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Asymmetric Synthesis of Letermovir Using a Novel Phase-Transfer-Catalyzed Aza-Michael Reaction

Guy R. Humphrey,* Stephen M. Dalby,* Teresa Andreani, Bangping Xiang, Michael R. Luzung,† Zhiguo Jake Song, Michael Shevlin, Melodie Christensen, Kevin M. Belyk, and David M. Tschaen

Department of Process Chemistry, Merck and Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: The development of a concise asymmetric synthesis of the antiviral development candidate letermovir is reported, proceeding in >60% yield over a total of seven steps from commercially available materials. Key to the effectiveness of this process is a novel cinchonidine-based PTC-catalyzed aza-Michael reaction to configure the single stereocenter.

Despite advances in modern antiviral treatment, human cytomegalovirus (HCMV) remains associated with serious morbidity and mortality in immunocompromised patients, particularly those with advanced HIV and those undergoing organ transplant, up to 75% of whom experience HCMV infection or reactivation without appropriate antiviral treatment.[1] Existing therapies almost universally target DNA polymerase and thus suffer from severe toxicity and increasingly prevalent drug resistance.[2] Novel therapeutic agents are therefore urgently sought-after, combining efficacy with a unique mode of action to circumvent cross-resistance with available HCMV agents.

Letermovir (**1**, Figure 1) shows great promise in this respect for the next-generation treatment of HCMV infection.[3] Endowed with potent anti-HCMV activity (cell culture EC_{50} = ca. 5 nM) with no observed dose-dependent toxicity, it functions uniquely through inhibition of the DNA terminase, via a mechanism distinct from other compounds targeting this enzyme complex.[3,4] Letermovir was granted both fast track and orphan drug status in 2011 and has since progressed to PhIII clinical trials. Herein we describe the first enantioselective synthesis of letermovir to support ongoing clinical trials and ultimately a manufacturing process.

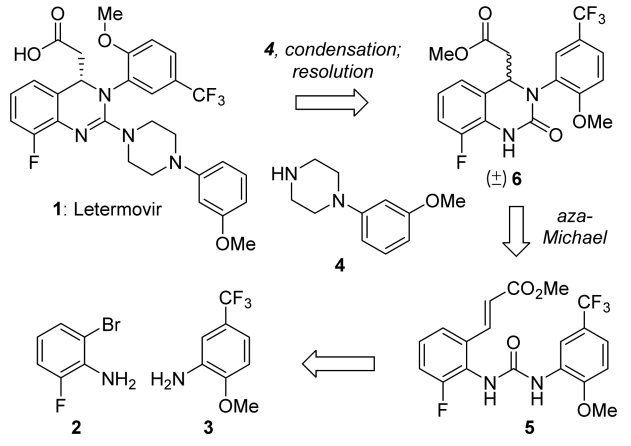
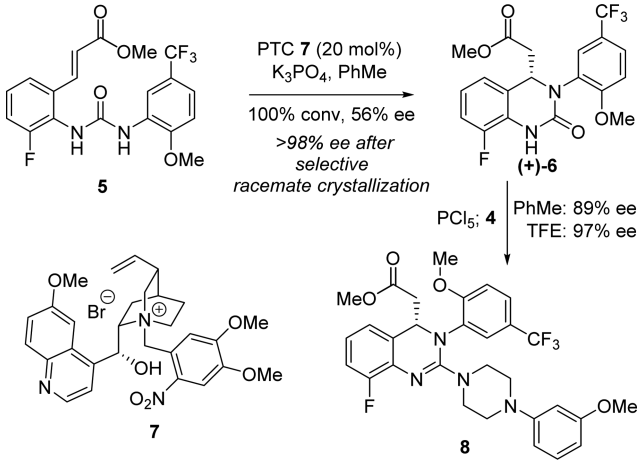


Figure 1. Retrosynthetic analysis of letermovir (**1**).

From a structural perspective, letermovir presents a fluorinated dihydroquinazoline core functionalized with a piperazine and a trifluoromethylanisole together with a stereogenic C4-acetate. Retrosynthetically, this structure is most straightforwardly distilled down to the commercially accessible building blocks **2**, **3**, and **4**, which may be assembled to generate the central dihydroquinazoline ring (Figure 1). This had previously been established, whereby base-mediated cyclization of urea **5** provided racemic dihydroquinazolinone **6**, which was then condensed with piperazine **4** and subject to a classical resolution to provide enantioenriched material.[3a,c] While this proved sufficient for initial supplies of letermovir, in view of its racemic mode and significant raw material costs, we sought to define a more efficient and cost-effective route, appropriate for more sustainable long-term supply.

Central to this effort would be the development and implementation of an asymmetric method to define the C4-acetate stereocenter. Initial work focused on catalysis of the urea cyclization reaction, and some success was realized utilizing cinchona alkaloid-based phase transfer catalysis (PTC, Scheme 1).[5−7] Treatment of urea **5** in a biphasic

Scheme 1. PTC Aza-Michael Cyclization of Urea 5



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mixture of toluene and aqueous K_3PO_4 with 20 mol % PTC **7** led to the smooth formation of quinazolinone **6** with moderate levels of stereoinduction (56% ee). Further screening failed to elevate the enantioselectivity, however, and although selective crystallization of the residual racemate did enable the isolation of highly enantioenriched material (>98% ee), epimerization of the newly formed stereocenter was observed in the subsequent Vilsmeier-type condensation with piperazine **4**. While this could be alleviated by the use of TFE as solvent,[8] the need for a more fundamentally revised approach was evident.

