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Practical Synthetic Method for the Preparation of Pyrone Diesters: An Efficient Synthetic Route for the Synthesis of Dolutegravir Sodium

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Supporting Information

ABSTRACT: A highly efficient and practical synthetic method for the preparation of pyrone diesters was established. The pyrone diester **3c** can be prepared from readily available starting materials on a multihundred gram scale. The pyrone diester **3c** can easily be converted to dolutegravir sodium (**1**). The synthetic route demonstrated herein provides an efficient and atom-economical synthetic method for preparing this potent anti-HIV agent.

KEYWORDS: *dolutegravir sodium, pyrone diester, hydroquinone cocrystal, intramolecular aminolysis*

INTRODUCTION

Dolutegravir sodium, an inhibitor of HIV integrase, is a promising drug for the treatment of HIV infection and is being used worldwide (see Figure 1). Dolutegravir has a highly functionalized pyridone substructure, and the construction of its core structure has been a key issue in the development of a method to synthesize it. As pyridones can be readily prepared from corresponding pyrones, many synthetic methods for preparing dolutegravir via a pyrone intermediate have been explored and reported thus far.[1]

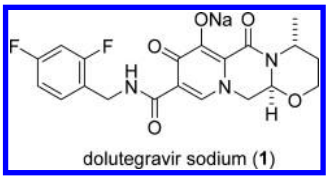

Figure 1. Dolutegravir sodium (**1**).

A medicinal chemistry-based synthetic route to dolutegravir employing maltol, which has a pyrone moiety, was applied to preparative scale manufacturing as reported in the preceding paper.[1d−f] However, the methods used require relatively long synthetic steps and also include a cryogenic reaction. Therefore, there has been a search for more efficient synthetic methods not using maltol.[2,3] We have already reported synthetic routes for preparing dolutegravir via a highly functionalized pyrone intermediate without using maltol, but no practical synthetic method for pyrone intermediates has yet been reported.[4] In this paper, we disclose a preparative scale synthetic method of pyrone intermediates which can offer an efficient synthetic route to dolutegravir sodium.

RESULTS AND DISCUSSION

A preparation method for an appropriately functionalized pyrone intermediate in short synthetic steps is desired. The previously developed synthetic method starting from maltol includes oxidative conversion of the methyl moiety of maltol into carboxylate, resulting in more synthetic steps and is less atom-economical (Scheme 1).[1] One promising intermediate is pyrone diester **3**, which can be readily prepared from enamine **4** and oxalate **5** without any oxidation steps.[5] Furthermore, one of the ester moieties of pyrone **3** can easily be converted into amide, leading to a more efficient synthetic method for the preparation of **1** (Scheme 2).

Treatment of enamine **4a** and diethyl oxalate (**5a**) furnished the corresponding pyrone **3a** (Table 1). In the case of THF solvent, a considerable amount of phenolic byproduct **6** was found to be formed (entries 1−3). This byproduct was speculated to be formed by dimerization of enamine **4a** under the basic condition (Scheme 3). To suppress the side reaction between enamine **4a** and its enolate, the reaction conditions were extensively explored.

We first examined the solvent for acceleration of the enolate formation and found aprotic polar solvents with more dissolving ability to be effective for suppressing byproduct **6**

