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Practical Synthesis of the Bicyclic Darunavir Side Chain: (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol from Monopotassium Isocitrate

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Supporting Information

ABSTRACT: A practical synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol—a key intermediate in the synthesis of darunavir—from monopotassium isocitrate is described. The isocitric acid salt, obtained from a high-yielding fermentation fed by sunflower oil, was converted in several steps to a tertiary amide. This amide, along with the compound's ester functionalities, was reduced with lithium aluminum hydride to give, on acidic workup, a transient aminal-triol. This was converted *in situ* to the title compound, the bicyclic acetal furofuranol side chain of darunavir, a protease inhibitor used in treatment of HIV/AIDS. Key to the success of this process was identifying an optimal amide that allowed for complete reaction and successful product isolation. *N*-Methyl aniline amide was identified as the most suitable substrate for the reduction and the subsequent cyclization to the desired product. Thus, the side chain is produced in 55% overall yield from monopotassium isocitrate.

INTRODUCTION

Global health guidelines recommend darunavir as a preferred protease inhibitor (PI) in PI-based regimens for the treatment of HIV-AIDS.[1] It offers lower toxicity and a better resistance profile in comparison to other PIs, and for these reasons it has seen significant usage in the developed world. However, darunavir is presently too expensive for wide use in resource-limited settings despite its clinical advantages. The lack of use in these settings in turn limits the interest of generic manufacturers. Subsequently, production volumes remain low, thus limiting economies of scale necessary to drive prices down to levels that would encourage wider use. We propose that development of more economical synthetic routes to manufacture darunavir could break this impasse. Cost analysis of current synthetic routes used to manufacture darunavir indicates that the bicyclic side chain, (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol (**7**), constitutes as much as half of the cost of the active pharmaceutical ingredient.

This small molecule, containing three contiguous chiral centers, has been the focus of numerous synthetic studies. Some synthetic routes involve preparation of the racemic **7** followed by enzymatic resolution to provide optically pure material.[2] Xie et al. reported a cycloaddition of dihydrofuran and glycolaldehyde to give **7** in high diastereoselectivity and modest enantioselectivity; optically pure **7** was obtained after enzymatic resolution.[3] A diastereo- and enantioselective synthesis of **7** using an Evans–Mukaiyama aldol reaction was also reported by Xie et al.[4] Recently, a highly efficient synthesis of **7** by a diphenylprolinol-catalyzed enantio- and diastereoselective cross aldol reaction was reported by Ikemoto et al.[5] Syntheses of **7** using chiral pool materials were also reported. Quaedflieg et al. demonstrated a stereoselective synthesis of optically pure **7** via a diastereoselective Michael addition of nitromethane to a D-glyceraldehyde derivative (itself derived from ascorbic acid).[6] Kulkarni et al. employed a Wittig olefination–Claisen rearrangement strategy starting with the same glyceraldehyde derivative, in syntheses of optically pure **7** and of its isomers.[7]

Our goal was to develop a practical stereospecific synthesis of furofuranol **7** without the need for enzymatic resolution and/or expensive reagents to maximize cost-effectiveness. We decided that isocitric acid could be a suitable chiral pool starting material, as it is readily produced by fermentation of sunflower oil using the Jen41 strain of yeast *Yarrowia lipolytica*.[8] We report herein the development of a practical and cost-effective synthesis of optically pure furofuranol **7** from isocitric acid, in five simple steps and employing inexpensive reagents under mild conditions. Contributing to our organization's goal of wider access to affordable darunavir, this synthetic route to the side chain is free of intellectual property restrictions.

RESULTS AND DISCUSSION

Original literature reports. A stereoselective synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol (**7**) from the monopotassium salt of (2*R*,3*S*) isocitric acid (**1**) via hemiester **4** was reported by Chen as shown in Scheme 1.[9] In a similar context, the conversion of isocitric acid to a *tert*-butyl analogue of hemiester **4** was demonstrated by Giannis et al.[8] Our initial work focused on attempts to reproduce these reported results, and to optimize the reported procedures to enable larger scale manufacturing of the side chain furofuranol **7**.

We were able to obtain comparable results for the conversion of **1** to lactone-diacid **2** and subsequently to hemiester **4** via cyclic anhydride **3** as described by Chen[9] and Giannis et al.[8] Hemiester **4** was readily converted to morpholine amide **5a** using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) as the coupling agents.[8] However, we were unable to obtain the reported yield at 71% for the

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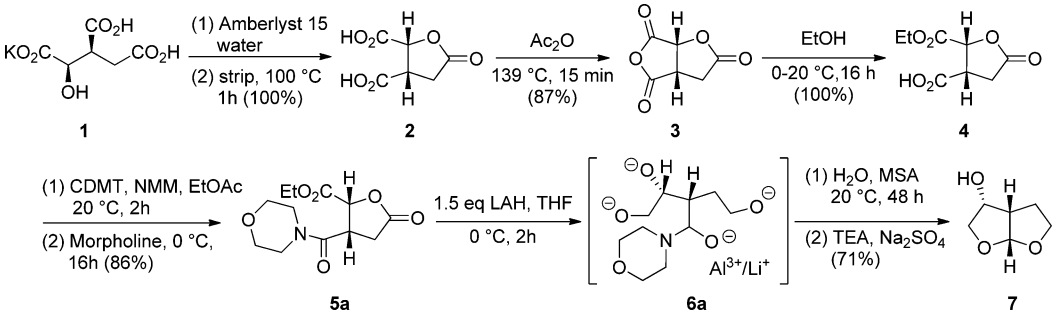
Scheme 1. Literature Process[8] from Potassium Isocitrate to (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol



conversion of morpholine amide **5a** to furofuranol **7**. The reported reaction conditions and product isolation procedure[9] were carefully repeated, and isolated yields were typically in the range 30−35%. Quenching the lithium aluminum hydride (LAH) reduction reaction mixture with either aqueous methanesulfonic acid (MSA) or aqueous $NaHSO_4$ produced gel-like mixtures, which made isolation of the product from the byproduct salts difficult. Various changes in the reaction and isolation conditions, including the number of equivalents of LAH used, reaction temperatures, and quench agents were investigated. None of these changes led to significant improvement in yield. We decided that more fundamental changes in the reduction and cyclization reactions were required to develop this reported approach into a practical manufacturing route which could provide meaningful cost savings in darunavir production.

The conversion of amide **5a** to furofuranol **7** formally involves five reactions:

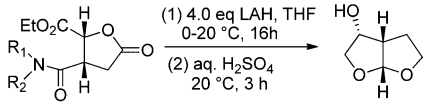
(1) reduction of ethyl ester to alcohol (and byproduct ethanol)
(2) reduction of lactone to a diol
(3) reduction of tertiary amide to hemiaminal **6a** (a masked aldehyde shown here as a metal salt complex)
(4) neutralization of **6a** and acid-catalyzed cyclization with a pendant alcohol to form the first tetrahydrofuran ring, and
(5) acid-catalyzed cyclization of the second pendant alcohol to form the fused tetrahydrofuran ring as an acetal. (We have not determined whether the final intermediate of this sequence is the hemiacetal or aminal.)

