Organic Process Research & Development **2011,** *15,* 73–83

Development of a Second-Generation, Highly Efficient Manufacturing Route for the HIV Integrase Inhibitor Raltegravir Potassium

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Abstract:

A manufacturing route for the synthesis of raltegravir potassium 1 was developed via a thermal rearrangement of amidoxime DMAD adducts 6 to construct the key, highly functionalized hydroxypyrimidinone core 7. Utilizing this route 1 was prepared in nine linear chemical steps with 22% overall yield. A second-generation synthesis was subsequently developed that solved the key chemical, productivity, and environmental impact issues of the initial synthesis. Highlights of the new synthesis include a highly selective methylation, 3−4-fold higher productivity, and a 65% reduction of combined organic and aqueous waste produced. The efficient second-generation manufacturing route provides raltegravir potassium 1 in 35% overall yield.

Introduction

HIV/AIDS remains a significant cause of morbidity and mortality worldwide. The Joint United Nations Program on HIV/AIDS estimated in 2007 that more than 33 million people lived with the disease worldwide and that AIDS killed more than 2 million people, including 330,000 children.[1,2] In the United States alone, the Centers for Disease Control estimated in 2006 that more than a million people were living with HIV infection.[3] Raltegravir potassium, or Isentress (**1**), was the first FDA-approved inhibitor of HIV integrase. Launched in 2007, raltegravir was originally indicated for combination therapy with other antiretroviral agents in treatment-experienced adults with evidence of viral replication and multidrug-resistant HIV-1 strains. In July 2009, the FDA approved an expanded indication for raltegravir to include treatment-naive adult patients, and in December 2009, the United States Department of Health and Human Services revised its HIV treatment guidelines to add a raltegravir combination to the preferred regimens for treatment-naive HIV patients.[4]

The medicinal chemistry synthesis of free phenol **1** was carried out in 10 linear steps in 3% overall yield (Scheme 1).[5] Strecker reaction of acetone cyanohydrin **2** followed by Cbz-protection of **3** and hydroxylamine addition to the nitrile group gave amidoxime **5**. The subsequent two-component coupling reaction between **5** and dimethyl acetylenedicarboxylate (DMAD) afforded a *Z/E* mixture of adducts **6**. Thermal rearrangement of **6** provided the key hydroxypyrimidinone intermediate **7**. Selective hydroxyl group protection, *N*-methylation using dimethylsulfate and lithium hydride then hydrogenation to cleave the Cbz-group, gave free amine **10**. Amide coupling of **10** with oxadiazole carbonyl chloride **11** provided intermediate **12**, which was converted to raltegravir free phenol **1** by amidation with 4-fluorobenzylamine (4-FBA).

The synthesis utilizes inexpensive starting materials and reagents and constructs the highly functionalized hydroxypyrimidinone core **7** in an efficient and atom-economical fashion. However, several steps, including the Strecker reaction, the thermal rearrangement, the unselective *N*-methylation, and the final amidation gave low yields, were therefore unproductive, and required substantial optimization for a multikilogram route. Repeated use of solvents such as chloroform, dichloromethane, and 1,4-dioxane was undesirable for large-scale use due to environmental concerns, toxicity, and cost.

While suitable, with minor modifications, for a small drug delivery to enable the start of initial safety assessment work, we desired a higher-yielding, more environmentally friendly and robust route for large-scale manufacturing purposes.

Results and Discussion

First-Generation Process for the Synthesis of 1. To address the aforementioned chemical and environmental issues, we began by investigating the synthesis of the key hydroxypyrimidinone **7**. The synthesis of amidoxime **5** was optimized

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(1) Kallings, L. O. *J. Intern. Med.* **2008**, *263* (3), 218–243.

(2) AIDS epidemic update: December 2007 *Joint United Nations Program on HIV/AIDS (UNAIDS) WHO*; UNAIDS/07.27E/JC1322E; ISBN: 978 92 9 173621 8, **2007**

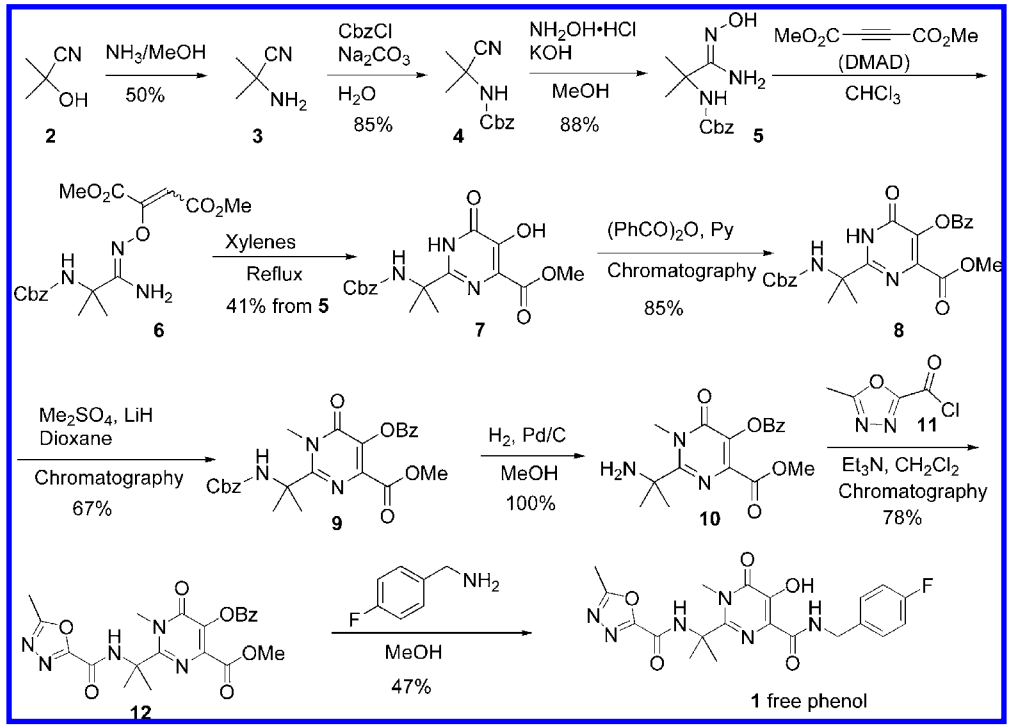
(3) *HIV/AIDS Surveillance Report - 2006*; Centers for Disease Control and Prevention, **2008**; Vol. 18.

(4) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Panel on Antiretroviral Guidelines for Adults and Adolescents; U.S. Department of Health and Human Services. December 1, 2009; pp 1−161. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

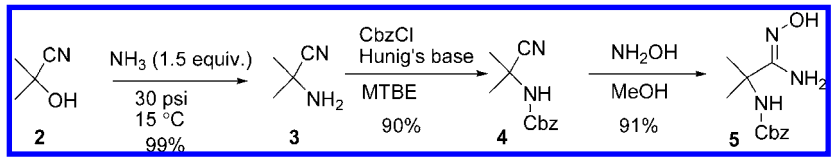
(5) (a) Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Gardelli, C.; Gonzalez Paz, O.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M. J. *J. Med. Chem.* **2008**, *51*, 5843–5855. (b) Belyk, K. M.; Morrison, H. G.; Jones, P.; Summa, V. Preparation of *N*-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidine-4-carboxamide potassium salts as HIV integrase inhibitors. PCT Int. Appl. WO/2006/060712, 2006.

10.1021/op100257r
Published on Web 11/16/2010

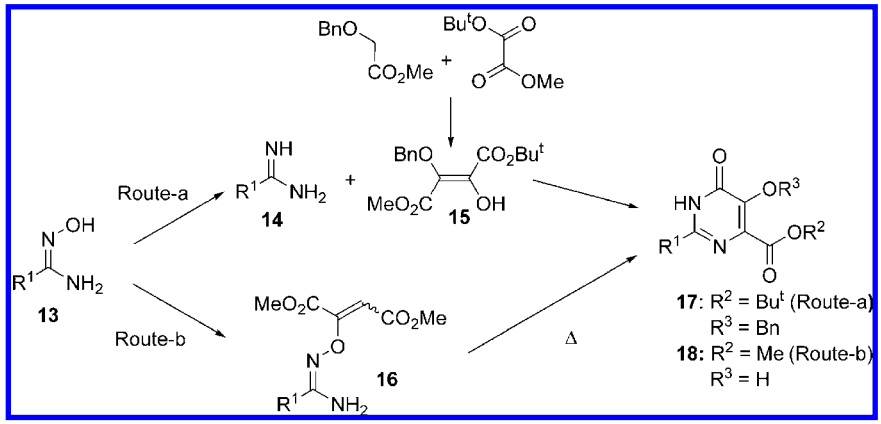
Scheme 1. **Medicinal chemistry route for the synthesis of free phenol 1**



Scheme 2. **Optimized synthesis of amidoxime 5**



Scheme 3. **Synthetic methods for the construction of hydroxypyrimidinone 7**



from acetone cyanohydrin **2**. Under the new conditions, the Strecker reaction was achieved in 99% yield using 1.5 equiv of neat liquid ammonia at 30 psi and 15 °C. Aminonitrile **3** was converted to the *N*-Cbz-protected intermediate **4** by treatment with benzyl chloroformate in 90% assay yield. Hydroxylamine addition to the nitrile **4** provided amidoxime **5** as a crystalline solid in 91% isolated yield. The overall isolated yield for the three-step sequence to **5** was increased from 37% to 81% (Scheme 2).