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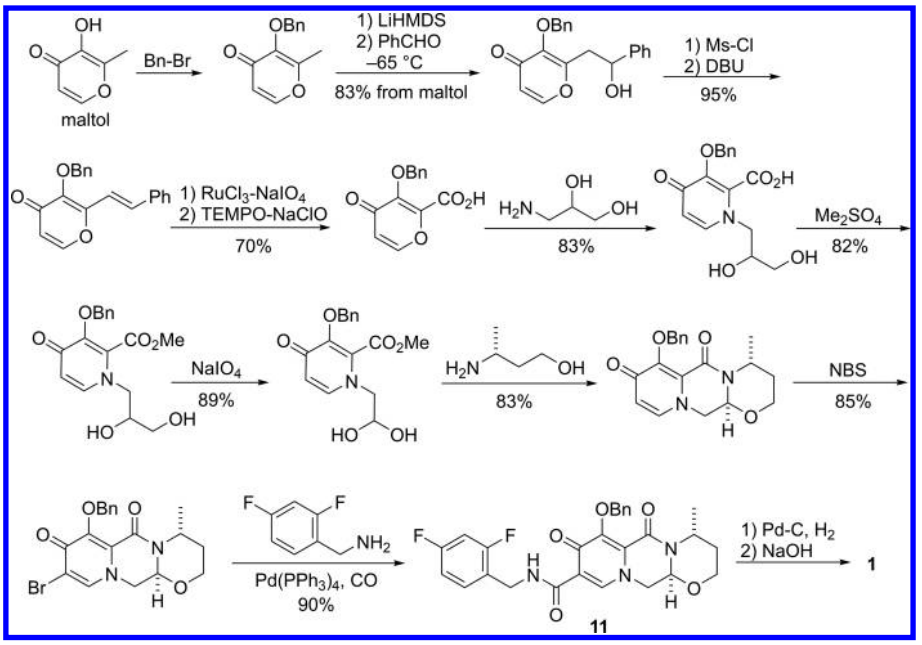
Scheme 1. Synthetic Route to Dolutegravir Sodium (1) Starting from Maltol



Scheme 2. Retrosynthetic Pathway for Dolutegravir Sodium (1) through a Pyrone Diester Intermediate 3

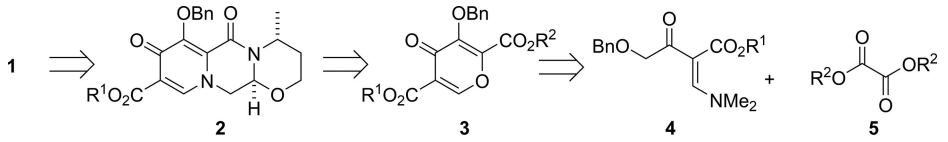
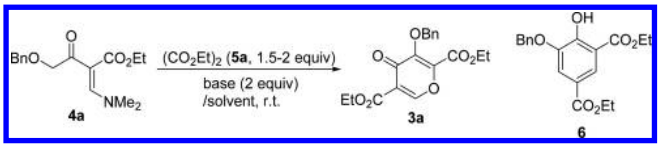


Table 1. Optimization of Pyrone Formation



entry	base	solvent	yield of **3a** (%)	yield of **6** (%)[a]
1[b]	NaH	THF	19	(34)
2[b]	NaO*t*-Bu	THF	12	(7)
3[b]	KO*t*-Bu	THF	trace	(55)
4[b]	NaH	DMA	30	(10)
5[b]	NaH	DMI	26	4 (2)
6[c]	NaO*t*-Bu	DMI	35	8 (6)
7[c]	NaO*t*-Bu	THF	26	14

[a]Values in parentheses are LC–MS peak area %. [b]**5a** was added to the mixture of **4a** and base. [c]Mixture of **4a** and **5a** was added to the base.

(Table 1, entries 4 and 5). When *N*,*N*-dimethylacetamide (DMA) was used as a solvent, another byproduct (ethyl 4-(dimethylamino)-2,4-dioxobutanoate) was formed due to condensation of the anion of DMA with diethyl oxalate. This byproduct formation could be suppressed by adopting 1,3-dimethyl-2-imidazolidinone (DMI) with no acidic protons as a solvent. Therefore, DMI was considered to be the better solvent.

We next explored the addition method and the bases used. Addition of the enamine and oxalate into the solution of NaO*t*-Bu in DMI improved the yield of **3a** (entry 6). This indicates that an enolate generated from **4a** should be allowed to immediately react with an oxalate. Using THF with the same addition method decreased the yield of **3a** along with an increase of byproduct **6**, indicating that use of an aprotic polar solvent is beneficial for pyrone formation (entry 7).

