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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00389 • Publication Date (Web): 28 Nov 2019

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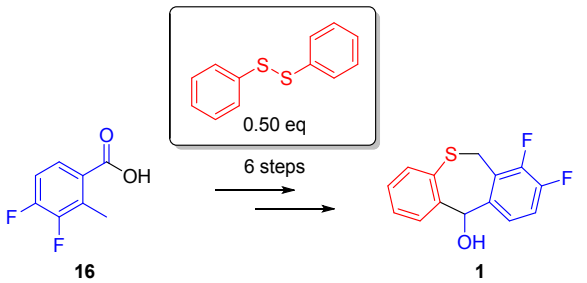


16 **1**

>98% purity by HPLC
up to 75% overall yield

ABSTRACT:

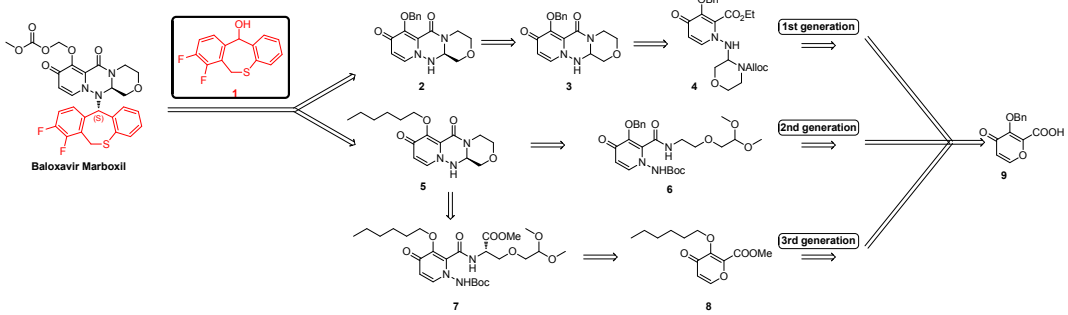
A novel 6-step synthesis of 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol (**1**) is described. Starting with 3,4-difloro-2-methylbenzoic acid and using diphenyl disulfide as an ideal sulfur source effectively solve the problems such as harsh reaction conditions, usage of smelly thiophenol, which might restrict the known process from pilot plant application. Large-scale applicability of this new route has been successfully demonstrated on kilogram-scale production to afford **1** with 98.04% purity in 75% overall yield. Meanwhile, the corresponding impurity profile was thus studied in detail and well documented.

Key words: Baloxavir marboxil; Diphenyl disulfide; Thiophenol; impurity profile; process

INTRODUCTION

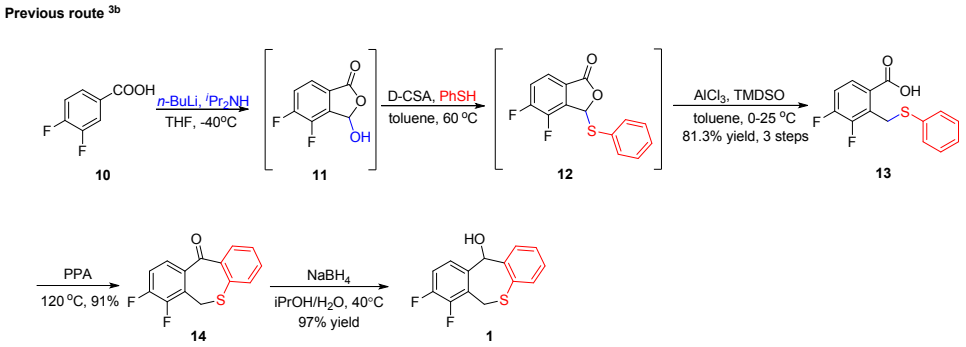
Baloxavir marboxil (Xofluza; baloxavir), which had been developed by Roche and Shionogi, was a small molecule cap-dependent endonuclease inhibitor and exhibited broad and potent antiviral activity against clinically isolated influenza A and B virus, including viruses harboring NAI-resistance mutation.[1] Baloxavir marboxil was first approved for the treatment of influenza A or B virus infections in Japan in February 2018,[1b] and then approved by the U.S. Food and Drug Administration (FDA) on October 24, 2018.[2]

Scheme 1. Three Synthetic Routes towards Baloxavir Marboxil (Xofluza)



Since the discovery of Baloxavir marboxil, three generations of synthetic route have been developed by Shionogi & CO., LTD to satisfy different needs during the drug development process.[3] As outlined in Scheme 1, these three approaches shared a similar retrosynthetic strategy of combining two major parts of the molecule, key intermediate **1** and the other motif **2** or **5**, by an S_N2 substitution reaction. Notably, an asymmetric directing group was introduced in the third generation route disclosed by Shionogi recently to improve overall yield and avoid cumbersome operations. Fragment **2** or **5** can both be prepared from compound **9** by intermolecular aminolysis or acetalization according to known methodologies. However, when refers to the production of **1** there has been relatively few reports by far.[3b,4]

