Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information-I

Design, Synthesis and Biological Evaluation of Optically Pure Functionalized Spiro[5,5]undecane-1,5,9-triones as HIV-1 Inhibitors

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Materials and Methods for Synthetic Studies:

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by

irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

The enantiomeric excess (*ee*) of the *DTCDA* products was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column and hexane/2-propanol as the eluent. Retention times and solvent ratios are indicated in the respective entries.

Materials: All solvents and commercially available chemicals were used as received. Highly functionalized chiral aldehydes **3a-f** was prepared according to literature procedures.[1] First time these chiral aldehydes **3a-f** were utilized as starting material for chiral dienophile source in proline-catalyzed *DTCDA* reactions.

General Experimental Procedures for the Cascade DTCDA Reactions:

Procedure A: *L-/D-Proline-catalyzed cascade DTCDA reactions*:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the enone **2**, 0.3 mmol of chiral aldehyde **3** and 0.3 mmol of CH-acid **4** was added 1.0 mL of CH_3CN, and then the catalyst L-/D-proline **7a**/**7b** (0.06 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1-4. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure products **1** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure B: *L-Proline-catalyzed TCRA reaction*:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the spiro ketone *cis*-(−)-**1ncb**, 0.3 mmol of CH-acid **4b** and 0.3 mmol of Hantzsch ester was added 1.0 mL of solvent, and then the catalyst L-proline **7a** (0.06 mmol) was added and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot product (−)-**9ncb** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure C: ***Synthesis of ethyl*** **(4'*S*,7*R*,9*R*,11*S*)-9-cyano-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-1,5-dioxo-2,4-dioxa-spiro[5.5]undec-9-yl carbonate *[(–)-8jca]*:**

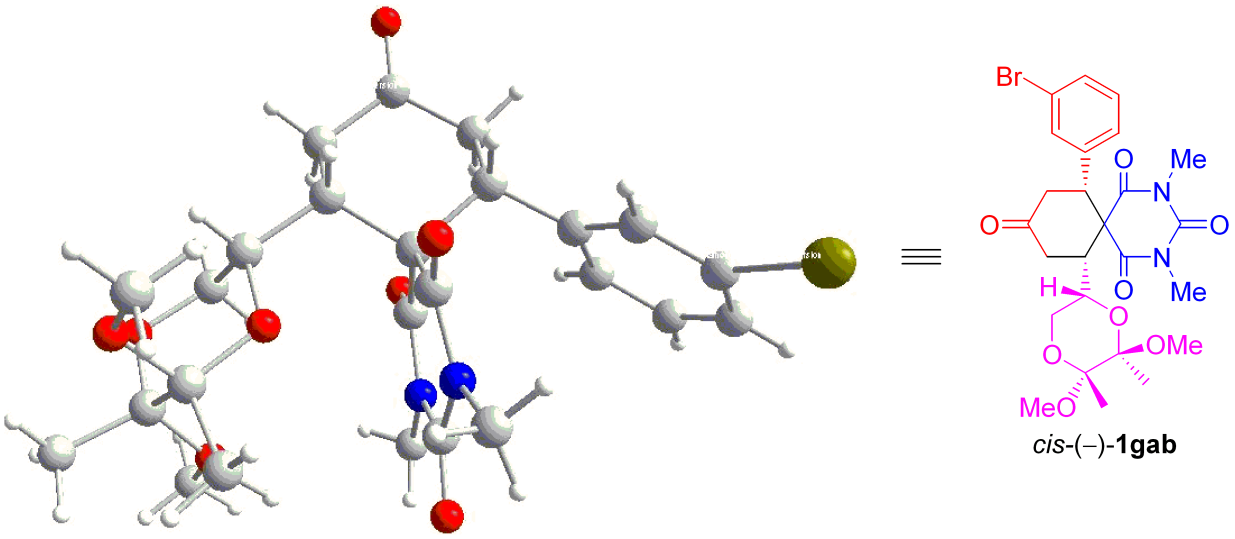
To a stirring solution of 0.5 mmol diisopropylamine in 3 mL of THF, *n*-BuLi (2.0 M, 0.22 mL) was added at 0 °C and stirring continued for 15 min. The reaction mixture was cooled to –78 °C, 0.3 mmol of spiro ketone *cis*-(–)-**1jca** in 3 mL of THF was added, following 15 min additional stirring, 0.45 mmol of ethyl cyanoformate was added and the reaction was allowed to stir at –78 °C for 2 h. The crude reaction mixture was diluted with ether then quenched with aqueous NH_4Cl solution and aqueous layer was extracted with ether. The combined organic layers dried over Na_2SO_4, filtered and concentrated. Pure product **(–)-8jca** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure D: ***Synthesis of 4-phenyl-2-trimethyl-siloxybuta-1,3-diene:***

To the mixture of benzylidene acetone (1.0 mmol) and chlorotrimethylsilane (1.2 mmol) in dichloromethane (1.0 mL) was added DBU (1.4 mmol) and stirred at 25 °C for 1 h. Then the mixture was diluted with pentane and washed successively with dilute HCl and $NaHCO_3$ solutions and dried over Na_2SO_4, evaporation of the solvent furnished the 4-phenyl-2-trimethyl-siloxybuta-1,3-diene **5a** (80% yield).

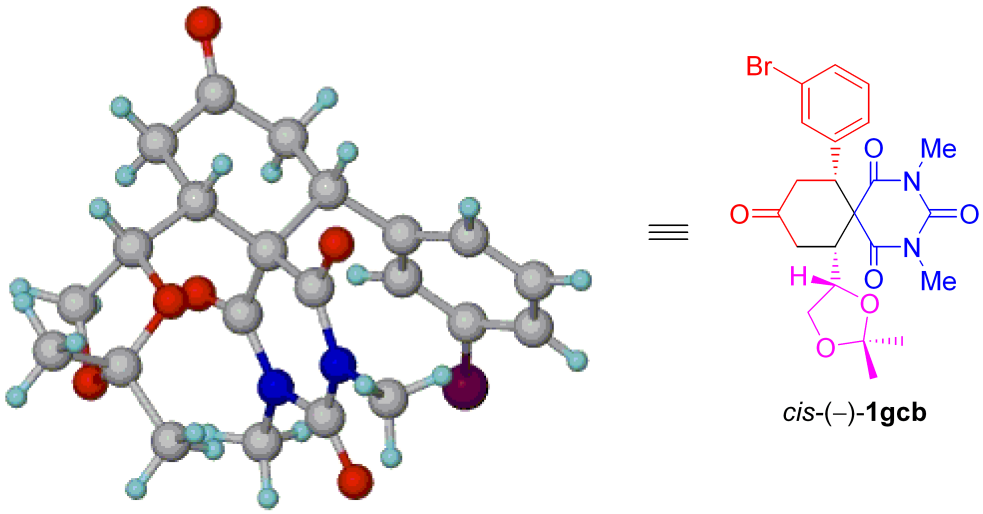
Procedure E: ***Diels-Alder reaction of 4-phenyl-2-trimethyl-siloxybuta-1,3-diene with preformed olefin 6ca:***

Mixture of 4-phenyl-2-trimethyl-siloxybuta-1,3-diene **5a** (0.6 mmol) and (4'*S*)-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6ca** (0.3 mmol) in dry CH_3CN (1 mL) was stirred at 25 °C for 24 h. The crude reaction mixture worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane. Pure products *cis*-**1aca** and *cis*-**1'aca** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



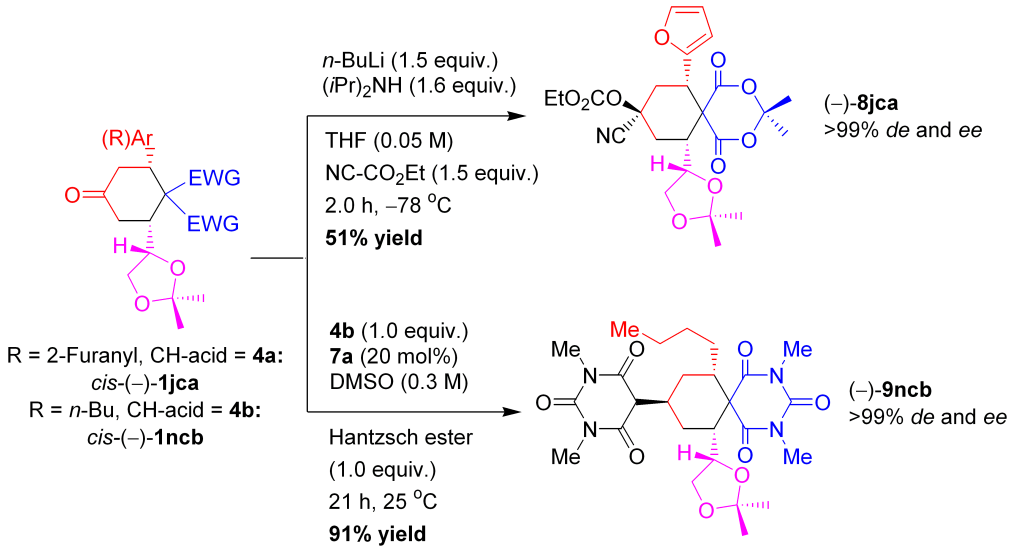
cis-(–)-**1gab**

Figure S1. X-Ray crystal structure of chiral spiro compound *cis*-(–)-**1gab**.



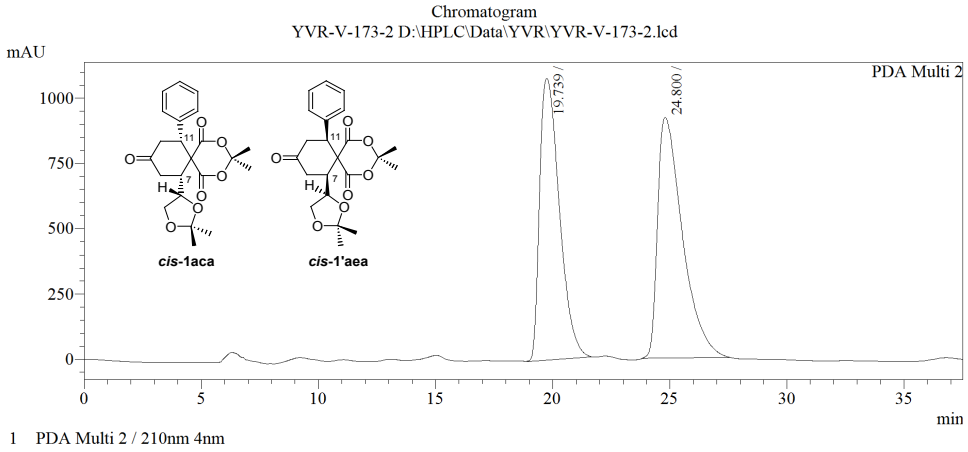
cis-(–)-**1gcb**

Figure S2. X-Ray crystal structure of chiral spiro compound *cis*-(–)-**1gcb**.