Preparation of pyrone **3** was further examined using NaO*t*-Bu and dimethyl oxalate (**5b**) in DMI (Table 2). Increasing the amount of **5b** to 3 equiv drastically improved the yield of the desired pyrone **3b**, whereas the amount of NaO*t*-Bu did not affect the yield of **3b** (entries 2 and 3). The drastic improvement of the yield of **3b** by increasing the amount of oxalate **5b** from 2 equiv to 3 equiv would be attributed to the suppression of the competitive side reaction of the enamine

Scheme 3. Speculated Mechanism for the Formation of Byproduct 6

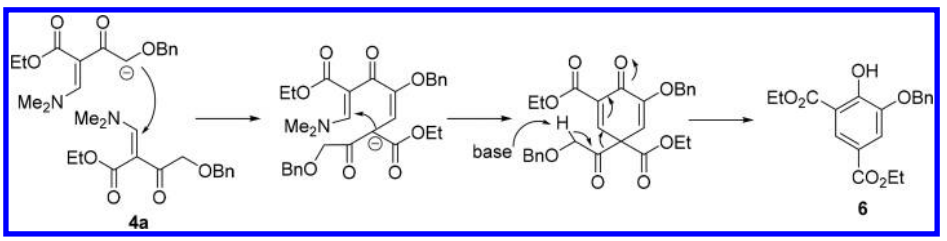


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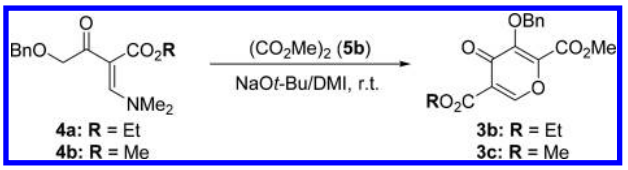
Table 2. Pyrone Formation Using Dimethyl Oxalate (5b) and NaO*t*-Bu



entry	R	NaO*t*-Bu (equiv)	**5b** (equiv)	product	yield of **3** (%)
1	Et	2.0	2.0	**3b**	39
2	Et	3.0	3.0	**3b**	86
3	Et	1.5	3.0	**3b**	85
4[a]	Et	1.5	3.0	**3b**	86
5	Et	3.0[b]	3.0	**3b**	57
6	Me	1.5	3.0	**3c**	85

[a]Carried out in 100 mmol scale. [b]Sodium *tert*-pentoxide was used as a base.

including its dimerization as shown in Scheme 3. Additionally, 1.5 equiv of base was found to be sufficient for enolate formation of enamine **4**. The high yield of **3b** was also be reproduced in the preparative scale synthesis (entry 4). Employing more sterically bulky base, sodium *tert*-pentoxide, resulted in a decrease of the yield of **3b** (entry 5). By using methyl ester substrate **4b**, pyrone **3c** with dimethyl ester moiety was also obtained in high yield (entry 6).

For preparation of pyrone dimethyl ester **3c**, NaOMe, a less expensive base than NaO*t*-Bu, can be used because there is no possibility of transesterification occurring. Using NaOMe as a base allows preparative scale synthesis of **3c**, with multi-hundred grams of **3c** being obtained starting from the inexpensive and readily available *β*-ketoester **7** (Scheme 4).

