An Improved Synthesis of Elvitegravir

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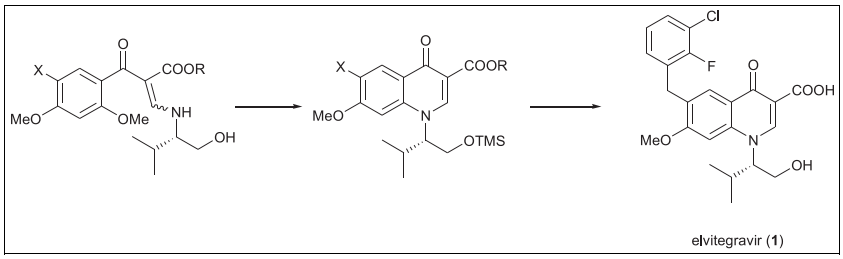
Dedicated to the memory of Prof. Alan R. Katritzky.



An improved process for the active pharmaceutical ingredient of a new HIV integrase inhibitor elvitegravir (**1**) has been developed. It starts from commercially available 2,4-dimethoxyacetophenone, which is selectively halogenated into the position 5. The 5-halo acetophenones are condensed with dialkyl carbonates to give the corresponding benzoylacetates. Their treatment with *N*,*N*-dimethylformamide dimethyl acetal followed by (*S*)-valinol then provided the corresponding intermediate benzoyl acrylates. Cyclization to the required 1,4-dihydroquinolin-4-oxo derivatives by aromatic nucleophilic substitution of the 2-methoxy group was achieved by treatment with *N*,*O*-bis(trimethylsilyl)-acetamide, which also protected the OH group as the trimethylsilyl derivative. Finally, the Negishi coupling with 2-fluoro-3-chlorobenzylzinc bromide and the following hydrolysis provided elvitegravir (**1**). The preferred variant, the seven-step procedure starting from 2,4-dimethoxyacetophenone, provides elvitegravir in 29.3% yield.

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INTRODUCTION

Elvitegravir (**1**) is an oral HIV integrase inhibitor used for the treatment of HIV infections [1]. Owing to its fast metabolic deactivation, elvitegravir must be used together with a cytochrome P450 inhibitor. Currently, the drug is approved as a fixed dose combination with such inhibitor cobicistat (**2**) and two anti-HIV drugs emtricitabine and tenofovir disoproxil fumarate known as Stribild [2] (Fig. 1).

When we started development of a generic equivalent of elvitegravir, besides general paper on novel HIV-1 integrase inhibitors [3] derived from antibacterial quinolones, only patent information of its synthesis was available. The basic patent procedure [4] starts from 2,4-difluorobenzoic acid (Scheme 1), a common intermediate of the synthesis of antibacterial quinolones [5]. However, the penultimate intermediate **6** is a common problematic impurity of this process. A process-dependent dimeric impurity has also been described [6].

A process patent procedure (Scheme 2) starts from 2,4-dimethoxybenzoic acid, which is in three steps transformed into intermediate **8** [7]. Disadvantage of this approach is the fact that the most expensive compound (2-fluoro-3-chlorobenzyl bromide) is used in an early stage of the synthesis.

For the reasons given earlier, we decided to develop a new synthesis of elvitegravir (**1**) starting from easily available 2,4-dimethoxyacetophenone. We also decided to introduce the 2-fluoro-3-chlorobenzyl group in a late step of the synthesis. Our retrosynthetic scheme is shown in Scheme 3.

RESULTS AND DISCUSSION

Selective bromination/iodination of 2,4-dimethoxy acetophenone (12). Direct bromination of acetophenone under common conditions is known to go selectively to the side acetyl group. Similar preference is known for most acetophenones, including 2,4-dimethoxyacetophenone [8]. A mixture of the corresponding product of monobromination in the side chain with 2-bromo-1-(5-bromo-2,4-dimethoxyphenyl)ethanone, the product of dibromination, was obtained by bromination in diethyl ether in the presence of $AlCl_3$ [8c]. However, selective aromatic bromination of 2,4-dimethoxyacetophenone (**12**) into the position 5 giving compound **13a** is described either with bromine in acetic acid at −20°C [9a] or with *N*-bromosuccinimide in the presence of p-toluenesulfonic acid (PTSA) without solvent [9b]. Although the solvent-free reactions are considered to be a perspective green approach, the scale-up from using trituration in a porcelain mortar into an industrially useful setup could be difficult. Therefore, reproduction of the bromination in acetic acid at lower temperature was performed. While at temperature

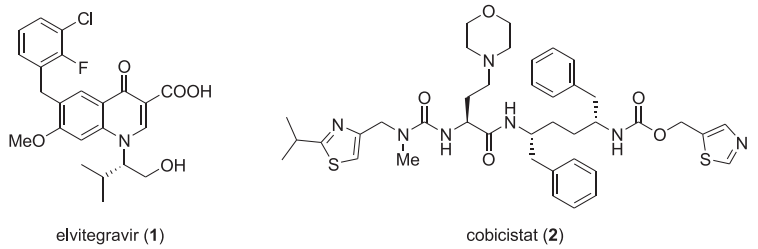
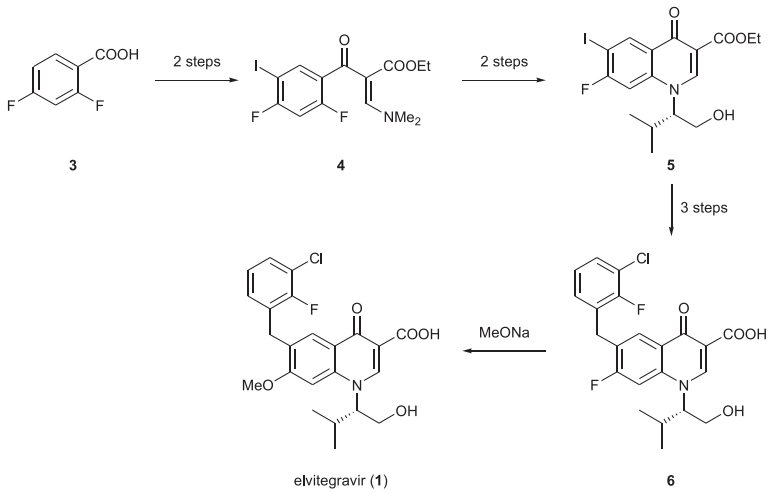
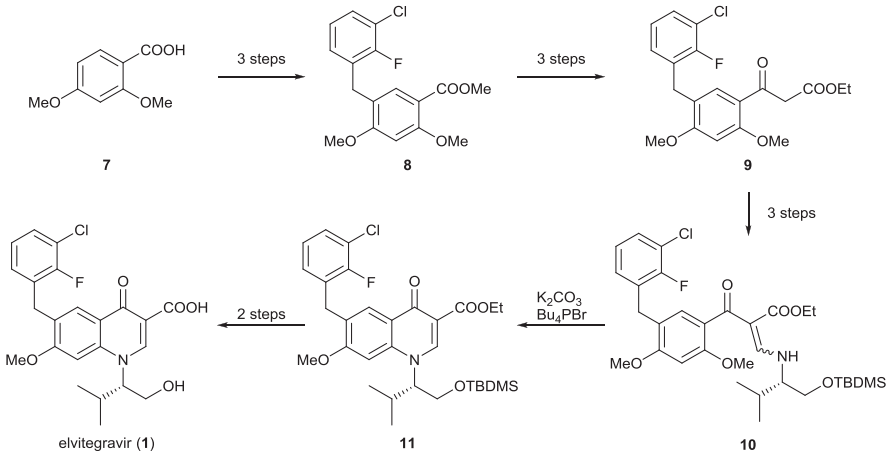


Figure 1. Structures of elvitegravir (**1**) and cobicistat (**2**).

Scheme 1. Synthesis of elvitegravir (**1**) from 2,4-difluorobenzoic acid.

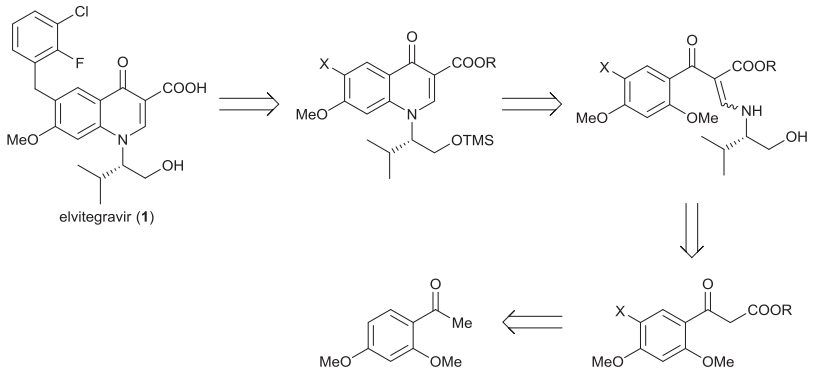


Scheme 2. Synthesis of elvitegravir (**1**) from 2,4-dimethoxybenzoic acid.



under −5°C the reaction mixture totally solidified, at 0°C, the hardly mechanically stirrable mixture provided complex mixtures containing mainly polybrominated compounds [liquid chromatography–mass spectrometry (LC–MS)]. Therefore, we have studied the bromination in solvent mixtures containing acetic acid. The best results were obtained using mixtures of acetic acid and acetonitrile. However, optimization of the ratio of acetonitrile–acetic acid led to the conclusion that comparable results could be obtained by also using acetonitrile as the only solvent. We have also found that the reaction is sufficiently selective up to −10°C, a rapid increase of the amounts of impurities at higher temperatures was observed. Although in gram quantities the sufficient selectivity at −10°C was repeatedly achieved, in 100 g scale, bromination at −20°C was preferred. Iodination of 2,4-dimethoxyacetophenone with

Scheme 3. Retrosynthetic scheme of the Zentiva synthesis of elvitegravir (**1**) from 2,4-dimethoxyacetophenone.