With the amidoxime **5** in hand, the synthesis of hydroxypyrimidinone **7** was investigated. A survey of the literature showed two ways of constructing the hydroxypyrimidinone core, both methods starting from an amidoxime intermediate (Scheme 3). Route-a involved a three-step sequence that included hydrogenation of **13** to prepare amidine **14**. Claisen condensation of commercially available α-benzyloxy acetate and methyl *tert*-butyl oxalate provided the dihydroxyfumarate derivative **15**, and subsequent condensation between **14** and **15** provided the benzyl-protected pyrimidinone **17**.[6] However, the moderate yield for this sequence, the stability concerns with **15**, and the overall poor atom-economy were not suitable for our long-term synthesis. On the other hand, route-b starts with a Michael reaction between **13** and DMAD, followed by a thermal rearrangement to hydroxypyrimidinone **18**.[7] Although the initial yield for the thermal rearrangement step was only 41%, the high atom-economy and simplicity were very attractive

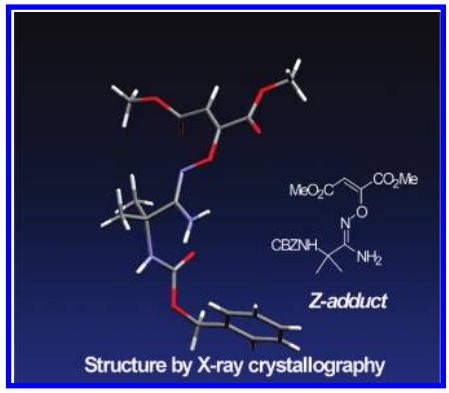


Figure 1

from a long-term route development perspective and warranted further investigation.

Addition of amidoxime **5** to DMAD typically afforded a mixture of *E*/*Z* adducts **6**. A solvent screen showed that, with nonpolar solvents such as *o*-xylene or xylenes,[8] the rearrangement reaction provided a higher assay yield and proved to be a better solvent choice. Initial experiments for the thermal rearrangement of a mixture of *E*- and *Z*-adducts **6** in *o*-xylene at 125 °C indicated that one of the isomers was consumed faster than the other. In order to understand the chemistry, the two isomers were separated using chromatography and the structure of *Z*-adduct **6*Z*** determined by the X-ray crystallography (Figure 1). The *E*- and *Z*-adducts were separately subjected to the thermal rearrangement conditions (Scheme 4). The thermal rearrangement of **6*Z*** was completed at a lower temperature (125 °C) and gave a 72% assay yield of product **7**. On the other hand, thermal rearrangement of **6*E*** required higher temperature (135 °C) to reach full conversion and afforded a lower assay yield.[9]

In order to improve the yield and minimize the reaction time and temperature, *Z*-selective amidoxime addition was investigated. While **6*E*** was favored in strongly aprotic polar solvents such as DMF and DMSO (Table 1, entries 1 and 2), **6*Z*** was obtained as the major component in methanol (entry 6). The stereoselectivity of **6*Z*** vs **6*E*** was improved in MeOH at lower temperature (entry 7). A similar result was observed when the reaction was run in THF or dichloroethane in the presence of catalytic amount DABCO (entries 9 and 10). Isomerization of **6*E*** to **6*Z*** was unsuccessful under typical double bond isomerization conditions such as heating with catalytic acids, bases, or iodine/trialkylphosphines.[10] The *Z*/*E* stereoselectivity was lower using diethyl acetylenedicarboxylate instead of DMAD.

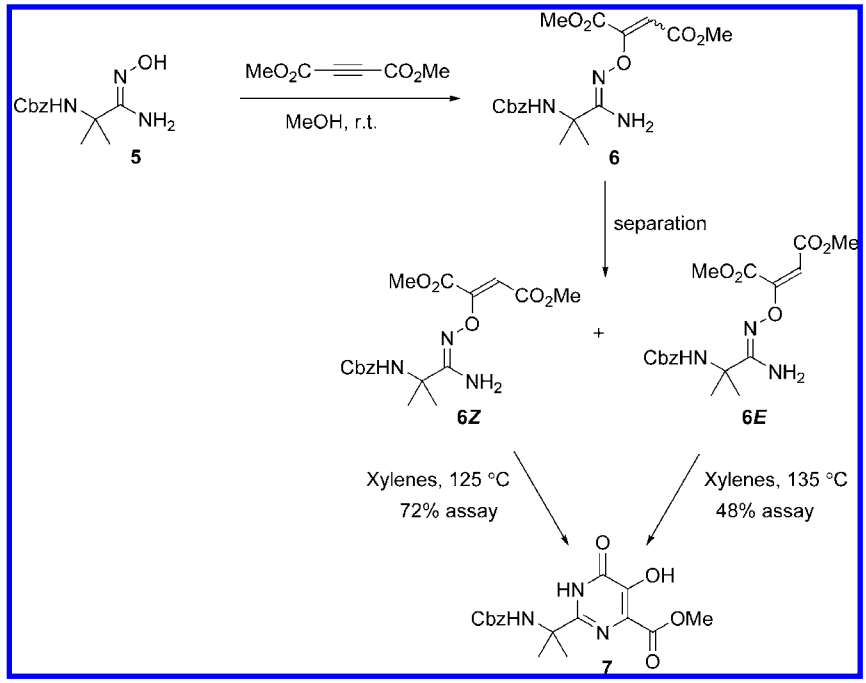
Table 1. **Optimization of stereoselective amidoxime 5 addition to DMAD**

entry	solvent	additive (mol %)	*T* (°C)	conversion (%)	*Z*/*E* ratio[a]
1	DMF	N/A	rt	100	2:98
2	DMSO	N/A	rt	100	1:99
3	MeCN	N/A	rt	100	20:80
4	DCM	N/A	rt	70	31:69
5	Xylenes	N/A	80	100	21:79
6	MeOH	N/A	rt	100	65:35
7	MeOH	N/A	−10	100	75:25
8	AcOH	N/A	rt	30	50:50
9	THF	DABCO (15)	−70	100	79:21
10	1,2-DCE	DABCO (5)	rt	100	74:26

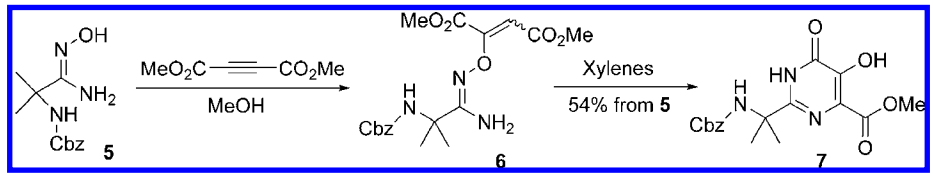
[a] *Z*/*E* ratio determined by NMR and HPLC analysis.