Sodium *tert*-pentoxide was used as a base for the preparation of **8** from **7**, since using sodium *tert*-butoxide gave considerable amount (~10%) of *tert*-butyl ether as a byproduct. Additionally, enamine **4b** can also be prepared from **8** using *N*,*N*-dimethylformamide dimethyl acetal as reported previously.[2b,c,6]

The resulting pyrone dimethyl ester **3c** can be easily transformed into dolutegravir sodium (**1**) in short synthetic steps (Scheme 5). Pyrone **3c** was converted to pyridone **9** by using aminoacetaldehyde dimethyl acetal. The reaction proceeded smoothly and **9** can be isolated from the reaction mixture by crystallization. The resulting pyridone **9** was then transformed into a tricyclic intermediate **10** by acid-catalyzed hydrolysis of acetal and the subsequent reaction with 3-(*R*)-aminobutan-1-ol. The resulting tricyclic intermediate **10** did not crystallize but could be isolated as hydroquinone cocrystal **10**·$^1/_2$hydroquinone with high diastereoselectivity (dr 98.5:1.5) by treating the workup solution with hydroquinone. The diastereoselectivity of the tricyclic scaffold formation would be due to the difference of reaction rates of the intramolecular aminolysis between the intermediary diastereomeric aminals **12** and **13** in the same manner as reported previously,[7] that is, **12** with a methyl moiety at the axial position is sterically more favored than **13** due to its lesser steric hindrance (Figure 2).

Amidation of the ester moiety of **10**·$^1/_2$hydroquinone was accomplished by direct aminolysis by 2,4-difluorobenzylamine to afford amide intermediate **11**.[2b,c] Acetic acid was essential for successful completion of the aminolysis. Hydroquinone was removed by the workup procedure, and no hydroquinone was detected in **11** by ^{1}H NMR analysis. Dolutegravir sodium (**1**) was obtained by removal of the benzyl protecting group of **11** followed by sodium salt formation according to the reported procedure.[1d,e] Taking into consideration the quality of API, the free form of **1** was isolated as an intermediate to remove solvents and catalyst used in debenzylation step before sodium salt formation.

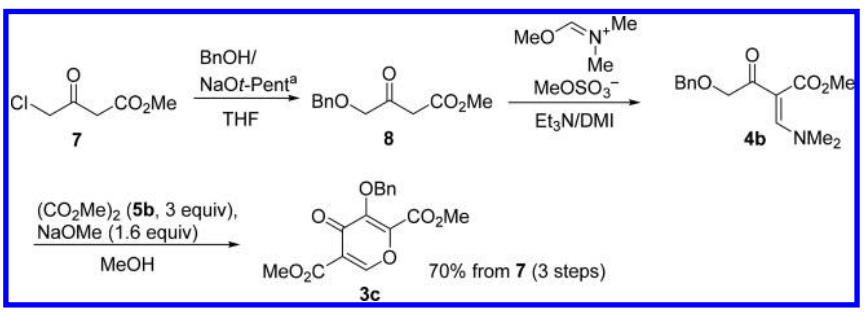
The synthetic route for the preparation of **1** developed herein has advantages that it has short synthetic steps (9 steps) and only requires an inexpensive and readily available starting material and base (*β*-ketoester **7** and NaOMe).

CONCLUSION

We successfully developed an efficient synthetic route for preparing dolutegravir sodium through a pyrone diester intermediate **3c**. A large-scale synthetic method of dimethyl 3-(benzyloxy)-4-oxo-4*H*-pyran-2,5-dicarboxylate (**3c**) was demonstrated starting from the inexpensive and readily available starting material methyl 4-chloro-3-oxobutanoate (**7**) using NaOMe as a base. The synthetic route from **3c** to **1** was also established via the intermediate of the cocrystal of **10** and hydroquinone.

The synthetic route demonstrated herein has the advantage of efficiency as it has short synthetic steps (9 synthetic steps) along with its each crystalline intermediate. Furthermore, this synthetic route does not include any oxidation or cryogenic reaction, which are often troublesome for scale-up. Also, this route offers a highly atom-efficient property as the waste from the process consists of only low molecular weight compounds (water, methanol, dimethylamine, and toluene). Compare to the synthetic route starting from maltol (Scheme 1) that contains oxidative cleavage of styrene and glycol, bromination for amidation, and use of heavy metal reagents, this synthetic route is atom-efficient and would be a manufacturing method with more atom-economical property.

