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Synthesis and Process Optimization of Boceprevir: A Protease Inhibitor Drug

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Supporting Information

ABSTRACT: Efforts toward the synthesis and process optimization of boceprevir **1** are described. Boceprevir synthesis was optimized by telescoping the first three steps and last two steps of the five-step process. Optimization of oxidation, which is one of the critical steps in the total synthesis, is discussed. A control strategy for the three impurities is described. A novel process for the synthesis of fragment A (**2**) has been developed, which is the key starting material for the synthesis of boceprevir.

INTRODUCTION

Hepatitis C virus (HCV) chronically infects more than 200 million people worldwide, and current treatment options have been very limited.[1] Boceprevir, a protease inhibitor, which is a drug molecule approved in 2011, is useful for the treatment of human hepatitis C virus infections. It is an amorphous mixture of two diastereomers in the ratio 1.15:1, which differ in their stereochemical configuration at the third carbon atom (see Figure 1, **1**) from the ketoamide end of the molecule. Boceprevir is used in combination with interferon α-2b and ribavirin in the treatment of chronic HCV genotype 1 infection.[2]

Boceprevir is a peptidomimetic with three moieties: fragment A is a *tert*-leucine urea **2**,[3] fragment B is the dimethylcyclopropylproline analogue **3**,[4] and fragment C is a racemic β-aminoamide **4**.[4b]

Herein we report our efforts to develop a simple and new process for the synthesis of **2** and a telescoped process for the synthesis of boceprevir **1**.

RESULTS AND DISCUSSION

Synthesis of Fragment A (2). The literature approach for the synthesis of **2** consists of coupling the amino acid derivatives with isocyanate or phosgene which are highly toxic, unstable, and difficult to handle.[3,5−7] Our approach to prepare **2** is simple and process-friendly (Scheme 1).

The developed process involved the coupling of *tert*-butylamine with *N,N*-carbonyldiimidazole (CDI) in the presence of toluene to make the CDI activated complex (X), followed by further treatment with *tert*-leucine to give 82% of urea **2**. The isolated product (**2**) showed 99% HPLC purity and 99.9% chiral purity.

Synthesis of Boceprevir 1. Literature precedence approaches[8−10] for the synthesis of boceprevir are shown in Scheme 2. The first route is the coupling of **2** with **3** in the presence of base and EDC·HCl followed by hydrolysis with LiOH to get acid **5**. The acid further couples with **4** in the presence of base, EDC·HCl, and HOBt followed by oxidation under Moffatt conditions to give boceprevir **1** (Scheme 2, route 1). The second route is the coupling of Boc protected *tert*-leucine **7** with **3** followed by isocyanate addition and hydrolysis to get acid **5** (Scheme 2, route 2). The third route is the reaction of acid **5** with oxidized fragment C **9** to get boceprevir **1** (Scheme 2, route 3).

In our initial attempts to make boceprevir, we started our synthesis with the coupling of Boc protected fragment B (**10**) with amine **4** to gave **11** followed by oxidation under Moffatt condition as shown in Scheme 3. The oxidized intermediate **12**, however, was unstable and not isolable. All of the attempts to move further were unsuccessful; thus, this route was abandoned. In an alternate approach to make boceprevir **1**, the intermediate **11** was deprotected and coupled with **2** to get intermediate **6**, which was further oxidized under Moffatt conditions. After Boc deprotection, the intermediate is unstable, and the conversion of **11** to **6** gave 20−30% inconsistent yield; therefore, we did not optimize this route further.

The literature method[8] for the synthesis of boceprevir **1** involves five steps including purification. On a large scale, workup and isolation of intermediates are always cumbersome and not viable on economic and environment grounds. All of these schemes involve CH_2Cl_2/acetonitrile solvents in the coupling stages and THF in the hydrolysis. CH_2Cl_2 is a restricted solvent in the industry, and there is a problem of recovery with acetonitrile and THF as these are the water-miscible solvents. There is thus a need to develop a new and telescoped process which would be viable on an industrial scale. Herein we describe the cost-effective and scalable process for boceprevir **1** as shown in Scheme 4.

In the first step, we screened different solvents and coupling reagents as shown in Table 1. With coupling reagents like CDI, TBTU, DCC, and BOP, the yield and purity were less and required longer reaction times (entries 1−4). Eventually

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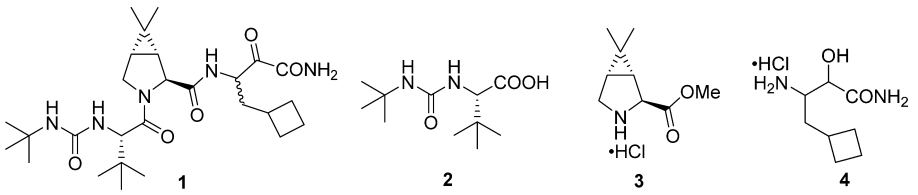
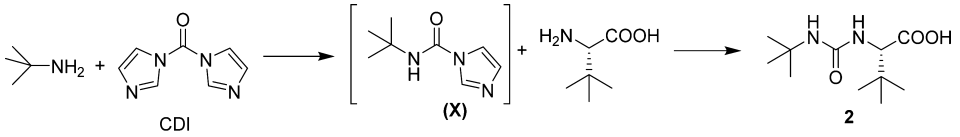


