Development of a manufacturing process toward the convergent synthesis of the COVID-19 antiviral Ensitrelvir

Takahiro Kawajiri[*†], Akihito Kijima[†], Atsuhiro Iimuro[‡], Eisaku Ohashi[†], Katsuya Yamakawa[†], Kazushi Agura[†], Kengo Masuda[‡], Kensuke Kouki[‡], Koji Kasamatsu[‡], Shuichi Yanagisawa[†], Sho Nakashima[†], Setsuya Shibahara[†], Takashi Toyota[†], Takafumi Higuchi[†], Takahiro Suto[‡], Tadashi Oohara[†], Toshikatsu Maki[†], Naoto Sahara[†], Nobuaki Fukui[†], Hisayuki Wakamori[†], Hidaka Ikemoto[†], Hiroaki Murakami[†], Hiroyasu Ando[†], Masahiro Hosoya[†], Mizuki Sato[†], Yusuke Suzuki[†], Yuta Nakagawa[†], Yuto Unoh[‡], Yoichi Hirano[†], Yoshitomo Nagasawa[†], Satoshi Goda[†], Takafumi Ohara[†], and Takayuki Tsuritani[†]*

[†]API R&D Laboratory, Research Division, Shionogi & Co., Ltd., 1-3, Kuise Terajima 2-Chome, Amagasaki, Hyogo 660-0813, Japan

[‡]Laboratory for Medicinal Chemistry Research, Research Division, Shionogi & Co., Ltd., 1-1, Futaba-cho 3-Chome, Toyonaka, Osaka 561-0825, Japan

KEYWORDS: Ensitrelvir, S-217622, SARS-CoV-2 antiviral, convergent strategy, scalable process

ABSTRACT: We describe the development of the practical manufacturing of Ensitrelvir, which was discovered as a SARS-CoV-2 antiviral candidate. Scalable synthetic methods of indazole,

1,2,4-triazole and 1,3,5-triazinone structures were established, and convergent couplings of these fragments enabled the development of a concise and efficient scale-up process to Ensitrelvir. In this process, introducing a *meta*-cresolyl moiety successfully enhanced the stability of intermediates. Compared to the initial route in the medicinal synthetic stage, the overall yield of the longest linear sequence (six steps) was improved by approximately 7-fold. Furthermore, nine out of the twelve isolated intermediates were crystallized directly from each reaction mixture without any extractive work-up (direct isolation). This led to an efficient and environmentally friendly manufacturing process that minimizes waste of organic solvents, reagents, and processing time. This practical process for manufacturing Ensitrelvir should contribute to protection against COVID-19.

INTRODUCTION: The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to threaten unfettered human activity around the world.[1)] COVID-19 has been recognized as one of the illnesses for which a cure is the most strongly desired in human history. Until now, two novel oral antiviral drugs, Molnupiravir[2-4)] (MK-4482 from Merck, formerly EIDD-2801 from Drug Innovations at Emory, LLC) and Nirmatrelvir[5)] (PF-07321332 from Pfizer), have been available and have helped reduce the risk of hospitalization or death.[6,7)] These breakthrough drugs based on small molecules can be supplied affordably, thus offering a remedy for a broad range of patients including those in developing countries.

Here we introduce another clinical candidate for treating COVID-19, Ensitrelvir (a non-proprietary name for S-217622, **1**, Figure 1), which was discovered through a collaboration research of Shionogi & Co., Ltd. and Hokkaido university, as the first nonpeptidic, noncovalent $3CL^{pro}$ inhibitor.[8)] **1** exhibited significant properties in terms of potent antiviral activity and high

bioavailability arising from a favorable drug metabolism and pharmacokinetic (DMPK) profile as a once-daily oral medicine to treat COVID-19. Therefore, unlike Nirmatrelvir, **1** can be used alone, without a pharmacokinetic booster like Ritonavir. Treatment using **1** will offer a therapeutic option not only for severe or high-risk patients but also low-risk patients without underlying disease and should help to curb the spread of COVID-19. Recently, the therapeutic value of **1** against Omicron variants of SARS-CoV-2 has also been reported.[9-11] Given the high demand for this medication, it is critical to develop a practical and sustainable manufacturing process of **1**.

Structurally, Ensitrelvir (**1**) consists of a central 1,3,5-triazinone core structure and three (hetero)aromatic components including a nitrogen atom rich 1,2,4-triazole and an indazole motif. As shown in Figure 1, the strategy of sequential introduction of the three (hetero)aromatic compounds into the 1,3,5-triazinone core is an efficient and rational approach. From the viewpoint of manufacturing scale, the shown convergent synthetic strategy[12,13] was also beneficial for reducing lead time for the supply of **1**. Namely, manufacturing time could be shortened by individual preparations of 1,3,5-triazinone, indazole, 1.2.4-triazole and 2,4,5-trifluorobenzene parts in parallel, followed by coupling of the fragments. The convergent approach was applied to the synthetic route, however, insufficient yield and the use of expensive compounds or cumbersome reagents were required in the medicinal chemistry synthetic stage, resulting in difficulty for large-scale synthesis (Scheme 1).

To overcome these problems, we established a practical and sustainable synthetic process of Ensitrelvir (**1**) by a convergent approach.

