An Efficient and Highly Diastereoselective Synthesis of GSK1265744, a Potent HIV Integrase Inhibitor

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Supporting information

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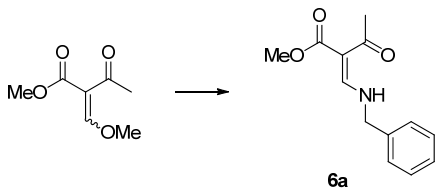
Experimental Details

General. Unless otherwise indicated, solvents and reagents were obtained from commercial sources and used without further purification. All reactions were conducted under a nitrogen atmosphere. All reactions were not optimized. Silica gel chromatographic purifications were performed using RediSep® silica gel-packed columns on a Teledyne Isco CombiFlash® system. Low resolution mass spectra were recorded on an Agilent 1100 series (SL) LC/MSD instrument. ^{1}H NMR, ^{13}C and ^{19}F NMR spectra were recorded at 25 ºC on a Bruker AVANCE 300 system at 300, 75 and 282 MHz respectively. Chemical shifts are reported as δ in ppm relative to chloroform-*d.* Elemental analyses were performed by Intertek QTI Laboratory in Whitehouse, New Jersey. High resolution mass spectra (HRLC-MS) were recorded using a Waters Q-TOF premier quadrupole orthogonal acceleration time-of-flight mass spectrometer coupled to an Agilent 1100 LC system. High performance liquid chromatographic (HPLC) analyses were carried out using an Agilent 1100 series HPLC instrument.



6a

Preparation of (E)-methyl 2-((benzylamino)methylene)-3-oxobutanoate (6a): Methyl 2-(methoxymethylene)-3-oxobutanoate[1] (826 mg, 5.22 mmol) was dissolved in CH_2Cl_2 (8 mL) and benzylamine (630 µL, 5.76 mmol, 1.1 equiv) was added. The mixture was stirred at rt overnight, concentrated and the product was purified by chromatography (eluted with 10%-40% EtOAc in hexanes, 1.106 g, 4.74 mmol, 91%). The product was a pale yellow solid. ES-MS: m/z 234 ($M+H^+$). ^{1}H NMR showed two isomers. The minor isomer was estimated to be ~4% from doublets at 8.10 ppm (major isomer) and 8.27 ppm (minor isomer) as well as singlets at 3.74 ppm (major) and 3.80 ppm (minor). The double bond geometry is inconsequential in the subsequent cyclization as the two isomers should be readily interconverting via an imine-enamine equilibrium, but the major isomer was assigned the (E)-configuration based on the assumption of intramolecular H bond between the ketone and the N-*H*.[2] The ^{1}H NMR data are also in agreement with reported values.[3] The major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.31 (br. s., 1 H), 8.10 (d, *J* = 13.6 Hz, 1 H), 7.42-7.25 (m, 5 H), 4.53 (d, *J* = 6.1 Hz, 2 H), 3.74 (s, 3 H), 2.50 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1, 167.3, 159.8, 136.1, 128.7, 127.9, 127.0, 100.0, 53.4, 50.6, 30.6. Anal calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00; found: C, 66.81; H, 6.51; N, 5.85.

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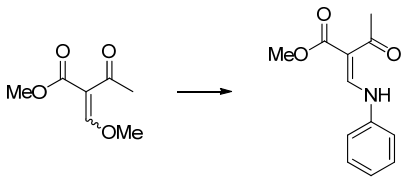
[1] Crombie, L.; Games, D. E.; James, A. W. G. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 464.
[2] Michalik, M. *J. Prakt. Chem* **1985**, *327*, 908.
[3] Ganem, B. *J. Am. Chem. Soc.* **1976**, *98*, 224.

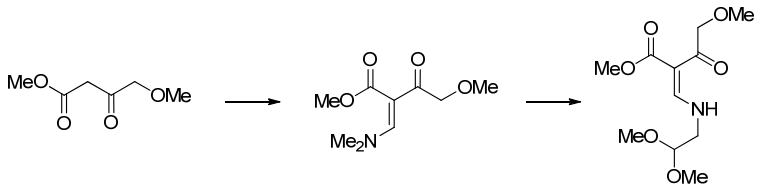


6b

Preparation of (E)-methyl 3-oxo-2-((phenylamino)methylene)butanoate (6b): Methyl 2-(methoxymethylene)-3-oxobutanoate (405 mg, 2.56 mmol) was dissolved in CH_2Cl_2 (4 mL) and aniline (260 μL, 2.85 mmol, 1.1 equiv) was added. The mixture was stirred at rt overnight, concentrated and the product was purified by chromatography (eluted with 10%-30% EtOAc in hexanes, 558.2 mg, 2.55 mmol, 99%). The product was a pale yellow solid. ES-MS: m/z 220 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, *J* = 13.2 Hz, 1 H), 7.43-7.37 (m, 2 H), 7.23-7.18 (m, 3 H), 3.79 (s, 3 H), 2.57 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.0, 167.1, 151.8, 138.8, 129.7, 125.4, 117.6, 102.1, 51.0, 31.0. Anal calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39; found: C, 65.57; H, 5.90; N, 6.34. The ^{1}H NMR data are in agreement with reported values.[3]

6c

Preparation of (E)-methyl 2-((isopropylamino)methylene)-3-oxobutanoate (6c): Methyl 2-(methoxymethylene)-3-oxobutanoate (1.098 g, 6.94 mmol) was dissolved in CH_2Cl_2 (10 mL) and isopropylamine (650 μL, 7.63 mmol, 1.1 equiv) was added. The mixture was stirred at rt overnight, concentrated and the product was purified by chromatography (eluted with 15%-30% EtOAc in hexanes, 1.216 g, 6.56 mmol, 94%). The product was a clear oil but solidified into a white solid. ES-MS: m/z 186 ($M+H^+$). ^{1}H NMR showed two isomers. The minor isomer was estimated to be ~10% from doublets at 8.02 ppm (major isomer) and 8.20 ppm (minor isomer) as well as singlets at 3.71 ppm (major) and 3.77 ppm (minor). The major isomer was assigned the (E)-configuration based on the assumption of intramolecular H bond between the ketone and the N-*H*. Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.04 (br. s., 1 H), 8.02 (d, *J* = 13.8 Hz, 1 H), 3.71 (s, 3 H), 3.64-3.51 (m, 1 H), 2.45 (s, 3 H), 1.29 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.7, 167.3, 157.5, 99.0, 51.2, 50.3, 30.4, 23.0. HRMS (ES) calcd for $C_9H_{15}NO_3$ $[M+H]^+$: 186.1130, found 186.1135.

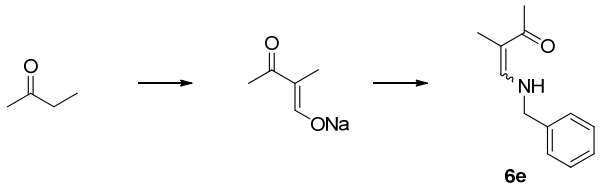


8 **4b** **6d**

Preparation of (Z)-methyl 2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (4b): Methyl 4-methoxy-3-oxobutanoate (**8**) (3.9 mL, 30.2 mmol, 1 equiv) was dissolved in 20 mL of toluene and DMF DMA (6.4 mL, 48.2 mmol, 1.6 equiv) was added. The mixture was heated to reflux for 4 h, and concentrated under vacuum. The product was purified by Kugelrohr distillation to give a light orange oil (5.5 g, 27.3 mmol, 90%). ES-MS: m/z 202 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (s, 1 H), 4.38 (s, 2 H), 3.73 (s, 3 H), 3.40 (s, 3 H), 3.26 (br. s., 3

H), 2.88 (br. s., 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.7, 166.7, 157.3, 98.2, 76.3, 57.9, 49.9, 46.8, 41.4. HRMS (ES) calcd for $C_9H_{15}NO_4$ $[M+H]^+$: 202.1079, found 202.1085.

Preparation of (E)-methyl 2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (6d): The tertiary vinylogous amide **4b** (292.6 mg, 1.45 mmol) was dissolved in 3 mL of CH_2Cl_2, and aminoacetaldehyde dimethyl acetal (170 μL, 1.58 mmol, 1.1 equiv) was added. The mixture was stirred at rt overnight, concentrated and the product was purified by chromatography (eluted with 0-60% EtOAc in hexanes, 371.6 mmol, 1.42 mmol, 98%). The product was an off-white solid. ES-MS: m/z 262 ($M+H^+$). ^{1}H NMR showed two isomers. The minor isomer was estimated to be ~8% from doublets at 7.96 ppm (major isomer) and 8.18 ppm (minor isomer). The major isomer was assigned the (E)-configuration based on the assumption of intramolecular H bond between the ketone and the N-*H*. The major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.97 (br. s., 1 H), 7.96 (d, *J* = 13.7 Hz, 1 H), 4.58 (s, 2 H), 4.42 (t, *J* = 5.3 Hz, 1 H), 3.72 (s, 3 H), 3.47 (s, 3 H), 3.43 (s, 6 H), 3.46-3.41 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 166.4, 160.5, 102.3, 97.8, 76.7, 58.6, 54.4, 51.3, 50.3. HRMS (ES) calcd for $C_{11}H_{19}NO_6$ $[M+H]^+$: 262.1291, found 262.1290.



6e

Preparation of 4-(benzylamino)-3-methylbut-3-en-2-one (6e): Sodium 2-methyl-3-oxobut-1-en-1-olate was prepared following literature procedure[4]: methyl formate (12.3 mL, 199 mmol, 2.5 equiv) was added to NaOMe (8.53 g, 158 mmol, 2 equiv) in ether (60 mL) at 0 °C. Butanone (7.0 mL, 78.1 mmol, 1 equiv) was added slowly over 5 min. The mixture was warmed to rt and stirred for 8 h. The solid product was collected by filtration and dried under vacuum at 50 °C (11.34 g). The sodium salt thus prepared (2.156 g, 17.6 mmol) was suspended in 20 mL of MeOH. HOAc (1.2 mL, 20.9 mmol, 1.2 equiv) and benzylamine (2.2 mL, 20.1 mmol, 1.1 equiv) were added. The mixture was stirred at rt overnight and the product purified by chromatography (eluted with gradient from hexanes to EtOAc, 1.896 g, 10.0 mmol, 68% over 2 steps). The product was a yellow solid. ES-MS: m/z 190 ($M+H^+$). ^{1}H NMR showed that the product was a mixture of two isomers in a 1.3:1 ratio. The major isomer was assigned as the Z-isomer based on the more downfield chemical shift of the N-*H* signal due to intramolecular hydrogen bonding. The assignments of the ^{1}H and ^{13}C NMR signals were based on ^{1}H signal integration, GASPE and correlation experiments (HMQC and HMBC).[5] Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.98 (br. s., 1 H), 7.39-7.22 (m, 5 H), 6.62 (d, *J* = 12.3 Hz, 1 H), 4.32 (d, *J* = 6.1 Hz, 2 H), 2.09 (s, 3 H), 1.82 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.1, 151.7, 99.9, 52.0, 27.9, 17.1. Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.22 (m, 6 H), 5.08 (br. s., 1 H), 4.41 (d, *J* = 5.8 Hz, 2 H), 2.16 (s, 3 H), 1.70 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 148.7, 107.6, 51.8, 24.1, 8.4. The ^{13}C NMR signals for the phenyl protons for both isomers: δ 138.45, 138.42, 128.6, 128.5, 127.5, 127.3, 126.9, 126.8. Anal calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40; found: C, 75.77; H, 8.15; N, 7.22.

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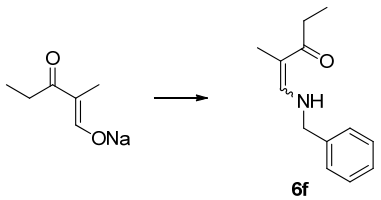
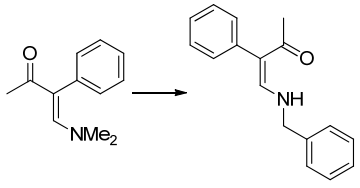
[4] Hjelmgaard, T.; Søtofte, I.; Tanner, D. *J. Org. Chem.* **2005**, *70*, 5688.

[5] The NMR data as well as the assignments for the two isomers are in agreement with the literature: Zhuo, J.; *Magn. Reson. Chem.* **1998**, *36*, 565.



6f

Preparation of 1-(benzylamino)-2-methylpent-1-en-3-one (6f): Sodium 2-methyl-3-oxopent-1-en-1-olate[6] (1.158 g, 8.51 mmol) was suspended in 12 mL of MeOH. HOAc (0.60 mL, 10.5 mmol, 1.2 equiv) and benzylamine (1.00 mL, 9.15 mmol, 1.1 equiv) were added. The mixture was stirred at rt overnight. MeOH was removed and the residue was diluted with 15 mL of CH_2Cl_2, washed with 20 mL of water. The aqueous layer was back extracted with CH_2Cl_2 (15 mL×2). The combined organic layers were dried and concentrated. The product was purified by chromatography (eluted with gradient from hexanes to EtOAc, 0.794 g, 3.91 mmol, 46%). The product was a light yellow solid. ES-MS: m/z 204 ($M+H^+$). ^{1}H NMR showed the product was a mixture of two isomers in a 2.7:1 ratio. The major isomer was assigned as the Z-isomer based on the more downfield chemical shift of the N-*H* signal due to intramolecular hydrogen bonding. The assignments of the ^{1}H and ^{13}C NMR signals were based on ^{1}H signal integration, GASPE and correlation experiments (HMQC and HMBC).[7] Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.95 (br. s., 1 H), 7.42-7.24 (m, 5 H), 6.62 (d, *J* = 12.3 Hz, 1 H), 4.34 (d, *J* = 6.1 Hz, 2 H), 2.41 (q, *J* = 7.3 Hz, 2 H), 1.83 (d, *J* = 0.6 Hz, 3 H), 1.10 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.0, 151.5, 99.6, 52.2, 32.8, 16.6, 8.3. Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.24 (m, 6 H), 4.51 (br. s., 1 H), 4.43 (d, *J* = 5.7 Hz, 2 H), 2.53 (q, *J* = 7.4 Hz, 2 H), 1.71 (d, *J* = 0.9 Hz, 3 H), 1.12 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.4, 147.4, 106.9, 52.0, 29.4, 10.1, 8.7. The ^{13}C NMR signals for the phenyl protons for both isomers: δ 138.6, 138.5, 128.8, 128.6, 127.8, 127.4, 127.1. Anal calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89; found: C, 76.74; H, 8.77; N, 6.76.