Among the range of potential approaches considered, those targeting catalytic asymmetric cyclization of guanidine substrates (which might thus circumvent epimerization during piperazine condensation) were deemed most attractive. As shown in Figure 2, the principal approaches explored involved

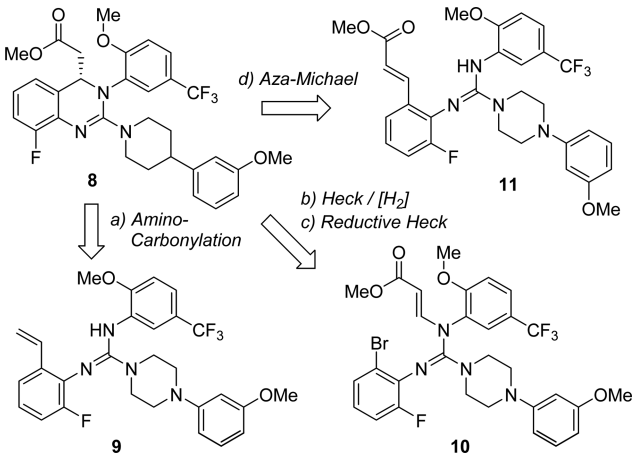


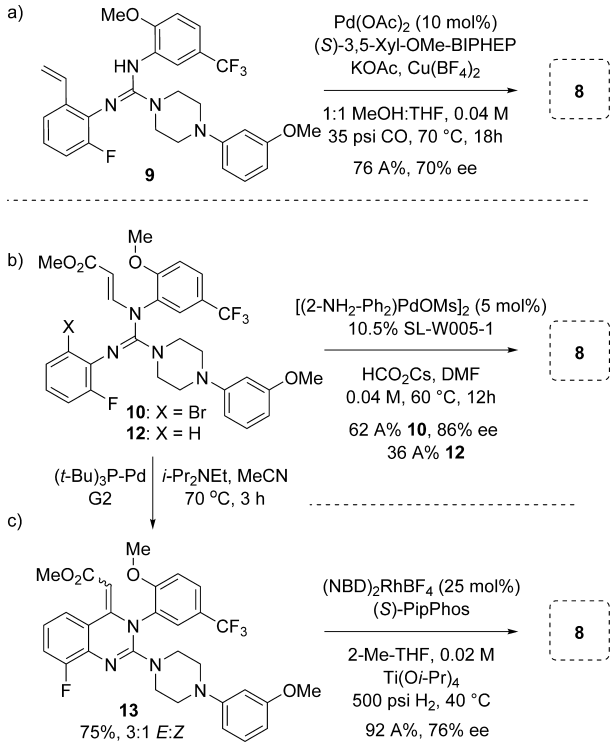
Figure 2. Principal asymmetric approaches considered.

(a) amino-carbonylation;[9] (b) Heck cyclization[10]/hydrogenation; (c) reductive Heck reaction;[11] (d) PTC aza-Michael reaction, aiming to exploit the initial success with urea **5**.

The amino-carbonylation substrate, styrenyl guanidine **9** (Scheme 2a),[12] was exposed to a range of Pd-mediated oxidative carbonylative conditions based on the work of Sasai.[9] Further screening of chiral ligands and additives led to the identification of the conditions shown in Scheme 2a, which provided dihydroquinazoline **8** in 76 A% (HPLC area %) and 70% ee. Relatively high Pd-loadings (10 mol %) were required to attain full conversion, however, even at elevated temperature (18h, 70 °C). While an attractive approach, attaining the necessary improvements for process viability was expected to be highly challenging.

Preparation of the *tetra*-substituted guanidine **10** proved more complicated than for **9**,[12] which was ultimately reflected in its reactivity profile. Pleasingly, screening of conditions for the asymmetric reductive Heck cyclization of **10** did identify a reagent set under which the desired dihydroquinazoline **8** could be prepared in up to 86% ee (Scheme 2b). Competitive reductive debromination to form **12** proved prohibitively problematic, however, and was unable to be suppressed beyond a ca. 2:1 product ratio of **8**:**12**. In response, the stepwise Heck reaction/hydrogenation strategy was explored, which might offer more synthetic control. Accordingly, Heck cyclization delivered the exocyclic acrylate **13** (Scheme 2c), which was isolated as an equilibrating ca. 3:1 mixture of *E*:*Z* isomers. Acrylate **13** also exhibited a propensity for alkene hydration, presumably to alleviate allylic strain with the adjacent anisole,

Scheme 2. Metal-Catalyzed Asymmetric Cyclizations[12]



which likely also contributes to the difficulties suppressing debromination in the reductive Heck reaction.[13] Despite these issues, productive asymmetric hydrogenation of **13** to provide **8** could be achieved, after optimization with 76% ee and 92 A%.

Evaluation of the asymmetric PTC aza-Michael cyclization of guanidine **11** commenced with the conditions developed for the analogous cyclization of urea **5** (20 mol % PTC, aq. K_3PO_4, PhMe, 0 °C). The success of this approach would rely in part upon the susceptibility of guanidine **11** to background cyclization, which was particularly prominent in alcoholic solvents.[14] Fortunately, this was suppressed using toluene, and no background cyclization was observed in the absence of the PTC. Pleasingly, *mono*-quaternized PTCs were generally found to effect a smooth cyclization reaction with encouraging levels of enantioselectivity (10−40% ee). The corresponding *bis*-quaternized catalysts offered immediate enhancements in both reaction rate and enantioselectivity, however.[15] Screening of this catalyst manifold (Table 1) revealed acute sensitivity to both the quinoline (R^1, **14j**, **14k**) and quinuclidine (R^2, **14h**, **14l**) substituents, leading to the identification of catalyst **14f**, which provided dihydroquinazoline **8** in almost quantitative yield and 76% ee after 3 h at 0 °C at 5 mol % loading. Notably, a range of other catalyst types proved ineffectual by comparison,[16] highlighting the utility of these new PTCs for asymmetric synthesis.