Although the highest ratio of **6*Z*** to **6*E*** was obtained in THF at −70 °C with a catalytic amount of DABCO, further experiments showed that DABCO must be removed prior to the thermal rearrangement.[11] Due to the minimal impact on overall yield and ease of processing, the Michael addition was run in methanol at 15−20 °C to afford a mixture of the *Z*- and *E*-adducts **6** in quantitative yield. The resulting solution of adducts **6** was solvent-switched to xylenes, then heated at 125 °C for 2 h, and at 135 °C for 4 h to give a 62% assay yield of desired product **7**. The reaction mixture was concentrated and

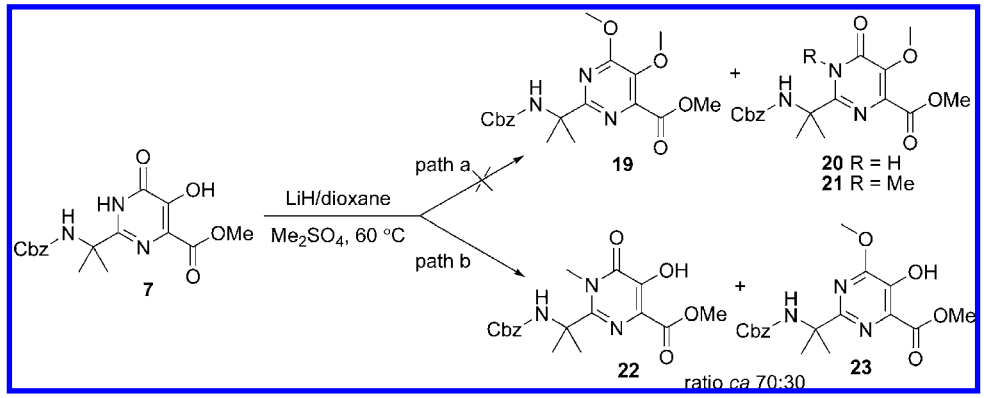
Scheme 4. **Thermal rearrangement of *E*- and *Z*-amidoxime-DMAD adducts 6*E* and 6*Z***



Scheme 5. **Synthesis of hydroxypyrimidinone core 7**



Scheme 6. **Direct *N*-methylation of hydropyrimidinone 7**



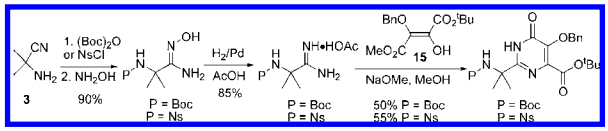
hydroxypyrimidinone **7** obtained by direct crystallization in 54% isolated yield as a white crystalline solid (Scheme 5).[12]

With the key hydroxypyrimidinone **7** in hand, optimization of the *N*-methylation was performed. In the initial medicinal chemistry route the phenolic OH was protected as a benzoate ester prior to *N*-methylation. In order to minimize the use of protecting groups, the direct *N*-methylation of hydroxypyrimidinone **7** was investigated. Unexpectedly, methylation of **7** gave a clean mixture of desired *N*-methyl product **22** and undesired *O*-methyl byproduct **23** as a 70:30 mixture (path-b, Scheme 6). HPLC and NMR analysis revealed that methyl ethers **19**−**21** were not formed in this reaction (path-a, Scheme 6).

The optimization of the methylation reaction was further investigated to improve the regioselectivity and yield and to eliminate the use of 1,4-dioxane and LiH (Table 2). Interestingly, the selectivity was significantly improved by addition of 1 equiv of $MgBr_2 \cdot OEt_2$ to the reaction in DMF (entry 6). The study showed the best performance came from the use of methyl iodide and $Mg(OMe)_2$ in DMSO at 60 °C (entry 13). Under these conditions, **22** was obtained in high purity (<1% **23**) in a 70% isolated yield, after isolation by crystallization from aqueous DMSO. A possible mechanism involving chelation between the hydroxypyrimidinone **7** and $Mg(OMe)_2$ was proposed (**24** and **25** in Scheme 7).

The initial medicinal chemistry route installed the oxadiazole fragment prior to introduction of the 4-fluorobenzylamine (4-FBA). Chromatography was required, and the product was obtained in a low 37% overall yield. In an attempt to improve the chemical yield, amidation of **22** with 4-FBA prior to

(6) (a) Johnson, T. B.; Caldwell, W. T. *J. Am. Chem. Soc.* **1929**, *51*, 873–880. (b) Budesinsky, I.; Jelinek, V.; Prikryl, J. *J. Collect. Czech. Chem. Commun.* **1962**, *27*, 2550–2560. (c) Sunderland, C. J.; Botta, M.; Aime, S.; Raymond, K. N. *Inorg. Chem.* **2001**, *40*, 6746–6756. (d) Dreher, S. D.; Ikemoto, N.; Gresham, V.; Liu, J.; Dormer, P. G.; Balsells, J.; Mathre, D.; Novak, T. J.; Armstrong, J. D., III *Tetrahedron Lett.* **2004**, *45*, 6023–6025. (e) Employed this three-step sequence, the hydroxypyrimidinones were prepared in 38−42% overall yields from **3** as shown below:



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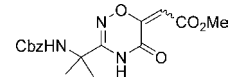
(8) For solvent screening on the reaction, please see: reference 7e.

(9) For details of the thermal rearrangement mechanism of **6**, please see: Pye, P. J.; Zhong, Y.-L.; Jones, G. O.; Reamer, R. A.; Houk, K. N.; Askin, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 4134.

(10) Treatment of **6** with sodium methoxide afforded a *Z*/*E* mixture of methyl [3-(2-{[(benzyloxy)carbonyl]amino}propan-2-yl)-5-oxo-4,5-dihydro-6*H*-1,2,4-oxadiazin-6-ylidene]ethanoate, which could not be converted to hydroxypyrimidinone **7** in the typical thermal rearrangement conditions and decomposed at higher temperature.



(11) In one instance the thermal isomerization in the presence of DABCO resulted in an uncontrolled exotherm causing product decomposition and low yield.

(12) About 5% of the imidazole was generated from the reaction.

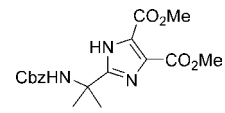
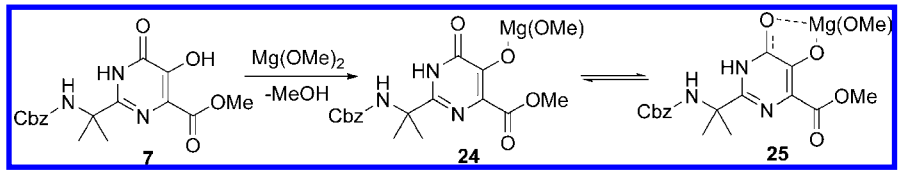


Table 2. **Optimization of direct methylation of hydroxypyrimidinone 7**

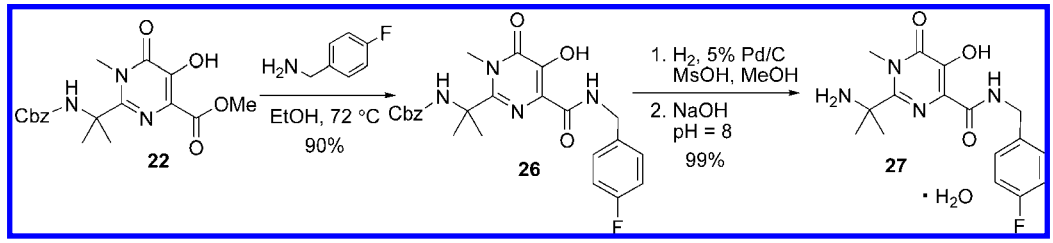
entry	reagent	base	solvent	additive	*T* (°C)	conversion (%)	**22:23** ratio[a]
1	Me_2SO_4	$LiOBu^t$	MeOH	N/A	50	25	16:84
2	Me_2SO_4	$LiOBu^t$	Toluene	N/A	50	40	48:52
3	Me_2SO_4	$LiOBu^t$	THF	N/A	50	74	47:53
4	Me_2SO_4	$LiOBu^t$	DMSO	N/A	50	100	12:88
5	Me_2SO_4	$LiOBu^t$	DMF	N/A	80	100	9:91
6	Me_2SO_4	$LiOBu^t$	DMF	$MgBr_2 \cdot OEt_2$	80	86	48:52
7	MeI	$LiOBu^t$	DMF	N/A	80	65	36:64
8	MeI	$Mg(OMe)_2$	THF	N/A	20	16	52:48
9	MeI	$Mg(OMe)_2$	DMF	N/A	35	58	64:36
10	MeI	$Mg(OMe)_2$	NMP	N/A	20	70	63:37
11	MeI	$Mg(OMe)_2$	DMAc	N/A	20	68	61:39
12	MeI	$Mg(OMe)_2$	DMSO	N/A	35	56	78:22
13	MeI	$Mg(OMe)_2$	DMSO	N/A	60	100	78:22

[a] Determined by ^{1}H NMR and HPLC analysis.

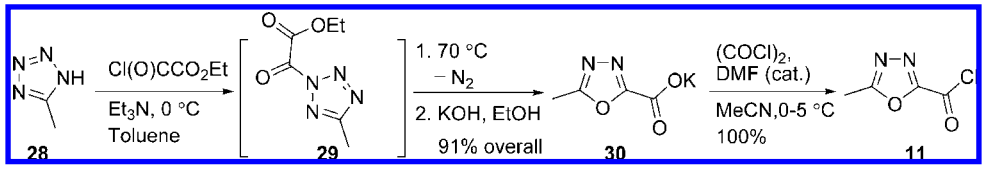
Scheme 7. **Proposed chelation of 7 with Mg^{2+}**



Scheme 8. **Synthesis of free amine 27**



Scheme 9. **Preparation of oxadiazole carbonyl chloride fragment 11**



installing the oxadiazole moiety was investigated. Thus, treatment of intermediate **22** with 2.2 equiv of 4-FBA in EtOH at 72 °C afforded **26** in 90% isolated yield (Scheme 8). Hydrogenation of **26** in the presence of 5% of Pd/C and 1 equiv of MsOH, to efficiently remove the Cbz-protected group, followed by neutralization of the crude reaction mixture with NaOH, afforded crystalline free amine **27** in 99% isolated yield as a monohydrate. Unfortunately, the hydrate was very stable and conventional oven-drying techniques failed to provide anhydrous amine suitable for the acylation reaction. Thus, azeotropic water removal using THF was used to dry the amine prior to use in the acylation reaction.

