16]

Once the chirally pure **19** was accessed, the corresponding acid chloride **21** was prepared using thionyl chloride and catalytic amount of DMF in toluene. The crude product **21** obtained was treated with aqueous ammonia to afford the amide **22**. Owing to

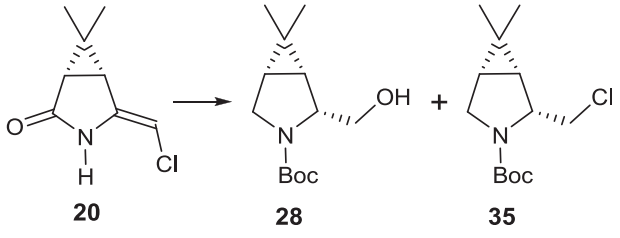


Scheme 6. *Reagents and conditions*: (a) (i) (*R*)-Phenylethylamine, IPA, Reflux, 30 min; (ii) 2 N HCl, water, 40%; (b) $SOCl_2$,toluene, 25 °C, 3 h; (c) aq. NH_3, toluene, 0–10 °C, 2–3 h, (d) *t*-BuOK, THF, 25 °C, 2–3 h, 80% (from **19**); (e,f) (i) BH_3·THF or $NaBH_4$, BF_3·THF, 50–60 °C, 2–3 h; (ii) 30% H_2O_2, 10% NaOH (*aq.*), 0–10 °C, 2 h; then $(Boc)_2O$, 25 °C, 1–2 h; (g) (i) NaOCl, KBr, TEMPO, DCM, 0 °C, 15 min (ii) $NaHSO_3$, 25–35 °C, then Na_2CO_3, 7–8 h; 55% (from **20**); (h,i) K_2CO_3, MeOH, 2–3 h, 25 °C, then I_2, 25 °C, 2–3 h; (j) 1 M HCl in EtOAc, 25 °C, 2 h, 70% (From **29**).

potential hazards associated with the use of sodium hydride in large-scale processes,[17] selected bases (such as NaOMe, *t*-BuOK, NaOH and Cs_2CO_3) were screened to study their suitability as an alternative to NaH in promoting the cyclization of **22** to **20**. We concluded that this transformation could be effected using either sodium methoxide or potassium *tert*-butoxide in THF or DMAc as the solvent. In the light of our observations, the first two steps, *viz.* synthesis of the amide **22** and its subsequent conversion to **20** using *t*-BuOK in THF, were efficiently telescoped to synthesize **20** from **19** in 80% yield.

We subsequently investigated the possibility of reducing the number of synthetic steps developed in the initial route. In lieu of the originally developed acidic-resin catalyzed addition of peroxide and silyl hydride reduction sequence on **20**, we decided to explore a simultaneous borane reduction of the vinyl chloride as well as the amide moiety in **20** to potentially obtain an unprotected variant of the aldehyde **29**. Quite surprisingly, as indicated by LC-MS of the crude reaction mixture, treatment of **20** with BH_3·THF, followed by oxidative workup gave the hydroxymethyl pyrrolidine intermediate **27** in place of the expected aldehyde **29**. No attempts were made to isolate **27** owing to the potential risk of aziridine formation. The reaction mixture, obtained after the hydroboration-oxidation reaction, was instead treated with $(Boc)_2O$ which enabled trapping of the secondary amine and allowed characterization of the alcohol **28** as the major product. However, a significant amount of a minor product, presumably the exocyclic methyl chloride **35**, was also detected in the reaction mixture (Scheme 7).[18]

In a bid to obtain as clean conversion of **20** to **28** as possible, we studied the effect of molar equivalents of borane, temperature and different sources of borane on the preferential formation of **28** over aberrant products, especially **35**. When the hydroboration reaction



Scheme 7. *Reagents & Conditions:* (a) BH_3·THF; (b) 30% H_2O_2, 10% NaOH (*aq.*), 0–10 °C, 2 h; (c) $(Boc)_2O$, 25–35 °C, 1–2 h.

on **20** was performed at low temperatures (*e.g.* −40 °C or 0–5 °C), it was observed that the undesired product **35** was formed in preference to the required **28**. On the other hand, performing the hydroboration at either room temperature or at 55 °C resulted in a cleaner reaction profile and afforded **28** as the major product. In addition, we found that unless the reaction was carried out at a very low temperature, employing three equivalents of BH_3 was typically enough in all cases to ensure complete consumption of the starting material **20**. Indeed, when the reaction were carried out at 55 °C, adding borane in excess of 3 equivalents neither resulted in a better reaction profile nor afforded any further improvement in the ratio of **28** to **35**.

In the screening experiments, no intermediate, bearing a pyrrolidone moiety (such as **24** or **26**), could be discerned. This pointed towards a probable mechanism for the borane induced formation of **27** from **20** in which the γ-lactam ring in **20** was reduced first, followed by a well-known transformation of the vinyl chloride intermediate to the primary alcohol **27** under hydroboration-oxidation conditions.[19] In addition, the high degree of diastereoselection observed in the formation of **27** from **20** indicated that the stereochemistry of the newly generated chiral center in the postulated second step of this transformation (*i.e.* vinyl chloride to primary alcohol) was being controlled by the topology of the rigid *cis*-fused bicyclic pyrrolidine framework.