Scheme S1: Synthetic application of chiral DTCDA products.

HPLC of Racemic Products of *cis*-1aca and *cis*-1'aea:



1 PDA Multi 2 / 210nm 4nm

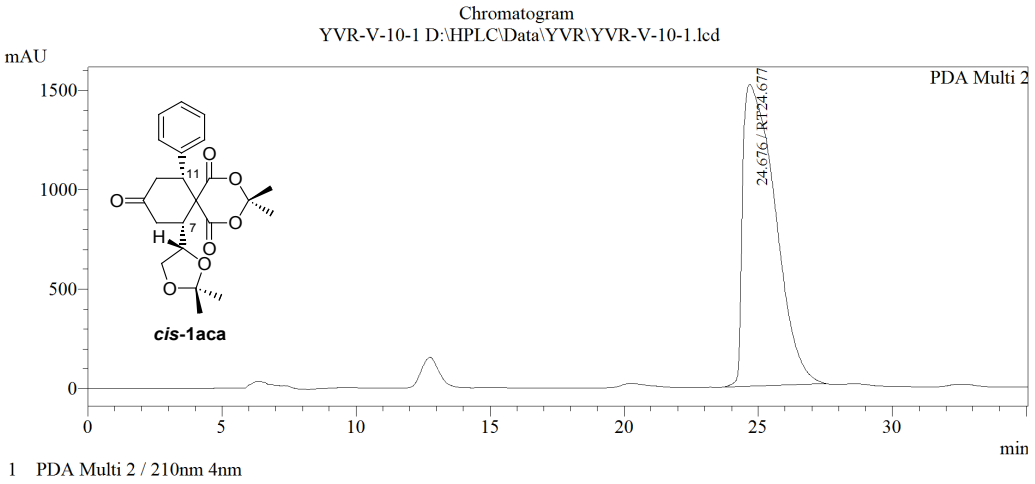
DAICEL CHIRALCEL OD-H COLUMN, Hexane/ i-PrOH =90:10, Flow Rate 0.5 mL/Min
λ_{max} 210nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1		19.739	63039789	1079369	48.052	53.914
2		24.800	68151349	922660	51.948	46.086
Total			131191138	2002028	100.000	100.000

Chiral-***cis*-1aca:**



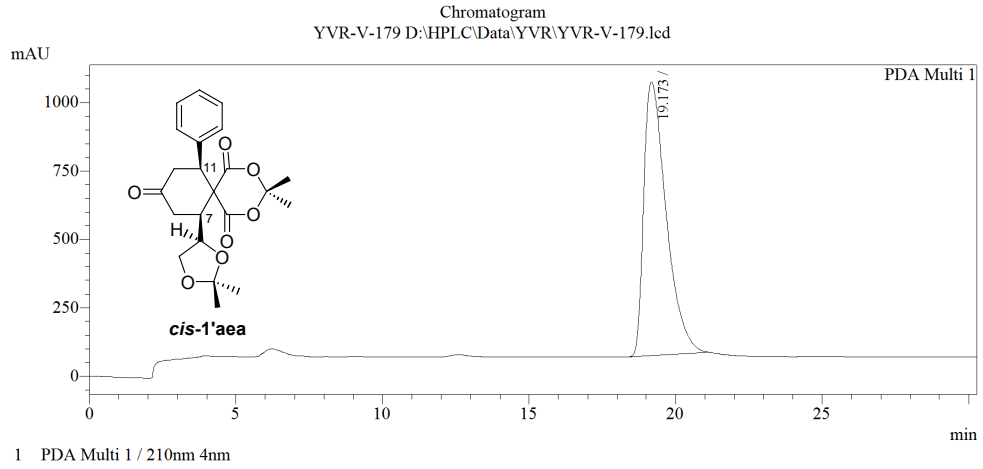
DAICEL CHIRALCEL OD-H COLUMN, Hexane/ i-PrOH =90:10, Flow Rate 0.5 mL/Min
λ_{max} 210nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT24.677	24.676	127325430	1518767	100.000	100.000
Total			127325430	1518767	100.000	100.000

Chiral-***cis*-1'aea:**



DAICEL CHIRALCEL OD-H COLUMN, Hexane/ i-PrOH =90:10, Flow Rate 0.5 mL/Min
λ_{max} 210nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1		19.173	53105028	1000292	100.000	100.000
Total			53105028	1000292	100.000	100.000

Materials and Methods for Biological Studies:

Compounds - AZT- 3'-azido-2', 3'-dideoxythymidine, a known HIV-1 reverse transcriptase inhibitor was taken as a reference compound.[2] MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was purchased from Himedia. ELISA p24 kit was purchased from Advanced BioSciences Labratories, USA.

Cells and viruses - 293T cells were used for production of HIV-1 virus NL4-3. SupT1 cells - a T cell lymphoblastic lymphoma, was used for infection assays. SupT1 cells were subcultured twice a week at a density of 3 X 10^5 cells/ml in RPMI 1640 medium with 10% FBS, 100 U of penicillin per ml, and 100 µg of streptomycin per ml. Pro-viral DNA pNL4-3 and 293T cells were used for virus production as explained in protocol by Kutner R.H et al.[3] The virus batches were quantified for p24 levels by ELISA and stored appropriately in -80ºC until used.

Cytotoxicity assay - The synthesized compounds were checked for their cytotoxic effect on the cells by MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. In brief SupT1 0.2x10^6 (200ul each) were seeded into 96 well plates. Increasing concentration of these synthesized compounds were added and incubated for 18 h at 37 °C, 5% CO_2. Next day, 150µl media was removed and 20µl of MTT was added to each well and incubated for 4 h at 37 °C in dark. Thereafter 100µl of DMSO was used to thoroughly dissolve the purple formazan crystals. The plate was read immediately at 570 nm and background absorbance values at 650 were subtracted from the data obtained. Each experiment was done in triplicate and the data are represented as an average with standard deviations.

Inhibition assay- Anti HIV activities by the test compounds were assayed as described earlier.[4] In brief SupT1 0.2x10^6 (200ul each) were seeded into 96 well plates in RPMI1640 without FBS and antibiotic. Virus NL4-3, at a concentration of 1ng/ml equivalent of p24, without or with increasing concentrations of these compounds [***cis*-1aaa**, ***cis*-1aca**, ***cis*-1jca** and **AZT**] was added simultaneously to the cells. The cells were then incubated for 5 h at 37 °C in 5% CO_2 incubator. The infected cells were then washed twice with PBS and re-suspended in fresh media with 10% FBS. After 96 hours, cells were collected for MTT assays for cell viability and the supernatant were collected for p24 ELISA to check for virus titers. The experimental set-up with no

compound added was taken as zero inhibition and percentage inhibition was calculated for the rest.

Results for biological studies:

The optically pure compounds *cis*-1aca and *cis*-1jca are less cytotoxic than anti-retroviral molecule AZT:

After successful high-yielding synthesis of optically pure single isomer of functionalized spiroundecanes **1** library, we further showed interest to screen them as anti-retroviral properties. A cell culture based HIV infection model was used for this purpose and differences in HIV turnovers in presence and absence of these compounds were monitored. For all the assays, AZT, a known anti-HIV compound, was used as a positive control. Before checking for anti-HIV activities, the compounds were checked for cytotoxicity in the Sup-T1 cells by MTT assay. The assay is based on the reduction of yellow color tetrazolium salt MTT by a mitochondrial dehydrogenase of viable or live cells, that converts this compound to a purple coloured formazan product that is measured spectrometrically at a wavelength of 570nm.[5] The amount of formazan formed is proportional to the number of living cells. For each set of experiment, the cells with mock treatment with equal volume of absolute ethanol were checked for viability by MTT assay and these values were considered as 100% viable background for each experiment. The percentage viability of the cells treated with different concentration of the three compounds, ***cis*-1aaa**, ***cis*-1aca**, ***cis*-1jca** and the control compound **AZT** were calculated against the 100% viability of cells (**Fig. S3**). The cells were monitored for 16 h to check for cell death. It was interesting to observe that **AZT**, the molecule that is used for retroviral treatment, was more cytotoxic than ***cis*-1aca** and ***cis*-1jca**. The compound ***cis*-1jca** had the least cytotoxicity in our conditions, with almost 90% alive even after 16 h of treatment. 100 pico molar (pm), 100 nano molar (nm) and 10 micro molar (μm) concentrations were selected for subsequent assays to check the anti-HIV properties of these compounds.

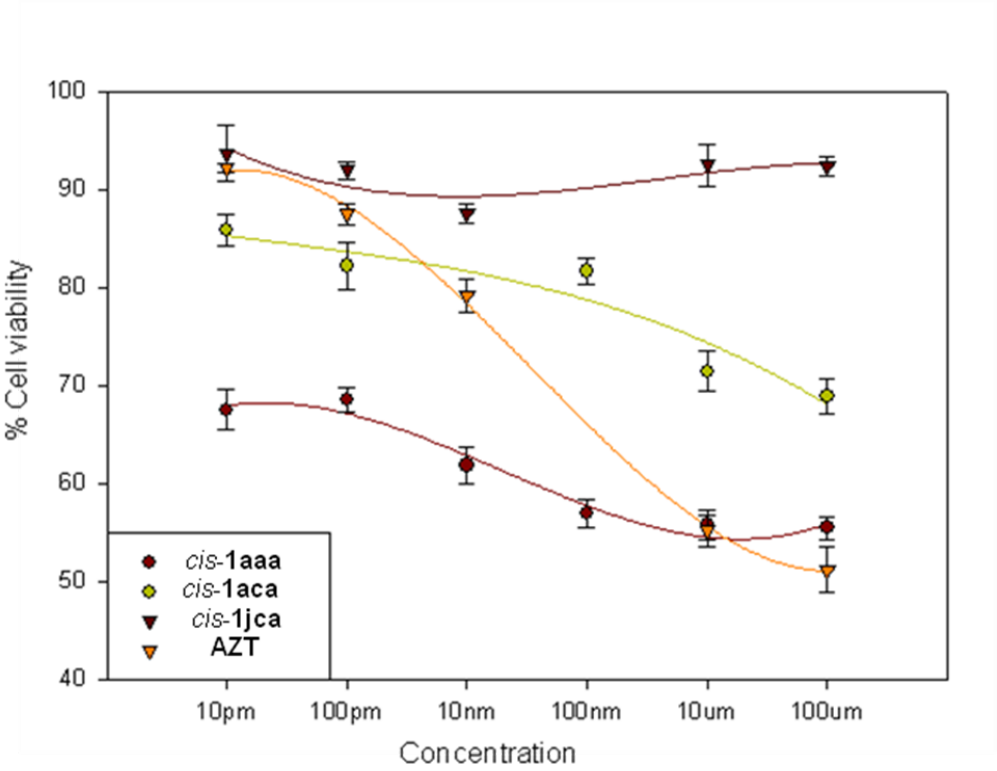


Figure S3: Concentration dependent cytotoxicity expressed as percentage cell-viability of the synthesized compounds. **AZT** was used as a reference compound. Higher percentage cell-viability refers to less cytotoxicity.

