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Synthesis of Filibuvir. Part II. Second-Generation Synthesis of a 6,6-Disubstituted 2*H*-Pyranone via Dieckmann Cyclization of a β-Acetoxy Ester

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Supporting Information

ABSTRACT: This paper describes an improved sequence for the conversion of an oxazolidinone (**3**) to a β-keto lactone (**5**). The primary drivers behind this change were the modest and variable yields observed in the intramolecular cyclization to generate the β-keto lactone. Changing the cyclization substrate from oxazolidinone to alkyl ester offered a significantly improved cyclization, as well as improvements in the alkyne hydrogenation. Selection of the optimal substrates for methanolysis and intermediate salt formation are also described.

INTRODUCTION

In the previous paper (Synthesis of Filibuvir. Part I) we described an approach to filibuvir (**1**) in which control of the C−O chirality was achieved through Evans aldol methodology. This led to a diastereoselective synthesis of propargylic alcohol **3** (Scheme 1). Through a sequence of Sonogashira coupling, acylation, and hydrogenation, this intermediate was converted to acetate **4**, which in turn served as a substrate for a Dieckmann-type cyclization to form β-keto lactone **5**. There were several problems encountered with this route, the most significant being low and variable yields in the cyclization of **4** to form **5**, particularly upon scale-up. Our analysis of the competing elimination pathways in this reaction suggested that changing the acyl oxazolidinone to a less acidic carbonyl group might improve the efficiency of the cyclization. This paper describes the results of these studies, leading to a more efficient conversion of **3** to β-keto lactone **5** via Dieckmann cyclization of a β-acetoxy methyl ester.

ALTERNATIVE ROUTE INVESTIGATION

In addition to the successful ester Dieckmann route (vide infra), we also considered a convergent Dieckmann approach in which the triazolopyrimidine fragment was present in the cyclization substrate (in the route ultimately developed, this fragment is installed via a reductive coupling after formation of the β-keto lactone; see the subsequent paper in this series, Synthesis of Filibuvir. Part III). Two substrates were prepared to study this cyclization, as shown in Scheme 1 (see Supporting Information for details on their preparation as well as evaluation of some related substrates). With oxazolidinone **7**, only trace amounts of **1** were formed by HPLC analysis. With ethyl ester **8**, a reasonable 76% in situ yield of **1** was observed. However, the lengthy synthesis of substrate **8** was not competitive with the route ultimately developed (vide infra).

OPTIMIZATION OF THE CYCLIZATION SUBSTRATE

As discussed in the preceding paper, elimination via C_2 deprotonation to form α,β-unsaturated acyloxazolidinones was problematic during the base-mediated cyclization (Scheme 3). We reasoned that changing the oxazolidinone to other carbonyl groups might alter the relative acidities of C_2 and C_3' and reduce the level of elimination byproducts, thereby improving the efficiency of the desired cyclization.

We prepared several carboxylic acid derivatives and studied their cyclizations, as summarized in Table 1 (see Supporting Information for details on preparation of substrates **10**−**13**). The substrates are arranged in order of decreasing elimination. Entry 2 represents the original cyclization substrate (**4**). Thioester **10** exhibited more elimination than the oxazolidinone. Weinreb amide **11** gave comparable results to the oxazolidinone. Ethyl ester **12** gave the best results with 90% cyclization and 7% elimination. Pyrrolidine amide **13** suffered no elimination, but also failed to cyclize (likely reflecting the poor leaving group ability of the pyrrolidinyl anion). This trend tracks reasonably well with the estimated acidity of C_2 (these estimates reflect the consensus evaluation of several chemists on the team, with guidance from the literature where available).[1]

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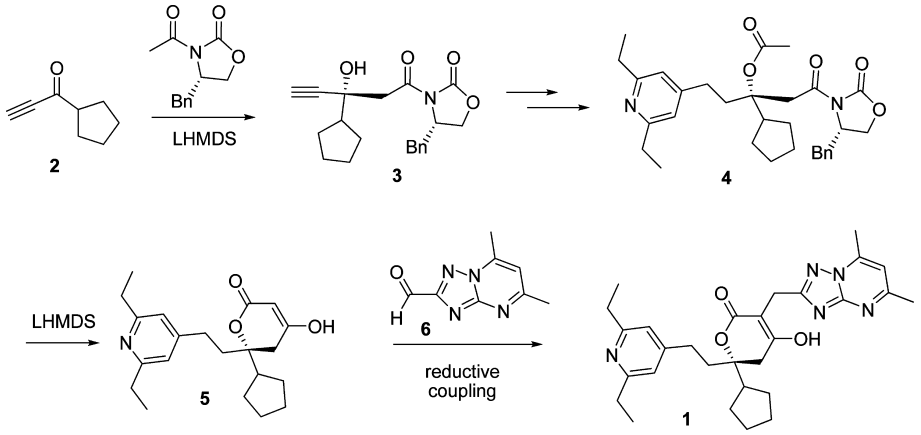
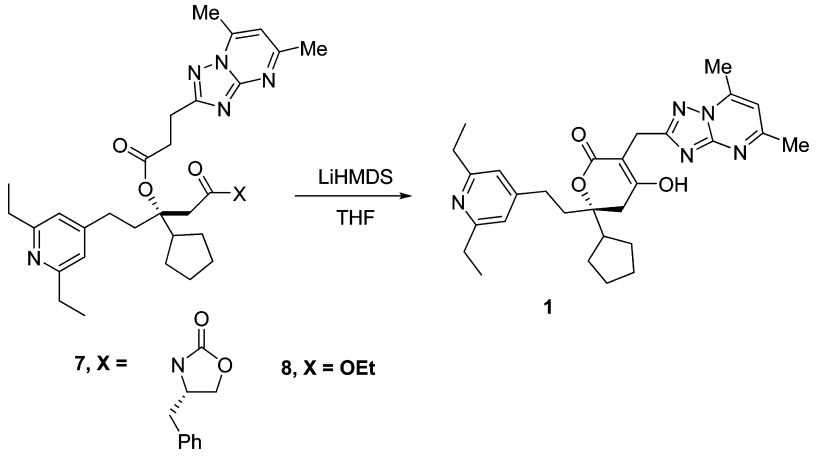
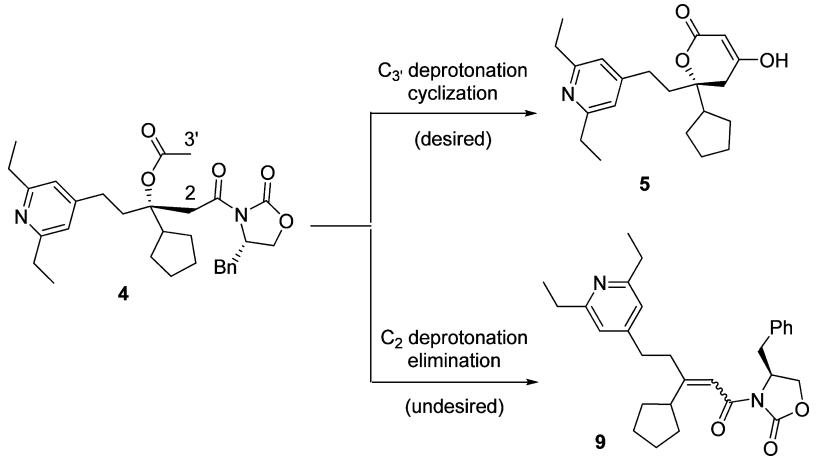
Scheme 1. Evans aldol approach to filibuvir (1)