Unfortunately, defining structure−activity relationships to guide further PTC refinement to access **8** in >90% ee proved unsuccessful and will likely rely upon greater mechanistic understanding. Several general features were apparent however: electron-deficient aromatic groups afforded much improved catalyst performance; CF_3 substituents tended to be beneficial (**14c**); 2-substituted quinuclidine substituents led to diminished activity and even reversal of enantioselectivity (**14d**), and cinchonidine-based catalysts were superior to the corresponding quinidine, quinine, and cinchonine-based catalysts (**14i**,

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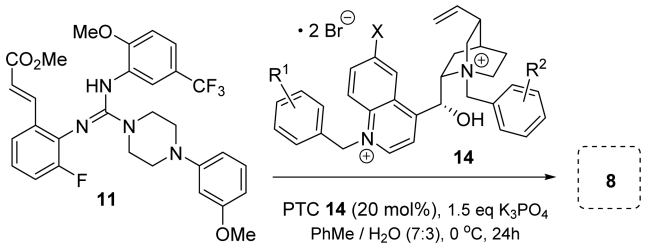
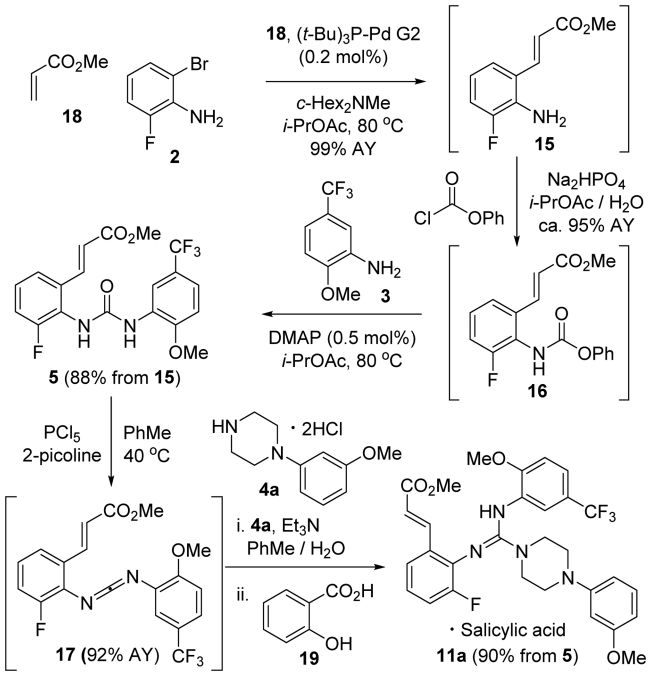
Table 1. Optimization of the Phase-Transfer-Catalyst[a]



PTC	X	R^1	R^2	ee (%)[b]
14a	H	2-Br, 5-OMe	3-NO_2	24
14b	H	″	3,5-F	24
14c	H	″	3,5-CF_3	58
14d	H	″	2-CF_3	−13
14e	H	3,5-NO_2	3,5-CF_3	51
14f	H	3-CF_3	″	76
14g	H	4-CF_3	″	67
14h	H	3,5-CF_3	″	74
14i	OMe	3,5-CF_3	″	<30
14j	H	2-F, 5-OCF_3	″	71
14k	H	3-F, 6-OCF_3	″	<10
14l	H	3,5-CF_3	3-CF_3	50
14m	OMe	3-F, 5-CF_3	3-F, 5-CF_3	45

[a]Subset of >200 PTC catalysts screened. [b]Enantioselectivity was determined by chiral HPLC analysis of the crude reaction mixtures.

Scheme 3. Preparation of Guanidine Salicylate 11a



14m). The corresponding benzyl or *t*-butyl ester substrates offered no selectivity benefits.

Contrasting the remarkable operational simplicity and effectiveness of the PTC aza-Michael reaction against the preparative, stability, and reactivity issues associated with alternative approaches led to its selection as the cornerstone of the new synthesis of letermovir, where refined PTCs may be directly implemented as they become available.[17] Accordingly, an effective means for preparation of guanidine **11** was developed and optimized (Scheme 3). This commenced with Heck reaction of commercially available bromoaniline **2** to provide acrylate **15** in 99% assay yield (AY), utilizing just 0.2 mol % Pd precatalyst.[18] Acylation under Schotten−Baumann conditions afforded phenyl carbamate **16**, which underwent smooth condensation with aniline **3** to provide urea **5**, whose high crystallinity enabled it to be isolated directly from the reaction stream. In practice, this sequence could be efficiently carried out as a single solvent through-process, proceeding in 87% yield over the three steps. Dehydration of urea **5** with PCl_5 in PhMe at 40 °C cleanly provided the carbodiimide **17**. This intermediate proved remarkably stable with respect to hydrolysis, yet underwent rapid reaction with piperazine **4a** as part of a second through-process. The targeted guanidine **11** was then conveniently isolated from the crude reaction stream as the corresponding salicylate salt (**11a**) in 90% yield from urea **5**. The combination of carbodiimide stability and piperazine nucleophilicity underpinned the success of this approach, in contrast to other permutations of urea/aniline condensation, while the use of toluene as a nonpolar solvent proved critical to preserving the acyclic integrity of guanidine **11** (<1% cyclization observed).

Process development of the aza-Michael cyclization revealed a number of intriguing features which might suggest an atypical PTC-type mechanism is operative. Both reaction rate and enantioselectivity were found to be sensitive to (i) agitation rate, where sharp drop-offs were observed below a critical point (Figure 3a);[19] (ii) the concentration and equivalents of aqueous base, where superstoichiometric amounts of K_3PO_4 (1.5 eq, 0.4 M aqueous) proved optimal (Figure 3b); (iii) PTC/base counterions, where deviation from Br^- or PO_4^{3-}, respectively, proved detrimental.[20] Relatively constant enantioselectivity was observed over the course of the reaction, suggesting a single active catalytic species. PTC loading could be reduced to 3 mol % with minimal effect (6 h, 72% ee).[21]

Having defined suitable operating parameters, the critical aza-Michael reaction was successfully implemented on multikilogram scale to deliver, after aqueous workup, a toluene solution of dihydroquinazoline **8** (Scheme 4). Upgrading the optical purity from 76 to >99% ee could be conveniently achieved through formation of the chiral DTTA (di-*p*-toluoyl-(*S*,*S*)-tartaric acid, **20**) salt **8a**.[3a,c] In practice, this was accomplished directly from the crude organic stream following aqueous workup, providing **8a** in 82% overall yield and 99.6% ee[22] and critically sufficient purity in preparation for generating amorphous drug substance. Accordingly, free-basing of DTTA salt **8a** followed by ester saponification (NaOH, 70 °C) provided letermovir (**1**), which was finally isolated through precipitation as an amorphous white solid (94%).