The chiral compounds *cis*-1aca and *cis*-1jca could decrease HIV-1 turnover:

The anti-HIV-1 activity of the compounds were tested for 100pm, 100nm and 10μm concentrations as described in materials and methods. Cells without any compound treatment, but infected with NL4-3 viruses were taken as background control. As virus infection was expected to increase cell death, the cells were treated with different compounds along with infection for 5 hours only, which was sufficient for viral entry and drug adsorption/absorption. The percentage inhibition (decrease in HIV-1 [here, NL4-3] turnover) as a function of concentration was plotted (**Fig. S4**). Higher percentage inhibition indicates enhanced decrease in HIV-1 turnover and therefore is indicative of more effective anti-retroviral molecule. We observed that all the three test compounds reduced the NL4-3 turnover on an average by 45%, which was comparable with **AZT**, the drug in use for HIV-1 treatment. The compound ***cis*-1aaa**, even though decreased NL4-3 turnover by 50%, the cells at the end of the experiments was only

69% ± 5% viable. The chiral compound ***cis*-1aca** could reduce NL4-3 turnover rate by as much as 58% at a concentration of 10μm, which was marginally more than the anti-retroviral affect of **AZT** at that concentration. In both the cases a cell viability of about 77% ± 8% were maintained. The compound ***cis*-1jca** at a concentration of 100nm showed comparatively improved anti-retroviral activity over **AZT**. The percentage inhibition of ***cis*-1jca** was 56% ± 0.4% with cell viability of 82% ± 5.6%, while that of **AZT** at 100nm is 51.7% ± 3% with almost equal cell viability. The % inhibition of NL4-3 turnover by ***cis*-1jca** increased to 59% ± 1% at 10μm, which was the highest amongst all the four compounds used. From these experiments, it could be concluded that the newly synthesized chiral compounds, especially ***cis*-1aca** and ***cis*-1jca** are bioactive molecules that bear the property of decreasing HIV-1 turnover upon 5 h of treatment, while maintaining more than 75% cell viability.

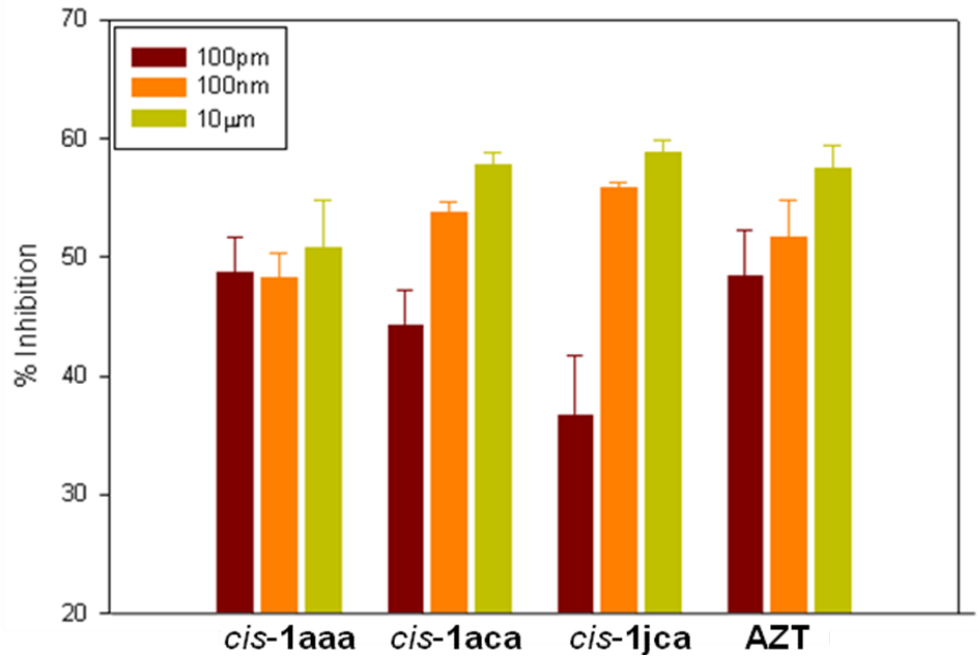
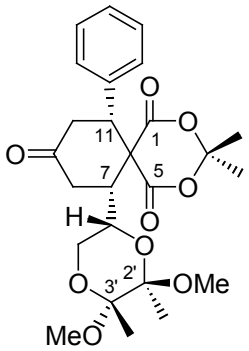


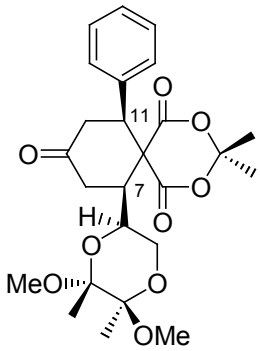
Figure S4: Percentage inhibition, measured in terms of decease in NL4-3 virus, upon treatment with 100pm, 100nm and 10μm of compounds ***cis*-1aaa**, ***cis*-1aca** and ***cis*-1jca** for 5 h. **AZT** was used as a reference compound.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1aaa): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 128 °C; **$[\alpha]^{25}_D = -98.4$ (*c* 1.1, $CHCl_3$);** IR (neat): ν_{max} 2993, 1761 (O-C=O), 1726 (C=O), 1378, 1282, 1138, 1038, 879, 734 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34-7.27 (3H, m), 7.19-7.17 (2H, m), 3.99 (1H, td, *J* = 11.2, 3.6 Hz), 3.76 (1H, dd, *J* = 14.4, 3.6 Hz), 3.62-3.55 (2H, m), 3.31 (1H, dd, *J* = 11.2, 2.8 Hz), 3.22 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.26-3.16 (1H, m), 3.01 (1H, td, *J* = 14.0, 4.0 Hz), 2.53 (2H, ddd, *J* = 18.8, 14.8, 2.8 Hz), 1.72 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.6 (C, C=O), 168.0 (C, O=C-O), 165.4 (C, O=C-O), 137.0 (C), 129.2 (3 x CH), 128.8 (CH), 128.7 (CH), 107.0 (C, O-C-O), 99.7 (C, O-C-O), 98.0 (C, O-C-O), 67.1 (CH, OCH), 60.2 (CH_2, OCH_2), 55.1 (C), 50.3 (CH_3, OCH_3), 48.8 (CH_3, OCH_3), 47.6 (CH), 46.7 (CH), 43.0 (CH_2), 38.5 (CH_2), 28.9 (CH_3), 28.2 (CH_3), 17.4 (2 x CH_3); LRMS m/z 475.45 ($M-H^+$), calcd $C_{25}H_{32}O_9$ 476.2046; Anal. calcd for $C_{25}H_{32}O_9$ (476.2046): C, 63.01; H, 6.77. Found: C, 63.21; H, 6.65%.



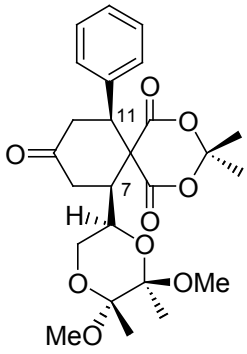
***cis*-1aaa**

(2'*R*,3'*R*,6'*S*,7*S*,11*S*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1'aaa): Prepared following procedure **A** in DMSO solvent and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. **$[\alpha]^{25}_D = -77.4$ (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 1728 (C=O), 1375, 1282, 1242, 1121, 1039, 878, 663 and 621 cm^{-1}; ^1H NMR ($CDCl_3$, isolated as mixture of isomer with *cis*-**1aaa**) δ 7.36-7.30 (3H, m), 7.20-7.18 (2H, m), 4.02-4.00 (1H,m), 3.66 (1H, t, *J* = 11.6 Hz), 3.51-3.39 (2H, m), 3.33-3.26 (2H, m), 3.21 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.05-2.96 (1H, m), 2.59-2.48 (2H, m), 1.76 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.45 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, isolated as mixture of isomer with *cis*-**1aaa**) δ 207.5 (C, C=O), 168.8 (C, O=C-O), 164.7 (C, O=C-O), 136.9 (C), 129.4 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 107.3 (C, O-C-O), 100.4 (C, O-C-O), 98.3 (C, O-C-O), 69.6 (CH, OCH), 60.9 (CH_2, OCH_2), 54.0 (C), 50.9 (CH_3, OCH_3), 48.2 (CH_3, OCH_3), 47.6 (CH), 47.0 (CH), 43.1 (CH_2), 42.0 (CH_2), 28.8 (CH_3), 28.3 (CH_3), 17.6 (CH_3), 17.5 (CH_3).