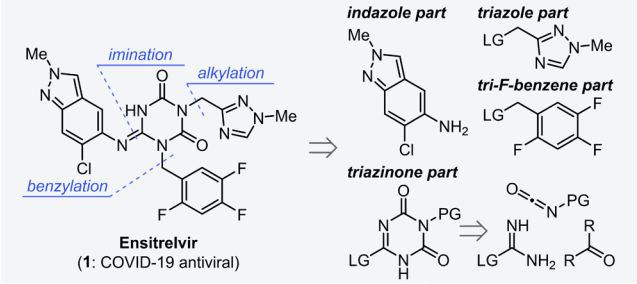
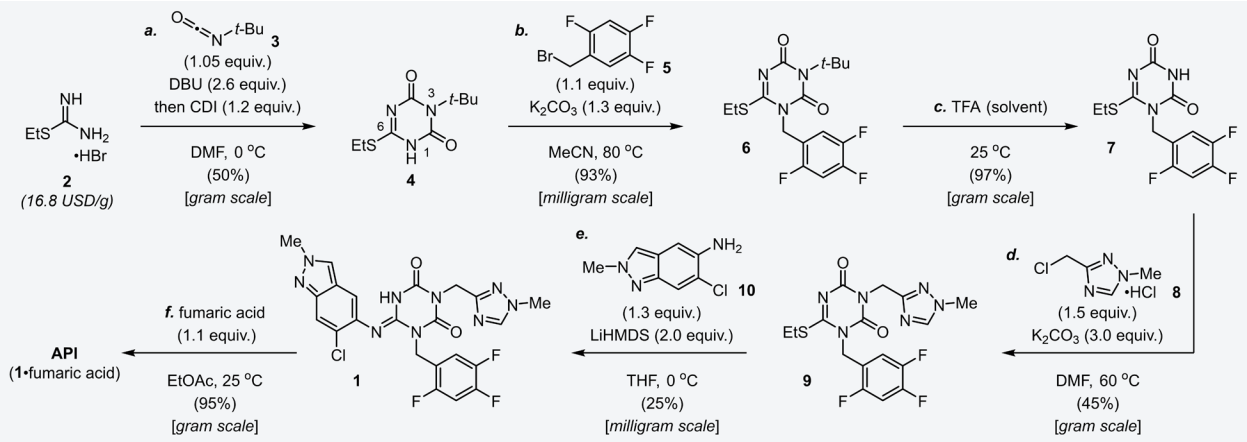


Figure 1. Chemical structure and synthetic strategy of Ensitrelvir (**1**). LG: leaving group, PG: protecting group.

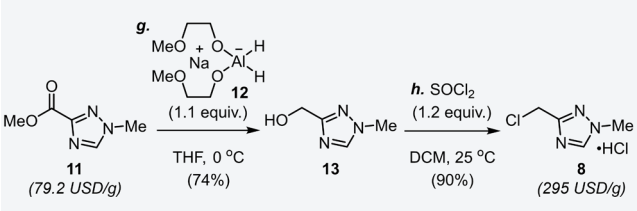
RESULTS AND DISCUSSION: **Outline of the synthetic route of Ensitrelvir in the medicinal stage**: In the medicinal stage, the convergent synthetic strategy of Ensitrelvir (**1**) was also conducted for a structure-activity relationship (SAR) study (Scheme 1).[8] According to the protocol reported previously,[14] 1,3,5-triazinone derivative (**4**) was constructed from a commercially available material (**2**) in one step (step a). 2,4,5-Trifluorobenzyl bromide (**5**) as the first aromatic fragment was introduced into **4** in the presence of potassium carbonate (K_2CO_3), and the *N*-benzylated compound (**6**) was obtained in high yield (step b). The *tert*-butyl group on the 3-position of compound **6** was removed in trifluoroacetic acid (TFA) as solvent to afford the corresponding compound (**7**, step c). Fragment coupling of **7** with 3-chloromethyl-1-methyl-1*H*-1,2,4-triazole (**8**) was performed under basic condition to provide **9** in moderate yield (45%, step d). Subsequentially, **9** was coupled with 2*H*-2-methyl-5-amino-6-chloro-indazole (**10**) and the target molecule **1** was obtained in 25% yield (step e). Finally, **1** was converted into a co-crystal form with fumaric acid to obtain an active pharmaceutical ingredient (step f). While the medicinal synthetic route was short and retrosynthetically reasonable, for sustainable manufacture of **1**, we needed to develop the process further. Specifically, the medicinal route gave an insufficient total yield for a steady supply of medications (4.8% from **2**). In addition, heteroaromatic compounds (**8**

and **10**) were expensive, and their suppliers were limited. Therefore, an efficient synthetic method for these compounds was required. Furthermore, there were issues blocking scale-up synthesis, such as the evaporation of corrosive acid (TFA, step c), the noxious odors generated from thiol derivatives (steps a and e), and purification by silica gel column chromatography (steps b, d, and e).



Scheme 1. Medicinal synthetic route to Ensitrelvir (**1**).

Preparation of the 1,2,4-triazole motif: To establish a refined manufacturing process, synthesis of 1,2,4-triazole derivative (**8**) was initially investigated (Scheme 2). Starting from a commercially available compound (**11**), reduction of the ester moiety was smoothly performed by sodium bis(2-methoxyethoxy)aluminum dihydride (**12**), which can be purchased as a toluene solution and does not have the hazardous pyrophoric nature like $LiAlH_4$.[15,16] Given the high solubility in water of the generated alcohol (**13**), an extractive process had to be avoided. Therefore, potassium sodium tartrate known as Rochelle salt was added directly into the reaction mixture to form a chelate complex with aluminum.[17] After removal of the aluminum residue by filtration, the crystals of **13** were directly isolated in 74% yield by switching to methyl *tert*-butyl ether (MTBE) as an antisolvent. Alcohol **13** was chlorinated immediately at room temperature using thionyl chloride ($SOCl_2$) to afford the desired **8** in high yield.[18]



Scheme 2. Manufacturing route to 1,2,4-triazole motif (**8**) *via* ester reduction and deoxychlorination.