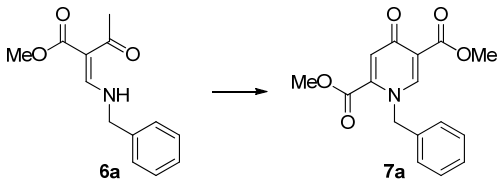


6g

Preparation of (Z)-4-(benzylamino)-3-phenylbut-3-en-2-one (6g): 4-(dimethylamino)-3-phenylbut-3-en-2-one [8] (637.4 mg, 3.37 mmol) was dissolved in 7 mL of MeOH and benzylamine (0.410 mL, 3.75 mmol, 1.1 equiv) was added. The mixture was heated to reflux for 22 h. Another portion of benzylamine (0.200 mL) was added and the reflux was continued for another 12 h. The mixture was cooled to rt, concentrated and the product was isolated by chromatography (eluted with 0-15% EtOAc in hexanes, 686.9 mg, 2.73 mmol, 81%). The product was a light orange oil. ES-MS: m/z 252 ($M+H^+$). ^{1}H NMR showed the product was a mixture of two isomers. A ratio of 9:1 was estimated from doublets at 6.86 ppm (major isomer)

[6] Myles, D. C.; Bigham, M. H. *Org. Synth.* **1992**, *70*, 231.
[7] The NMR data as well as the assignments for the two isomers are in agreement with the literature: Zhuo, J.; *Magn. Reson. Chem.* **1998**, *36*, 565.
[8] Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

and 7.70 ppm (minor isomer). The major isomer was assigned as the Z-isomer based on the downfield chemical shift of the N-*H* signal: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.55 (br. s., 1 H), 7.42-7.19 (m, 10 H), 6.86 (d, *J* = 12.6 Hz, 1 H), 4.44 (d, *J* = 6.1 Hz, 2 H), 2.09 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.5, 153.2, 140.0, 137.7, 130.0, 128.4, 127.9, 127.3, 126.8, 125.7, 110.3, 52.2, 28.2. HRMS (ES) calcd for $C_{17}H_{17}NO$ $[M+H]^+$: 252.1388, found 252.1387.



General procedure of oxalate cyclization in Table 2. Enamine **6a** (346.8 mg, 1.49 mmol) and dimethyl oxalate (617.6 mg, 5.23 mmol, 3.5 equiv) were dissolved in MeOH (1.1 mL) and a MeOH solution of NaOMe (25 wt%, 0.850 mL, 3.72 mmol, 2.5 equiv) was added. The mixture was heated to 30 ^{0}C for 36 h. The reaction was cooled to 0 ^{0}C and quenched with 1 N HCl (4.2 mL) and extracted with EtOAc (10 mL×3). The combined organic layers were dried and concentrated. The product was purified by chromatography (eluted with 40-60% acetone in TBME, 318.4 mg, 1.06 mmol, 71%) to give an off-white solid.

Dimethyl 1-benzyl-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (7a): ES-MS: m/z 302 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1 H), 7.41-7.34 (m, 3 H), 7.13-7.10 (m, 3 H), 5.46 (s, 2 H), 3.91 (s, 3 H), 3.78 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 165.0, 162.1, 149.4, 138.9, 134.6, 129.0, 128.6, 127.0, 126.7, 119.1, 58.2, 53.3, 52.2. Anal calcd for $C_{16}H_{15}NO_5$: C, 63.78,; H, 5.02; N, 4.65; found: C, 63.60,; H, 4.93; N, 4.33.

Dimethyl 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylate (7b): Tan solid (182.5 mg), prepared from **6b** (201.8 mg). ES-MS: m/z 288 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (s, 1 H), 7.48-7.43 (m, 3 H), 7.26-7.20 (m, 2 H), 7.06 (s, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 164.6, 161.4, 148.5, 141.8, 139.9, 129.7, 129.4, 124.9, 124.8, 118.9, 53.2, 52.2. HRMS (ES) calcd for $C_{15}H_{13}NO_5$ $[M+H]^+$: 288.0872, found 288.0861.

Dimethyl 1-isopropyl-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (7c): Off-white solid (195.3 mg), prepared from **6c** (203.1 mg). ES-MS: m/z 254 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (s, 1 H), 6.80 (s, 1 H), 4.77 (septet, *J* = 6.7 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 1.40 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 165.0, 162.2, 143.2, 140.0, 125.3, 119.3, 54.4, 53.3, 52.0, 22.7. HRMS (ES) calcd for $C_{12}H_{15}NO_5$ $[M+H]^+$: 254.1028, found 254.1037.

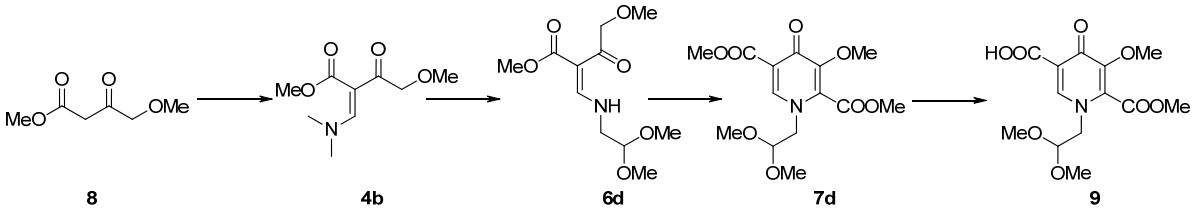
Dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (7d): prepared as an orange oil starting from 11.3 g of methyl 4-methoxyacetoacetate (see below for the synthesis of **6d**). ES-MS: m/z 330 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (s, 1 H), 4.51 (t, *J* = 4.9 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.94 (d, *J* = 4.9 Hz, 2 H), 3.91 (s, 3 H), 3.41 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 164.6, 161.8, 149.6, 145.7, 133.6, 117.6, 102.2, 59.9, 56.0, 55.2, 52.8, 51.6. HRMS (ES) calcd for $C_{14}H_{19}NO_8$ $[M+H]^+$: 330.1189, found 330.1184.

Methyl 1-benzyl-5-methyl-4-oxo-1,4-dihydropyridine-2-carboxylate (7e): light orange solid (203.5mg), prepared from **6e** (223.3 mg). ES-MS: m/z 258 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.31 (m, 4 H), 7.11-7.08 (m, 2 H), 6.95 (s, 1 H), 5.37 (s, 2 H), 3.79 (s, 3 H), 2.06 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.3, 162.7, 140.8, 138.6, 135.7, 128.9, 128.7, 128.0, 126.6, 119.8, 57.0, 52.9, 13.6. Anal calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44; found: C, 69.73; H, 5.97; N, 5.31.

Methyl 1-benzyl-3,5-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylate (7f): yellow oil (178.5 mg), prepared from **6f** (223.2 mg). ES-MS: m/z 272 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.34 (m, 3 H), 7.28 (m, 1 H), 7.15-7.12 (m, 2 H), 4.99 (s, 2 H), 3.73 (s, 3 H), 2.05 (d, J = 0.9 Hz, 3 H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.8, 163.9, 139.2, 137.8, 134.9, 128.9, 128.5, 127.0, 125.2, 123.3, 57.8, 52.6, 13.9, 12.1. HRMS (ES) calcd for $C_{16}H_{17}NO_3$ $[M+H]^+$: 272.1287, found 272.1293.

Methyl 1-benzyl-4-oxo-5-phenyl-1,4-dihydropyridine-2-carboxylate (7g): off-white solid (170.3 mg), prepared from **6g** (225.2 mg). ES-MS: m/z 320 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64-7.61 (m, 3 H), 7.44-7.32 (m, 6 H), 7.17-7.14 (m, 3 H), 5.48 (s, 2 H), 3.83 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.1, 162.5, 142.0, 138.1, 135.5, 133.7, 130.7, 128.8, 128.2, 128.1, 127.7, 126.7, 122.8, 57.3, 53.0. HRMS (ES) calcd for $C_{20}H_{17}NO_3$ $[M+H]^+$: 320.1287, found 320.1282.

Methyl 1-benzyl-4-oxo-1,4-dihydropyridine-2-carboxylate (7h): light yellow solid (76.7 mg), prepared from 4-(benzylamino)-but-3-en-2-one (**6h**, 241.6 mg)[9]: ES-MS: m/z 244 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, J = 7.6 Hz, 1 H), 7.39-7.30 (m, 3 H), 7.10 (m, 2 H), 6.94 (d, J = 2.7 Hz, 1 H), 6.47 (dd, J = 7.6, 2.7 Hz, 1 H), 5.36 (s, 2 H), 3.79 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.2, 162.3, 143.4, 139.6, 135.2, 128.6, 128.0, 126.6, 121.8, 118.9, 57.1, 52.9. HRMS (ES) calcd for $C_{14}H_{13}NO_3$ $[M+H]^+$: 244.0974, found 244.0963.



8 **4b** **6d** **7d** **9**

One pot synthesis of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (9): A round-bottom flask was charged with methyl 4-methoxyacetoacetate (**8**, 12.0 mL, 92.9 mmol, 1 equiv) and DMF-DMA (18.5 mL, 139 mmol,

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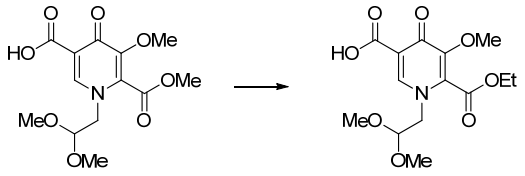
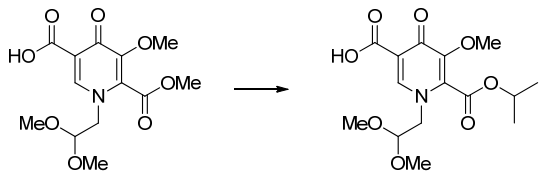
[9] (a) Murphy, J. P.; Hadden, M.; Stevenson, P. J. *Tetrahedron* 1997, 53, 11827. (b) You, L.; Hsung, R. P.; Bedermann, A. A.; Kurdyumov, A. V.; Tang, Y.; Buchanan, G. S.; Cole, K. P. *Adv. Synth. Catal.* **2008**, *350*, 2885.

1.5 equiv). The mixture was stirred at room temperature overnight and concentrated to remove excess DMF-DMA. The crude product oil was dissolved in MeOH (70 mL) and the resultant solution was cooled to ~5 °C. Aminoacetaldehyde dimethyl acetal (10 mL, 92.7 mmol, 1.0 equiv) was added while maintaining temperature below 10 °C. The mixture was warmed to 20 °C for 2 h, and concentrated. Dimethyl oxalate (38.35 g, 324 mmol, 3.5 equiv) was added followed by LiOMe (2.2 M solution in MeOH, 63 mL, 139 mmol, 1.5 equiv). The mixture was heated to 46 °C for 20.5 h and cooled to -5 °C. LiOH (13.33 g, 557 mmol, 6.0 equiv) was added while maintaining internal temperature below 0 °C. The mixture was stirred at -2 °C for 4.5 h, and quenched with aqueous HCl (2.0 M, 313 mL, 626 mmol, 6.75 equiv) while maintaining internal temperature below 0 °C. When the addition was complete, the mixture was warmed to 10 °C and EtOAc (280 mL) was added. The mixture was filtered and the organic layer was separated. Water (130 mL) was added to the EtOAc layer and mixture was concentrated to remove EtOAc. The resulting slurry was filtered. The product was washed with water, and dried in a vacuum oven at 55 °C to give **9** as a white solid (17.70 g, 56.1 mmol, 61%). ES-MS: m/z 316 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1 H), 4.53 (t, J = 4.6 Hz, 1 H), 4.11 (d, J = 4.6 Hz, 2 H), 4.03 (s, 3 H), 4.02 (s, 3 H), 3.42 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 165.8, 161.4, 148.5, 145.3, 136.4, 116.4, 102.2, 60.8, 57.1, 55.8, 53.6. Anal calcd for $C_{13}H_{17}NO_8$: C, 49.52; H, 5.43; N, 4.44; found: C, 49.50; H 5.47; N 4.32.



9 **10**

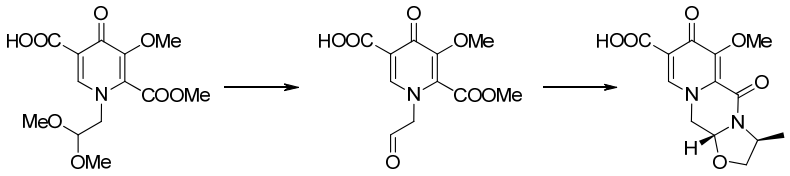
Preparation of 1-(2,2-dimethoxyethyl)-6-(ethoxycarbonyl)-5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid (10): LiH (206.1 mg, 25.9 mmol, 1.3 equiv) was dissolved in ethanol (60 mL). The methyl ester **9** (6.40 g, 20.3 mmol) was added after the off-gassing had subsided. The mixture was stirred at rt for 3 h. A second portion of LiH (28.4 mg) was added and the stirring was continued for another 2 h. TBME (100mL) was added followed by HCl (1 N, 100 mL). The aqueous layer was extracted a second time with 100 mL of TBME. The combined organic layers were concentrated. The product precipitated out of residual water (~8 mL). TBME (15 mL) was added and the mixture was stirred at rt for 30 min, filtered and dried (5.435 g, 16.5 mmol, 81%) to give a white solid. ES-MS: m/z 330 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1 H), 4.55 (t, J = 4.7 Hz, 1 H), 4.49 (q, J = 7.2 Hz, 2 H), 4.10 (d, J = 4.6 Hz, 2 H), 4.03 (s, 3 H), 3.41 (s, 6 H), 1.44 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 165.8, 160.9, 148.4, 145.2, 136.8, 116.4, 102.2, 63.3, 60.7, 57.1, 55.7, 14.0. Anal calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25; found: C, 51.02; H 5.94; N 4.17.



9 **11**

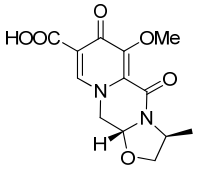
Preparation of 1-(2,2-dimethoxyethyl)-6-(isopropoxycarbonyl)-5-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid (11): NaH (505.6 mg, 60 wt%, 12.6 mmol, 1.6 equiv) was

added to anhydrous IPA (20 mL) and the mixture was stirred at rt for 1 h. The methyl ester **9** (2.49 g, 7.90 mmol) was added. The mixture was stirred at rt overnight and a second portion of NaH (523.0 mg) was added. The mixture was stirred at rt for 5 h. The methyl ester was consumed, however, formation of a large amount of the 2,5-diacid was observed. The reaction was quenched with 2 N HCl and extracted with iPAC (×2). The combined organic layers were washed with water until the 2,5-diacid was completely removed. The organic layer was dried, concentrated and the product crystallized from iPAC/TBME as a white solid (370.3 mg, 1.08 mmol, 14%). ES-MS: m/z 344 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (s, 1 H), 5.35 (spt, *J* = 6.3 Hz, 1 H), 4.57 (t, *J* = 4.9 Hz, 1 H), 4.08 (d, *J* = 4.9 Hz, 2 H), 4.02 (s, 3 H), 3.42 (s, 6 H), 1.43 (d, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 165.9, 160.4, 148.2, 145.0, 137.1, 116.5, 102.2, 71.9, 60.7, 57.1, 55.7, 21.6. HRMS (ES) calcd for $C_{15}H_{21}NO_8$ $[M+H]^+$: 344.1345, found 344.1353.



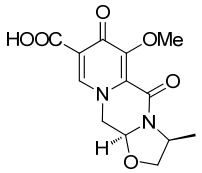
9 **12**

Preparation of (3S,11aR)-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxylic acid (12): Acetal **9** (22.54 g, 71.5 mmol) was dissolved in 220 mL of CH_3CN. HOAc (20 mL, 349 mmol, 4.9 equiv) and CH_3SO_3H (1.4 mL, 21.6 mmol, 0.3 equiv) were added at rt and the mixture was heated to 58-65 °C for 19.5 h. Alaninol (7.511 g, 100 mmol, 1.4 equiv) in CH_3CN (15 mL) was added slowly and the resultant mixture was stirred at 64 °C for 18.5 h. The mixture was concentrated, and the residue was redissolved in CH_2Cl_2 (170 mL). HCl (1 N, 170 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (170 mL×2) and the organic layers were combined and concentrated. MeOH (50 mL) was added and the resultant mixture was again concentrated. MeOH (80 mL) was added and the resultant mixture was heated at reflux for 4 h, gradually cooled to 20 °C and held at 20 °C for 15 h. The product was collected by filtration and dried under vacuum (15.67 g, 74% yield, 95.2% de) to give a white solid.