Scheme 2. Previous Route to intermediate 1



In 2017, Shionogi[3b] developed an intramolecular Friedel-Crafts acylation process to construct intermediate **1** from 3,4-difluorbenzoic acid **10** (Scheme 2). The methylene phenyl sulfide part in the derivative was introduced from *N,N*-Dimethylformamide (DMF) and thiophenol in 3 steps**.** As an original route to acquire sufficient amount of **1** for follow-up research, the drawbacks were obvious. Large-scale synthesis of **1** was limited by ultra-low reaction temperature and usage of moisture-sensitive base lithium diisopropylamide (LDA). Besides, thiophenol was so smelly and air-sensitive that it was not suitable for scale-up procedure. Furthermore, when we repeated this reported procedure a defluorinated impurity **15** was detected and proved difficult to remove. Moreover，the corresponding impurity originated from **15** was found in the final active pharmaceutical ingredient (API) and therefore affect the product quality (Figure 1). Thus, it is still highly desirable to develop an efficient and readily scalable process for the synthesis of this key intermediate **1** with high purity which could meet the quality remand for Baloxavir marboxil .

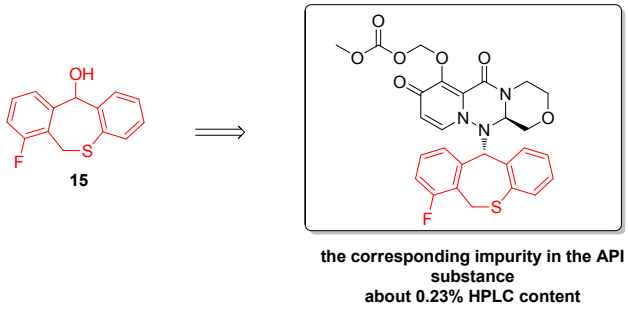
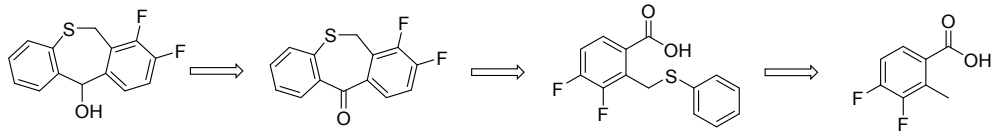


Figure 1. Key impurity 15 and the corresponding impurity in the final API

To overcome all the above disadvantages, we wished to develop a convenient and readily scalable

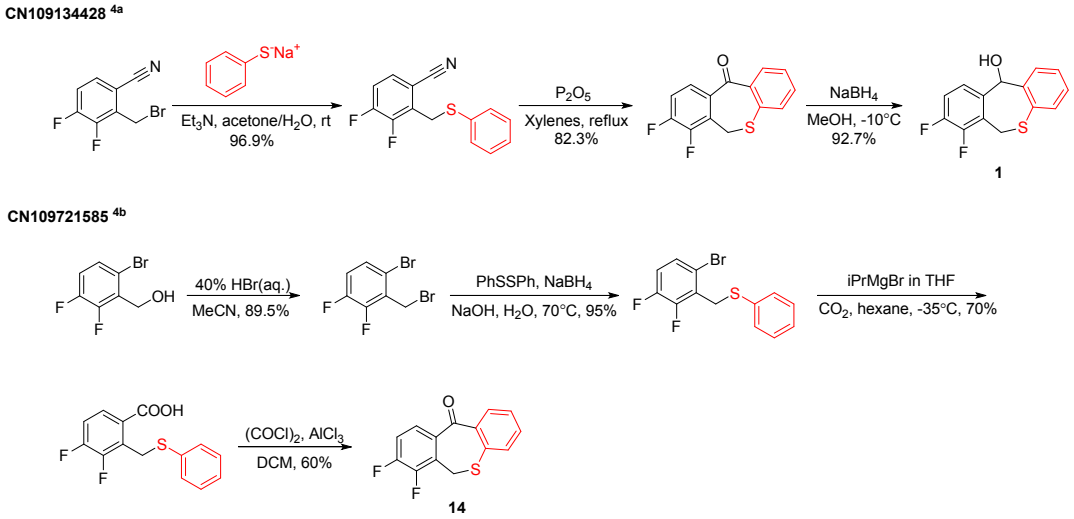
approach for the synthesis of **1** based on the retrosynthetic strategy depicted in Scheme 3. It was envisioned that with introduction of a methyl group in *ortho*-position to the carboxylic acid beforehand, alkylation under ultra-low temperature could be avoided. Then after bromination of the benzylic position, substitution by a thiol nucleophile would be implemented to afford a cyclization precursor. Another 2 steps were needed to complete the route after the intramolecular cyclization.