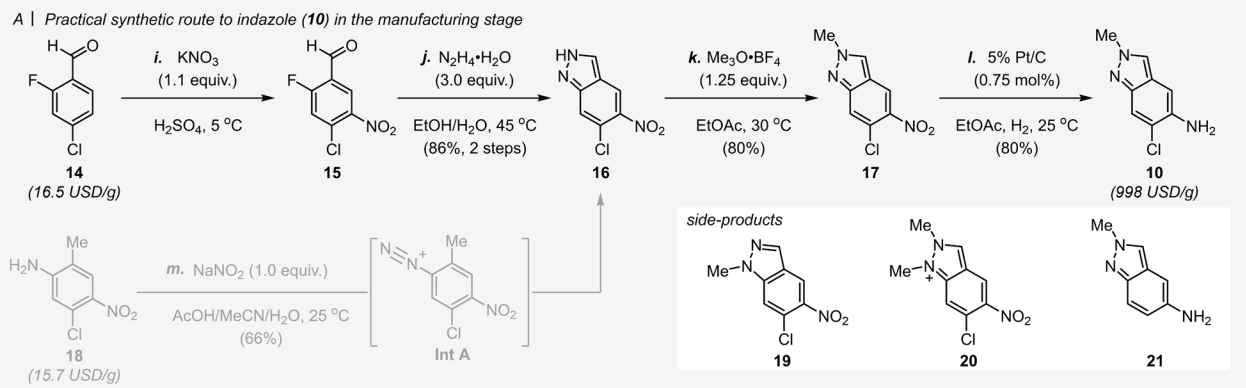
Preparation of the indazole motif: Indazoles as pharmacophores have a broad variety of biological utilities, which have encouraged the development of novel synthetic methodologies of indazole derivatives.[19-21] Several unique synthetic methods of indazoles have been reported, but most require harsh conditions and/or inaccessible starting compounds making it difficult to design scalable processes.[22-26] Therefore, a mild preparation of indazole needed to be optimized in anticipation of scale-up.

Our synthesis began with electrophilic aromatic nitration of inexpensive feedstock aromatic aldehyde (**14**) under classical but reliable conditions (Scheme 3A, step i).[27] Crystallization was directly conducted in the reaction mixture to afford the corresponding compound (**15**), which could be used in the next reaction without drying. With reference to the pioneering study,[25] cyclization of **15** was performed in the presence of hydrazine to form indazole motif (**16**) *via* formation of a hydrazone intermediate and a subsequent S_NAr reaction (step j). Through optimization of the reported protocol, we identified an excess amount of hydrazine as the important key to achieving mild conditions and **16** was directly obtained from EtOH/water co-solvent in 86% yield (from **14**, over two steps). While indazole **16** could be prepared from tetra-substituted benzene (**18**) *via* the diazonium compound (**Int A**) in one step (step m),[26] the former synthetic route from **14** was superior in terms of yield and feasibility of scale-up.

The proposed reaction mechanism in step j is shown in Scheme 3B. The aromatic aldehyde **15** reacted with hydrazine to afford the corresponding hydrazone (**22**). A reactive intermediate (**Int B**) was generated by substitution of the aryl fluoride **22** with another molecule of hydrazine, followed by the immediate cyclization of **Int B**. In the present step, excess hydrazine is expected to accelerate this S_NAr reaction. Indeed, when using 1.1 equiv. of hydrazine, high temperature (ca. 150 ^oC) was needed to proceed. Although impurity **23** was generated by the reaction with **15** and **22**, water as co-solvent enabled the equilibration between **22** and **23** to re-generate **22**. In addition, impurities **24** and **25** were formed *via* an intermediate (**Int C**). To support our proposed mechanism, all impurities **22**, **23**, **24**, and **25** were identified to control the quality of the final product.

With a scalable assembly method of indazole **16** in hand, the subsequent *N*-methylation was examined (Scheme 3C, top). Using trimethyloxonium tetrafluoroborate ($Me_3O\cdot BF_4$, known as Meerwein reagent) gave the best result compared with other methylation reagents, such as methyl iodide, dimethyl sulfate, dimethyl carbonate, and methyl 2,2,2-trichloroacetimidate.[28,29] The present reaction conditions using $Me_3O\cdot BF_4$ could suppress the generation of side-products (**19** and **20**) to an acceptable level. It has been reported that the regioselectivity between two nitrogen atoms on the indazole depends on the nature of the alkylating reagents.[30] As a matter of fact, a trend of low regioselectivity was observed under basic conditions, and the acidic reagents improved the regioselectivity. Because methylation of **16** in tetrahydrofuran (THF) caused a problem in stirring due to a sticky slurry, we chose ethyl acetate (EtOAc) as an optimal reaction solvent to afford **17** in sufficient isolated yield (80%). Next, the practical reduction conditions of the nitro group were explored (Scheme 3C, bottom).[31] Although Béchamp reduction using iron under acidic condition was a powerful tool for converting aromatic nitro compounds into the corresponding anilines,[32] iron-derived insoluble materials adhered to the reactor and were difficult

to remove. Reduction by $NaBH_4$ and catalytic $NiCl_2$ was unsafe due to the difficulty of controlling hydrogen gas and the exothermic reaction.[33] Various other conditions using $Na_2S_2O_4$, $HSiCl_3$, or palladium on carbon (Pd/C) under hydrogen atmosphere were investigated but resulted in insufficient conversion or failure to suppress the undesired de-chlorination (generation of **21**). Fortunately, the desired reduction proceeded in the presence of Pd/C catalyst and N_2H_4 as a hydrogen source to give the aniline derivative (**10**) in 71% isolated yield. After screening of the heterogeneous catalyst and hydrogen source, 0.75 mol% of platinum on carbon (Pt/C) was found to perform effectively under hydrogen atmosphere to reduce the nitro group selectively as a scalable process (80% isolated yield).[34] The scalability of this manufacturing process of **10** from **14** was demonstrated on the scale of several hundred kilograms.