Scheme 4. Synthesis of Pyrone Dimethyl Ester 3c Using NaOMe



[a]NaO*t*-Pent: sodium *tert*-pentoxide

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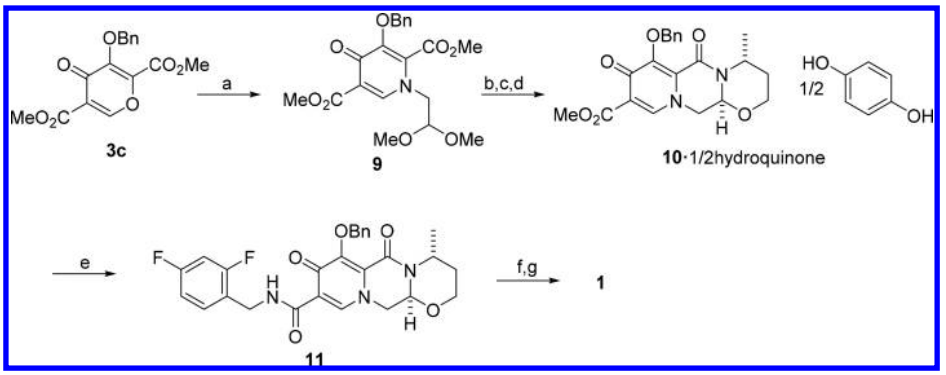
Scheme 5. Synthetic Route to Dolutegravir Sodium (1) from Pyrone Diester Intermediate 3c



[a]Aminoacetaldehyde dimethyl acetal, MeOH, reflux (83%). [b]$HCO_2H-H_2SO_4$ aq, r.t. [c]3-(*R*)-aminobutan-1-ol, AcOH, toluene/MeOH, 100 °C. [d]Hydroquinone, AcOEt (66%, dr 98.5:1.5, 3 steps). [e]2,4-Difluorobenzylamine, AcOH, toluene, 100 °C (62%). [f]Pd−C, H_2, THF/MeOH (92%). [g]NaOH aq, EtOH (99%).

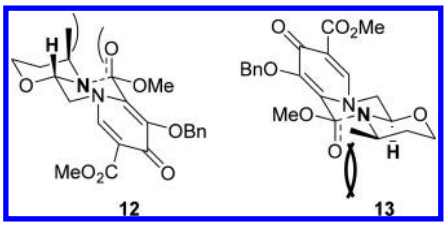


Figure 2. Intermediary aminals for intramolecular aminolysis.

EXPERIMENTAL SECTION

General. All materials were purchased from commercial suppliers. Unless otherwise specified, all reagents and solvents were used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in the solvent indicated on a Bruker AVANCE III HD 400 spectrometer, and mass spectra were determined on a Shimadzu LCMS-2010EV spectrometer.

*5-Ethyl 2-methyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (**3b**).* To a suspension of dimethyl oxalate (354.3 mg, 3.0 mmol) and sodium *tert*-butoxide (144.2 mg, 1.5 mmol) in 1,3-dimethyl-2-imidazolidinone (1.4 mL) was added to a solution of **4a** (291.3 mg, 1.0 mmol) in 1,3-dimethyl-2-imidazolidinone at 0 °C, and the whole was stirred at room temperature for 2 h. After completion of the reaction, 2 M hydrochloric acid aq (10 mL) was added, and the mixture was stirred for 0.5 h. The resulting precipitate was collected, washed with water, and dried under reduced pressure to give **3b** (283.9 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.50−7.45 (m, 2H), 7.41−7.30 (m, 3H), 5.34 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 162.2, 159.8, 159.8, 150.2, 145.2, 136.0, 129.0, 128.6, 128.5, 120.8, 75.1, 61.8, 53.2, 14.2.

*Dimethyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (**3c**).* To a suspension of sodium *tert*-pentoxide (424 g, 3.66 mol) in tetrahydrofuran (790 mL) was added a solution of benzyl alcohol (152 mL, 1.46 mol) in tetrahydrofuran (474 mL) at 15 °C, and the whole was stirred at 40 °C for 2 h, then cooled with an ice bath. A solution of methyl 4-chloro-3-oxobutanoate (**7**) (189 mL, 1.61 mol) in tetrahydrofuran (474 mL) was added at the ice bath temperature, and the reaction mixture was stirred at 40 °C for 2 h. A solution of **7** (17.2 mL, 0.146 mol) in tetrahydrofuran (10 mL) was added and stirred for an additional 40 min. After cooling to room temperature, a solution of citric acid monohydrate (307 g) in water (1900 mL) was added to the reaction mixture and extracted with ethyl acetate (1600 mL). The organic layer was washed successively with aqueous solution of 5% sodium hydrogen carbonate (1400 mL) and saturated aqueous sodium chloride solution (1400 mL). The organic layer was concentrated under reduced pressure to give **8** (386.06 g) as a yellow oil. This crude material was used for next step without further purification.

Dimethylformamide (182 mL, 2.34 mol) was added to dimethyl sulfate (210 mL, 2.19 mol) and stirred at 80 °C for 4 h. The resultant solution was cooled to give the methoxydimethylmethanaminium methyl sulfate[8] (443.4 g) as a yellow oil. To this was added 1,3-dimethyl-2-imidazolidinone (10 mL) and cooled to the ice bath temperature. The crude oil of **8** (386.06 g) was added and the resultant yellow solution was stirred at ice bath temperature for 4 h. Triethylamine (345 mL, 2.49 mol) was added and stirred at room temperature for an additional 1.5 h. Cold water (975 g) and 20% aqueous sodium chloride solution was added and extracted with ethyl acetate (1950 mL). The organic layer was washed successively with 2% sodium chloride aq (1300 mL) and 0.4% sodium chloride aq (1500 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous magnesium sulfate, concentrated to give **4b** (438.1 g) as a brown oil. This crude material was used for next step without further purification.

To 1,3-dimethyl-2-imidazolidinone (1000 mL) was added 28% methanolic solution of sodium methoxide (438 mL, 2.16 mol) and cooled to the ice bath temperature. To the solution was added dimethyl oxalate (509 g, 4.31 mol) portionwise and stirred at room temperature for 30 min. To this was added crude oil of **4b** (430.7 g) and stirred at room temperature for 2.5 h. Methanolic solution of sodium methoxide (29 mL, 0.14 mol) was added and stirred for an additional 1.5 h. The reaction mixture was added to the mixture of ethyl acetate (1600 mL), 2 M aqueous hydrochloric acid (2000 mL), and cold water (798 g) and extracted. The organic layer was washed with 5% aqueous sodium hydrogen carbonate (2000 mL) and 2% aqueous sodium chloride (2000 mL). The aqueous layer was extracted with ethyl acetate (2000 mL), and the combined organic layer was dried over magnesium sulfate and concentrated. To the resultant brown oil was added diisopropyl ether (600 mL) and *n*-hexane (400 mL) with stirring, and the precipitated solid was collected by filtration,

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washed with diisopropyl ether (200 mL × 3), and dried to give **3c** (314.82 g) as a pale yellow solid. Additional **3c** (7.55 g) was obtained from the concentrated mother liquor by column chromatography (silica gel, chloroform/ethyl acetate = 99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.49−7.45 (m, 2H), 7.40−7.30 (m, 3H), 5.34 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 162.9, 160.2, 159.7, 150.2, 145.2, 135.9, 129.0, 128.6, 128.5, 120.6, 75.1, 53.2, 52.7.