In summary we have developed a concise and efficient asymmetric synthesis of letermovir, a potent and selective new treatment for infections of HCMV. A novel asymmetric aza-Michael cyclization reaction was devised and implemented for this purpose, exploiting *bis*-quaternized PTC catalysis. The entire synthesis proceeds in >60% yield over seven steps, including five steps incorporated into two single solvent through-processes, without need for chromatography, and has already enabled the preparation of over 1 t of letermovir for further clinical development.

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources

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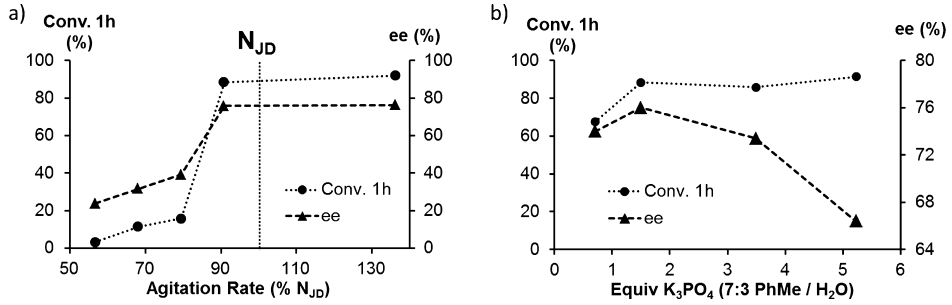
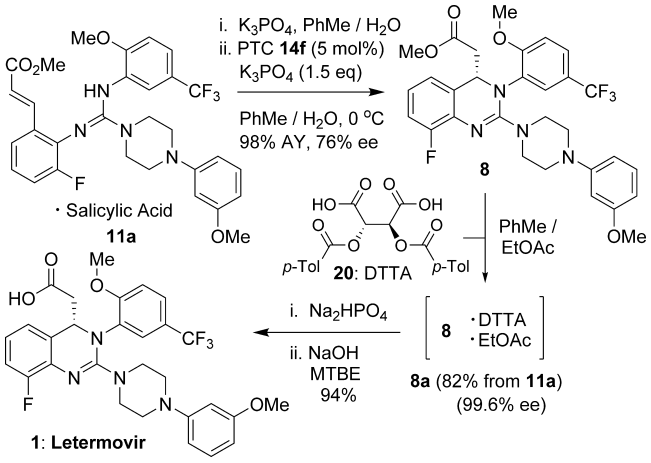


Figure 3. Aza-Michael reaction agitation/base sensitivity.

Scheme 4. Completion of the Synthesis of Letermovir (1)



and were used without further purification. ^{1}H and ^{13}C NMR chemical shifts were reported relative to residual proton solvent peaks. Melting points were determined on TA Instruments Density Scanning Calorimetry Q20. All yields are corrected for purity and determined by reverse-phase HPLC assay using purified standards. High-resolution mass spectra (HR-MS) were recorded using Waters Acquity UPLC and Waters Synapt G1Mass Spectroscopy under positive ESI conditions.

Methyl-(*E*)-3-(2-amino-3-fluorophenyl)acrylate (15). A stirred slurry of 2-bromo-6-fluoroaniline (**2**) (1.30 kg, 6.82 mol), methyl acrylate (1.24 L, 13.6 mol), *c*-Hex$_2$NMe (1.75 L, 8.18 mol), and Solka-floc (ca. 250 g) in *i*-PrOAc (10.4 L) was thoroughly degassed (N_2 sparge) before addition of (*t*-Bu)$_3$P–Pd G2 (26.2 g, 5.12 mol). The solution was heated to 80 °C and aged for 5 h before being cooled to RT and filtered (filter cake washed with *i*-PrOAc, 7.80 L). The filtrate was washed with citric acid (1 M aq., 2 × 2.00 L) to provide a crude *i*-PrOAc solution of acrylate **15** (16.2 kg, 8.2 wt % **15**, 99% assay yield) which was used directly without further purification. For the purposes of characterization, a sample of pure acrylate **15** was isolated by crystallization from a partially concentrated sample of the crude solution. Mp 48–50 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.79 (1H, d, J = 15.9 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.98 (1H, m), 6.67 (1H, td, J = 8.0, 5.3 Hz), 6.36 (1H, d, J = 15.9 Hz), 4.07 (2H, br s), 3.79 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 167.3, 151.9 (d, J_{CF} = 238.6 Hz), 139.0 (d, J_{CF} = 3.9 Hz), 134.2 (d, J = 12.7 Hz), 123.1 (d, J_{CF} = 3.2 Hz), 121.8 (J_{CF} = 3.4 Hz), 118.8, 117.9 (J_{CF} = 7.9 Hz), 116.1 (J_{CF} = 19.1 Hz), 51.7; HR-MS calcd for $C_{10}H_{11}FNO_2^+$ $[M + H]^+$ 196.0768, found 196.0773 (Δ = 0.5 mmu).