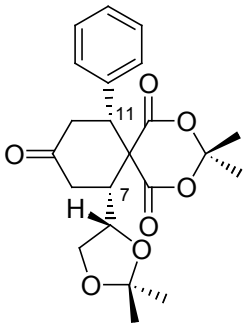
***cis*-1'aaa**

(2'*R*,3'*R*,6'*R*,7*S*,11*S*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1'aba): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as gummy oil. **$[\alpha]^{25}_{D}$ = –53.4 (*c* 0.8, $CHCl_3$);** IR (neat): ν_{max} 1759 (O-C=O), 1726 (C=O), 1375, 1284, 1209, 1064, 704 and 648 cm^{-1}; ^1H NMR ($CDCl_3$, **3:1 ratio of isomers, major**) δ 7.32-7.27 (3H, m), 7.18-6.70 (2H, m), 4.01-3.98 (1H,m), 3.75 (1H, dd, *J* = 14.4, 3.6 Hz), 3.64-3.54 (2H, m), 3.30 (1H, dd, *J* = 11.6, 3.2 Hz), 3.26-3.21 (1H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.03-2.97 (1H, m), 2.57-2.47 (2H, m), 1.71 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.20 (3H, s, CH_3), 0.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, major**) δ 207.8 (C, C=O), 168.2 (C, O=C-O), 165.6 (C, O=C-O), 137.1 (C), 129.4 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 107.2 (C, O-C-O), 99.8 (C, O-C-O), 98.1 (C, O-C-O), 67.3 (CH, OCH), 60.3 (CH_2, OCH_2), 55.3 (C), 50.5 (CH_3, OCH_3), 48.9 (CH_3, OCH_3), 47.8 (CH), 46.8 (CH), 43.1 (CH_2), 38.7 (CH_2), 29.0 (CH_3), 28.3 (CH_3), 17.5 (2 x CH_3); ^1H NMR ($CDCl_3$, **3:1 ratio of isomers, minor**) δ 7.32-7.27 (3H, m), 7.18-6.70 (2H, m), 3.97-3.92 (1H, m), 3.75 (1H, dd, *J* = 14.4, 3.6 Hz), 3.64-3.54 (2H, m), 3.30 (1H, dd, *J* = 11.6, 3.2 Hz), 3.26-3.21 (1H, m), 3.19 (3H, s, OCH_3), 3.14 (3H, s, OCH_3), 3.03-2.97 (1H, m), 2.57-2.47 (2H, m), 1.74 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.44 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, minor**) δ 207.5 (C, C=O), 168.8 (C, O=C-O), 164.7 (C, O=C-O), 137.9 (C), 129.4 (2 x CH), 129.0 (2 x CH), 128.9 (CH), 107.2 (C, O-C-O), 100.4 (C, O-C-O), 98.3 (C, O-C-O), 69.6 (CH, OCH), 60.9 (CH_2, OCH_2), 54.0 (C), 50.9 (CH_3, OCH_3), 48.2 (CH_3, OCH_3), 47.6 (CH), 46.9 (CH), 43.0 (CH_2), 41.9 (CH_2), 28.8 (CH_3), 28.3 (CH_3), 17.4 (2 x CH_3); LRMS m/z 475.45 ($M\text{-}H^+$), calcd $C_{25}H_{32}O_9$ 476.2046; Anal. calcd for $C_{25}H_{32}O_9$ (476.2046): C, 63.01; H, 6.77. Found: C, 63.15; H, 6.71%.



***cis*-1'aba**

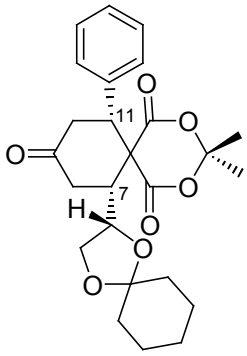
(4'*S*,7*R*,11*R*)-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (*cis*-1aca): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 118 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 210 nm), t_R = 24.68 min (major); for racemic compound peaks observed at t_R = 19.74 min and t_R = 24.80 min. **$[\alpha]^{25}_{D}$ = –35.3 (*c* 0.4, $CHCl_3$, >99% ee);** IR (neat): ν_{max} 2925, 1755 (O-C=O), 1726 (C=O), 1377, 1283, 1247, 1207, 1050, 704 and 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.26 (3H, m), 7.20-7.18 (2H, m), 4.22-4.21 (1H, m), 4.01 (1H, t, *J* = 7.6 Hz), 3.80 (1H, dd, *J* = 14.0, 4.0 Hz), 3.74 (1H, dd, *J*



***cis*-1aca**

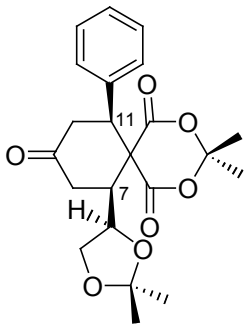
= 8.8, 5.2 Hz), 3.58 (1H, t, *J* = 14.4 Hz), 3.32 (1H, t, *J* = 14.4 Hz), 2.81 (1H, dd, *J* = 14.0, 1.6 Hz), 2.58 (1H, dd, *J* = 15.2, 4.0 Hz), 2.48 (1H, dd, *J* = 15.6, 3.2 Hz), 1.63 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.25 (3H, s, CH_3), 0.65 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 168.9 (C, O=C-O), 164.0 (C, O=C-O), 136.7 (C), 129.2 (2 x CH), 128.7 (CH), 128.6 (2 x CH), 110.5 (C, O-C-O), 106.7 (C, O-C-O), 74.0 (CH, OCH), 66.2 (CH_2, OCH_2), 56.5 (C), 50.1 (CH), 47.8 (CH), 42.9 (CH_2), 36.3 (CH_2), 28.9 (CH_3), 28.5 (CH_3), 25.5 (CH_3), 24.5 (CH_3); LRMS m/z 403.40 ($M+H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.51; H, 6.68%.

(2'*S*,7*R*,11*R*)-7-(1,4-Dioxa-spiro[4.5]dec-2-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1ada): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 110 °C; **[α]$^{25}_D$ = –38.2 (*c* 0.8, $CHCl_3$);** IR (neat): ν_{max} 2938, 1727 (C=O), 1678, 1376, 1280, 1111, 1069, 1038, 810 and 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35-7.29 (3H, m), 7.20 (2H, d, *J* = 4.0 Hz), 4.22 (1H, t, *J* = 4.8 Hz), 4.03 (1H, dd, *J* = 8.8, 6.8 Hz), 3.78 (2H, ddd, *J* = 18.4, 14.0 4.4 Hz), 3.60 (1H, t, *J* = 14.8 Hz), 3.33 (1H, t, *J* = 14.4 Hz), 2.85-2.80 (1H, m), 2.58 (1H, dd, *J* = 15.6, 4.0 Hz), 2.49 (1H, dd, *J* = 15.6, 3.6 Hz), 1.68 (3H, s, CH_3), 1.66-1.46 (10H, m), 0.64 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, C=O), 169.0 (C, O=C-O), 164.1 (C, O=C-O), 136.8 (C), 129.2 (2 x CH), 128.8 (CH), 128.6 (2 x CH), 111.4 (C, O-C-O), 106.7 (C, O-C-O), 73.9 (CH, OCH), 65.9 (CH_2, OCH_2), 56.6 (C), 50.1 (CH), 48.0 (CH), 42.9 (CH_2), 36.6 (CH_2), 35.2 (CH_2), 34.3 (CH_2), 29.1 (CH_3), 28.4 (CH_3), 25.0 (CH_2), 23.7 (2 x CH_2); LRMS m/z 443.25 ($M+H^+$), calcd $C_{25}H_{30}O_7$ 442.1992; Anal. calcd for $C_{25}H_{30}O_7$ (442.1992): C, 67.86; H, 6.83. Found: C, 67.91; H, 6.78%.



***cis*-1ada**

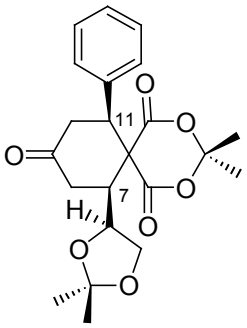
(4'*R*,7*S*,11*S*)-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-dimethyl-11-phenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (*cis*-1'aea): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 119 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 210 nm), t_R = 19.17 min (major); for racemic compound peaks observed at t_R = 19.74 min and t_R = 24.80 min. **[α]$^{25}_D$ = +34.1 (*c* 0.3, $CHCl_3$, >99% ee);** IR (neat): ν_{max} 1759 (O-C=O), 1725 (C=O), 1375, 1285, 1121, 1063, 647 and 616 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36-7.27 (3H, m), 7.22-7.20 (2H, m), 4.24 (1H, br t, *J* = 4.8 Hz), 4.03 (1H, t, *J* = 8.8 Hz), 3.82 (1H, dd, *J* = 14.0, 4.4 Hz), 3.76 (1H, dd, *J* = 9.2, 5.2



***cis*-1'aea**

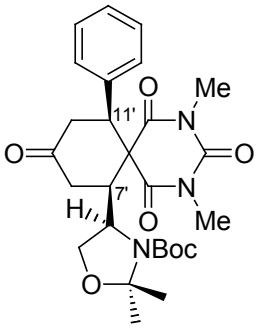
Hz), 3.60 (1H, t, *J* = 14.8 Hz), 3.33 (1H, t, *J* = 14.8 Hz), 2.82 (1H, br dd, *J* = 14.0, 2.0 Hz), 2.60 (1H, dd, *J* = 15.6, 4.4 Hz), 2.50 (1H, dd, *J* = 15.6, 4.0 Hz), 1.64 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.27 (3H, s, CH_3), 0.66 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.3 (C, C=O), 169.0 (C, O=C-O), 164.1 (C, O=C-O), 136.8 (C), 129.2 (2 x CH), 128.8 (CH), 128.6 (2 x CH), 110.6 (C, O-C-O), 106.7 (C, O-C-O), 74.1 (CH, OCH), 66.2 (CH_2, OCH_2), 56.6 (C), 50.2 (CH), 47.8 (CH), 42.9 (CH_2), 36.4 (CH_2), 29.0 (CH_3), 28.5 (CH_3), 25.5 (CH_3), 24.5 (CH_3); LRMS m/z 401.20 ($M\text{-}H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.58; H, 6.56%.

(4'*R*,7*S*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3,3-dimethyl-11-phenyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1'aca): Prepared following procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. IR (neat): ν_{max} 1746 (O-C=O, C=O), 1375, 1285, 1217, 1155, 1068, 841 and 611 cm^{-1}; ^{1}H NMR ($CDCl_3$, **3:1 ratio of isomers, minor isomer**) δ 7.33-7.26 (3H, m), 7.19-7.16 (2H, m), 4.11 (1H, dd, *J* = 8.4, 6.4 Hz), 3.94-3.91 (1H, m), 3.81-3.72 (1H, m), 3.67 (1H, dd, *J* = 8.4, 6.0 Hz), 3.46 (1H, t, *J* = 14.8 Hz), 3.13-3.06 (1H, m), 2.89 (1H, t, *J* = 14.4 Hz), 2.47 (1H, dd, *J* = 15.6, 2.8 Hz), 2.22 (1H, dd, *J* = 14.4, 3.6 Hz), 1.64 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.27 (3H, s, CH_3), 0.49 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, minor isomer**) δ 206.3 (C, C=O), 168.0 (C, O=C-O), 165.1 (C, O=C-O), 136.5 (C), 129.1 (2 x CH), 128.8 (CH), 128.7 (2 x CH), 110.8 (C, O-C-O), 107.4 (C, O-C-O), 76.1 (CH, OCH), 68.3 (CH_2, OCH_2), 54.9 (C), 50.5 (CH), 48.7 (CH), 42.5 (CH_2), 40.0 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 25.4 (CH_3), 25.0 (CH_3); LRMS m/z 403.25 ($M+H^+$), calcd $C_{22}H_{26}O_7$ 402.1679; Anal. calcd for $C_{22}H_{26}O_7$ (402.1679): C, 65.66; H, 6.51. Found: C, 65.71; H, 6.48%.



