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(Chloromethyl)dimethylchlorosilane-KF a Two-Step Solution to the Selectivity Problem in the Methylation of a Pyrimidone Intermediate en route to Raltegravir.

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ABSTRACT: The present work describes a two-step process, namely silylation with (chloromethyl)dimethylchlorosilane and desilylation, to address the selectivity problem in the *N*-methylation of a pyrimidone intermediate towards the synthesis of raltegravir API. The said methodology delivers the desired drug substance in which the *O*-methylated impurity content is below detection limit by HPLC analysis. Moreover, this two-step one-pot procedure provides an apparent advantage in terms of environmental impact with respect to the optimum approach described in the literature, while it compares equally well in terms of cost and operational simplicity.

KEYWORDS: Raltegravir, amide methylation, (chloromethyl)dimethylchlorosilane, industrial preparations.

INTRODUCTION

Raltegravir, in the form of its potassium salt (**1**; Figure 1), is an antiretroviral drug developed by Merck & Co, for the treatment of HIV infection and is marketed under the trade name *Isentress*®. It is the first member of a new class of antiretroviral drugs interfering with the integration process of the viral encoded DNA into the host cell genome by inhibiting the enzyme *integrase*.[1] This new mode of action has certain advantages over other strategies currently followed (such as reverse transcriptase inhibition) as it suffers to much lesser extent from resistance due to virus mutations.[2] In addition, the new biological target, HIV integrase, has no equivalent in the human cell, which substantially lowers the risk of side effects.[3]

Chemically, raltegravir (**1**) can be regarded as an *N*-methyl hydroxy-pyrimidone core, bearing a hydrophobic benzylic moiety at C4 amide substituent, a crucial structural feature for binding to the active site of the enzyme (Figure 1). Furthermore, the chelation of the triad consisting of the amidic carbonyl of the C4 substituent and the two consecutive oxygen atoms on the pyrimidone ring with two Mg^{++} metal ions is important as it resides within the catalytic pocket. Finally, a second amide substituent, encompassing an oxadiazolyl moiety, is located at the bottom-left side of the molecule, i.e. at the C2 position of the pyrimidone.

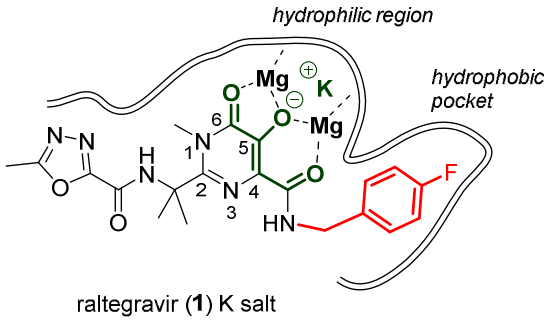
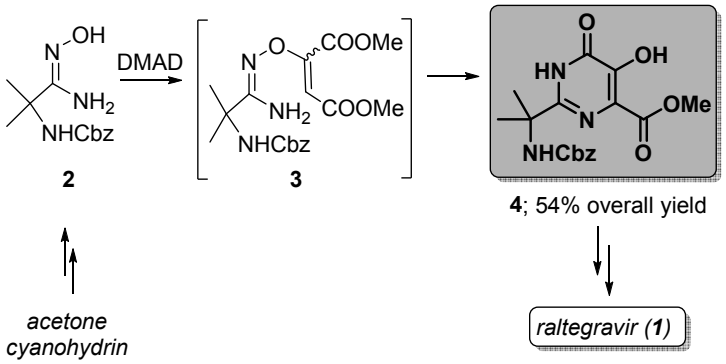