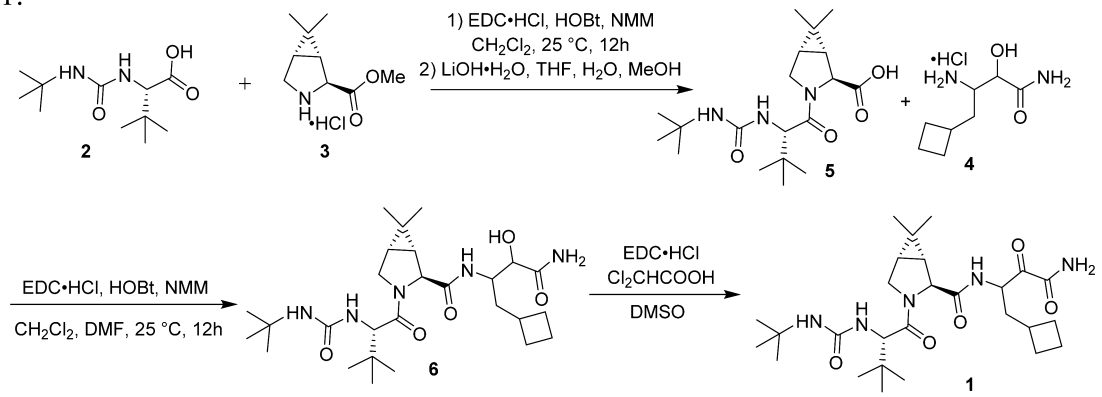
Figure 1. Structure of boceprevir and its fragments.

Scheme 1. Synthesis of 2

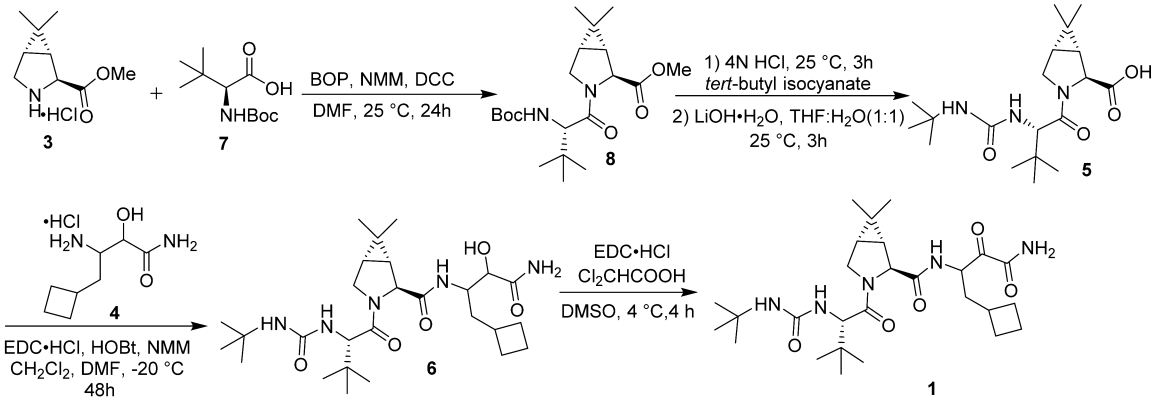


Scheme 2. Precedented approach to the synthesis of boceprevir

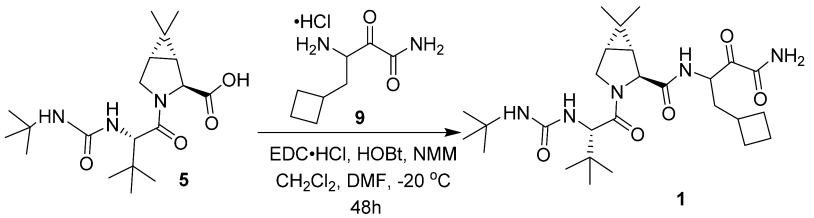
Route 1:



Route 2:



Route 3:



EDC·HCl was found to be a good coupling reagent in the presence of NMM with 1:1 mixture of toluene and DMF as solvents at 0−10 °C (entry 5). The advantage of EDC·HCl is that the byproduct is water-soluble which simplified the purification process to get 90% yield and 99.3% purity. We screened different solvents to avoid mixture of solvents but all attempts failed (entries 8−13). To fix the ratio of DMF and toluene, we studied different combinations and 1:1 ratio of DMF and toluene was found to give good results (entry 5). With less DMF quantity reaction mass becomes gummy. In