Given the flammability of borane and obvious risks associated with handling the material in bulk,[20] we decided to examine next the possibility of obtaining **28** (via **27**) from **20** with *in situ* generated BH_3 using $NaBH_4$ in combination with several Lewis acids such as I_2,[21] TMSCl[22] and BF_3·THF.[23] Among all the reagents studied, $NaBH_4/BF_3$·THF was found to be suitable process amenable replacement for BH_3·THF (Scheme 6). Moving forward, the primary alcohol **28** was oxidized to the aldehyde **29** using TEMPO and sodium hypochlorite. The required product **29** was quite conveniently isolated in pure form from the reaction mixture by sodium bisulphite adduct formation. For converting **29** to the methyl ester **31**, we decided to forgo employing the earlier developed three step sequence (epimerization of aldehyde, oxidation to acid and esterification) in favor of a one-pot epimerization - oxidative esterification[24] strategy. Accordingly, epimerization of **29** in presence of potassium carbonate and methanol gave **30**, which was then treated with iodine at ambient temperature to furnish the methyl ester **31**. Boc-removal in **31** with 1 M HCl in EtOAc, followed by recrystallization from 1:4 *i*-PrOH-MTBE, afforded **3** as a

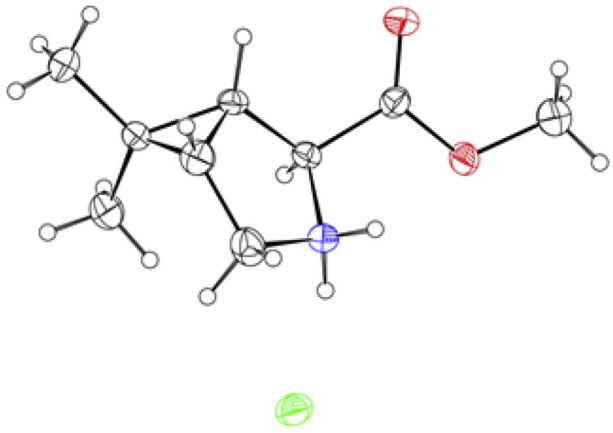


Fig. 3. ORTEP diagram of **3**·**HCl** drawn at 30% probability level.

hydrochloride salt with high chemical (~99%) and chiral (>99%) purity. Finally, stereostructure of the chiral **3**·**HCl** thus isolated was unambiguously secured by single crystal X-ray diffraction analysis (Fig. 3).[25]

3. Conclusion

In short, we have demonstrated herein on a multi-gram scale a novel telescoped diastereoselective synthesis of a key boceprevir fragment **3** from *cis*-cypermethric acid ***rac*-19**, an inexpensive pyrethroid that forms the synthetic precursor of several well-known insecticides such as cypermethrin. Unlike other known syntheses of **3**, wherein the cyclopropyl ring of **3** is derived from a pyrethroid, our synthetic route exemplifies a carbon conservative approach wherein the entire carbon backbone of the pyrethroid **19** is retained and simply re-structured into the bicyclic [3.1.0] proline moiety, present in **3**. In addition, the functional group transformations required for effecting the construction of the proline ring from **19** are operationally simple, atom economical and do not require any exotic reagent or a customized biocatalytic transformation.

4. Experimental section

4.1. General information

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were monitored by thin layer chromatography (TLC) performed on Merck TLC silica gel 60 F254 aluminium plates. Visualization of the spots on the TLC plates was achieved by exposure to UV radiation (254 nm) or by using an appropriate TLC staining reagent (such as PMA, anisaldehyde or ninhydrin). Chromatographic purification of products was carried out by flash column chromatography on silica gel (60–120 mesh or 100–200 mesh or 230–400 mesh as the case required). Melting points were determined using a Differential Scanning Calorimeter (DSC, Q-2000, TA) apparatus. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts (δ) in ppm are reported relative to Me_4Si (= 0 ppm) by using residual solvent signals as internal reference [$CDCl_3$: δ = 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR); CD_3OD: δ = 3.31 ppm (^{1}H NMR) and 49.2 ppm (^{13}C NMR); DMSO-d_6: δ = 2.50 ppm (^{1}H NMR) and 39.5 ppm (^{13}C NMR)]. LRMS data were recorded on an Agilent 1200 Series liquid chromatography module hyphenated to a 6430 Triple Quad LC/MS system. HRMS spectra were recorded on Micromass LCT Premier mass spectrometer equipped with an ESI lock spray source for accurate mass values. Specific optical rotation was recorded on an Anton Paar MCP 200 polarimeter.

4.2. Experimental procedures

4.2.1. (1S*,3S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxamide (*rac*-22)

Ammonia gas was passed for 2–3 h into a solution of *cis*-cypermethric acid chloride ***rac*-21** (300 g, 1.318 mol) in DCM (3.0 L) maintained at −10 °C. After the completion of reaction as monitored by TLC, water (2.0 L) was added to the reaction mixture. Both the layers formed were separated and the aqueous layer was further extracted with DCM (900 mL). Both the organic layers were combined, washed with brine solution (1.5 L), dried over anhydrous sodium sulfate and concentrated under reduced pressure below 45 °C. The crude material was purified by trituration with hexane (600 mL) to afford the title compound ***rac*-22** as a white solid (226 g, 82.4%); R_f (20% ethyl acetate in hexane): 0.2; ν_{max} ($CHCl_3$, cm^{-1}): 3489, 3332, 1681, 1658, 1611, 1441, 915; δ_H (400 MHz, DMSO-d_6): 7.54 (s, 1H), 6.81 (s, 1H), 6.50 (d, J = 8.8 Hz, 1H), 1.76–1.85 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H); δ_C (100 MHz, DMSO-d_6): 171.7, 127.8, 117.1, 32.8, 31.2, 28.5, 26.3, 15.2; HRMS (ESI-MS): MH^+, found 208.0287. $C_8H_{12}NOCl_2$ requires 208.0296.