Figure 1. Structure of raltegravir (**1**) potassium salt

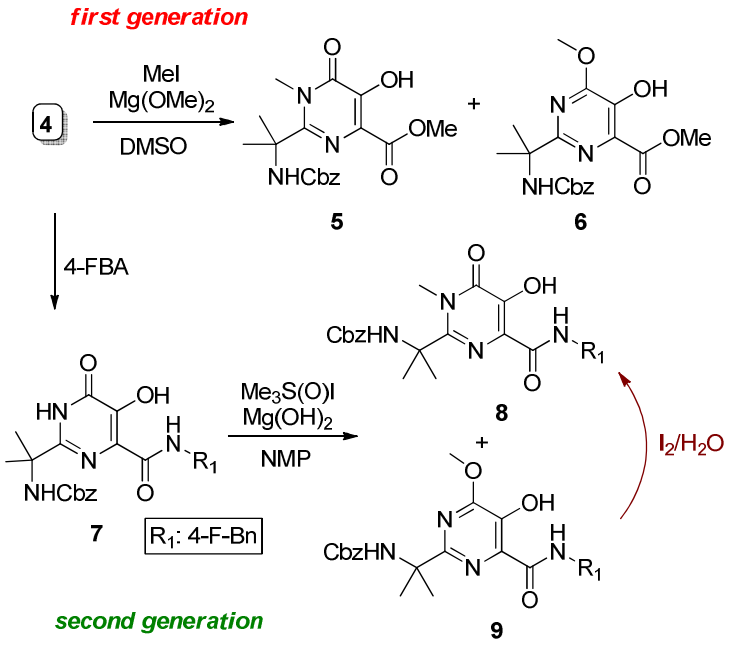
The first chemical synthesis of the free phenol **1** was accomplished in 10 linear steps and low overall yield (3%; Scheme 1).[4] This early synthetic attempt suffered from many drawbacks which were partially overcome in the improved first generation process for the synthesis of raltegravir by Merck.[5] In the latter, ta robust and atom-economical method was established for the construction of the key hydroxy-pyrimidone core **4**, via a thermal rearrangement of **3** (the adduct of amidoxime **2** to dimethyl acetylenedicarboxylate; Scheme 1).



Scheme 1. Preparation of the hydroxy-pyrimidone intermediate **4**. DMAD; Dimethyl acetylenedicarboxylate.

The attempted direct *N*-methylation of **4**, however, proved troublesome, as the isomeric *O*-methylated compound **6** was also obtained. In many cases this undesired species was the major product (Scheme 2; first generation route). After extensive experimentation the best result achieved with this approach was a 78:22 ratio in favor of the desired **5** (MeI, $Mg(OMe)_2$, DMSO, 60 ^oC). From this crude material, pure **5** was isolated in 70% yield after tedious purification still contaminated by the isomeric **6** (approx. 1% by HPLC). With the poor selectivity in the methylation reaction identified as the major issue in the synthesis of raltegravir, alternative approaches were investigated. In the second generation process reported by Merck's laboratories,[6] the optimum methylation conditions described above were applied to the more

chemically stable amide **7** and delivered a mixture of products in similar ratio of *N*-methyl **8** to *O*-methyl **9** (80:20; Scheme 2). However, prolonged reaction time and addition of traces of water to the reaction mixture, in combination with molecular iodine produced *in situ*, led to recycling of the *O*-methyl isomer **9** in favor of the *N*-methyl compound **8**. After further optimization (2 equivs. $Mg(OH)_2$, 2 equivs. $Me_3S(O)I$, NMP, 100 °C, 6 h), the desired *N*-methyl intermediate **8** was isolated in 89% yield and >99% purity.

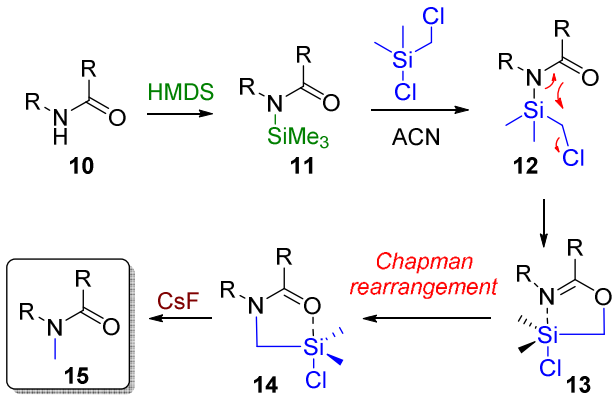


Scheme 2. First and second generation methylation processes by Merck

Despite the indisputable improvement of the methylation process, undesirable features for a multikilogram production still existed. Among them, one can include the *in situ* production of the extremely toxic MeI which, under the harsh reaction conditions (100°C for 6h), raises major concerns due to safety and environmental risk. In addition, the reaction media, namely NMP (*N*-methylpyrrolidone), is not among the most desirable solvents for industrial applications.[7] To add to this, in an effort to evaluate the process in our laboratory, we found out that very careful