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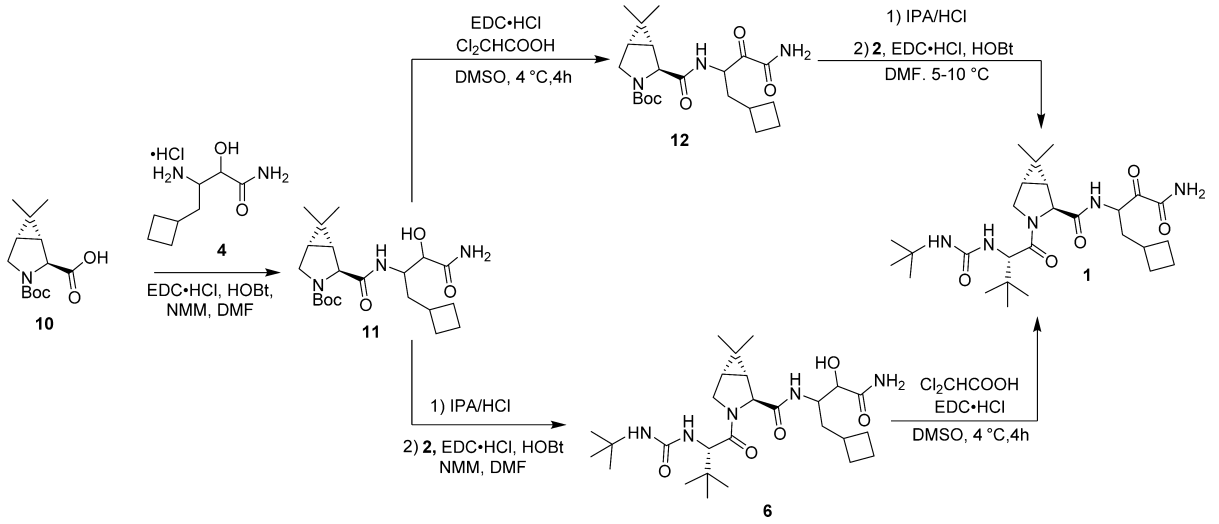
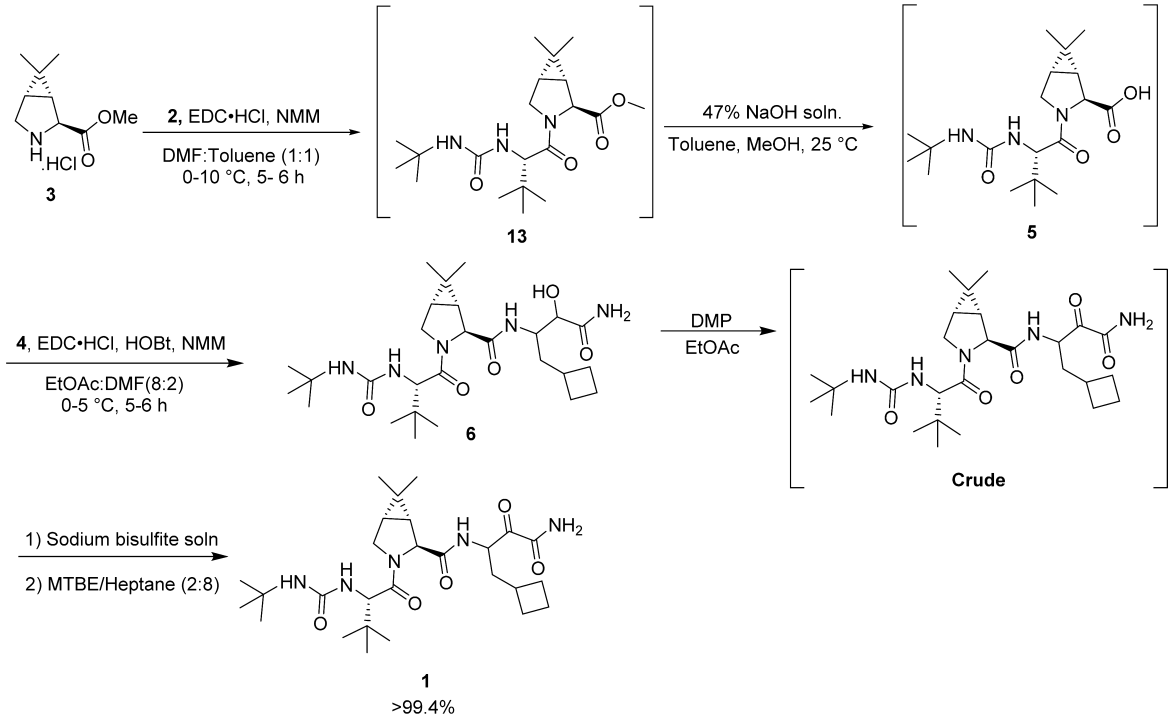
Scheme 3. Novel approaches to the synthesis of boceprevir



Scheme 4. Improved process for the synthesis of boceprevir 1



essence, DMF plays a crucial role in accelerating the reaction rate and reduced the reaction time from 24 to 5 h with 90% yield.

In the second step, we replaced the THF with toluene and screened different bases for the hydrolysis as shown in Table 2. Under the conditions reported for the reaction, lower yields and purities were obtained. In the presence of Bu_4NOH as an additive, reactions gave product in good yield and purity (entries 3−4). When reaction was carried out in the presence of methanol and NaOH as a base, additive Bu_4NOH was not required, and the reaction gave a good yield and purity (entry 6). Further, we optimized the reaction conditions and reduced the quantity of methanol. We found 47% NaOH solution in the presence of 1 volume of methanol gave 92% yield of **5** at room temperature (entry 9). Here methanol played a crucial role to accelerate the reaction rate and conversion (entries 9 and 10).

In the third coupling step, we used EDC·HCl as a coupling reagent with 0.2 equiv of HOBt and 2.5 equiv of NMM with a 8:2 mixture of ethyl acetate and DMF as solvents at 0−10 °C to get 90% yield of amide **6**. Here we found that, in the absence of HOBt, impurities were increased and the starting material did not get fully consumed. The fourth step is oxidation where we screened different oxidizing reagents such as DMSO/EDC·HCl, TEMPO, $KMnO_4$, and DMP as shown in Table 3. Under Moffatt conditions, we found that the reaction gave a displeasing odor of dimethyl sulfide generated from DMSO which is difficult to avoid on larger scale (entry 1). TEMPO oxidation required 1 equiv of reagent and has the additional problem of genotoxicity associated with it (entry 2).[12] A

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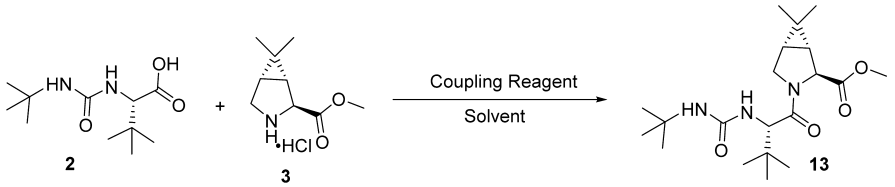
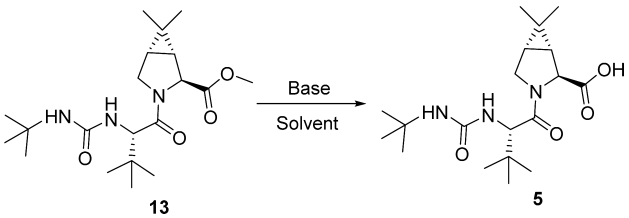
Table 1. Optimization of reaction conditions for the coupling reaction[a,b]