Scheme 2. Convergent Dieckmann approach with oxazolidinone (7) and ester (8) substrates



Scheme 3. Deprotonation regioselectivity impact on cyclization vs elimination pathways



METHANOLYSIS OF THE OXAZOLIDINONE

These studies demonstrated that changing the oxazolidinone to an alkyl ester would offer a significant yield improvement. We first considered hydrolysis of the oxazolidinone substrates followed by esterification of the resultant acids to prepare the ester substrate. Interestingly, the saponification (aq LiOH, H_2O_2)[2] of oxazolidinone **14**, an intermediate in our first-generation process, led to isolation of enol lactone **16** (Scheme 4). This product apparently arises from spontaneous cyclization of alkynyl acid **15**, and precludes approaches wherein an alkynyl pyridine is formed in the presence of the free acid. This cyclization could also be metal-catalyzed, as there are numerous literature examples of such transformations, including with palladium.[3]

On the other hand, we could hydrolyze oxazolidinone **3** to form acid **17**, which was isolated as the crystalline dicyclohexylamine salt in 75% yield (Scheme 5). Although the Sonogashira reaction of acid **17** with bromopyridine did not provide any

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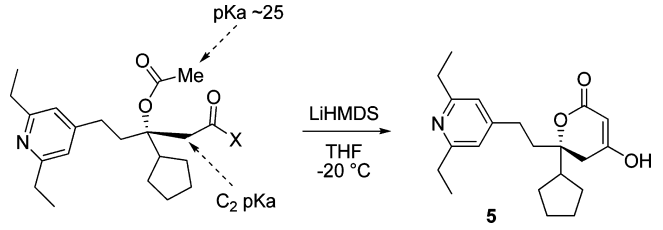
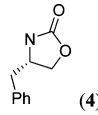
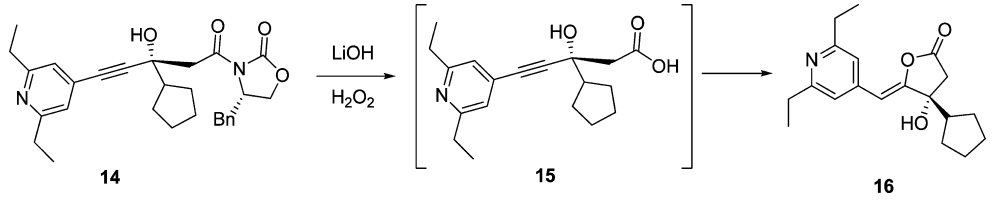
Table 1. Base-mediated cyclization of several carboxylic acid derivatives



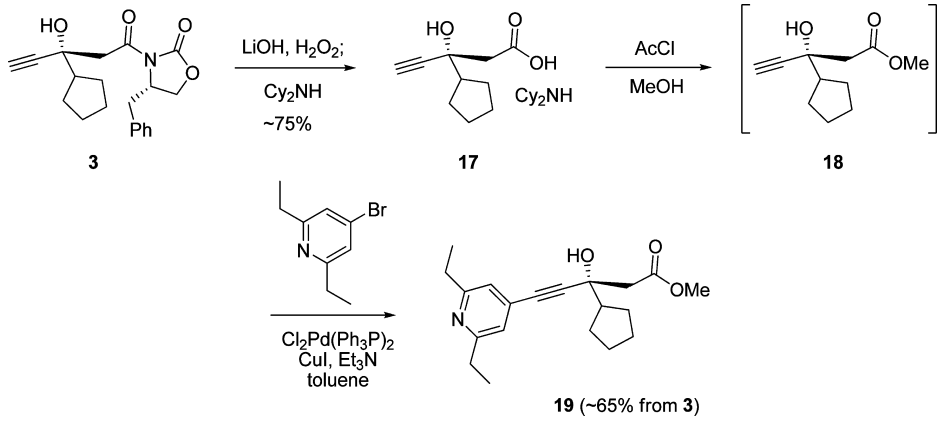
Entry	X	Elimination (%)	Cyclization (%)[a]	Estimated C_2 pKa
1	SCH_2CH_3 (**10**)	25	72	~20
2	 (**4**)	15	75	~23
3	N(Me)OMe (**11**)	15	74	~23
4	OCH_2CH_3 (**12**)	7	90	~25
5	 (**13**)	<2	<2[b]	~28

[a]Cyclization yields in toluene followed the same trend as above, but were 6−14% lower than in THF due to increased formation of elimination products. [b]The only observed product was deacetylation to form the tertiary alcohol.