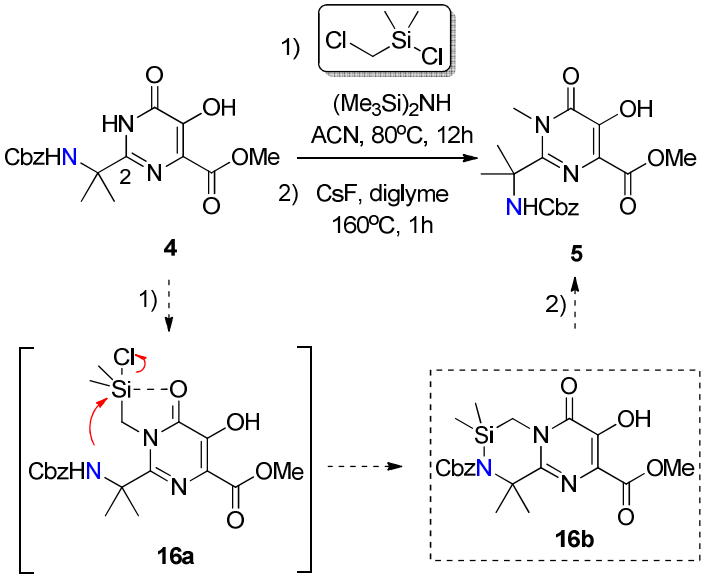
removal of the solvent (< 1000 ppm) is essential for the following catalytic hydrogenation step to be successful. For the same reason, removal of *in situ* generated DMSO, with a stricter limit of detection (<100 ppm), proving necessary. Finally, a less energy consuming procedure would be highly desirable.

Seeking for alternative methods for the selective *N*-methylation of amides we came across a report by Taylor *et al.*, where (chloromethyl)dimethylchlorosilane was employed for the chemoselective methylation of amides and heterocycles.[8] According to the proposed mechanism, the initial activation of the nitrogen atom by hexamethyldisilazine (HMDS, Scheme 3), is followed by a transilylation event to intermediate **12** and, thereafter, an intramolecular *O*-alkylation to the stabilized imidate **13**.[9] The desired *N*-alkylation product **14**, comprising a pentacoordinate silicon atom, is effected after a Chapman-type rearrangement.[10] The authors found out that treatment of this silicon species with CsF afforded the *N*-methylated amides **15** in good yields. They also demonstrated that the reaction sequence can operate equally well in the presence of other nucleophiles.



Scheme 3. The proposed mechanism by Pestunovich *et al.* for the selective *N*-methylation of amides using (chloromethyl)dimethylchlorosilane[9]

In fact, we envisioned that the nitrogen atom of the carbamate substituent at C2 position could react intramolecularly with the pentacoordinated silicon atom in **16a** leading to a cyclic intermediate (Scheme 4; suggested structure **16b**), thus offering additional stabilization to the system. Our hypothesis was further supported by analogous examples in the literature involving suitable tethered sulfonamides that served as nucleophiles that eventually led to similar cyclic products.[11]

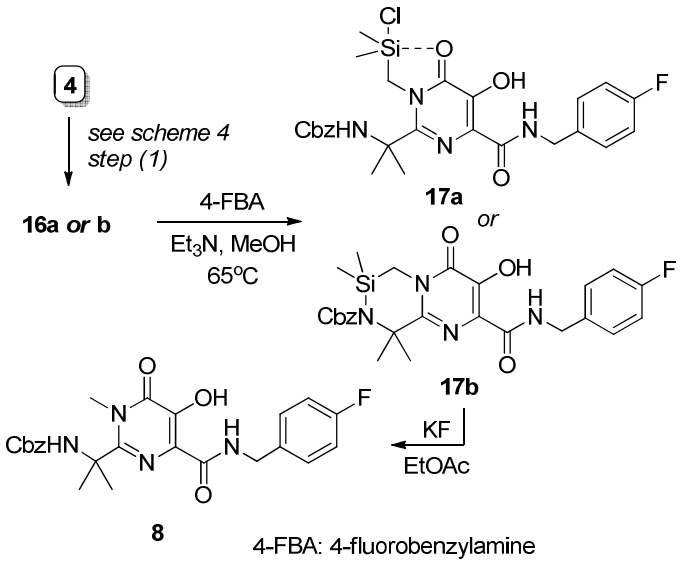


Scheme 4. *N*-Methylation of **4** using (chloromethyl)dimethylchlorosilane. Proposed structures of intermediates **16**.