Scheme 3. Retrosynthetic Analysis of Baloxavir marboxil Key Intermediate 1



Following this line of retrosynthetic reasoning, we set out to develop this synthetic strategy. During our production for this procedure on kilogram-scale, some Chinese patents using similar strategies were disclosed earlier this year (Scheme 4).[4] However, whether these processes could be scaled up in batch mode was still suspicious due to commercial unavailability of starting materials 6-Cyano-2,3-difluorobenzyl bromide[4a] or (6-bromo-2,3-difluorophenyl)mechanol.[4b] Besides, carboxyl group introduction by reaction between Grignard reagent and CO_2 might not be easily manipulated and the yield was less than moderate.[4b] Moreover, no quality researches concerning impurities profiles were presented in the patents. Therefore, we still continued our ongoing work to seek an industrial solution which could meet the corresponding quality demand for the API substance.

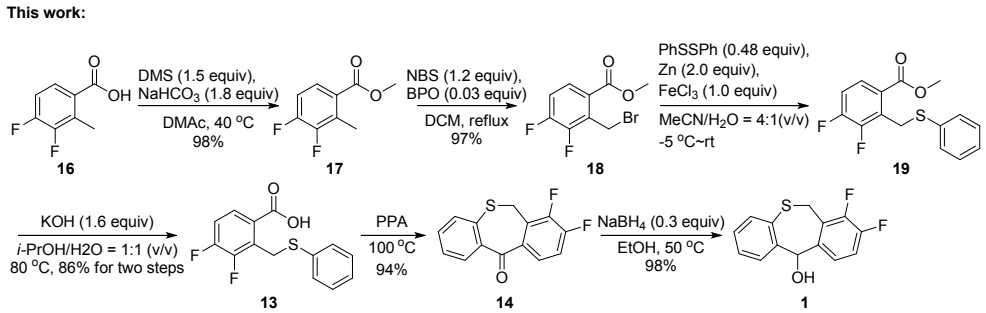
Scheme 4. Relative Chinese patents for intermediate 1 and intermediate 14



RESULTS AND DISCUSSION

Herein we report our readily scalable process for the synthesis of intermediate **1** (Scheme 5). Initial esterification with 3,4-difloro-2-methylbenzoic acid (**16**) and dimethyl sulfate (DMS) in dimethylacetamide (DMAc) gave compound **17** in nearly quantitative yield. Slow crystallization proved to be critical to remove the defluorinated impurity (<0.08% detected by HPLC). MeOH/$SOCl_2$ was also an alternative for methylation but led to an oily product, which had brought difficulties to the subsequent purification procedure.

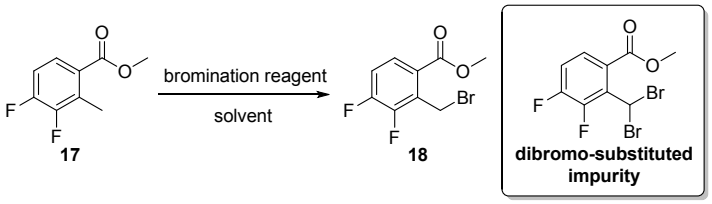
Scheme 5. New Synthetic Route to 1



CCl_4[5] was the best solvent for the following Wohl-Ziegler Reaction to furnish **18** due to its immiscibility with N-bromosuccinimide (NBS) and resulting succinimide, reaching a 97% yield in only 18 h (Table 1, entry 1). The poor solubility of NBS in CCl_4 successfully kept the concentration of the reagent low and the insolubility of byproduct succinimide also promoted the reaction. However, high

toxicity of CCl_4 made it unsuitable for industrial scale-up. In addition, other solvents such as acetonitrile (MeCN) and ethyl acetate, which could lead to an undesired dibromo-substituted byproduct, failed to provide product **18** in good yield or satisfying quality. Thus, it prompted us to choose dichloromethane (DCM) as the reaction solvent, with which **18** was obtained in 97% yield after 36 h (Table 1, entries 2-4). Other bromination reagent such as 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) led to an inferior result, same as an reduced reaction temperature to 40 ^oC (Table 1, entries 5-6). Therefore, benzylic bromination of **17** with NBS using dibenzoyl peroxide (BPO) as free-radical initiator in DCM at reflux was preferred as the optimal conditions. Together with esterification with DMS, both steps could be scaled up to multi-kilogram batch size.

Table 1. Effect of solvent, reagent, and temperature on bromination reaction [a]



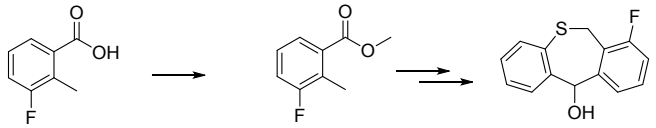
entry	solvent	bromination reagent	T (^oC) [b]	Yield of **18**[c](%)
1	CCl_4	NBS	80	97[d]
2	DCM	NBS	50	97
3	MeCN	NBS	80	58(24[e])
4	ethyl acetate	NBS	60	63
5	DCM	DBDMH	50	85
6	DCM	NBS	40	81

[a] reaction conditions: **17** (0.11 mol), reagent (1.2 equiv), and solvent (8.0 mL/g) , for 36 h; [b] reactor jacket temperature; [c] isolated yield; [d] for 24 h; [e] the content of dibromo-substituted impurity.