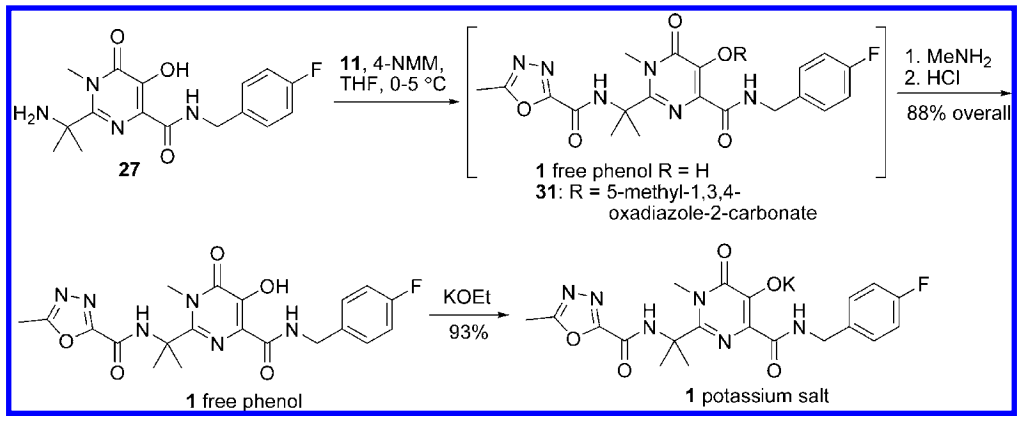
Modification of a literature procedure[13] provided an efficient process for the oxadiazole fragment (Scheme 9). Acylation of tetrazole **28** with ethyl oxalyl chloride afforded intermediate **29**, which was heated at 70 °C to form the oxadiazole ester. Direct KOH-mediated hydrolysis afforded the corresponding potassium salt **30** as a crystalline solid, in 91% overall yield. Treatment of **30** with oxalyl chloride in the presence of a catalytic amount of DMF provided 5-methyl-1,3,4-oxadiazole-2-carbonyl chloride **11** in quantitative yield.

Finally, coupling reaction of free amine **27** with acid chloride **11** was conducted in the presence of *N*-methylmorpholine (4-NMM) to generate a mixture of the desired free phenol **1** and the ester **31** in 10:1 ratio (Scheme 10). Treatment of the crude reaction mixture with aqueous methylamine to cleave the ester linkage in **31**, followed by acidification with HCl provided free phenol **1** in 88% isolated yield. Raltegravir **1** was isolated as a crystalline potassium salt (1:1 molar ratio) by addition of KOEt to a solution of the free phenol **1** in a 93% yield and 99.5% purity (Scheme 10). This process for the manufacture of **1** was used to produce API through launch.

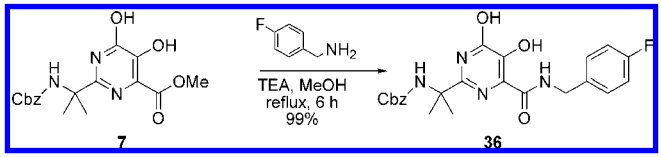
Second-Generation Process for the Synthesis of 1. The construction of the hydroxypyrimidinone **7** via the cycloisomerization chemistry used inexpensive and readily available raw materials, provided the complex core in a single step with high efficiency, and was robust and simple to perform with a direct crystallization to afford the product **7** with good purity. Thus, the majority of the synthesis redesign was targeted at the

(13) Ogilvie, W.; Rank, W. *Can. J. Chem.* **1987**, *65*, 166.

Scheme 10. **Complete synthesis of raltegravir potassium 1**



Scheme 11. **Preparation of amide 36**



subsequent chemical steps. Evaluation of each step of the existing route with respect to yield, productivity, efficiency, waste generation (PMI),[14] and solvent use was carried out, and a number of potential areas for improvement were identified.

Considerable work on the methylation reaction was carried out in the first-generation route development. Apart from the moderate yield (70%), the reaction suffered from lower than ideal productivity and very high solvent use, resulting in the production of a large amount of waste. In fact the PMI for this single step was over 100. Since, based on our prior work, complete kinetic regioselectivity was unlikely to be achieved, our attention shifted to the demethylation of **23** followed by a *N*-methylation recycle, which would theoretically permit an eventual 100% overall yield (Scheme 6). Unfortunately, attempted demethylation of **23** under a variety of conditions resulted in extensive decomposition, due in part to the lability of the methyl ester functionality. In order to stabilize the intermediate to the relatively harsh demethylation conditions, we decided to look at reversing the step order and to prepare the amide prior to methylation.

Amide **36** was prepared from hydroxypyrimidinone **7** using 1.2 equiv of 4-FBA in the presence of one equiv of triethylamine in methanol at reflux for 6 h. Addition of acetic acid and water to induce crystallization provided amide **36** in 99% isolated yield after filtration and drying (Scheme 11).

Methylation of amide **36** under the previously optimized conditions [MeI, $Mg(OMe)_2$, DMSO] used for ester **7** provided similar *N*-Me to *O*-Me regioselectivity (78:22). With the increased stability of amide **36** vs ester **7**, higher temperatures and longer reaction times were investigated. Heating the mixture for 4 h at 65 °C gave an 80:20 selectivity for the desired *N*-methylated product **26**. Remarkably, extended heating (20 h) provided a 99:1 selectivity for **26** (Scheme 12). In order to explore the *O*-Me to *N*-Me recycle strategy further, design of experiments (DOE) and extensive use of high-throughput screening was utilized. DOE evaluation of a number of variables including reaction concentration, temperature, time, and equivalents of reagents showed that higher reaction temperature, higher concentration, and higher equivalents of reagents all lead to higher *N*-Me selectivity. Under optimum conditions [4 equiv of $Mg(OMe)_2$, 4 equiv of MeI, 20 h, 65 °C, 1.0 M] *N*-methyl amide **26** was obtained in 90% assay yield in a 99:1, *N*-Me vs *O*-Me ratio.

With successful proof of concept on the in situ conversion of *O*-Me **37** to *N*-Me **26**, we used high-throughput reaction screening to optimize the reaction conditions. Magnesium hydroxide [$Mg(OH)_2$] was selected as the base for optimization due to ready availability and very low cost. Trimethylsulfoxonium iodide [$Me_3S(O)I$] was selected as the methylation reagent[15] due to relative cost, safety profile, and ease of handling when compared with methyl iodide. Both DMSO and DMF were suitable as reaction solvents; however, NMP was chosen for intrinsic safety reasons.

The optimized methylation conditions [2 equiv of $Mg(OH)_2$, 2 equiv of $Me_3S(O)I$, NMP, 100 °C, 6 h) provided >99% conversion and 92% isolated yield of **26** after in situ crystallization, filtration, and drying. Addition of at least 1 equiv of water was essential for complete conversion of the *O*-Me to the *N*-Me product. Under these reaction conditions MeI is released at the reaction temperature resulting in an initial 4:1 mixture of **26**:**37**. In situ, iodide-promoted demethylation of **37** followed by remethylation recycles the undesired *O*-methyl isomer to **26** in a single-pot reaction. The reaction was generally complete after 5 h at 100 °C.[16]

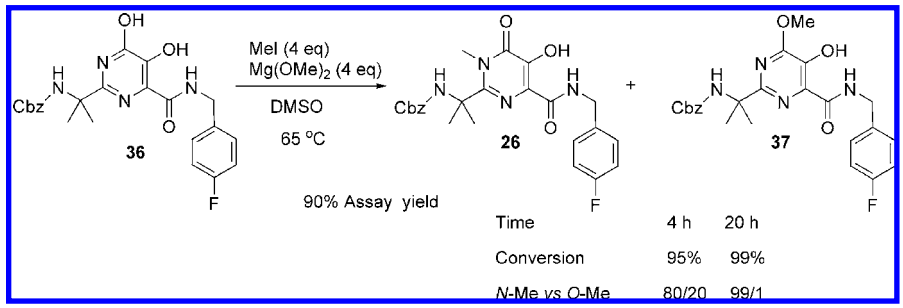
During the final coupling reaction between free amine **27** and oxadiazole **11**, unselective acylation of the phenolic OH occurs to give the bis-acylated compound **31**. Hydrolysis of **31** using $MeNH_2$ or KOH furnishes the coupled phenol **1**. Attempts to overcome the unselective acylation issue using alternative coupling reagents were unsuccessful. Thus, in order to reduce the need for 2.2 equiv of expensive oxadiazole **11** to obtain high conversion/yield, protection of the OH group in amine **27** was employed. Selection of the 'right' protecting group was critical. The group needed to be easily and economically installed in essentially quantitative yield and provide a stable,

(14) PMI = product mass intensity [total raw material input (kg)/quantity of bulk API (kg)]. Augé, J. *Green Chem.* **2008**, *10*, 225.