step k

deviation from above	HPLC area% 16	17	19	20
MeI, K_2CO_3 in DMF	1	29	70	0
Me_2SO_4	42	48	2	8
Me_2CO_3, MsOH	96	3	0	0
methyl 2,2,2-trichloroacetimidate, TfOH in DCM	1	79	2	18
$Me_3O•BF_4$ in THF	3	75	3	19
none	3	76	<1	13

step l

deviation from above	HPLC area% 17	10	21
Fe powder, NH_4Cl, heat	1	66	4
$NiCl_2•6H_2O$, $NaBH_4$	0	81	0
$Na_2S_2O_4$, heat	100	0	0
$HSiCl_3$, DIPEA	0	46	0
cat. Pd/C, H_2	75	16	6
cat. Pd/C, $N_2H_4•H_2O$	1	87	12
none	1	91	3

Scheme 3. (A) Practical synthetic route to indazole motif (**10**) in the manufacturing stage. (B) Proposed reaction mechanism in step j. (C) Optimizations of steps k and l.

Manufacturing process of Ensitrelvir: Having established an efficient synthesis of 1,2,4-triazole derivative (**8**) and indazole derivative (**10**), we next turned to the synthesis of a 1,3,5-triazinone scaffold for the final convergent coupling. As described in Scheme 4A, our synthetic route of the 1,3,5-triazinone motif began with a multi-component reaction of 1-amidinopyrazole (**26**), *tert*-butyl isocyanate (**3**), and 1,1'-carbonyldiimidazole (CDI) in *N*,*N*-dimethylacetamide (DMA, step n).[14] To avoid the generation of the noxious sulfurous odor, the starting material *S*-ethylisothiourea (**2** in Scheme 1) used in the medicinal stage was replaced by **26**. Compared with **2** (16.8 USD/g, more than 60 suppliers), **26** was inexpensive and easily available (5.7 USD/g, more than 90 suppliers).[35] After the cyclization reaction of **26** with **3** and CDI, addition of 10% aqueous H_2SO_4 to the reaction mixture delivered the target 1,3,5-triazinone derivative (**27**) in 81% yield. For this neutralization, H_2SO_4 was better than HCl as a neutralizer because 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-HCl salt was insoluble in DMA/water solution and there was the possibility of contaminating the **27** crystals. Notably, it was found that the yield of **27** was improved by the fractional addition of DBU, i.e., two separate additions before and after the formation of the intermediate (**Int D**). This simple manipulation seems to minimize the decomposition of **3** caused by excess DBU to afford **Int D** with high conversion. *N*-Benzylation of **27** with 2,4,5-trifluorobenzyl bromide (**5**) proceeded smoothly using *N*,*N*-diisopropylethylamine (DIPEA) as a scalable organic base (step o). Direct isolation was also effective in step o, and the crystals of the desired molecule (**28**) could be obtained with high purity by simply adding water to the reaction medium.

Next, we investigated the removal of *tert*-butyl moiety at the 3-position of compound **28** enabling avoidance of the evaporation of corrosive acid, i.e., TFA. Unfortunately, only TFA (as solvent) could remove the *tert*-butyl group, with failure of the desired deprotection using alternative acids (methanesulfonic acid, H_2SO_4, HCl, and $BF_3 \cdot Et_2O$). With the above results, a scalable neutralization method was explored to remove TFA, however, the deprotected compound bearing a pyrazolyl moiety was unstable under neutralization conditions. Thus, an alternative substituent to the pyrazolyl moiety was required to enhance the stability of the intermediate toward hydrolysis. After detailed investigations, *meta*-cresol was strategically substituted at the pyrazolyl position. In other words, the deprotection at the 3-position and the protection of the 6-position were conducted simultaneously in the presence of *meta*-cresol in TFA to give the corresponding compound (**29**, step p). Interestingly, an excess amount of *meta*-cresol also played a role in capturing the *tert*-butyl cation derived from the deprotection, and unexpected side-reactions could be prevented.[36,37)]