4.2.2. (1S*,5R*)-4-(chloromethylene)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (*rac*-20)

To a suspension of sodium hydride (115.2 g, 2.8 mol) in *N,N*-dimethylacetamide (1.0 L) was added ***rac*-22** (200 g, 0.961 mol) at 0 °C under nitrogen atmosphere. The reaction mixture temperature was raised to 25–35 °C and stirred for further 5–6 h. Upon the completion of the reaction (as indicated by TLC), the reaction mixture was slowly poured into cold water (3.5 L). The pH of reaction mixture was adjusted to 2 to 2.5 with 2 N HCl. The solid obtained was collected by filtration and the cake was washed with water (1.6 L). The material was dried below 45 °C to afford the title compound ***rac*-20** as a yellow colored solid (102 g, 61.8%); R_f (30% ethyl acetate in hexane): 0.6;ν_{max} ($CHCl_3$, cm^{-1}): 3226, 1684, 1375; δ_H (400 MHz, $CDCl_3$): 7.26 (brs, 1H), 5.24 (s, 1H), 2.30 (d, J = 5.8 Hz, 1H), 2.11 (dd, J = 4.4 Hz, J = 1.4 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H); δ_C (100 MHz, DMSO-d_6): 173.8, 139.0, 89.8, 33.6, 31.3, 26.1, 25.4, 15.2; HRMS (ESI-MS): MH^+, found 172.0564. $C_8H_{11}NOCl$ requires 172.0529.

4.2.3. (1S*,4R*,5R*)-4-(chloromethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (*rac*-24)

To a solution of ***rac*-20** (110 g, 0.641 mol) in hydrogen peroxide (2.2 L) was added Amberlite IR120 resin (110 g) at ambient temperature. The resulting mixture was stirred for 5 h at the same temperature. Upon the completion of the reaction (as indicated by TLC), the reaction mixture was added to water (1.0 L) and extracted with ethyl acetate (3×1 L). The organic layers were combined and washed with brine solution (1.0 L). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 50 °C to afford **23** as a pale yellow solid (110 g). This material was taken forward to next step without any further purification. δ_H (400 MHz, $CDCl_3$): 10.72 (s, 1 H), 7.27 (s, 1H), 3.88 (d, J = 12.2 Hz, 1H), 3.70 (d, J = 12.4 Hz, 1H), 2.1 (d, J = 5.6 Hz, 1H), 1.94 (dd, J = 5.6 Hz, J = 1.2 Hz, 1H), 1.29 (s, 3H), 1.18 (s, 3H); δ_C (100 MHz, $CDCl_3$): 177.94, 94.86, 42.45, 33.15, 32.56, 27.06, 26.42, 16.06.

To a solution of **23** (100 g) in dichloromethane (1.5 L) was added triethylsilane (101.75 g, 0.8771 mol) at 5–10 °C. Trifluoroacetic acid (633.3 g, 5.555 mol) was added slowly to this reaction mixture at 5–10 °C and the whole contents were stirred for 16 h at 25–35 °C.

After the completion of reaction as monitored by TLC, Saturated $NaHCO_3$ sol. (3.0 L) was added to the reaction mixture. Both the layers formed were separated and the aqueous layer was further extracted with DCM (2×500 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C to afford the crude compound which was purified by the silica gel column chromatography (eluted with 50% ethyl acetate in hexane) to furnish ***rac-24*** as a colorless liquid (65 g, 65.8%); ν_{max} ($CHCl_3$, cm^{-1}): 3433, 3216, 3018, 1693, 1216; δ_H (400 MHz, DMSO-d_6): 7.61 (brs, 1H), 3.99–3.94 (m, 1H), 3.72–3.67 (m, 1H), 3.57–3.52 (m, 1H), 1.71–1.70 (m, 1H), 1.65–1.63 (m, 1H), 1.22 (s, 3H), 1.02 (s, 3H); δ_C (100 MHz, DMSO-d_6): 174.1, 56.3, 44.2, 33.6, 28.4, 26.7, 22.2, 17.6; HRMS (ESI-MS): MH^+, found 174.0690. $C_8H_{13}NOCl$ requires 174.0686.

4.2.4. ((1R*,2R*,5S*)-6,6-dimethyl-4-oxo-3-azabicyclo[3.1.0]hexan-2-yl)methyl acetate(*rac-25*)

To a solution of compound ***rac-24*** (80.0 g, 0.462 mol) in toluene (800 mL) was added sodium acetate (151.6 g, 1.85 mol) and tetrabutylammonium bromide (149 g, 0.462 mol) at 25–35 °C. The resulting mixture was heated to reflux and stirred continuously for 16 h. After the completion of reaction as monitored by TLC, The reaction mixture temperature was cooled to 35 °C and water (1.5 L) was added to the reaction mixture. Both the layers formed were separated and the aqueous layer was extracted with ethyl acetate (3×750 mL). The organic layers were combined, washed with brine solution (500 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure below 50 °C. The crude material obtained was purified by triturating with hexane (100 mL) at RT. The solid obtained was filtered and dried below 40 °C under vacuum to afford the title compound ***rac-25*** as a pale yellow solid (59 g, 64%); R_f (ethyl acetate) 0.5;ν_{max} ($CHCl_3$, cm^{-1}): 3211, 2954, 1738, 1694, 1368, 1227; δ_H (400 MHz,DMSO-d_6): 7.62 (brs, 1H), 4.16–4.04 (m, 2H), 3.99–3.95 (m, 1H), 2.02 (s, 3H), 1.68–1.62 (m, 2H), 1.20 (s, 3H), 1.03 (s, 3H); δ_C (100 MHz, DMSO-d_6): 174.3, 170.6, 63.5, 53.4, 33.2, 27.5, 26.7, 21.9, 21.1, 17.7; HRMS (ESI-MS): MH^+, found 198.1137. $C_{10}H_{16}NO_3$ requires 198.1130.