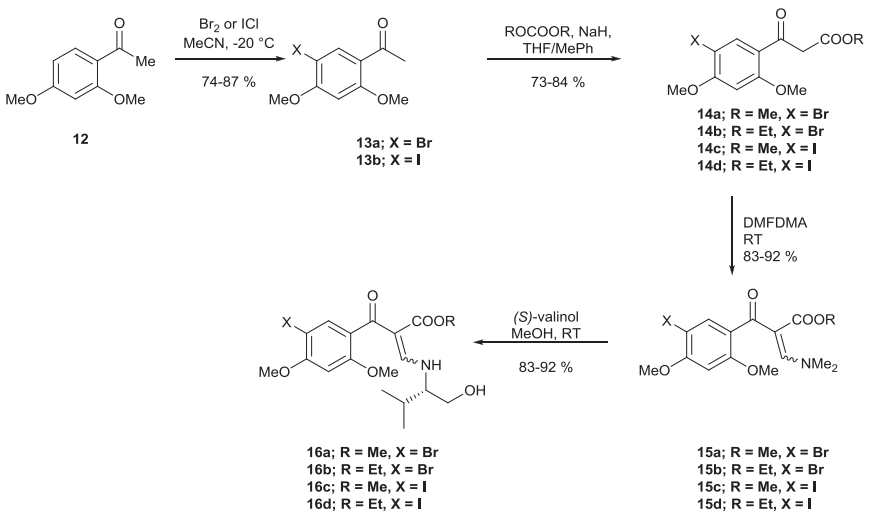
iodine monochloride under similar conditions provided the corresponding 5-iodo compound **13b** (Scheme 4).

Synthesis of benzoylacetates 14 from 2,4-dimethoxy acetophenones 13. In the next step, 1-(5-halo-2,4-dimethoxyphenyl)ethanones **13** are transformed into benzoylacetates **14**. This type of transformation is usually performed by condensation with corresponding dialkyl carbonates in the presence of sodium hydride [10], usually in benzene, toluene, or tetrahydrofuran (THF). We have studied the reaction of acetophenones **13** with NaH as the base using dimethyl and diethyl carbonate in several solvents (THF, toluene, DMF, and mixtures of the mentioned solvents). Dialkyl carbonates are considered as cheap and green compounds, and therefore, finally, we used them as reagents and solvents with no additional solvent used. Attempts to substitute NaH by a different base (MeONa, *t*-BuOK, $(Me_3Si)_2NNa$, $(Me_3Si)_2NLi$) under similar conditions failed to obtain comparable results.

Transformation of benzoyl acetates 14 into (*S*)-methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylates 16. Transformation of benzoylacetates into alkylaminomethylene benzoylacetates is well known and often used in the synthesis of antibacterial quinolones [5]. It is usually performed via the corresponding ethoxymethylene or dimethylaminomethylene intermediates. For our purpose, we decided to use the latter possibility because the treatment of the starting benzoylacetate with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) is performed under milder conditions. We screened the reaction of **14a** with DMFDMA in several solvents (DMF, toluene, MeOH, mixtures of toluene–MeOH) and also in neat DMFDMA. As the reaction in most solvents was not quite clean and the reaction times necessary for full conversion were usually high (>10 h), reaction in neat DMFDMA at 80°C was selected for further development. Under these conditions, all compounds **15** were prepared in good yields.

Reaction of *N*,*N*-dimethylaminomethylene benzoylacetates with a wide range of primary amines providing the corresponding alkylaminomethylene derivatives is well documented [5]. In case of valinol, the reaction proceeded well without necessity to protect the hydroxyl group. Simple stirring of **15** with L-valinol in methanol at room

Scheme 4. Synthesis of (*S*)-methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylates **16.**



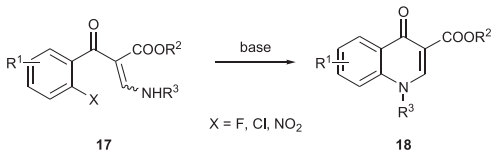
temperature provided 80–90% yields of compounds **16** (Scheme 4).

Cyclization of intermediates 16 into corresponding 4-oxo-1,4-dihydro-quinoline-3-carboxylates. Synthesis of a wide range of 4-oxo-1,4-dihydro-quinoline-3-carboxylates from corresponding benzoyl aminoacrylates under basic conditions (Scheme 5) is well documented and is even industrially used for production of some antibacterial quinolones. Usually, leaving groups X = F, Cl are used [5]. This procedure was applied also in the synthesis of elvitegravir intermediate **5** described in the basic patent (Scheme 1) [4]. Several examples of the denitrocyclization reaction (X = NO_2) are also described [11]. Nevertheless, there is only one example describing aromatic nucleophilic substitution of the methoxy group (X = OMe) in scientific literature. Grohe and Heitzer [12a] described cyclization of **17** (R^1 = H, R^2 = Et, R^3 = cyclopropyl) by heating of **17** with K_2CO_3 in DMF leading to **18**, an intermediate of synthesis of a ciprofloxacin analog. On the other hand, there are several such reactions described in patents [12b,c] and especially conditions discovered by Mundla and Randall [12b] using *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) as the cyclization agent seems to be quite advantageous.

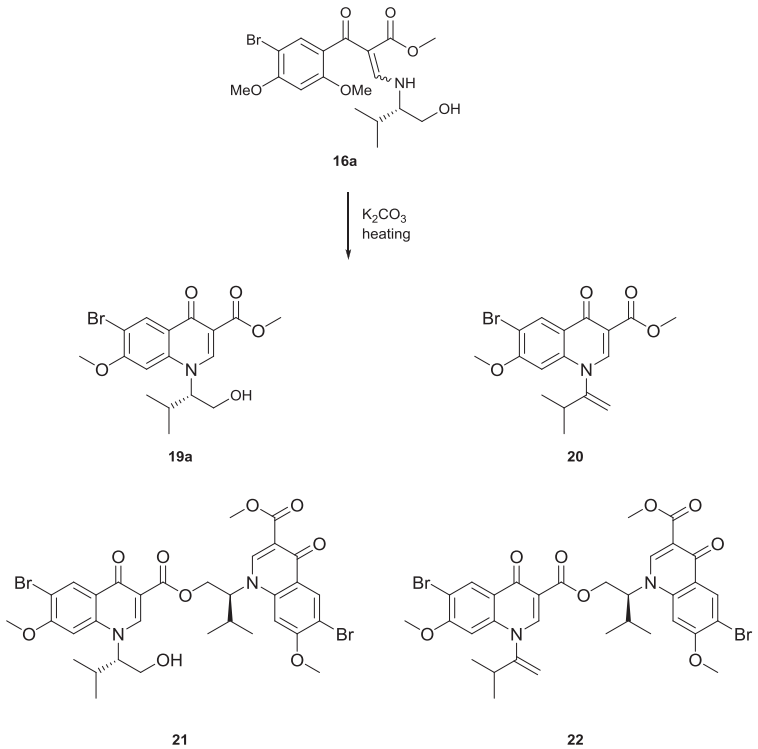
When we treated compound **16a** with K_2CO_3 in DMF under the conditions described by Grohe and Heitzer [12a], after 1 h, a complex mixture containing about 36% of the required product **19a** was formed. According to LC–MS, a product of elimination **20** and dimeric products **21** and **22** were also present in amounts of about 7, 24, and 12%, respectively (Scheme 6).

It is evident that the hydroxy group in intermediates **16** should be protected. We decided to apply conditions described by Mundla and Randall [12] using BSA as a cyclization agent. This approach has been described for cyclization of ethyl ester **16b** with BSA providing after workup corresponding compound **19b**, which was then protected with *tert*-butyldimethylsilyl (TBDMS) group [12b]. We have applied this approach, and compounds **19a** and **24a** were prepared. For full conversion of compounds **16** [high-performance liquid chromatography (HPLC)], at least 2.5 equivalents of BSA must be used, and DMF was selected as a solvent of choice. We also tried to develop a mild workup to be able to isolate directly the trimethylsilyl intermediate **23a**. Finally, we succeeded

Scheme 5. Synthesis of 4-oxo-1,4-dihydro-quinoline-3-carboxylates from corresponding benzoyl aminoacrylates.



Scheme 6. K_2CO_3 mediated cyclization of **16a**.