Scheme 4. Hydrolysis of the acyloxazolidinone 14 and enol lactone formation



Scheme 5. Hydrolysis of oxazolidinone 3, esterification, and Sonogashira reaction



Scheme 6. Alcoholysis of acyloxazolidinone 4

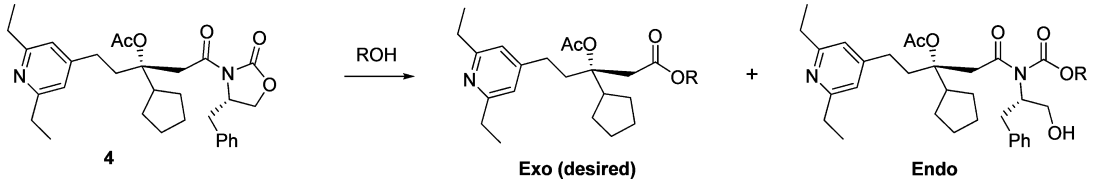


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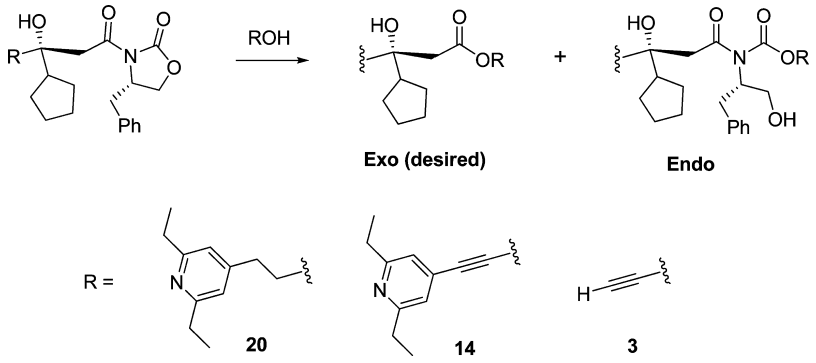
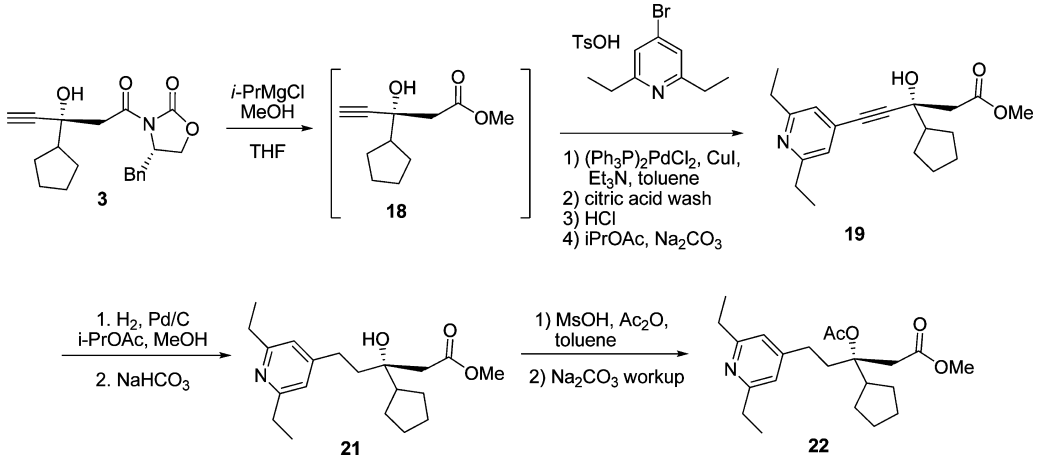
Table 2. Substrate and reagent optimization for the alcoholysis



entry	substrate	conditions	exo/endo (%)
1	**20**	MeMgBr, MeOH, THF	45/49
2	**14**	NaOMe, MeOH	50/25
3		$MgBr_2$ or $MgCl_2$, MeOH/THF	60–80/8–20
4		MeMgBr, MeOH/THF	85/8
5		$Mg(OMe)_2$, MeOH/THF	80/13
6		$Me(OMe)_2$, AcCl, MeOH/THF	86/7
7	**3**	***i*-PrMgCl, MeOH/THF**	**93–95/2–5**
8		**$Mg(OMe)_2$, AcCl, MeOH/THF**	**93–95/2–5**

Scheme 7. Telescoped methanolysis, Sonogashira, and hydrogenation sequence to 22



coupling product, the Fischer esterification of **17** followed by the Sonogashira reaction of the resultant ester **18** afforded coupling product **19** cleanly. The overall in situ yield from **3** to **19** was a modest 65%, which was not competitive with the direct methanolysis approach (vide infra).

We then studied alcoholysis, hoping to form the desired ester directly. Our initial studies focused on oxazolidinone **4**, based on our desire to make use of the large quantities of this intermediate that had previously been prepared in our pilot plant (Scheme 6). Unfortunately, **4** was not a good substrate for alcoholysis. Most conditions either provided minimal reaction or gave significant levels of endocyclic product.[4] Gadolinium triflate ($Gd(OTf)_3$)[5−7] was the only effective Lewis acid that gave a reasonable 91:9 exo/endo selectivity, but at least 10% loading of the catalyst was required. While this result was mechanistically interesting, it was unlikely to be viable on a multikilogram scale. We soon found improved results with magnesium alkoxide reagents and other substrates (Table 2).

Several other substrates were next evaluated in magnesium-mediated methanolyses (Table 2). Endocyclic alcoholysis was a significant byproduct with substrate **20** (entry 1). With the alkynyl pyridine **14**, NaOMe/MeOH gave significant endocyclic product (entry 2), but showed reasonable selectivities with magnesium salts (entries 3−6). The best results were obtained with terminal alkyne **3**, which provided >20:1 exo selectivity with MeOMgCl (entries 7−8).[8−10] This reagent was conveniently prepared in situ either by addition of methanol to commercial *i*-PrMgCl in THF or treatment of a methanol solution of $Mg(OMe)_2$ with HCl (generated in situ with AcCl). We chose the Grignard method due to its consistency and lower cost. We also found that 0.5 equiv of MeOMgCl were sufficient to achieve the same selectivity and reaction rate as a full equivalent. Further lowering the amount of MeOMgCl not only slowed the reaction but also gave more endocyclic byproduct.