To test our theory we applied the suggested experimental conditions directly on the hydroxy-pyrimidone compound **4** (Scheme 4). Thus, refluxing of an acetonitrile solution[12] of the latter with HMDS for 3 h and then, addition of (chloromethyl)dimethylchlorosilane and further heating for 16 h gave a new compound as evidenced by TLC.[13] By solvent exchange to diglyme and heating at 160°C, in the presence of CsF, we were pleased to find out that the desired *N*-methylated product was afforded in 65% isolated yield. We were even more excited to note that

the undesirable *O*-methylated pyrimidone **6**, was below the detection limit by HPLC analysis (0.01% w/w based on signal-to-noise = 3 criterion).

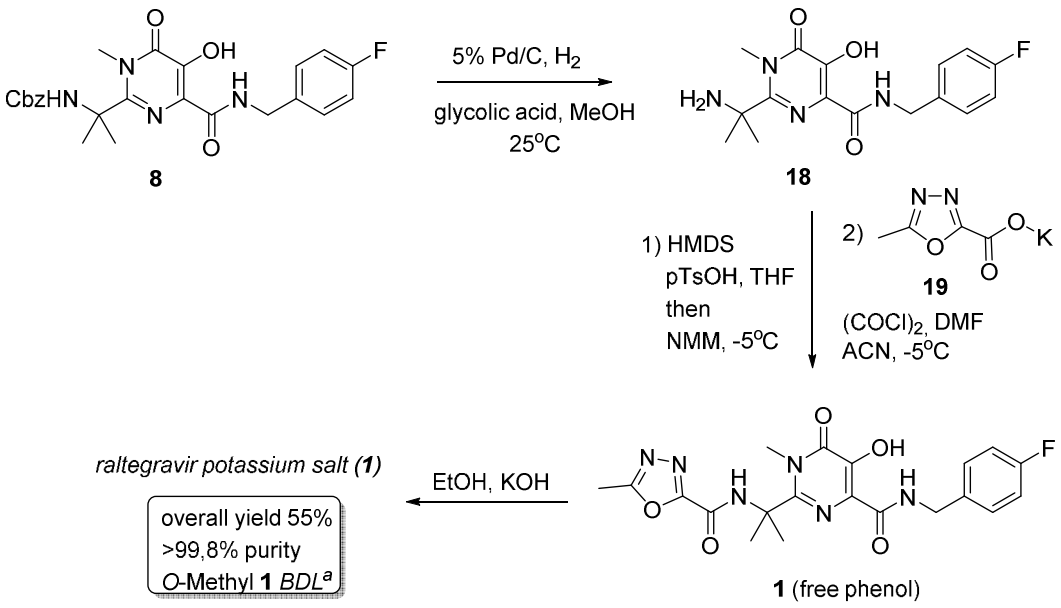
This initial achievement, although quite encouraging, called for improvement in many aspects of the process (solvents, temperature, cost of reagents etc). Much effort was expended to these factors, to deliver a much more industrially friendly process with an upgraded efficiency (78% isolated yield). In particular, reaction time for the first step was shortened, while the desilylation step could be conducted in a solvent of much lower boiling point (THF; 65°C). We found that the more manufacturing friendly solvent ethyl acetate could be employed for this purpose. Ethyl acetate also resulted in a simplified work up process. Furthermore, we were happy to discover that KF, a much more economical source of fluoride anions, could be utilized as the desilylation agent instead of the costly CsF.



Scheme 5. The silylation-amidation-desilylation sequence on **4**

As a further development to our process, we were keen to explore the possibility of carrying out the *N*-4-fluorobenzylamide formation step before the desilylation event; thus combining two

steps without any isolation of intermediates (Scheme 5). Hence, starting material **4** was treated successively with HMDS and (chloromethyl)dimethylchlorosilane in boiling acetonitrile, followed by solvent exchange to methanol and addition of 4-fluorobenzylamine and triethylamine as base. Upon exposure to these conditions, the initially formed intermediate **16(a** or **b)** was fully converted within 30 mins to a new compound **17(a** or **b)**,[14] which was then subjected to desilylation with KF after a second solvent exchange to ethyl acetate. A simple acidic work-up afforded the desired *N*-methylated amide **8** in 75-80% yield after recrystallization. Once again, optimization of the process revealed that the desilylation step could be carried out by direct addition of solid KF in the amidation reaction mixture in hot MeOH. The formation of a colorless precipitate is indicative of the completion of the reaction. Demineralized water is then added to the slurry and stirred for 1 h further. Crude amide **8** was collected as a colorless solid by filtration under vacuum. To our delight, once again, HPLC analysis of **8** showed no detected *O*-methyl isomer **9**, though, contamination by small amounts (3-4%) of non-methylated compound **7** was observed, which was partially removed after recrystallization (0.5-2% of **7** in the final product **8**; overall yield 80-85%).[15]