4.2.5. (1S*, 4R*, 5R*)-4-(hydroxymethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (*rac-26*)

To a solution of ***rac-25*** (59.0 g, 0.299 mol) in methanol (600 mL) was added potassium carbonate (49.59 g, 0.3593 mol) at 25–35 °C and stirred for 2 h at the same temperature. Upon completion of the reaction (as indicated by TLC), the reaction mixture was filtered through Celite and the cake was washed with methanol (2×75 mL). The filtrate was collected and concentrated under reduced pressure below 55 °C to get the crude residue. The crude compound was dissolved in water (40 mL) and extracted with ethyl acetate (3×300 mL). The organic layers were combined, washed with brine solution (75 mL) and then dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure below 50 °C to furnish the title compound ***rac-26*** as a pale yellow color solid (40 g, 86%); R_f (ethyl acetate) 0.2; ν_{max} ($CHCl_3$, cm^{-1}): 3293, 2935, 2869, 1685, 1446, 1364, 1323; δ_H (400 MHz, DMSO-d_6): 7.30 (brs, 1H), 4.80 (brs, 1H), 3.79–3.74 (m, 1H), 3.52–3.41 (m, 2H), 1.63–1.55 (m, 2H), 1.16 (s, 3H), 1.02 (s, 3H); δ_C (100 MHz, DMSO-d_6): 174.2, 61.2, 57.3, 33.2, 28.0, 26.9, 21.8, 17.9; HRMS (ESI-MS): MH^+, found 156.1040. $C_8H_{14}NO_2$ requires 156.1025.

4.2.6. (1R*,2R*,5S*)-tert-butyl 2-(hydroxymethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (*rac-28*)

To the suspension of lithium aluminium hydride (69.13 g, 1.8193 mol) in dry THF (500 mL) was added ***rac-26*** (47 g, 0.303 mol) in THF (440 mL) at 25–35 °C under nitrogen atmosphere. The reaction mixture temperature was raised to 65 °C and maintained for additional 16 h. Upon completion of reaction (as indicated by TLC), the reaction mixture was quenched with saturated aqueous sodium sulfate solution (200 mL). The reaction mixture was diluted with ethyl acetate (1 L) and filtered through celite bed. The cake was washed with ethyl acetate (2×500 mL). The resulting filtrate was concentrated under reduced pressure below 50 °C to afford the crude material ***rac-27*** which was taken directly for N–Boc protection (40 g).

Boc_2O (68.1 g, 0.312 mol) was added to a solution of ***rac-27*** (40 g, 0.283 mol) in dichloromethane (400 mL) at 25–35 °C under nitrogen atmosphere and stirred for 2 h at the same temperature. After the completion of reaction as monitored by TLC, the solvent was concentrated under reduce pressure below 40 °C. Methanol (300 mL) was added to the residue followed by addition of potassium carbonate (30 g) and the reaction mixture was stirred for further 1 h at ambient temperature. The solid obtained was filtered and the cake was washed with methanol (50 mL). The filtrate was concentrated under reduced pressure. The crude compound was dissolved in DCM (400 mL) and washed with water (2×200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude compound which was purified by the silica gel column chromatography (10–15% ethyl acetate in hexane) to afford the title compound ***rac-28*** as yellow solid (40 g, 55% from ***rac-26***). ν_{max} ($CHCl_3$, cm^{-1}): 3483, 2975, 1676, 1372, 1135, 1031; δ_H (400 MHz, $CDCl_3$): 5.62 (d, J = 10.2 Hz, 1H), 4.05 (t, J = 5.9 Hz, 1H), 3.81–3.72 (m, 2H), 3.78–3.72 (m, 1H), 3.36 (d, J = 11.7 Hz, 1H), 1.44 (s, 9H), 1.42 (d, J = 2.0 Hz, 1H), 1.23 (t, J = 5.9 Hz, 1H), 1.06 (s, 3H), 0.98 (s, 3H); δ_C (100 MHz, $CDCl_3$): 156.7, 80.3, 65.2, 64.5, 48.9, 32.4, 28.3, 26.9, 25.1, 19.5, 16.3; HRMS (ESI-MS): MH^+, found 242.1754 $C_{13}H_{24}NO_3$ requires 242.1856.

4.2.7. (1R*,2R*,5S*)-tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (*rac-29*)

To a solution of oxalyl chloride (10.27 g, 0.08 mol) in dichloromethane (50 mL) was added DMSO (6.8 g, 0.0871 mol) at −78 °C under nitrogen atmosphere and stirred continuously at the same temperature for 30 min. The solution of ***rac-28*** (15 g, 0.062 mol) in dichloromethane (200 mL) was added to this reaction mixture at −78 °C followed by addition of triethylamine (31.49 g, 0.3112 mol). The reaction mixture temperature was slowly raised to 30–35 °C and stirred for further 45 min. After completion of reaction as monitored by TLC, cool water was added to the reaction mixture (200 ml) and both the layers formed were separated. Aqueous layer was further extracted with DCM (100 mL) and all the organic layers were combined and washed with 1 N HCl (200 mL) followed by saturated $NaHCO_3$solution (200 mL). The organic layer was concentrated under reduced pressure below 40 °C to afford the title compound ***rac-29*** as brown color liquid (14.0 g, 94%); [Note: Compound ***rac-29*** exists as mixture of two conformers, so that every unique ^1H or ^{13}C signal appears pair wise] R_f (20% ethyl acetate in hexane) 0.6; ν_{max} ($CHCl_3$, cm^{-1}): 2819, 1730, 1682, 1413, 1388, 1139; δ_H (400 MHz, $CDCl_3$): 9.61 (d, J = 3.4 Hz, 1H), 4.27–4.18 (m, 1H), 3.68–3.44 (m, 2H), 1.68–1.65 (m, 1H), 1.51 (m, 1H), 1.40 (s, 9H), 1.15 (s, 3H), 1.01 (s, 3H); δ_C (100 MHz, $CDCl_3$): 201.8, 153.8, 81.0, 66.9, 47.0, 32.8, 29.3, 28.1, 27.4, 26.4, 20.5, 17.4; HRMS (ESI-MS): MH^+, found 240.1606. $C_{13}H_{22}NO_3$ requires 240.1600.