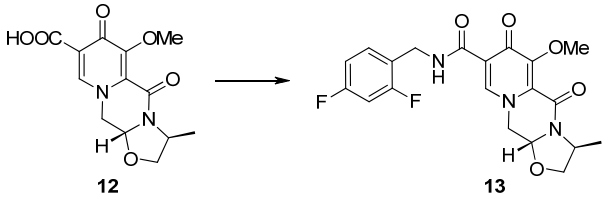
12a

The major isomer: (3S,11aR)-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxylic acid (12a). ES-MS: m/z 295 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1 H), 5.40 (dd, *J* = 9.9, 3.7 Hz, 1 H), 4.55-4.39 (m, 3 H), 4.12 (s, 3 H), 3.98 (dd, *J* = 12.1, 9.9 Hz, 1 H), 3.74 (dd, *J* = 8.2, 6.5 Hz, 1 H), 1.46 (d, *J* = 6.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 165.7, 153.8, 152.6, 143.0, 131.5, 116.1, 82.4, 73.2, 61.6, 55.8, 52.2, 17.0. Anal calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52; found: C, 53.02; H, 4.74; N, 9.45.



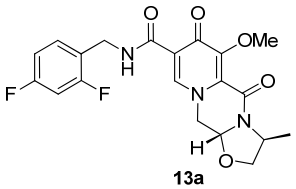
12b

The minor isomer (3S,11aS)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxylic acid (12b) was isolated from reaction mixtures by prep HPLC (Chiralpak IC 25×1 cm, 20 μm dp, with CH_3CN as the mobile phase at 3 mL/min, rt). An off-white solid was obtained. ES-MS: m/z 295 ($M+H^+$). ^1H NMR ($CDCl_3$, 300MHz) δ 8.48 (s, 1 H), 5.26 (dd, *J* = 3.0, 10.1 Hz, 1 H), 4.76 (dd, *J* = 3.0, 12.2 Hz, 1 H), 4.33 (m, 1 H), 4.16-4.11 (m, 1 H), 4.04 (s, 3 H), 4.07-4.00 (m, 2 H), 1.49 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 165.8, 152.9, 152.8, 143.6, 131.6, 115.7, 82.8, 73.6, 61.4, 57.2, 52.6, 18.1. HRMS (ES) calcd for $C_{13}H_{14}N_2O_6$ $[M+H]^+$: 295.0930, found 295.0927.



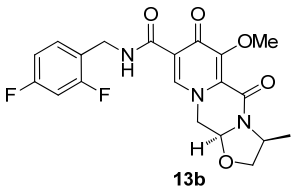
12 13

Preparation of (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (13): Acid **12** (3.00 g, 10.2 mmol) and CDI (2.15 g, 13.2 mmol, 1.3 equiv) were slurried in DME (30 mL). The mixture was heated to 80 °C for 1 h. The resulting solution was cooled to 20 °C, then treated with 2,4-difluorobenzylamine (1.45 mL, 12.2 mmol, 1.2 equiv). After stirring for 1 h, the mixture was quenched with water (30 mL) and DME was removed under reduced pressure. The product was collected by filtration and dried in a vacuum oven overnight at 50 °C. Amide **13** was obtained as a white solid (4.06 g, 9.68 mmol, 95%).



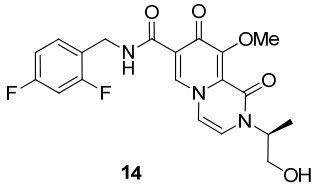
13a

The major isomer (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (13a): ES-MS: m/z 420 ($M+H^+$). ^1H NMR ($CDCl_3$, 300 MHz) δ 10.33 (t, *J* = 5.7 Hz, 1 H), 8.41 (s, 1 H), 7.36 (td, *J* = 8.7, 6.4 Hz, 1 H), 6.86-6.77 (m, 2 H), 5.32 (dd, *J* = 9.9, 3.7 Hz, 1 H), 4.70-4.56 (m, 2 H), 4.49-4.33 (m, 3 H), 4.07 (s, 3 H), 3.90 (dd, *J* = 12.3, 9.8 Hz, 1 H), 3.71 (dd, *J* = 8.5, 6.8 Hz, 1 H), 1.45 (d, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 163.8, 162.2 (dd, *J* = 248, 12 Hz), 160.7 (dd, *J* = 249, 12 Hz), 154.6, 153.2, 142.4, 130.5 (dd, *J* = 9.7, 5.8 Hz), 130.0, 121.3 (dd, *J* = 15, 3.9 Hz), 118.9, 111.1 (dd, *J* = 21, 3.6 Hz), 103.7 (t, *J* = 25 Hz), 82.4, 73.0, 61.3, 55.2, 52.0, 36.5, 17.1. ^{19}F NMR ($CDCl_3$, 282 MHz) δ -111.5 (d, *J* = 6.9 Hz), -114.3 (d, *J* = 6.9 Hz). Anal calcd for $C_{20}H_{19}F_2N_3O_5$: C, 57.28; H, 4.57; N, 10.02; found: C, 57.37; H, 4.48; N, 9.92.



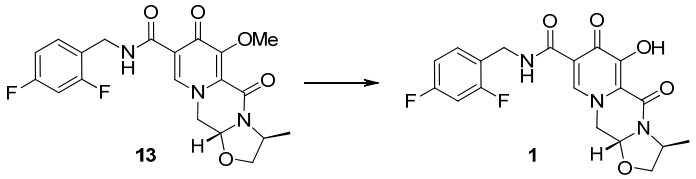
13b

The minor isomer (3S,11aS)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (13b) was prepared analogously from the corresponding acid **12b** (47.7 mg of **12b** gave 33.8 mg of **13b** in 50% yield). ES-MS: m/z 420 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.33 (t, *J* = 5.8 Hz, 1 H), 8.44 (s, 1 H), 7.37-7.25 (m, 1 H), 6.86-6.74 (m, 2 H), 5.12 (dd, *J* = 3.1, 10.0 Hz, 1 H), 4.67-4.51 (m, 3 H), 4.31 (m, 1 H), 4.11-3.85 (m, 3 H), 4.03 (s, 3 H), 1.49 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 163.9, 162.2 (dd, *J* = 248, 12 Hz), 160.7 (dd, J = 249, 12 Hz), 153.8, 153.6, 142.6, 130.5 (dd, *J* = 9.6, 5.9 Hz), 129.9, 121.3 (dd, *J* = 15.3, 3.7 Hz), 118.8, 111.1 (dd, *J* = 21, 3.6 Hz), 103.8 (t, J = 25.3 Hz), 83.0, 73.6, 61.2, 56.9, 52.5, 36.5 (d, *J* = 3.6 Hz), 18.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ -111.5 (d, *J* = 7.6 Hz), -114.3 (d, *J* = 6.9 Hz). HRMS (ES) calcd for $C_{20}H_{19}F_2N_3O_5$ $[M+H]^+$: 420.1371, found 420.1362.



14

(S)-N-(2,4-difluorobenzyl)-2-(1-hydroxypropan-2-yl)-9-methoxy-1,8-dioxo-2,8-dihydro-1H-pyrido[1,2-a]pyrazine-7-carboxamide (14) was isolated as a yellow solid from reaction mixtures and characterized: ES-MS: m/z 420 ($M+H^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.55 (t, *J* = 5.9 Hz, 1 H), 8.57 (s, 1 H), 7.42-7.34 (m, 1 H), 6.88-6.78 (m, 2 H), 6.73 (d, *J* = 6.4 Hz, 1 H), 6.59 (d, *J* = 6.3 Hz, 1 H), 5.04-4.93 (m, 1 H), 4.63 (d, *J* = 5.8 Hz, 2 H), 3.98 (s, 3 H), 3.92-3.87 (m, 1 H), 3.80-3.72 (m, 1 H), 3.25 (br. s., 1 H), 1.37 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 163.5, 162.0 (dd, *J* = 248, 12 Hz), 160.2 (dd, *J* = 249, 12 Hz), 154.1, 152.8, 137.7, 130.4 (dd, *J* = 9.7, 5.8 Hz), 129.1, 120.9 (dd, *J* = 15, 3.9 Hz), 120.0, 115.8, 111.1 (dd, *J* = 21, 3.5 Hz), 110.8, 103.5 (t, *J* = 25 Hz), 63.5, 60.8, 52.2, 36.4 (d, *J* = 2.8 Hz), 14.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ -111.1 (d, *J* = 7.6 Hz), -114.2 (d, *J* = 6.9 Hz). HRMS (ES) calcd for $C_{20}H_{19}F_2N_3O_5$ $[M+H]^+$: 420.1371, found 420.1374.

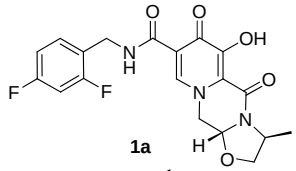


13 1

GSK1265744 Enol ether **13** (1.324 g, 3.16 mmol) was dissolved in CH_3CN (10 mL) at 50 °C and $MgBr_2$ (1.168 g, 6.34 mmol, 2 equiv) was added. The mixture was heated at 50 °C for 2.5 h, cooled to rt and quenched with HCl (1 N, 10 mL). The resultant slurry was stirred at rt overnight. The product was collected by filtration and dried to give a white solid (1.154 g, 2.85 mmol, 90%).

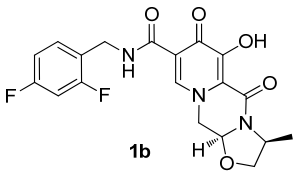
The demethylation was better accomplished with LiBr on large scale. A representative procedure is as following: Enol ether **13** (4.609 g, 11.0 mmol) was dissolved in THF (45 mL). LiBr (2.10 g, 24.2 mmol, 2.2 equiv) and water (0.26 g, 14.4 mmol, 1.3 equiv) were added. The mixture was heated at reflux overnight, and cooled to rt. HOAc (1.98 g, 33.0 mmol, 3 equiv) in

water (38 mL) was added slowly. The resultant suspension was stirred at rt for 2.5 h, filtered and reslurried in aq THF (25 mL/25 mL) at rt for 2 h. The product was collected by filtration and dried to give a white solid (4.14 g, 2.85 mmol, 10.2 mmol, 93%).



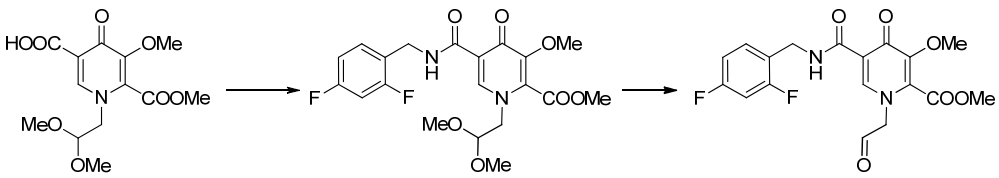
1a

GSK1265744 (1a): ES-MS: m/z 406 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.47 (s, 1 H), 10.31 (t, *J* = 5.9 Hz, 1 H), 8.47 (s, 1 H), 7.40 (td, *J* = 8.6, 6.8 Hz, 1 H), 7.25 (ddd, *J* = 10.4, 9.5, 2.6 Hz, 1 H), 7.06 (td, *J* = 8.5, 2.4 Hz, 1 H), 5.39 (dd, *J* = 10.1, 4.1 Hz, 1 H), 4.89 (dd, *J* = 12.3, 4.1 Hz, 1 H), 4.54 (d, *J* = 5.8 Hz, 2 H), 4.40 (dd, *J* = 8.4, 6.8 Hz, 1 H), 4.29 (sxt, *J* = 6.4 Hz, 1 H), 4.00 (dd, *J* = 11.9, 10.2 Hz, 1 H), 3.66 (dd, *J* = 8.4, 6.6 Hz, 1 H), 1.34 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.4, 163.6, 161.5 (dd, *J* = 245, 12 Hz), 160.2 (dd, *J* = 247, 12 Hz), 158.9, 153.1, 141.5, 130.8 (dd, *J* = 9.8, 6.2 Hz), 122.4 (dd, *J* = 15.2, 3.6 Hz), 117.4, 114.9, 111.4 (dd, *J* = 21, 3.4 Hz), 103.8 (t, *J* = 26 Hz), 81.7, 72.4, 52.9, 51.4, 35.8 (d, *J* = 3.0 Hz), 16.6. ^{19}F NMR (DMSO-d_6, 282 MHz) δ -111.9 (d, *J* = 7.6 Hz), -114.5 (d, *J* = 6.9 Hz). Anal calcd for $C_{19}H_{17}F_2N_3O_5$: C, 56.30; H, 4.23; N, 10.37; found: C, 55.99; H, 4.12; N, 10.21.



1b

The minor diastereomer (3S,11aS)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (1b) was prepared analogously from the corresponding methyl ether **13b** (71.2 mg): solid (38.0 mg, 55%). ES-MS: m/z 406 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.86 (br. s., 1 H), 10.33 (t, *J* = 5.9 Hz, 1 H), 8.45 (s, 1 H), 7.39 (td, *J* = 8.6, 6.8 Hz, 1 H), 7.23 (ddd, *J* = 10.5, 9.4, 2.5 Hz, 1 H), 7.06 (tdd, *J* = 8.5, 2.5, 0.9 Hz, 1 H), 5.21 (dd, *J* = 10.3, 3.4 Hz, 1 H), 4.96 (dd, *J* = 12.0, 3.4 Hz, 1 H), 4.54 (d, *J* = 5.9 Hz, 2 H), 4.30-4.22 (m, 1 H), 4.12 - 3.99 (m, 3 H), 1.36 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.4, 163.7, 161.5 (dd, *J* = 245, 12 Hz), 160.2 (dd, *J* = 247, 12 Hz), 159.2, 153.9, 141.6, 130.8 (dd, *J* = 9.7, 6.1 Hz), 122.4 (dd, *J* = 15.2, 3.6 Hz), 117.1, 114.9, 111.4 (dd, *J* = 21.0, 3.3 Hz), 103.8 (t, *J* = 25.8 Hz), 83.0, 73.0, 54.1, 51.4, 35.8 (d, *J* = 3.0 Hz), 17.9. ^{19}F NMR (DMSO-d_6, 282 MHz) δ -111.9 (d, *J* = 6.9 Hz), -114.5 (d, *J* = 6.9 Hz). HRMS (ES) calcd for $C_{19}H_{17}F_2N_3O_5$ $[M+H]^+$: 406.1215, found 406.1215.