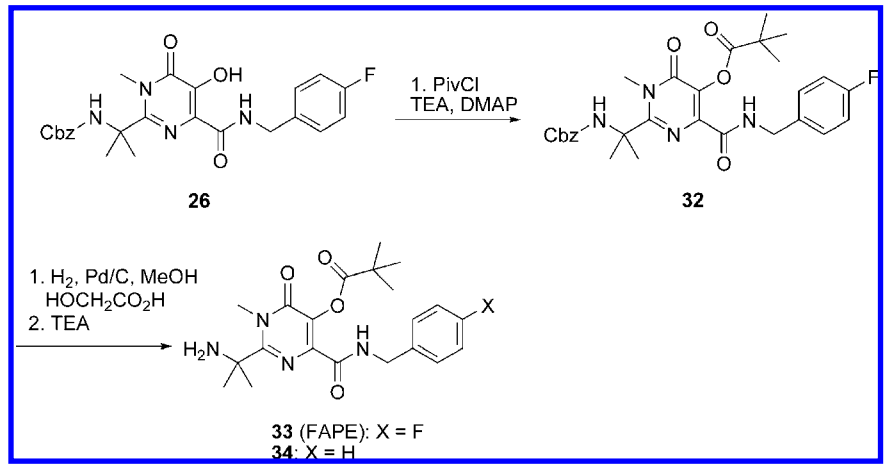
(15) Malik, S.; Nadir, U. K.; Pandey, P. S. *Synth. Commun.* **2008**, *38*, 3074.

(16) The scope, generality, and mechanism of the *O*-Me to *N*-Me rearrangement is under investigation and will be reported separately in due course.

Scheme 12. **Methylation of 36 and conversion of *O*-Me to *N*-Me in situ using MgI_2**



Scheme 13. **Preparation of free-amine pivalate ester 33**



isolable intermediate that could be stored and used directly in the coupling reaction. Ideally the intermediate would be crystalline and nonhygroscopic, obviating the tedious and expensive drying step of amine **27** in the existing process. Last the protecting group would ideally be cleaved under the same conditions (or milder) as used in the current process. The oxadiazole side chain is unstable under basic conditions and care is needed to avoid decomposition. Consequently, a number of acyl protecting groups were evaluated including acetate, propionate, benzoate, and pivalate. A combination of positive attributes led us to select the pivalate ester derivative **33** for further development.[17]

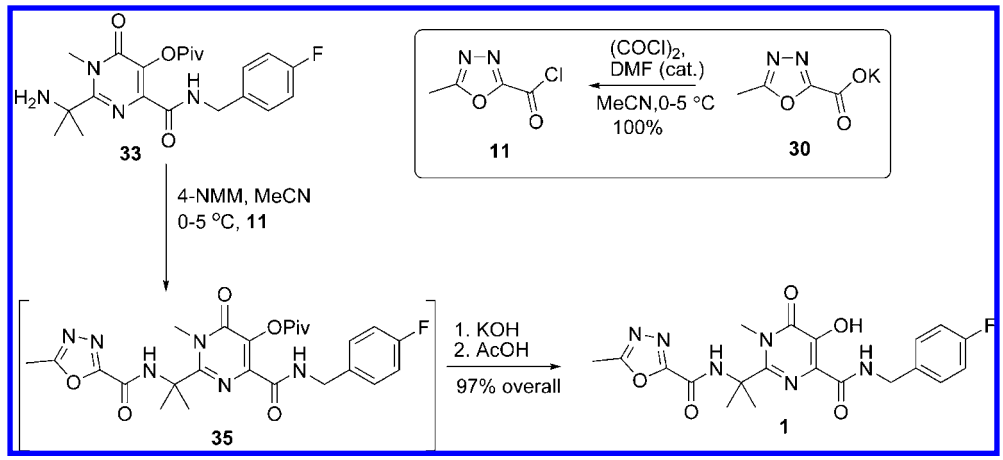
Pivalate ester **33** was prepared in excellent yield (99%) and purity using a highly optimized through-process (Scheme 13). Cbz-amide **26** was acylated with pivaloyl chloride in the presence of triethyl amine and a catalytic amount (0.01 mol %) of DMAP in ethyl acetate. Without DMAP, the reaction was sluggish and typically stalled at 90−95% conversion. Attempted hydrogenation of **32** using the previously employed conditions (Pd/C, MsOH, MeOH) was complicated due to the insolubility of the MsOH salt of the amine **33** in the reaction medium, making catalyst filtration impossible. After screening several different acids, glycolic acid was identified as a suitable counterion with excellent solubility properties for the resulting salt. Glycolic acid proved to be an essential additive allowing complete conversion to the amine without formation of the des-fluoro impurity **34** and maintaining solubility of the free amine in the reaction mixture.[18] In practice, after pivalate ester formation, the crude reaction mixture was washed with water to remove the $NEt_3 \cdot HCl$. Methanol, glycolic acid, and Pd/C were added, and the mixture hydrogenated at 5 psi of hydrogen for 2−3 h, at 20−25 °C. Upon complete conversion, the catalyst was filtered, and the pH of solution was adjusted to pH 9 with triethylamine to crystallize the pivalate ester, **33**, as the free base. The isolated solid was a high-melting, crystalline solid that proved stable to storage in the solid state and gratifyingly was nonhygroscopic between 0 and 95% relative humidity and could be dried easily using conventional drying oven technology.

With crystalline, dry, nonhygroscopic **33** in-hand, reoptimization of the final amide coupling was carried out (Scheme 14). In the original manufacturing route a mixture of solvents was required. THF was used to azeotropically dry the amine **27**, acetonitrile was used to prepare the acyl chloride **11** and IPA/water used to crystallize the free phenol **1.** The volume productivity was low, while solvent waste generation was high and the multisolvent waste mixture produced was difficult to recycle. In order to simplify the process and increase productivity, the coupling and isolation were optimized to a single solvent. Thus, acyl chloride preparation was carried out in acetonitrile at 0−5 °C. A slurry of **33** and NMM in acetonitrile was added to **11** at −10 °C. On completion of the reaction aqueous potassium hydroxide was added to convert **35** into crude **1**. Acetic acid was then added followed by water to crystallize the free phenol **1** in 97% overall isolated yield from **33**. When compared to the original process to couple **11** with **27**, the new process is less complex from a process standpoint, uses

(17) Humphrey, G. R.; Miller, R. A.; Maligres, P. E.; Weissman, S. Process for preparing *N*-substituted hydroxypyrimidinone carboxamides. PCT Int. Appl. WO/2009/088729, 2009.

(18) Des-F **34** results in formation of des-F **1**, an impurity not rejected by crystallization.

Scheme 14. **Optimized synthesis of free phenol 1**



approximately 80% less solvent, and is about 3 times more productive. The new process also uses only 1.15 equiv of expensive acid chloride **11** (vs 2.2 equiv), does not employ any solvent switches or time-consuming concentrations, and provides API **1** in almost quantitative yield.

Conclusion

The first-generation manufacturing process was rapidly and successfully scaled up to provide multiton quantities of bulk drug with consistently high purity. This route satisfied API requirements from Phase II to initial commercial manufacturing batches. The yield of the key hydroxypyrimidinone **7** was increased from 15% in the initial medicinal chemistry route to 44%.

Improvements in the conversion of hydroxypyrimidinone **7** to raltegravir **1** resulted in an increase in overall yield from only 20% in the original medicinal chemistry synthesis to 51% in the first-generation manufacturing route and finally to 84% for the second-generation manufacturing route. The described process was successfully demonstrated at the multihundred kilogram scale. In addition to reducing the overall cost to produce raltegravir, the improvement in overall yield, coupled with a 3- to 5-fold increase in productivity for most steps, resulted in an overall reduction of organic and aqueous waste generation by 65%.

Experimental Section

General. NMR data were obtained using a Bruker AM400 or AM500 spectrometer. HPLC assays were carried out using a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile. All isolated yields reflect correction for purity based on HPLC assays. All reagents and solvents were used as received without further purification.