4.2.8. (1R*,2S*,5S*)-tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (*rac-30*)

To a solution of ***rac-29*** (14 g, 0.058 mol) in dichloromethane (140 mL) was added DBU (4.45 g, 0.0292 mol) under nitrogen atmosphere at ambient temperature and stirred for 2–3 h. After the completion of reaction as monitored by TLC, cold water (200 mL) was added to the reaction and both the layers formed were

separated. The aqueous layer was extracted with DCM (100 mL). The organic layers were combined, washed with brine solution (100 mL) and concentrated under reduced pressure below 40 °C to afford the title compound ***rac-30*** (14 g) as pale yellow liquid; [Note: Compound ***rac-30*** exist as mixture of two conformers, so that every unique ^{1}H or ^{13}C signal appears pair wise] R_f (20% ethyl acetate in hexane) 0.6; ν_{max} ($CHCl_3$, cm^{-1}): 2819, 1730, 1682, 1413, 1388, 1139; δ_H (400 MHz, $CDCl_3$): δ 9.71 (d, J = 1.2 Hz, 1H), 4.19–4.01 (m, 1H), 3.76–3.66 (m, 1H), 3.59–3.48 (m, 1H), 1.55–1.33 (m, 11H), 1.09 (s, 3H), 1.05 (s, 3H); δ_C (100 MHz, $CDCl_3$): 201.7, 153.8, 81.0, 66.9, 47.0, 32.8, 31.7, 28.2, 28.1, 27.4, 26.5, 20.5, 17.3; HRMS (ESI-MS): MH^+, found 240.1606. $C_{13}H_{22}NO_3$ requires 240.1600.

4.2.9. (1R*,2S*,5S*)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (***rac-31***)

To the mixture of ***rac-30*** (14 g, 0.0585 mol) in acetone (280 mL) was added Jones reagent (42 mL) in acetone (30 mL) under nitrogen atmosphere at −30 °C. The reaction mixture temperature was warmed to 0–5 °C and stirred for 1 h. After the completion of reaction as monitored by TLC, isopropyl alcohol (30 mL) was added to the reaction mixture and stirred for 1 h at room temperature. Reaction mixture was filtered through Celite bed and washed with acetone (20 mL). The filtrate was concentrated under reduced pressure below 40 °C. Saturated sodium bicarbonate solution was added to the residue and washed with ethyl acetate (2×100 mL). The pH of the aqueous layer was adjusted to 3.5 to 3.0 with saturated citric acid solution and extracted with ethyl acetate (2×100 mL). The organic layers were combined and concentrated under reduced pressure below 50 °C to afford the title compound ***rac-31*** as a white colored solid (8.6 g, 58%); R_f (ethyl acetate) 0.1; ν_{max} ($CHCl_3$, cm^{-1}): 3019, 2981, 1721, 1694, 1414, 1174; δ_H (400 MHz, DMSO-d_6): 12.7 (brs, 1H), 3.92–3.88 (m, 1H), 3.50–3.46 (m, 1H), 3.34–3.23 (m, 1H), 1.36–1.23 (m, 11H), 0.95 (s, 3H), 0.90 (s, 3H); δ_C (100 MHz, DMSO-d_6): 173.6, 152.9, 79.3, 59.4, 46.4, 30.7, 28.3, 26.2, 26.1, 19.0, 12.6; Mass: m/z = 254 $[M\text{-}H]^-$

4.2.10. (1R*,2S*,5S*)-3-tert-butyl 2-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (***rac-32***)

To a suspension of ***rac-31*** (8.0 g, 0.313 mol), potassium carbonate (21.65 g, 0.156 mol) in acetone (240 mL) was added methyl iodide (22.27 g, 0.156 mol) at ambient temperature under nitrogen atmosphere and stirred for 16 h. Upon the completion of reaction (as indicated by TLC), the reaction mixture was filtered through Celite bed and the cake was washed with acetone (2×50 mL). The filtrates were combined and concentrated under reduced pressure below 40 °C. Water (100 mL) was added to the residue and extracted with ethyl acetate (2×100 mL). The organic layers were combined and concentrated under reduced pressure to obtain the crude product which was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford the title compound ***rac-32*** as colorless liquid (7.1 g, 84.2%); [Note: Compound ***rac-32*** exists as mixture of two conformers, so that every unique ^{1}H or ^{13}C signal appears pair wise[26]]; R_f (30% ethyl acetate in hexane) 0.6; ν_{max} ($CHCl_3$, cm^{-1}): 2975, 2954, 2930, 1753, 1706, 1390, 1175; δ_H (400 MHz, $CDCl_3$): 4.21–4.09 (m, 1H), 3.72 (s, 3H), 3.63–3.53 (m, 1H), 3.47–3.38 (m, 1H), 1.67 (t, J = 7.4 Hz, 1H), 1.47 (m, 1H), 1.45 (s, 9H), 1.10 (s, 3H), 0.99 (s, 3H); δ_C (100 MHz, $CDCl_3$): 173.1, 153.7, 153.1, 79.9, 59.7, 52.1, 46.4, 31.9, 28.3, 27.3, 26.6, 26.2, 19.3, 12.5; HRMS (ESI-MS): MH^+, found 270.1692. $C_{14}H_{24}NO_4$ requires 270.1705.