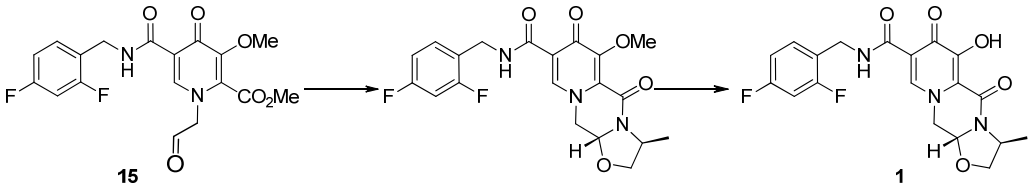


9 **19** **15**

Preparation of methyl 5-((2,4-difluorobenzyl)carbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (19): The 5-acid **9** (3.059 g, 9.70 mmol) and CDI (1.904 g, 11.7 mmol, 1.2 equiv) were dissolved in 30 mL of THF and the resultant mixture was heated to reflux for 2.5 h. A second portion of CDI (516 mg) was added and the

reflux was continued for another 2 h. The mixture was cooled to rt and 2,4-difluorobenzylamine (1.3 mL, 10.9 mmol, 1.1 equiv) was added. The mixture was stirred at rt overnight. The reaction mixture was diluted with TBME (30 mL), and washed with HCl (1 N, 30 mL), NaOH (1 N, 30 mL) and brine (30 mL). The organic layer was concentrated and used directly in the next step. A pure sample of the amide-acetal can be obtained by chromatography: ES-MS: m/z 441 ($M+H^+$). ^1H NMR ($CDCl_3$, 300 MHz) δ 10.38 (t, *J* = 5.7 Hz, 1 H), 8.41 (s, 1 H), 7.41-7.33 (m, 1 H), 6.85-6.75 (m, 2 H), 4.61 (d, *J* = 5.9 Hz, 2 H), 4.49 (t, *J* = 4.8 Hz, 1 H), 4.04 (d, *J* = 4.8 Hz, 2 H), 3.98 (s, 3 H), 3.95 (s, 3H), 3.38 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 163.9, 162.0 (dd, *J* = 248, 12 Hz), 162.0, 160.6 (dd, *J* = 249, 12 Hz), 149.2, 144.4, 134.8, 130.5 (dd, *J* = 9.5, 5.9 Hz), 121.4 (dd, *J* = 15, 3.6 Hz), 119.1, 110.9 (dd, *J* = 21, 3.6 Hz), 103.5 (t, *J* = 25 Hz), 102.5, 60.5, 56.5, 55.4, 53.2, 36.2 (d, *J* = 3.0 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ -111.8 (d, *J* = 6.9 Hz), -114.4 (d, *J* = 6.9 Hz). HRMS (ES) calcd for $C_{20}H_{22}F_2N_2O_7$ $[M+H]^+$: 441.1473, found 441.1475.

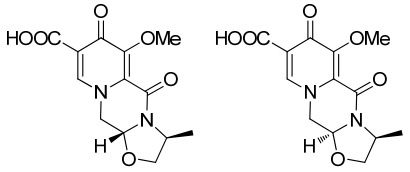
Preparation of methyl 5-((2,4-difluorobenzyl)carbamoyl)-3-methoxy-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-2-carboxylate (15): The crude amide-acetal (**19**) prepared above was dissolved in 25 mL of HCOOH and the mixture was heated to 60 ºC for 3 h. The solvent was removed. The residue was diluted with NaH_2PO_4 (10%, 25 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layer was concentrated and reslurried in 15 mL of TBME overnight. The product was isolated by filtration. The product was shown to contain 70% hydrate (3.541 g, 8.70 mmol, 90%). The hydrate does not affect the subsequent reactions, although a pure sample of the aldehyde can be obtained by chromatography: white solid. ES-MS: m/z 413 ($M+H_2O+H^+$), 395 ($M+H^+$). ^1H NMR ($CDCl_3$, 300MHz) δ 10.35 (t, *J* = 5.7 Hz, 1 H), 9.62 (s, 1 H), 8.42 (s, 1 H), 7.39-7.31 (m, 1 H), 6.87-6.77 (m, 2 H), 4.95 (s, 2 H), 4.62 (d, *J* = 5.9 Hz, 2 H), 4.00 (s, 3 H), 3.94 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.3, 173.5, 164.0, 162.3, 162.2 (dd, *J* = 248, 12 Hz), 160.7 (dd, *J* = 249, 11 Hz), 150.4, 144.7, 133.7, 130.4 (dd, *J* = 9.3, 6.5 Hz), 121.2 (dd, *J* = 15, 3.6 Hz), 119.4, 111.2 (dd, *J* = 21, 3.4 Hz), 103.8 (t, *J* = 25 Hz), 63.6, 60.8, 53.6, 36.5 (d, J = 3.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ -111.5 (d, *J* = 6.9 Hz), -114.3 (d, *J* = 7.6 Hz). HRMS (ES) calcd for $C_{18}H_{16}F_2N_2O_6$ $[M+H]^+$: 395.1055, found 395.1067.



One pot synthesis of 1 from 15 by Mg^{2+} mediated cyclization and demethylation: A mixture of aldehyde **15** (1.3136 g, contained ~70% hydrate, 3.23 mmol), $Mg(OTf)_2$ (1.157 g, 3.59 mmol, 1.1 equiv) and l-alaninol (0.280 mL, 3.60 mmol, 1.1 equiv) in CH_3CN (15 mL) was heated to 60 ºC for 21 h, and NaBr (457 mg, 4.44 mmol, 1.4 equiv) was added. The mixture was heated at 60 ºC for another 15 h and cooled to rt. H_2SO_4 (0.5 M, 15 mL) was added and the mixture as stirred at rt for 7 h. The product was collected by filtration and dried to give a white solid (681.4 mg, 1.68 mmol, 52% yield, 99.3% de).

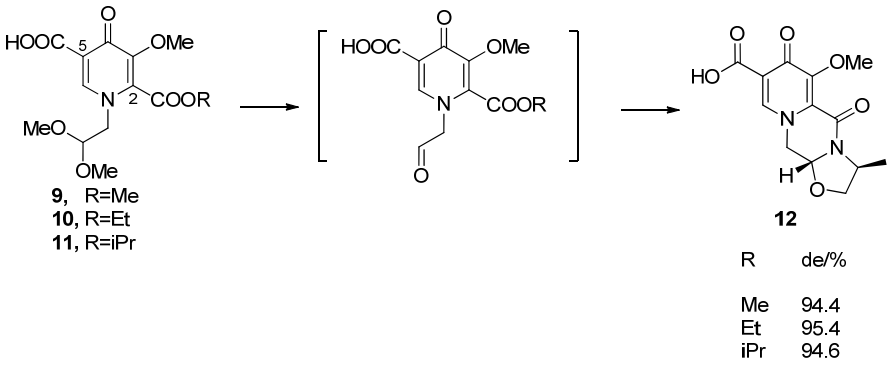
Diastereomeric excess values for the pairs **12a/b**, **13a/b** and **1a/b** were measured by integrations of HPLC peaks. An analytically pure sample of minor isomer **12b** was separated from crude reaction mixture by prep HPLC. Analytically pure samples of minor isomers **13b** and **1b** were synthesized from **12b** using the standard procedure. The de's measured by HPLC ratio were also consistent with those observed by ^{1}H NMR.

The diastereomeric excess for the pair 12a/12b was measured by integrations of HPLC peaks. HPLC: Agilent 1100 series; column: Zorbax Bonus-RP (3.5 μm, 4.6×150 mm); flow rate: 1 mL/min; solvent: 0.05% TFA in water - 0.05% TFA in CH_3CN (gradient, from 88:12 to 5:95). t_R: **12a** 5.1 min, **12b** 4.8 min.



12a **12b**

The HPLC traces of the reaction mixtures for the following transformation (formation of **12** from **9-11,** Scheme 2) are included on page S15 to page S17.



9, R=Me
10, R=Et
11, R=iPr

12

R	de/%
Me	94.4
Et	95.4
iPr	94.6

Data File C:\CHEM32\2\DATA\13JUL2012\GSK1265744_IPM 2012-07-13 13-55-31\040-0401.D
Sample Name: HW212905-049R4

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Acq. Operator   :                                  Seq. Line :   4
                                                    Location : Vial 40
Injection Date  : 13-Jul-12, 15:36:28                    Inj :   1
                                                  Inj Volume : 2 µl
Acq. Method     : GSK1265744_IPM.M
Analysis Method : C:\CHEM32\2\DATA\GSK1265744_IPM 2012-07-10 14-17-06\11JUL2012\
                  GSK1265744_IPM 2012-07-11 10-04-58\GSK1265744_IPM.M
Last changed    : 7/11/2012 1:05:27 PM
                  (modified after loading)
Method Info     : GSK1265744 IPM method using Bonus RP column,150 x 4.6mm, 3.5um

Sample Info     : Me 50C 17h
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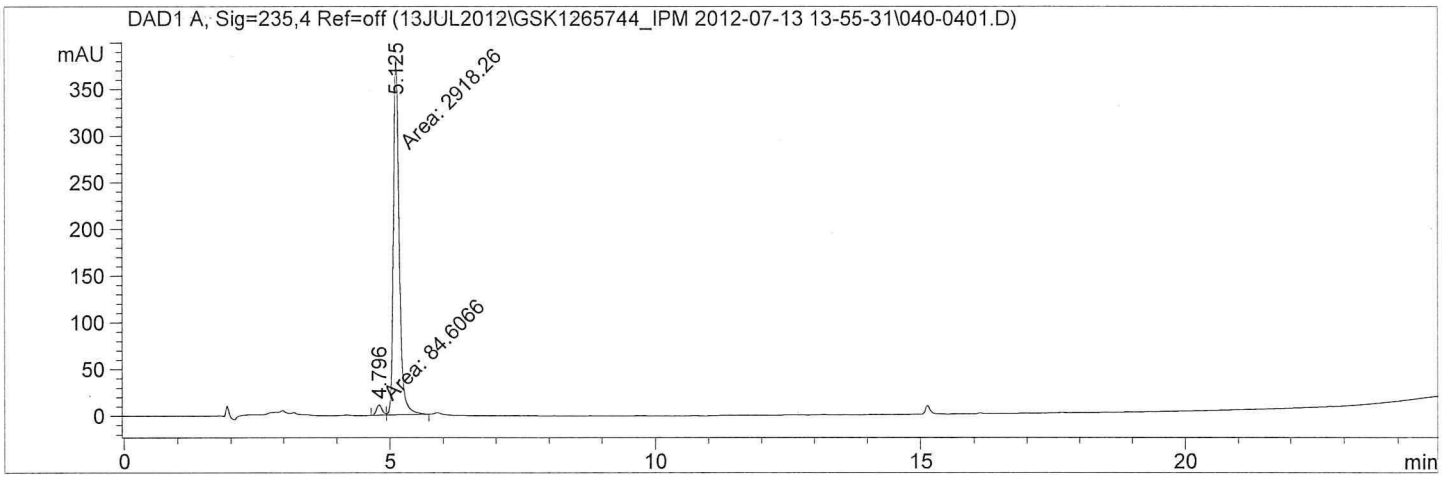


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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=235,4 Ref=off

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   1   4.796 MF    0.1252   84.60658   11.26268   2.8175
   2   5.125 FM    0.1274 2918.26392  381.63705  97.1825

Totals :                   3002.87050  392.89973

==========================================================================
                        *** End of Report ***
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Data File C:\CHEM32\2\DATA\13JUL2012\GSK1265744_IPM 2012-07-13 17-19-11\041-0101.D
Sample Name: HW212905-049R5

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Injection Date  : 7/13/2012 5:25:22 PM                  Inj :   1
                                                  Inj Volume : 2 µl
Acq. Method     : C:\CHEM32\2\DATA\13JUL2012\GSK1265744_IPM 2012-07-13 17-19-11\
                  GSK1265744_IPM.M
Last changed    : 5/16/2012 2:45:41 PM by sg
Analysis Method : C:\CHEM32\2\DATA\GSK1265744_IPM 2012-07-10 14-17-06\11JUL2012\
                  GSK1265744_IPM 2012-07-11 10-04-58\GSK1265744_IPM.M
Last changed    : 7/11/2012 1:05:27 PM
                  (modified after loading)
Method Info     : GSK1265744 IPM method using Bonus RP column,150 x 4.6mm, 3.5um

Sample Info     : Et 50C 17h
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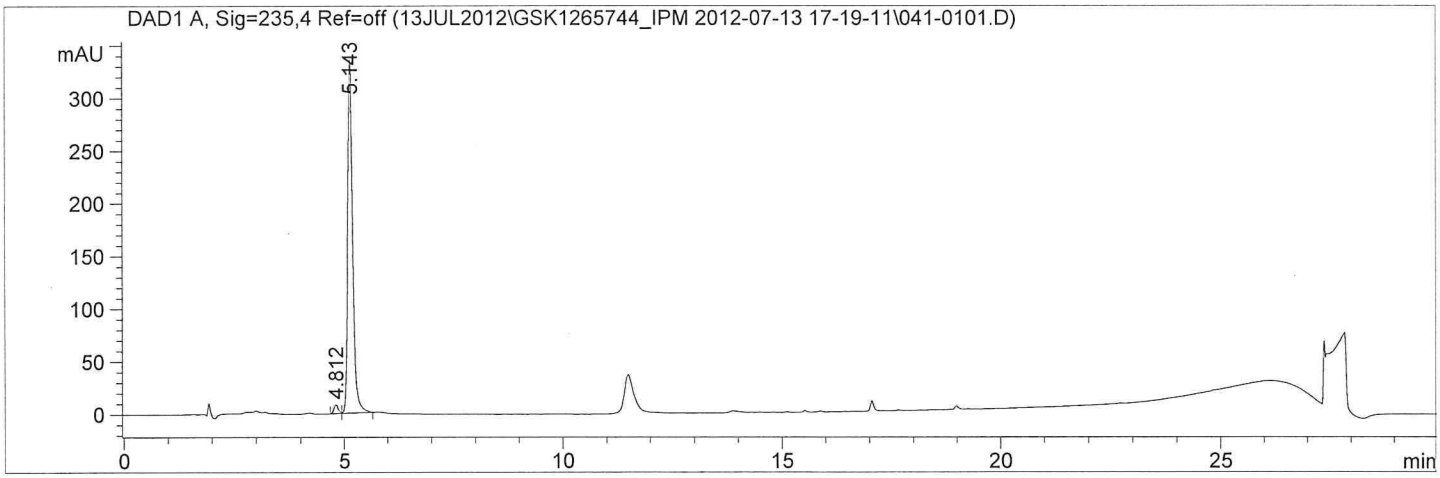


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                          Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=235,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   4.812 BV    0.1130   60.25024    8.26978   2.2895
   2   5.143 VB    0.1172 2571.37158  336.38025  97.7105