Additionally, during the investigation of this step the defluorinated impurity in **17** was considered material-related rather than process-related as 0.3% of 3-fluoro-2-methylbenzoic acid had been found in 3,4-difluoro-2-methylbenzoic acid **16**. After the optimization of the first step, the corresponding defluorinated impurity was easy to purge and remained only 0.08% determined by HPLC. Moreover,

no **15** could be detected in **1** followed by successive steps in the later studies (Scheme 6). Therefore, by controlling the amount of 3-fluoro-2-methylbenzoic acid in starting material 3,4-difluoro-2-methylbenzoic acid **16,** defluorinated impurity **15** can be well avoided in key intermediate **1**.

Scheme 6. The origin of impurity 15

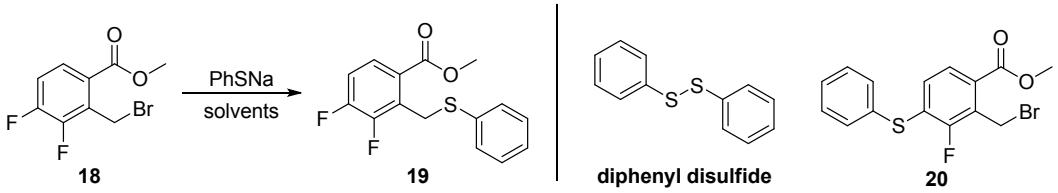


3-fluoro-2-methylbenzoic acid corresponding deflorinated impurity in **17** impurity **15**

For the subsequent step, it is known that most of the sulfur nucleophiles are not suitable for pilot plant production due to horrible smells. To solve this problem, we tried to choose a solid and non-volatile sulfur source as a nucleophile. We initially examined sodium thiophenolate for its strong nucleophility and alkalinity. However, it proved more challenging than anticipated as sodium thiophenolate turned out to have a poor solubility in organic solvents and was instable under reaction conditions with a possible mechanism shown in Scheme 7.[6] After 17 hours of reaction, only 39% of **18** was converted into product **19**, with a content of about 15% of hydrolysis product **13** and 10% of diphenyl disulfide. Significant efforts including usage of other solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), acetonitrile (MeCN), DCM and toluene were not able to provide acceptable results, nor were elevated temperature (50 ^{o}C) or increased dosage of the sodium thiophenolate (3.0 equiv). Although the reaction proceeded under nitrogen, the content of diphenyl disulfide still increased considerably while the reaction temperature was raised. Another impurity, methyl 2-(bromomethyl)-3-fluoro-4-(phenylthio)benzoate **20**, was also detected in reaction mixture (Scheme 7). In addition, excessive sodium thiophenolate would result in a large amount of smelly thiophenol after acidic work-up which might pass on to the crystallization of **13**. Thus, sodium

thiophenolate was not a good sulfur nucleophile for this reaction and had to be replaced.

Scheme 7. Impurities and possible formation mechanism of diphenyl disulfide in the thiol etherification reaction



Possible mechanism of diphenyl disulfide formation from sodium thiophenolate

$$2PhS^-Na^+ + O_2 \longrightarrow 2PhS\cdot + O_2^{2-} + 2Na^+$$

$$2PhS\cdot \longrightarrow PhSSPh$$

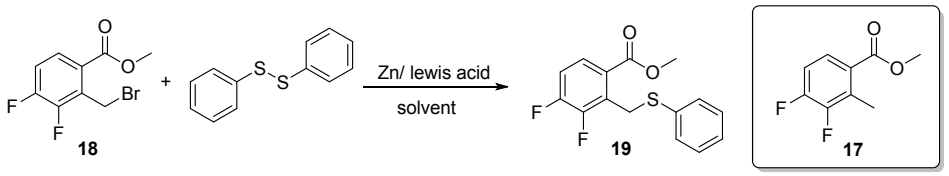
$$H_2O + O_2^{2-} + 2Na^+ \longrightarrow 2NaOH + 0.5O_2$$

All the mentioned difficulties led us to pursue an alternative method of preparing thiol ether **19**. In the original procedure, diphenyl disulfide was an undesired but intrinsic impurity possibly attributed to air oxidation. From another perspective, diphenyl disulfide is also an odorless solid sulfur-containing compound. Thus, we were interested in the possibility to utilize diphenyl disulfide as a sulfur source in the synthesis of intermediate **1** as several benefits could be envisioned. And to our delight, a research by S. Roy *et. al*[7] was later found to support this idea, which clearly described a new radical assisted synthesis to sulfides from disulfides via in-situ generated organocobalt(III) intermediates. Moreover, **18** might still be suitable for this reaction system.[8] Based on that, we set out to verify our proposal. To prove our concept (Table 2), **18** was treated with diphenyl disulfide in the presence of Lewis acid $AlCl_3$ together with zinc powder in DMF/H_2O. Gratifyingly, the reaction was clean and **19** was achieved successfully in 83% yield at 65 °C. Although the yield of **19** was not affected by lowering the loading of diphenyl disulfide to 0.5 equiv (Table 2, entries 1-3), different kinds of Lewis acid had a great influence on the conversion of **18**, among which $FeCl_3$ gave the best result (85% yield, Table 2, entries 4-8).