***cis*-1'aca**

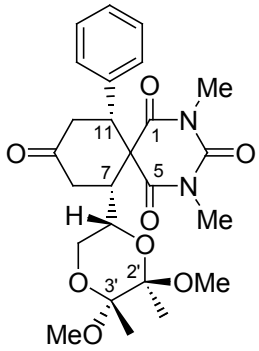
(4*R*,7'*S*,11'*S*)-4-(2,4-Dimethyl-1,3,5,9-tetraoxo-11-phenyl-2,4-diaza-spiro[5.5]undec-7-yl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (*cis*-1'afb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 160 °C; **$[\alpha]^{25}_D$ = +6.6 (*c* 0.8, $CHCl_3$)**; IR (neat): ν_{max} 2360, 2336, 1711 (C=O), 1676 (N-C=O), 1450, 1422, 1382, 1374, 1263, 1103, 1065, 809 and 658 cm^{-1}; ^{1}H NMR ($CDCl_3$, **4:1 ratio of isomers, major**) δ 7.27-7.25 (3H, m), 6.90-6.88 (2H, m), 4.12 (1H, d, *J* = 6.4 Hz), 3.99 (1H, dd, *J* = 9.2, 7.2 Hz), 3.78 (1H, d, *J* = 9.6 Hz), 3.63-3.50 (2H, m), 3.27-3.13 (2H, m), 3.02 (6H, s, 2 x *N*CH_3), 2.66 (1H, dd, *J* = 15.6, 3.6 Hz), 2.50 (1H, dd, *J* = 15.2, 2.8 Hz), 1.52 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.38 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT-



***cis*-1'afb**

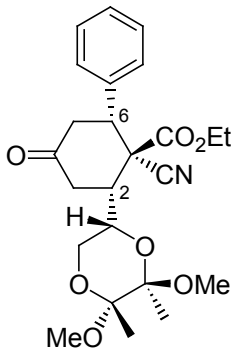
135, **4:1 ratio of isomers, major**) δ 208.8 (C, C=O), 170.8 (C, O=C-N), 168.4 (C, O=C-N), 154.3 (C), 150.4 (C), 136.0 (C), 129.0 (CH), 128.3 (2 x CH), 127.2 (2 x CH), 95.0 (C, Me_3C-O), 80.8 (C, N-C-O), 67.7 (CH_2, OCH_2), 57.8 (C), 57.5 (CH, NCH), 54.0 (CH), 47.9 (CH), 42.0 (CH_2), 39.0 (CH_2), 28.3 (3 x CH_3), 28.2 (CH_3), 27.9 (CH_3), 26.2 (CH_3), 23.8 (CH_3); LRMS m/z 514.00 ($M+H^+$), calcd $C_{27}H_{35}N_3O_7$ 513.2475; Anal. calcd for $C_{27}H_{35}N_3O_7$ (513.2475): C, 63.14; H, 6.87; N, 8.18. Found: C, 63.25; H, 6.79; N, 8.22%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-Dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-phenyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1aab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 114 °C; **$[\alpha]^{25}_D$ = –50.1 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 2954, 1716 (C=O), 1667 (N-C=O), 1422, 1379, 1124, 1038, 879 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27-7.24 (3H, m), 6.94-6.93 (2H, m), 4.01-3.96 (1H, m), 3.64 (1H, t, *J* = 11.2 Hz), 3.59 (1H, dd, *J* = 14.4, 3.6 Hz), 3.43 (1H, t, *J* = 14.8 Hz), 3.31-3.19 (3H, m), 3.16 (6H, s, 2 x OCH_3), 3.06 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.48-2.44 (2H, m), 1.16 (3H, s, CH_3), 1.01 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.9 (C, C=O), 171.1 (C, O=C-N), 169.5 (C, O=C-N), 150.2 (C), 135.9 (C), 128.9 (CH), 128.6 (2 x CH), 127.0 (2 x CH), 99.3 (C, O-C-O), 97.8 (C, O-C-O), 66.7 (CH, OCH), 59.7 (CH_2, OCH_2), 55.5 (C), 52.1 (CH), 48.1 (2 x CH_3, OCH_3), 44.5 (CH), 42.3 (CH_2), 38.6 (CH_2), 28.3 (CH_3, NCH_3), 27.9 (CH_3, NCH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 489.00 ($M+H^+$), calcd $C_{25}H_{32}N_2O_8$ 488.2159; Anal. calcd for $C_{25}H_{32}N_2O_8$ (488.2159): C, 61.46; H, 6.60; N, 5.73. Found: C, 61.32; H, 6.68; N, 5.65%.



***cis*-1aab**

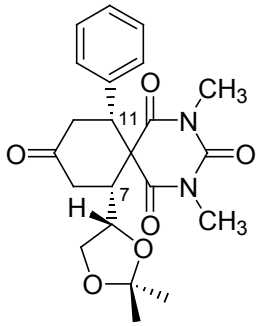
Ethyl (1*R*,2*R*,2'*R*,3'*R*,6'*S*,6*R*)-1-cyano-2-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-4-oxo-6-phenyl-cyclohexanecarboxylate (*cis*-1aac): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as oil. **$[\alpha]^{25}_D$ = –71.5 (*c* 2.0, $CHCl_3$);** IR (neat): ν_{max} 2965, 1746 (O-C=O), 1729 (C=O), 1374, 1262, 1232, 1141, 1036, 878 and 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.27 (3H, m), 7.10-7.09 (2H, m), 4.31-4.26 (3H, m), 3.97-3.87 (2H, m), 3.58 (1H, t, *J* = 10.8 Hz), 3.34 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.30-3.18 (2H, m), 2.98-2.85 (2H, m), 2.64-2.59 (1H, m), 1.27 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.03 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.3 (C, C=O), 166.4 (C, O=C-O), 136.6 (C), 128.7 (2 x CH), 128.6 (CH), 128.4 (2 x CH), 117.9 (C, CN), 99.5 (C, O-C-O), 97.9 (C, O-C-O), 66.9 (CH, OCH), 63.0 (CH_2, OCH_2CH_3), 60.4 (CH_2, OCH_2), 51.9 (C), 48.6



***cis*-1aac**

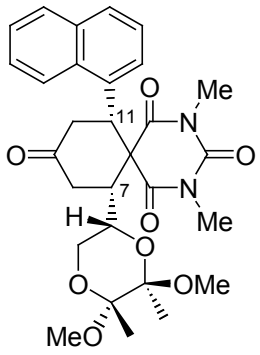
(CH_3, OCH_3), 48.2 (CH_3, OCH_3), 48.0 (CH), 41.7 (CH_2), 38.2 (CH), 37.0 (CH_2), 17.4 (CH_3), 17.3 (CH_3), 13.5 (CH_3, OCH_2CH_3); LRMS m/z 445.05 (M^+), calcd $C_{24}H_{31}NO_7$ 445.2101; Anal. calcd for $C_{24}H_{31}NO_7$ (445.2101): C, 64.70; H, 7.01; N, 3.14. Found: C, 64.71; H, 7.11; N, 3.22%.

(4'*S*,7*R*,11*R*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-phenyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1acb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 132 °C; **$[\alpha]^{25}_D = -19.1$ (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2926, 2855, 1718 (C=O), 1674 (N-C=O), 1446, 1422, 1378, 1254, 1210, 1125, 1060, 704 and 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (3H, br s, Ph-*H*), 6.99 (2H, br s, Ph-*H*), 3.99-3.98 (1H, m), 3.86 (1H, t, *J* = 8.4 Hz), 3.75-3.66 (2H, m), 3.54 (1H, t, *J* = 14.8 Hz), 3.27 (1H, t, *J* = 14.4 Hz), 3.13-3.05 (1H, m), 3.13 (3H, s, NC*H*$_3$), 3.05 (3H, s, NC*H*$_3$), 2.56-2.47 (2H, m), 1.26 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 171.2 (C, O=C-N), 168.5 (C, O=C-N), 150.2 (C), 136.3 (C), 128.7 (3 x CH), 127.3 (2 x CH), 109.7 (C, O-C-O), 74.7 (CH, OCH), 66.0 (CH_2, OCH_2), 56.8 (C), 51.3 (CH), 46.4 (CH), 42.7 (CH_2), 37.4 (CH_2), 28.4 (CH_3, NC*H*$_3$), 28.1 (CH_3, NC*H*$_3$), 25.6 (CH_3), 24.7 (CH_3); LRMS m/z 415.20 ($M+H^+$), calcd $C_{22}H_{26}N_2O_6$ 414.1791; Anal. calcd for $C_{22}H_{26}N_2O_6$ (414.1791): C, 63.76; H, 6.32; N, 6.76. Found: C, 65.85; H, 6.28; N, 6.63%.



***cis*-1acb**

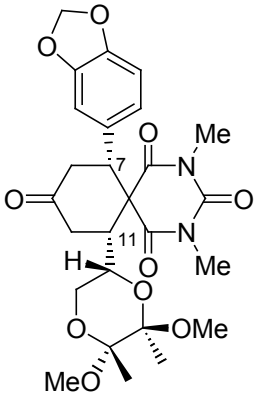
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-naphthalen-1-yl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1bab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D = -260.7$ (*c* 1.5, $CHCl_3$);** IR (neat): ν_{max} 3011, 1718 (C=O), 1672 (N-C=O), 1448, 1423, 1377, 1272, 1128, 1036, 879, 802 and 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.82 (1H, d, *J* = 6.8 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.53-7.48 (2H, m), 7.38 (1H, t, *J* = 7.6 Hz), 7.18 (1H, d, *J* = 7.2 Hz), 4.56 (1H, dd, *J* = 14.0, 3.6 Hz), 4.05 (1H, ddd, *J* = 11.6, 6.8, 3.2 Hz), 3.74 (1H, t, *J* = 11.6 Hz), 3.68-3.61 (1H, m), 3.57 (1H, t, *J* = 14.4 Hz), 3.42 (1H, t, *J* = 14.4 Hz), 3.25 (1H, dd, *J* = 11.6, 3.2 Hz), 3.20 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.05 (3H, s, NCH_3), 2.55 (2H, d, *J* = 14.8 Hz), 2.27 (3H, s, NCH_3), 1.17 (3H, s, CH_3), 0.96 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.2 (C, C=O), 170.6 (C, O=C-N), 169.9 (C, O=C-N), 150.0 (C), 133.7 (C), 132.4 (C), 130.5 (C), 129.4 (CH), 128.8 (CH), 126.5 (CH), 126.1 (CH), 124.4 (CH), 123.8 (CH), 122.7 (CH), 99.4 (C, O-C-O), 97.8 (C, O-C-O), 66.4 (CH, OCH), 59.9 (CH_2, OCH_2),