Scheme 6. Completion of the synthesis of raltegravir. [a] BDL; below detection limit (0.01% w/w based on signal-to-noise = 3 criterion)

Despite the presence of trace amounts of **7**, the material produced by the method described above was able to ultimately deliver our pharmaceutical compound in superior quality. According to our synthetic plan (Scheme 6), the advanced intermediate **8**, was deprotected to free amine **18** using catalytic hydrogenation under acidic conditions (glycolic acid).[16] When this transformation was first reported, it was mentioned that the resulting amine was obtained in its dihydrate form, a fact that necessitated the use of excess (2.2 equivs) of the expensive heterocyclic carboxylic acid potassium salt **19** to force the following amidation reaction to completion.[5] Utilizing our modified isolation conditions, amine **18** is reproducibly accessed with much lower water content (< 1.5% by Karl-Fischer titration).[17]

The next step, the direct peptide coupling of free amine **18** with the chloride derived from salt **19**, has been the center of interest for other research groups, as it represents the shortest path to raltegravir free phenol. In their patent published in 2012, Mylan Pharmaceuticals reported the

use of TMSCl, among other agents, for the transient protection of the phenolic group in **18** and the trapping of excess water.[18] Their process utilized more than 6 equivalents of TMSCl in order to reduce the loading of **19** to 1.5 equivalents (compared to the 2.2 previously reported). According to our assessment, the same result could be achieved using HMDS (2.0 equivs) as the silylating agent. However, we observed that a portion of salt **19** (approximately 20%) was lost to an undesirable reaction with HMDS. After much experimentation, we discovered that the employment of 0.8 equivalents of HMDS in the presence of catalytic amounts of p-toluenesulfonic acid could lead to a more controllable protection of hydroxyl group in compound **18**. This improvement restricts the requirement in salt **19** to as low as 1.25 equivalents. Under the optimized conditions raltegravir free phenol is obtained in very high purity (>99.8%) by precipitation from the reaction mixture. Finally, a typical treatment with EtOK (Scheme 6), led to the respective potassium salt as a colorless solid, whose specifications met all the standards of pharmacopeia with respect to the specific API.

In conclusion, we have successfully implemented and extensively modified a previously reported methodology for the selective *N*-methylation of a common pyrimidone-type intermediate of raltegravir, employing (chloromethyl)dimethylchlorosilane as silylating agent and KF as an inexpensive source of fluoride anion for the desilylation step. The method has been properly adjusted to reduce the safety and environmental risks and to fit for multikilogram production. Furthermore, for the rest of the synthesis, the shortest path, which involves Cbz deprotection and direct coupling with the oxadiazoloyl moiety, has been followed. Problems associated with water removal and wasteful use of expensive salt **19** have been addressed to eventually deliver raltegravir potassium salt (**1**) in high overall yield and excellent purity.

EXPERIMENTAL DETAILS

General Remarks. All grade quality reagents commercially available were used without further purification. All reactions were monitored on commercial available pre-coated TLC plates (layer thickness 0.25mm) of Kieselgel 60 F254. Compounds were visualized by use of UV lamp or/and Seebach stain solution and heating. NMR spectra were recorded on a 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 126 MHz). Chemical shifts are given in ppm and J in *Hz* using residual solvent as an internal reference. IR spectra were recorded on an FTIR instrument as indicated. Mass spectra were obtained by electro spray technique, positive mode (ES-MS). Melting points were determined with a capillary apparatus and are uncorrected.

Methyl 2-(2-(((benzyloxy)carbonyl)amino)propan-2-yl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (5). A 500 ml 3-necked round bottom flask, equipped with a reflux condenser and a thermometer is charged with 15.0 g (41.5 mmol) methyl 2-(2(((benzyloxy)carbonyl)amino)propan-2-yl)-5,6-dihydroxy-1,6dihydropyrimidine-4-carboxylate (**4**) and 150 ml acetonitrile under inert atmosphere at 20-30^{o}C. To the resulting suspension is added with stirring 8.7 ml HMDS (41.5 mmol; 1.0 equiv) (suspension turns into clear solution) and mixture is heated at 80^{o}C for 1 h. While still hot, 6.0 ml (chloromethyl)-dimethylchlorosilane (45.7 mmol, 1.10 equivs) is added and heating is maintained for 2 h. Reaction progress is monitored by TLC (DCM/MeOH= 95/5; double development). Upon completion, the volatiles are evaporated off and the residue is further dried under high vacuum for at least 30 min. To the residue is added 75 ml EtOAc and the mixture is heated and stirred until a clear solution arises (approximately 60^{o}C). 3.0 g KF (51.9 mmol; 1.25 equivs) is added and stirring is maintained for approximately 1h. Upon completion, 50 ml demineralized water is added. After stirring for 10 min, the mixture is left to settle. The upper organic phase is collected