On the other hand, a drastic drop of yield to only 14% of **19** occurred when the Zn loading was

reduced to 1.5 equiv and no product was observed when lowered to 1.0 equiv (Table 2, entries 9-11). An abundant of zinc powder demonstrated to be necessary for good yields implying a potential different mechanism from Roy's methodology. Meanwhile, the yield decreased dramatically when the Lewis acid loading is reduced to less than 1 equivalent (Table 2, entries 12-13). A subsequent solvent screening indicated MeCN/H_2O as the optimal solvent system for this conversion, with a product yield of 91% (Table 2, entries 14-18). Besides, water played an important role in this process by showing only 46% yield of **19** and a content of **17** up to 38% when absent (Table 2, entry 18). We were also glad to find that by-product generation could be suppressed by decline of reaction temperature, with only 0.25% of **17** was detected while **19** was obtain in 91% yield under room temperature (Table 2, entry 19).

Table 2. Investigation of the optimized conditions for synthesizing 19[a]



entry	PhSSPh (equiv)	solvent[b]	Zn/ lewis acid (mol ratio)	T (°C)	Yield of **19**[c]:**17**[d] (%)
1	1.0	DMF/H_2O	$AlCl_3$ (2:1)	65	83:2.0
2	0.8	DMF/H_2O	$AlCl_3$ (2:1)	65	84:2.0
3	0.5	DMF/H_2O	$AlCl_3$ (2:1)	65	83:2.0
4	0.5	DMF/H_2O	$FeCl_3$ (2:1)	65	85:3.0
5	0.5	DMF/H_2O	$CuCl_2$ (2:1)	65	31:36
6	0.5	DMF/H_2O	$CoCl_2$ (2:1)	65	82:4.0
7	0.5	DMF/H_2O	$MgCl_2$ (2:1)	65	78:2.0
8	0.5	DMF/H_2O	$BF_3{\cdot}Et_2O$ (2:1)	65	80:3.0
9	0.5	DMF/H_2O	$FeCl_3$ (2.5:1)	65	84:2.0
10	0.5	DMF/H_2O	$FeCl_3$ (1.5:1)	65	14:3.0
11	0.5	DMF/H_2O	$FeCl_3$ (1:1)	65	N/A
12	0.5	DMF/H_2O	$FeCl_3$ (1.6:0.8)	65	62:2.0
13	0.5	DMF/H_2O	$FeCl_3$ (1.0:0.5)	65	45:3.0
14	0.5	THF/H_2O	$FeCl_3$ (2:1)	65	85:3.0
15	0.5	MeCN/H_2O	$FeCl_3$ (2:1)	65	91:2.0

16	0.5	toluene/H_2O	$FeCl_3$ (2:1)	65	30:2.0
17	0.5	MeOH/H_2O	$FeCl_3$ (2:1)	65	88:2.0
18	0.5	MeCN	$FeCl_3$ (2:1)	65	46:38
19	0.5	MeCN/H_2O	$FeCl_3$ (2:1)	rt	91:0.25
20	0.5	MeCN/H_2O	$FeCl_3$ (2:1)	40	90:1.0
21	0.5	MeCN/H_2O	$FeCl_3$ (2:1)	50	87:3.0
22	0.5	MeCN/H_2O	$FeCl_3$ (2:1)	80	81:4.0

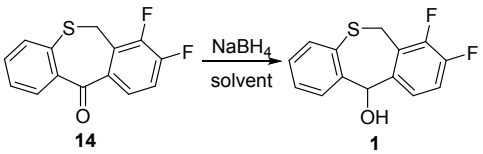
[a] reaction conditions: **18** (3.8 mmol), lewis acid (1.0 equiv), and solvent (10 mL/g) , for 3 h; [b] unless otherwise stated, all reactions were carried out using organic solvent : H_2O = 4 : 1 (v/v) as solvent; [c] isolated yield; [d] detected by HPLC.

Subsequently, an investigation on solvents of the saponification for crude product **19** to provide **13** was carried out (Step 4, Scheme 5). According to the experiment results, isopropyl alcohol was preferred over MeOH or EtOH. This might probably be attributed to Le Chatelier's principle as methanol is also produced during this hydrolysis process. Furthermore, higher temperature accelerated the reaction while iPrOH has a higher boiling point over MeOH. Although KOH was considered as the optimal base for this reaction, other bases such as K_2CO_3 and NaOH were acceptable while a reaction time of at least 18 hours was demanded to guarantee a complete conversion. Ultimately, acid **13** was achieved smoothly as a white solid, with an overall yield up to 85% over two steps from compound **18**.