2-Amino-2-methyl-propionitrile (3). A solution of acetone cyanohydrin **2** (75.0 kg, 882 mol) and MTBE (10 kg, from a line flush) was cooled to 10 °C, and anhydrous ammonia (22.6 kg, 1329 mol) was charged over 2 h, maintaining the reaction temperature between 10−25 °C and the pressure below 30 psi. Once complete conversion was obtained (>99% as determined by GC assay), the vessel was vented to a thermal oxidizer and purged with nitrogen for 15 min to remove residual ammonia. MTBE (73 kg) was added and the batch flushed at constant volume with MTBE to remove residual ammonia to provide **3**[5b,19] (∼50 wt % in MTBE, 73.3 assay kg) in 99% yield.

(Cyano-dimethyl-methyl)carbamic Acid Benzyl Ester (4). A mixture of aminonitrile **3** (36.8 assay kg, 437 mol) and MTBE (307 kg) was cooled to 10 °C and benzylchloroformate (86.1 kg, 505 mol) added over 1 h at 10−25 °C. Diisopropylethylamine (73.1 kg, 566 mol) was added over 1 h at 10−25 °C and the batch aged at 25 °C for 1 h. Water (83.8 kg) was added, the phases were agitated for 30 min, and the lower aqueous layer was separated. The organic phase was washed with water (83.9 kg) and concentrated under reduced pressure and solvent switched to heptane at a volume of about 550 L. The resultant slurry was filtered and washed with heptane (300 kg). The cake was dried to afford **4**[5b,20] (85.6 kg, > 99.9 wt %, > 99.9 LCAP%) in 90% yield, mp 101.0−101.7 °C.

[1-(*N*-Hydroxycarbamimidoyl)-1-methyl-ethyl]carbamic Acid Benzyl Ester (5). A mixture of Cbz-aminonitrile **4** (109 kg, 499 mol) and IPA (220 kg) was warmed to 58 °C and 50% (w/w) aqueous hydroxylamine (35.9 kg, 544 mol) added over 25 min. The solution was aged at 60 °C for 5 h and cooled to −2 °C, and heptane (198 kg) was added over 30 min. The resultant slurry was filtered and washed with heptane (300 kg). The cake was dried at 40 °C under reduced pressure to afford **5**[5] (114.1 kg, >99.9 wt %, 99.8 LCAP%) in 91% yield, mp 160.0−160.5 °C.

2-(1-Benzyloxycarbonylamino-1-methyl-ethyl)-5,6-dihydroxy-pyrimidine-4-carboxylic Acid Methyl Ester (7). A slurry of amidoxime **5** (63.1 kg, 251 mol) and methanol (180 kg) was cooled to 15 °C. Dimethyl acetylenedicarboxylate (38.8 kg, 273 mol) was added over 30 min, maintaining the batch temperature between 15 and 25 °C. The resultant solution was aged at 25 °C for 2 h to obtain >99% conversion and gave Michael adducts **6Z/6E** (ratio ∼65:35 by ^{1}H NMR).

For characterization purposes, a small sample was purified by flash chromatography (silica gel, EtOAc/hexanes) to give

(19) (a) Taillades, J.; Commeyras, A. *Tetrahedron* **1974**, *30*, 3407–3414. (b) Rousset, A.; Lasperas, M.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, *36*, 2649–2661.

(20) (a) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525–2527. (b) Crescenzi, B.; Gardelli, C.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Petrocchi, A.; Poma, M.; Rowley, M.; Scarpelli, R.; Summa, V. Preparation of N-substituted hydroxypyrimidinone carboxamide inhibitors of HIV integrase. PCT Int. Appl. WO/2003/035077, 2003.

6Z and ***6E***. ***6Z*** as colorless needles, mp 76.5−77.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38−7.26 (m, 5 H), 5.75 (s, 1 H), 5.66 (br s, 3 H), 5.08 (s, 2 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 1.54 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 163.2, 161.2, 155.6, 154.9, 136.0, 128.6 (2 C), 128.3, 128.1 (2 C), 102.3, 66.9, 54.3, 52.6, 51.5, 25.9 (2 C). HRMS (ESI) calculated for $C_{18}H_{23}N_3O_7$ $(M + Na)^+$ 416.1434, found 416.1438. ***6E*** as colorless needles, mp 65.0−66.1 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38−7.26 (m, 5 H), 5.83 (s, 1 H), 5.40 (br s, 2 H), 5.08 (s, 1 H), 5.07 (s, 2 H), 3.88 (s, 3 H), 3.69 (s, 3 H), 1.56 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.9, 163.4, 161.3, 160.6, 155.6, 135.8, 128.6 (2 C), 128.3 (2 C), 128.1, 94.9, 67.0, 54.5, 52.8, 51.4, 26.0 (2 C). HRMS (ESI) calculated for $C_{18}H_{23}N_3O_7$ $(M + Na)^+$ 416.1434, found 416.1430.

The solution was concentrated to about 160 L under reduced pressure and solvent switched, by feed and bleed at constant volume, to xylenes. The final batch temperature was maintained below 70 °C during the solvent switch. The mixture was heated to 125 °C, aged for 2 h, warmed to 135 °C for 5 h to complete the reaction and then cooled to 60 °C. Methanol (45 kg) was added and the resultant slurry aged at 35 °C for 1 h. MTBE (145 kg) was added over 1 h at 20−25 °C. The slurry was cooled to −10 °C over 2 h and aged overnight. The slurry was filtered, the cake washed with 9:1 of MTBE:methanol (140 kg) and dried at 40 °C under reduced pressure to afford **7** (49.6 kg, > 99.5 wt %, 98.4 LCAP%) in 54% overall yield, mp 186.3−187.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.23 (br s, 1 H), 10.75 (br s, 1 H), 7.24 (m, 5 H), 6.10 (br s, 1 H), 4.98 (s, 2 H), 3.98 (s, 3 H) 1.69 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.9, 159.4, 155.1, 153.5, 149.4, 136.2, 128.3 (2 C), 128.0, 127.9 (2 C), 126.1, 66.7, 55.6, 53.2, 26.4 (2 C). HRMS (ESI) calculated for $C_{17}H_{19}N_3O_6$ $(M + H)^+$ 362.1352, found 362.1352.

2-(1-Benzyloxycarbonylamino-1-methyl-ethyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic Acid Methyl Ester (22). To a mixture of hydroxypyrimidinone **7** (2.00 kg, 5.53 mol) and DMSO (16 L) was added a solution of 8 wt % of $Mg(OMe)_2$ in MeOH (13.4 L, 11.1 mol, 2.0 equiv). Excess MeOH was then evaporated under vacuum (30 mmHg) at 40 °C. After cooling to 20 °C, MeI (1.38 L, 22.2 mol) was added dropwise, and the mixture was stirred at 20−25 °C for 2 h, then at 60 °C for 5 h and cooled to 20 °C.

2 M HCl (20 L) was added followed by 5 wt % sodium bisulfite (2 L). Water (40 L) was added over 40 min, and the slurry was stirred for 40 min and the resultant slurry cooled to 5 °C. The crystalline product was collected by filtration, washed with water (20 L) and then with 9:1 of MTBE/MeOH (30 L) to remove the *O*-Me byproduct. The product was dried overnight at rt under vacuum with N_2 sweep to give **22** (1.49 kg) in 70% yield, as an off-white crystalline solid, mp 198.5−199.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.35 (br s, 1 H), 7.38−7.26 (m, 5 H), 5.41 (br s, 1 H), 5.01 (s, 2 H), 3.96 (s, 3 H), 3.64 (s, 3 H), 1.70 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.7, 159.5, 154.3, 151.0, 147.9, 136.0, 128.5 (2 C), 128.2 (2 C), 128.1, 123.5, 66.9, 60.3, 53.0, 32.9, 27.8 (2 C). HRMS (ESI) calculated for $C_{18}H_{21}N_3O_6$ $(M + H)^+$ 376.1509, found 376.1507.

For characterization, a small sample of the mother liquors was purified by flash chromatography (silica gel, hexane/EtOAc) to give *O*-methylated byproduct **23** as colorless needles, mp 103.0−103.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.45 (s, 1 H), 7.37−7.26 (m, 5 H), 6.56 (br s, 1 H), 5.10 (s, 2 H), 4.06 (s, 3 H), 4.00 (s, 3 H), 1.74 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.5, 161.4, 161.2, 155.2, 143.6, 137.3, 131.1, 128.4 (2 C), 128.1 (2 C), 128.0, 66.1, 57.2, 54.7, 53.3, 26.9 (2 C). HRMS (ESI) calculated for $C_{18}H_{21}N_3O_6$ $(M + Na)^+$ 398.1328, found 398.1321.