We preferred to avoid isolation of methyl ester **18** due to its noncrystalline nature and lack of UV chromophore. Fortunately, we found that the methanolysis product solution could be taken directly into the Sonogashira coupling to provide alkynyl pyridine **19** with excellent conversions (Scheme 7). The

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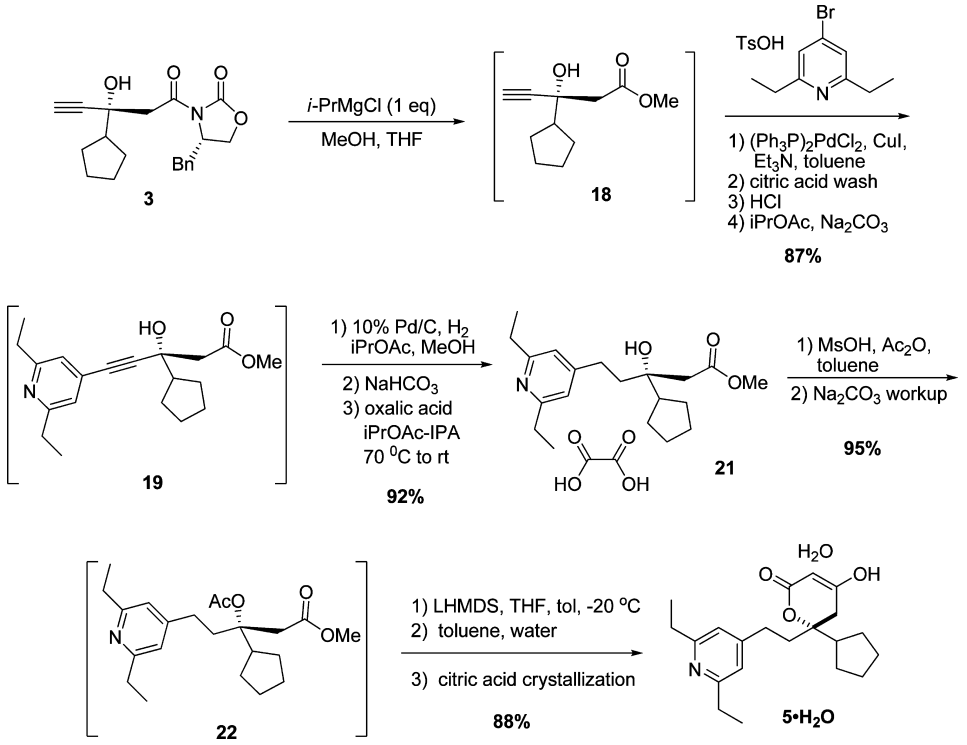
Scheme 8. Optimized process for conversion of oxazolidinone 3 to β-keto lactone 5



magnesium salts from the methanolysis reaction did not interfere with the copper and palladium reagents used in the Sonogashira coupling. As described in the previous paper (Synthesis of Filibuvir. Part I), the alkyne hydrogenation in the oxazolidinone series (i.e., **19** to **21**, where OMe in the ester is replaced with the benzyloxazolidinone) had required high loadings of Pd/C catalyst (25 wt %), a result we attributed to the presence of residual phosphine and copper species from the Sonogashira coupling. With the change from oxazolidinone to methyl ester, we now found that the solubility properties of alkynyl alcohol **19** were such that it could be extracted from the organic phase with aqueous HCl (this was not possible with the less polar oxazolidinone). This allowed for a more robust cleanup of the Sonogashira product via the following sequence: (i) aqueous citric acid wash (pH 4−5) to remove inorganic salts; (ii) aqueous HCl extraction of pyridine **19**; (iii) neutralization with aq base and extraction of **19** into a fresh organic phase (toluene or *i*-PrOAc). This sequence provided an effective purge of residual phosphine and copper impurities from the Sonogashira coupling, and allowed for significantly lower catalyst loadings in the alkyne hydrogenation (5 wt %).

The hydrogenation of **19** occurred smoothly in a variety of solvents (MeOH, toluene, EtOAc, *i*-PrOAc, *i*-PrOH, THF), although the rate was faster in alcohol solvents. A variety of catalysts were screened with several commercially available catalysts giving good conversions at 30 °C and 50 psi H_2 (e.g., Johnson-Mathey type A402028−10). On scale the hydrogenation was run in 15 volumes of *i*-PrOAc containing 3% MeOH, with 92% isolated yield (15 kg scale) following isolation of the oxalate salt of **21** (vide infra) (pilot plant yields for all reactions are presented in Scheme 8). Acylation of the alcohol was achieved under similar conditions to those used in the earlier sequence (Synthesis of Filibuvir. Part I), with acetic anhydride and methanesulfonic acid in toluene providing clean conversion to the desired product **22**. These conditions were identified after initial screening showed $Cu(OTf)_2$ to be an effective catalyst for acylation of this hindered, tertiary alcohol.[11] Subsequent experiments demonstrated that the copper triflate could be replaced by a strong acid such as methanesulfonic acid, suggesting that the role of the copper triflate was to provide catalytic quantities of trifluoromethanesulfonic acid.

SELECTION OF AN INTERMEDIATE FOR ISOLATION

With the four step sequence to convert **3** to **22** defined, we next turned to selection of the optimal isolation strategy (Scheme 7). There were three potential isolation points, as crystalline salts of pyridines **19**, **21**, and **22** had been isolated. Ideally we sought a single isolation point that would minimize filtrations and isolations by telescoping two of the three steps. A variety of salts were screened, from which several promising leads emerged, including the D-DBTA (dibenzoyl tartaric acid) and oxalic acid salts of **19**, the D-DBTA, L-DBTA and oxalic acid salts of **21**, and the D- and L-DBTA salts of **22**. From these studies, the preferred salt emerged as the oxalate of **21**. This was based on its ease of isolation (reasonably fast filtrations), its chemical stability, the low cost of oxalic acid, and the high potency of the resulting salt (i.e., the low molecular weight of oxalic acid relative to the pyridine).