Considering the disavantage of the high reaction temperature, different cyclization conditions from the reported ones by Shiongi [3b] were evaluated initially. Standard conditions using $SOCl_2/AlCl_3$/DCM as a Lewis acid system was supposed to be suitable for this following Friedel-Crafts acylation cyclization to afford **14**. However, contrary to our initial expectation, it failed with only a 35% conversion. Tremendous efforts had been made with the attempt to improve the yield of **14** under standard conditions by changing solvents into $ClCH_2CH_2Cl$, $PhNO_2$, $CHCl_3$ or CCl_4 at different temperatures including 50 °C, 60 °C and 70 °C. To our disappointment, only moderate yield (73%) was achieved in CCl_4 at 60 °C. The difficulty in this cyclization urged us to pursue an alternative sequence. Finally, when we came to a Brønsted acid system adopting neat polyphosphoric acid (PPA) as reaction

reagent which was the same as that proposed by Shiongi,[3b] a successful cyclization of compound **13** was furnished and the desired **14** was given in 94% yield. Lower reaction temperature, a simplified work-up procedure and a slightly higher yield were achieved through the improvements of this step compared to the original conditions.

Table 3. Optimization of reduction conditions[a]



14 **1**

entry	$NaBH_4$ (equiv)	solvent	Yield of **1** (%)[b]
1	1.0	MeOH	89
2	1.0	i-PrOH	97
3	1.0	EtOH	98
4	0.50	EtOH	97
5	0.30	EtOH	98
6	0.25	EtOH	76

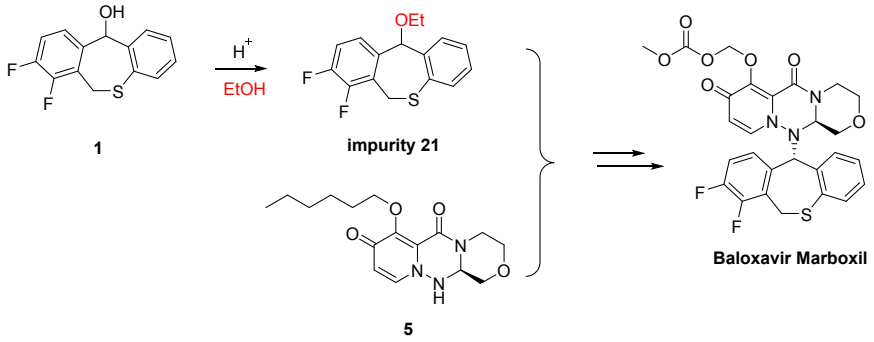
[a] reaction conditions: **14** (46 mmol), solvent (3 mL/g) , 50 °C , for 3 h; [b] isolated yield;

For the last step, compound **14** was reduced to form key intermediate **1** as presented in Table 3. EtOH was more favored over MeOH or iPrOH in terms of yields while MeOH was the least beneficial, partly due to a better solubility of product in methanol (Table 3, entries 1-3). When above 0.30 equiv, loading of $NaBH_4$ had no big influence on the reaction yield (Table 3, entries 3-5), whereas the yield slumped to 76% as the loading lowered to 0.25 equiv (Table 3, entry 6). This indicated that at least 0.25 equivalent of sodium borohydride was required for a clean and complete reaction. After an easy crystallization by simply adding water to the reaction mixture at 50 °C, product **1** was collected through a smooth filtration with high quality (>98% pure by HPLC). No sodium hydroxide was needed for the reaction compared to the original conditions.[3b]

For the optimization of the last step, ethyl ether impurity **21** was one of the major impurities that had been observed during acidic work-up of **1**, which was owe to an ether formation between hydroxyl

group of **1** and the solvent ethanol under treatment of aqueous hydrochloride. By quenching the reaction with water instead of aqueous hydrochloride, **21** was finally avoided. Even if trace **21** was found in intermediate **1,** it still had no effect on the quality of final API substance as the mentioned impurity could also react with **5** to deliver the same final product (Scheme 8).

Scheme 8. The formation and control strategy of impurity 21



Impurity control is an important part of drug development and regulatory assessment for efficiency and safety reasons. The impurity **15** and **21** were initially found critical for the quality of **1**, thus the formation and control strategies for these two were carefully studied and well documented during this process development. Based on that, **1** was well obtained from **16** via six steps with 98.04% purity in 75% overall yield. Moreover, the process has been successfully applied for multikilo-gram scale production showing reproducible and consistent results all along the development.

CONCLUSIONS

We have developed an effective and scalable process to synthesize key motif **1**, that avoids harsh reaction conditions by starting from 3,4-difloro-2-methylbenzoic acid and addresses smelly issue by using diphenyl disulfide as a stable sulfur source compared to the known process. This six-step procedure has been demonstrated in multikilo-gram scale production to afford **1** with 98.04% purity in 75% overall yield while the corresponding impurity file is thus studied in detail. It is expected to be designated as the manufacturing route in large quantities and therefore supports the kilogram-scale preparation of the baloxavir marboxil that meets drug substance standards for future research and commercialization.