***cis*-1bab**

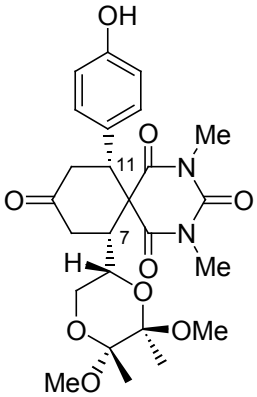
55.1 (C), 48.1 (2 x CH_3, OCH_3), 44.5 (CH), 44.1 (CH), 43.6 (CH_2), 38.8 (CH_2), 27.9 (CH_3, NCH_3), 27.8 (CH_3, NCH_3), 17.3 (CH_3), 17.0 (CH_3); LRMS m/z 537.35 ($M-H^+$), calcd $C_{29}H_{34}N_2O_8$ 538.2315; Anal. calcd for $C_{29}H_{34}N_2O_8$ (538.2315): C, 64.67; H, 6.36; N, 5.20. Found: C, 64.55; H, 6.28; N, 5.16%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-Benzo[1,3]dioxol-5-yl-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1cab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 138 °C; **$[\alpha]^{25}_D$ = –67.4 (*c* 0.4, $CHCl_3$);** IR (neat): ν_{max} 2926, 2854, 1721 (C=O), 1673 (N-C=O), 1445, 1376, 1284, 1257, 1120, 1037, 880, 817 and 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.66 (1H, d, *J* = 7.6 Hz), 6.44-6.41 (2H, m), 5.93 (2H, br s, OCH_2O), 4.00-3.97 (1H, m), 3.63 (1H, t, *J* = 11.2 Hz), 3.54 (1H, dd, *J* = 14.4, 3.2 Hz), 3.40-3.31 (2H, m), 3.29-3.25 (2H, m), 3.22 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.08 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 2.44 (2H, d, *J* = 12.8 Hz), 1.18 (3H, s, CH_3), 1.04 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.8 (C, C=O), 172.2 (C, O=C-N), 169.6 (C, O=C-N), 150.4 (C), 148.0 (C), 147.7 (C), 129.7 (C), 120.8 (CH), 108.2 (CH), 106.9 (CH), 101.4 (CH_2, OCH_2O), 99.4 (C, O-*C*-O), 97.8 (C, O-*C*-O), 66.7 (CH, OCH), 59.6 (CH_2, OCH_2), 55.5 (C), 51.8 (CH), 48.2 (2 x CH_3, OCH_3), 44.5 (CH), 42.8 (CH_2), 38.6 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 533.00 ($M+H^+$), calcd $C_{26}H_{32}N_2O_{10}$ 532.2057; Anal. calcd for $C_{26}H_{32}N_2O_{10}$ (532.2057): C, 58.64; H, 6.06; N, 5.26. Found: C, 58.72; H, 6.13; N, 5.19%.



***cis*-1cab**

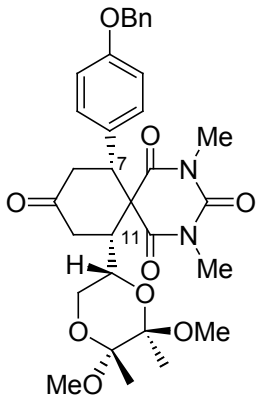
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-11-(4-hydroxy-phenyl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1dab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as solid. mp.: 108 °C; **$[\alpha]^{25}_D$ = –70.4 (*c* 0.6, $CHCl_3$);** IR (neat): ν_{max} 1711 (C=O), 1672 (N-C=O), 1425, 1379, 1274, 1137, 1034, 879, 756 and 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (2H, d, *J* = 8.4 Hz), 6.67 (2H, d, *J* = 8.4 Hz), 3.95-3.93 (1H, m), 3.59 (1H, t, *J* = 11.6 Hz), 3.50 (1H, dd, *J* = 14.0, 3.2 Hz), 3.38-3.29 (2H, m), 3.26-3.19 (2H, m), 3.14 (3H, s, OCH_3), 3.12 (3H, s, OCH_3), 3.03 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 2.43-2.40 (2H, m), 1.13 (3H, s, CH_3), 0.99 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, C=O), 171.3 (C, O=C-N), 169.6 (C, O=C-N), 156.6 (C), 150.4 (C), 128.2 (2 x CH), 127.1 (C), 115.4 (2 x CH), 99.3 (C, O-C-O), 97.8 (C, O-C-O), 66.6 (CH, OCH), 59.6 (CH_2, OCH_2), 55.6 (C), 51.4 (CH),



***cis*-1dab**

48.0 (2 x CH_3, OCH_3), 44.2 (CH), 42.6 (CH_2), 38.5 (CH_2), 28.3 (CH_3, NCH_3), 27.9 (CH_3, NCH_3), 17.2 (CH_3), 17.1 (CH_3); LRMS m/z 505.00 ($M+H^+$), calcd $C_{25}H_{32}N_2O_9$ 504.2108; Anal. calcd for $C_{25}H_{32}N_2O_9$ (504.2108): C, 59.51; H, 6.39; N, 5.55. Found: C, 59.42; H, 6.45; N, 5.48%.

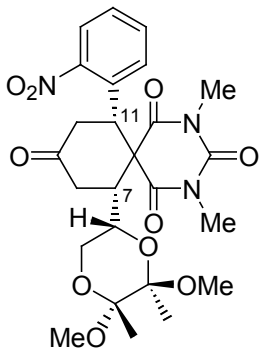
(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(4-Benzyloxy-phenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1eab): Prepared following procedure **A**



***cis*-1eab**

and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_D$ = –74.3 (*c* 1.2, $CHCl_3$);** IR (neat): ν_{max} 2960, 1717 (C=O), 1673 (N-C=O), 1469, 1446, 1424, 1378, 1261, 1131, 1036, 876, 812 and 629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.31 (5H, m), 6.86-6.80 (4H, m), 5.00 (2H, s, O*C*H_2Ph), 3.98-3.95 (1H, m), 3.62 (1H, t, *J* = 11.6 Hz), 3.56 (1H, dd, *J* = 14.4, 4.0 Hz), 3.42-3.22 (4H, m), 3.160 (3H, s, OCH_3), 3.157 (3H, s, OCH_3), 3.06 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 2.45-2.42 (2H, m), 1.17 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.7 (C, C=O), 171.0 (C, O=C-N), 169.4 (C, O=C-N), 158.6 (C), 150.0 (C), 136.3 (C), 128.4 (2 x CH), 128.0 (2 x CH), 127.8 (CH), 127.2 (2 x CH), 127.2 (C), 114.7 (2 x CH), 99.1 (C, O-C-O), 97.6 (C, O-C-O), 69.6 (CH_2, O*C*H_2Ph), 66.5 (CH, OCH), 59.4 (CH_2, OCH_2), 55.4 (C), 51.2 (CH), 47.9 (2 x CH_3, OCH_3), 44.2 (CH), 42.4 (CH_2), 38.4 (CH_2), 28.1 (CH_3), 27.7 (CH_3), 17.1 (CH_3), 17.0 (CH_3); LRMS m/z 593.00 ($M-H^+$), calcd $C_{32}H_{38}N_2O_9$ 594.2577; Anal. calcd for $C_{32}H_{38}N_2O_9$ (594.2577): C, 64.63; H, 6.44; N, 4.71. Found: C, 64.45; H, 6.58; N, 4.78%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-(2-nitro-phenyl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1fab): Prepared following procedure **A** and

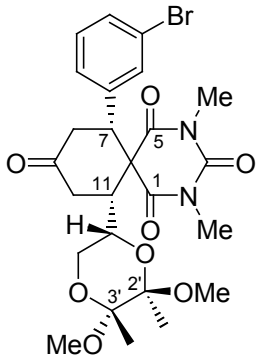


***cis*-1fab**

purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. mp.: 72 °C; **$[\alpha]^{25}_D$ = –269.2 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 1719 (C=O), 1675 (N-C=O), 1533, 1446, 1377, 1189, 1126, 1038, 878, 736, 702 and 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (1H, dd, *J* = 7.6, 1.2 Hz), 7.49 (1H, dt, *J* = 7.2, 1.2 Hz), 7.43 (1H, dt, *J* = 7.6, 1.6 Hz), 7.20 (1H, dd, *J* = 7.6, 0.8 Hz), 4.49 (1H, dd, *J* = 14.0, 4.0 Hz), 4.00-3.95 (1H, m), 3.57 (1H, t, *J* = 11.2 Hz), 3.40-3.33 (3H, m), 3.25 (3H, s, OCH_3), 3.26-3.24 (1H, m), 3.16 (3H, s, OCH_3), 3.03 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.67 (1H, dd, *J* = 15.2, 4.0 Hz), 2.48 (1H, dd, *J* = 15.2, 4.4 Hz), 1.16 (3H, s, CH_3), 0.98 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.0 (C, C=O), 170.3 (C, O=C-N), 169.8 (C, O=C-N), 150.3 (C), 150.1 (C), 132.3 (CH), 130.2

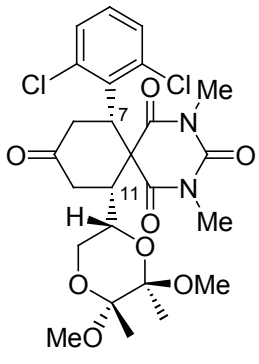
(C), 129.5 (CH), 127.4 (CH), 124.9 (CH), 99.4 (C, O-C-O), 97.9 (C, O-C-O), 66.6 (CH, OCH), 59.3 (CH_2, OCH_2), 54.5 (C), 48.2 (2 x CH_3, OCH_3), 45.1 (CH), 44.4 (CH), 42.0 (CH_2), 38.2 (CH_2), 28.7 (CH_3), 28.2 (CH_3), 17.2 (CH_3), 17.1 (CH_3); LRMS m/z 533.40 (M^+), calcd $C_{25}H_{31}N_3O_{10}$ 533.2009; Anal. calcd for $C_{25}H_{31}N_3O_{10}$ (533.2009): C, 56.28; H, 5.86; N, 7.88. Found: C, 56.41; H, 5.80; N, 7.81%.