and washed with 50 ml water, then dried over anhydrous Na_2SO_4, filtered and evaporated down to afford **5** as off-white solid (12.1 g; 78% yield; >98% purity).

Benzyl (2-(4-((4-fluorobenzyl)carbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl)carbamate 8. A 2 L 3-necked round bottom flask, equipped with a mechanical stirrer, a reflux condenser and a thermometer is charged with 150.0 g (0.42 mol) methyl 2-(2(((benzyloxy)carbonyl)amino)propan-2-yl)-5,6-dihydroxy-1,6dihydropyrimidine-4-carboxylate (**4**) and 0.75 L acetonitrile under inert atmosphere at 20-30 ^oC. To the resulting suspension is added with stirring 87 ml HMDS (0.42 mol; 1.0 equiv), the suspension slowly turns into a clear solution and the mixture is heated at 80 ^oC for 1 h. While still hot, 60.4 ml (chloromethyl)-dimethylchlorosilane is added over 10-15 min and heating is maintained for 2 h. Reaction progress is monitored by TLC (DCM/MeOH= 95/5; double development). Upon completion, the mixture is evaporated down and the residue is further dried under vacuum for at least 30 min. To the residue is added 0.75 L MeOH and the mixture stirred until a clear solution arises. 69.7 ml (0.50 mol; 1.20 equivs) Et_3N is added followed by 57.2 ml (0.50 mol; 1.20 equivs) 4-F-benzylamine and the resulting mixture is heated to 65 ^oC for 1 h. While still hot, KF (30.8 g; 0.53 mol; 1.25 equivs) is added in one portion and heating maintained for 1-2 h. Upon completion of the desilylation, a colorless solid precipitates from the reaction mixture. Reaction is cooled down to ambient temperature and 1.12 L demineralized water is added and the slurry is stirred for 1 h. Crude Benzyl (2-(4-((4-fluorobenzyl)carbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl)carbamate (**8**) is afforded by filtration under vacuum. The wet cake is washed with 0.45 L MeOH/H_2O (1:2) and pulled dry on the filter for 1 h. The colorless solid is collected and dried further under vacuum at 30^oC for 10 h. After recrystallization with MeOH/H_2O= 3:1, pure **8** is obtained as colorless solid (159.8 g, 82%). IR

(film) 3346, 3237, 3145, 1712, 1674, 1533 cm^{-1}, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 11.89 (br, 1 H), 7.77 (br, 1 H), 7.32-7.29 (m, 7H), 7.06-7.03 (m, 2 H), 5.21 (s, 1H), 5.00 (s, 1H), 4.56 (d, J = 6.0 Hz, 2H), 3.64 (s, 3H), 1.66 (s, 6 H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.4, 163.3 (d, J_{CF}=246 Hz), 161.4, 150.9, 133.1, 129.5, 129.4, 128.7, 128.2, 115.7 (d, J_{CF}=21 Hz), 57.3, 42.4, 32.9, 28.0, ^{19}F-NMR (470 MHz, $CDCl_3$) δ -114.5 (br s), HRMS (ESI) calculated for $C_{24}H_{25}FN_4O_5$ $(M+H)^+$ 469.1887, found 469.1880.