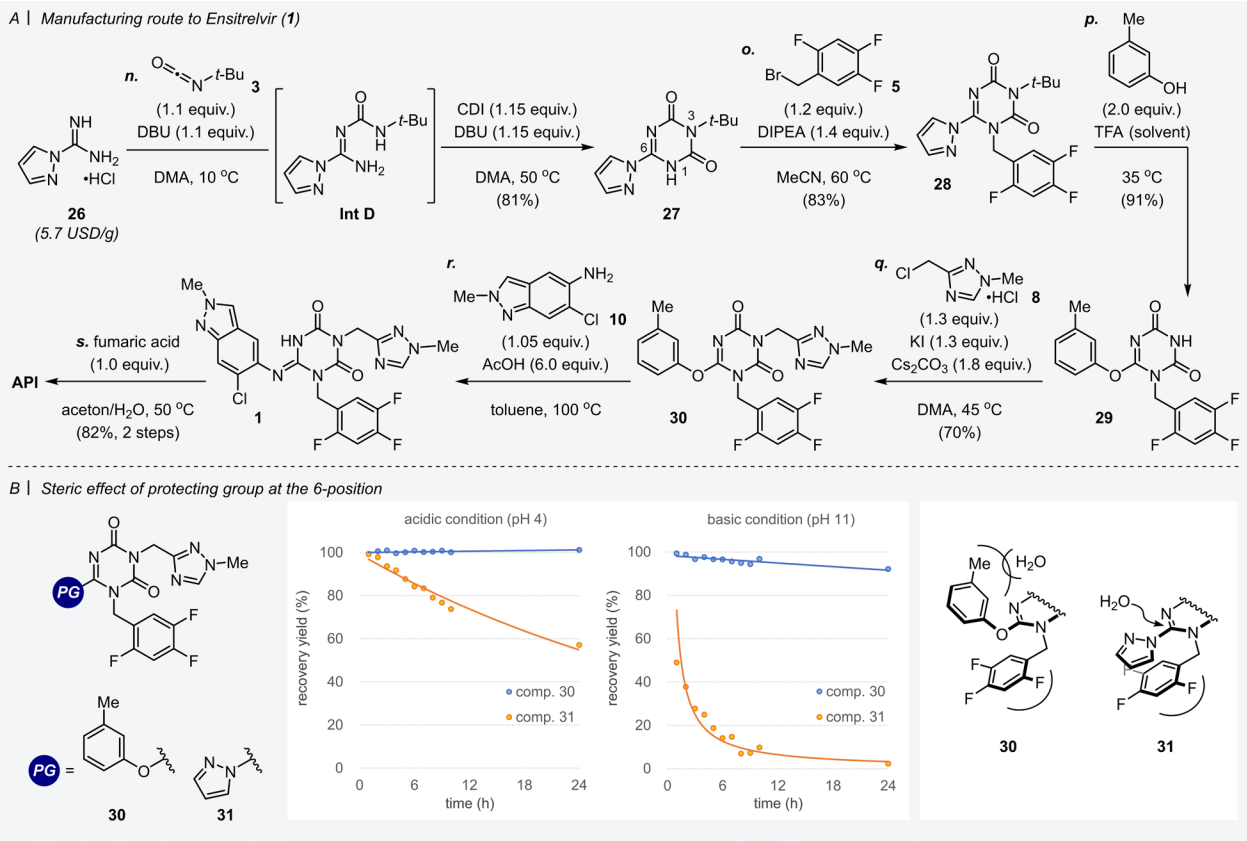
Since the target compound (**29**) had better stability, the appropriate work-up conditions for the removal of TFA were examined again. Aqueous sodium acetate (NaOAc) could neutralize TFA and target compound **29** was crystalized directly from the reaction medium without an extraction procedure. In this case, the decomposition of **29** was suppressed, but **29** was obtained as co-crystals with *meta*-cresol, which affected the next alkylation step. The neutralization using triethylamine (Et_3N) and subsequent extraction were unacceptable from the standpoint of loss of **29** during the extraction process. Neutralization by aqueous tripotassium phosphate (K_3PO_4) or trisodium citrate showed good performance without marked loss or decomposition of **29**. Finally, a practical work-up method was established by neutralization and extraction using aqueous sodium hydroxide

(NaOH), and subsequent crystallization from EtOAc/*n*-heptane. The present process without evaporation of TFA could facilitate equipment selection.

The strategy of introducing a *meta*-cresolyl moiety to improve hydrolysis resistance also had a pivotal impact on the next *N*-alkylation (step q). A preliminary stability test between the compounds bearing different substituents (**30** and **31**) revealed the significance of protecting groups at the 6-position (Scheme 4B). Namely, 1,3,5-triazinone bearing a *meta*-cresolyl moiety (**30**) was more stable than **31** under both weak acidic (pH 4) and basic (pH 11) conditions that mimicked step q (Scheme 4B, center). Differences in stability might be manifested by electronic effects and/or steric factors. In particular, steric hindrance of the *meta*-cresolyl moiety compared to the flat pyrazolyl moiety probably enhances the stability toward hydrolysis (Scheme 4B, right). In addition to the above results, using cesium carbonate (Cs_2CO_3) instead of K_2CO_3 improved the reproducibility of the reaction. Moreover, **30** could be crystallized directly from the reaction mixture to obtain 70% yield.

Installation of indazole **10** was the most important step affecting the quality of Ensitrelvir (**1**). Therefore, both high efficiency and robustness were required in the final step. The *meta*-cresolyl moiety also had the crucial role of a good leaving group in this step, and the targeted **1** was generated smoothly after heating in toluene with **10** in the presence of acetic acid (step r). When using other substrates bearing different leaving groups, such as ethylsulfanyl (**9**) or pyrazolyl (**31**) moieties instead of the *meta*-cresolyl moiety, the yield of **1** was insufficient and/or unapplicable reagents were required for scalable processes (see the supporting information). The present results indicated that the synthetic strategy using *meta*-cresol, which was irreplaceable not only as a protecting group but also as a leaving group, was essential. **1** was directly isolated from the reaction mixture after cooling and then used in the next step without drying. Crystallization of **1** with

fumaric acid in co-solvent (acetone and water) gave co-crystals of **1** with sufficient purity for pharmaceutical medicine (step s). This described process to **1** involving the preparation of **8** and **10**, showed good to excellent yield at each step, and was successfully applied to synthesis on the scale of several hundred kilograms. All the target compounds were isolated by crystallization, completely avoiding purification by column chromatography.