*Dimethyl 3-(benzyloxy)-1-(2,2-dimethoxyethyl)-4-oxo-1,4-dihydropyridine-2,5 -dicarboxylate (**9**).* To a solution of **3c** (19.56 g, 61.5 mmol) in methanol (117 mL) was added a solution of aminoacetaldehyde dimethyl acetal (7.11 g, 67.6 mmol) in methanol (20 mL) at room temperature and stirred under reflux for 6 h. After completion of the reaction, the reaction mixture was concentrated and water was added to the concentrate with stirring. The precipitated solid was collected and dried under reduced pressure to give **9** (18.10 g, 73%). Mother liquor was concentrated and extracted with ethyl acetate. The extract was concentrated and cooled to the ice bath temperature. The precipitate was collected and dried under reduced pressure to give **9** (2.51 g, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.44−7.41 (m, 2H), 7.36−7.30 (m, 3H), 5.29 (s, 2H), 4.47 (t, J = 4.9 Hz, 1H), 3.93 (s, 3H), 3.91 (d, J = 4.9 Hz, 2H), 3.80 (s, 3H), 3.38 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.6, 162.3, 149.4, 146.2, 137.0, 134.0, 128.8, 128.3, 128.2, 118.3, 102.9, 74.2, 56.9, 55.8, 53.1, 52.4. MS m/z 406 $[M + H]^+$.

*Methyl (4R,12aS)-7-(benzyloxy)-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro- 2H-pyrido[1′,2′:4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylate (**10**) hemi hydroquinone cocrystal.* To a solution of **9** (2.0 g, 4.93 mmol) in 98% formic acid (18 mL) was added 62% aqueous sulfuric acid (1.80 mL) and stirred at 5 °C for 2.5 h. Saturated aqueous solution of sodium hydrogen carbonate was added at 5 °C and extracted with dichloromethane. The extract was concentrated and the concentrate was dissolved in toluene (16 mL). To this was added methanol (0.6 mL, 14.8 mmol), 3-(*R*)-aminobutan-1-ol (484 mg, 5.43 mmol), and acetic acid (326 mg, 5.43 mmol) successively and stirred at 100 °C for 2.5 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The extract was washed with water and concentrated to give yellow oil (2.37 g). The resultant oil was dissolved in ethyl acetate (14 mL), hydroquinone (272 mg, 2.47 mmol) added, then cooled to 5 °C, and allowed to stand for 1.5 h. The precipitate was collected, washed with ethyl acetate (10 mL), and dried under reduced pressure to give **10**·$^1/_2$hydroquinone (1.46 g, 66%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.66−7.63 (m, 2H), 7.35−7.25 (m, 3H), 6.71 (s, 2H), 5.35 (brs, 1H), 5.34 (d, J = 10.2 Hz, 1H), 5.27 (d, J = 10.2 Hz, 1H), 5.12 (dd, J = 6.0, 3.7 Hz, 1H), 5.00−4.93 (m, 1H), 4.14 (dd, J = 13.5, 3.7 Hz, 1H), 3.99 (dd, J = 13.5, 6.0 Hz, 1H), 3.92 (dd, J = 8.8, 2.4 Hz, 2H), 3.90 (s, 3H), 2.18−2.08 (m, 1H), 1.47 (ddd, J = 14.0, 4.7, 2.4 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.35, 165.48, 155.71, 154.44, 149.68, 143.68, 136.98, 129.30, 128.77, 128.21, 128.06, 117.46, 116.19, 76.04, 74.13, 62.52, 53.47, 52.42, 44.48, 29.42, 16.02. MS m/z 399 $[M + H]^+$. mp 159 °C.