Each of these five reactions and the product isolation have to be highly efficient to give a good overall yield. Due to the lack of chromophores and the complexity of the reaction mixture, HPLC-UV monitoring did not yield useful information. A GC-MS method was useful in monitoring the amide starting material **5a** and product **7** but not the intermediate **6a** or related species. An attempt was made to use Raman spectroscopy to monitor the reaction *in situ*, but preliminary results were not conclusive.[10] Successful modifications of this synthesis must address the efficiencies of the three reductions and the two cyclizations as well as the ease of product isolation.

Studies on the substrate effect on the reduction of amide 5. The reduction of tertiary amides in many cases gives aldehydes in poor to modest yields, while over-reductions to alcohol or amine are typical side-reactions.[11] Studies on LAH reduction of tertiary amides of butyric acid to butyraldehyde by Brown and Tsukamoto provided relevant data and theoretical interpretation.[12] It was reported that under a standard set of reduction conditions (0.25 equiv of LAH, Et_2O, 0 °C), *N*,*N*-diethylbutyramide, piperidinobutyramide, and *N*-methyl-*N*-phenylbutyramide gave butyraldehyde in 22%, 33%, and 58% yield, respectively.[12] These results were rationalized on electronic grounds: delocalization of the nitrogen lone pair into the phenyl ring would make the amide carbonyl more electrophilic and hence more susceptible to hydride addition. The lack of such electronic delocalization could explain the lower yield of butyraldehyde from the reductions of diethylbutyramide and piperidinobutyramide. Using Brown's procedure, we carried out the LAH reductions of *N*-methyl-*N*-phenylbutyramide and morpholinobutyramide and isolated butyraldehyde (as its 2,4-dinitrophenylhydrazone) in 52% and 27% yield, respectively. These results suggest that *N*-alkylaniline versions of amide **5a** may give a cleaner, higher-yielding reduction.

Three novel *N*-alkylaniline amides (**5b**, **5c**, and **5d**) and Weinreb amide **5e** (Table 1) were prepared to probe the electronic, steric, and chelation effects in the reduction. The reduction was carried out using 4 equiv of LAH in THF at −10 to 20 °C. Upon completion of the reduction, the reaction mixture containing excess hydride was quenched by addition of 10 wt % aqueous sulfuric acid, giving a clear solution. The acidic aqueous solution was stirred at ambient temperature for 3 h for the cyclizations to give **7**. Solvent (THF) was partially removed by evaporation, and the water-soluble product was isolated by multiple extractions with ethyl acetate until **7** was undetectable in the organic extract by GC-MS. The crude product was purified by silica gel chromatography. The isolated yields of furofuranol **7** in the reduction of these amides are shown in Table 1.

Table 1. Substrate Effect on the Conversion of Amide 5 to Furofuranol 7



amide	R_1	R_2	Yield[a] of 7 (%)
5a	-$CH_2CH_2OCH_2CH_2$-		34
5b	Ph	Me	70
5c	Ph	Et	54
5d	Ph	^{i}Pr	24
5e	Me	OMe	50

[a]Yield of product after purification by flash chromatography on silica gel with EtOAc-hexanes.

Based on the yields of bicyclic acetal **7**, we presume that the reduction of *N*-methyl aniline amide **5b** was more efficient than

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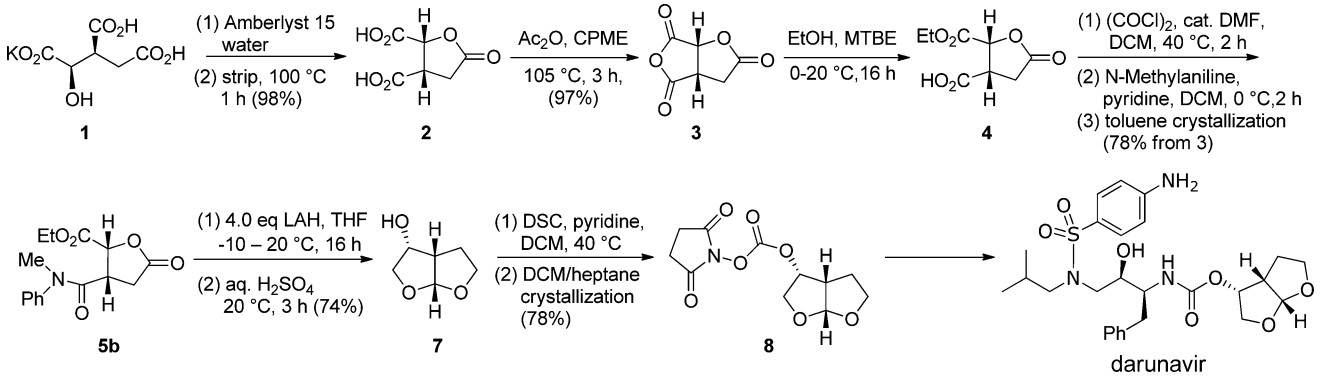
Scheme 2. Optimization of the Synthetic Process from Isocitrate to (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol



reduction of the morpholine amide **5a**. This trend is indeed similar to that reported by Brown and Tsukamoto.[12] The higher yield of this reduction may be attributed to the enhanced reactivity of the *N*-methyl aniline amide compared to morpholine amide. Furthermore, the change in steric hindrance may slow down the addition of the second hydride to the tetrahedral intermediate, which causes over-reduction to amine or alcohol. The ethyl-analogue **5c** gave a lower yield than **5b** while it still compares favorably to morpholine amide **5a**. Increased steric hindrance in the *N*-isopropyl aniline amide **5d** is implicated in the lower yield of product 7. This observation is very similar to the lack of reaction in the LAH reduction of *N*,*N*-diisopropylbutyramide as report by Brown.[13]

It is well-known that Weinreb amides can be selectively reduced to aldehyde using LAH or diisobuytlaluminum hydride (DIBAL).[14] The tetrahedral intermediate resulting from the first hydride addition to Weinreb amide is stabilized by chelation and hence is unreactive to the addition of the second hydride.[14] In our case, the Weinreb amide **5e** gave a moderate yield of 50%. It appears that the overall yield of product 7 is the outcome of a balance of activation of the amide to first hydride addition and deactivation of the tetrahedral intermediate toward second hydride addition. In light of the higher cost of *N*,*O*-dimethylhydroxlamine compared to the inexpensive *N*-methyl aniline, and the fact that **5e** was not a crystalline intermediate, **5b** was chosen for further development.

Optimization of the synthetic process from isocitrate to (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol. We re-examined the literature procedures[8,9] and made several changes to make the synthetic sequence more practical (as shown in Scheme 2). As reported, the neutralization of potassium isocitrate by the ion-exchange resin Amberlyst 15 was effective. The resultant aqueous solution of free isocitric acid was concentrated under reduced pressure to dryness, and the resultant solid was heated to 95−100 °C in a heated bath to furnish lactone diacid **2** in 98% yield. The use of ion-exchange resin to generate the free acid requires a substantial amount of water, which then must be removed in order to drive the lactonization to completion. While this procedure provided material for downstream research, it would be challenging at scale, even with recycling of the resin, so we developed a more scalable alternative.