Scheme 4. (A) Manufacturing route to Ensitrelvir (**1**). (B) Steric effect of protecting group at the 6-position. Conditions of the stability test: To a mixture of **30** (or **31**) (10 mg), DMA (100 μL) and water (50 μL) was added acetic acid (2 μL, 1.5 equiv., acidic condition) or DIPEA (5 μL, 1.5 equiv., basic condition). After stirring for an adequate time at 25ºC, the recovery yield of **30** (or **31**) measured by HPLC was plotted.

CONCLUSION: We have developed a practical route to Ensitrelvir (**1**). The unprecedented strategy utilizing a *meta*-cresolyl moiety enhanced the stability of intermediate compounds and enabled scalable manufacturing of **1**. A six step longest linear sequence (from **26**) delivers the target molecule in 35.1% yield. This overall yield was improved by approximately 7-fold compared to the earlier process used in the medicinal stage (4.8%). Our convergent approach to the synthesis of **1** made the manufacturing process concise, streamlined, and short. Direct crystallization was achieved in nine out of the twelve steps, thus establishing a greener process without silica-gel chromatographic purification.[38] In addition, the present practical process settled all the issues that made large-scale synthesis difficult, i.e., removal of corrosive acid by evaporation and the generation of noxious odors from thiol derivatives. We believe the development of this practical process for manufacturing of **1** contributes to re-establishing the safety and security of society and address the COVID-19 pandemic.

ASSOCIATED CONTENT

Supporting Information. Spectrum charts are available free of charge *via* Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

*E-mail: takahiro.kawajiri@shionogi.co.jp

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): All authors were full-time employees of Shionogi & Co., Ltd. at the time when this study was performed.

ACKNOWLEDGMENT

We are grateful to Drs. Hasegawa, A. and Fukuda, T. for helpful discussion and their contribution to this research.

REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/ accessed Oct. 1st, 2022.

2. Wahl, A.; Gralinski, L. E.; Johnson, C. E.; Yao, W.; Kovarova, M.; Dinnon, K. H.; Liu, H.; Madden, V. J.; Krzystek, H. M.; De, C.; White, K. K.; Gully, K.; Schäfer, A.; Zaman, T.; Leist, S. R.; Grant, P. O.; Bluemling, G. R.; Kolykhalov, A. A.; Natchus, M. G.; Askin, F. B.; Painter, G.; Browne, E. P.; Jones, C. D.; Pickles, R. J.; Baric, R. S.; Garcia, J. V. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature* **2021**, *591*, 451–457.

3. McIntosh, J. A.; Benkovics, T.; Silverman, S. M.; Huffman, M. A.; Kong, J.; Maligres, P.; Itoh, T.; Yang, H.; Verma, D.; Pan, W.; Ho, H.; Vroom, J.; Knight, A. M.; Hurtak, J. A.; Klapars, A.; Fryszkowska, A.; Morris, W. J.; Strotman, N.; Murphy, G.; Maloney, K.; Fier, P. Engineered Ribosyl-1-Kinase Enables Concise Synthesis of Molnupiravir, an Antiviral for COVID-19. *ACS Cent. Sci.* **2021**, *7*, 1980–1985.

4. Fier, P. S.; Xu, Y.; Poirier, M.; Brito, G.; Zheng, M.; Bade, R.; Sirota, E.; Stone, K.; Tan, L.; Humphrey, G. R.; Chang, D.; Bothe, J.; Zhang, Y.; Bernardoni, F.; Castro, S.; Zompa, M. A.; Taylor, J.; Sirk, K. M.; Santana, A. D-.; Diribe, I.; Emerson, K. M.; Krishnamurthi, B.; Zhao, R.; Ward, M.; Xiao, C.; Ouyand, H.; Zhan, J.; Morris. W. J. Development of a Robust Manufacturing

Route for Molnupiravir, an Antiviral for the Treatment of COVID-19, *Org*. *Process Res*. *Dev*. **2021**, *25*, 2806–2815.

5. Owen, D. R.; Allerton, C. M. N.; Anderson, A. S.; Aschembrenner, L.; Avery, M.; Berritt, S.; Boras, B.; Cardin, R. D.; Carlo, A.; Coffman, K. J.; Dantonio, A.; Di, L.; Eng, H.; Ferre, R.; Gajiwala, K. S.; Gibson, S. A.; Greasley, S. E.; Hurst, B. L.; Kadar, E. P.; Kalgutkar, A. S.; Lee, J. C.; Lee, J.; Liu, W.; Mason, S. W.; Noell, S.; Noval, J. J.; Obach, R. S.; Ogilvie, K.; Patel, N. C.; Pettersson, M.; Rai, D. K.; Reese, M. R.; Sammons, M. F.; Sathish, J. G.; Singh, R. S. P.; Steppan, C. M.; Stewart, C. M.; Tuttle, J. B.; Updyke, L.; Verhoest, P. R.; Wei, L.; Yang, Q.; Zhu, Y. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science* **2021**, *374*, 1586–1593.

6. Bernal, A. J.; Silva, M.M.G.; Musungaie, D. B.; Kovalchuk, E.; Gonzalez, A.; Reyes, V. D.; Quirós, A. M-.; Caraco, Y.; Diaz, A. W-.; Brown, M. L.; Du, J.; Pedley, A.; Assaid, C.; Strizki, J.; Grobler, J. A.; Shamsuddin, H. H.; Tipping, R.; Wan, H.; Paschke, A.; Butterton, J. R.; Johnson, M. G.; Anda, C. D. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N*. *Engl*. *J*. *Med*. **2022**, *386*, 509–520.