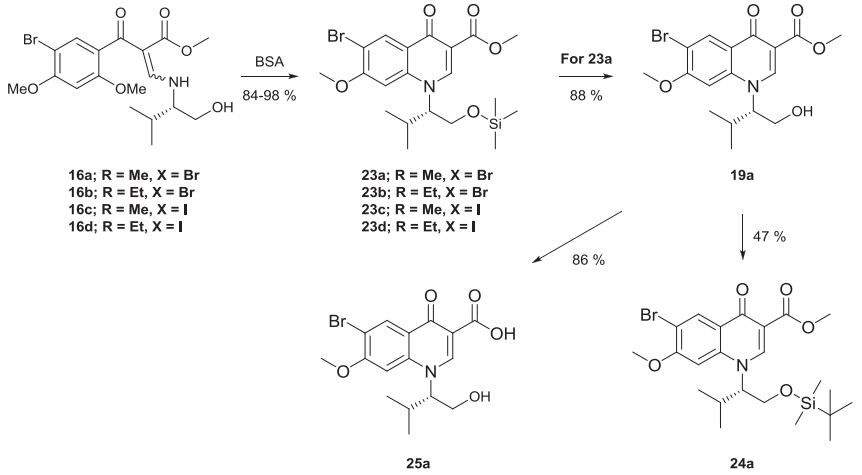


using aqueous workup at about 0°C. Alkaline hydrolysis of ester **19a** provided the corresponding acids **25a** (Scheme 7). The corresponding ethyl ester **23b**, as well as iodo derivatives **23c** and **23d**, was obtained similarly.

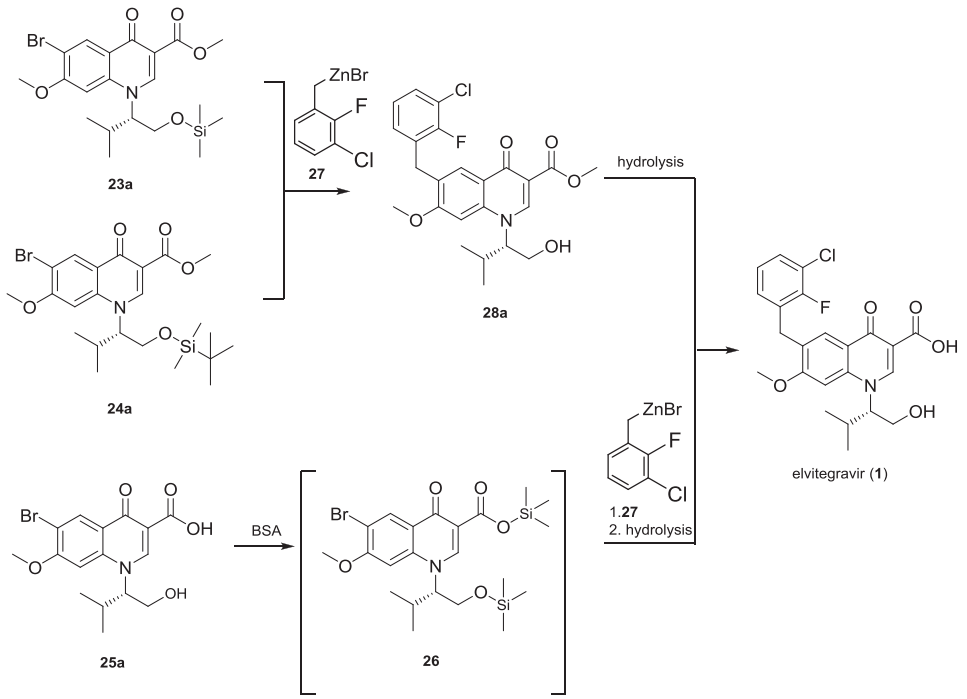
For the introduction of 2-fluoro-3-chlorobenzyl group into the quinolone skeleton, we applied Negishi coupling with 3-chloro-2-fluorobenzylzinc bromide (**27**) used in the elvitegravir patents [4,7]. The Negishi coupling of both 6-bromo and 6-iodo derivatives provided good yields of compounds **28**, but in the case of iodo derivatives, the purity achieved was lower. Therefore, we finally used compound **23a** as the intermediate of choice. We also tested the possibility to use acid **25a,** protect both the OH and COOH groups as the trimethylsilyl derivatives **26**, and to use the formed disilylated compound without isolation directly to the Negishi coupling. This approach was found viable, but the final elvitegravir (**1**) was not so pure (Scheme 8).

The developed procedure was used also for the synthesis of (*R*)-elvitegravir starting from intermediate bromo derivative **15a** and (*R*)-(−)-valinol. (*R*)-Elvitegravir and the

Scheme 7. Synthesis of 4-oxo-1,4-dihydro-quinoline-3-carboxylates by BSA promoted cyclization.



Scheme 8. Synthesis of elvitegravir (**1**).



corresponding (*R*)-enantiomer of **28a** were used as standards for the chiral purity HPLC determination, which proved that no evident racemization takes place during the reaction sequences used.

CONCLUSION

We have developed a robust processes for synthesis of elvitegravir (**1**) starting from 2,4-dimethoxyacetophenone. The starting compound was transformed into (*S*)-3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-halo-2,4-dimethoxybenzoyl)-acrylates **16**, which were cyclized with BSA to suitable 5-halo 4-oxo-1,4-dihydro-quinoline-3-carboxylates. Introduction of the 2-fluoro-3-chlorobenzyl group by Negishi coupling provides finally elvitegravir (**1**). The principal advantage of the process is the fact that the most expensive intermediate (3-chloro-2-fluorobenzyl bromide) is used in the penultimate step. The preferred variant, the seven-step procedure starting from 2,4-dimethoxyacetophenone and using for the Negishi coupling methylester **23a**, provides elvitegravir (**1**) in 29.3% yield. The same procedure was used for the synthesis of the opposite (*R*)-elvitegravir using bromo derivative **15a** as the key intermediate.

EXPERIMENTAL

All chemicals used in the synthesis were purchased from Sigma-Aldrich (Milwaukee, WI, USA) and were used without purification.

Melting points were measured on a Kofler block or Stuart (Bibby Scientific, Stone, UK) melting point apparatus SMP30 and are uncorrected. NMR experiments were carried out on a Bruker Avance 500 (Rheinstetten, Germany) at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C). Reference for ^{1}H δ ($CDCl_3$) = 7.26 ppm, δ ($DMSOd_6$) = 2.50 ppm and for ^{13}C δ ($CDCl_3$) = 77.00 ppm, δ ($DMSOd_6$) = 39.50 ppm. IR spectra were measured on a Fourier transform infrared spectrometer Nicolet Nexus (Thermo, Waltham, MA) using ZnSe attenuated total reflection crystal technique by accumulation of 64 scans with two 1/cm resolution. The UV spectra were recorded in methanol on a Lambda 25 spectrophotometer (PerkinElmer, Waltham, MA) in the range of 200–700 nm. Optical rotation measurements were recorded on a PerkinElmer model 341 polarimeter in MeOH (*c* approx. 1%) using a 10-cm cell. The mass spectra (MS/MS; ionization mode atmospheric-pressure chemical ionization (APCI)(+)) were measured on an active pharmaceutical ingredient 3000 PE machine (Sciex Instruments, Applied Biosystems, Framingham, MA, USA). The purity of the prepared substances was evaluated by thin-layer chromatography on silica gel (FP KG F 254, Merck, Darmstadt, Germany) and by HPLC system HP 1050 with UV detection (column Phenomenex Luna 5μ C18(2) length: 0.25 m, internal diameter 4.6 mm; Phenomenex, Torrance, CA, USA). Gradient elution with mobile phase A [phosphate buffer (1. 2 g NaH_2PO_4) diluted in 1000 mL of water, pH adjusted to 3.0 with 50% phosphoric acid], and mobile phase B (methanol) was used. Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was performed using Cyclograph instrument (Analtech, Newark, DE, USA) with silica gel pre-scraped rotors.

1-(5-Bromo-2,4-dimethoxyphenyl)ethanone (13a). Bromine (50 g) was added during 2 h to a solution of 2,4-dimethoxyacetophenone (**12**, 45 g, 0.25 mol) in acetonitrile (500 mL) stirred at −20°C. The resulting suspension was stirred for additional 3 h at this temperature and then poured to a mixture of ice (200 g) and water (200 mL). The insoluble portion was filtered and washed with water. The product was dried *in vacuo* at 50°C to give 62.2 g (96.4%) of pink crystals containing according to HPLC 93.5% of **13a** and 1.7% of starting compound **12**, which was used for the next step without further purification. Mp 136–138°C (Ref. [8b] mp 138–139°C). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.04 (s, 1H, H-6), 6.45 (s, 1H, H-3), 3.96 (s, 3H, MeO), 3.94 (s, 3H, MeO), 2.56 (s, 3H, MeCO). ^{13}C NMR ($CDCl_3$) δ (ppm): 196.3, 160.4, 160.1, 135.2, 121.6, 102.8, 95.8, 56.4, 55.8, 31.8. IR: ν(C–H) 2974, 2838, ν(C=O) 1647, $\nu(C{=}C)_{AR}$ 1594, 1470, ν(C–O) 1275 cm^{-1}. UV λ_{max} (log ε): 219 (4.32), 229 (4.34), 265 (4.14), 314 (3.92).