*(4R,12aS)-7-(Benzyloxy)-N-(2,4-difluorobenzyl)-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1′,2′:4,5]-pyrazino[2,1-b][1,3]oxazine-9-carboxamide (**11**).* To a solution of **10**·$^1/_2$hydroquinone (800 mg, 1.76 mmol) in toluene (20 mL) was added 2,4-difluorobenzylamine (505 mg, 3.53 mmol) and acetic acid (212 mg, 3.53 mmol), and the whole solution was stirred at 100 °C for 5 h. Water (8 mL) was added, and the organic layer was separated and washed with 4% aqueous sodium hydroxide (4 mL × 3) and water (4 mL × 1). The organic layer was concentrated, ethanol was added, and the solution was cooled to the ice bath temperature. The precipitate was collected, washed with cold ethanol, and dried under reduced pressure to give **11** (561 mg, 62%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (t, J = 6.0 Hz, 1H), 8.35 (s, 1H), 7.62−7.59 (m, 2H), 7.39−7.27 (m, 4H), 6.85−6.77 (m, 2H), 5.30 (d, J = 10.2 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 5.14 (dd, J = 5.9, 3.8 Hz, 1H), 5.03−4.95 (m, 1H), 4.63 (d, J = 6.0 Hz, 2H), 4.22 (dd, J = 13.5, 3.8 Hz, 1H), 4.08 (dd, J = 13.5, 5.9 Hz, 1H), 3.95−3.92 (m, 2H), 2.19−2.10 (m, 1H), 1.50 (ddd, J = 13.9, 4.6, 2.3 Hz, 1H), 1.32 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 164.1, 162.8 (dd, J_{C-F} = 147.8, 12.1 Hz), 160.3 (dd, J_{C-F} = 148.9, 11.7 Hz), 155.6, 153.3, 142.2, 136.8, 130.6 (dd, J_{C-F} = 9.9, 5.5 Hz), 129.5, 129.0, 128.3, 128.1, 121.6 (dd, J_{C-F} = 14.7, 3.7 Hz), 118.8, 111.2 (dd, J_{C-F} = 21.3, 3.7 Hz), 103.8 (dd, J_{C-F} = 25.3 Hz), 76.1, 74.4, 62.5, 53.5, 44.6, 36.5 (d, J_{C-F} = 3.7 Hz), 29.4, 16.0. MS m/z 510 $[M + H]^+$.

*Dolutegravir Sodium (**1**).* Under hydrogen atmosphere, a mixture of **11** (28.0 g, 55.0 mmol) and 10% Pd−C (5.6 g) in THF (252 mL) and MeOH (28 mL) was stirred for 1 h. After the precipitate (Pd−C) was filtered and washed with THF (45 mL), 10% Pd−C (5.6 g) was added and the mixture was stirred for 1.5 h under a hydrogen atmosphere. After the Pd−C was filtered and washed with $CHCl_3$/MeOH (9/1, 150 mL), the filtrate was concentrated. After dissolution of the residue in EtOH (1.38 L) by heating, the solution was gradually cooled to room temperature. After filtration, the filtrate was concentrated and cooled. Filtration, washing with EtOH, and drying provided debenzylated product (21.2 g, 92%) as a crystal.

After dissolving of the debenzylated product (18.0 g) in EtOH (54 mL) by heating, followed by filtration, 2 N NaOH aq (21.5 mL) was added to the solution at 80 °C. The solution was gradually cooled to room temperature. Filtration, washing with EtOH (80 mL), and drying provided **1** (18.8 g, 99%) as a crystal. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (t, J = 6.0 Hz, 1H), 7.89 (s, 1H), 7.40−7.30 (m, 1H), 7.25−7.16 (m, 1H), 7.06−6.98 (m, 1H), 5.22−5.12 (m, 1H), 4.87−4.74 (m, 1H), 4.51 (d, J = 5.4 Hz, 2H), 4.35−4.25 (m, 1H), 4.16 (dd, J = 1.8, 14.1 Hz, 1H), 4.05−3.90 (m, 1H), 3.86−3.74 (m, 1H), 2.00−1.72 (m, 1H), 1.44−1.32 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00410.

^{1}H NMR spectrum for compound **3c**; ^{1}H, ^{13}C NMR and MS spectra for compound **9**, **10**·$^1/_2$hydroquinone, and **11**; LC−MS chromatogram and a powder X-ray diffraction spectrum for **10**·$^1/_2$hydroquinone (PDF)

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Notes

The authors declare no competing financial interest.

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