Methyl-(*E*)-3-(3-fluoro-2-((phenoxycarbonyl)amino)-phenyl)acrylate (16). To a stirred crude *i*-PrOAc solution of acrylate **15** (15.9 kg, 8.2 wt % **15**, 6.66 mol) was added H_2O (6.50 L) and Na_2HPO_4 (1.42 kg, 10.0 mol) followed by phenyl chloroformate (1.04 L, 8.33 mol) dropwise over 30 min. The reaction mixture was stirred at RT for 12 h before being heated to 60 °C and stirred for a further 2 h. The mixture was then diluted with *i*-PrOAc (7.00 L) and held at 60 °C until all solids were dissolved. The aqueous phase was then separated and the organics washed with H_2O (2.60 L) before being cooled to RT to afford a crude *i*-PrOAc slurry of carbamate **16** (ca. 95% assay yield) which was used directly without further purification. For the purposes of characterization, a sample of pure carbamate **16** was isolated by crystallization from a sample of the crude solution diluted with heptane. NMR spectra were complicated by persistent rotamers—peaks are reported as observed. Mp 154–158 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.97/9.57 (1H, br s), 7.98–7.80 (1H, m), 7.75 (1H, m), 7.50–7.32 (4H, m), 7.29–7.02 (3H, m), 6.75 (1H, m), 6.54/6.44/5.63 (minor rotamers), 3.80–3.70 (3H, s); ^{13}C NMR (500 MHz, DMSO-d_6) δ_C 166.5, 158.0 (d, J_{CF} = 247.6 Hz), 157.2, 152.8, 150.8, 139.6 (d, J_{CF} = 3.7 Hz), 138.6 (d, J_{CF} = 3.2 Hz), 133.4, 129.6, 129.5, 128.6, 125.6, 122.8 (d, J_{CF} = 3.1 Hz), 121.6, 120.7, 118.9, 117.7 (d, J_{CF} = 20.6 Hz), 116.7, 116.2 (d, J_{CF} = 18.8 Hz), 115.7 (d, J_{CF} = 7.6 Hz), 115.3, 51.8, 51.3; HR-MS calcd for $C_{17}H_{15}FNO_4^+$ $[M + H]^+$ 316.0980, found 316.0971 (Δ = 0.9 mmu).

Methyl-(*E*)-3-(3-fluoro-2-(3-(2-methoxy-5-(trifluoromethyl)phenyl)ureido)phenyl)acrylate (5). To a stirred crude *i*-PrOAc solution of carbamate **16** (<6.66 mol) was added 2-methoxy-5-(trifluoromethyl)aniline **3** (1.40 kg, 7.33 mol). The slurry was diluted with *i*-PrOAc, heated to 40–45 °C, and a constant volume distillation carried out to azeotropically dry the mixture (KF < 400 ppm). DMAP (40.5 g, 331 μmol) was added, and the solution was heated to reflux for 5 h. The ensuing slurry was then cooled to RT and aged for 2 h before being filtered. The cake was washed with *i*-PrOAc (4.00 L) and air-dried to afford urea **5** (2.43 kg, 5.89 mol, 99 wt %, 88% from acrylate **15**) as an off white crystalline solid. Mp 212–216 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.01 (1H, s), 8.78 (1H, s), 8.46 (1H, s), 7.76 (1H, d, J = 16.1 Hz), 7.72 (1H, d, J = 6.4 Hz), 7.31–7.35 (1H, m), 7.21 (1H, d, J = 8.4 Hz), 6.69 (1H, d, J = 16.1 Hz), 3.99 (3H, s), 3.72 (3H, s); ^{13}C NMR (500 MHz, DMSO-d_6) δ_C 166.5, 157.8 (d, J_{CF} = 245.6 Hz), 152.9, 150.1, 139.1 (d, J_{CF} = 2.5 Hz), 133.2, 129.2, 127.5 (d, J_{CF} = 8.1 Hz), 124.8 (d, J_{CF} = 13.7 Hz), 124.5 (q, J_{CF} = 271.2 Hz), 122.5, 121.1 (q, J_{CF} = 31.5 Hz), 119.9, 119.0 (q, J_{CF} = 4.1 Hz), 117.3 (d, J_{CF} = 20.8 Hz), 114.1 (q, J_{CF} = 3.6 Hz), 110.9, 56.3, 51.6; HR-MS calcd for $C_{19}H_{17}F_4N_2O_4^+$ $[M + H]^+$ 413.1119, found 413.1112 (Δ = 0.7 mmu).

Methyl-(*E*)-3-(3-fluoro-2-((((2-methoxy-5-(trifluoromethyl)phenyl)imino)methylene)amino)-

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phenyl)acrylate (17). To a stirred suspension of urea **5** (2.00 kg, 4.85 mol) in toluene (28.0 L) at RT was added 2-picoline (1.47 L, 14.6 mol) followed by PCl_5 (1.24 kg, 5.82 mol) portionwise over 30 min. The reaction mixture was heated to 40 °C for 5 h before being cooled to 0 °C and quenched by dropwise addition of KOH (2 M aq., 14.6 L, 29.1 mol), maintaining internal temperature <20 °C. The mixture was then filtered (2.00 L toluene vessel rinse), allowed to warm to RT, and stirred for a further 2 h. The aqueous phase was separated, and the organic phase was washed with citric acid (1 M aq., 7.28 L) and H_2O (7.28 L) to afford a crude toluene solution of carbodiimide **17** (27.5 kg, 6.4 wt % **17**, 92% assay yield) which was used directly without further purification. For the purposes of characterization, a sample of pure carbodiimide **17** was isolated by crystallization from a sample of the crude solution diluted with heptane. Mp 80−84 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 7.95 (1H, d, J = 16.1 Hz), 7.70 (1H, d, J = 8.0 Hz), 7.59 (1H, dd, J = 8.7, 1.9 Hz), 7.46 (1H, d, J = 2.1 Hz), 7.40 (1H, ddd, J = 10.4, 8.4, 1.2 Hz), 7.23−7.31 (2H, m), 6.76 (1H, d, J = 16.2 Hz), 3.91 (3H, s), 3.74 (3H, s); ^{13}C NMR (500 MHz, DMSO-d_6) δ_C 166.8, 157.9 (d, J_{CF} = 247.5 Hz), 157.1, 138.7 (d, J_{CF} = 3.5 Hz), 135.4, 130.4, 126.8 (d, J_{CF} = 8.4 Hz), 126.3, 125.7 (d, J_{CF} = 13.7 Hz), 124.7 (q, J_{CF} = 3.9 Hz), 124.4 (q, J_{CF} = 271.1 Hz), 123.9 (d, J_{CF} = 3.1 Hz), 122.1 (q, J_{CF} = 32.7 Hz), 121.8 (q, J_{CF} = 3.7 Hz), 121.0, 117.8 (d, J_{CF} = 19.5 Hz), 112.7, 57.2, 52.1; HR-MS calcd for $C_{16}H_{15}O_3N_2F_4^+$ $[M + H]^+$ 395.1008, found 395.1013 (Δ = 0.5 mmu).