1-(5-Iodo-2,4-dimethoxyphenyl)ethanone (13b). A solution of iodine monochloride (10 g) in acetonitrile (5 mL) was added during 1 h to a solution of 2,4-dimethoxyacetophenone (**12**, 9 g, 50 mmol) in acetonitrile (75 mL) stirred at −20°C. The resulting suspension was stirred for additional 4 h at this temperature and then poured to a mixture of ice (25 g) and water (25 mL). The insoluble portion was filtered, washed with water, and dried *in vacuo* to give 14.2 g of crude product. Crystallization from methanol provided 11.3 g (73.8%) of yellowish crystals; mp 139–143°C (Ref. [13] mp 145°C) and HPLC purity of 99.6%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.23 (s, 1H, H-6), 6.39 (s, 1H, H-3), 3.94 (s, 3H, MeO), 3.93 (s, 3H, MeO), 2.55 (s, 3H, MeCO). ^{13}C NMR ($CDCl_3$) δ (ppm): 196.3, 162.3, 161.5, 141.3, 122.5, 95.0, 75.0, 56.5, 55.7, 31.7. IR: ν(C–H) 2973, 2839, ν(C=O) 1645, $\nu(C{=}C)_{AR}$ 1588, 1470, ν(C–O) 1270, 1230 cm^{-1}. UV λ_{max} (log ε): 208 (4.62), 234 (4.45), 265 (4.18), 318 (3.93).

Methyl 3-(5-bromo-2,4-dimethoxyphenyl)-3-oxopropanoate (14a). Hexane (100 mL) was added to a 60% w/w sodium hydride dispersion in mineral oil (12 g, 300 mmol), and the mixture was stirred under nitrogen for 10 min. Then the stirring was stopped, hexane was removed with syringe, and another portion of hexane (100 mL) was added and after 10 min again removed. Then toluene was added (100 mL) followed by dimethyl carbonate (18 g, 200 mmol), and the mixture was heated to reflux. A solution of 5-bromo-2,4-

dimethoxyacetophenone (**13a**, 26 g, 100 mmol) in THF (24 mL) was added dropwise over 1 h, and the mixture was refluxed for additional 2 h. After cooling, the mixture was poured onto a mixture of ice (100 g) and water (100 mL), and the mixture was acidified with 10% HCl to pH 5–6. The mixture was extracted with ethyl acetate (2 × 200 mL), the extract was washed with brine (3 × 100 mL) and dried with $MgSO_4$. The residue after evaporation (34 g) was purified by crystallization from methanol to give 23.2 g (73.4%) of off-white crystals; mp 109–111°C (HPLC purity 98.8). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.14 (s, 3H, H-6), 6.43 (s, 3H, H-3), 3.96 (s, 3H, MeO), 3.91 (s, 5H, MeO + CH_2), 3.71 (s, 3H, COOMe). ^{13}C NMR ($CDCl_3$) δ (ppm): 189.8, 168.6, 160.9, 160.5, 135.6, 119.9, 103.5, 95.6, 56.5, 55.7, 52.1, 50.2. IR: ν(C–H) 2924, 2831, ν(C=O) 1734, 1652, $\nu(C{=}C)_{AR}$ 1593, 1456, ν(C–O) 1270, 1214 cm^{-1}. UV λ_{max} (log ε): 217 (4.34), 234 (4.35), 269 (4.19), 318 (4.03). High-resolution mass spectrometry (HRMS) for $C_{12}H_{14}BrO_5$ $(M+H)^+$ Calcd: 317.0025, found: 317.0025. *Anal* Calcd. for $C_{12}H_{13}BrO_5$: C, 45.57; H, 4.15; Br, 24.97. Found: C, 45.12; H, 4.44; Br, 24.55.

Ethyl 3-(5-bromo-2,4-dimethoxyphenyl)-3-oxopropanoate (14b). Using diethyl carbonate and the procedure described for the synthesis of **14a**, ethyl ester **14b** was obtained in 75.0% yield as off-white crystals; mp 77–84°C (ethanol). HPLC purity 97.7%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.14 (s, 1H, H-6), 6.43 (s, 1H, H-3), 4.18 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 3.96 (s, 3H, MeO), 3.91 (s, 3H, MeO), 3.89 (s, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 190.0, 168.2, 160.8, 160.4, 135.6, 120.0, 103.4, 95.6, 60.9, 56.5, 55.7, 50.5, 14.1. IR: ν(C–H) 2987, ν(C=O) 1733, 1666, $\nu(C{=}C)_{AR}$ 1588, 1472, ν(C–O) 1256, 1216, 1146 cm^{-1}. UV λ_{max} (log ε): 208 (4.76), 232 (4.35), 269 (4.18), 317 (4.00). HRMS for $C_{13}H_{16}$ BrO_5 (M^+) Calcd: 331.0181, found: 331.0173. *Anal* Calcd. for $C_{13}H_{15}BrO_5$: C, 47.27; H, 4.58; Br, 23.91. Found: C, 46.85; H, 4.72; Br, 23.65.

Methyl 3-(5-iodo-2,4-dimethoxyphenyl)-3-oxopropanoate (14c). Starting from iodo derivative **13b** adhering to the process described for the synthesis of **14a**, iodo derivative **14c** was obtained in 83.6% yield as off-white crystals; mp 120–123°C (methanol). HPLC purity 99.2%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.34 (s, 1H, H-6), 6.36 (s, 1H, H-3), 3.95 (s, 3H, MeO), 3.91 (s, 3H, MeO), 3.90 (s, 2H, CH_2), 3.71 (s, 3H, COOMe). ^{13}C NMR ($CDCl_3$) δ (ppm): 189.8, 168.7, 163.1, 161.5, 141.8, 120.7, 94.7, 75.7, 56.6, 55,6, 52.1, 50.1. IR: ν(C–H) 2922, 2829, ν(C=O) 1730, 1649, $\nu(C{=}C)_{AR}$ 1583, 1446, ν(C–O) 1265, 1213 cm^{-1}. UV λ_{max} (log ε): 237 (4.51), 270 (4.25), 322 (4.06). *Anal* Calcd. for $C_{12}H_{13}IO_5$: C, 39.58; H, 3.60. Found: C, 39.27; H, 4.09.

Ethyl 3-(5-iodo-2,4-dimethoxyphenyl)-3-oxopropanoate (14d). Using diethyl carbonate and starting from iodo derivative **13b** adhering to the process described for the synthesis of **14a**, ethyl ester **14d** was obtained in 78.6% yield as off-white crystals; mp 87–89°C (ethanol). HPLC purity 94.7%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.31 (s, 1H, H-6), 6.35 (s, 1H, H-3), 4.16 (q, J = 7.2 Hz, 2H, O$\underline{CH_2}CH_3$), 3.93 (s, 3H, MeO), 3.90 (s, 3H, MeO), 3.87 (s, 2H, CH_2), 1.22 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 189.9, 168.2, 163.0, 161.5, 141.7, 120.8, 94.7, 75.5, 60.9, 56.6, 55.5, 50.3, 14.1. IR: ν(C–H) 2975, ν(C=O) 1735, 1658, $\nu(C{=}C)_{AR}$ 1581, 1447, ν(C–O) 1278, 1256, 1140 cm^{-1}. UV λ_{max} (log ε): 237 (4.48), 270 (4.21), 323 (4.02). *Anal* Calcd. for $C_{13}H_{15}IO_5$: C, 41.29; H, 4.00. Found: C, 41.07; H, 3.88.

Methyl 2-(5-bromo-2,4-dimethoxybenzoyl)-3-(dimethylamino)-acrylate (15a). A mixture of methyl 3-(5-bromo-2,4-dimethoxyphenyl)-3-oxopropanoate (**14a**; 12.5 g, 39.4 mmol) and DMFDMA (30 mL) was stirred at 80°C under nitrogen for 3 h. The mixture was evaporated under reduced pressure, and the residue was crystallized from methanol to 12.7 g (86.6%) of yellow crystals; mp 122–124°C (HPLC purity 99.1%). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.83 (bs, 1H, –CH=), 7.64 (s, 1H, H-6), 6.40 (s, 1H, H-3), 3.93 (s, 3H, MeO), 3.81 (s, 3H, MeO), 3.04 (s, 3H, COOMe), 3.11 (bs, 6H, Me_2N). ^{13}C NMR ($CDCl_3$) δ (ppm): 188.0, 168.8, 158.9, 158.5, 155.9, 134.6, 125.3, 103.2, 102.1, 95.7, 56.3, 55.9, 50.9, 41.8. IR: ν(C–H) 2942, ν(C=O) 1668, $\nu(C{=}C)_{AR}$ + ν(C=C) 1572, $\nu(C{=}C)_{AR}$ 1435, ν(C–O) 1281, 1208, 1088 cm^{-1}. UV 210 (4.37), 233 (4.29), 270 (4.26), 328 (4.28). *Anal* Calcd. for $C_{15}H_{18}BrNO_5$: C, 48.40; H, 4.87; N, 3.76. Found: C, 48.28; H, 5.07; N, 3.93.

Ethyl 2-(5-bromo-2,4-dimethoxybenzoyl)-3-(dimethylamino)-acrylate (15b). Using procedure described for the synthesis of **15a**, ethyl ester **15b** was obtained in 92.0% yield as yellow crystals; mp 134–140°C (ethanol). HPLC purity 98.8%. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (bs, 1H, –CH=), 7.64 (s, 1H, H-6), 6.39 (s, 1H, H-3), 3.95 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 3.92 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.09 (bs, 6H, Me_2N), 0.95 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 188.2, 168.6, 158.8, 158.4, 156.1, 134.3, 125.7, 103.4, 101.9, 95.7, 59.6, 56.3, 55.8, 41.7, 14.0. IR: ν(C–H) 2978, ν(C=O) 1692, ν(C=C) 1620, $\nu(C{=}C)_{AR}$ 1592, ν(C–O) 1276, 1205, 1117 cm^{-1}. UV λ_{max} (log ε): 209 (4.53), 233 (4.26), 269 (4.25), 328 (4.25). *Anal* Calcd. for $C_{16}H_{20}BrNO_5$: C, 49.76; H, 5.22; N, 3.63. Found: C, 49.55; H, 5.37; N, 3.77.