ACYLATION AND DIECKMANN CYCLIZATION

Acylation of alcohol **21** could be performed directly on the oxalate salt, avoiding the need for a separate salt break. Acylation conditions were similar to those with the analogous oxazolidinone substrate; attempts to replace methanesulfonic acid with other acid catalysts (HCl, H_2SO_4) or to directly use acetyl chloride with no added acid were unsuccessful. The equivalents of MsOH and Ac_2O in the acylation were studied,

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and optimal conditions were found to be >1.5 equiv of MsOH and >2 equiv Ac_2O.

Off-gassing was observed during the addition of MsOH and Ac_2O to the oxalate salt, consistent with literature reports.[12−14] We quantified the volume of gas generated and found it to be ∼20% of the theoretical volume of CO_2 and CO that would form from complete decomposition of oxalic acid (Figure 1). Although full decomposition was not observed, risk/hazard analyses for scale-up were predicated on the complete conversion of oxalic acid to CO_2 and CO.

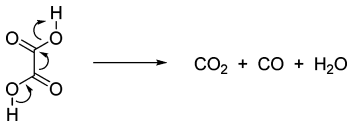
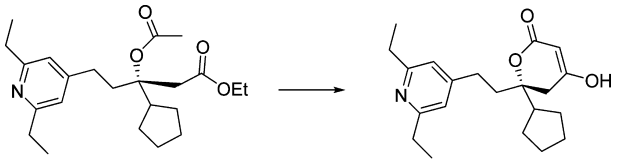


Figure 1. Decomposition of oxalic acid.

The Dieckmann cyclization was more efficient in THF than in toluene (90% vs 76% yield), but we found that up to 1−2 volumes (mL/g substrate) of toluene, the optimal solvent for acylation of **21**, were well tolerated. Thus, following addition of aqueous sodium carbonate, a water wash, and phase separation, the toluene phase was distilled to 1−2 volumes, and THF was added prior to execution of the next reaction. This operation also served as an effective method for removal of any trace water following the workup.

Optimization of the base used in the Dieckmann cyclization is summarized in Table 3. Although optimized on the ethyl ester **23**, comparable results were observed with the methyl ester. These experiments indicated that LHMDS was the preferred reagent, consistent with observations made with the analogous oxazolidinone substrate.

Table 3. Evaluation of base in the Dieckmann cyclization



23 **5**

cyclization conditions	in situ yield of **5** (%)	other products
LiHMDS, THF, −20 °C	**90**	**5−6% elimination**
LiHMDS, Et_3N, THF, −20 °C	89	7−8% elimination
NaHMDS, THF, −20 °C	43	50% elimination
KHMDS, THF, −20 °C	31	35% elimination, other byproducts
KO*t*-Bu, THF, −20 °C	8	15% SM, 60% elimination, other byproducts
LiO*t*-Bu, THF, −20 to 0 °C	8	20% SM, 70% elimination
LDA, THF, −20 to −10 °C	30	15% elimination, other byproducts
LiTMP, THF, −20 to −10 °C	40	15% elimination, other byproducts

Although the yields with the ester substrate were consistently higher than those with oxazolidinone, we did observe some yield dependence on mode of addition and source of LHMDS, similar to those observed with the oxazolidinone substrate (Synthesis of Filibuvir. Part I). These are summarized in Table 4. For rapid additions (<10 min), little if any difference was observed. However, for longer addition times (5 h), as would be required for larger scale campaigns, the dual stream addition developed for the oxazolidinone substrate was clearly preferred, as it exhibited no variation between 1 and 5 h addition times. The mass balances for all the experiments in Table 4 were excellent, with the reduced yield of *β*-keto lactone corresponding to an increase in the level of elimination byproducts.

Table 4. Time variations for three addition protocols

mode of addition	addition time	isolated yield (%)
normal addition (LHMDS to substrate)	5−10 min	87−88
	30 or 90 min	85−87
	5 h	81
inverse addition (Substrate to LHMDS)	5−10 min	86
	5 h	65
dual stream addition	1 or 5 h	88−90

We also observed a source-dependence for the LHMDS, similar to that observed with the oxazolidinone substrate. With LHMDS prepared from *n*-BuLi and $HN(TMS)_2$ the yield was consistently 88−90%. However, in the case of one supplier using a lithium metal process (Li metal, 2-methyl-1,3-butadiene, $HN(TMS)_2$), a consistently lower yield of 81% was observed. Similar observations with LDA prepared from *n*-BuLi vs Li metal/styrene have also been reported.[15,16] In the course of investigating the cause of this variation, we identified two additional suppliers who used the lithium metal process, but with those sources the higher yield was consistently obtained (88−90%). We also found that if the "low olefin content" grade of LHMDS was used from the initial supplier, the yield improved to 85−87%. We studied several potential culprits, including the presence of residual 2-methyl-2-butene and small quantities of other metal contaminants (e.g., sodium amide bases, LiCl, and Li-alkoxides), but none of these accounted for the observed discrepancy. In all cases where the yield decreased, an increased level of elimination impurities was observed (i.e., the total mass balance was consistent). While these results continue to intrigue us, our successful identification of at least three viable commercial suppliers (Optima, BASF, and Chemetall "Low Olefin Content" LHMDS) for the reagent and the relatively modest yield variations have attenuated our concern with this unexplained LHMDS source variation.

Gratifyingly, the outcome of these studies upon scale-up to 15−30 kg batches in our pilot plant were dramatic and positive, as shown in Table 5. Although fewer batches have been processed with this new substrate, the average yield difference is significant (58.1% over 14 batches for the oxazolidinone substrate, vs 79.7% over 3 batches for ester **23**).