Methyl-(2*E*)-3-(3-fluoro-2-((((2-methoxy-5-(trifluoromethyl)phenyl)amino)(4-(3-methoxyphenyl)-piperazin-1-yl)methylene)amino)phenyl)acrylate 2-Hydroxybenzoate (11a). To a stirred solution of carbodiimide **17** in PhMe (27.5 kg, 6.4 wt % **17**, 4.46 mol) was added a solution of piperazine *bis*-hydrochloride **4a** (1.38 kg, 5.09 mmol) in H_2O (13.0 L) followed by Et_3N (1.49 L, 10.7 mol). The reaction mixture was stirred at RT for 30 min before being heated to 40 °C and held for 1 h. The aqueous phase was separated and the organic phase washed with NaH_2PO_4 (2 × 9.70 L) and H_2O (7.30 L) to afford a solution of crude guanidine free base **11**. Salicylic acid (**19**, 744 g, 5.34 mol) was then added, and the solution was stirred at RT for 1 h before being cooled to 0 °C and stirred for a further 2 h. The ensuing slurry was filtered and the cake washed with cold (0 °C) PhMe (4.00 L) and dried under air to afford guanidine salicylate **11a** (3.16 kg, 4.36 mol, 98 wt %, 90% from **5**) as a white crystalline solid. mp 112−118 °C; ^{1}H NMR (500 MHz, CD_3CN) δ_H 12.9 (1H, br s), 7.75 (1H, dd, J = 7.8, 1.8 Hz), 7.72 (1H, d, J = 16.1 Hz), 7.40 (1H, td, J = 7.2, 1.7 Hz), 7.27 (1H, d, J = 7.8 Hz), 7.17 (1H, m), 7.16 (1H, t, J = 8.2 Hz), 7.02 (1H, br s), 6.95 (1H, t, J = 8.6 Hz), 6.88−6.81 (3H, m), 6.78 (1H, br s), 6.60 (1H, dd, J = 8.2, 2.0 Hz), 6.54 (1H, m), 6.48 (1H, d, J = 16.1 Hz), 6.43 (1H, dd, J = 8.0, 2.1 Hz), 3.73 (3H, s), 3.71 (3H, s), 3.69 (4H, br s), 3.68 (3H, s); ^{13}C NMR (125 MHz, CD_3CN) δ_C 173.1, 166.4, 161.9, 160.7, 156.6, 156.5 (d, J_{CF} = 247.7 Hz), 155.4, 152.0, 137.7, 134.4, 130.5, 129.9, 127.9 (d, J_{CF} = 8.2 Hz), 127.9, 126.2, 125.0 (q, J_{CF} = 3.7 Hz), 124.8 (d, J_{CF} = 12.8 Hz), 123.5 (q, J_{CF} = 273.1 Hz), 122.3, 122.0 (q, J_{CF} = 34.8 Hz), 121.4, 121.0, 118.4, 117.2 (d, J_{CF} = 11.8 Hz), 116.6, 115.5, 115.3, 112.1, 108.8, 105.4, 102.5, 56.1, 54.8, 51.4, 48.0, 47.9; HR-MS calc for $C_{30}H_{31}F_4N_4O_4^+$ $[M + H]^+$ 587.2276, found 587.2272 (Δ = 0.4 mmu).