7. Hammond, J.; Tebbe, H. L-.; Gardner, A.; Abreu, P.; Bao, W.; Wisemandle, W.; Baniecki, M.; Hendrick, V. M.; Damle, B.; Campos, A. S-.; Pypstra, R.; Rusnak, J. M. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N*. *Engl*. *J*. *Med*. **2022**, *386*, 1397–1408.

8. Unoh, Y.; Uehara, S.; Nakahara, K.; Nobori, H.; Yamatsu, Y.; Yamamoto, S.; Maruyama, Y.; Taoda, Y.; Kasamatsu, K.; Suto, T.; Kouki, K.; Nakahashi, A.; Kawashima, S.; Sanaki, T.; Toba, S.; Uemura, K.; Mizutare, T.; Ando, S.; Sasaki, M.; Orba, Y.; Sawa, H.; Sato, A.; Sato, T.; Kato, T.; Tachibana, Y. Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CLProtease Inhibitor Clinical Candidate for Treating COVID-19. *J*. *Med*. *Chem*. **2022**, *65*, 6499–6512.

9. Uraki, R.; Kiso, M.; Imai, M.; Yamayoshi, S.; Ito, M.; Fujisaki, S.; Takashita, E.; Ujie, M.; Furusawa, Y.; Yasuhara, A.; Horimoto, K. I-.; Tagawa, Y. S-.; Watanabe, S.; Hasegawa, H.; Kawaoka, Y. Therapeutic efficacy of monoclonal antibodies and antivirals against SARS-CoV-2 Omicron BA.1 in Syrian hamsters. *Nat*. *Microbiol*. **2022**, DOI: 10.1038/s41564-022-01170-4.

10. S-217622, a Therapeutic Drug for COVID-19, Shows High In Vitro Antiviral Activity Against Omicron Subvariants BA.4 And BA.5. Press Release from Shionogi & Co., Ltd., Jul. 14th, 2022.

11. Ensitrelvir Fumaric Acid (S-217622), a Therapeutic Drug for COVID-19, Shows High In Vitro Antiviral Activity Against Omicron Subvariants BA.2.75. Press Release from Shionogi & Co., Ltd., Aug. 10th, 2022.

12. Hansen, M. M.; Kallman, N. J.; Koenig, T. M.; Linder, R. J.; Richey, R. N.; Rizzo, J. R.; Ward, J. A.; Yu, H.; Zhang, T. Y.; Mitchell, D. Double Heck Route to a Dibenzoxepine and Convergent Suzuki Cross-Coupling Strategy for the Synthesis of an MR Antagonist. *Org*. *Process Res*. *Dev*. **2017**, *21*, 208–217.

13. Urabe, D.; Asaba, T.; Inoue, M. Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem*. *Rev*. **2015**, *115*, 9207–9231.

14. Kai, H.; Kameyama, T.; Horiguchi, T.; Asahi, K.; Endoh, T.; Fujii, Y.; Shintani, T.; Nakamura, K.; Matsumoto, S.; Hasegawa, T.; Oohara, M.; Tada, Y.; Maki, T.; Iida, A. Preparation of Triazine Derivatives and Pharmaceutical Compound that Contains Same and Exhibits Analgesic Activity. WO 2012020749 A1, Feb. 16th, 2012.

15. Bazant, V.; Capka. M.; Cerny, M.; Chvalovsky, V.; Koehloefl, K.; Kraus, M.; Malek, J. Properties of Sodium-bis-(2-methoxyehyoxy) Alminiumhydride. I. Reduction of Some Organic Functional Groups. *Tetrahedron Lett*. **1968**, *29*, 3303–3306.

16. Gugelchuk, M.; Silva III, L. F.; Vasconcelos, R. S.; Quintiliano, S. A. P. Sodium Bis(2-methoxyethoxy)aluminum Hydride. *e-EROS*, **2007**, DOI: 10.1002/9780470842898.rs049.pub2.

17. Burgstahler, A. W.; Nordin I. C. Stereospecific Angular Alkylation. A New Application of the Claisen Rearrangement[1]. *J. Am. Chem. Soc*. **1961**, *83*, 198–206.

18. Harit, T.; Bellaouchi, R.; Rokni, Y.; Riahi, A.; Malek, F.; Asehraou, A. Synthesis, Characterization, Antimicrobial Activity, and Docking Studies of New Triazolic Tripodal Ligands. *Chem. Biodiversity* **2017**, *14*, e1700351.

19. Schmidt, A.; Beutler, A.; Snovydovych, B. Recent Advances in the Chemistry of Indazoles. *Eur. J. Org. Chem*. **2008**, *24*, 4073–4095.

20. Kusakabe, K.; Ide, N.; Daigo, Y.; Tachibana, Y.; Itoh, T.; Yamamoto, T.; Hashizume, H.; Hato, Y.; Higashino, K.; Okano, Y.; Sato, Y.; Inoue, M.; Iguchi, M.; Kanazawa, T.; Ishioka, Y.; Dohi, K.; Kido, Y.; Sakamoto, S.; Yasuo, K.; Maeda, M.; Higaki, M.; Ueda, K.; Yoshizawa, H.; Baba, Y.; Shiota, T.; Murai, H.; Nakamura, Y. Indazole-Based Potent and Cell-Active Mps1 Kinase Inhibitors: Rational Design from Pan-Kinase Inhibitor Anthrapyrazolone (SP600125). *J. Med. Chem*. **2013**, *56*, 4343–4356.