The alternative procedure neutralized the potassium isocitrate with aqueous hydrochloric acid, and water was then removed by azeotropic distillation with 2-methyl tetrahydrofuran (MeTHF) to drive the formation of lactone-diacid **2**. Precipitation of potassium chloride was observed during the solvent exchange; the salt, which appears to inhibit subsequent lactonization, is easily removed by filtration. The lactonization progressed to completion upon continuation of heating of the filtrate with further distillation of MeTHF. The product **2** can then be precipitated by addition of an antisolvent (e.g., toluene), or carried forward as a concentrated solution to preparation of the anhydride **3**. The solvent selection was key here, with MeTHF providing a medium where the triacid and the lactone are solubilized, where the byproduct salt is essentially insoluble, and where removal of water by azeotropic Dean−Stark distillation is possible. As well, MeTHF is a suitable solvent for the subsequent reaction.

The literature procedure for preparation of cyclic anhydride **3** used refluxing neat acetic anhydride (at 139 °C); the product crystallized and was filtered from the anhydride/acetic acid liquors.[8,9] However, these conditions seemed unnecessarily harsh for scale-up. We first employed a milder procedure in which the MeTHF solution of lactone diacid **2** was treated with stoichiometric trifluoroacetic anhydride (TFAA) at ambient temperature to give the anhydride **3**. This precipitated from the solvent and was readily isolated in 68% yield (unoptimized). Alternatively, the cyclic anhydride formation was carried out by reacting isolated **2** with 1.2 equiv of acetic anhydride in cyclopentyl methyl ether (CPME) at 105 °C for ∼3 h. After cooling the reaction mixture to ambient temperature, the cyclic anhydride **3** was isolated in 97% yield by filtration. The higher reaction temperature possible in CPME allowed the use of acetic anhydride, which has a cost advantage over TFAA. Performing this reaction with acetic anhydride in MeTHF alone (boiling point 80 °C) was less successful.

The isolated cyclic anhydride **3** was suspended in CPME (or in MTBE) and treated with ethanol in a regioselective anhydride-opening reaction to give hemiester **4**, which was isolated as an oil after solvent evaporation. In cases where levels of **2** as an impurity were unacceptably high (>10%), it was found that washing the product solution with a 20% solution of monopotassium phosphate successfully reduced levels of **2** with minimal loss of **4**.

For the formation of amide, the higher cost of the CDMT coupling reagent, and challenges with the removal of CDMT coupling byproducts, prompted us to seek an alternative. Oxalyl chloride with a catalytic amount of *N*,*N*-dimethylformamide (DMF) in dichloromethane (DCM) was found to be suitable for the acyl chloride formation. The acyl chloride thus formed was reacted *in situ* with *N*-methylaniline in the presence of pyridine to give crude amide **5b**. Crystallization from toluene or

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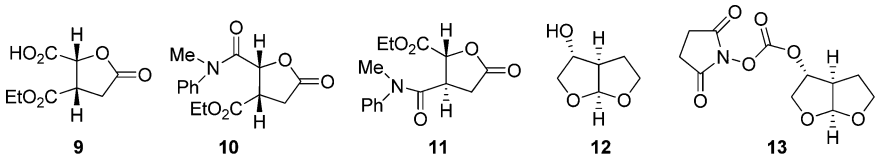

Figure 1. Impurities of hemiester **4**, amide **5b**, **7**, and **8**.

ethyl acetate/heptane gave amide **5b** as a crystalline solid in 80% yield from the cyclic anhydride **3**.

Some efforts have been made toward streamlining the conversion from lactone-diacid **2** to amide **5b** by using cyclopentyl methyl ether (CPME) as the solvent in three reactions. Lactone-diacid **2** was treated with acetic anhydride in CPME at 105 °C for 2 h to complete cyclic anhydride formation. Additional CPME was charged and distilled off to remove acetic acid. The resultant slurry containing the cyclic anhydride **3** was cooled and treated with ethanol in the anhydride-opening reaction. Upon completion of the anhydride-opening reaction, CPME was charged and distilled off to remove excess ethanol. The resultant hemiester **4** solution in CPME was treated with oxalyl chloride and a catalytic amount of DMF to generate the acyl chloride which was quenched with *N*-methylaniline and pyridine to give amide **5b** in the same pot. After aqueous workup and ethyl acetate/heptane crystallization, the amide **5b** was obtained in 56% overall yield from lactone-diacid **2**. Developing such a telescoped procedure, ultimately incorporating the initial salt-break/lactonization transformation from **1** to **2**, provides interesting opportunities in optimization for cost reduction.

In the optimized reduction/cyclization process, the crystallized amide **5b** was treated with LAH (1 M solution in THF) at −10 to 20 °C for 16 h. The reaction mixture was quenched with 10 wt % aqueous sulfuric acid and the resultant aqueous mixture was stirred at 20 °C for 3 h for conversion of putative hemiaminal to furofuranol **7**. The quenched solution was concentrated under reduced pressure (∼80 Torr and at ∼30 °C) to remove most of the THF to facilitate product extraction. Multiple extractions (typically 10) of the aqueous solution (at pH 1−2) with ethyl acetate gave about 70−75% yield of furofuranol **7**. However, the product **7** typically contained ∼5−10 wt % of *N*-methylaniline (released in cyclization of hemiaminal to **7**), which necessitated purification by silica gel chromatography. In order to resolve this issue, the pH of the quenched acidic aqueous solution was adjusted to 4−5 using aqueous sodium hydroxide after holding the cyclization mixture for 3 h. This slightly acidic solution was extracted with toluene to remove *N*-methylaniline. Furofuranol **7** has a poor partition to toluene in the toluene/water biphasic system (ca. 2:98), so loss of product **7** was minimal. After toluene extractions, the aqueous solution was extracted multiple times (typically 10) with ethyl acetate. Furofuranol product **7** was isolated in ∼70% yield containing only 1−2 wt % of *N*-methylaniline. As an alternative to the tedious multiple extractions, continuous extraction of the aqueous solution was carried out with DCM in a continuous extractor for 16 h, and furofuranol **7** was isolated in 74% yield (diastereomeric ratio = 98.4:1.6), for an overall yield of 55% from **1**.

The use of 4 equiv of LAH gave the highest isolated yield of furofuranol **7** at ∼70%. The cost of LAH and large volume of sulfuric acid used in the reduction quench are not desirable. In comparing experiments, the reduction was carried out using 4.0 equiv, 2.75 equiv, and 1.5 equiv of LAH, and furofuranol **7** was obtained in 74%, 68% and 61% yield, respectively. These data would be useful in deciding the optimum cost/yield balance for LAH usage in a manufacturing setting.