(1*S*,2*S*,4*S*,5*R*)-1-(3,5-*Bis*(trifluoromethyl)benzyl)-2-((*R*)-hydroxy(1-(3-(trifluoromethyl)benzyl)quinolin-1-ium-4-yl)methyl)-5-vinylquinuclidin-1-ium Bromide 14f. To a stirred solution of cinchonidine (51.5 g, 175 mmol) in MeCN/*i*-PrOH (7:1, 840 mL) was added 3,5-*bis*-trifluoromethylbenzyl bromide (22, 32.2 mL, 175 mmol). The mixture was degassed (N_2 sparge) then heated to 50 °C and aged for 5 h or until cinchonidine was consumed. 3-(Trifluoromethyl)benzyl bromide (40.1 mL, 263 mmol) was then added, and the reaction mixture was heated to 70 °C and aged for 12 h. The solution was then cooled to RT and concentrated in vacuo to ca. 250 mL. The residue was diluted with EtOAc (3.00 L), seeded with *bis*-Quat PTC **14f** (1.46 g, 1.74 mmol), and the ensuing slurry was stirred for a further 12 h at RT. The slurry was filtered and the cake washed with ethyl acetate (500 mL) before being air-dried to afford *bis*-Quat PTC **14f** as a yellow solid (133.6 g, 159 mmol, 99 A%, 91%). An analogous procedure was used for the preparation of *bis*-quaternized catalysts **14a−m**. Mp 178−181 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H δ 9.92 (1H, d, J = 6.2 Hz), 8.86 (1H, dd, J = 8.7, 1.3 Hz), 8.65 (1H, s), 8.62 (1H, d, J = 9.0 Hz), 8.53 (1H, d, J = 6.1 Hz), 8.33 (1H, s), 8.27 (1H, ddd, J = 8.6, 7.0, 1.2 Hz), 8.12 (1H, t, J = 7.7 Hz), 7.97 (1H, s), 7.74 (1H, d, J = 7.7 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.62 (1H, t, J = 7.8 Hz), 7.25 (1H, d, J = 5.2 Hz), 6.85 (1H, d, J = 4.4 Hz), 6.57 (1H, d, J = 15.7 Hz), 6.51 (1H, d, J = 15.7 Hz), 5.70−5.62 (1H, m), 5.55 (1H, d, J = 12.3 Hz), 5.24 (1H, dt, J = 17.3, 1.3 Hz), 4.93 (1H, dt, J = 10.5, 1.3 Hz), 4.46 (1H, t, J = 13.5 Hz), 4.12 (1H, d, J = 12.3 Hz), 4.08 (1H, t, J = 9.5 Hz), 3.44−3.38 (2H, m), 3.31 (1H, td, J = 11.6, 4.8 Hz), 2.65 (1H, s), 2.14−2.03 (1H, m), 2.03−1.99 (1H, m), 1.82 (1H, t, J = 13.5 Hz), 1.43 (1H, ddd, J = 12.8, 9.1, 4.8 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C 158.5, 150.3, 138.1, 137.5, 135.7, 135.3, 135.0, 132.0, 131.6, 131.4, 131.2 (q, J_{CF} = 33.4 Hz), 130.5, 130.2 (q, J_{CF} = 31.9 Hz), 127.5, 126.6, 125.9, 125.0, 124.2 (q, J_{CF} = 272.8 Hz), 124.2, 123.6 (q, J_{CF} = 272.8 Hz), 122.1, 120.3, 116.8, 68.0, 65.1, 60.4, 59.7, 59.5, 51.1, 37.3, 26.5, 24.6, 21.8; HR-MS calc for $C_{36}H_{33}F_9N_2O^{2+}$ $[M]^{2+}$ 340.1219, found 340.1208 (Δ = 1.1 mmu).

Methyl-(*S*)-2-(8-fluoro-3-(2-methoxy-5-(trifluoromethyl)phenyl)-2-(4-(3-methoxyphenyl)-piperazin-1-yl)-3,4-dihydroquinazolin-4-yl)acetate (2*S*,3*S*)-2,3-*bis*((4-Methylbenzoyl)oxy)succinate Ethyl Acetate Solvate (8a). To a stirred suspension of guanidine salicylate **11a** (498 g, 687 mmol) in PhMe (5.30 L) was added K_3PO_4 (1 M aq., 1.03 L, 1.03 mol). The biphasic slurry was heated to 45 °C and stirred for 1 h or until all solids were dissolved. The aqueous layer was then separated; fresh K_3PO_4 (0.43 M aq., 2.40 L, 1.03 mmol) was added and the mixture cooled to 0 °C. Vigorous stirring was maintained while a solution of *bis*-Quat PTC **14f** (28.9 g, 34.4 mmol) in DMF (53.0 mL) was added rapidly and continued for a further 5 h at 0 °C. The aqueous phase was then separated, glycolic acid (1 M aq., 1.03 L, 1.03 mol) was added, and the mixture was heated to 50 °C and stirred for 2 h. Without cooling, the aqueous phase was separated and the organics washed with H_2O (687 mL). Darco KB-G (ca. 50 g) was then added and the suspension stirred for 2 h while being allowed to cool to RT before being filtered through Celite. The solution was concentrated in vacuo to ca. 3.50 L with concomitant azeotropic removal of water to provide a crude toluene solution (KF < 200 ppm) of dihydroquinazaline 8 (4.98 L, 13.5 wt % **8**, 98% assay yield, 76% ee). The solution was heated to 45 °C and a solution of (*S*,*S*)-di-*p*-toloyltartaric acid (**20**, DTTA, 53.1 g, 137 mmol) in EtOAc (160 mL) was then added and the mixture seeded with dihydroquinazaline DTTA salt **8a** (1.00 g, 943 μmol). The mixture was stirred for 2 h at 45 °C during which time a thin

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slurry formed. Further DTTA (212 g, 550 mmol) in EtOAc (640 mL) was then added via syringe pump over 12 h. The slurry was allowed to cool to RT and stirred for 3 h before being filtered. The cake was washed with EtOAc (3 × 500 mL) and air-dried to afford dihydroquinazaline DTTA salt **8a** (597 g, 563 mmol, 99 wt %, 82%, 99.6% ee) as a crystalline white solid. Mp 126−133 °C; ^{1}H NMR (600 MHz, CD_3CN) δ_H 7.87 (4H, d, J = 8.2 Hz), 7.62 (1H, dd, J = 8.8, 2.2 Hz), 7.23 (4H, d, J = 8.0 Hz), 7.16 (1H, m), 7.14−7.08 (3H, m), 6.95 (1H, dd, J = 7.1, 1.7 Hz), 6.42 (1H, dd, J = 8.1, 2.3 Hz), 6.36 (1H, dd, J = 8.2, 2.3 Hz), 6.31 (1H, t, J = 2.4 Hz), 5.81 (2H, s), 5.05 (1H, t, J = 7.0 Hz), 4.08 (2H, q, J = 7.1 Hz), 3.77 (3H, bs), 3.74 (3H, s), 3.66 (3H, s), 3.52−3.41 (4H, m), 3.08 (1H, dd, J = 15.7, 7.3 Hz), 2.93−2.72 (4H, m), 2.70 (1H, dd, J = 15.7, 7.3 Hz), 2.35 (6H, s), 2.00 (3H, s), 1.23 (3H, t, J = 7.1 Hz); ^{13}C NMR (150 MHz, CD_3CN) δ_C 170.7, 170.5, 168.7, 165.2, 160.6, 156.6, 154.3, 153.2 (d, J_{CF} = 249.1 Hz), 152.0, 144.4, 132.4, 129.8, 129.7, 129.5, 129.4 (d, J_{CF} = 13.6 Hz), 129.2, 126.7, 126.0 (q, J_{CF} = 3.0 Hz), 125.7, 124.3, 124.0 (q, J_{CF} = 271.0 Hz), 122.9 (q, J_{CF} = 33.2 Hz), 121.2, 117.3, 115.4 (d, J_{CF} = 18.6 Hz), 113.4, 108.6, 104.9, 102.3, 71.7, 60.1, 60.0, 56.3, 54.7, 51.6, 47.7, 47.6, 39.1, 20.7, 20.2, 13.5; HR-MS calcd for $C_{30}H_{31}F_4N_4O_4^+$ $[M + H]^+$ 587.2286, found 587.2276 (Δ = 1.0 mmu); R_t 5.1 min (undesired)/6.3 min (desired) (Chiral Pack IC-3, 150 × 4.6 mm, 3.0 μm), 70/30 MeCN/(0.05% aqueous TFA with 5 mM Na2B4O7), 0.9 mL·min^{-1}, λ = 210 nm.