entry	coupling reagent	base	solvent	time (h)	isolated yield (%)	HPLC purity[11] (%)
1	CDI	NMM	THF	8	62	90.0
2	TBTU	2,6-lutidine	DMF:toluene (1:1)	15	85	86.7
3	DCC	2,6-lutidine	DMF:toluene (1:1)	15	88	91.2
4	BOP	NMM	toluene	15	75	90.3
5	EDC·HCl	NMM	DMF:toluene (1:1)	5	90	99.3
6	EDC·HCl	NMM	acetonitrile	6	84	99.7
7	EDC·HCl	NMM	DMAC	6	40	99.7
8	EDC·HCl	NMM	DCM	6	68	99.6
9	EDC·HCl	NMM	EtOAc	6	66	99.0
10	EDC·HCl	NMM	DMF	6	60	99.4
11	EDC·HCl	NMM	2-MeTHF	6	75	98.9
12	EDC·HCl	NMM	toluene	24	62	96.8
13	EDC·HCl	NMM	DMF:toluene (1:9)	6	88	99.8
14	EDC·HCl	NMM	DMF:toluene (2:8)	6	88	99.5
15	EDC·HCl	NMM	DMF:toluene (3:7)	6	88	99.4
16	EDC·HCl	NMM	DMF:toluene (4:6)	6	89	99.5

[a]The reaction was carried out using 1.0 equiv of **2**, 1.0 equiv of **3**, 1.3 equiv of coupling reagent, and 2.5 equiv of base in solvent at 0−10 °C for the mentioned time. [b]DMAc = *N,N*-dimethylacetamide, DMSO = dimethyl sulfoxide, MTBE = methyl-*tert*-butyl ether, THF = tetrahydrofuran, DCM = dichloromethane, EtOAc = ethyl acetate, DMF = *N,N*-dimethylformamide, CDI = 1,1′-carbonyldiimidazole, EDC·HCl = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, TBTU = *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate, DCC = *N,N′*-dicyclohexylcarbodiimide, BOP = (benzotriazol-1-yloxy)tri(dimethylamino)phosphonium hexafluorophosphate, NMM = *N*-mehtylmorpholine, DIPEA = *N,N*-diisopropylethylamine.

Table 2. Optimization of reaction conditions for hydrolysis[a]



entry	base	additives	solvent[c]	isolated yield (%)	HPLC purity[11] (%)
1	LiOH·H_2O		THF:water (3:2)	89	96.3
2	LiOH·H_2O	Bu_4NOH	toluene:water (9:1)	78	95.3
3	NaOH	Bu_4NOH	toluene:water (9:1)	94	99.7
4	KOH	Bu_4NOH	toluene:water (9:1)	97	99.7
5	*t*-BuOK		toluene:MeOH:water (1:1:1)	96	77.3
6	NaOH		toluene:MeOH:water (1:1:1)	93	99.5
7	KOH		toluene:MeOH:water (1:1:1)	86	99.7
8	LiOH·H_2O		toluene:MeOH:water (1:1:1)	93	99.8
9	47% NaOH soln.		toluene:MeOH (9:1)	92	99.8
10	47% NaOH soln.[b]		toluene	55	98.5

[a]The reaction was carried out using 1.0 equiv of **13**, 1.5 equiv of base, and 1.0 equiv of additive in solvent at 25−30 °C for 4 h. [b]The reaction was carried out using 1.0 equiv of **13** and 1.5 equiv of base in toluene at 25−30 °C for 24 h. [c]THF = tetrahydrofuran, MeOH = methanol.

reaction with $KMnO_4$ and oxone did not go to completion, and all of the attempts to drive the reaction to complete conversion were unsuccessful (entries 3−4). Dess−Martin periodinane (DMP) in the presence of ethyl acetate as a solvent was found to be a good oxidizing reagent (entry 9). In this step we obtained 70% crude yield of boceprevir **1**. But 0.2−0.5% starting material remained unreacted which made the product very difficult to purify. Different reaction conditions were screened in order to drive the reaction to completion, but all of the attempts proved to be unsuccessful (entries 4−12). When the reaction was carried out with more than 1.6 equiv of DMP or for longer times, α,β-unsaturated carbonyl compound **14** was forming as a major impurity (entries 10−11). All of the attempts for the purification of boceprevir **1** through solvent

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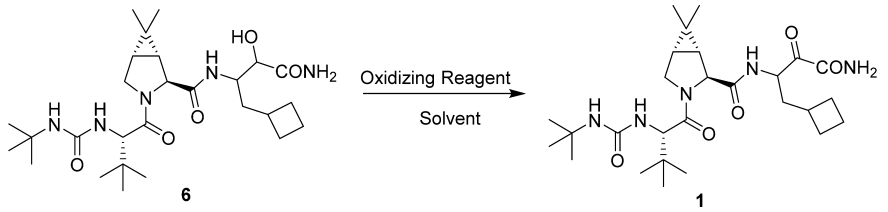
Table 3. Optimization of reaction conditions for oxidation[a]



entry	reagent	solvent	isolated yield (%)	HPLC purity[11] (%) 1	6
1	EDC·HCl/$Cl_2CHCOOH$[b]	DMSO:toluene (1:1)	77	92	1.2
2	TEMPO/NaOCl[c]	MTBE:water (1:1)	65	91	2.6
3	$KMnO_4$/TEMPO[d]	MTBE:water (1:1)	55	86	11
4	oxone/TBAB/TEMPO[e]	acetonitrile	60	78	20
5	DMP[f]	acetonitrile	82	91	1.2
6	DMP[f]	2-MeTHF	75	94	0.4
7	DMP[f]	THF	65	84	8
8	DMP[f]	DCM	78	91	4
9	DMP[f]	EtOAc	80	95	0.3
10	DMP[g]	EtOAc	74	86	0.2
11	DMP[h]	EtOAc	77	90	2.4
12	DMP[i]	EtOAc	76	92	0.3