Totals :                   2631.62182  344.65003

==========================================================================
                          *** End of Report ***
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Data File C:\CHEM32\2\DATA\13JUL2012\GSK1265744_IPM 2012-07-13 17-19-11\042-0201.D
Sample Name: HW212905-049R6

```
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                                                   Inj Volume : 2 µl
Acq. Method     : C:\CHEM32\2\DATA\13JUL2012\GSK1265744_IPM 2012-07-13 17-19-11\
                  GSK1265744_IPM.M
Last changed    : 5/16/2012 2:45:41 PM by sg
Analysis Method : C:\CHEM32\2\DATA\GSK1265744_IPM 2012-07-10 14-17-06\11JUL2012\
                  GSK1265744_IPM 2012-07-11 10-04-58\GSK1265744_IPM.M
Last changed    : 7/11/2012 1:05:27 PM
                  (modified after loading)
Method Info     : GSK1265744 IPM method using Bonus RP column,150 x 4.6mm, 3.5um

Sample Info     : iPr 50C 17h
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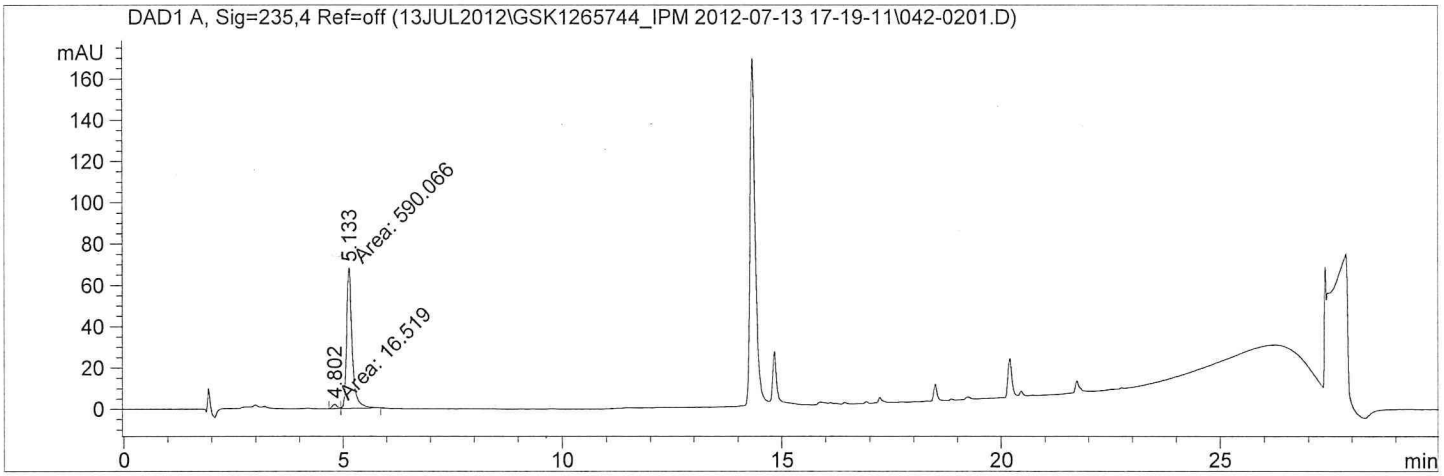


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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=235,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.802 MF    0.1358   16.51898    2.02695   2.7233
   2   5.133 FM    0.1445  590.06592   68.03947  97.2767

Totals :                   606.58489   70.06643

==========================================================================
                        *** End of Report ***
```
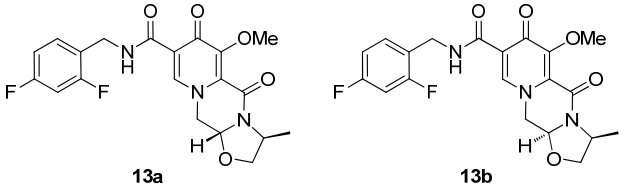
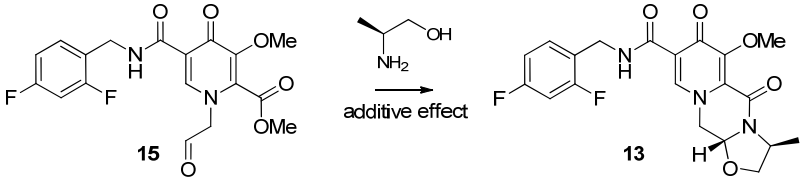

The diastereomeric excess for the pair 13a/13b was measured by integrations of HPLC peaks. HPLC: Agilent 1100 series; column: Waters XTerra MS C_{18} (3.5 μm, 4.6×150 mm); flow rate: 1 mL/min; solvent: 0.1% aqueous NH_4OH-CH_3CN (gradient, from 7:93 to 95:5). t_R: **13a** 12.3 min, **13b**: 12.0 min.



13a **13b**

The HPLC traces of the reaction mixtures for the following transformation (formation of **13** from **15,** Table 3) are included on page S19 to page S26.



15 **13**

Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\011-0401.D
Sample Name: HW212835-011R1

```
==========================================================================
Acq. Operator    : HW                                Seq. Line :   4
Acq. Instrument  : HP1100-4                           Location : Vial 11
Injection Date   : 7/12/2011 5:52:33 PM                    Inj :   1
                                                    Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   011-0401.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 12/23/2009 2:44:03 PM
Method Info      : for HIV Integrase amide isomers

Sample Info      : no additive 60C 16.5h
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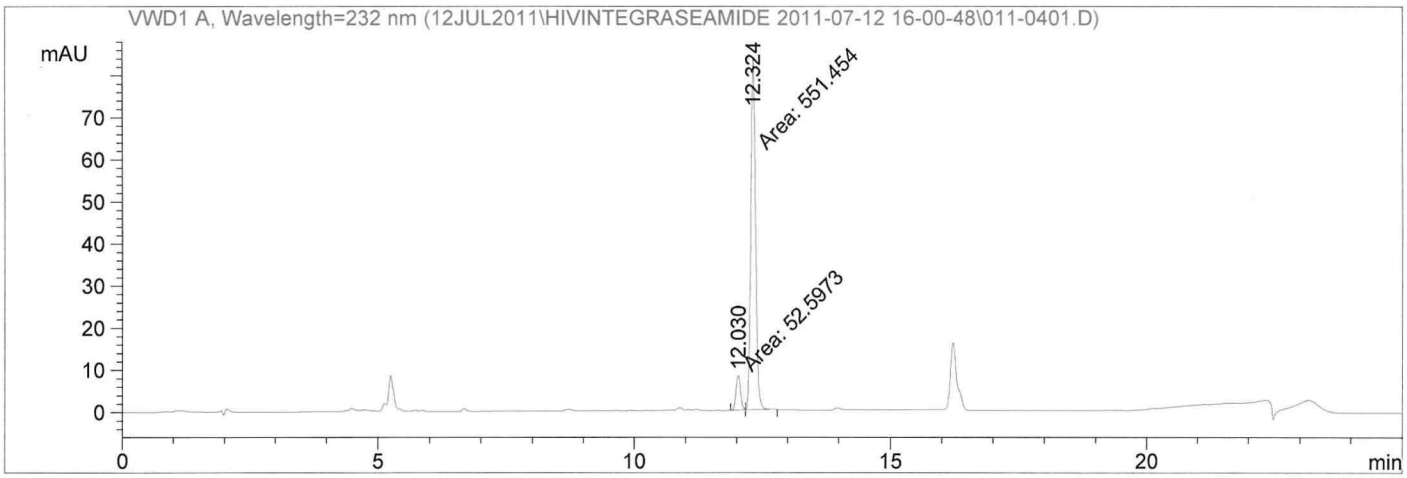


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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.030 MF    0.1062   52.59728    8.25123   8.7074
   2  12.324 FM    0.1103  551.45410   83.32913  91.2926

Totals :                   604.05138   91.58036

==========================================================================
                        *** End of Report ***
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Data File C:\CHEM32\2\DATA\18SEP09\HIVINTEGRASE2 2009-09-18 13-26-33\012-0401.D
Sample Name: HW211473-001R2

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================================================================================
Acq. Operator    : CY                                  Seq. Line :   4
Acq. Instrument  : UM28-009                             Location : Vial 12
Injection Date   : 9/18/2009 2:47:07 PM                      Inj :   1
                                                      Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\2\DATA\18SEP09\HIVINTEGRASE2 2009-09-18 13-26-33\
                   HIVINTEGRASE2.M
Last changed     : 9/18/2009 11:23:52 AM by CY
Analysis Method  : C:\CHEM32\2\DATA\18SEP09\HIVINTEGRASE2 2009-09-18 13-26-33\001-0101.
                   D\DA.M (HIVINTEGRASE2.M)
Last changed     : 9/19/2009 8:24:10 AM by CY
                   (modified after loading)
Method Info      : HIV Integrasr _OMe isomers IPM

Sample Info      : 12h MSOH
```

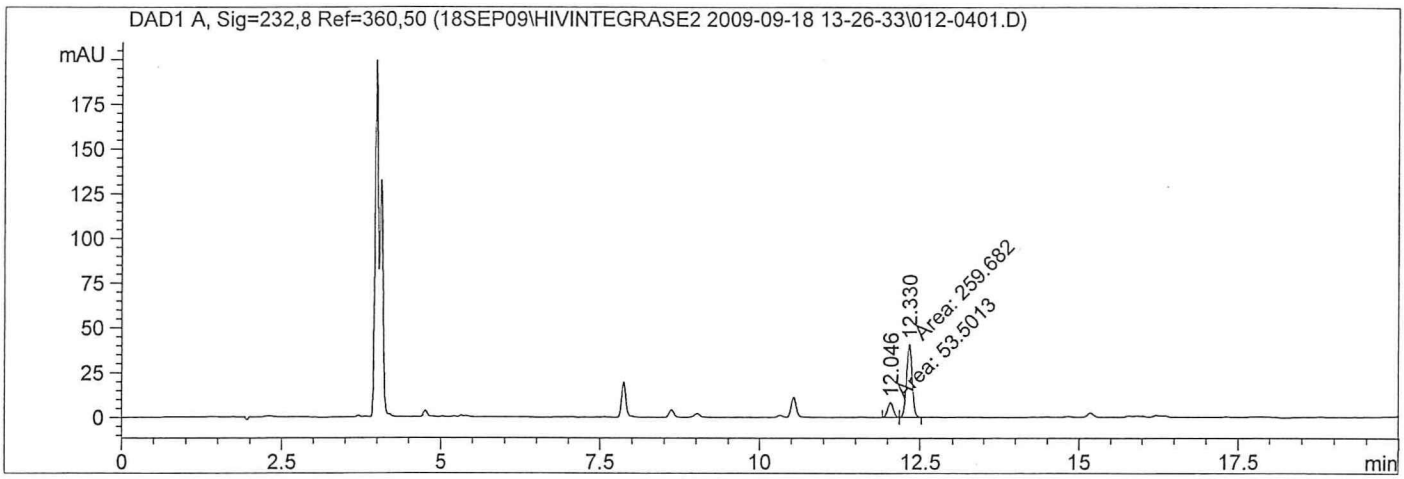


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                          Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=232,8 Ref=360,50

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.046 MF    0.1056   53.50127    8.44706  17.0830
   2  12.330 FM    0.1057  259.68240   40.95332  82.9170

Totals :                   313.18367   49.40037

================================================================================
                          *** End of Report ***
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Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\020-1301.D
Sample Name: HW212835-011R10

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Injection Date   : 7/12/2011 9:49:26 PM                      Inj :   1
                                                      Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   020-1301.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 6/7/2012 8:26:05 AM by LMO
                   (modified after loading)
Method Info      : for HIV Integrase amide isomers

Sample Info      : tfa 60C 16.5h
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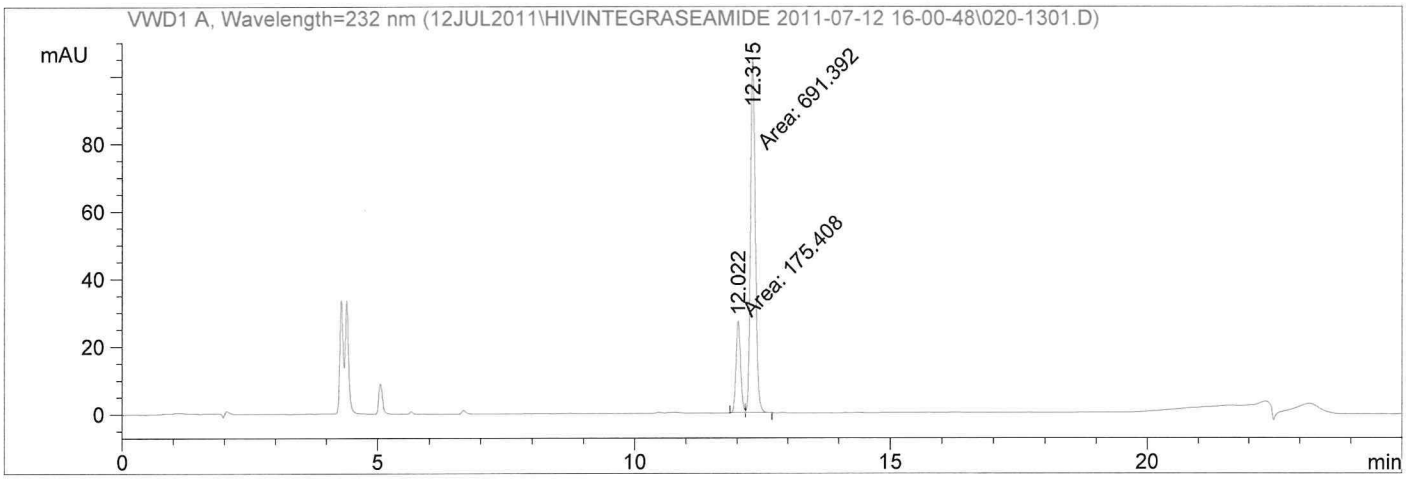


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==========================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.022 MF    0.1080  175.40779   27.07558  20.2363
   2  12.315 FM    0.1101  691.39172  104.67611  79.7637

Totals :                  866.79951  131.75169

==========================================================================
                        *** End of Report ***
```

Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\019-1201.D
Sample Name: HW212835-011R9

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Acq. Instrument  : HP1100-4                         Location : Vial 19
Injection Date   : 7/12/2011 9:23:07 PM                Inj :   1
                                                  Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   019-1201.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 6/7/2012 9:13:04 AM by LMO
                   (modified after loading)
Method Info      : for HIV Integrase amide isomers

Sample Info      : CHCl2COOH 60C 16.5h
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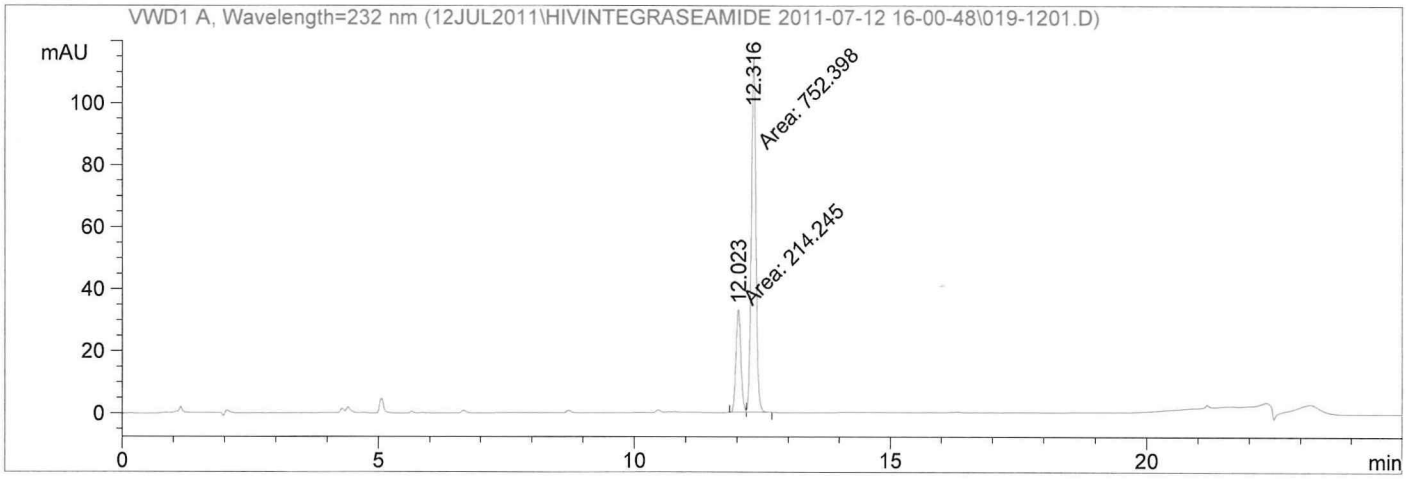


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==========================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.023 MF    0.1077  214.24475   33.14441  22.1638
   2  12.316 FM    0.1100  752.39801  113.94874  77.8362

Totals :                  966.64276  147.09314

==========================================================================
                        *** End of Report ***
```
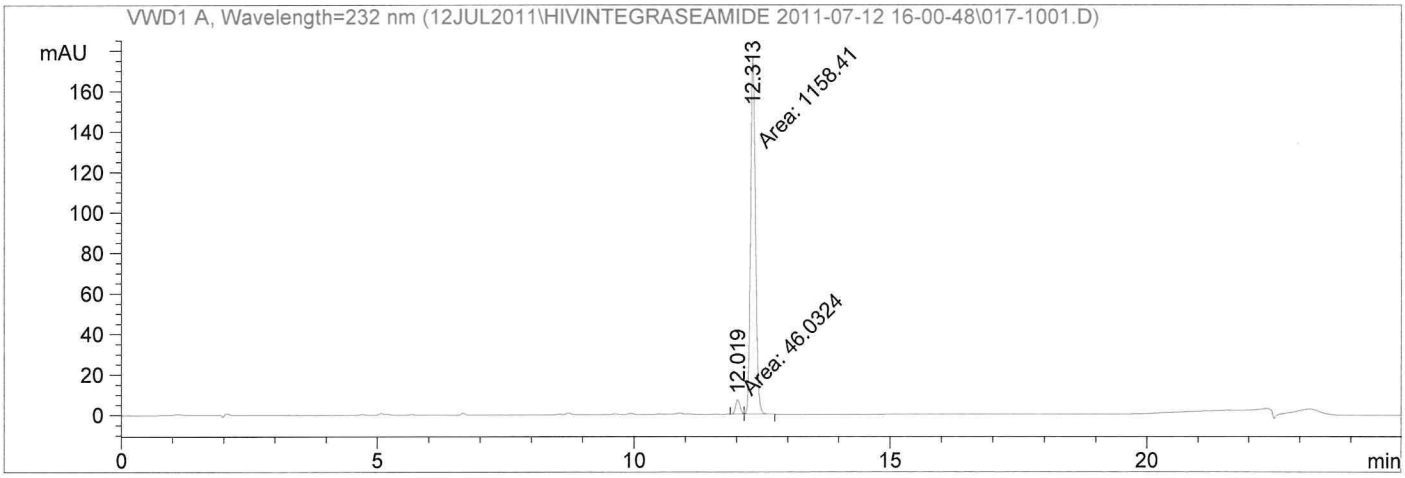

Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\017-1001.D
Sample Name: HW212835-011R7

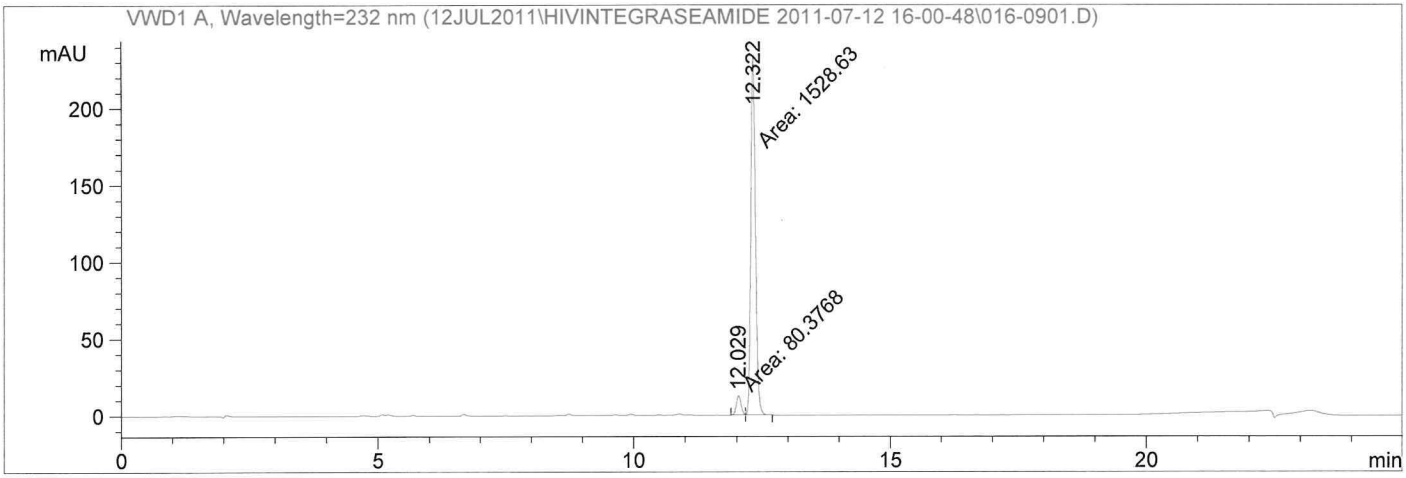
```
==========================================================================
Acq. Operator    : HW                                  Seq. Line :  10
Acq. Instrument  : HP1100-4                             Location : Vial 17
Injection Date   : 7/12/2011 8:30:25 PM                      Inj :   1
                                                      Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   017-1001.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 12/23/2009 2:44:03 PM
Method Info      : for HIV Integrase amide isomers

Sample Info      : HOAc 60C 16.5h
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.019 MF    0.1063   46.03238    7.21466   3.8219
   2  12.313 FM    0.1097 1158.41455  175.94485  96.1781

Totals :                  1204.44693  183.15952

==========================================================================
                        *** End of Report ***
```

Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\016-0901.D
Sample Name: HW212835-011R6

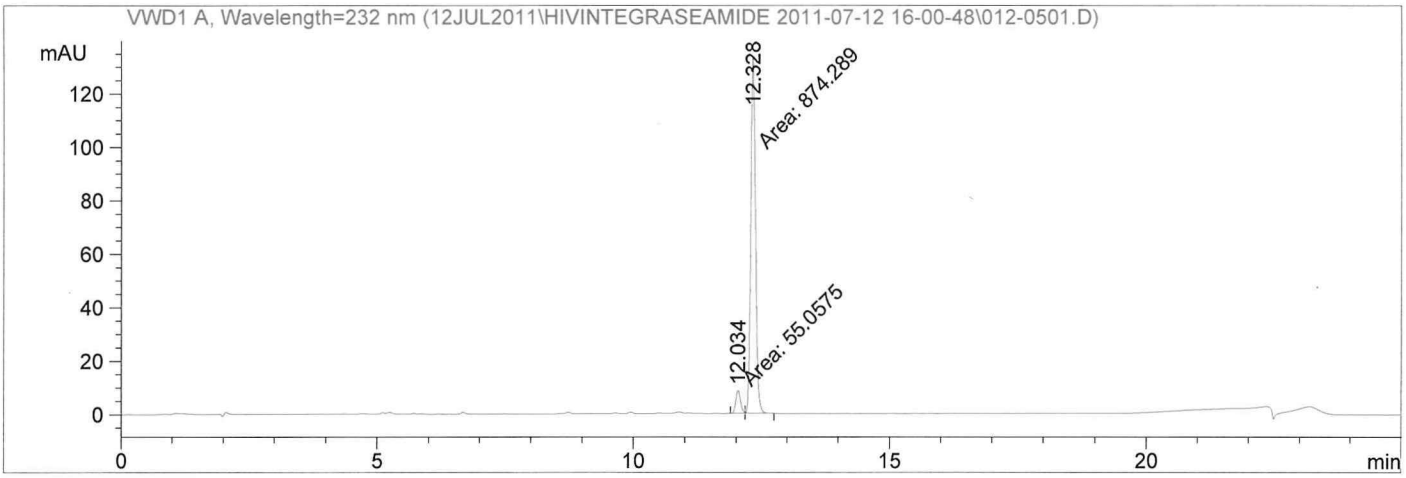
```
==========================================================================
Acq. Operator    : HW                                  Seq. Line :   9
Acq. Instrument  : HP1100-4                             Location : Vial 16
Injection Date   : 7/12/2011 8:04:05 PM                      Inj :   1
                                                      Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   016-0901.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 12/23/2009 2:44:03 PM
Method Info      : for HIV Integrase amide isomers

Sample Info      : IBA 60C 16.5h
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.029 MF    0.1065   80.37677   12.57614   4.9954
   2  12.322 FM    0.1097 1528.63416  232.32300  95.0046

Totals :                  1609.01093  244.89914

==========================================================================
                        *** End of Report ***
```

Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\012-0501.D
Sample Name: HW212835-011R2

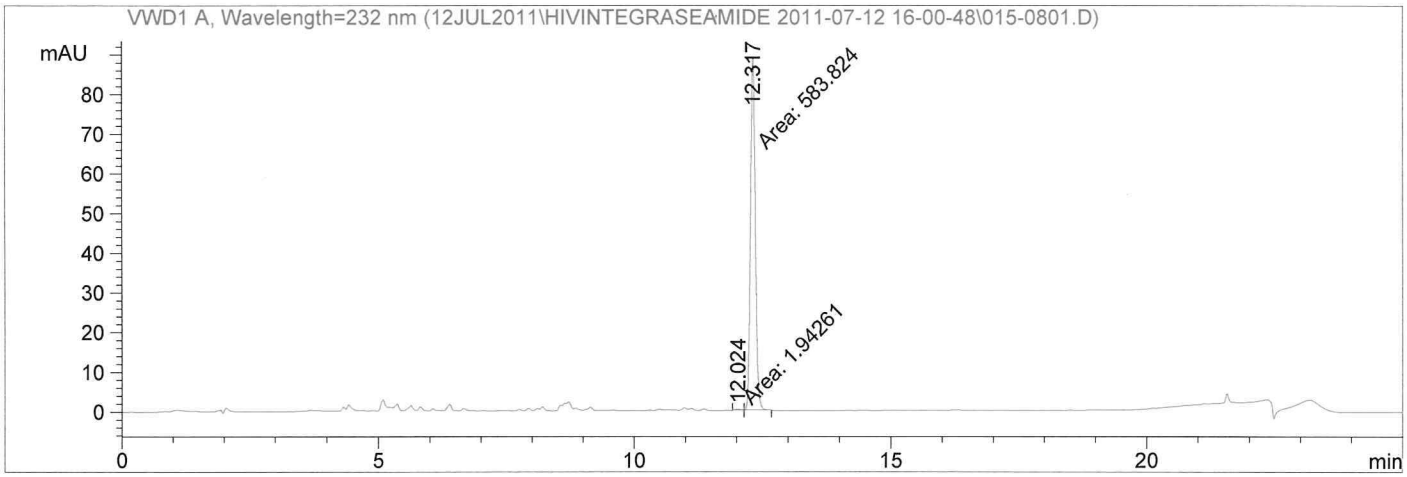
```
==========================================================================
Acq. Operator    : HW                              Seq. Line :   5
Acq. Instrument  : HP1100-4                         Location : Vial 12
Injection Date   : 7/12/2011 6:18:52 PM                Inj :   1
                                                  Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   012-0501.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 6/7/2012 9:18:47 AM by LMO
                   (modified after loading)
Method Info      : for HIV Integrase amide isomers

Sample Info      : pivalic acid 60C 16.5h
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.034 MF    0.1066   55.05747    8.60756   5.9243
   2  12.328 FM    0.1097  874.28882  132.81303  94.0757

Totals :                   929.34629  141.42060

==========================================================================
                        *** End of Report ***
```

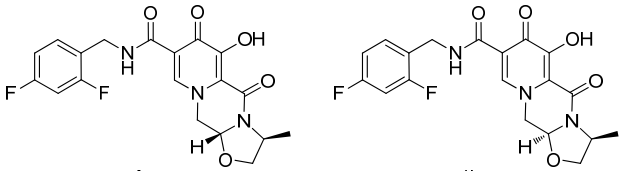
Data File C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\015-0801.D
Sample Name: HW212835-011R5

```
==========================================================================
Acq. Operator    : HW                              Seq. Line :   8
Acq. Instrument  : HP1100-4                         Location : Vial 15
Injection Date   : 7/12/2011 7:37:47 PM                Inj :   1
                                                  Inj Volume : 2 µl
Acq. Method      : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   HIVINTEGRASEAMIDE.M
Last changed     : 12/23/2009 2:44:03 PM
Analysis Method  : C:\CHEM32\1\DATA\12JUL2011\HIVINTEGRASEAMIDE 2011-07-12 16-00-48\
                   015-0801.D\DA.M (HIVINTEGRASEAMIDE.M)
Last changed     : 12/23/2009 2:44:03 PM
Method Info      : for HIV Integrase amide isomers

Sample Info      : Mg(OTf)2 60C 16.5h
```



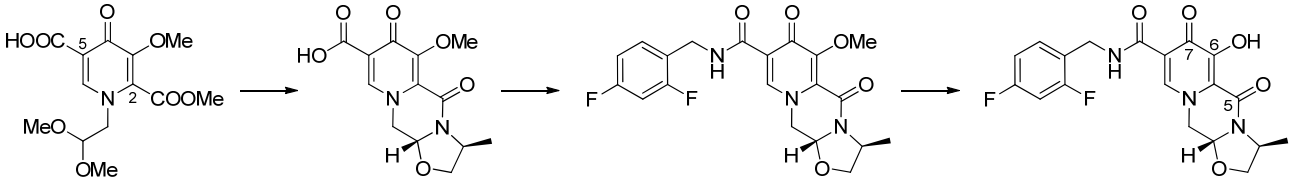

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=232 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.024 MF    0.1030    1.94261 3.14408e-1   0.3316
   2  12.317 FM    0.1098  583.82373   88.58716  99.6684