Generation of potential process impurities and comparison to authentic darunavir. In order to confirm the specificity of our analytical methods, diastereomeric and regioisomeric impurities of key intermediates were prepared and characterized (Figure 1). Preparation of the regioisomeric amide, ethyl (2*R*,3*S*)-2-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-3-carboxylate (**10**) started with a reaction of the cyclic anhydride **3** with ethanol at 70 °C. In this anhydride opening reaction at elevated temperature, the desired hemiester **4** was formed together with some of the purported regioisomeric hemiester, (2*R*,3*S*)-3-(ethoxycarbonyl)-5-oxotetrahydrofuran-2-carboxylic acid (**9**), as a side-product. Without further purification, the mixture was converted to the corresponding amides using the same procedure as described. The regioisomeric amide **10** was isolated by silica gel chromatography in 5% yield from **3**.[15]

The diastereomeric amide, ethyl (2*R*,3*R*)-3-(methyl(phenyl)-carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**11**), was prepared by heating a solution of **5b** in DMF in the presence of DBU at 50 °C for 16 h, which resulted in partial epimerization to give a mixture of **5b** and **11** in a 56:44 ratio (by GC-MS). A sample enriched in **11** was obtained by silica gel chromatography of the mixture.[15] If carried forward, **11** provides **12**, the (3*R*,3a*R*,6a*S*) diastereomer of furofuranol **7**, and subsequently the diastereomeric carbonate **13**.

With amide impurity markers **10** and **11** in hand, HPLC and GC-MS methods were refined to assay the purity of amide **5b**. Typically, the crude amide **5b** contained less than 2% of the regioisomer **10** and less than 0.5% of the diastereomer **11**, as determined by GC-MS analysis. These impurities were effectively purged by recrystallization from toluene to give **5b** in 99.5 A% purity by GC-MS.

For comparison to authentic darunavir, side chain **7** was coupled to the darunavir backbone according to the procedure described by Goyvaerts et al.[16] In this manner, **7** was reacted with disuccinimidyl carbonate to give the activated carbonate **8** in 78% yield after crystallization from DCM/hexanes, with the ratio of diastereomers **8** and **13** = 99.8:0.2. This compares well to the material produced by the Ikemoto process, reported at >99:1.[5] The carbonate **8** obtained from our route was then coupled to the penultimate, 4-amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide, to furnish darunavir drug substance in a nonsolvate form. The NMR spectroscopic[17] and chromatographic properties of this material matched those of an authentic sample of darunavir.[18]

■ CONCLUSION

A practical synthesis of furofuranol **7** from potassium isocitrate (**1**) was developed. Selection of the optimal amide substrate **5b** was crucial in achieving an efficient LAH reduction and, hence, higher yield of furofuranol **7**. The synthetic sequence was carried out starting from potassium isocitrate (**1**) to give pure

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activated carbonate **8**, a key intermediate in the manufacturing of darunavir, in 43% overall yield without chromatographic purification. While potassium isocitrate (**1**) is not currently a product of large-scale commerce, we have received material produced at two suppliers at 1−2 kg scale to date, and we see no impediment to scale-up of the fermentation process. Assuming a modest production scale, isocitric acid should cost as low as $50/kg, which by this route would produce the furofuranol side chain at about one-third the current cost for this intermediate. We are hopeful that, with further development, this route will be effective for reducing the cost of darunavir in the developing world.

EXPERIMENTAL SECTION

General remarks. ^{1}H NMR and ^{13}C NMR spectra were obtained at the field strengths of 400 and 100.6 MHz, respectively. HPLC Method 1: Agilent Eclipse XDB-C18, 5 μM (4.6 × 150 mm) mobile phase 5:95 MeOH: 0.1% H_3PO_4 and UV detection at 210 nm, flow = 1.0 mL/min, temp = 25 °C. HPLC method 2, YMC ODS_AQ 3 μM C-18 (4.6 × 150 mm) mobile phase = 0.1% H_3PO_4 at flow = 0.75 mL/min, UV detection at 210 nm, temp = 20 °C. HPLC method 3: Agilent Eclipse XDB-C18, 5 μM (4.6 × 150 mm) mobile phase 20:80 ACN: 0.1% H_3PO_4 and UV detection at 210 nm, flow = 1.5 mL/min, temp = 30 °C. HPLC method 4: Agilent Extend C18, 5 μM (4.6 × 150 mm) mobile phase gradient of ACN vs 0.1% H_3PO_4 time: 0 to 5 min ACN from 25 to 40%, 5−15 min from 5 to 15 min, increase to 58% ACN between 15 and 30 min, then to 70% ACN in 2 min, 5 min re-equilibration. UV detection at 264 nm, flow = 1.5 mL/min, temp = 20 °C. GC-MS method: Agilent HP-5MS 5% Phenylmethylsiloxane: 30 m × 0.25 mm ID, 0.25 μM. Initial oven temperature was 100 °C with ramp to 250 °C at 7.5 min and hold for 7.5 min.

(1*R*,2*S*)-1-Hydroxypropane-1,2,3-tricarboxylic acid (isocitric acid). An ion exchange column was formed with Amberlyst 15 hydrogen form dry resin (66.4 g, 312 mmol) wetted with water (300 mL) prior to packing and flushed with deionized water (1.5 L) until the eluent was clear and neutral. Potassium salt of (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (**1**) (45.33 g, 195 mmol) was dissolved in water (60 °C, 450 mL). The warm solution (500 mL, 45 °C) was loaded onto the column and eluted with deionized water (2.0 L). The eluent solution (2.5 L) was shown to contain (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (isocitric acid) with 99.4 A% purity by HPLC method 1.

(2*R*,3*S*)-5-Oxotetrahydrofuran-2,3-dicarboxylic acid (2). The aqueous solution containing free (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (2.0 L, obtained from 36 g, 156 mmol of potassium salt of (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (**1**) after passing through ion-exchange resin) was concentrated at 25 Torr on a rotary evaporator (bath temperature = 55 °C) to give 56.5 g of oil (theoretical yield of free isocitric acid = 30.0 g). This oil was coevaporated with MeTHF (2 × 200 mL) on a rotary evaporator to remove water. The oil was then heated under reduced pressure (25 Torr) in a water bath at 95−100 °C for 2 h to give (2*R*,3*S*)-5-oxotetrahydrofuran-2,3-dicarboxylic acid (**2**) as an off-white solid (27.3 g, 96.3 A% purity by HPLC method 1, 151 mmol, 96.5% yield). Mp = 151−152 °C (literature mp = 148−152 °C).[8] ^{1}H NMR (DMSO-d_6): 2.69 (dd, J = 17.4, 7.1 Hz, 1H), 2.82 (dd, J = 17.4, 9.1 Hz, 1H), 3.70 (ddd, J = 9.1, 8.0, 7.1 Hz, 1H), 5.12 (d, J = 8.0, 1H), 13 (bs, 2H). ^{13}C NMR (DMSO-d_6): 174.96, 171.46, 169.65, 76.56, 42.99, 31.08. HPLC (method 1) retention time = 2.1 min. GC-MS retention time = 4.72 min.