Methyl 2-(5-iodo-2,4-dimethoxybenzoyl)-3-(dimethylamino)-acrylate (15c). Using procedure described for the synthesis of **15a**, iodo derivative **15c** was obtained in 83.4% yield as yellow crystals; mp 153–157°C (methanol). HPLC purity 98.8%. ^{1}H NMR ($CDCl_3$) δ (ppm):8.02 (bs, 1H, –CH=), 7.66 (s, 1H, H-6), 6.37 (s, 1H, H-3), 3.93 (s, 3H, MeO), 3.84 (s, 3H, MeO), 3.53 (s, 3H, COOMe), 3.10 (bs, 6H, Me_2N). ^{13}C NMR ($CDCl_3$) δ (ppm): 188.0, 168.9, 160.9, 160.1, 155.9, 140.4, 126.1, 103.2, 94.9, 56.4, 74.4, 55.8, 50.9, 44.6. IR: ν(C–H) 2941, ν(C=O) 1665, $\nu(C{=}C)_{AR}$ + ν(C=C) 1569,

ν(C=C)$_{AR}$ 1434, ν(C–O) 1278, 1206, 1088 cm^{-1}. UV λ_{max} (log ε): 208 (4.52), 238 (4.38), 269 (4.30), 331 (4.29). *Anal* Calcd. for $C_{15}H_{18}INO_5$: C, 42.98; H, 4.33; N, 3.33. Found: C, 42.73; H, 4.53; N, 3.64.

Ethyl 2-(5-iodo-2,4-dimethoxybenzoyl)-3-(dimethylamino)-acrylate (15d). Using procedure described for the synthesis of **15a**, iodo derivative **15d** was obtained in 86.6% yield; yellow crystals, mp 151–156°C (ethanol). HPLC purity 97.8%. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.00 (bs, 1H, –CH=), 7.64 (s, 1H, H-6), 6.34 (s, 1H, H-3), 3.95 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 3.91 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.09 (bs, 6H, Me_2N), 0.95 (t, J = 7.1 Hz, 3H, OCH$_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 188.6, 168.1, 160.8, 160.0, 156.0, 140.3, 126.6, 103.3, 94.9, 74.1, 59.6, 56.4, 55.7, approx. 40 (observed at 50°C, not at 25°C), 14.1. IR: ν(C–H) 2969, ν(C=O) 1692, ν(C=C) 1619, ν(C=C)$_{AR}$ 1585, ν(C–O) 1272, 1203, 1112 cm^{-1}. UV λ_{max} (log ε): 208 (4.60), 238 (4.36), 269 (4.28), 331 (4.27). *Anal* Calcd. for $C_{16}H_{20}INO_5$: C, 44.36; H, 4.65; N, 3.23. Found: C, 44.55; H, 4.37; N, 3.49.

(*S*)-Methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylate (16a). A solution of (*S*)-(+)-valinol (5 g, 48.5 mmol) in methanol (20 mL) was added to a suspension of 2-(5-bromo-2,4-dimethoxybenzoyl)-3-(dimethylamino)acrylate (**15a**; 16.4 g, 44 mmol) in methanol (120 mL), and the mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure to 1/3 of the original volume, the mixture was stirred in ice bath for 1 h, and insoluble portion was filtered off. The crystals were washed with hexane (25 mL) and water (2 × 25 mL) and dried to provide 18.2 g (96.0%) of off-white crystals; mp 141–145°C. HPLC purity 98.5%. ^{1}H NMR ($CDCl_3$) δ (ppm): 10.85 (dd, J = 13.0, 10.2 Hz, 0.8H, NH), 9.17 (dd, J = 14.3, 9.7 Hz, 0.2H, NH), 7.98 (d, J = 13.6 Hz, 0.8H, –CH=), 7.88 (d, J = 14.2 Hz, 0.2H, –CH=),7.55 (s, 0.2H, H-6), 7.47 (s, 0.8H, H-6), 6.401 (s, 0.8H, H-3), 6.396 (s, 0.2H, H-3), 3.92 + 3.91 (s, 3H, MeO), 3.67–3.76 (m, 5H, MeO + $\underline{CH_2}$OH), 3.53 + 3.54 (s + s, 3H, COOMe), 3.05–3.12 (m, 1H, $\underline{CH}$N), 2.57 (t, J = 5.7 Hz, 0.8H, OH), 2.39 (t, J = 5.7 Hz, 0.2H, OH), 1.92–2.00 (m, 1H, $\underline{CH}Me_2$), 0.95–1.01 (m, 6H, CH$\underline{Me_2}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.2, 189.1, 169.8, 168.0, 160.4, 159.8, 157.7, 157.4, 157.6, 157.0, 133.6, 132.6, 126.1, 125.8, 101.9, 101.8, 101.71, 101.69, 95.8, 95.6, 68.8, 68.2, 63.4, 63.3, 56.3, 56.2, 56.0, 55.8, 50.8, 50.6, 29.4, 29.3, 19.57, 19.55, 18.2, 18.1. IR: ν(O–H) 3491, ν(C–H) 2969, ν(C=O) 1662, ν(C=C)$_{AR}$ + ν(C=C) 1595, ν(C=C)$_{AR}$ 1434, ν(C–O) 1284, 1204 cm^{-1}. UV λ_{max} (log ε): 206 (4.79), 236 (4.35), 317 (4.30). $[\alpha]_D^{20}$ (MeOH) = −38.8°. *Anal* Calcd. for $C_{18}H_{24}BrNO_6$: C, 50.24; H, 5.62; N, 3.26. Found: C, 50.51; H, 5.78; N, 3.44.

(*R*)-Methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylate (*R*-16a). Starting from 11.2 g (30 mmol) of 2-(5-bromo-2,4-dimethoxybenzoyl)-3-(dimethylamino)acrylate (**15a)** and 3.2 g (31 mmol) of (*R*)-(−)-valinol using procedure described for the synthesis of compound **16a**, 11.5 g (89.1%) of the corresponding *R*-isomer was obtained as slightly yellowish crystals; mp 140–143°C (HPLC purity 99.6%). $[\alpha]_D^{20}$ (MeOH) = +39.5°.

(*S*)-Ethyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylate (16b). Starting from ethyl ester **15b** and using procedure described for the synthesis of **16a**, compound **16b** was obtained in 88.8% yield as yellowish crystals; mp 113–116°C (ethanol). HPLC purity 95.7%. ^{1}H NMR ($CDCl_3$) δ (ppm): 10.82 (dd, J = 13.0, 10.2 Hz, 0.8H, NH), 9.18 (dd, J = 14.3, 9.7 Hz, 0.2H, NH), 7.96 (d, J = 13.6 Hz, 0.8H, –CH=), 7.91 (d, J = 14.2 Hz, 0.2H, –CH=),7.47 (s, 0.2H, H-6), 7.41 (s, 0.8H, H-6), 6.388 (s, 0.2H, H-3), 6.380 (s, 0.8H, H-3), 3.87–3.98 (m, 5H, O$\underline{CH_2}$Me + MeO), 3.61–3.74 (m, 5H, MeO + $\underline{CH_2}$OH), 3.04–3.09 (m, 1H, $\underline{CH}$N), 2.85 (m, 0.8H, OH), 2.60 (m, 0.2H, OH), 1.90–1.95 (m, 1H, $\underline{CH}Me_2$), 0.89–1.00 (m, 9H, CH$\underline{Me_2}$, OCH$_2\underline{Me}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.6, 189.6, 169.1, 167.7, 160.0, 159.8, 157.5, 157.4, 157.3, 156.9, 134.9, 133.0, 126.5, 126.4, 102.6, 101.8, 101.59, 101.56, 95.9, 95.8, 68.7, 68.1, 63.1, 59.5, 56.3, 56.2, 55.9, 55.8, 55.7, 50.0, 29.3, 29.2, 20.5, 19.5, 18.0, 14.0, 13.7. IR: ν(O–H) 3419, ν(C–H) 2967, ν(C=O) 1665, ν(C=C)$_{AR}$ + ν(C=C) 1594, ν(C=C)$_{AR}$ 1428, ν(C–O) 1272, 1205 cm^{-1}. UV λ_{max} (log ε): 206 (4.70), 316 (4.26). *Anal* Calcd. for $C_{19}H_{26}BrNO_6$: C, 51.36; H, 5.90; N, 3.15. Found: C, 51.11; H, 6.08; N, 3.33.