(*S*)-2-(8-Fluoro-3-(2-methoxy-5-(trifluoromethyl)-phenyl)-2-(4-(3-methoxyphenyl)piperazin-1-yl)-3,4-dihydroquinazolin-4-yl)acetic Acid (Letermovir, 1). Dihydroquinazaline DTTA salt **8a** (40.0 g, 37.7 mmol) was slurried in MTBE (80 mL) and Na_2HPO_4 (0.5 M aq., 188 mL, 94.0 mol) added. The mixture was stirred for 2 h before the aqueous layer was separated and NaOH (1 M aq., 151 mL, 151 mmol) added. The stirred mixture was then heated to 60 °C, with concomitant removal of MTBE by distillation. The resulting aqueous reaction mixture was stirred at 60 °C for 5 h before being cooled to RT. H_2O (80 mL) and MTBE (200 mL) were then added, and the organic phase was separated (discarded). Further MTBE (200 mL) was added to the aqueous residue, which was then acidified (pH 5−6) with HCl (3 M aq., ca. 40 mL). The organic phase was separated and concentrated to ca. 100 mL. Removal of MTBE through constant volume solvent switch with acetone (600 mL) was carried out, providing a final solution of ca. 60 mL. This solution was then added over 30 min to H_2O (320 mL), and the ensuing slurry was stirred for a further 1 h before being filtered. The cake was washed with H_2O (3 × 50 mL) and air-dried to provide letermovir (**1**, 20.2 g, 35.3 mmol, 100 wt %, 94%) as an amorphous white powder. ^{1}H NMR (DMSO-d_6, 600 MHz) δ_H 7.52 (dd, J = 8.7, 1.7 Hz, 1H), 7.40 (brs, 1H), 7.21 (m, 1H), 7.07 (t, J = 8.2 Hz, 1H), 7.04 (m, 1H), 6.87 (m, 2H), 6.44 (dd, J = 8.2, 1.9 Hz, 1H), 6.40 (t, J = 2.3 Hz, 1H), 6.36 (dd, J = 8.0, 2.0 Hz, 1H), 4.89 (t, J = 7.2 Hz, 1H), 3.80 (brs, 3H), 3.68 (s, 3H), 3.39−3.48 (m, 4H), 2.82−2.95 (m, 4H), 2.80 (dd, J = 14.8, 7.4 Hz, 1H), 2.46 (dd, J = 14.9, 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ_C 171.8, 160.2, 156.5, 154.6 (d, J_{CF} = 246.3 Hz), 153.2, 152.2, 134.2, 132.3 (d, J_{CF} = 11.2 Hz), 129.6, 124.1 (q, J_{CF} = 271.3 Hz), 123.8 (q, J_{CF} = 3.7 Hz), 122.4, 122.1 (q, J_{CF} = 7.1 Hz), 121.4 (q, J_{CF} = 29.2 Hz), 120.8, 114.5 (d, J_{CF} = 19.5 Hz), 113.3, 108.3, 104.6, 101.9, 59.0, 56.3, 54.8, 47.9, 45.6, 40.0; HR-MS calcd for $C_{29}H_{29}F_4N_4O_4^+$ $[M + H]^+$ 573.2119, found 573.2117 (Δ = 0.2 mmu).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00076.

^{1}H and ^{13}C NMR spectra, further characterization data, ligand structures for Scheme 2, and expansions of Figure 3 (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: stephen.dalby@merck.com.

*E-mail: guy_humphrey@merck.com.

Present Address

†M.R.L.: Process Research and Development, The Bristol-Myers Squibb Pharmaceutical Research Institute, 1 Squibb Drive, New Brunswick, New Jersey 08903.

Notes

The authors declare no competing financial interest.

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(13) DFT ground state energy calculations at the B3LYP 6-31G** level for the corresponding quinazalinone indicated the (*E*)-acrylate to be + 4.0 kcal mol^{-1} relative to its hydrate—see the Supporting Information for details. We note the competetive reductive debromination process may also relate to the relative inaccessibility of an intermediate arylpalladium complex conformer appropriate for migratory insertion of the acrylate group.
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(20) Alternative PTC counterions included: Cl^- (70% ee), NO_3^- (61% ee), BF_4^- (51% ee), OTf^- (27% ee), SbF_6^- (23% ee). Spiking KBr led to increasingly diminished reaction rate and enantioselectivity (0.25 eq KBr − 77% conv after 14 h, 60% ee) together suggesting that counterion exchange plays a critical role in this process.
(21) 1 mol% PTC loading led to diminished rate and selectivity (18 h, 60% ee). Slow catalyst degradation via Hoffmann elimination was observed during the reaction; this degradate was only weakly catalytically active.
(22) The application of asymmetric catalysis thus translates into a significant yield enhancement compared to resolution of racemic **11** (ref 3a). An 82% isolated yield of **8a** (99.6% ee) from **11a** via **8** (76% ee, 88:12 er) represents an effective overall yield of 93% for this transformation.

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