(3a*S*,6a*R*)-Dihydrofuro[3,4-*b*]furan-2,4,6(3*H*)-trione (3) from potassium salt of (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (1). To a 400 mL jacketed reactor were added 46.7 g (200 mmol) of potassium salt of (1*R*,2*S*)-1-hydroxypropane-1,2,3-tricarboxylic acid (**1**) and a mixture of concentrated hydrochloric acid (18.0 mL, 210 mmol) in water (18.0 mL). Water was removed by distillation at 75 °C under 80−100 Torr, collecting ∼21 mL of distillate. To the resulting thick oil was added MeTHF, (50 mL). The reactor was fixed with a Dean−Stark distillation trap, and the mixture brought to reflux. The lower layer and some upper layer were periodically drained from the trap, ultimately collecting ∼40 mL of a mixture with ∼4 mL of the lower, aqueous phase. Additional MeTHF (30 mL) was added and the reaction mixture, containing KCl, was cooled to 50 °C. This was filtered while warm on a coarse frit funnel, rinsing the reactor and salt cake with an additional MeTHF (40 mL). The filtrates were returned to the reactor flask, rinsing in with additional MeTHF (30 mL). Drying the isolated salt provided 14.1 g (95% of theoretical yield) of KCl-containing minimal isocitrate-based material by HPLC method 1. At this point, HPLC of the reaction mix showed a 45:55 mixture of open chain isocitric acid to lactone **2**. The reaction was set again for atmospheric distillation. The collected distillate (∼30 mL) showed small amounts of aqueous phase. Distillation was continued, increasing the jacket temperature and adding two portions of MeTHF (2 × 30 mL) when needed to maintain a stirrable reactor mass, until the batch temperature reached 98 °C. At this point, HPLC analysis (method 1) showed <5% of the open chain form. The batch was cooled and additional MeTHF (30 mL) was added to loosen the resulting solution.

The batch was cooled to 5 °C, and trifluoroacetic anhydride (28.9 mL, 208 mmol) was added over ∼30 min. Precipitation of product began almost immediately, and the batch temperature rose to 12 °C before falling back when addition was nearly complete. The batch was then stirred at 10 °C for 60 min. The batch was filtered, rinsing the reactor and cake with a mixture of *tert*-butyl methyl ether (20 mL) and heptanes (30 mL), providing an off-white cake. This was quickly transferred to a drying dish and dried under vacuum without heat. The resulting solid (**3**) weighed 25.1 g (67.9% yield). ^{1}H NMR (DMSO-d_6) of **3** in mixture with **2** (as a result of hydrolysis in NMR solvent): 2.81 (m, 2H), 3.98 (m, 1H) 5.38 (d, J = 8.0, 1H). It was generally best to use the wet product **3** immediately for the subsequent reaction due to the reactive nature with atmospheric moisture reverting to **2**.

(3a*S*,6a*R*)-Dihydrofuro[3,4-*b*]furan-2,4,6(3*H*)-trione (3) from (2*R*,3*S*)-5-oxotetrahydrofuran-2,3-dicarboxylic acid (2). (2*R*,3*S*)-5-Oxotetrahydrofuran-2,3-dicarboxylic acid (**2**) (22.0 g, 116 mmol) was suspended in CPME (170 mL) at room temperature. The slurry was warmed to 50−60 °C and treated with acetic anhydride (14.06 g, 138 mmol) over 5 min. The reaction mixture was heated to 100−105 °C to give a clear solution. After the solution was held at 105 °C for ∼5 min, precipitation of white solid was observed. The slurry was heated at 105 °C for 3 h. A sample of the slurry was taken and quenched into neat methanol for GCMS analysis. GCMS showed a major peak at 5.51 min (at 93 A%) which corresponds to the methyl hemiester. The reaction was deemed complete. The slurry was cooled to 10 °C and held at that temperature for 30 min. The solid was collected by filtration

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under nitrogen blanket and the wet cake was washed with CPME (40 mL). (3a*S*,6a*R*)-dihydrofuro[3,4-*b*]furan-2,4,6(3*H*)-trione (**3**) was obtained as an off-white solid (19.95 g, 87.1 A% purity by HPLC, 118 mmol, 97% yield). Mp = 187−190 °C (literature mp = 190−193 °C).[8] GC-MS purity was determined as methyl hemiester (GC retention time = 5.59 min) by dissolving anhydride **3** into methanol. HPLC retention time (method 2) of the methyl hemiester = 8.1 min.

(2*R*,3*S*)-2-(Ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (4). (3a*S*,6a*R*)-Dihydrofuro[3,4-*b*]furan-2,4,6(3*H*)-trione (**3**) (19.95 g, 118 mmol) was suspended CPME (132 mL) at room temperature. Anhydrous ethanol (55.8 g, 1211 mmol) was added to the suspension at 0 °C over 15 min. The resultant slurry was stirred at room temperature for 16 h. At this point, a solution was observed and was evaporated under reduced pressure to dryness. (2*R*,3*S*)-2-(Ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) was obtained as colorless oil (26.8 g, 93.9 A% purity by GC-MS, 127 mmol, 105% yield). ^{1}H NMR ($CDCl_3$): 1.29 (t, *J* = 7.1, 3H), 2.83 (dd, *J* = 17.8, 9.3 Hz, 1H), 3.03 (dd, *J* = 17.8, 8.7 Hz, 1H), 3.82 (ddd, *J* = 9.3, 8.7, 8.3, 1H), 4.24 (overlapping q, *J* = 7.1. 2H), 5.13 (d, *J* = 8.3 Hz, 1H), 9.7 (bs, 1H). ^{13}C NMR ($CDCl_3$): 174.46, 176.65, 167.82, 76.38, 62.59, 43.21, 30.42, 13.85. GC retention time of **4** = 5.83 min. HPLC retention time (method 3) = 1.6 min. When MTBE was used as the reaction solvent, product (**4**) was isolated in similar yield and purity.

Ethyl (2*R*,3*S*)-3-(morpholine-4-carbonyl)-5-oxotetrahydrofuran-2-carboxylate (5a). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (12.1 g, 68.9 mmol) was suspended in ethyl acetate (200 mL). *N*-Methylmorpholine (6.17 g, 78.6 mmol) was added to this suspension at room temperature and stirred for 30 min. The reaction mixture was cooled to 0 °C and morpholine (5.67 g, 65.2 mmol) was added at 0- 5 °C. A solution of (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) (12.3 g, 60.9 mmol) in ethyl acetate (70 mL) was added to the reaction mixture at 5−7 °C. The reaction mixture was stirred at 5 °C for 1 h and at room temperature for 16 h. A white precipitate in the reaction mixture was removed by filtration. The filtrate was washed with 2N aqueous hydrochloric acid (2 × 50 mL) and brine (50 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered, and evaporated under 50−60 Torr to give an off-white solid. The crude product was purified by silica gel column chromatography using heptane/ethyl acetate 1:1 (v/v) to neat ethyl acetate as eluent. Pure fractions were evaporated to give ethyl (2*R*,3*S*)-3-(morpholine-4-carbonyl)-5-oxotetrahydrofuran-2-carboxylate (**5a**) (5.91 g, 96.8 A% purity by GC-MS, 23.0 mmol, 38%) as a white solid. Mp 94−96 °C. $C_{12}H_{17}NO_6$, GC-MS (EI): *m*/*z* 271 (M). ^{1}H NMR ($CDCl_3$): 1.29 (t. *J* = 7.1, 3H), 2.61 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.23 (dd, *J* = 17.6, 9.9 Hz, 1H), 3.6−3.9 (m, 8H), 4.01 (apparent q, *J* = 9.8 Hz, 1H), 4.24 (overlapping q, *J* = 7.1. 2H), 5.02 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 174.70, 167.58, 166.15, 75.94, 66.51, 66.36, 62.32, 46.06, 42.69, 41.35, 30.60, 14.11. GC retention time of **5a** = 8.79 min.