[a]DMSO = dimethyl sulfoxide, MTBE = methyl-*tert*-butyl ether, THF = tetrahydrofuran, DCM = dichloromethane, EtOAc = ethyl acetate, TEMPO = 2,2,6,6-tetramethylpiperidinyloxy, DMP = Dess−Martin periodinane, TBAB = tetra-*n*-butylammonium bromide, NaOCl = sodium hypochlorite, EDC·HCl = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride. [b]The reaction was carried out using 1.0 equiv of **6**, 5.0 equiv of EDC·HCl, and 10 equiv of trichloroacetic acid addition at 0 °C in DMSO:toluene (1:1) followed by maintenance at 25 °C for 15 h. [c]The reaction was carried out using 1.0 equiv of **6**, 1.0 equiv of TEMPO, equiv of NaOCl in MTBE, and water at 0 °C. [d]The reaction was carried out using 1.0 equiv of **6**, 1.0 equiv of TEMPO, and $KMnO_4$ in MTBE and water at 0 °C. [e]The reaction was carried out using 1.0 equiv of **6**, 2.2 equiv of oxone, 1 equiv of TEMPO, and 0.5 equiv of TBAB in MTBE and water at 0−5 °C. [f]The reaction was carried out using 1.0 equiv of **6**, 1.6 equiv of DMP, and 10 volume of solvent at 5−15 °C for 6 h. [g]The reaction was carried out using 1.0 equiv of **6**, 2.5 equiv of DMP, and EtOAc at 5−15 °C for 6 h. [h]The reaction was carried out using 1.0 equiv of **6**, 1.6 equiv of DMP, and EtOAc at 5−15 °C for 10 h. [i]The reaction was carried out using 1.0 equiv of **6**, 2.5 equiv of DMP, and EtOAc at 5−15 °C for 4 h.

extraction and crystallization methods were unsuccessful. Finally, we moved towards sodium bisulfite adduct formation of boceprevir by using saturated sodium bisulfite solution to achieve >99.4% purity with a single maximum unknown impurity less than 0.15%.

In our endeavour, with various screening and optimization techniques we were successful in telescoping the process and avoiding the isolation of intermediates in first two steps. In the telescoped process, after completion of the first step, the reaction was quenched by addition of water, and after layer separation, the toluene layer was carried forward to the hydrolysis step. After completion of hydrolysis, water was added, and the layers were separated. The aqueous layer was acidified to pH 1−2 with 5 N HCl and the desired compound extracted into ethyl acetate. The ethyl acetate layer was carried forward to the next coupling step without isolation. After completion of the third step, the reaction mixture was quenched by adding water, and the ethyl acetate layer was given acidic and basic washings. The ethyl acetate layer was distilled off up to 80% of its volume and charged to the cooled heptane solution to isolate the product **6** with 88% overall yield. The isolated product gave >98% purity by HPLC. The fourth oxidation step was carried out in ethyl acetate with DMP at 5−18 °C. After completion of the reaction, the reaction mass was filtered through Celite, and ethyl acetate layer was washed 3−4 times with water to remove inorganic salts. The ethyl acetate layer was treated with a saturated solution of sodium bisulfite, and the solution was stirred overnight at room temperature. The layers were separated, and the ethyl acetate layer was distilled under vacuum followed by addition of cyclohexane to precipitate out the boceprevir bisulfite adduct in 80% yield. The adduct was regenerated to boceprevir with >99.4% purity and 40% yield. In the total process the final purification step was challenging, and there is still scope to improve the yield.

The overall yield of the telescoped process of boceprevir was found to be 35% in comparison to the 23% yield obtained from the stepwise isolation process, and the details are summarized in Table 4.

Impurity Control Strategy. In the final oxidation process, we found that one of the major impurity was formed due to the over-oxidation of boceprevir **1** to α,β-unsaturated carbonyl compound **14** (Scheme 5). To control this impurity, we studied different equivalents of DMP and monitored the reaction

Table 4. Comparison of yield and cost of isolated and telescoped process

sr. no.	step no.	stepwise yield (%) in isolated process	stepwise yield (%) in telescoped process
1	1	90	
2	2	92	
3	3	90	88
4	4	70	
5	5	44	40
6	overall yield	23	35
7	cost (USD/kg)[a]	29984	21882

[a]Considering current exchange rates.