{1-[4-(4-Fluoro-benzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl]-1-methyl-ethyl}carbamic Acid Benzyl Ester (26). To a slurry of *N*-methylpyrimidinone **22** (1.40 kg, 3.73 mol) in EtOH (14 L) at 4 °C was slowly added 4-fluorobenzylamine (1.05 kg, 8.14 mol) over 15 min. The slurry becomes very thick, and vigorous stirring is required. The reaction mixture was warmed to 72 °C over 2 h and kept at this temperature for 2 h (>99.5% conversion).

The reaction mixture was cooled to 60 °C, and AcOH (0.55 L) was added over 30 min. Water (6.7 L) was added over 30 min to afford a slurry. After 30 min at 60 °C, the remaining 7.3 L water was added over 30 min, and the reaction mixture was allowed to cool to ambient temperature. The crystalline solid was collected by filtration, slurry washed with 1:1 of water/EtOH (2 × 4 L), and dried on the filter pot under vacuum with N_2 sweep to constant weight to afford Cbz-amide **26** (1.60 kg, 99 LCAP%) in 90% yield, as white crystalline solid, mp 182.0−182.8 °C. (NMR spectra were acquired at 0 °C: the major carbamate rotamer is reported.) ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.95 (br s, 1 H), 7.83 (t, J = 6.0 Hz, 1H), 7.36−7.28 (m, 7 H), 7.07−7.03 (m, 2 H), 5.42 (s, 1 H), 5.00 (s, 2 H), 4.57 (d, J = 6.0 Hz, 2 H), 3.65 (s, 3 H), 1.67 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 162.4 (d, J_{CF} = 246 Hz), 159.8, 154.5, 151.1, 146.7, 135.9, 133.1 (d, J_{CF} = 3 Hz), 129.6 (d, J_{CF} = 8 Hz), 128.8, 128.7, 128.4, 124.4, 115.9 (d, J_{CF} = 21 Hz), 67.2, 57.3, 42.5, 33.1, 28.1. HRMS (ESI) calculated for $C_{24}H_{25}FN_4O_5$ $(M + H)^+$ 469.1887, found 469.1882.

2-(1-Amino-1-methyl-ethyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic Acid 4-Fluoro-benzyl-amide (27). A solution of amide **26** (1.60 kg, 3.41 mol), methanesulfonic acid (0.20 kg, 3.41 mol, 1.0 equiv), and 5% Pd/C (0.16 kg, 10 wt %) in methanol (12.6 L) at 12 °C was hydrogenated at 15 psi for 2−3 h (>99.5% conversion). The reaction mixture was filtered through Solka Floc (0.72 kg), then washed with 4.5:1 of methanol/water (24 L). The combined filtrate was concentrated to a total volume 15.4 L at 10−23 °C and neutralized by 2.5 NaOH to pH = 8 at 5−23 °C. The resulting slurry was aged at 0−5 °C for 1 h. The crystalline solid was collected by filtration, rinsed with cold water (5.0 L), and dried under vacuum with nitrogen sweep to afford monohydrated free amine **27** (1.19 kg, 99.7 LCAP% purity, 100.2 wt % by $HClO_4$ titration) in 99% yield, mp 188.0−189.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.86 (br s, 1 H), 7.35 (dd, J = 8.6, 5.6 Hz, 2 H), 7.15 (bt, J = 8.6 Hz, 2 H), 4.48 (d, J = 6.0 Hz, 2 H), 3.58 (s, 3 H), 1.63 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.3, 164.2, 162.2 (d, J_{CF} = 243 Hz), 154.9, 153.2, 137.0 (d, J_{CF} = 2 Hz), 130.2 (d, J_{CF} = 8 Hz), 123.3, 116.1 (d, J_{CF} = 22), 57.4, 42.4, 33.9, 27.6 (2 C). HRMS (ESI) calculated for $C_{16}H_{19}FN_4O_3$ $(M + H)^+$ 335.1519, found 335.1517.

Potassium 5-Methyl-[1,3,4]oxadiazole-2-carboxylate (30). Ethyl oxalyl chloride (4.01 kg, 29.4 mol) was slowly added to a mixture of methyl tetrazole **28** (2.50 kg, 29.7 mol; [while 5-methyl-tetrazole is not rated an explosive material (see: http://www.chemicalbook.com/ChemicalProductProperty_EN_CB4290179.htm), it is an irritant and highly flammable. It should be handled only after all hazard data has been reviewed and proper PPE obtained]) and triethylamine (3.03 kg, 30.0 mol) in toluene (32 L) at 0 °C at such a rate that the temperature stayed below 5 °C at all times. (Caution: **29** is a potentially explosive intermediate that will quickly generate nitrogen gas at <50 °C. Conduct this chemistry only after training for handling explosive compounds, and conduct the heating only behind a shield.) The slurry was stirred for 1 h at 0−5 °C. The triethylamine hydrogen chloride salt was filtered off. The solid was washed with 27 L of cold toluene (5 °C). The combined filtrates were kept at 0 °C at all times and were slowly added to a hot solution of toluene (50 °C, 15 L) over 40−50 min. (Caution: N_2 gas evolves. Use the same precautions during heating as above.) Most of the intermediate **29** had been converted to the corresponding non-explosive oxadiazole ester at this moment. The solution was continually stirred at 70 °C for 1 h. After cooling to 20 °C, the toluene solution was washed with 5 L of 10% brine, and solvent was switched to ethanol. EtOH was added to adjust the final volume to approximately 40 L.

The solution was cooled to 10 °C and aqueous KOH (8.0 L) was added over 30 min. The resulting thick slurry was then stirred for 40 min at room temperature while the oxadiazole K salt crystallized. The solid was collected by filtration and washed with EtOH (11 L) and MTBE (15 L). The crystalline solid was dried overnight under vacuum at 20 °C with nitrogen sweep to give oxadiazole K salt **30** (4.48 kg) in 91% yield, mp 258.3 °C dec. ^{1}H NMR (400 MHz, CD_3OD/D_2O = 2:1) δ: 2.62 (S, 3 H); ^{13}C NMR (100 MHz, CD_3OD/D_2O = 2:1) δ: 165.8, 161.8, 158.3, 9.8. MS (FAB) *m/z* 129 (corresponding to free acid, M + H, 100%).

Raltegravir (1) from Amine (27). A slurry of oxadiazole K salt **30** (22.8 g, 96.1 wt %, 132 mmol) in acetonitrile (200 mL) and DMF (0.3 mL) was cooled to 0−5 °C and oxalyl chloride (16.7 g, 132 mmol) added keeping the internal temperature <5 °C. The slurry was aged for 1 h at 0−5 °C.

A slurry of free amine monohydrate **27** (22.2 g, 63 mmol) and THF (260 mL). was azeotropically dried at 45−55 °C to a KF of <150 ppm. The resulting slurry (about 280 mL) was cooled to 0−5 °C and NMM (33.4 g, 330 mmol) added. The acetonitrile slurry of **11** was added slowly maintaining the reaction temperature below 5 °C. The slurry was aged for 1 h. The reaction mixture was quenched with 40% $MeNH_2$ aqueous (31 g, 396 mmol) and the yellow slurry stirred for 30 min at 5 °C. The mixture was acidified to pH 4.3 with 2 N HCl, followed by addition of water (210 mL). EtOAc (200 mL) was added, and the mixture was heated to 30 °C until all solids dissolved. The organic layer was separated. The aqueous layer was extracted with EtOAc (150 mL) at 30 °C. The combined organic layers were washed with brine (200 mL) and water (100 mL). The organics were concentrated to a volume of (100 mL) under vacuum and solvent-switched to MeOH to a final volume of 150 mL. The resulting slurry was then cooled to 0−5 °C and stirred for 1 h. The crystalline solid was collected by filtration and washed with MeOH (70 mL) and water (3 × 100 mL) The product was dried overnight under vacuum with nitrogen sweep at room temperature. Raltegravir **1** (free phenol) was obtained as a white crystalline solid (24.6 g, 99 wt %) in 88% yield, mp 143.0−144.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.20 (br s, 1 H), 9.86 (br s, 1 H), 9.10 (t, J = 6.4 Hz, 1 H), 7.43 (dd, J = 8.6, 5.7 Hz, 2 H), 7.19 (app. t, J = 8.6 Hz, 2 H), 4.54 (d, J = 6.4 Hz, 2 H), 3.52 (s, 3 H), 2.59 (s, 3 H), 1.77 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.5, 166.9, 162.4 (d, J_{CF} = 243 Hz), 159.8, 159.2, 153.7, 152.9, 146.8, 135.9 (d, J_{CF} = 3 Hz), 130.6 (d, J_{CF} = 8 Hz), 125.6, 116.2 (d, J_{CF} = 22), 58.7, 42.8, 34.1, 28.1 (2 C), 11.8. HRMS (ESI) calculated for $C_{20}H_{21}FN_6O_5$ $(M + H)^+$ 445.1636, found 445.1633.