FINAL PROCESS DESCRIPTION

The optimized sequence to convert alkyne **3** to *β*-keto lactone **5** is shown in Scheme 8, including yields on pilot plant scale (16 kg of oxazolidinone **3**).

The key features of the optimized synthesis relative to the previous route are as follows: (1) An improved yield for the Dieckmann cyclization (**22** to **5**·H_2O) from an average of 58% to 80% on multi-kilogram-scale; (2) reduced catalyst load in the alkyne hydrogenation (the enhanced solubility of alkynyl alcohol **19** in aqueous acid relative to the analogous oxazolidinone acetate allowed for a more robust purge of copper and phosphine contaminants from the Sonogashira coupling, and thus a reduced catalyst requirement from 25 to 5

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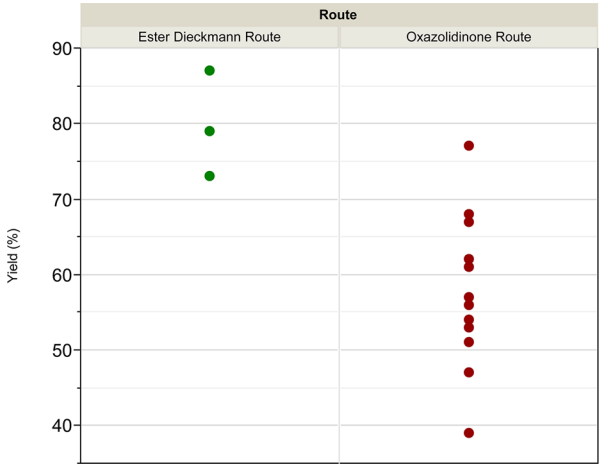
Table 5. Campaign yields for cyclization of ester vs oxazoidinone substrates



wt %; (3) an efficient conversion of oxazolidinone **3** to methyl ester **18** with MeOMgCl, conveniently prepared from *i*-PrMgCl and MeOH.

Development of a reductive coupling for the conversion of *β*-keto lactone **5**·H_2O to filibuvir (**1**) will be described in the next paper in this journal (Synthesis of Filibuvir. Part III).

EXPERIMENTAL SECTION

Analytical Methods. The UPLC method used for reaction monitoring and analysis of isolated intermediates employed a Waters Acquity series instrument (Waters Corp., Milford, MA), an Acquity BEH C8 column (100 × 2.1 mm, 1.7 μm particle size), and a 10 mM ammonium acetate/acetonitrile gradient as shown in the table below with a re-equilibration time of approximately 2 min. The flow rate was 0.4 mL/min and the column temperature was 30 °C. The injection volume was 2 μL and UV detection was performed at 220 nm.

Gradient Program for UPLC Analysis. See Table 6

Table 6. Gradient program for UPLC analysis

time (min)	% mobile phase A	% mobile phase B
0	95	5
10	5	95
10.5	5	95

Sample Solution Preparation. See Table 7.

The approximate retention times are listed in Table 8.

*(R)-Methyl 3-Cyclopentyl-5-(2,6-diethylpyridin-4-yl)-3-hydroxypent-4-ynoate (**19**).* A 250 L reactor was charged with dry THF (32 L) and cooled to 0 to 5 °C. Isopropyl magnesium chloride (20.6 wt % in THF, 11.1 kg, 22.3 mol) was added, and the resulting solution was cooled to −5 to 0 °C. A solution of methanol (1.35 L, 33.4 mol) in THF (16 L) was added to the Grignard solution over 20 min (CAUTION: this addition was highly exothermic and evolved propane gas; the addition was done at a rate such that the internal temperature remained <25 °C). An additional 32 L portion of methanol was then added, and the solution of MeOMgCl was stirred until the temperature had returned to −5 to 0 °C (1−2 h required). Solid acyl oxazolidinone **3** (16.0 kg, 95 wt %, 44.5 mol) was added, and the solution was stirred for 3 h at −5 to 0 °C, then warmed to

Table 7. Sample solution preparation

sample	quantity	volume (mL)	dissolving solvent
3 to **18** reaction mixture	0.5 g	50	acetonitrile/water (50/50, v/v)
18 to **19** reaction mixture	0.5 g	100	acetonitrile/water (80/20, v/v)
19 product solution	0.5 g	100	acetonitrile/water (80/20, v/v)
19 to **21** reaction mixture	0.5 g	25	acetonitrile/water (80/20, v/v)
21 oxalic acid salt	50 mg	25	acetonitrile/water (80/20, v/v)
21 to **22** reaction mixture	0.5 mL	25	acetonitrile
22 product solution	0.5 g	100	acetonitrile
22 to **5** reaction mixture	0.5 mL each layer	25	acetonitrile/water (80/20, v/v)
5·H_2O	20 mg	25	acetonitrile/water (80/20, v/v)

Table 8. Approximate retention times

cmpd	retention time (min)
3	6.6
18	4.8
4	3.4
4-bromo-2,6-diethylpyridine	6.0
19	6.8
21	6.5
22	7.4
5	3.9

15 °C over 2 h. A sample was analyzed by UPLC for reaction completion.

Upon complete methanolysis (<0.1% acyloxazolidinone **3**), the vessel was charged with 4-bromo-2,6-diethylpyridine *p*-toluenesulfonic acid (17.3 kg, 99.6 wt %, 44.5 mol), toluene (41.5 L), and triethylamine (13.5 L, 134 mol). The reactor was then purged with nitrogen. Bis(triphenylphosphine) palladium-(II) chloride (312 g, 0.445 mol) was charged, and the reactor purged with nitrogen. The resulting slurry was stirred at 25 to 30 °C for 30 min, and copper(I) iodide (127 g, 0.666 mol) was added. The system was purged with nitrogen and warmed to 60 to 65 °C for 10 h.