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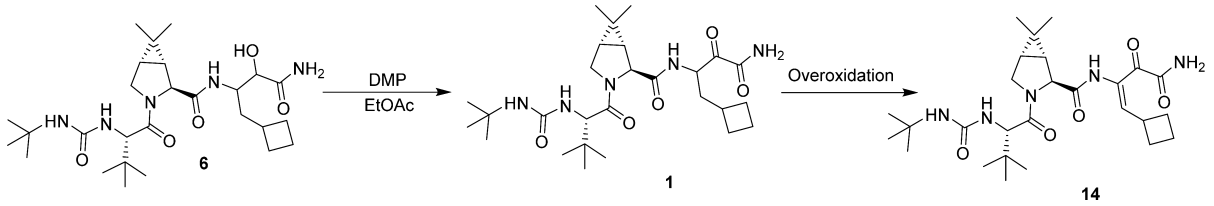
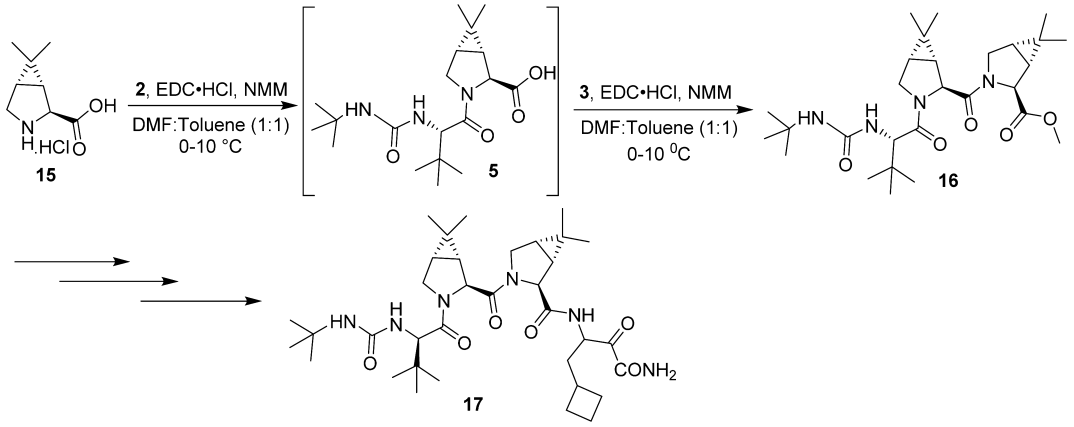
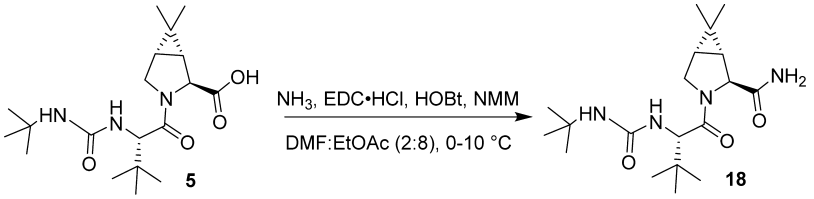
Scheme 5. Formation of impurity 14



Scheme 6. Formation of impurity 17



Scheme 7. Formation of impurity 18



progress over the period of time. We found that this impurity kept on increasing with the increase in the equivalents of DMP, longer reaction time, and higher temperature. This impurity was controlled by adding 1.6 equiv of reagent in three lots at equal intervals of 45 min at 5−10 °C and then maintaining the reaction at 12−18 °C for 3 h.

The impurity **17** had its origin in starting material **3** containing some acid **15** as an impurity formed by ester hydrolysis during storage. Acid **15** is coupled with **2** followed by coupling with **3** to form ester **16** (Scheme 6). This ester behaves similarly to the first step intermediate **13** of the boceprevir. Ester **16** reacts further in the subsequent stages to form the impurity **17** in the final stage. This impurity can be controlled by keeping tight specification of ester **3** and storing it under dry conditions. Alternatively, we have developed a crystallization process for the purification of **5** in ethyl acetate/MTBE to wash out this impurity.

The amide impurity **18** is formed during the coupling of acid **5** with **4** due to the presence of ammonia in **4** (Scheme 7). When we used **4** as such without purification, we found that the impurity **18** formed around 70%. We controlled this impurity below 0.1% by crystallization of **4** from methanol, keeping the level of ammonia below 0.05% in the specification for **4**. Further this impurity was removed during the bisulfite purification in the final stage.

Polymorphism. The isolated product was found to be amorphous.

CONCLUSION

We have developed an improved synthesis for (**2**) which was further used for the synthesis of boceprevir. Further we have also developed an industrially scalable process for the synthesis of boceprevir **1** by telescoping the process and avoiding industrially restricted solvents. The critical oxidation step was optimized by using Dess−Martin periodinane as an oxidizing reagent by adding the reagent in three lots. The overall yield of the telescoped process is increased from 23% to 35%.

EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}C spectra were measured in DMSO-d_6 using 400 MHz on Varian Gemini and Varian Mercury plus 2000 FT NMR spectrometers; the chemical shifts were reported in δ ppm. IR spectra were recorded in the solid state as a KBr dispersion using a PerkinElmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on HP 5989 A LC/MS spectrometer. The melting points were determined by using the capillary method on Polmon (model MP-96) melting point apparatus.

Synthesis of (*S*)-2-(3-(*tert*-Butyl)ureido)-3,3-dimethylbutanoic Acid 2. To a stirred solution of *tert*-butylamine (333 g, 4.50 mol, 1.2 equiv) in toluene (2.5 L) was slowly added CDI (736 g, 4.50 mol, 1.2 equiv) at 0−5 °C. The mixture was stirred at that temperature for 2−3 h to make the complex (X). In another RBF *tert*-leucine (500 g, 3.78 mol, 1.0 equiv) was

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added in water (5.0 L), and the solution was basified to pH 10−11 by adding 15% NaOH solution (~0.8 L). This solution was added to the complex (X) at 5−10 °C, and the temperature was slowly raised to 25−30 °C. The mixture was stirred at 25−30 °C for 10−12 h. Layers were separated, and the aqueous layer was washed with toluene. The aqueous layer was acidified with 5 N HCl solution (2.6 L) up to pH 1−2 at 0−10 °C and was stirred at 25−30 °C for 3−4 h. The solid was filtered on a Buchner funnel under vacuum and sucked dried for 2 h followed by dried 18 h in vacuum oven at 60 °C to get the acid **2** 700 g (82% yield) as a white solid with >99% HPLC purity. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.36 (br s, 1H), 5.95 (d, J = 10 Hz, 2H), 3.88 (d, J = 10 Hz, 1H), 1.80 (s, 9H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.2, 157.4, 60.7, 49.4, 34.0, 29.7, 27.0. MS (m/z): 231 [M + H]$^+$. Mp 185−192 °C.