4.2.11. (1R*,2S*,5S*)-methyl 6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxylate hydrochloride (***rac-3***·HCl)

To a solution of ***rac-3*** (7 g, 0.026 mol) in 1,4-dioxane (35 mL) was added 1 M HCl in ethyl acetate solution (105 mL) at 10 °C under nitrogen atmosphere. The reaction mixture temperature was warmed to 25–35 °C and stirred for 4 h. After the completion of reaction as monitored by TLC, the solvent was evaporated under reduced pressure below 55 °C and co evaporated with toluene (15 mL). The crude product was triturated with MTBE (20 mL) and the solid was collected by filtration to afford the title compound as light brown colored solid (5.0 g, 94%); R_f (30% ethyl acetate in hexane) 0.6; ν_{max} ($CHCl_3$, cm^{-1}): 2564, 1759, 1267, 1214, 1029; δ_H (400 MHz, DMSO-d_6): 9.81 (brs, 1H) 4.13 (d, J = 1.6 Hz, 1H), 3.79 (s, 3H), 3.61–3.57 (m, 1H), 3.03 (dd, J = 10.8 Hz, J = 2 Hz, 1H), 1.90–1.87 (m, 1H), 1.74–1.78 (m, 1H), 1.07 (s, 3H), 1.04 (s, 3H); δ_C (100 MHz, CD_3OD): 170.1, 61.4, 54.3, 47.2, 34.4, 30.7, 26.2, 23.5, 14.0; HRMS (ESI-MS): MH^+, found 170.1188, $C_9H_{16}NO_2$ requires 170.1181.

4.2.12. (1R*,2R*,5S*)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (***rac-33***)

To a solution of Jones reagent (60 mL) in acetone (70 mL) was added ***rac-28*** (10 g, 0.0415 mol) in acetone (70 mL) at 0–5 °C under nitrogen atmosphere. The reaction mixture temperature was warmed to 25–35 °C and stirred for 16 h. The progress of the reaction was monitored by TLC. Isopropyl alcohol (20 mL) was added to the reaction mixture and stirred for 1 h at the same temperature. The reaction mixture was filtered through celite bed and the cake was washed with acetone (20 mL). The resulting filtrate was concentrated under reduced pressure below 40 °C. Saturated sodium bicarbonate solution (50 mL) was added to the residue and it was washed with ethyl acetate (2×50 mL). The aqueous layer was acidified with saturated citric acid solution (pH 3 to 3.5) and extracted with ethyl acetate (2×75 mL). The organic layers were combined and concentrated under reduced pressure to afford the title compound ***rac-33*** as colorless liquid (5.0 g, 47.3%); R_f (ethyl acetate) 0.1; δ_H (400 MHz, $CDCl_3$): 8.5 (brs, 1H), 4.60–4.45 (m, 1H), 3.65–3.61 (m, 1H), 3.47–3.35 (m, 1H), 1.76–1.71 (m, 1H), 1.39 (s, 9H), 1.26–1.24 (m, 1H), 1.05 (s, 3H), 1.02 (s, 3H); δ_C NMR (100 MHz, $CDCl_3$): 176.7, 173.0, 82.1, 61.5, 48.5, 31.4, 30.9, 28.3, 26.8, 26.3, 20.8, 14.4; Mass: m/z = 254.0 $[M\text{-}H]^-$.

4.2.13. (1R*,2R*,5S*)-3-tert-butyl 2-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (***rac-34***)

To a solution of ***rac-33*** (1.0 g, 0.004 mol) in DMF (10 mL) was added cesium carbonate (1.78 g, 0.005 mol) followed by addition of methyl iodide (1.0 g, 0.007 mol) at 25–35 °C under nitrogen atmosphere. The resulting reaction mixture was stirred for 4 h at the same temperature. After the completion of reaction, cold water (30 mL) was added to the reaction mixture and extracted with MTBE (3×20 mL). The combined organic layers were washed with brine solution and the organic layer was concentrated under reduced pressure below 50 °C. The crude compound was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the title compound ***rac-34*** as a pale yellow liquid (0.35 g, 33%); R_f (30% ethyl acetate in hexane) 0.6; δ_H (400 MHz, $CDCl_3$): 4.49–4.42 (m, 1H), 3.72–3.71 (m, 3H), 3.71–3.58 (m, 1H), 3.46–3.37 (m, 1H) 1.69–1.62 (m, 1H), 1.44–1.42 (m, 1H) 1.40 (s, 9H), 1.09 (s, 3H), 0.98 (s, 3H); δ_C (100 MHz, $CDCl_3$): 171.5, 154.0, 79.9, 60.3, 51.6, 47.4, 31.7, 28.3, 27.2, 26.8, 26.5, 20.8, 20.7, 14.3; Mass: m/z = 170.0 $[M\text{-Boc}+H]^+$

4.2.14. (1R*,2S*,5S*)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (***rac-31***)