EXPERIMENTAL SECTION

If no specially indicated, all reagents and solvents were used as commercially available without further purification. NMR spectra were measured on a BrukerAvance 400 spectrometer in the solvents indicated; chemical shifts are reported in units (ppm) by assigning TMS resonance in the 1H spectrum as 0.00ppm. Coupling constants are reported in Hz with multiplicities denoted as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. HRMS were performed on Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Analytical HPLC for liquid phase was carried out on an Agilent HPLC workstation, equipped with a Water Xbridge-C18 (4.6x 75mm, 2.5μm) column. Gradient elution from 65:35 to 20:80 (0.1% H_3PO_4 in water)/(acetonitrile) over 19 min, from 20:80 to 10:90 (0.1% H_3PO_4 in water)/(acetonitrile) over 1 min, hold for 4 min, then gradient from 10:90 to 65:35 over 4 min; flow rate 1.0 mL/min; temperature, 50 ^oC; wave length 216 nm.

Preparation of methyl 3,4-difluoro-2-methylbenzoate (17). To a stirred solution of 3,4-difluoro-2-methylbenzoic acid (2 kg, 11.6 mol) in *N,N*-dimethylacetamide (DMAc, 6L) was added

dimethyl sulfate (DMS, 2.2 kg, 17.4 mol) and $NaHCO_3$ (1.8 kg, 20.9 mol). The reaction mixture was stirred at 40 °C for 4 h. After fully conversion of the starting material, the reaction mixture was cooled to room temperature and H_2O (18L) was added dropwise over at least 3 hours. The white solid product was collected by filtration and dry under vacuum at room temperature to yield the titled compound (2.12 kg, 98% yield). HPLC purity: 99.86%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (ddd, *J* = 8.6, 5.2, 1.7 Hz, 1H), 7.04 (dd, *J* = 16.9, 8.8 Hz, 1H), 3.91 (s, 3H), 2.55 (d, *J* = 2.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.57 (d), 154.23 (d), 151.70 (d), 150.60 (d), 148.16 (d), 130.58 (d), 126.89 (dt), 113.99 (d), 52.22, 12.25 (dd). HRMS (ESI) calcd for $C_9H_9F_2O_2$ $[M+H]^+$ 187.0560, found 187.0565.

Preparation of methyl 2-(bromomethyl)-3,4-difluorobenzoate (18). To a solution of methyl 3,4-difluoro-2-methylbenzoate **17** (2 kg, 10.7 mol) in dichloromethane (DCM, 16 L) was added N-bromosuccinimide (NBS, 2.3 kg, 12.9 mol) and dibenzoyl peroxide (BPO, 78.1 g, 0.3 mol), the resulting mixture was stirred for about 36 h at 50 °C. After fully conversion of the starting material, the insoluble matters were removed by filtration and the organic layer was washed with 10% of Na_2SO_3 aqueous solution (1 L), then with water (1L). The organic layer was concentrated under vacuum (40 °C) to give 2.7 kg product as yellow oil, yield 97%. HPLC purity: 92.29%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 8.8, 5.0, 1.9 Hz, 1H), 7.19 (ddd, *J* = 13.5, 8.4, 6.3 Hz, 1H), 5.01 (d, *J* = 2.2 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.41 (d), 154.18 (d), 151.63 (d), 150.56 (d), 148.05 (d), 130.88 (m), 128.96, 127.90 (dd), 116.88 (d), 52.67, 21.06 (dd). HRMS (ESI) calcd for $C_9H_8BrF_2O_2$ $[M+H]^+$ 264.9615, found 264.9670.

Preparation of methyl 3,4-difluoro-2-((phenylthio)methyl)benzoate (19). In a 30 L reaction kettle, diphenyl disulfide (450 g, 2.06 mol), zinc powder (564 g, 8.63 mol) and MeCN-H_2O (12L, 4:1, v/v) were placed. The solution was cooled to -5 °C, then $FeCl_3$ (696 g, 4.3 mol) was added by portions over

1 h. After that, the reaction was allowed to reach room temperature and stirred for 3 h, and then methyl 2-(bromomethyl)-3,4-difluorobenzoate **18** (1.2 kg, 4.3 mol) was added. The reaction was stirred at room temperature until conversion was completed (about 8 h). The residue was removed by filtration, the filter cake was washed with ethyl acetate (500 mL×3), and the filtrate was concentrated under vacuum to give a crude product. The crude product was dissolved in the mixture of ethyl acetate-H_2O (12 L, 1:1, v/v). After stirring for 30 min, the aqueous phase was removed and the organic layer was washed with water (2L) before being concentrated. The product was used in the next step directly without further purification. HPLC purity: 84.35%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 8.8, 5.1, 1.9 Hz, 1H), 7.40-7.29 (m, 2H), 7.26-7.16 (m, 3H), 7.05 (td, *J* = 9.0, 7.8 Hz, 1H), 4.55 (d, *J* = 1.9 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.00 (d), 153.87 (d), 151.33 (d), 150.18 (d), 147.71 (d), 134.84, 132.55, 131.00 (d), 128.87, 127.61, 127.36 (dd), 126.31 (dd), 115.30 (d), 52.38, 29.89 (dt). HRMS (ESI) calcd for $C_{15}H_{13}F_2O_2S$ $[M+H]^+$ 295.0568, found 295.0599.