Synthesis of Methyl (1*R*,2*S*,5*S*)-3-((*S*)-2-(3-(*tert*-Butyl)-ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate 13. To a stirred solution of (*S*)-2-(3-(*tert*-butyl)ureido)-3,3-dimethylbutanoic acid (**2**, 336 g, 1.46 mol, 1.0 equiv) and methyl (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**3**, 300 g, 1.46 mol, 1.0 equiv) in a 1:1 mixture of DMF and toluene (3.0 L) at 0−10 °C was added EDC·HCl (363 g, 1.89 mol, 1.3 equiv) and NMM (369 g, 3.64 mol, 2.5 equiv). The reaction mixture was stirred at 0−10 °C for 4−5 h and after completion of reaction (based on TLC), water (3.0 L) was added slowly at 0−10 °C. The layers were separated, and the organic layer was washed with 1 N HCl solution (1.5 L), 10% $NaHCO_3$ (1.5 L) solution, water (1.5 L), and brine (1.5 L). The organic layer distilled off under vacuum (670−700 mmHg) to get the title compound **13** 501 g (90% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.95 (s, 1H), 5.89 (d, J = 10 Hz, 1H), 4.19 (s, 1H), 4.15 (d, J = 10 Hz, 1H), 4.02 (d, J = 10.4 Hz, 1H), 3.75−3.77 (m, 1H), 3.64 (s, 3H), 1.50−1.52 (m, 1H), 1.39 (d, J = 7.64, 1H), 1.17 (s, 9H), 1.00 (s, 3H), 0.91 (s, 9H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.2, 173.7, 160.2, 61.2, 59.3, 53.2, 51.2, 36.3, 31.9, 30.4, 29.1, 30.1, 27.5, 27.4, 26.9, 21.0, 13.4. IR (KBr, cm^{-1}): 3392, 2959, 1754, 1641, 1618, 1530, 1435, 1198, 1178. MS (m/z): 382 [M + H]$^+$, 404 [M + Na]$^+$. Mp 158−162 °C.

Synthesis of (1*R*,2*S*,5*S*)-3-((*S*)-2-(*tert*-Butyl)ureido-3,3-dimethylbutanoyl-6,6-dimethyl-3-azabicylo[3.1.0]-hexane-2-carboxylic Acid 5. To a stirred solution of **13** (500 g, 1.31 mol, 1.0 equiv) in toluene (5.0 L) was added methanol (500 mL) and 47% sodium hydroxide solution (158 mL) at 0−10 °C. After addition the temperature was slowly raised to 25−30 °C, and the reaction mass was stirred at that temperature for 3−4 h. After completion of the reaction (based on TLC), water (2.5 L) was added to the reaction mixture, and layers were separated. The aqueous layer was acidified with 1 N HCl solution (2.5 L) to pH 2, and the product was extracted in ethyl acetate (2 × 2.5 L). The organic layer was concentrated under vacuum up to 80% and was added to a precooled solution of MTBE (2.5 L) at 5−10 °C. The mass was stirred at 5−10 °C for 2−3 h and was filtered under vacuum to get the compound **5** 449 g (92% yield) as a white solid with 99.8% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.95 (s, 1H), 5.88 (d, J = 10 Hz, 1H), 4.15 (d, J = 10 Hz, 1H), 4.10 (s, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.72−3.76 (m, 1H), 1.46−1.49 (m, 1H), 1.36−1.39 (m, 1H), 1.17 (s, 9H), 1.00 (s, 3H), 0.91 (s, 9H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1, 171.6, 157.7, 59.2, 57.0, 49.4, 47.4, 34.6, 30.3, 29.6, 27.3, 26.8, 26.3, 19.2, 12.8. IR (KBr, cm^{-1}): 3396, 2961, 1720, 1633, 1552, 1554, 1365, 1214, 1198. MS (m/z): 368 [M + H]$^+$, 390 [M + Na]$^+$. Mp 135−140 °C.

Synthesis of (1*R*,2*S*,5*S*)-*N*-(4-Amino-1-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((*S*)-2-(3-(*tert*-butyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicylo[3.1.0]-hexane-2-carboxamide 6. To a stirred solution of **5** (400 g, 1.08 mol, 1.0 equiv) and 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride (**4**, 250 g, 1.19 mol, 1.1 equiv) in a 8:2 mixture of EtOAc and DMF (4.0 L) at 0−10 °C was added EDC·HCl (250 g, 1.30 mol, 1.2 equiv), HOBt (30 g, 0.22 mol, 0.2 equiv), and NMM (275 g, 2.71 mol, 2.5 equiv). The reaction mixture was stirred at 0−10 °C for 5−6 h, and after completion of the reaction (based on TLC), water (3.0 L) was added at 0−10 °C. The layers were separated, and the organic layer was washed with 1 N HCl (2.0 L) solution followed by 10% $NaHCO_3$ solution (2.0 L). The organic layer was distilled under vacuum (670−700 mmHg) up to 80% and then slowly added to the cooled solution of heptane (2.4 L) at 0−10 °C. The precipitated solid was filtered under vacuum to get compound **6** 511 g (90% yield) as a white to off-white solid with >98.5% HPLC purity (2.3:1.2:1 dr). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14−7.60 (m, 3H), 5.84−5.96 (m, 2H), 5.35−5.60 (m, 1H), 3.83−4.23 (m, 4H), 3.74−3.80 (m, 2H), 2.25−2.39 (m,1H), 1.90−1.94 (m, 2H), 1.67−1.74 (m, 2H), 1.50−1.56 (m, 4H), 1.33−1.45 (m, 2H), 1.17−1.27 (m, 9H), 0.97−1.00 (m, 3H), 0.85−0.91 (m, 9H), 0.80−0.83 (m, 3H). IR (KBr, cm^{-1}): 3378, 2961, 1720, 1660, 1549, 11480, 1436, 1364, 1215. MS (m/z): 522 [M + H]$^+$, 544 [M + Na]$^+$. Mp 162−168 °C.