(*S*)-Methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-iodo-2,4-dimethoxybenzoyl)-acrylate (16c). Starting from iodo derivative **15c** and using procedure described for the synthesis of **16a**, compound **16c** was obtained in 83.2% yield as yellowish crystals; mp 115–119°C (methanol). HPLC purity 97.2%. ^{1}H NMR ($CDCl_3$) δ (ppm): 10.82 (dd, J = 13.0, 10.2 Hz, 0.8H, NH), 9.15 (dd, J = 14.3, 9.7 Hz, 0.2H, NH), 7.96 (d, J = 13.6 Hz, 0.8H, –CH=), 7.85 (d, J = 14.2 Hz, 0.2H, –CH=), 7.72 (s, 0.2H, H-6), 7.64 (s, 0.8H, H-6), 6.34 (s, 0.2H, H-3), 6.33 (s, 0.8H, H-3), 3.89 + 3.88 (s, 3H, MeO), 3.69 + 3.72 (m, 5H, MeO + $\underline{CH_2}$OH), 3.51 + 3.62 (s + s, 3H, COOMe), 3.07–3.09 (m, 1H, $\underline{CH}$N), 3.04–3.06 (m, 0.8H, OH), 2.94 (m, 0.2H, OH), 1.91–1.95 (m, 1H, $\underline{CH}Me_2$), 0.93–0.98 (m, 6H, CH$\underline{Me_2}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.4, 189.0, 169.7, 168.0, 160.4, 160.0, 159.8, 159.7, 158.7, 158.2, 139.4, 138.3, 127.0, 126.6, 101.6, 101.5, 95.1, 94.9, 774.1, 73.9, 68.7, 68.1, 63.22, 63.20, 56.4, 56.3, 55.9, 55.6, 50.8, 50.5, 29.6, 29.31, 29.29, 19.52, 18.1. IR: ν(O–H) 3368, ν(C–H) 2958, ν(C=O) 1664, ν(C=C) 1618, ν(C=C)$_{AR}$ 1589, 1442, ν(C–O) 1251, 1204 cm^{-1}. UV λ_{max} (log ε): 208 (4.70), 238 (4.42), 316 (4.27). *Anal* Calcd. for

$C_{18}H_{24}INO_6$: C, 45.30; H, 5.07; N, 2.93. Found: C, 45.69; H, 5.27; N, 3.15.

(*S*)-Ethyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-iodo-2,4-dimethoxybenzoyl)-acrylate (16d). Starting from ethyl ester **15d** and using procedure described for the synthesis of **16a**, compound **16d** was obtained in 86.8% yield as yellowish crystals; mp 111–116°C (ethanol). HPLC purity 99.5%. ^{1}H NMR ($CDCl_3$) δ (ppm): ^{1}H NMR ($CDCl_3$) δ (ppm): 10.78 (dd, J = 13.0, 10.2 Hz, 0.8H, NH), 9.15 (dd, J = 14.3, 9.7 Hz, 0.2H, NH), 7.92 (d, J = 13.6 Hz, 0.8H, –CH=), 7.89 (d, J = 14.2 Hz, 0.2H, –CH=), 7.61 (s, 0.2H, H-6), 7.56 (s, 0.8H, H-6), 6.286 (s, 0.2H, H-3), 6.280 (s, 0.8H, H-3), 3.83–3.93 (m, 5H, CH_2 + MeO), 3.58–3.70 (m, 5H, MeO + $\underline{CH_2}$OH), 3.00–3.04 (m, 1H, $\underline{CH}$N), 2.85 (m, 0.8H, OH), 2.78 (m, 0.2H, OH), 1.86–1.90 (m, 1H, $\underline{CH}Me_2$), 0.85–0.96 (m, 9H, $CH\underline{Me_2}$, $OCH_2\underline{Me}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.5, 189.6, 169.2, 167.7, 161.9, 160.9, 159.8, 159.7, 158.6, 158.1, 140.9, 138.1, 127.4, 122.8, 101.9, 101.6, 95.1, 95.0, 68.7, 68.1, 63.2, 56.4, 56.3, 55.8, 55.7, 55.6, 49.9, 29.6, 29.3, 20.5, 19.5, 18.1, 14.1, 13.8. IR: ν(O–H) 3436, ν(C–H) 2963, ν(C=O) 1656, $\nu(C{=}C)_{AR}$ + ν(C=C) 1587, $\nu(C{=}C)_{AR}$ 1431, ν(C–O) 1265, 1205 cm^{-1}. UV λ_{max} (log ε): 208 (4.84), 237 (4.38), 313 (4.22). *Anal* Calcd. for $C_{19}H_{26}INO_6$: C, 46.45; H, 5.33; N, 2.85. Found: C, 46.72; H, 5.57; N, 3.01.

(*S*)-Methyl 6-bromo-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylate (19a). To a solution of (*S*)-methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylate (**16a**; 1.72 g, 4 mmol) in DMF (25 mL) was added *N*,*O*-bis(trimethylsilyl)-acetamide (3 g), and the mixture was stirred at 100°C for 5 h. The mixture was diluted with water and stirred at room temperature overnight. The insoluble portion was filtered off, washed with water, and dried to give 1.4 g (87.9%) of white crystals; mp 140–146°C (HPLC purity 99.4%). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.55 (s, 1H, H-2), 7.71 (s, 1H, H-5), 6.85 (s, 1H, H-8), 5.84 (t, J = 7.1 Hz, 1H, OH), 4.22–4.32 (m, 2H, $\underline{CH_2}$OH), 4.08–4.13 (m, 1H, $\underline{CH}$N), 4.05 (s, 3H, MeO), 3.84 (s, 3H, COOMe), 2.43–2.52 (m, 1H, $\underline{CH}Me_2$), 1.24 (d, J = 6.4 Hz, 3H, $CH\underline{Me_2}$), 0.71 (d, J = 6.4 Hz, 3H, $CH\underline{Me_2}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.0, 165.1, 159.3, 146.8, 141.4, 130.9, 122.6, 110.6, 109.4, 96.7, 68.9, 60.8, 56.7, 51.7, 28.5, 20.4, 19.5. IR: ν(O–H) 3219, ν(C–H) 2943, ν(C=O) 1690, $\nu(C{=}C)_{AR}$ 1607, 1576, 1432, ν(C–O) 1258, 1239 cm^{-1}. UV λ_{max} (log ε): 209 (4.62), 253 (4.64), 270 (4.58), 319 (4.16), 332 (4.16). $[\alpha]_D^{20}$ (MeOH) = −28.6°. *Anal* Calcd. for $C_{17}H_{20}BrNO_5$: C, 51.27; H, 5.06; N, 3.52. Found: C, 50.89; H, 5.33; N, 3.67.

(*S*)-Methyl 6-bromo-1,4-dihydro-1-(1-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylate (24a). A solution of (*S*)-methyl 6-bromo-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylate (**19a**, 1 g, 2.5 mmol), imidazole (1.5 g, 22 mmol) and *tert*-butyldimethylsilyl chloride (1.,5 g, 10 mmol) in DMF (15 mL) was stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate (50 mL), and the solution was washed with water and then dried with $MgSO_4$. Crystallization of the residue after evaporation from toluene provided 0.6 g (46.6%) of white solid; mp 227–235°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.70 (s, 1H, H-5), 8.66 (s, 1H, H-2), 6.86 (s, 1H, H-8), 4.17–4.19 (m, 1H, $\underline{CH}$N), 3.93–4.05 (m, 2H, $\underline{CH_2}$O), 4.00 (s, 3H, MeO), 3.88 (s, 3H, COOMe), 2.38–2.45 (m, 1H, $\underline{CH}Me_2$), 1.17 (d, J = 6.5 Hz, 3H, $CH\underline{Me_2}$), 0.86 (d, J = 6.5Hz, 3H, $CH\underline{Me_2}$), 0.76 (s, 9H, *tert*-Bu), −0.06 (s, 3H, SiMe), −0.09 (s, 3H, SiMe). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.3, 166.0, 158.9, 146.1, 141.6, 132.7, 124.0, 111.0, 110.2, 96.9, 66.7, 62.6, 56.5, 52.0, 29.2, 25.5, 19.9, 19.6, −5.7, −5.9. IR: ν(C–H) 2949, ν(C=O) 1721, $\nu(C{=}C)_{AR}$ 1606, 1581, 1481, ν(C–O) 1263, 1196, ν(Si–O) 1101 cm^{-1}. UV λ_{max} (log ε): 253 (4.63), 270 (4.59), 319 (4.16), 332 (4.18).

(*S*)-6-Bromo-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylic acid (25a). *N*,*O*-bis (Trimethylsilyl)-acetamide (5 g, 25 mmol) was added to a suspension of compound **16a** (4.8 g, 10 mmol) in acetonitrile (10 mL), and the suspension was stirred at r. t. for 30 min and at 70–75°C for 4 h. After addition of water (5 mL), the mixture was stirred at 70°C for 2 h and then at r.t. overnight. Then 20% aqueous solution of KOH (5 mL) was added and stirred at r.t. for additional 4 h. Precipitate formed after acidification with acetic acid was filtered off, washed with acetonitrile (2 × 2 mL) and water (5 mL) and dried to provide 3.3 g (85.9%) of off-white solid; mp 259–262°C. HPLC purity 99.6%. ^{1}H NMR (DMSOd_6) δ (ppm): 15.12 (s, 1H), 8.92 (s, 1H, H-2), 8.49 (s, 1H, H-5), 7.55 (s, 1H, H-8), 5.22 (t, J = 4.6 Hz, 1H, OH), 4.90 (m, 1H, CHN), 4.10 (s, 3H, MeO), 3.99 (m, 1H, $\underline{CH_2}$OH), 3.80 (m, 1H, $\underline{CH_2}$OH), 2.38 (m, 1H, CH), 1.16 (m, J = 6.5 Hz, 3H, Me), 0.74 (m, J = 6.5 Hz, 3H, Me). ^{13}C NMR (DMSOd_6) δ (ppm): 175.6, 165.9 159.6, 146.2, 141.6, 129.8, 120.1, 111.1, 107.8, 100.0, 66.5, 60.1, 57.7, 29.2, 19.1, 18.9. IR: ν(O–H) 3436, ν(C–H) 2968, ν(C=O) 1722, $\nu(C{=}C)_{AR}$ 1609, 1536, 1451, ν(C–O) 1271 cm^{-1}. UV λ_{max} (log ε): 255 (4.62), 269 (4.60), 318 (4.10), 330 (4.09). *Anal* Calcd. for $C_{16}H_{18}BrNO_5$: C, 50.02; H, 4.72; N, 3.65. Found: C, 50.33; H, 5.00; N, 3.73.