Preparation of 3,4-difluoro-2-((phenylthio)methyl)benzoic acid (13). Crude product of methyl 3,4-difluoro-2-((phenylthio)methyl)benzoate **19** was dissolved in a mixed solution of ^{i}PrOH-H_2O (10.05 L, 2:1, v/v), then KOH (383 g, 6.84 mol, dissolved in 3.35 L of H_2O) was added. The resulting solution was heated to 80 °C and stood for 8 h, then cooled to 50 °C. The solvent was removed under reduced pressure to give crude product as a gray solid. The crude product was dissolved in water (6.7 L), then the pH was adjusted to 1 with HCl (2 M) and stirred for another hour at 15 °C. After filtration a solid was observed and then suspended in *n*-hexane (6.7 L), stirred for 1 h, then filtered and dried to give pure product as a white solid (1.1 kg, 86% yield over two steps). HPLC purity: 97.37%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.80 (m, 1H), 7.35 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.30-7.20 (m, 3H), 7.12 (dd, *J* = 16.7, 8.7 Hz, 1H), 4.61 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.16, 154.72 (d), 152.16 (d), 150.38

(d), 147.91 (d), 134.60, 133.02, 132.22 (d), 129.05, 128.58 (dd), 127.96, 125.20-124.14 (m), 115.57 (d), 30.11 (d). NMR were in accordance with literature.[3b] HRMS (ESI) calcd for $C_{14}H_{11}F_2O_2S$ $[M+H]^+$ 281.0399, found 281.0442.

Preparation of 7,8-difluorodibenzo[b,e]thiepin-11(6H)-one (14). A mixture of 3,4-difluoro-2-((phenylthio)methyl)benzoic acid **13** (1.0 kg, 3.57 mol) and polyphosphoric acid (PPA, 4.8 kg) was heated to 100 °C. After 10 h, the reaction mixture was cooled to room temperature, and ice-water (10 kg) was added. The solid product was filtrated and was suspended in saturated $NaHCO_3$ solution (3 L), stirred for 8 h, then filtered and dried in vacuum to yield the titled compound as a gray solid (880 g, 94% yield). HPLC purity: 98.43%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.38 (dddd, *J* = 18.1, 9.1, 6.4, 1.5 Hz, 3H), 7.28 (ddd, *J* = 12.8, 7.1, 3.6 Hz, 1H), 7.12 (dt, *J* = 16.6, 8.3 Hz, 1H), 4.13 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.42 (d), 153.86 (d), 151.33 (d), 146.60 (d), 144.13 (d), 140.51 (s), 137.59 (d), 135.14, 133.10, 132.68, 129.41, 128.04 (d), 126.02, 125.78 (dd), 116.34 (d), 27.30 (dd). NMR were in accordance with literature.[3b] HRMS (ESI) calcd for $C_{14}H_9F_2OS$ $[M+H]^+$ 263.0350, found 263.0337.

Preparation of 7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-ol (1). Compound 7,8-difluorodibenzo[b,e]thiepin-11(6H)-one **14** (2.0 kg, 7.63 mol) was dissolved in EtOH (6 L) and $NaBH_4$ (87 g, 2.29 mol) was added by portions over 1 h at room temperature. The resulting solution was stirred for 4 h at 50 °C, then water (18 L) was added dropwise under this temperature. The reaction mixture was then cooled to 0 °C and stirred for a further hour, then filtered and dried to give pure product as a white solid (1.98 kg, 98% yield). HPLC purity: 98.04%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.35 (m, 1H), 7.21-7.06 (m, 4H), 6.99 (dd, *J* = 17.8, 8.4 Hz, 1H), 6.01 (s, 1H), 4.61 (d, *J* = 14.5 Hz, 1H), 4.14 (dd, *J* = 14.5, 0.7 Hz, 1H), 2.97 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.61 (d),

149.13 (d), 148.61 (d), 146.15 (d), 138.73, 137.74 (d), 133.40, 129.57, 128.53, 127.44, 126.16, 123.15 (d), 121.20 (dd), 115.69 (d), 74.60, 25.16 (dd). NMR were in accordance with literature.[3b] HRMS (ESI) calcd for $C_{14}H_{11}F_2OS$ $[M\text{-}OH]^+$ 247.0388, found 247.0372.

SUPPORTING INFORMATION

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^1H and ^{13}C NMR spectra for these compounds are given.

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ACKNOWLEDGMENT

This work was financially supported by the Anti-infective Drug National Key Laboratory Open Grant (No. SKLAID201805). We also gratefully acknowledge financial support from the Key Science & Technology Brainstorm Project of Dongguan (No. 2019622102009) and The Hunan Provincial Natural Science Foundation of China (No. 2017JJ2240). We gratefully thank Guozhu Liu (HEC Pharm Co., Inc.) for NMR assistance, and Meiyan Qiu(HEC Pharm Co., Inc.) for HPLC assistance.

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