Upon reaction completion (UPLC analysis, <3% bromopyridine), the reaction mixture was cooled to ambient temperature and quenched into a solution of citric acid monohydrate (5.20 kg, 24.5 mol) and water (80 L). The reactor was rinsed with toluene (22 L). The two-phase quench solution was stirred for 15 min, and the layers were separated. The dark brown organic layer was cooled to 0 to 5 °C and extracted with two portions of prechilled aqueous HCl (1 M, 66.8 L for each extraction). The first aq HCl addition was exothermic, and was added at a rate such that the temperature remained <10 °C. To the combined product-containing aqueous extractions was added isopropyl acetate (128 L), and the two-phase mixture was cooled to 0 to 5 °C. Aqueous sodium carbonate (20%, 77 L) was added at such a rate that off-gassing was controlled. The layers were separated, and the lower aqueous phase was checked for pH (target pH 8−9). The product-containing organic phase was washed with water (64 L), and the organic was assayed by HPLC (12.7 kg of **19**, yield 86.9%) and used directly in the next reaction.

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An aliquot of **19** was isolated for characterization by flash chromatography (20% to 40% EtOAc in hexanes) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 2H), 4.45 (s, 1H), 3.74 (s, 3H), 2.83 (d, 1H, J = 15.8), 2.74 (q, 4H, J = 7.6 Hz), 2.68 (d, 1H, J = 15.8), 2.19 (m, 1H), 1.90−1.60 (m, 5H), 1.60−1.50 (m, 3H), 1.25 (t, 6H, J = 7.6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 162.9, 131.0, 121.0, 93.1, 82.6, 71.6, 51.9, 49.5, 44.7, 31.5, 31.3, 28.2, 27.4, 25.8, 13.9. IR (KBr pellet, thin film, cm^{-1}): 3493 (br), 2954, 2868, 1723, 1597, 1548, 1406, 1349, 1202, 1169. HRMS (ESI+): m/z calcd. for $C_{20}H_{28}NO_3$ 330.20637; found 330.20642.

*(R)-Methyl 3-Cyclopentyl-5-(2,6-diethylpyridin-4-yl)-3-hydroxypentanoate, oxalic acid salt (**21**).* A 250 L hastelloy pressure reactor was charged with a solution consisting of alkyne **19** (12.3 kg, 37.2 mol) and isopropyl acetate (total solution weigh 135.2 kg, ∼155 L), rinsing with an additional portion of isopropyl acetate (37 L). 10% Pd/C (0.613 kg, 5 wt %, 50% water wet, Johnson−Mathey Type A402028−10) was charged, followed by methanol (4.9 L). The vessel was purged with nitrogen (3×), and then hydrogen (3×) at 25 °C, pressurized to 50 psig (4.5 barg) of hydrogen and stirred at 30 °C for 4 h, at which time hydrogen uptake was complete. The vessel was depressurized and purged with nitrogen, and an aliquot was analyzed for reaction completion (<1% cis-olefin). The reaction mixture was filtered through a glass fiber filter, rinsing with 49 L of isopropyl acetate.

The solution of free base was washed sequentially, first with 25 L of aqueous $NaHCO_3$ (1.09 kg $NaHCO_3$ (13.0 mol) dissolved in 25 L water), and then with 25 L of water. The organic layer was concentrated under vacuum (0.6 bar) to a volume of ∼98 L (8 L/kg substrate). An additional 86 L of isopropyl acetate was added and distillation resumed to a volume of ∼12.3 L (10 L/kg substrate). Water content of an aliquot was assayed by Karl−Fischer titration (target <0.1%). Isopropanol (22 L) was added, and the solution was heated to 80 °C. A solution of oxalic acid (4.02 kg, 44.6 mol, 1.2 equiv) in 122.5 L isopropyl acetate was added over 5−10 min, such that the internal temperature remained >75 °C. The reaction was cooled to 74 °C at 0.25 °C/min, and seed crystals (61.3 g) were added. The resulting slurry was stirred at 74 °C for 60 min, then cooled to 66 °C at 0.1 °C/min. The slurry was reheated to 70 °C at 0.25 °C/min, and granulated for at least 60 min. The slurry was cooled to 55 °C at 0.1 °C/min, then to 20 °C at 0.25 °C/min. Solids were collected by filtration, rinsing with two portions of isopropyl acetate (49 L each). The solids were dried at 0.1 bar and 60 °C for 24 h to provide the product oxalate salt of **21** (**21**·$(CO_2H)_2$) as white, fluffy solids (14.2 kg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0−10.0 (b, 2H), 7.24 (s, 2H), 3.69 (s, 3H), 3.02 (q, 4H, J = 7.6), 2.86 (m, 2H), 2.61 (d, 1H, J = 15.2), 2.52 (d, 1H, J = 15.2), 2.05 (m, 1H), 1.85 (m, 2 H), 1.70−1.45 (m, 5H), 1.45−1.35 (m, 3H), 1.30 (t, 6H, J = 7.6). ^{13}C (100 MHz, $CDCl_3$): δ 173.1, 163.1, 162.5, 158.4, 122.6, 73.9, 51.9, 47.9, 40.9, 38.3, 30.6, 26.6, 26.5, 26.4, 25.64, 25.58, 13.2. IR (KBr pellet, thin film, cm^{-1}): 3558 (br), 3074, 2948, 2870, 2661, 1714, 1632, 1323, 1193, 1164. HRMS (ESI +): m/z calcd. for $C_{20}H_{32}NO_3$ 334.23767; found 334.23779. HPLC purity (achiral): 98.9%; oxalic acid content 21.5% (theory 21.3%); water <0.1%; residual solvents <0.1%.