(2'*R*,3'*R*,6'*S*,7*R*,11*R*)-7-(3-Bromophenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1gab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 128 °C; **$[\alpha]^{25}_D$ = –74.3 (*c* 1.0, $CHCl_3$)**; IR (neat): ν_{max} 1721 (C=O), 1672 (N-C=O), 1426, 1381, 1133, 1084, 1039, 881, 798, 665 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (1H, d, *J* = 8.0 Hz), 7.13 (1H, s), 7.13 (1H, t, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 4.02-3.98 (1H,m), 3.64 (1H, t, *J* = 11.6 Hz), 3.58 (1H, dd, *J* = 14.4, 3.6 Hz), 3.44-3.36 (2H, m), 3.32-3.23 (2H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.08 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 2.46 (2H, td, *J* = 14.4, 4.0 Hz), 1.18 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.2 (C, C=O), 170.9 (C, O=C-N), 169.4 (C, O=C-N), 150.1 (C), 138.2 (C), 132.0 (CH), 130.3 (CH), 130.1 (CH), 125.7 (CH), 122.8 (C), 99.4 (C, O-C-O), 97.8 (C, O-C-O), 66.6 (CH, OCH), 59.6 (CH_2, OCH_2), 55.3 (C), 51.6 (CH), 48.2 (2 x CH_3, OCH_3), 44.6 (CH), 42.1 (CH_2), 38.6 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 17.3 (CH_3), 17.2 (CH_3); LRMS m/z 565.35 ($M\text{-}H^+$), calcd $C_{25}H_{31}BrN_2O_8$ 566.1264; Anal. calcd for $C_{25}H_{31}BrN_2O_8$ (566.1264): C, 52.92; H, 5.51; N, 4.94. Found: C, 52.85; H, 5.59; N, 5.07%.



***cis*-1gab**

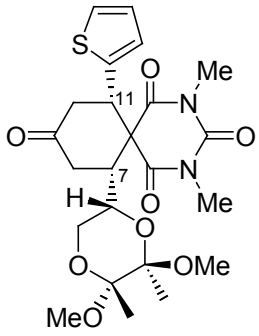
(2'*R*,3'*R*,6'*S*,7*S*,11*R*)-7-(2,6-Dichlorophenyl)-11-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1hab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 192 °C; **$[\alpha]^{25}_D$ = –78.3 (*c* 0.7, $CHCl_3$)**; IR (neat): ν_{max} 1719 (C=O), 1676 (N-C=O), 1442, 1425, 1375, 1265, 1129, 1108, 1038, 875 and 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (1H, d, *J* = 8.0 Hz), 7.19 (1H, d, *J* = 8.0 Hz), 7.08 (1H, t, *J* = 8.0 Hz), 4.62 (1H, dd, *J* = 14.8, 3.2 Hz), 4.04-3.96 (2H, m), 3.72 (1H, t, *J* = 11.6 Hz), 3.59-3.52 (1H, m), 3.33-3.24 (1H, m), 3.28 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.20-3.14 (1H, m), 3.04 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.53 (1H, dd, *J* = 15.6, 5.2 Hz), 2.41 (1H, dd, *J* = 15.6, 2.4 Hz), 1.14 (3H, s, CH_3), 0.96 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.6 (C, C=O), 169.5 (C, O=C-



***cis*-1hab**

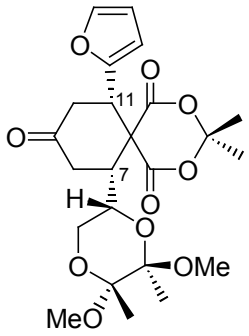
N), 169.2 (C, O=C-N), 150.7 (C), 137.2 (C), 135.2 (C), 131.6 (C), 130.8 (CH), 130.0 (CH), 129.5 (CH), 99.5 (C, O-C-O), 97.8 (C, O-C-O), 66.2 (CH, OCH), 59.9 (CH_2, OCH_2), 53.8 (C), 48.3 (CH_3, OCH_3), 48.1 (CH_3, OCH_3), 47.5 (CH), 44.8 (CH), 40.1 (CH_2), 38.8 (CH_2), 28.9 (CH_3), 28.4 (CH_3), 17.3 (CH_3), 17.0 (CH_3); LRMS m/z 557.00 ($M+H^+$), calcd $C_{25}H_{30}Cl_2N_2O_8$ 556.1379; Anal. calcd for $C_{25}H_{30}Cl_2N_2O_8$ (556.1379): C, 53.87; H, 5.42; N, 5.03. Found: C, 53.65; H, 5.48; N, 5.12%.

(2'*R*,3'*R*,6'*S*,7*R*,11*S*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-2,4-dimethyl-11-thiophen-2-yl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1iab): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as light yellow oil. **$[\alpha]^{25}_D$ = –84.7 (*c* 1.3, $CHCl_3$);** IR (neat): ν_{max} 2954, 1674 (N-C=O), 1595, 1386, 1253, 1122, 1037, 1002, 879, 732 and 648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (1H, d, *J* = 5.2 Hz), 6.88 (1H, t, *J* = 4.0 Hz), 6.72 (1H, d, *J* = 3.2 Hz), 3.99 (2H, dd, *J* = 14.0, 4.0 Hz), 3.60 (1H, t, *J* = 11.2 Hz), 3.38 (1H, t, *J* = 14.8 Hz), 3.26-3.21 (3H, m), 3.21 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 2.63 (1H, dd, *J* = 15.2, 4.4 Hz), 2.45 (1H, d, *J* = 10.8 Hz), 1.19 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.8 (C, C=O), 171.3 (C, O=C-N), 169.4 (C, O=C-N), 150.5 (C), 139.0 (C), 126.9 (CH), 125.8 (CH), 125.6 (CH), 99.4 (C, O-C-O), 97.9 (C, O-C-O), 66.9 (CH, OCH), 59.6 (CH_2, OCH_2), 55.9 (C), 48.2 (2 x CH_3, OCH_3), 47.6 (CH), 44.6 (CH), 44.2 (CH_2), 38.4 (CH_2), 28.6 (CH_3, NCH_3), 28.3 (CH_3, NCH_3), 17.3 (2 x CH_3); LRMS m/z 463.50 ($M-OMe^+$), calcd $C_{23}H_{30}N_2O_8S$ 494.1723; Anal. calcd for $C_{23}H_{30}N_2O_8S$ (494.1723): C, 55.86; H, 6.11; N, 5.66. Found: C, 55.92; H, 6.03; N, 5.58%.



***cis*-1iab**

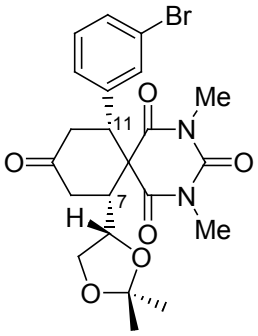
(2'*R*,3'*R*,6'*S*,7*R*,11*S*)-7-(2,3-dimethoxy-2,3-dimethyl-[1,4]dioxan-6-yl)-11-furan-2-yl-3,3-dimethyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1jaa): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_D$ = –71.5 (*c* 1.4, $CHCl_3$);** IR (neat): ν_{max} 2986, 1766 (O-C=O), 1730 (C=O), 1377, 1281, 1207, 1129, 1037, 879, 657 and 611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (1H, s), 6.28 (1H, s), 6.17 (1H, d, *J* = 2.8 Hz), 3.97-3.95 (1H, m), 3.88 (1H, dd, *J* = 14.4, 4.0 Hz), 3.54 (1H, t, *J* = 11.6 Hz), 3.49 (1H, t, *J* = 9.6 Hz), 3.27 (1H, dd, *J* = 9.6, 2.8 Hz), 3.20 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.08 (1H, t, *J* = 14.4 Hz), 2.87-2.83 (1H, m), 2.51 (2H, dt, *J* = 16.0, 2.8 Hz), 1.76 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.19 (3H, s, CH_3), 0.84 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.8 (C, C=O), 168.2 (C, O=C-O), 165.2 (C, O=C-O), 150.5 (C), 142.7 (CH), 111.0 (CH), 109.6 (CH),



***cis*-1jaa**

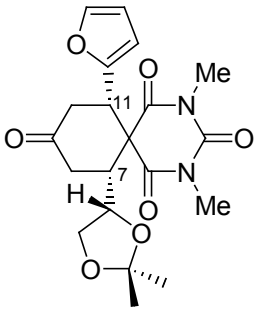
106.8 (C), 99.6 (C, O-C-O), 98.0 (C, O-C-O), 66.7 (CH, OCH), 60.2 (CH_2, OCH_2), 53.9 (C), 48.9 (CH_3, OCH_3), 47.8 (CH_3, OCH_3), 46.5 (CH), 44.0 (CH), 41.4 (CH_2), 38.2 (CH_2), 28.7 (CH_3), 28.6 (CH_3), 17.4 (2 x CH_3); LRMS m/z 465.45 ($M-H^+$), calcd $C_{23}H_{30}O_{10}$ 466.1839; Anal. calcd for $C_{23}H_{30}O_{10}$ (464.1839): C, 59.22; H, 6.48. Found: C, 59.35; H, 6.41%.

(4'*S*,7*R*,11*R*)-7-(3-Bromo-phenyl)-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1gcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 122°C; **$[\alpha]^{25}_D$ = –21.2 (*c* 1.1, $CHCl_3$);** IR (neat): ν_{max} 1722 (C=O), 1672 (N-C=O), 1424, 1379, 1265, 1205, 1047, 858, 800 and 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, s), 7.13-7.08 (2H, m), 6.89 (1H, d, *J* = 5.6 Hz), 3.94 (1H, br s), 3.85-3.81 (1H, m), 3.68-3.64 (2H, m), 3.48-3.40 (1H, m), 3.24-3.17 (1H, m), 3.20-3.06 (1H, m), 3.12 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 2.45 (2H, t, *J* = 20.0 Hz), 1.22 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.4 (C, C=O), 170.9 (C, O=C-N), 168.2 (C, O=C-N), 149.9 (C), 138.6 (C), 131.7 (CH), 130.4 (CH), 130.1 (CH), 125.8 (CH), 122.7 (C), 109.6 (C, O-C-O), 74.4 (CH, OCH), 65.8 (CH_2, OCH_2), 56.4 (C), 50.5 (CH), 46.5 (CH), 42.3 (CH_2), 37.1 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 25.4 (CH_3), 24.6 (CH_3); LRMS m/z 493.00 ($M+H^+$), calcd $C_{22}H_{25}BrN_2O_6$ 492.0896; Anal. calcd for $C_{22}H_{25}BrN_2O_6$ (492.0896): C, 53.56; H, 5.11; N, 5.68. Found: C, 53.45; H, 5.18; N, 5.61%.