(*S*)-Methyl 6-bromo-1,4-dihydro-7-methoxy-1-(3-methyl-1-(trimethylsilyloxy)butan-2-yl)-4-oxo-quinoline-3-carboxylate (23a). To a solution of (*S*)-methyl 3-(1-hydroxy-3-methylbutan-2-ylamino)-2-(5-bromo-2,4-dimethoxybenzoyl)-acrylate (**16a**; 17.2 g, 40 mmol) in DMF (150 mL) was added *N*,*O*-bis(trimethylsilyl)-acetamide (20 g), and the mixture was stirred at 100°C under nitrogen for 5 h. The mixture was

cooled down to 5°C and placed in an ice bath, and then water was added (200 mL). The formed precipitate was filtered off, washed with cold water, and dried *in vacuo* at 20–22°C to give 18.5 g (98.3%) of **23a** as white solid; mp 193–196°C (HPLC purity 94,5%), which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.72 (s, 1H, H-5), 8.67 (s, 1H, H-2), 6.89 (s, 1H, H-8), 4.09–4.17 (m, 1H, CHN), 3.93–4.01 (m, 2H, CH_2O), 4.00 (s, 3H, MeO), 3.91 (s, 3H, COOMe), 2.36–2.43 (m, 1H, $CHMe_2$), 1.15 (d, J = 6.5 Hz, 3H, $CHMe_2$), 0.81 (d, J = 6.5Hz, 3H, $CHMe_2$), −0.02 (s, 9H, $SiMe_3$). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.3, 166.0, 158.9, 146.2, 141.6, 132.5, 123.9, 110.8, 110.2, 97.1, 66.6, 61.9, 56.5, 52.0, 29.3, 19.9, 19.5, −0.9. IR: ν(C–H) 2950, ν(C=O) 1722, ν(C=C)$_{AR}$ 1608, 1583, 1482, ν(C–O) 1262, 1195, ν(Si–O) 1099 cm^{-1}. UV λ_{max} (log ε): 253 (4.74), 270 (4.70), 319 (4.25), 331 (4.26). $[\alpha]_D^{20}$ (MeOH) = −38.2°.

(*R*)-Methyl 6-bromo-1,4-dihydro-7-methoxy-1-(3-methyl-1-(trimethylsilyloxy)butan-2-yl)-4-oxo-quinoline-3-carboxylate (*R*-23a). Starting from 10 g (23.2 mmol) of derivate **(*R*)-16a** and using procedure described for the synthesis of compound **23a**, 10.4 g (95.1%) of the corresponding *R*-isomer was obtained as white solid; mp 191–194°C (HPLC purity 92.1%). $[\alpha]_D^{20}$ (MeOH) = +38.5°.

(*S*)-Ethyl 6-bromo-1,4-dihydro-7-methoxy-1-(3-methyl-1-(trimethylsilyloxy)butan-2-yl)-4-oxo-quinoline-3-carboxylate (23b). Starting from ethyl ester **16b** and using procedure described for the synthesis of **23a**, compound **23b** was obtained in 91.8% yield as white crystals, mp 154–174°C (HPLC purity 96.6%), which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.68 (s, 1H, H-5), 8.46 (s, 1H, H-2), 6.83 (s, 1H, H-8), 4.01–4.12 (m, 1H, CHN), 3.99–4.11 (m, 2H, CH_2O), 3.97 (s, 3H, MeO), 3.95 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 2.33–2.45 (m, 1H, $CHMe_2$), 1.11 (d, J = 6.5 Hz, 3H, $CHMe_2$), 0.96 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.78 (d, J = 6.5Hz, 3H, $CHMe_2$), −0.05 (s, 9H, $SiMe_3$). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.2, 165.6, 159.0, 146.7, 142.7, 133.8, 122.8, 109.5, 107.3, 98.4, 67.8, 61.9, 59.8, 55.2, 28.8, 19.8, 19.6, 14.1, −0.7. IR: ν(C–H) 2960, ν(C=O) 1720, ν(C=C)$_{AR}$ 1607, 1584, 1480, ν(C–O) 1262, 1195, ν(Si–O) 1097 cm^{-1}. UV λ_{max} (log ε): 253 (4.58), 270 (4.55), 319 (4.13), 332 (4.13).

(*S*)-Methyl 6-iodo-1,4-dihydro-7-methoxy-1-(3-methyl-1-(trimethylsilyloxy)-butan-2-yl)-4-oxo-quinoline-3-carboxylate (23c). Starting from iodo derivate **16c** and using procedure described for the synthesis of **23a**, compound **23c** was obtained in 86.8% yield; off-white crystals, mp 192–194°C (HPLC purity 98.4%), which was used for the next step without further purification.

(*S*)-Ethyl 6-iodo-1,4-dihydro-7-methoxy-1-(3-methyl-1-(trimethylsilyloxy)-butan-2-yl)-4-oxo-quinoline-3-carboxylate (23d). Starting from iodo derivate **16d** and using procedure described for the synthesis of **23a**, compound **23d** was obtained in 83.7% yield; off-white crystals, mp 167–171°C (HPLC purity 98.2%), which was used for the next step without further purification. IR: ν(C–H) 2958, ν(C=O) 1717, ν(C=C)$_{AR}$ 1622, 1581, 1472, ν(C–O) 1253, 1195, ν(Si–O) 1094 cm^{-1}. UV λ_{max} (log ε): 228 (4.43), 254 (4.64), 272 (4.61), 322 (4.15), 335 (4.16).

Preparation of a 1*M* solution of 3-chloro-2-fluorobenzylzinc bromide (27) in THF. A solution of 1,2-dibromoethane (0.8 g) and trimethylsilyl chloride (0.8 mL) in dry THF (10 mL) was added to a suspension of granular Zn (12 g; 30–100 mesh) in dry THF (150 mL) stirred under argon at 60°C. After 1 h, a solution of 3-chloro-2-fluorobenzyl bromide (36.4 g, 163 mmol) in THF (150 mL) was added with syringe pump during 1 h, and the mixture was stirred at this temperature for additional 1 h (most of the metal was dissolved).

(*S*)-Methyl 6-(3-chloro-2-fluorobenzyl)-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylate (28a)

Method A. To a solution of compound **23a** (3.3 g, 7 mmol) in THF (35 mL) under argon atmosphere was added $PdCl_2(PPh_3)_2$ (0.2 g). Then the temperature was elevated to 60°C, and a 1*M* solution of 3-chloro-2-fluorobenzylzinkbromide in THF (10 mL) was added by syringe pump during 1 h, and the mixture was stirred at this temperature for an additional 1 h. After cooling, the mixture was poured into a mixture of saturated aqueous solution of NH_4Cl (50 mL) and ethyl acetate (50 mL). After thorough shaking, the layers were separated, and the organic layer was consecutively washed with saturated aqueous NH_4Cl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The formed dark solution was stirred with charcoal (2 g) for 4 h, charcoal was removed through celite, and the filtrate was evaporated to give yellowish residue (4.5 g). The residue was dissolved in methanol (50 mL), 5% aqueous HCl (0.5 mL) was added, and the mixture was stirred at room temperature for 24 h (white precipitate). After cooling, the precipitate was filtered off providing after drying 2.8 g of crude product containing 94% of **28a**. Recrystallization from toluene then provided 2.1 g (64.9%) of white crystals; mp 192–194°C. HPLC purity 98.3%. ^{1}H NMR (DMSOd_6) δ (ppm): 8.63 (s, 1H, H-2), 7.89 (s, 1H, H-5), 7.47 (m, 1H, Ar-H), 7.27 (s, 1H, H-8), 7.17–7.22 (m, 2H, Ar-H), 5.11 (t, J = 5.0 Hz, 1H, OH), 4.60–4.68 (m, 1H, CHN), 4.05 (s, 2H, CH_2), 3.92–3.98 (m, 4H, MeO, CH_2OH), 3.78 (m, 1H, CH_2OH), 3.72 (s, 3H, COOMe), 2.29–2.35 (m, 1H, $CHMe_2$), 1.14 (d, J = 6.6 Hz, 3H, $CHMe_2$), 0.74 (d, J = 6.6 Hz, 3H, $CHMe_2$). ^{13}C NMR (DMSOd_6) δ (ppm): 171.7, 160.6, 165.4, 155.6, 145.7, 141.6, 130.2, 128.7, 128.6, 127.2, 125.5, 125.3, 121.7, 119.6, 109.5, 97.5, 65.2, 60.2, 56.5, 51.2, 29.0, 28.4, 19.2, 19.1. IR: ν(O–H) 3438, ν(C–H) 2948, ν(C=O) 1716, ν(C=C)$_{AR}$ 1609, 1580, 1460, ν(C–O) 1256 cm^{-1}. UV λ_{max} (log ε):

211 (4.69), 254 (4.79), 269 (4.73), 315 (4.32). $[\alpha]_D^{20}$ (DMSO) = −29.5°.