Ethyl (2*R*,3*S*)-3-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (5b). Oxalyl chloride (68.5 mL of 2 M solution in DCM, 137 mmol) was added to a solution of (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) (25.3 g, 114 mmol estimated based on quantitative yield from previous step) in DCM (80 mL) at room temperature. Three drops of DMF was added to the reaction mixture at 10 °C and gas evolution was observed. The reaction mixture was stirred at room temperature for 1 h and then heated to 35 °C for 3 h. The reaction mixture was evaporated under 50−60 Torr to orange oil. The oil was coevaporated with DCM-toluene (2x 40 mL) to remove residual oxalyl chloride. The resultant oil was dissolved in DCM (120 mL) and cooled to −5 °C. *N*-Methyl-aniline (12.24 g, 114 mmol) and pyridine (9.03 g, 114 mmol) were dissolved in DCM (120 mL). This solution was added dropwise to the acyl chloride solution at −5 °C over 45 min. The reaction mixture was stirred at room temperature overnight for convenience. The reaction mixture was diluted with DCM (100 mL) and then washed with 1N aqueous hydrochloric acid (2 × 100 mL), water (100 mL) and brine (50 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under 50−60 Torr to dryness to give a light brown solid (32.9 g). The solid was suspended in a toluene (130 mL) at room temperature. The slurry was heated to 85 °C to dissolve and then allowed to cool to room temperature, filtered and the filter cake washed with toluene (40 mL) to give 22.15 g as the first crop. A second crop (3.85 g) was obtained from combined filtrates after concentration under 30−40 Torr and crystallization from toluene (40 mL). Ethyl (2*R*,3*S*)-3-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5b**) was obtained from the combined solids as a white solid (26.0 g, 99.6% A% purity by GC-MS, 89 mmol, 80% yield from cyclic anhydride **3**). Mp = 123−125 °C. $C_{15}H_{17}NO_5$, GC-MS (EI): *m*/*z* 291 (M). ^{1}H NMR ($CDCl_3$): 1.36 (t, *J* = 7.1 Hz, 3H), 2.41 (dd, *J* = 17.5, 8.5, 1H), 3.23 (dd, *J* = 11.2, 17.6 Hz, 1H), 3.28 (s, 3H), 3.53 (m, 1H), 4.29 (ab mult, 2H), 4.62 d, *J* = 8.8 Hz, 1H), 7.3 (bd, 2H), 7.49 (m, 3H). ^{13}C NMR ($CDCl_3$): 174.56, 167.81, 167.05, 142.61, 130.36 (2C), 128.98, 127.23 (2C), 76.34, 62.24, 42.49, 37.85, 30.69, 14.09. HPLC retention time (method 3) = 10.3 min. GC retention time of **5b** = 9.10 min.

One-pot procedure for conversion of (2*R*,3*S*)-5-oxotetrahydrofuran-2,3-dicarboxylic acid (2) to Ethyl (2*R*,3*S*)-3-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (5b). (2*R*,3*S*)-5-Oxotetrahydrofuran-2,3-dicarboxylic acid (**2**) (1.00 g, 5.75 mmol) was suspended in CPME, (10 mL) at room temperature. The slurry was heated to 50−60 °C and acetic anhydride (703.8 mg, 6.90 mmol) was added dropwise at this temperature. The slurry turned into a clear solution upon complete addition. The clear solution was heated to 100−106 °C under reflux. After 10 min heating under reflux, a white solid separated. The slurry was heated under reflux at 100−106 °C for 2 h as the slurry thickened. The slurry was distilled under atmospheric pressure to remove ∼4 mL of distillate. Fresh CPME (10 mL) was added, and the slurry was distilled to remove 8 mL of distillate. The resultant light yellow slurry was cooled to room temperature. An aliquot of the slurry was quenched into methanol and GC-MS showed a major peak at 5.51 min (91 A %) which corresponds to the methyl hemiester, indicating the formation of (3a*S*,6a*R*)-dihydrofuro-[3,4-*b*]furan-2,4,6(3*H*)-trione (**3**).The cyclic anhydride **3** slurry was charged with anhydrous ethanol (793 mg, 17.2 mmol) at −5 to −8 °C over 20 min. The resultant slurry was warmed to room temperature and stirred for 16 h. At this point the reaction mixture was a solution. GC-MS of the solution showed major peak at 5.81 min (91 A%) which corresponds to (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**). The solution of hemiester **4** was distilled under atmospheric pressure to remove ∼4 mL of distillate (batch temperature at 106 °C, head temperature at 80 °C). Fresh CPME (5 mL) was

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added, and solution was distilled to remove ~5 mL of distillate (batch temperature at 108 °C, head temperature at 104 °C). The hemiester **4** solution was sampled and GC-MS showed a major peak at 5.81 min (94 area %). The hemiester **4** solution was cooled to 5 °C. Oxalyl chloride (3.45 mL of 2 M solution in DCM, 6.90 mmol) was added at 5 °C over 5 min. Two drops of DMF was added and gas evolution was observed. The reaction mixture was heated to 45 °C for 2 h. The reaction mixture was distilled under atmospheric pressure to remove 2 mL of distillate. Fresh DCM (10 mL) was added and the solution was distilled to remove 10 mL of distillate. The resultant acyl chloride solution was cooled to 0 °C. *N*-Methyl-aniline (616 mg, 5.75 mmol) and pyridine (455 mg, 5.75 mmol) were dissolved in DCM (5 mL). The aniline/pyridine solution was added dropwise to the acyl chloride solution at 0 °C. Upon complete addition of the aniline/pyridine solution, brown oil separated from the reaction mixture. DCM (3 mL) was added to dissolve the oil and the solution was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (25 mL). The solution was washed with 1N aqueous hydrochloric acid (15 mL), saturated sodium carbonate (15 mL), water (2 × 25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give the ethyl (2*R*,3*S*)-3-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5b**) as a light brown solid (960 mg, 96.2 A% purity by GC-MS, 3.30 mmol, 57% yield from (2*R*,3*S*)-5-oxotetrahydrofuran-2,3-dicarboxylic acid (**2**). HPLC retention time (method 3) = 10.3 min