Totals :                   585.76634   88.90157

==========================================================================
                        *** End of Report ***
```

The diastereomeric excess for the pair 1a/1b was measured by integrations of HPLC peaks. HPLC: Agilent 1100 series; column: Chiralcel OD-RH; flow rate: 1 mL/min; solvent: 0.1% TFA in water - CH_3CN (isocratic, 60:40). t_R: **1a** 8.3 min, **1b** 9.7 min.

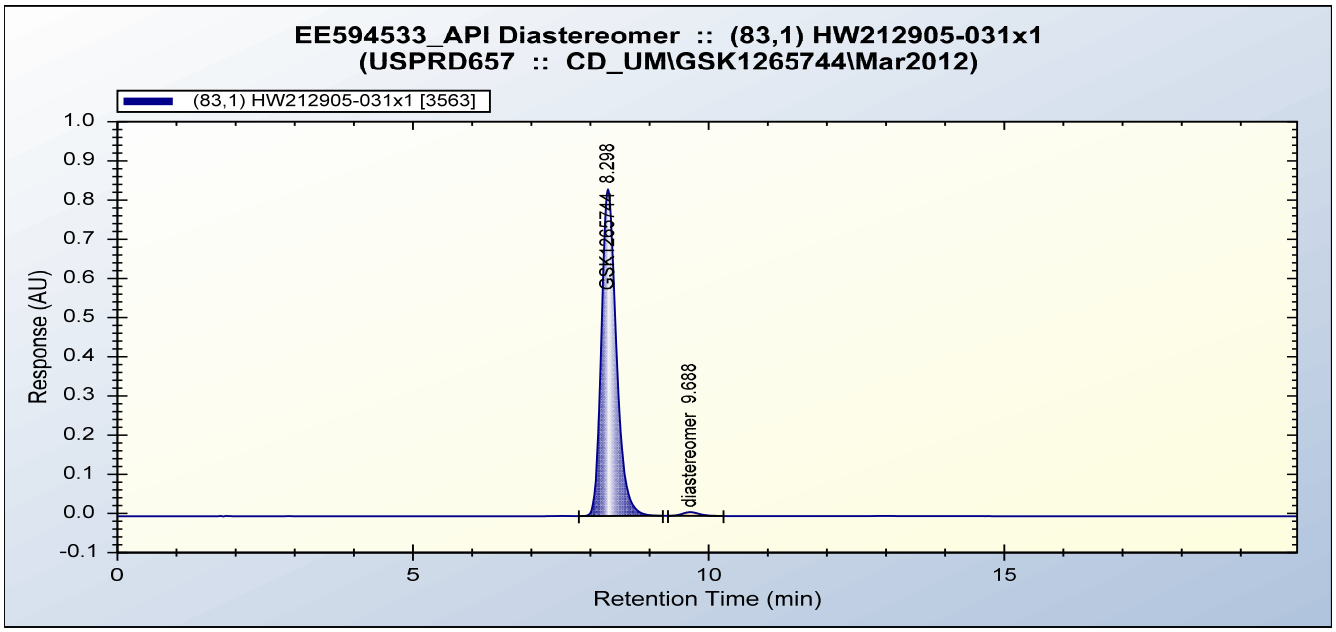


1a 1b

The HPLC trace of a typical batch of **1a** prepared by the sequence in Scheme 2:

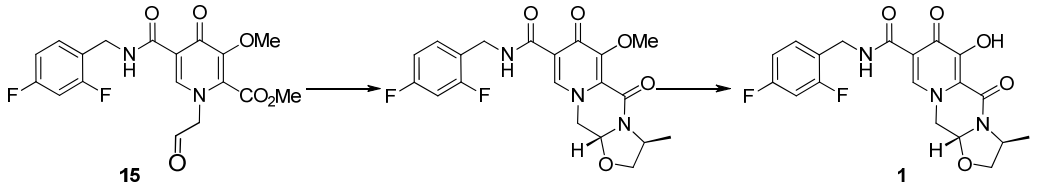


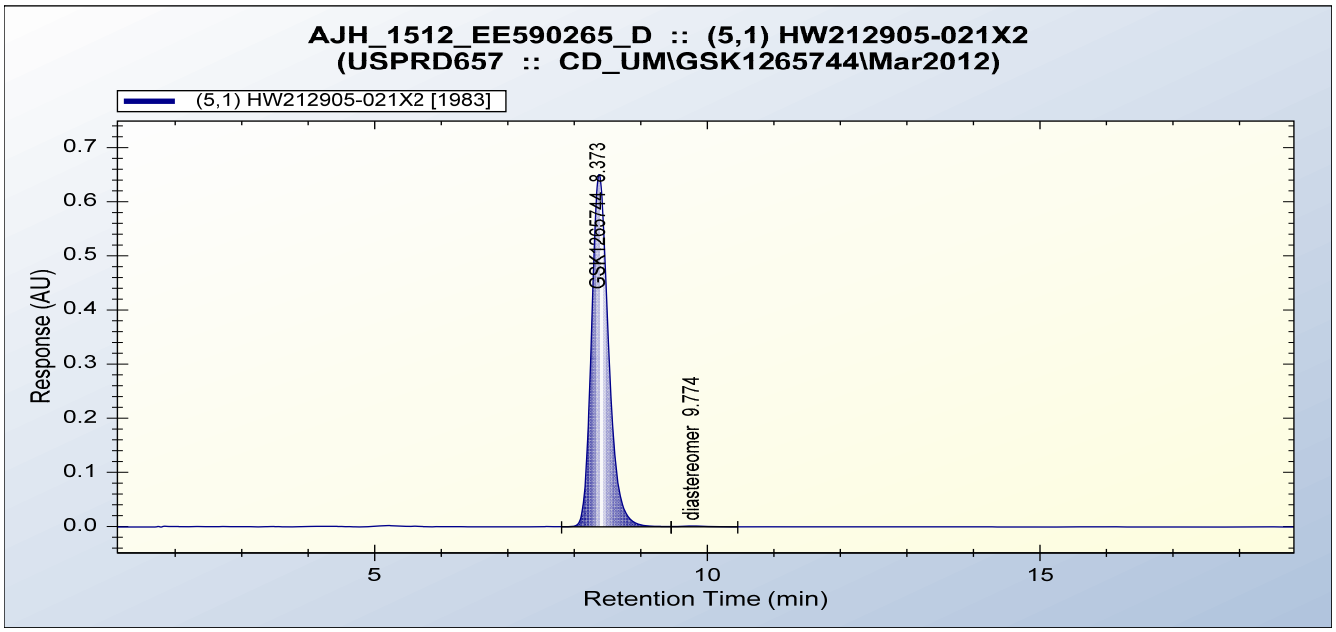
9 **12** **13** **1a**



RT	Name	Height	Area	Area %
8.298	GSK1265744	833004.089	14704851.135	98.705
9.688	diastereomer	9600.641	192879.920	1.295

The HPLC trace of a typical batch of **1a** prepared by the sequence in Scheme 4:





RT	Name	Height	Area	Area %
8.373	GSK1265744	650993.420	11650529.173	99.664
9.774	diastereomer	1538.878	39264.200	0.336

Computational Methods:

To calculate various energetic states of the final product **13** and the isomers of intermediate **16**, the bound bioactive conformation of related drug Dolutegravir, as determined by crystallographic structure 3S3M (PDB code), was used as a strarting template conformation. The Jaguar software suite distributed with Maestro v9.3.5 was used to run *ab initio* density functional energy calculations. The B3LYP/lacvp** basis set was used for full structural optimization. The energy difference between the two diastereomers of **13** by DFT calculation (B3LYP/lacvp**) is 0.7 kcal/mol favoring the desired trans isomer (**13a**); and, the cis isomer **16b** is more stable by 1.0 kcal/mol by DFT calculation (B3LYP/lacvp**).

Jaguar input command file:

```
&gen
basis=lacvp**
igeopt=1
dftname=b3lyp
&
&zmat
```

Optimized XYZ coordinate files:

16a_trans

```
                     3D
 Structure written by MMmdl.
 55 57  0  0  1  0            999 V2000
   -1.5377   -1.4712    2.1446 C   0  0  0  0  0  0
   -1.3380   -2.1879    0.9123 O   0  0  0  0  0  0
   -2.2933   -3.0722    0.5276 C   0  0  0  0  0  0
   -1.8670   -4.3220    0.1465 C   0  0  0  0  0  0
   -0.3901   -4.6251    0.1578 C   0  0  0  0  0  0
   -0.0798   -5.5717    1.0606 O   0  0  0  0  0  0
    1.3067   -5.9763    1.0645 C   0  0  0  0  0  0
    0.4116   -4.0748   -0.5614 O   0  0  0  0  0  0
   -0.5393   -6.2710   -2.5141 N   0  0  0  0  0  0
   -0.1364   -6.9931   -3.7313 C   0  0  2  0  0  0
   -0.5271   -6.3096   -5.0495 C   0  0  0  0  0  0
   -0.8805   -8.3138   -3.4869 C   0  0  0  0  0  0
   -2.0657   -7.9464   -2.7647 O   0  0  0  0  0  0
   -1.9399   -6.6127   -2.2940 C   0  0  1  0  0  0
   -2.3431   -6.6054   -0.8064 C   0  0  0  0  0  0
   -2.7630   -5.2783   -0.3124 N   0  0  0  0  0  0
   -4.0779   -4.9542   -0.3919 C   0  0  0  0  0  0
   -4.5852   -3.7317   -0.0390 C   0  0  0  0  0  0
   -6.0716   -3.5828   -0.2341 C   0  0  0  0  0  0
   -6.7565   -4.5257   -0.6388 O   0  0  0  0  0  0
   -6.5678   -2.3524    0.0570 N   0  0  0  0  0  0
   -7.9690   -2.0343   -0.1136 C   0  0  0  0  0  0
   -8.7193   -1.8300    1.1924 C   0  0  0  0  0  0
   -8.2390   -2.2501    2.4353 C   0  0  0  0  0  0
   -8.9729   -2.0646    3.6082 C   0  0  0  0  0  0
  -10.2123   -1.4446    3.5241 C   0  0  0  0  0  0
  -10.9348   -1.2580    4.6482 F   0  0  0  0  0  0
  -10.7382   -1.0048    2.3148 C   0  0  0  0  0  0
   -9.9711   -1.2126    1.1771 C   0  0  0  0  0  0
  -10.4648   -0.7943   -0.0127 F   0  0  0  0  0  0
   -3.7075   -2.6784    0.4437 C   0  0  0  0  0  0
   -4.0827   -1.5264    0.7542 O   0  0  0  0  0  0
   -0.6201   -0.8998    2.2940 H   0  0  0  0  0  0
```

```
  -1.6666   -2.1729    2.9779 H   0  0  0  0  0  0
  -2.4006   -0.8102    2.0761 H   0  0  0  0  0  0
   1.3851   -6.7368    1.8406 H   0  0  0  0  0  0
   1.9499   -5.1233    1.2894 H   0  0  0  0  0  0
   1.5736   -6.3847    0.0870 H   0  0  0  0  0  0
  -0.3712   -5.2700   -2.5655 H   0  0  0  0  0  0
   0.9483   -7.1497   -3.7105 H   0  0  0  0  0  0
  -1.6129   -6.1961   -5.1362 H   0  0  0  0  0  0
  -0.1820   -6.8951   -5.9088 H   0  0  0  0  0  0
  -0.0727   -5.3155   -5.1212 H   0  0  0  0  0  0
  -0.2814   -9.0059   -2.8821 H   0  0  0  0  0  0
  -1.1774   -8.8170   -4.4127 H   0  0  0  0  0  0
  -2.6497   -5.9684   -2.8481 H   0  0  0  0  0  0
  -1.5222   -6.9821   -0.1982 H   0  0  0  0  0  0
  -3.1981   -7.2731   -0.6906 H   0  0  0  0  0  0
  -4.7560   -5.7148   -0.7621 H   0  0  0  0  0  0
  -5.8912   -1.6579    0.3804 H   0  0  0  0  0  0
  -8.0704   -1.1342   -0.7300 H   0  0  0  0  0  0
  -8.4160   -2.8617   -0.6736 H   0  0  0  0  0  0
  -7.2658   -2.7277    2.4804 H   0  0  0  0  0  0
  -8.5986   -2.3908    4.5721 H   0  0  0  0  0  0
 -11.7056   -0.5207    2.2596 H   0  0  0  0  0  0
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 1 33  1  0  0  0
 1 34  1  0  0  0
 1 35  1  0  0  0
 2  3  1  0  0  0
 3  4  2  0  0  0
 3 31  1  0  0  0
 4  5  1  0  0  0
 4 16  1  0  0  0
 5  6  1  0  0  0
 5  8  2  0  0  0
 6  7  1  0  0  0
 7 36  1  0  0  0
 7 37  1  0  0  0
 7 38  1  0  0  0
 9 10  1  0  0  0
 9 14  1  0  0  0
 9 39  1  0  0  0
10 11  1  0  0  0
10 12  1  0  0  0
10 40  1  0  0  0
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11 42  1  0  0  0
11 43  1  0  0  0
12 13  1  0  0  0
12 44  1  0  0  0
12 45  1  0  0  0
13 14  1  0  0  0
14 15  1  0  0  0
14 46  1  0  0  0
15 16  1  0  0  0
15 47  1  0  0  0
15 48  1  0  0  0
16 17  1  0  0  0
```

```
 17 18  2  0  0  0
 17 49  1  0  0  0
 18 19  1  0  0  0
 18 31  1  0  0  0
 19 20  2  0  0  0
 19 21  1  0  0  0
 21 22  1  0  0  0
 21 50  1  0  0  0
 22 23  1  0  0  0
 22 51  1  0  0  0
 22 52  1  0  0  0
 23 24  1  0  0  0
 23 29  2  0  0  0
 24 25  2  0  0  0
 24 53  1  0  0  0
 25 26  1  0  0  0
 25 54  1  0  0  0
 26 27  1  0  0  0
 26 28  2  0  0  0
 28 29  1  0  0  0
 28 55  1  0  0  0
 29 30  1  0  0  0
 31 32  2  0  0  0
M  END

> <s_j_Task>
Optimization

> <s_j_QM_Basis>
lacvp**

> <s_j_QM_Method>
DFT(b3lyp)

> <i_j_Number_of_canonical_orbitals>
562

> <r_j_Gas_Phase_Energy>
-1629.34808634685

> <r_j_HOMO>
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> <r_j_LUMO>
-0.0526456820245516

$$$$
16b_cis
                    3D
 Structure written by MMmdl.
 55 57  0  0  1  0            999 V2000
   -1.4311   -1.4620    2.2271 C   0  0  0  0  0  0
   -1.2404   -2.1397    0.9714 O   0  0  0  0  0  0
   -2.2103   -2.9995    0.5627 C   0  0  0  0  0  0
   -1.8007   -4.2450    0.1572 C   0  0  0  0  0  0
   -0.3267   -4.5651    0.1588 C   0  0  0  0  0  0
```

```
 -0.0071   -5.4554    1.1120 O   0  0  0  0  0  0
  1.3787   -5.8648    1.1232 C   0  0  0  0  0  0
  0.4630   -4.0748   -0.6157 O   0  0  0  0  0  0
 -0.5040   -6.2525   -2.5486 N   0  0  0  0  0  0
 -0.2018   -6.9300   -3.8161 C   0  0  1  0  0  0
  1.2948   -7.0824   -4.0573 C   0  0  0  0  0  0
 -0.9549   -8.2460   -3.5792 C   0  0  0  0  0  0
 -2.0628   -7.8979   -2.7364 O   0  0  0  0  0  0
 -1.9051   -6.5549   -2.2977 C   0  0  1  0  0  0
 -2.2955   -6.5139   -0.8100 C   0  0  0  0  0  0
 -2.7026   -5.1767   -0.3345 N   0  0  0  0  0  0
 -4.0112   -4.8297   -0.4278 C   0  0  0  0  0  0
 -4.5029   -3.6068   -0.0542 C   0  0  0  0  0  0
 -5.9811   -3.4220   -0.2800 C   0  0  0  0  0  0
 -6.6708   -4.3289   -0.7526 O   0  0  0  0  0  0
 -6.4659   -2.2009    0.0640 N   0  0  0  0  0  0
 -7.8483   -1.8389   -0.1654 C   0  0  0  0  0  0
 -8.7127   -1.8340    1.0857 C   0  0  0  0  0  0
 -8.3417   -2.4383    2.2890 C   0  0  0  0  0  0
 -9.1813   -2.4321    3.4045 C   0  0  0  0  0  0
-10.4163   -1.8054    3.3029 C   0  0  0  0  0  0
-11.2399   -1.7907    4.3712 F   0  0  0  0  0  0
-10.8360   -1.1870    2.1304 C   0  0  0  0  0  0
 -9.9662   -1.2212    1.0495 C   0  0  0  0  0  0
-10.3554   -0.6277   -0.1044 F   0  0  0  0  0  0
 -3.6164   -2.5822    0.4752 C   0  0  0  0  0  0
 -3.9793   -1.4356    0.8182 O   0  0  0  0  0  0
 -0.5144   -0.8920    2.3871 H   0  0  0  0  0  0
 -1.5513   -2.1900    3.0389 H   0  0  0  0  0  0
 -2.2965   -0.8017    2.1853 H   0  0  0  0  0  0
  1.4611   -6.5875    1.9341 H   0  0  0  0  0  0
  2.0256   -5.0037    1.3026 H   0  0  0  0  0  0
  1.6373   -6.3195    0.1642 H   0  0  0  0  0  0
 -0.3041   -5.2556   -2.5660 H   0  0  0  0  0  0
 -0.6587   -6.4112   -4.6787 H   0  0  0  0  0  0
  1.7671   -7.5944   -3.2133 H   0  0  0  0  0  0
  1.7737   -6.1054   -4.1762 H   0  0  0  0  0  0
  1.4844   -7.6573   -4.9700 H   0  0  0  0  0  0
 -0.3190   -8.9775   -3.0629 H   0  0  0  0  0  0
 -1.3329   -8.6938   -4.5042 H   0  0  0  0  0  0
 -2.6023   -5.9053   -2.8650 H   0  0  0  0  0  0
 -1.4721   -6.8856   -0.2010 H   0  0  0  0  0  0
 -3.1514   -7.1769   -0.6742 H   0  0  0  0  0  0
 -4.6951   -5.5705   -0.8266 H   0  0  0  0  0  0
 -5.7850   -1.5330    0.4310 H   0  0  0  0  0  0
 -7.8889   -0.8499   -0.6337 H   0  0  0  0  0  0
 -8.2532   -2.5562   -0.8859 H   0  0  0  0  0  0
 -7.3714   -2.9197    2.3501 H   0  0  0  0  0  0
 -8.8919   -2.9022    4.3377 H   0  0  0  0  0  0
-11.8007   -0.6994    2.0599 H   0  0  0  0  0  0
1  2  1  0  0  0
1 33  1  0  0  0
1 34  1  0  0  0
1 35  1  0  0  0
2  3  1  0  0  0
3  4  2  0  0  0
```