To a solution of ***rac-34*** (0.14 g, 0.5 m mol) in methanol (5 mL) was added sodium methoxide (0.113 g, 0.0070 mol) under nitrogen atmosphere at ambient temperature. Reaction mixture temperature was heated to reflux and stirred for 16 h. After the completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure below 50 °C. Cold water (10 mL) was added to the residue and washed with ethyl acetate (10 mL). Aqueous

layer was acidified with saturated citric acid solution (pH 3.0–3.5) and extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with brine solution (5 mL) and concentrated under reduced pressure below 50 °C to afford the title compound ***rac-31*** as a off-white colored solid (0.11 g, 83%); R_f (ethyl acetate) 0.2; ν_{max} ($CHCl_3$, cm^{-1}): 3019, 2981, 1721, 1694, 1414, 1174; δ_H (400 MHz, $CDCl_3$): 12.7 (brs, 1H), 3.92–3.88 (m, 1H), 3.50–3.46 (m, 1H), 3.34–3.23 (m, 1H), 1.36–1.23 (m, 11H), 0.95 (s, 3H), 0.90 (s, 3H); δ_C (100 MHz, $CDCl_3$): 173.6, 153.2, 79.3, 59.7, 46.5, 31.6, 30.7, 28.4, 26.9, 26.2, 26.1, 19.0, 12.8; Mass: m/z = 254.1 $[M-H]^+$

4.2.15. (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (*19*)

To a stirred solution of (*R*)-phenylethyl amine (63.75 g, 0.526 mol) in isopropanol (2.5 L) was added *cis*-cypermethric acid ***rac*-19** (100 g, 0.478 mol) at 25 °C and stirred for 30 min at the same temperature. The reaction mixture was heated to reflux for 30 min and then slowly cooled to ambient temperature. The solid product obtained was filtered and recrystallized from IPA (800 mL) to afford the chirally pure salt. The salt was suspended in water (1.0 L) and the pH of the reaction mixture was adjusted to 2.0–2.5 using 2 N HCl. The solid obtained was collected by filtration, washed with water (100 mL) and dried at 50 °C under vacuum to afford the chirally pure acid **19** (20 g, 40%); $[\alpha]_{589}^{20}$−39.40 (*c* 1.5, CH_2Cl_2) [lit.[27] $[\alpha]_{589}^{20}$−38.0 (*c* 1.5, CH_2Cl_2)]; δ_H (400 MHz, $CDCl_3$): 11.3 (brs, 1H), 6.21 (d, J = 8.7 Hz, 1H), 2.10 (t, J = 8.7 Hz, 1H),1.84 (d, J = 8.3 Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H). Determination of the chiral purity of the product was carried out by chiral HPLC analysis [Column: Chiralpak-ADH, 250×4.6 mm, 5 μm particle size; Eluent: 1% TFA in 95:5 n-hexane-isopropanol; Flow rate: 0.6 mL/min; UV detection at 210 nm; retention times for **19** and ***ent*-19** were 7.1 and 7.9 min respectively]. Enantiomeric excess of **19** in the product was >99%.

4.2.16. (1S,5R)-4-(chloromethylene)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (*20*)

To a suspension of **19** (30.0 g, 0.143 mol) in toluene (60 mL) and DMF (0.15 mL), thionyl chloride (20.49 g, 0.172 mol) was added at 25–35 °C under nitrogen atmosphere and stirred for 3 h at the same temperature. The reaction mixture was added to aq. ammonia (300 mL) at 0–10 °C and stirred for further 2–3 h at 25 °C. Toluene (240 mL) was added to the reaction mass mixture and both the layers formed were separated. The aqueous layer was further extracted with toluene (150 mL). The organic layers were combined and washed with brine solution and evaporated under vacuum to afford **22** (26.9 g).

To a stirred solution of **22** (20.39 g, 0.098 mol) in toluene (180 mL), was added a solution of potassium *tert*-butoxide (40.26 g, 0.358 mol) in THF (150 mL) at 25–35 °C under nitrogen atmosphere and stirred for 2–3 h at the same temperature. The reaction mixture was quenched with saturated ammonium chloride solution at 0–10 °C. The both layers formed were separated and the aqueous layer was further extracted with toluene (2×100 mL). The organic layers were combined and evaporated under vacuum to afford **20** as off white colored solid (15.1 g, 80% yield from **19**); ν_{max} ($CHCl_3$, cm^{-1}): 3226, 1684, 1375; δ_H (400 MHz, $CDCl_3$): δ 7.26 (brs, 1H), 5.24 (s, 1H), 2.30 (d, J = 5.8 Hz, 1H), 2.11 (dd, J = 4.4 Hz, J = 1.4 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H); δ_C (100 MHz, DMSO-d_6): 173.8, 139.0, 89.8, 33.6, 31.3, 26.1, 25.4, 15.2; HRMS (ESI-MS): MH^+, found 172.0554. $C_8H_{11}NOCl$ requires 172.0529.

4.2.17. (1R,2R,5S)-tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (*29*)

To a stirred suspension of sodium borohydride (9.91 g, 0.262 mol) in THF (140 mL) was added BF_3·THF (45% BF_3) (41.5 mL, 0.349 mol) at 0 °C under nitrogen atmosphere. The reaction mixture temperature was raised to 25–35 °C and stirred for 2 h. The solution of the compound **20** (10 g, 0.058 mol) in THF (50 mL) was added to reaction at 25 °C and then the reaction mixture was heated to 50–60 °C and stirred continuously for 2–3 h. The mixture was cooled to 0–10 °C. The reaction mixture was quenched with water (100 mL) and then 10% aqueous sodium hydroxide (150 mL) solution was added followed by 30% hydrogen peroxide solution at 0 °C. The reaction mixture temperature was raised to 25–35 °C and stirred for 2 h. Boc_2O (16.6 mL, 0.0699 mol) was added to the reaction mixture at 25–35 °C and stirred for 1–2 h. The reaction mixture was filtered through Celite bed and the product was extracted with MTBE (2×50 mL). The organic layers were combined, washed with 20% sodium sulfite solution (2×50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get intermediate **28**. The obtained crude product (10 g) was taken for next step.