21. Tandon, N.; Luxami, V.; Kant, D.; Tandon, R.; Paul, K. Current Progress, Challenges and Future Prospects of Indazoles as Protein Kinase Inhibitors for the Treatment of Cancer. *RSC Adv*. **2021**, *22*, 25228–25257.

22. Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radosevich, A. T. A Biphilic Phosphetane Catalyzes N-N Bond-Forming Cadogan Heterocyclization *via* P^{III}/P^{V}=O Redox Cycling. *J. Am. Chem. Soc*. **2017**, *139*, 6839–6842.

23. Kumar, M. R.; Park, A.; Park, N.; Lee, S. Consecutive Condensation, C-N and N-N Bond Formations: A Copper- Catalyzed One-Pot Three-Component Synthesis of 2*H*-Indazole. *Org*. *Lett*. **2011**, *13*, 3542–3545.

24. Lu, Y.; Cole, K. P.; Fennell, J. W.; Maloney, T. D.; Mitchell, D.; Subbiah, R.; Ramadas, B. An alternative indazole synthesis for merestinib. *Org*. *Process Res*. *Dev*. **2018**, *22*, 409–419.

25. Lukin, K.; Hsu, M. C.;Fernando, D.; Leanna, M. R. New Practical Synthesis of Indazoles *via* Condensation of *o*-Fluorobenzaldehydes and Their *O*-Methyloximes with Hydrazine. *J. Org*. *Chem*. **2006**, 71, 8166–8172.

26. Souers A. J.; Gao, J.; Wodka, D.; Judd, A. S.; Mulhern, M. M.; Napier, J. J.; Brune, M. E.; Bush, E. N.; Brodjian, S. J.; Dayton, B. D.; Shapiro, R.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. Synthesis and evaluation of urea-based indazoles as melanin-concentrating hormone receptor 1 antagonists for the treatment of obesity. *Bioorg*. *Med*. *Chem*. *Lett*. **2005**, *15*, 2752–2757.

27. Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration Methods and Mechanisms*; VCH: New York, **1989**.

28. Cheung, M.; Boloor, A.; Stafford, J. A. Efficient and Regioselective Synthesis of 2-Alkyl-2*H*-indazoles. *J. Org*. *Chem*. **2003**, *68*, 4093–4095.

29. Clemens, J.; Bell, E. L.; Londregan, A. T. Selective N2-Alkylation of 1*H*-Indazoles and 1*H*-Azaindazoles. *Synthesis* **2022**, *54*, 3215–3226.

30. Baddama, S. R.; Kumara, N. U.; Reddy, A. P.; Bandichhor, R. Regioselective methylation of indazoles using methyl 2,2,2-trichloromethylacetimidate. *Tetrahedron Lett.* **2013**, *54*, 1661–1663.

31. Orlandi, M.; Brenna, D.; Harms, R.; Jost, S.; Benaglia, M. Recent Developments in the Reduction of Aromatic and Aliphatic Nitro Compounds to Amines. *Org*. *Process Res*. *Dev*. **2018**, *22*, 430–445.

32. Béchamp, A. J. De l'action des protosels de fer sur la nitronaphtaline et la nitrobenzine. nouvelle methode de formation des bases organiques artificielles de Zinin. *Ann. de Chimie et de Physique* **1854**, *42*, 186–196.

33. Ganem, B.; Osby, J. O. Synthetically useful reactions with metal boride and aluminide catalysts. *Chem*. *Rev*. **1986**, *86*, 763–780.

34. Hoogenraad, M.; van der Linden, J. B.; Smith, A. A.; Hughes, B.; Derrick, A. M.; Harris, L. J.; Higginson, P. D.; Pettman, A. J. Accelerated Process Development of Pharmaceuticals: Selective Catalytic Hydrogenations of Nitro Compounds. *Org*. *Process*. *Res*. *Dev*. **2004**, *8*, 469–476.

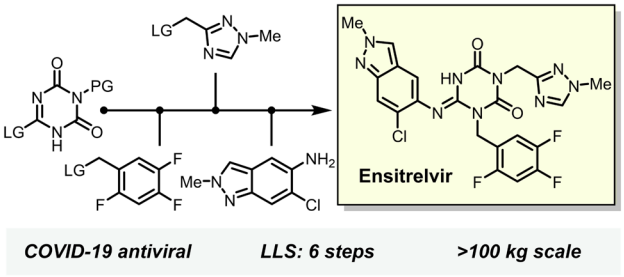
35. SciFinder^{n}, https://scifinder-n.cas.org/ accessed Oct. 1st, 2022.

36. Okano, K.; Okuyama, K.-i.; Fukuyama, T.; Tokuyama, H. Mild Debenzylation of Aryl Benzyl Ether with BCl_3 in the Presence of Pentamethylbenzene as a Non-Lewis-Basic Cation Scavenger. *Synlett* **2008**, 1977–1980.

37. Samacá, J.; Bautista, E. V-.; Tabares, L.; Escamilla, L.; Vanegas, M.; Patarroyo, M. -E. *p*-Methoxyphenol: A potent and effective scavenger for solid-phase peptide synthesis. *J. Pep*. *Sci*. **2020**, *26*, e3251.

38. Anderson, N. G. Assessing the Benefits of Direct Isolation Processes. *Org*. *Process Res*. *Dev*. **2004**, *8*, 260–265.

TABLE OF CONTENTS



SYNOPSIS: Ensitrelvir is a COVID-19 antiviral candidate with $3CL^{pro}$ inhibitory activity. Here we describe a practical synthetic process for Ensitrelvir by a convergent approach.