Ethyl (2*R*,3*S*)-3-(ethyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (5C). Oxalyl chloride (6.0 mL of 2 M solution in DCM, 12.0 mmol) was added to a solution of (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) (2.02g, 10.0 mmol) in DCM (4 mL) at room temperature. Two drops of dimethylformamide (DMF) was added to the reaction mixture and gas evolution was observed. The reaction mixture was stirred at 35−40 °C for 2 h. The reaction mixture was evaporated under reduced pressure to an orange oil. The oil was coevaporated with DCM (2 × 5 mL) to remove residual oxalyl chloride. The resultant oil was dissolved in DCM (10 mL) and cooled to −5 °C. *N*-Ethyl-aniline (1.454 g, 12.0 mmol) and pyridine (0.949 g, 12.0 mmol) were dissolved in DCM (10 mL) and added to the acyl chloride solution at −5 °C over 30 min. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (30 mL) and then washed with 1N aqueous hydrochloric acid (2 × 20 mL), water (20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give a light brown solid. The solid was suspended in a mixture of ethyl acetate (3 mL) and hexane (5 mL) at room temperature. The resultant slurry was heated to 70 °C for 1 h, cooled to 20 °C, and filtered. Ethyl (2*R*,3*S*)-3-(ethyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5c**) was obtained as a white solid (1.80 g, 99.9 A% purity by GC-MS, 5.89 mmol, 59% yield). Mp = 113−116 °C. $C_{16}H_{19}NO_5$, GC-MS (EI): *m*/*z* 305 (M). ^{1}H NMR ($CDCl_3$): 1.13 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 2.40 (dd, *J* = 17.5, 8.5, 1H), 3.28 (dd, *J* = 17.5, 11.1, 1H), 3.46 (dd, *J* = 11.1, 8.6 Hz, 1H), 3.65 (dd, *J* = 13.4, 7.1, 1H), 3.82 (dd, *J* = 13.4, 7.2, 1H), 4.28 (ab mult, *J* = 10.7, 7.1 Hz, 2H), 4.61, (d, *J* = 8.8 Hz, 1H), 7.3 (bs, 2H), 7.50 (m, 3H). ^{13}C NMR ($CDCl_3$): 174.70, 167.85, 166.44, 140.94, 130.23 (2C), 129.04, 128.26 (2C), 76.53, 62.29, 44.82, 42.78, 30.70, 14.10, 12.73. GC retention of **5c** = 9.41 min.

Ethyl (2*R*,3*S*)-3-(isopropyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (5d). Oxalyl chloride (6.0 mL of 2 M solution in DCM, 12.0 mmol) was added to a solution of (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) (2.02 g, 10.0 mmol) in DCM (4 mL) at room temperature. Two drops of DMF was added to the reaction mixture and gas evolution was observed. The reaction mixture was stirred at 35−40 °C for 2 h. The reaction mixture was evaporated under reduced pressure to an orange oil. The oil was coevaporated with DCM (2 × 5 mL) to remove residual oxalyl chloride. The resultant oil was dissolved in DCM (10 mL) and cooled to −5 °C. *N*-Ethyl-aniline (1.623 g, 12.0 mmol) and pyridine (0.949 g, 12.0 mmol) were dissolved in DCM (10 mL) andadded to the acyl chloride solution at −5 °C over 30 min. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (30 mL) and then washed with 1N aqueous hydrochloric acid (2 × 20 mL), water (20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give a brown oil. The oil was purified by silica gel column chromatography using ethyl acetate/hexane (1:1, v/v) as eluent. The pure fractions were collected and evaporated to give a light brown solid. The solid was dissolved in MTBE (7 mL) at reflux and the resultant solution was cooled to 20 °C while solids separated. The resultant slurry was stirred at 20 °C for 1 h and filtered. Ethyl (2*R*,3*S*)-3-(isopropyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5d**) was obtained as a white solid (1.18 g, 99.1 A% purity by GC-MS, 3.69 mmol, 37% yield). Mp = 94−95 °C. $C_{17}H_{21}NO_5$, GC-MS (EI): *m*/*z* 319 (M). ^{1}H NMR ($CDCl_3$): 1.07 (dd, J = 6.8, 11.2, 6H), 1.36 (t, J = 7.2, 3H), 2.38 (dd, J = 17.1, 8.1, 1H), 3.27 (ab mult, 2H), 4.28 (ab mult, 2H), 4.54 (d, *J* = 8.6 Hz, 1H), 4.91 (septet, *J* = 6.8 Hz, 1H), 7.15 (m, 1H), 7.5 (m, 4H). ^{13}C NMR ($CDCl_3$): 174.81, 167.89, 166.27, 137.23, 130.15 (2C), 129.77, 129.28 (2C), 76.63, 62.30, 47.11, 43.40, 30.65, 20.71, 14.10. GC retention time of **5d** = 9.66 min.

Ethyl (2*R*,3*S*)-3-(methoxy(methyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (5e). Oxalyl chloride (10.39 mL of 2 M solution in DCM, 20.8 mmol) was added to a solution of (2*R*,3*S*)-2-(ethoxycarbonyl)-5-oxotetrahydrofuran-3-carboxylic acid (**4**) (3.50 g, 17.3 mmol) in DCM (5 mL) at room temperature. Three drops of DMF was added to the reaction mixture and gas evolution occurred. The reaction mixture was stirred at 35−40 °C for 2 h. The reaction mixture was evaporated under 50−60 Torr to an orange oil. The oil was coevaporated with DCM (2x 5 mL) to remove residual oxalyl chloride. The resultant oil was dissolved in DCM (25 mL) and cooled to −5 °C. Dimethylhydroxylamine hydrochloride (1.856 g, 19.03 mmol) was added to the acyl chloride solution at 0 °C. Pyridine (3.01 g, 38.06 mmol) were dissolved in DCM (15 mL). The pyridine solution was added dropwise to the reaction mixture at −5 °C over 30 min. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (50 mL) and then washed with 1N aqueous hydrochloric acid (2 × 30 mL), water (20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give a brown oil. The oil was purified by silica gel column chromatography using ethyl acetate/hexane (1:1 v/v) was eluent. The pure fractions were collected and evaporated to give ethyl (2*R*,3*S*)-3-(methoxy-(methyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5e**), (3.51 g, 97.3 A% purity by GC-MS, 14.3 mmol, 82% yield), as a light brown oil. $C_{10}H_{15}NO_6$, GC-MS (EI): *m*/*z* 245 (M).

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^{1}H NMR ($CDCl_3$): 1.28 (m, 3H), 2.60 (m, 1H), 3.15 (m, 1H), 3.20 (s, 3H), 3.75 (m, 1H), 3.80 (s, 3H), 4.20 (m, 3H), 5.14 (d, J = 8.7, 1H). ^{13}C NMR ($CDCl_3$): 174.89, 168.61, 167.99, 75.89, 62.23, 41.59, 32.53, 29.68, 14.10. GC retention time of **5e** = 6.73 min.