2-(2-Aminopropan-2-yl)-*N*-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide 18. A slurry suspension of 500 g (1.07 mol) Benzyl (2-(4-((4-fluorobenzyl)carbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2yl) carbamate **8**, 190 ml (2.13 mol) glycolic acid (67% w/w) and 25g 5% Pd/C (50% w/w) in 5 L methanol was hydrogenated at 130 psi for 3-4 h. The reaction mixture was transferred to a 20 L glass reactor and diluted with 10 L MeOH, filtered through celite bed and washed with 0.5 L MeOH. The combined filtrates ware concentrated to a total volume of 5.5 L at 25-28 ^{o}C and neutralized by 325 ml Et_3N. The formed crystalline solid is collected by filtration, rinsed with 0.5L MeOH and dried under vacuum to afford 325 g (0.97 mol; 91% yield, 99.6% purity) of 2-(2-Aminopropan-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**18**). mp 190.6-190.8 ^{o}C, IR (film) 3666, 3199,2978, 1639, 1551, 1509 cm^{-1}, ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.16 (br, 1 H), 7.33-7.30 (m, 2H), 7.14-7.10 (m, 2H), 4.45 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H), 1.56 (s, 6H), ^{13}C-NMR (125 MHz, DMSO-d_6) δ 168.1, 162.1 (d, J_{CF}=243 Hz), 160.2, 135.6, 129.3 (d, J_{CF} = 8 Hz), 123.2, 115.0 (d, J_{CF} = 22 Hz), 55.9, 48.6, 41.3, 33.1, 28.2, ^{19}F-NMR (470 MHz, $CDCl_3$) δ -116.2 (tt), HRMS (ESI) calculated for $C_{16}H_{19}FN_4O_3$ $(M+H)^+$ 335.1419, found 335.1417.

Raltegravir (1) free phenol. A mixture of oxadiazole potassium salt **19** (238.5 g, 1.43 mol), acetonitrile (1.2 L), and DMF (7.4 ml) was cooled to -5 ^{o}C and oxalyl chloride (115.2 ml, 1.34 mol) is added over 30 min. The resulting slurry was aged at 0-5 ^{o}C for 1 h and then cooled to -10 ^{o}C. A slurry of 2-(2-Aminopropan-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (**18**) (300 g, 0.90 mol) and THF (3L) was stirred at room temperature and HMDS (148.5 ml, 0.72 mol) is added dropwise over a period of 5 min. To the resulting suspension 5.13 g *p*-TsOH (26.8 mmol) was added in one portion. The reaction mixture was heated at 60-65^{o}C for 2 h, then cooled down to around -5 ^{o}C and *N*-methylmorpholine (296.4 ml, 2.69 mol) was added. The resulting solution was aged at -5 ^{o}C for 20-30 min. The oxadiazole acid chloride, prepared above, was added dropwise to the amine containing slurry reaction mixture at -5^{o}C over 45 min. Reaction is monitored with HPLC and after completion 20% aq. potassium hydroxide (1.50 L) was added and the reaction mixture is stirred at 5^{o}C for 1 h. HCl 2N (1.11 L) was added over 10-15 min to adjust the pH at 3-4 and the reaction mass is warmed at 15 ^{o}C. 11.25 L water was added slowly over 1 h. The resulting white suspension was aged at 15 ^{o}C for 1 h and filtered. The cake was washed with 0.90 L H_2O/acetonitrile (2.5:1) and 0.90 L water. The colorless solid is dried further to afford raltegravir free phenol (337 g, 84% yield; 98.7% purity). This material was optionally recrystallized from 7.5 L H_2O/acetonitrile (2.5:1) to deliver raltegravir free phenol in 99.7% purity (recrystallization yield 91%). mp 141.0-145.2 ^{o}C. IR (film) 3583, 3492, 3340, 3302, 1703, 1686, 1637, 1597, 1505 cm^{-1}, ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.24 (s, 1 H), 9.90 (s, 1H), 9.12 (t, J = 6.4 Hz, 1 H), 7.41-7.38 (m, 2 H), 7.19-7.15 (m, 2 H), 4.51 (d, J = 6.4 Hz, 2 H), 3.48 (s, 3 H), 2.56 (s, 3 H), 1.74 (s, 6 H), ^{13}C-NMR (125 MHz, DMSO-d_6) δ 168.4, 165.8, 162.3 (d, J_{CF}=241 Hz), 158.6, 158.1, 152.6, 151.8, 145.8, 134.9, 129.7 (d, J_{CF}=6 Hz), 129.5 (d, J_{CF}=6 Hz), 124.5, 115.5, 57.6, 41.7, 33.1, 27.1, 10.9, 10.7,

^{19}F-NMR (470 MHz, $CDCl_3$) δ -115.7 (tt), HRMS (ESI) calculated for $C_{20}H_{21}FN_6O_5$ 445.1636 found 445.1631