{1-[4-(4-Fluoro-benzylcarbamoyl)-5,6-dihydroxy-pyrimidin-2-yl]-1-methyl-ethyl}-carbamic Acid Phenethyl Ester (36). A slurry of pyrimidine diol **7** (50.0 g, 136 mmol) in methanol (81 mL) was warmed to 55 °C and triethylamine (16.4 g, 163 mmol) added in one portion. The solution was warmed to 65 °C and 4-fluorobenzylamine (20.4 g, 163 mmol) added over 30−40 min at 65−68 °C. The mixture was aged at gentle reflux for 7 h. The solution was cooled to 55 °C and acetic acid (16.3 g, 271 mmol) added over 5 min. Water (17 mL) was added and the reaction solution seeded with product (50 mg) at 60 °C. The resultant slurry was aged at 60 °C for 30 min and the remaining water (65 mL) added over 30 min at 60 °C and then cooled to 20 °C over 2 h. The slurry was filtered, and the cake was washed with 1:1 of methanol/water (60 mL) and dried in a nitrogen stream overnight to afford amide **36** (62.3 g, 96 wt %, KF = 1.75% w/w) in 98% yield, mp 110.3−111.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 12.37 (br s, 2H), 7.95 (br t, J = 6.0 Hz, 1 H), 7.35−7.31 (m, 2 H), 7.25−7.19 (br m, 5 H), 7.08−7.04 (m, 2 H), 6.49 (s, 1 H), 4.96 (s, 2 H), 4.58 (d, J = 6.0 Hz, 2 H), 1.64 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.5, 162.6 (d, J_{CF} = 247 Hz), 160.0, 155.3, 154.1, 147.9, 136.5, 133.1 (d, J_{CF} = 3 Hz), 129.7 (d, J_{CF} = 8 Hz), 128.6, 128.1, 127.9, 127.1, 116.0 (d, J_{CF} = 22 Hz), 66.8, 55.5, 42.7, 26.7. HRMS (ESI) calculated for $C_{23}H_{23}FN_4O_5$ $(M + H)^+$ 455.1731, found 455.1737.

{1-[4-(4-Fluoro-benzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl]-1-methyl-ethyl}-carbamic acid phenethyl ester (26). A mixture of amide **36** (62.4 g, 95.4 wt %, 131 mmol), magnesium hydroxide (15.8 g, 271 mmol), trimethylsulfoxonium iodide (59.4 g, 271 mmol) and water (1.46 mL) was warmed to 100 °C over 2 h and maintained at 100 °C for 5 h. The mixture was cooled to 20 °C and methanol (108 mL) was added. 5 N HCl (54 mL) was added over 15 min followed by seed crystals of product (50 mg). The mixture was aged for 15 min and then a solution of 2.4 M aq sodium bisulfite (3 mL) was added over 1−2 min. The mixture was aged for 1−2 h at 31−35 °C. Five N HCl (54 mL) was added over 1 h. The slurry was gradually cooled to 10 °C over 1 h. The slurry was filtered and the filter cake washed with 1:1 of methanol/water (200 mL). The white granular, crystalline product was dried to a constant weight under a stream of nitrogen to give Cbz-amide **26 (**42 g, 99 wt % purity) in 89% yield, mp 181.8−182.5 °C.

2,2-Dimethyl-propionic Acid 2-(1-Amino-1-methyl-ethyl)-4-(4-fluorobenzylcarbamoyl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-5-yl Ester (33). To a slurry of Cbz-amide **26** (50.0 g, 98 wt %, 105 mmol) in ethyl acetate (150 mL) was added triethylamine (13.7 g, 136 mmol) and DMAP (12.7 mg, 0.15 mmol). The slurry was cooled to 10 °C and pivaloyl chloride (15.1 g, 126 mmol) added over about 30 min maintaining the reaction temperature 10−15 °C. On complete addition, the slurry was aged 15 min at 10−15 °C. Water (50 mL) was added and the mixture warmed to rt. The lower aqueous layer was cut. Methanol (100 mL) and 67 wt % glycolic acid (16.6 g, 125.5 mmol) were added to the organic layer and the crude mixture hydrogenated at 5 psi and 20 °C using 5 wt % Pd/C (1.15 g, 50% wet). On complete reaction, the catalyst was removed by filtration through a Celite plug and the cake washed with methanol (50 mL). The filtrates were combined, and triethylamine (15.8 g, 136 mmol) was added in one portion at rt. The mixture was seeded with amine product **33** (50 mg) and aged for 1 h. Water (150 mL) was added over 1 h at rt. The slurry was aged for 2 h and filtered. The cake was washed with 1:1 of methanol/water (100 mL) and dried to afford **33** (42.9 g, 99 wt %) in 98% yield, as a white crystalline solid, mp 210−211 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (br t, J = 6.0 Hz, 1 H), 7.29−7.25 (m, 2 H), 7.04−7.00 (m, 2 H), 4.53 (d, J = 6.0 Hz, 2 H), 4.01 (s, 3 H), 1.60 (br s, 2 H), 1.59 (s, 6 H), 1.43 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9, 162.4 (d, J_{CF} = 246 Hz), 161.9, 160.5, 160.4, 138.8, 136.6, 133.9 (d, J_{CF} = 3.1 Hz), 129.4 (d, J_{CF} = 7.9 Hz), 115.8 (d, J_{CF} = 21.4 Hz), 56.5, 42.6, 39.4, 34.4, 31.3, 27.3. HRMS (ESI) calculated for $C_{21}H_{27}FN_4O_4$ $(M + H)^+$ 419.2095, found 419.2099.

Raltegravir (1) from Amine (33). A mixture of oxadiazole K-salt **30** (45.7 g, 0.27 mol), acetonitrile (250 mL), and DMF (0.55 mL) was cooled to −5 °C and oxalyl chloride (33.4 g, 0.27 mol) added over 30 min. The slurry was aged at 0−5 °C for 1 h, then cooled to −10 °C.

A solution of amine **33** (99.9 g, 0.24 mol) and acetonitrile (150 mL) was cooled to −10 °C and *N*-methylmorpholine (28.9 g, 0.28 mol) added. The free amine/NMM slurry was added to the above oxadiazole acid chloride **11** at −10 °C over 45 min. 20% aq potassium hydroxide (389 g) was added and the reaction mixture aged at 0−5 °C. HOAc (137 mL) was added over 5 min and the reaction mixture warmed to 15 °C. Water (800 mL) was added slowly. Seed **1** (2 wt %) was added to prevent supersaturation. The slurry was aged for 1 h and filtered. The cake was washed with 2.5:1 water/acetonitrile (300 mL), water (300 mL) and dried to afford raltegravir **1** (104 g, >99.5 wt %) in 97% yield, mp 143.5−144.5 °C.

Raltegravir Potassium 1. To a suspension of phenol **1** (200 g, 4.50 mol) in ethanol (270 mL) and water (270 mL) was added aq KOH (45 wt %, 35.7 mL, 423 mmol) at 20 °C. After 30 min the cloudy solution was filtered through a 1μm filter, seeded, at rt with potassium salt **1** (9.0 g). The slurry was aged for 1 h and EtOH (2.9 L) added at 20 °C over 1 h. The slurry was cooled to <5 °C and aged for 2 h. The batch was filtered, washed with EtOH (500 mL), and dried to afford raltegravir potassium **1** (194 g, > 99 wt %) as a white crystalline solid in 94% yield, mp 274.2−275.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.65 (t, J = 6.0 Hz, 1 H), 9.75 (s, 1 H), 7.36 (dd, J = 8.6, 5.7 Hz, 2 H), 7.14 (app. t, J = 8.6 Hz, 2 H), 4.48 (d, J = 6.0 Hz, 2 H), 3.43 (s, 3 H), 2.58 (s, 3 H), 1.73 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.7, 167.0, 166.6, 162.1 (d, J_{CF} = 243 Hz), 159.7, 158.3, 153.1, 139.6, 138.0 (d, J_{CF} = 3 Hz), 130.2 (d, J_{CF} = 8 Hz), 123.7, 116.0 (d, J_{CF} = 22), 58.4, 42.1, 33.3, 28.1 (2 C), 11.7.

Acknowledgment

We thank the following individuals from Merck Research Laboratories for their support during this work: Richard G. Ball, Nancy Tsou, Jennifer R. Foley, Spencer Dreher, David L. Hughes, Tony Hudgens, Jaemoon Lee, Amar J. Mahajan, Dermot O'Brien, Michael Palucki, Paul Phillips, Vanessa M. Pruzinsky, Mary Stanik, Dietrich Steinhubel, and Timothy J. Wright.

Received for review September 22, 2010.

OP100257R