(3R,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (7). To ethyl (2*R*,3*S*)-3-(methyl(phenyl)carbamoyl)-5-oxotetrahydrofuran-2-carboxylate (**5b**) (22.15 g, 76 mmol) in dry THF (230 mL) was added a solution of 1.0 M LAH (303 mL, 303 mmol) in THF over 75 min at −10 to 3 °C. The reaction was warmed to room temperature and stirred for 16h. The reaction mixture was cooled to −8 °C and treated with 1.0 M sulfuric acid (910 mL, 910 mmol) over 2 h at <5 °C. Upon complete addition of sulfuric acid, the pH of the quenched solution was 1.3 (by pH paper). The ice bath was removed and reaction allowed to warm to room temperature and stirred for 5 h. The mixture was concentrated to remove organic solvent under ∼80 Torr and at ∼30 °C. The resultant aqueous solution was cooled in an ice bath and treated portion-wise with 1N sodium hydroxide (834 mL, 834 mmol) to adjust pH to 4−5. The neutralized solution was extracted with toluene (4 × 500 mL) to remove *N*-methylaniline byproduct. The aqueous phase containing the product furanofuranol **7** (1750 mL) was transferred to a continuous extractor and the distillation flask was charged with DCM (500 mL). The extraction was run for 44 h with internal temp at 40 °C and oil bath set to 80 °C in order to maintain a vigorous reflux. The DCM extract was evaporated to dryness to give crude furanofuranol **7** oil (8.75 g, 89 A% purity by GCMS). The crude oil was dissolved in EtOAc (100 mL) and filtered through a short pad of silica gel (20 g) and the pad was washed with EtOAc (100 mL). The combined filtrate and wash was evaporated to give (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol (**7**) as clear oil (7.8 g, 96.8 A % purity by GC-MS, 55.7 mmol, 74% yield). $C_6H_{10}O_3$, GC-MS (EI): *m*/*z* 100 (M- H_2CO). ^{1}H NMR ($CDCl_3$): 1.88 (m, 1H), 2.08 (bd, 1H, −OH), 2.31 (m, 1H), 2.87 (m, 1H), 3.64 (dd, J = 9.2, 7.0 Hz, 1H), 3.87−4.02 (abx system, 3H), 4.45 (m, 1H), 5.70 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): 109.54, 73.15, 71.00, 69.90, 46.58, 24.86. Diastereomeric ratio of **7** to **12** = 98.2:1.8. GC retention time of **7**= 3.20 min; **12** = 3.09 min.

2,5-Dioxopyrrolidin-1-yl((3*R*,3a*S*,6a*R*)-hexahydrofuro-[2,3-*b*]furan-3-yl)carbonate (8). (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (**7**) (5.0 g, 93 A% purity, 35.7 mmol) was dissolved in DCM (100 mL) at room temperature. *N*,*N*′-Disuccinimidyl carbonate (DSC, 14.3 g, 53.1 mmol) and pyridine (7.22 mL, 91 mmol) were charged to the furanofuranol **7** solution at room temperature. The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and charged with DCM (100 mL) and water (100 mL). The resultant biphasic mixture was stirred at room temperature for 30 min. The phases were separated and the organic phase was washed with water (100 mL), brine (100 mL), dried over anhyd $MgSO_4$, coevaporated with toluene (2 × 100 mL) to give a crude yellow solid (11.9 g). The solids were slurried in refluxing DCM (100 mL), cooled to room temperature, and insoluble material was removed by filtration. The solid was washed with fresh DCM (2 × 25 mL). The combined filtrate was filtered through a pad of silica gel and the pad was washed with DCM (2 × 25 mL) followed by EtOAc (25 mL). The combined filtrates were concentrated under 40−50 Torr to give a off-white crude solid (9.6 g). The crude solid was recrystallized from a mixture of DCM (40 mL) and hexane (80 mL) to give 2,5-dioxopyrrolidin-1-yl((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl)carbonate (**8**) as a white solid (8.0 g, 94.8 A% purity by GCMS, 27.8 mmol, 78% yield). Mp = 128−129 °C with gas evolution. ^{1}H NMR ($CDCl_3$): 2.0 (m, 1H), 2.14 (m, 1H), 2.85 (s, 4H), 3.14 (m, 1H), 3.94 (m, 2H), 4.03 (ddd, J = 8.4, 8.4, 2.4 Hz, 1H), 4.11 (dd, J = 10.2, 6.1 Hz, 1H), 5.25 (ddd, J = 8.4, 6.1, 6.1, 1H), 5.74 (d, J = 5.2, 1H). ^{13}C NMR ($CDCl_3$): 168.57 (2C), 151.19, 109.16, 79.66, 70.05, 69.65, 45.07, 25.94, 25.45 (2C). Diastereomeric ratio of **8** to **13** = 99.86:0.14. GC retention time of **8** = 8.84 min; **13** = 8.99 min.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl ((2*S*,3*R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (darunavir). 4-Amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (391.5 mg, 1.00 mmol) and 2,5-dioxopyrrolidin-1-yl((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl)carbonate (**8**) (271.2 mg, 1.00 mmol) were dissolved in acetonitrile (10 mL) at room temperature. Triethylamine (101 mg, 1.00 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under 40−50 Torr and diluted with MTBE (40 mL). The organic solution was washed with 10% aqueous Na_2CO_3 (20 mL), 10% aqueous H_2SO_4 (20 mL), and 10% aqueous Na_2CO_3 (20 mL). The organic solution was concentrated under 40−50 Torr to give a white foam. The white foam was dissolved in ethanol (3 mL) at room temperature and heated to reflux. The solution was cooled to room temperature and solid separated. The resultant slurry was stirred at room temperature for 16 h. The white solid was collected by filtration. The yield of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ((2*S*,3*R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-carbamate (darunavir) was 414 mg (76% yield, HPLC purity 99.2A%). ^{1}H NMR ($CDCl_3$): 0.89 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.45 (m, 1H), 1.62 (m, 1H), 1.77 (bs, 2H), 1.84 (m overlapping singlet, 1H), 2.7−3.2 (m, 6H), 3.7−4.0 (m, 6H) 4.21 (bs, 2H), 5.03 (m, 2H), 5.64 (d, J = 5.1, 1H), 6.68 (d, J = 7.9, 2H), 7.2−7.3 (m, 5H), 7.54 (d, J = 7.9, 2H). ^{13}C NMR ($CDCl_3$): 155.5, 150.83, 137.70, 129.51, 129.39, 128.51, 126.53, 125.90, 114.09, 109.30, 73.36, 72.84, 70.84, 69.63, 58.90, 55.10, 53.76, 45.35, 35.67, 27.29, 25.81, 20.18, 19.92. The ^{1}H NMR and ^{13}C NMR spectra and HPLC chromatogram of this sample matched those of an authentic sample.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00377.

^{1}H and ^{13}C NMR spectra and chromatographic (HPLC and GC-MS) data for **2**, **3**, **4**, **5a**−**e**, **7**, **8**, **10**, **11**, and darunavir (PDF)

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The authors declare no competing financial interest.

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