*(R)-6-Cyclopentyl-6-(2-(2,6-diethylpyridin-4-yl)ethyl)-dihyro-2H-pyran-2,4(3H)-dione hydrate (**5**). Acylation.* A 2500 L glass-lined reactor was charged with (*R*)-methyl 3-cyclopentyl-5-(2,6-diethylpyridin-4-yl)-3-hydroxypentanoate, oxalic acid salt (**21**·$(CO_2H)_2$) (140 kg, 330.6 mol) and dry toluene (1078 L), and cooled to 15 °C. Methanesulfonic acid (36.5 L, 562 mol, 1.70 equiv) was added at a rate such that the internal temperature remained below 25 °C. Acetic anhydride (93.8 L, 992 mol, 3.0 equiv) was charged rapidly (this addition was not exothermic). The resulting two-phase mixture was stirred at high agitation for at least 2 h. When complete by UPLC analysis (<2% SM), the reaction mixture was cooled to 10 °C and quenched by addition of aqueous KOH (296.8 kg of 50 wt % aq KOH, 2645 mol, diluted with 840 L water), added at a rate such that the internal temperature remained <30 °C. The resulting solution was stirred at 25 °C for 2 h, then allowed to settle for 15 min. The aqueous pH was confirmed to be in target (pH >6), and the phases were separated. The organic phase was washed with water (700 L), then vacuum concentrated (0.1 bar) to a volume of ∼350 L. The resulting toluene solution of product (**22**) was assayed for water content by Karl−Fischer titration (target <0.05%). When within target, it was transferred to a tared vessel, rinsing with THF (280 L), assayed for potency (∼117.9 kg, 95%), and held for use in the cyclization (it is stable to storage at this point up to 7 days).

Characterization data of **(*R*)-Methyl 3-acetoxy-3-cyclopentyl-5-(2,6-diethylpyridin-4-yl)pentanoate (22)** is from a sample isolated by flash chromatography (20% to 40% EtOAc in hexanes) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 2H), 3.69 (s, 3H), 3.08 (d, 1H, J = 14.7), 3.02 (d, 1H, J = 14.7), 2.78 (q, 4H, J = 7.5), 2.70−2.60 (m, 3H), 2.36 (m, 1H), 2.26 (m, 1 H), 2.05 (s, 3H), 1.80−1.40 (m, 8H), 1.30 (t, 6H, J = 7.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.4, 162.7, 151.3, 119.0, 85.0, 51.4, 47.2, 39.5, 37.0, 31.2, 29.9, 26.9, 26.7, 25.3, 25.1, 22.0, 14.1. IR (KBr pellet, thin film, cm^{-1}): 2962, 2871, 1731, 1605, 1565, 1435, 1366, 1242, 1205, 1161. HRMS (ESI+): m/z calcd. for $C_{22}H_{34}NO_4$ 376.24824; found 376.24827.

Cyclization. The following procedure involved the simultaneous addition of substrate and LHMDS solutions to a reactor vessel. Vessel #1 was the reactor vessel, vessel #2 was the substrate charge vessel, and vessel #3 was the LHMDS charge vessel. Vessel #1 was charged with anhydrous THF (193 L), and cooled to −15 to −20 °C. Vessel #2 was charged with a THF−toluene solution of **22**, prepared as described above, containing 117.9 kg (314 mol) of substrate in ∼554 L total solution volume, rinsing with 31 L anhydrous THF. This solution was cooled to −15 °C. Vessel #3 was charged with LHMDS (550 L of a 23.1 wt % THF solution, 691 mol, 2.2 equiv), rinsing with 35.4 L THF as a line rinse, and cooled to −10 °C. The contents of charge vessels #2 and #3 were simultaneously transferred to reactor vessel #1 at such a rate that the internal temperature remained <5 °C (on this scale the addition required 2 h). Upon complete addition, stirring was maintained at −15 °C for 30 min, and the reaction was sampled for completion (target <2% remaining SM). The reaction was warmed to −5 °C and quenched with cold (<5 °C) water (707 L), maintaining an internal temperature below 20 °C. Toluene (236 L) was then added, and the mixture stirred for 30 min at 0 to 5 °C. The mixture was warmed to 20 °C and allowed to settle. The aqueous phase (containing product at this pH) was removed, and the organic phase was rinsed with an additional 236 L portion of water. The aqueous phases were combined. A solution of citric acid monohydrate (66 kg, 314 mol, 1.0 equiv) in 236 L water was prepared in a separate vessel, and added to the aqueous product solution. The pH was monitored throughout the addition until a pH of 6.5−7.5 was reached (the first 40−50% of the citric acid solution was added rapidly,

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but then slowed to allow the pH to stabilize as the end point was approached). Product crystallization began, and the slurry was held with stirring for 60 min. Additional citric acid was added slowly until a pH of 5.5−6.5 was reached (target pH 6.0). 75−85% of the prepared citric acid solution was required to reach the final target pH. The resulting slurry was stirred for at least 30 min, and the solids were collected by filtration, rinsing the vessel and filter cake with water (2 × 236 L). The solids were dried at 35 °C under vacuum to provide the product (**5**·H_2O) as a white solid (94.6 kg, 87.5% yield).

Data obtained from a laboratory pilot: ^{1}H NMR (400 MHz, CD_3OD): (note that the protons on C_3 of the dihydropyrone are not visible due to deuterium exchange with solvent): δ 7.08 (s, 2H), 2.77 (q, 4H, J = 7.6), 2.70−2.65 (m, 3H), 2.43−2.42 (m, 2H), 2.09−2.06 (m, 2H), 1.75−1.4 (m, 8H), 1.27 (t, 6H, J = 7.6). ^{13}C NMR (100 MHz, CD_3OD): (note that the C_3 dihydropyrone resonance is broadened due to deuterium exchange): δ 175.9, 170.3, 161.9, 155.7, 120.5, 89 (br), 83.8, 47.0, 37.8, 33.6, 29.6, 29.5, 26.8, 26.7, 25.5, 13.4. IR (thin film, KBr disc, cm^{-1}): 3294 (br), 2963, 2870, 1656, 1605. MS (CI): 344.2 $(M - H)^+$. HPLC purity (achiral): 99.5%; 5.1% water (theory for monohydrate 5.0%); residual solvents 0.27% (MeTHF and MeOH).

■ ASSOCIATED CONTENT

Supporting Information

Preparation of alternative cyclization substrates **7** and **8** (Scheme 2) and other alternative cyclization studies. Preparation of cyclization substrates **10**−**13** (Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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