Raltegravir (1) potassium salt. To a suspension of raltegravir free phenol (100 g, 0.23 mol) in EtOH (1.0 L) a solution of KOH (17.7 g) in 0.75 L H_2O was added slowly over a period of 30 min. To the reaction mixture 1.0 L EtOH was then added over 30 min. The reaction was stirred at 25 ^oC for 90 min. A colorless solid was formed that was collected by filtration and rinsed with 0.5 L EtOH. The cake was dried further for 10 h at 50^oC under vacuum to afford raltegravir potassium salt (**1**) (95.0 g, 88% yield, 99.8% purity). mp 267.2-267.6 ^oC. IR (film) 3416, 3259, 1697, 1639, 1572, 1536, 1509, 1486 cm^{-1}, ^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 1 H), 9.75 (s, 1H), 7.34-7.31 (m, 2 H), 7.13-7.10 (m, 2 H), 4.45 (d, J = 6.0 Hz, 2 H), 3.40 (s, 3 H), 2.56 (s, 3 H), 1.70 (s, 6 H), ^{13}C-NMR (125 MHz, DMSO-d_6) δ167.3, 165.9, 165.4, 161.9 (d, J_{CF}=242 Hz), 159.9, 158.6, 157.4, 151.9, 137.9, 137.1 (d, J_{CF}=3 Hz), 129.0 (d, J_{CF}=8 Hz), 122.4, 114.9 (d, J_{CF}=22 Hz), 57.2, 40.9, 32.1, 26.9, 10.7. ^{19}F-NMR (470 MHz, $CDCl_3$) δ -116.7 (br s).

ASSOCIATED CONTENT

^{1}H, ^{13}C and ^{19}F NMR spectra of compounds **8**, **18** and **1** are listed in the Supporting Information. Experimental details of the performed HPLC method and the chromatograms of compound **8** and final API raltegravir (**1**) potassium salt are also included. The following files are available free of charge.

^{1}H, ^{13}C and ^{19}F NMR spectra (file type, i.e., PDF)

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ABBREVIATIONS

API, Active Pharmaceutical Ingredient; DMAD**,** dimethyl acetylenedicarboxylate; NMP, *N*-methyl-2-pyrrolidone; DMSO, dimethylsulfoxide; HPLC, high performance liquid chromatography; HMDS, hexamethyldisilazine; THF, tetrahydrofuran; TMSCl, trimethylchlorosilane; TLC, thin layer chromatography.

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[7] NMP belongs to Class 2 in the classification of Organic solvents (ICH Q3C, guideline for residual solvents, 2016).

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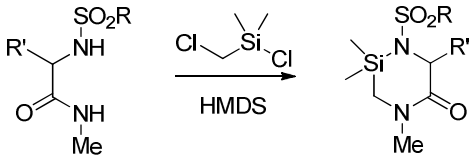

[12] Although acetonitrile belongs to Class 2 of organic solvents, as NMP does, its removal to the dictated limits is much more effective.

[13] The exact structure of the intermediate could not be unambiguously determined by common spectroscopic techniques (NMR, HPLC and LC-MS) due to the inherent instability of both suggested compounds.

[14] Intermediate **17** also proved too labile for its structure to be identified.

[15] Under these reaction conditions, the formation of **7** in crude **8** seemed inevitable. Suppression of impurity **7** was achieved by using TMSCl/Et_3N in place of HMDS, however the

material thus produced was of diminished purity. Efforts to improve the impurity profile of **8** obtained by the aforementioned modification are currently underway.

[16] The deprotected amine **18** was found to be free of the corresponding non-methylated impurity (< 0.1% by HPLC).

[17] Precipitation of compound **18** from a more dilute methanolic solution allows for more effective reduction of water content from the precipitate. For more details see experimental part.

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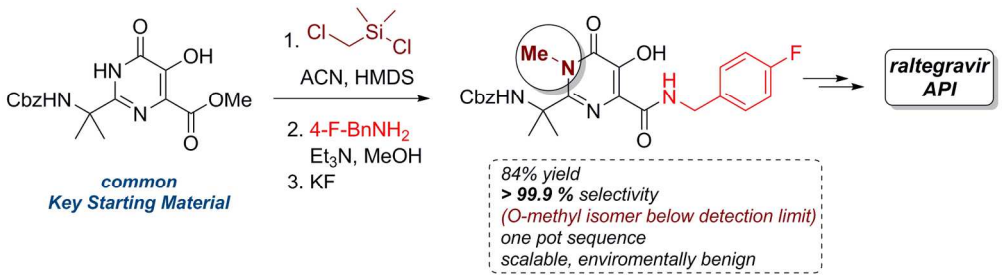

graphical abstract

173x47mm (300 x 300 DPI)