Telescoped Process for the Synthesis of (1*R*,2*S*,5*S*)-*N*-(4-Amino-1-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((*S*)-2-(3-(*tert*-butyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicylo[3.1.0]hexane-2-carboxamide 6. To a stirred solution of (*S*)-2-(3-(*tert*-butyl)ureido)-3,3-dimethylbutanoic acid (**2**, 223 g, 0.97 mol, 1.0 equiv) and methyl (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (**3**, 200 g, 0.97 mol, 1.0 equiv) in a 1:1 mixture of DMF and toluene (2.0 L) at 0−10 °C was added EDC·HCl (223 g, 1.16 mol, 1.2 eqiv) and NMM (246 g, 2.43 mol, 2.5 equiv). The reaction mixture was stirred at 0−10 °C for 4−5 h, and after completion of the reaction (based on TLC), water (3.0 L) was added slowly at 0−10 °C. The layers were separated, and to the organic layer was added methanol (0.40 L) and 47% NaOH solution (117 mL) at 0−10 °C. After addition the temperature was slowly raised to 25−30 °C, and the reaction mass was stirred for 3−4 h. After completion of the reaction (based on TLC), water (2.0 L) was added to the reaction mixture, and layers were separated. The aqueous layer was acidified with 1 N HCl solution (1.0 L) to pH 2, and product was extracted in ethyl acetate (2 × 1 L). To this ethyl acetate layer was added DMF (400 mL) and the reaction mixture cooled at 0−10 °C. To this was added EDC·HCl (223 g, 1.16 mol, 1.2 equiv), HOBt (26 g, 0.19 mol, 0.2 equiv), and NMM (246 g, 2.43 mol, 2.5 equiv) at 0−10 °C. The reaction mixture was stirred at 0−10 °C for 5−6 h, and after completion of the reaction (based on TLC), water (2.0 L) was added at 0−10 °C. The layers were separated, and the organic layer was washed with 1 N HCl (2.0 L) solution followed by 10% $NaHCO_3$ solution (2.0 L). The organic layer was distilled under vacuum up to 80% and then slowly added to the cooled solution of heptane (2.5 L) at 0−10 °C. The precipitated solid

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was filtered under vacuum to get compound **6** 446 g (88% yield) as a white to off-white solid with >98.5% HPLC purity (2.2:1.3:1 dr).

Synthesis of (1*R*,2*S*,5*S*)-*N*-(4-Amino-1-cyclobutyl-3,4-dioxobutan-2-yl)-3-((*S*)-2-(3-(*tert*-butyl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicylo[3.1.0]-hexane-2-carboxamide 7. To a stirred solution of **6** (200 g, 0.38 mol, 1.0 equiv) in ethyl acetate (2.0 L) was added Dess−Martin periodinane (DMP) (260 g, 0.61 mol, 1.6 equiv) in three lots at equal intervals of 45 min at 5−10 °C, and the reaction mass was stirred at 12−18 °C for 3 h. After the completion of the reaction (based on TLC), the reaction mass was filtered through a Celite bed under vacuum. The filtrate was washed with the water (2.0), and 40% sodium bisulfite solution (256 g sodium bisulfite in 640 mL water) was added to the organic layer. The solution was stirred at 25−30 °C for 12−15 h. The layers were separated, and the organic layer was concentrated under vacuum up to 80%, and cyclohexane (0.8 L) was added to this. The heterogeneous mass was stirred for 1 h at 25−30 °C, and the bisulfite adduct was filtered under vacuum. The bisulfite adduct was dissolved in water (0.5 L) and EtOAc (1.0 L) and cooled to 0−3 °C. The reaction mass was stirred at 0−3 °C for 10−15 min, and layers were separated. The aqueous layer was washed with ethyl acetate (0.5 L) at 0−3 °C. MTBE (1.0 L) was added to the aqueous layer, and the reaction mass was stirred at 25−30 °C for 2−3 h and the layers separated. The MTBE layer was concentrated under vacuum up to 80% and added to the precooled solution of heptane at 0−5 °C and stirred at that temperature for 30−45 min. The solid material was filtered under vacuum to get 80 g (40% yield) as a white solid with >99% purity (1.1:1 dr). ***Caution:*** *We completed all the DMP related operations at cooling conditions and did not have any accidents. It was reported that it could be explosive under impact or heating at >130* °C.[13] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−8.27 (m, 1H), 7.99 (m, 1H), 7.75 (m, 1H), 5.96 (s, 1H), 5.88 (m, 1H), 5.83−8.00−8.27 (m, 1H), 4.82−4.99 (m, 1H), 4.27 (d, 1H), 4.10−4.14 (m, 1H), 3.96−3.99 (m, 1H), 3.74−3.78 (m, 1H), 2.49−2.51 (m, 1H), 1.91−1.99 (m, 2H), 1.71−1.81 (m, 3H), 1.55−1.66 (m 3H), 1.41−1.45 (m, 2H), 1.26−1.29 (m, 9H), 0.90−1.19 (m, 3 H), 0.82−0.89 (m, 12 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.3, 197.3, 171.6, 171.4, 171.3, 171.2, 163.5, 163.3, 157.8, 157.8, 59.9, 59.6, 57.3, 52.6, 52.3, 49.4, 49.4, 47.9, 37.2, 37.1, 34.5, 32.6, 32.6, 31.1, 31.0, 29.6, 28.4, 28.2, 27.9, 27.5, 27.4, 27.3, 26.8. IR (KBr, cm^{-1}): 3383, 2961, 1665, 1547, 1436, 1214. MS (m/z): 520 $[M + H]^+$, 542 $[M + Na]^+$. Mp 118−125 °C.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, IR, mass spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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