To the solution of alcohol intermediate **28** (10 g, 0.041 mol) in DCM (200 mL) was added potassium bromide (0.98 g, 0.008 mol) in water (10 mL) at 0–5 °C. TEMPO (0.129 g, 0.00082 mol) followed by 9% sodium hypochlorite (pH was adjusted 9.3 by using sodium bicarbonate) was added to the reaction mixture at 0–10 °C and stirring continuously for 10 min. The both layers formed were separated and the organic layer was washed with 10% aq. sodium thiosulfate (100 mL). 25% of aq. sodium bisulphite solution (75 mL) was added to the organic layer and stirred for 7–8 h at 25–35 °C. Both layers formed were separated and the aqueous layer was washed with MTBE (2×50 mL). The pH of the aqueous layer was adjusted to 9.0 using sodium carbonate and extracted with MTBE (2×50 mL). The organic layers were combined and concentrated under vacuum to afford aldehyde **29** as a light brown color liquid (7.7 g, 55% yield from **20**); [Note: Compound **29** exists as mixture of two conformers, so that every unique ^1H or ^{13}C signal appears pair wise] ν_{max} ($CHCl_3$, cm^{-1}): 2819, 1730, 1682, 1413, 1388, 1139; δ_H (400 MHz, $CDCl_3$): 9.61 (d, J = 3.4 Hz, 1H), 4.27–4.18 (m, 1H), 3.68–3.44 (m, 2H), 1.68–1.65 (m, 1H), 1.51 (m, 1H), 1.40 (s, 9H), 1.15 (s, 3H), 1.01 (s, 3H); δ_C (100 MHz, $CDCl_3$): 201.8, 153.8, 81.0, 66.9, 47.0, 32.8, 29.3, 28.2, 27.4, 26.5, 26.0, 20.5, 17.3; HRMS (ESI-MS): MH^+, found 240.1603. $C_{13}H_{22}NO_3$ requires 240.1600.

4.2.18. (1R,2S,5S)-3-tert-butyl 2-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (*32*)

To a solution of aldehyde **29** (15 g, 0.063 mol) in methanol (150 mL) was added potassium carbonate (21.65 g, 0.156 mol) and the contents were stirred for 3 h at 25 °C. Upon completion of reaction as indicated by TLC, iodine (16.07 g, 0.063 mol) was added to the reaction mixture, which was then stirred for 3 h under dark conditions. 10% sodium thiosulfate solution (150 mL) was added to the reaction mixture the methanol present was evaporated under vacuum. The product was extracted with ethyl acetate (2×10 mL) and the organic layers were combined, washed with brine solution and distilled under vacuum to afford ester **32** (17.2 g crude); [Note: Compound **32** exists as mixture of two conformers, so that every unique ^1H or ^{13}C signal appears pair wise[26]] ν_{max} ($CHCl_3$, cm^{-1}): 2975, 2954, 2930, 1753, 1706, 1390, 1175;; δ_H (400 MHz, $CDCl_3$): 4.50–4.43 (m, 1H), 3.72 (s, 3H), 3.63–3.53 (m, 1H), 3.47–3.38 (m, 1H), 1.67 (t, J = 7.4 Hz, 1H), 1.47 (m, 1H), 1.45 (s, 9H), 1.10 (s, 3H), 0.99 (s, 3H); δ_C (100 MHz, $CDCl_3$): 173.1, 153.7, 79.9, 59.7, 52.1, 46.4, 31.9, 28.3, 27.3, 26.6, 26.2, 19.3, 12.5; HRMS (ESI-MS): MH^+, found 270.1696. $C_{14}H_{24}NO_4$ requires 270.1705.

4.2.19. (1R,2S,5S)-methyl 6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylate hydrochloride (*3*·HCl)

To a solution of ester **32**(10.0 g, 0.37 mol) in ethyl acetate (30 mL) was added 1 M HCl in ethyl acetate (30 mL) at 0 °C and stirred for 2 h. Charcoal was added to the reaction mixture and

filtered through Celite and then filtrate was concentrated under vacuum. The crude product obtained was re-crystallized from the mixture of IPA-MTBE (1:4) (100 mL) to afford compound **3** as an off-white colored solid (5.3 g, 70% overall yield from **29**, *ee* by chiral HPLC analysis >99%). MP: 162–164 °C; ν_{max} ($CHCl_3$, cm^{-1}): 2564, 1759, 1540, 1267, 1214, 1029; δ_H (400 MHz, DMSO-d_6): δ 9.81 (brs, 1H), 4.13 (d, $J = 1.6$ Hz, 1H), 3.79 (s, 3H), 3.61–3.57 (m, 1H), 3.03 (dd, $J = 10.8$ Hz, $J = 2$ Hz, 1H), 1.90–1.87 (m, 1H), 1.78–1.74 (m, 1H), 1.07 (s, 3H), 1.04 (s, 3H); δ_C (100 MHz, CD_3OD): 170.1, 61.4, 54.3, 47.2, 34.4, 30.7, 26.2, 23.5, 14.0; HRMS (ESI-MS): MH^+, found: 170.1182, $C_9H_{16}NO_2$ requires 170.1181. Determination of the chiral purity of the product was carried out by chiral HPLC analysis [Column: Chiralpak-IC, 250×4.6 mm, 5 μm particle size; Eluent: 0.05% diethylamine in 9:1 *n*-hexane-ethanol; Flow rate: 0.6 mL/min; UV detection at 210 nm; retention times for **3** and ***ent*-3** were 18.3 and 13.7 min respectively]. Enantiomeric excess of **3** in the product was >99%.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.05.080.

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