```
  3 31  1  0  0  0
  4  5  1  0  0  0
  4 16  1  0  0  0
  5  6  1  0  0  0
  5  8  2  0  0  0
  6  7  1  0  0  0
  7 36  1  0  0  0
  7 37  1  0  0  0
  7 38  1  0  0  0
  9 10  1  0  0  0
  9 14  1  0  0  0
  9 39  1  0  0  0
 10 11  1  0  0  0
 10 12  1  0  0  0
 10 40  1  0  0  0
 11 41  1  0  0  0
 11 42  1  0  0  0
 11 43  1  0  0  0
 12 13  1  0  0  0
 12 44  1  0  0  0
 12 45  1  0  0  0
 13 14  1  0  0  0
 14 15  1  0  0  0
 14 46  1  0  0  0
 15 16  1  0  0  0
 15 47  1  0  0  0
 15 48  1  0  0  0
 16 17  1  0  0  0
 17 18  2  0  0  0
 17 49  1  0  0  0
 18 19  1  0  0  0
 18 31  1  0  0  0
 19 20  2  0  0  0
 19 21  1  0  0  0
 21 22  1  0  0  0
 21 50  1  0  0  0
 22 23  1  0  0  0
 22 51  1  0  0  0
 22 52  1  0  0  0
 23 24  1  0  0  0
 23 29  2  0  0  0
 24 25  2  0  0  0
 24 53  1  0  0  0
 25 26  1  0  0  0
 25 54  1  0  0  0
 26 27  1  0  0  0
 26 28  2  0  0  0
 28 29  1  0  0  0
 28 55  1  0  0  0
 29 30  1  0  0  0
 31 32  2  0  0  0
M  END

> <s_j_Task>
Optimization
```

> <s_j_QM_Basis>
lacvp**

> <s_j_QM_Method>
DFT(b3lyp)

> <i_j_Number_of_canonical_orbitals>
562

> <r_j_Gas_Phase_Energy>
-1629.34969116351

> <r_j_HOMO>
-0.226462171532978

> <r_j_LUMO>
-0.0503860678562342

$$$$
13a_trans

```
                     3D
 Structure written by MMmdl.
 49 52  0  0  1  0            999 V2000
   -0.9409   -0.8190    1.9605 C   0  0  0  0  0  0
   -0.6649   -1.7673    0.9123 O   0  0  0  0  0  0
   -1.5880   -2.6640    0.5342 C   0  0  0  0  0  0
   -1.1594   -3.9264    0.1670 C   0  0  0  0  0  0
    0.2802   -4.3601    0.2415 C   0  0  0  0  0  0
    1.2254   -3.5888    0.1610 O   0  0  0  0  0  0
    0.4616   -5.7110    0.4503 N   0  0  0  0  0  0
    1.7975   -6.3243    0.3397 C   0  0  1  0  0  0
    2.7060   -6.0312    1.5307 C   0  0  0  0  0  0
    1.4103   -7.8086    0.1920 C   0  0  0  0  0  0
    0.0957   -7.8028   -0.3758 O   0  0  0  0  0  0
   -0.5776   -6.7137    0.2078 C   0  0  2  0  0  0
   -1.6043   -6.1632   -0.7684 C   0  0  0  0  0  0
   -2.0909   -4.8729   -0.2668 N   0  0  0  0  0  0
   -3.4068   -4.5777   -0.3184 C   0  0  0  0  0  0
   -3.9106   -3.3521    0.0310 C   0  0  0  0  0  0
   -5.4022   -3.2129   -0.1043 C   0  0  0  0  0  0
   -6.0995   -4.1808   -0.4354 O   0  0  0  0  0  0
   -5.8994   -1.9800    0.1464 N   0  0  0  0  0  0
   -7.3256   -1.6964    0.0338 C   0  0  0  0  0  0
   -8.1023   -1.9376    1.3154 C   0  0  0  0  0  0
   -7.4610   -2.3355    2.4970 C   0  0  0  0  0  0
   -8.1683   -2.5438    3.6796 C   0  0  0  0  0  0
   -9.5454   -2.3506    3.6708 C   0  0  0  0  0  0
  -10.2445   -2.5503    4.8071 F   0  0  0  0  0  0
  -10.2318   -1.9579    2.5292 C   0  0  0  0  0  0
   -9.4843   -1.7584    1.3740 C   0  0  0  0  0  0
  -10.1436   -1.3742    0.2555 F   0  0  0  0  0  0
   -3.0190   -2.2869    0.4488 C   0  0  0  0  0  0
   -3.3886   -1.1248    0.7168 O   0  0  0  0  0  0
    0.0441   -0.4864    2.2932 H   0  0  0  0  0  0
   -1.4666   -1.2951    2.7939 H   0  0  0  0  0  0
   -1.5330    0.0164    1.5917 H   0  0  0  0  0  0
```

```
   2.2719   -5.9526   -0.5771 H   0  0  0  0  0  0
   2.2415   -6.3581    2.4667 H   0  0  0  0  0  0
   2.9050   -4.9601    1.5900 H   0  0  0  0  0  0
   3.6603   -6.5564    1.4146 H   0  0  0  0  0  0
   1.4001   -8.3069    1.1731 H   0  0  0  0  0  0
   2.0643   -8.3637   -0.4828 H   0  0  0  0  0  0
  -1.0595   -7.0112    1.1547 H   0  0  0  0  0  0
  -2.4524   -6.8407   -0.8732 H   0  0  0  0  0  0
  -1.1229   -6.0399   -1.7451 H   0  0  0  0  0  0
  -4.0846   -5.3502   -0.6643 H   0  0  0  0  0  0
  -5.2290   -1.2702    0.4439 H   0  0  0  0  0  0
  -7.4398   -0.6560   -0.2758 H   0  0  0  0  0  0
  -7.7237   -2.3392   -0.7554 H   0  0  0  0  0  0
  -6.3836   -2.4677    2.4734 H   0  0  0  0  0  0
  -7.6745   -2.8514    4.5948 H   0  0  0  0  0  0
 -11.3051   -1.8126    2.5362 H   0  0  0  0  0  0
 1 31  1  0  0  0
 1 32  1  0  0  0
 1 33  1  0  0  0
 1  2  1  0  0  0
 2  3  1  0  0  0
 3  4  2  0  0  0
 3 29  1  0  0  0
 4  5  1  0  0  0
 4 14  1  0  0  0
 5  6  2  0  0  0
 5  7  1  0  0  0
 7  8  1  0  0  0
 7 12  1  0  0  0
 8 34  1  0  0  0
 8  9  1  0  0  0
 8 10  1  0  0  0
 9 35  1  0  0  0
 9 36  1  0  0  0
 9 37  1  0  0  0
10 38  1  0  0  0
10 39  1  0  0  0
10 11  1  0  0  0
11 12  1  0  0  0
12 40  1  0  0  0
12 13  1  0  0  0
13 41  1  0  0  0
13 42  1  0  0  0
13 14  1  0  0  0
14 15  1  0  0  0
15 43  1  0  0  0
15 16  2  0  0  0
16 17  1  0  0  0
16 29  1  0  0  0
17 18  2  0  0  0
17 19  1  0  0  0
19 44  1  0  0  0
19 20  1  0  0  0
20 45  1  0  0  0
20 46  1  0  0  0
20 21  1  0  0  0
```

```
 21 22  1  0  0  0
 21 27  2  0  0  0
 22 47  1  0  0  0
 22 23  2  0  0  0
 23 48  1  0  0  0
 23 24  1  0  0  0
 24 25  1  0  0  0
 24 26  2  0  0  0
 26 49  1  0  0  0
 26 27  1  0  0  0
 27 28  1  0  0  0
 29 30  2  0  0  0
M  END

> <s_j_Task>
Optimization

> <s_j_QM_Basis>
lacvp**

> <s_j_QM_Method>
DFT(b3lyp)

> <i_j_Number_of_canonical_orbitals>
514

> <r_j_Gas_Phase_Energy>
-1513.62603483402

> <r_j_HOMO>
-0.224289255692887

> <r_j_LUMO>
-0.0645261793384926

$$$$
```

13b_cis

```
                    3D
 Structure written by MMmdl.
 49 52  0  0  1  0            999 V2000
   -0.9530   -1.4425    2.0943 C   0  0  0  0  0  0
   -0.7156   -2.3081    0.9682 O   0  0  0  0  0  0
   -1.6825   -3.1110    0.5011 C   0  0  0  0  0  0
   -1.3239   -4.3628    0.0304 C   0  0  0  0  0  0
    0.0975   -4.8691    0.0634 C   0  0  0  0  0  0
    1.0754   -4.1374    0.1304 O   0  0  0  0  0  0
    0.2145   -6.2368    0.0178 N   0  0  0  0  0  0
    1.4876   -6.9524   -0.1734 C   0  0  2  0  0  0
    2.1963   -6.5737   -1.4772 C   0  0  0  0  0  0
    0.9627   -8.4025   -0.1664 C   0  0  0  0  0  0
   -0.3653   -8.3063   -0.7069 O   0  0  0  0  0  0
   -0.9168   -7.1471   -0.1391 C   0  0  2  0  0  0
   -1.9338   -6.5078   -1.0658 C   0  0  0  0  0  0
   -2.3122   -5.2077   -0.4914 N   0  0  0  0  0  0
   -3.6048   -4.8200   -0.5277 C   0  0  0  0  0  0
   -4.0342   -3.5949   -0.0904 C   0  0  0  0  0  0
```

```
  -5.5113   -3.3472   -0.2311 C   0  0  0  0  0  0
  -6.2680   -4.2418   -0.6302 O   0  0  0  0  0  0
  -5.9250   -2.1001    0.0912 N   0  0  0  0  0  0
  -7.3269   -1.7121   -0.0084 C   0  0  0  0  0  0
  -8.1206   -1.9630    1.2600 C   0  0  0  0  0  0
  -8.5893   -3.2422    1.5908 C   0  0  0  0  0  0
  -9.3034   -3.4785    2.7647 C   0  0  0  0  0  0
  -9.5489   -2.4089    3.6189 C   0  0  0  0  0  0
 -10.2398   -2.6213    4.7578 F   0  0  0  0  0  0
  -9.1062   -1.1221    3.3400 C   0  0  0  0  0  0
  -8.3953   -0.9333    2.1602 C   0  0  0  0  0  0
  -7.9561    0.3163    1.8796 F   0  0  0  0  0  0
  -3.0825   -2.6295    0.4227 C   0  0  0  0  0  0
  -3.3773   -1.4678    0.7741 O   0  0  0  0  0  0
   0.0436   -1.2128    2.4762 H   0  0  0  0  0  0
  -1.5317   -1.9545    2.8694 H   0  0  0  0  0  0
  -1.4764   -0.5371    1.7931 H   0  0  0  0  0  0
   2.1466   -6.7608    0.6797 H   0  0  0  0  0  0
   1.5788   -6.8415   -2.3408 H   0  0  0  0  0  0
   3.1481   -7.1096   -1.5533 H   0  0  0  0  0  0
   2.3986   -5.5021   -1.4997 H   0  0  0  0  0  0
   0.9273   -8.8134    0.8526 H   0  0  0  0  0  0
   1.5346   -9.0746   -0.8082 H   0  0  0  0  0  0
  -1.3792   -7.3699    0.8393 H   0  0  0  0  0  0
  -2.8319   -7.1198   -1.1584 H   0  0  0  0  0  0
  -1.4815   -6.3796   -2.0555 H   0  0  0  0  0  0
  -4.3284   -5.5174   -0.9349 H   0  0  0  0  0  0
  -5.2124   -1.4625    0.4486 H   0  0  0  0  0  0
  -7.3667   -0.6519   -0.2660 H   0  0  0  0  0  0
  -7.7655   -2.2858   -0.8283 H   0  0  0  0  0  0
  -8.3696   -4.0592    0.9104 H   0  0  0  0  0  0
  -9.6677   -4.4666    3.0231 H   0  0  0  0  0  0
  -9.3043   -0.2979    4.0141 H   0  0  0  0  0  0
 1  2  1  0  0  0
 1 31  1  0  0  0
 1 32  1  0  0  0
 1 33  1  0  0  0
 2  3  1  0  0  0
 3  4  2  0  0  0
 3 29  1  0  0  0
 4  5  1  0  0  0
 4 14  1  0  0  0
 5  6  2  0  0  0
 5  7  1  0  0  0
 7  8  1  0  0  0
 7 12  1  0  0  0
 8  9  1  0  0  0
 8 10  1  0  0  0
 8 34  1  0  0  0
 9 35  1  0  0  0
 9 36  1  0  0  0
 9 37  1  0  0  0
10 11  1  0  0  0
10 38  1  0  0  0
10 39  1  0  0  0
11 12  1  0  0  0
```

```
 12 13  1  0  0  0
 12 40  1  0  0  0
 13 14  1  0  0  0
 13 41  1  0  0  0
 13 42  1  0  0  0
 14 15  1  0  0  0
 15 16  2  0  0  0
 15 43  1  0  0  0
 16 17  1  0  0  0
 16 29  1  0  0  0
 17 18  2  0  0  0
 17 19  1  0  0  0
 19 20  1  0  0  0
 19 44  1  0  0  0
 20 21  1  0  0  0
 20 45  1  0  0  0
 20 46  1  0  0  0
 21 22  1  0  0  0
 21 27  2  0  0  0
 22 23  2  0  0  0
 22 47  1  0  0  0
 23 24  1  0  0  0
 23 48  1  0  0  0
 24 25  1  0  0  0
 24 26  2  0  0  0
 26 27  1  0  0  0
 26 49  1  0  0  0
 27 28  1  0  0  0
 29 30  2  0  0  0
M  END

> <s_j_Task>
Optimization

> <s_j_QM_Basis>
lacvp**

> <s_j_QM_Method>
DFT(b3lyp)

> <i_j_Number_of_canonical_orbitals>
515

> <r_j_Gas_Phase_Energy>
-1513.62490790329

> <r_j_HOMO>
-0.223543935955167

> <r_j_LUMO>
-0.0643165746209451

$$$$
```