Method B. Starting from iodo derivate **23c** (0.52 g, 1 mmol) using procedure described as *Method A*, the crude compound **28a** was obtained in 75.8% yield (HPLC purity 86.2%). Centrifugally accelerated axial chromatography (CH_2Cl_2–MeOH) provided 0.25 g (54.1%) of compound **28a**; white crystals, mp 195–201°C (methanol). HPLC purity 98.8%.

Method C. To a solution of compound **24a** (0.5 g, 1 mmol) in THF (5 mL) under argon atmosphere was added $PdCl_2(PPh_3)_2$ (0.1 g). Then the temperature was elevated to 60°C, and a 1*M* solution of 3-chloro-2-fluorobenzylzinkbromide in THF (1.5 mL) was added by syringe pump during 1 h, and the mixture was stirred at this temperature for additional 4 h. After cooling, the mixture was poured into 1*M* aqueous HCl (20 mL), and the mixture was stirred at room temperature for 4 h and then extracted with dichloromethane (4 × 20 mL). The extract was evaporated under reduced pressure and dissolved in methanol (5 mL), and after addition of a solution of sodium hydroxide (1 g) in water (10 mL), the mixture was stirred at room temperature for 15 h. Then the mixture was acidified with acetic acid, and the formed cloudy solution was left to stand in a refrigerator overnight. The insoluble portion was filtered off to provide 0.25 g (56%) of off-white product; mp 193–200°C (HPLC purity of 96.3%).

(*R*)-Methyl 6-(3-chloro-2-fluorobenzyl)-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylate (*R*-28a). Starting from 7.05 g (15 mmol) derivate **(*R*)-23a** and using procedure described as *Method A* in the synthesis of compound **28a**, 4.9 g (70.7%) of the corresponding *R*-isomer was obtained as a white crystals; mp 192–198°C (HPLC purity 95.7%). ^{1}H NMR (DMSOd_6) δ (ppm): 8.63 (s, 1H, H-2), 7.89 (s, 1H, H-5), 7.47 (td, J = 7.6, 1.8 Hz, 1H, Ar-H), 7.27 (s, 1H, H-8), 7.17–7.22 (m, 2H, Ar-H), 5.12 (t, J = 5.0 Hz, 1H, OH), 4.62–4.67 (m, 1H, CHN), 4.05 (s, 2H, CH_2), 3.97 (s, 3H, MeO), 3.94–3.95 (m, 1H, CH_2OH), 3.78 (m, 1H, CH_2OH), 3.72 (s, 3H, COOMe), 2.27–2.32 (m, 1H, $CHMe_2$), 1.13 (d, J = 6.6 Hz, 3H, $CHMe_2$), 0.74 (d, J = 6.6 Hz, 3H, $CHMe_2$). ^{13}C NMR (DMSOd_6) δ (ppm): 171.7, 160.6, 165.4, 155.6, 145.7, 141.6, 130.2, 128.7, 128.6, 127.2, 125.5, 125.3, 121.7, 119.6, 109.5, 97.5, 65.2, 60.2, 56.5, 51.2, 29.0, 28.4, 19.2, 19.1.

(*S*)-Ethyl 6-(3-chloro-2-fluorobenzyl)-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylate (28b). Starting from ethyl ester **23b** and using procedure described for the synthesis of **28a** (*Method A*), compound **28b** was obtained in 80.8% yield; mp 178–183°C (HPLC purity 93.8%), which was used for the next step without further purification.

(*S*)-6-(3-Chloro-2-fluorobenzyl)-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylic acid–elvitegravir (1)

Method A. A mixture of **28a** (4.6 g, 10 mmol), methanol (45 mL), water (45 mL), and NaOH (2.5 g, 62.5 mmol) was stirred at room temperature for 5 h. The slightly cloudy solution was diluted with water (25 mL) and filtered, and the clear solution was acidified with 10% aqueous HCl. The formed precipitate was filtered off, washed with water, and dried *in vacuo* to give 3.5 g (78.1%) of white solid; mp 153–156°C (Ref. [3], mp 151–152°C). $[\alpha]_D^{20}$ (MeOH) = −29.2° (Ref. [3] gives $[\alpha]_D^{25}$ (MeOH) = −29.7°). HPLC purity 98.9%. ^{1}H NMR (DMSOd_6) δ (ppm): 8.88 (s, 1H, H-2), 8.04 (s, 1H, H-5), 7.47 (s, 1H, H-8), 7.18–7.22 (m, 3H, Ar-H), 4.86–4.92 (m, 1H, CHN), 4.11 (s, 2H, CH_2), 4.04 (s, 3H, MeO), 3.98–4.00 (m, 1H, CH_2OH), 3.78–3.81 (m, 1H, CH_2OH), 2.36–2.39 (m, 1H, $CHMe_2$), 1.16 (d, J = 6.5 Hz, 3H, $CHMe_2$), 0.73 (d, J = 6.,5 Hz, 3H, $CHMe_2$). ^{13}C NMR (DMSOd_6) δ (ppm): 176.2, 166.3, 161.9, 155.7, 145.4, 142.4, 130.2, 128.8, 128.6, 127.7, 126.4, 125.3, 119.6, 118.9, 107.3, 98.1, 66.3, 60.1, 56.8, 29.2, 28.5, 19.1, 19.0. IR: ν(O–H) 3391, ν(C–H) 2969, ν(C=O) 1699, 1612, $\nu(C{=}C)_{AR}$ 1456, ν(C–O) 1256 cm^{-1}. UV λ_{max} (log ε): 209 (4.54), 258 (4.69), 313 (4.13). HRMS for $C_{23}H_{24}ClFNO_5$ $(M+1)^+$ Calcd: 448.1327, found: 448.1322.

Method B. Similar hydrolysis of **28b** provided elvitegravir (**1**) in 73.3% yield. HPLC purity 97.2%.

Method C. *N*,*O*-Bis(trimethylsilyl)-acetamide (2 g, 10 mmol) was added to a suspension of compound **25a** (1.3 g, 3.4 mmol) in anhydrous THF (15 mL), and the mixture was stirred at r.t. for 15 min under argon. $PdCl_2(PPh_3)_2$ (40 mg) was added, the temperature was elevated to 60°C, and a 1*M* solution of 3-chloro-2-fluorobenzylzinkbromide in THF (5 mL) was added by syringe pump during 1 h, and the mixture was stirred at this temperature for additional 1.5 h. After cooling to 25°C, water (10 mL) was added, followed by 5% HCl (0.5 mL) and saturated solution of NH_4Cl (10 mL), and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with saturated solution of NH_4Cl (10 mL) and brine (2 × 10 mL) and dried with $MgSO_4$. The residue after evaporation was crystallized from methanol (charcoal) to give 1.3 g (85.6%) of off-white crystals; mp 151–156°C (decomp.). HPLC purity 96.3%.

(*R*)-6-(3-Chloro-2-fluorobenzyl)-1,4-dihydro-1-(1-hydroxy-3-methylbutan-2-yl)-7-methoxy-4-oxo-quinoline-3-carboxylic acid–elvitegravir (*R*-1). Starting from 1.15 g (2.5 mmol) of derivate **(*R*)-28a** and using procedure described as *Method A* in the synthesis of elvitegravir (**1**), 0.75 g (66.9%) of *R*-isomer of elvitegravir was obtained as off-white solid; mp 149–153°C (HPLC purity 98.1%). ^{1}H NMR (DMSOd_6) δ (ppm): 8.88 (s, 1H, H-2), 8.04 (s, 1H, H-5), 7.46 (s, 1H, H-8), 7.18–7.38 (m, 3H, Ar-H), 4.86–

4.92 (m, 1H, CHN), 4.11 (s, 2H, CH_2), 4.04 (s, 3H, MeO), 3.99 (dd, $J = 12.4$, 5.3 Hz, 1H, CH_2OH), 3.78 (d, $J = 12.4$ Hz, 1H, CH_2OH), 2.36–2.39 (m, 1H, $CHMe_2$), 1.16 (d, $J = 6.5$ Hz, 3H, $CHMe_2$), 0.73 (d, $J = 6.,5$ Hz, 3H, $CHMe_2$). ^{13}C NMR (DMSOd_6) δ (ppm): 176.2, 163.3, 161.9, 155.7, 145.4, 142.4, 130.2, 128.9, 128.1, 126.5, 126.4, 125.3, 119.6, 118.9, 107.3, 98.1, 66.3, 60.1, 56.8, 29.1, 28.5, 19.1, 19.0. $[\alpha]_D^{20}$ (MeOH) = +29.5°. HRMS for $C_{23}H_{24}ClFNO_5$ $(M+1)^+$ Calcd: 448.1327, found: 448.1352.

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