***cis*-1gcb**

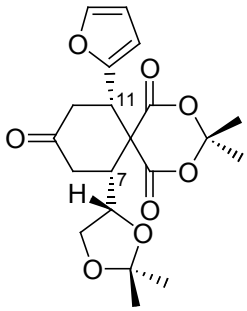
(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1jcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 98 °C; **$[\alpha]^{25}_D$ = –21.2 (*c* 1.3, $CHCl_3$);** IR (neat): ν_{max} 2926, 2361, 2335, 1714 (C=O), 1677 (N-C=O), 1451, 1422, 1378, 1282, 1150, 1061, 754 and 638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (1H, s), 6.22 (1H, d, *J* = 1.6 Hz), 5.99 (1H, d, *J* = 2.8 Hz), 3.95-3.83 (3H, m), 3.63 (1H, dd, *J* = 8.4, 6.0 Hz), 3.39 (1H, t, *J* = 14.0 Hz), 3.25 (3H, s, NCH_3), 3.18-3.13 (1H, m), 3.13 (3H, s, NCH_3) 2.94-2.90 (1H, m), 2.60 (1H, dd, *J* = 15.2, 4.4 Hz), 2.44-2.39 (1H, m), 1.25 (3H, s, CH_3), 1.16 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.4 (C, C=O), 171.3 (C, N- C=O), 168.0 (C, N=C-O), 151.1 (C), 150.5 (C), 142.5 (CH), 110.5 (CH), 109.8 (C), 107.4 (CH), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 55.3 (C), 46.3 (CH), 44.3 (CH), 41.0 (CH_2), 36.7 (CH_2), 28.7 (CH_3, N*C*H_3), 28.2 (CH_3, N*C*H_3),



***cis*-1jcb**

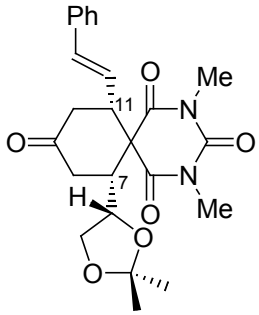
25.5 (CH_3), 24.6 (CH_3); LRMS m/z 405.00 ($M+H^+$), calcd $C_{20}H_{24}N_2O_7$ 404.1584; Anal. calcd for $C_{20}H_{24}N_2O_7$ (404.1584): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.51; H, 5.92; N, 6.85%.

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-2,4-dioxa-spiro[5.5]undecane-1,5,9-trione (*cis*-1jca): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 106 °C; **$[\alpha]^{25}_D$ = –41.6 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2928, 1726 (O-C=O), 1687, 1376, 1287, 1210, 1060 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (1H, br s), 6.34 (1H, s), 6.21 (1H, s), 4.25 (1H, br s), 4.03-3.96 (2H, m), 3.73 (1H, br s), 3.49 (1H, t, *J* = 14.8 Hz), 3.25 (1H, t, *J* = 14.42 Hz), 2.76 (1H, d, *J* = 13.6 Hz), 2.63 (1H, d, *J* = 15.6 Hz), 2.48 (1H, d, *J* = 15.6 Hz), 1.74 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.13 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.2 (C, C=O), 168.9 (C, O=C-O), 163.7 (C, O=C-O), 150.7 (C), 142.7 (CH), 110.8 (CH), 110.6 (C, O-C-O), 109.0 (CH), 106.7 (C, O-C-O), 73.9 (CH, OCH), 66.3 (CH_2, OCH_2), 54.9 (C), 47.1 (CH), 44.0 (CH), 41.3 (CH_2), 36.1 (CH_2), 28.8 (2 x CH_3), 25.5 (CH_3), 24.4 (CH_3); LRMS m/z 393.00 ($M+H^+$), calcd $C_{20}H_{24}O_8$ 392.1471; Anal. calcd for $C_{20}H_{24}O_8$ (392.1471): C, 61.22; H, 6.16. Found: C, 61.33; H, 6.21%.



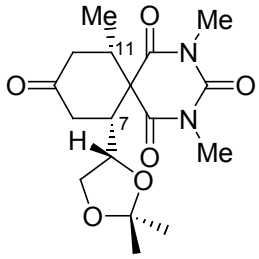
***cis*-1jca**

(4'*S*,7*R*,11*R*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-styryl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1kcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as white solid. mp.: 176 °C; **$[\alpha]^{25}_D$ = +12.6 (*c* 1.2, $CHCl_3$);** IR (neat): ν_{max} 2928, 1681 (N-C=O),1444, 1421, 1375, 1268, 1212, 1118, 1057, 850 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.22 (5H, m, Ph-*H*), 6.44 (1H, d, *J* = 15.6 Hz), 5.73 (1H, dd, *J* = 15.6, 8.8 Hz), 3.98 (1H, br s), 3.90 (1H, t, *J* = 8.4 Hz), 3.67 (1H, t, *J* = 6.4 Hz), 3.44-3.43 (1H, m), 3.30 (3H, s, NCH_3), 3.29 (3H, s, NCH_3), 3.21 (1H, t, *J* = 14.8 Hz), 3.10 (1H, t, *J* = 14.8 Hz), 2.86 (1H, d, *J* = 13.6 Hz), 2.49 (1H, dd, *J* = 15.6 4.8 Hz), 2.41 (1H, dd, *J* = 15.6 4.8 Hz), 1.31 (3H, s, CH_3), 1.21 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.1 (C, C=O), 171.4 (C, O=C-N), 168.6 (C, O=C-N), 150.8 (C), 135.7 (C), 134.6 (CH), 128.7 (2 x CH), 128.3 (CH), 126.4 (2 x CH), 124.5 (CH), 109.9 (C, O-C-O), 74.4 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 48.8 (CH), 47.0 (CH), 42.9 (CH_2), 36.5 (CH_2), 28.8 (CH_3, NCH_3), 28.5 (CH_3, NCH_3), 25.6 (CH_3), 24.7 (CH_3); LRMS m/z 441.55 ($M+H^+$), calcd $C_{24}H_{28}N_2O_6$ 440.1947; Anal. calcd for $C_{24}H_{28}N_2O_6$ (440.1947): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.29; H, 6.49; N, 6.28%.



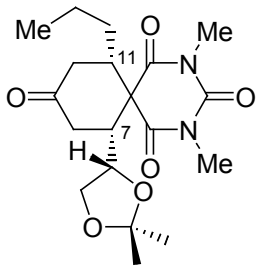
***cis*-1kcb**

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4,11-trimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1lcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 138 °C; **$[\alpha]^{25}_{D} = -20.0$ (*c* 0.2, $CHCl_3$);** IR (neat): ν_{max} 2928, 1713 (C=O), 1674 (N-C=O), 1446, 1422, 1376, 1275, 1058, 755 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (1H, dt, *J* = 6.0, 2.8 Hz), 3.87 (1H, dd, *J* = 8.8, 6.4 Hz), 3.62 (1H, dd, *J* = 8.8, 6.0 Hz), 3.39 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 3.02-2.88 (2H, m), 2.78-2.74 (2H, m), 2.37 (2H, m), 1.29 (3H, s, CH_3), 1.20 (3H, s, CH_3), 0.86 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, C=O), 172.0 (C, O=C-N), 168.6 (C, O=C-N), 151.0 (C), 109.9 (C, O-C-O), 74.4 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.4 (CH), 44.8 (CH_2), 40.3 (CH), 36.4 (CH_2), 28.9 (CH_3), 28.5 (CH_3), 25.6 (CH_3), 24.7 (CH_3), 16.8 (CH_3); LRMS m/z 352.85 ($M+H^+$), calcd $C_{17}H_{24}N_2O_6$ 352.1634; Anal. calcd for $C_{17}H_{24}N_2O_6$ (352.1634): C, 57.94; H, 6.86; N, 7.95. Found: C, 57.98; H, 6.79; N, 7.88%.



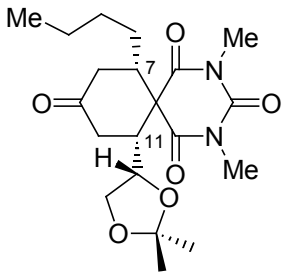
***cis*-1lcb**

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-propyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1mcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 92 °C; **$[\alpha]^{25}_{D} = -13.0$ (*c* 0.7, $CHCl_3$);** IR (neat): ν_{max} 2985, 2361, 1679 (C=O), 1449, 1420, 1376, 1269, 1058 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93-3.89 (1H, m), 3.86 (1H, t, *J* = 8.4 Hz), 3.60 (1H, dd, *J* = 8.0, 5.2 Hz), 3.37 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 2.99 (1H, t, *J* = 15.2 Hz), 2.79 (1H, dd, *J* = 14.8, 11.2 Hz), 2.72-2.61 (2H, m), 2.53 (1H, dd, *J* = 15.2, 4.8 Hz), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz), 1.36-1.30 (1H, m), 1.27 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.14-1.04 (3H, m), 0.81 (3H, t, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, C=O), 172.1 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.7 (CH), 44.5 (CH), 42.0 (CH_2), 36.4 (CH_2), 33.8 (CH_2), 28.9 (CH_3), 28.4 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 19.6 (CH_2), 13.7 (CH_3); LRMS m/z 381.35 ($M+H^+$), calcd $C_{19}H_{28}N_2O_6$ 380.1947; Anal. calcd for $C_{19}H_{28}N_2O_6$ (380.1947): C, 59.98; H, 7.42; N, 7.36. Found: C, 59.88; H, 7.37; N, 7.45%.



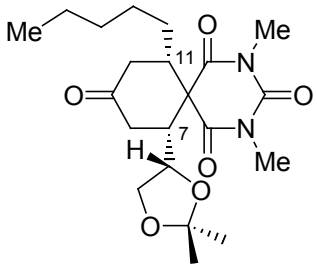
***cis*-1mcb**

(4'*S*,7*S*,11*R*)-7-Butyl-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1ncb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 90 °C; **$[\alpha]^{25}_{D}$ = –13.6 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2986, 2361, 1678 (C=O), 1450, 1377, 1275, 1266, 1060 and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90-3.86 (1H, m), 3.84 (1H, t, *J* = 8.0 Hz), 3.59 (1H, dd, *J* = 8.4, 5.6 Hz), 3.35 (3H, s, NCH_3), 3.26 (3H, s, NCH_3), 2.98 (1H, t, *J* = 14.4 Hz), 2.78 (1H, t, *J* = 12.8 Hz), 2.71-2.67 (1H, m), 2.62-2.48 (2H, m), 2.31 (1H, dd, *J* = 15.6, 4.0 Hz), 1.26 (3H, s, CH_3), 1.22-1.20 (2H, m), 1.16 (3H, s, CH_3), 1.16-1.10 (4H, m), 0.79 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, C=O), 172.0 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 56.1 (C), 47.6 (CH), 44.6 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.4 (CH_2), 28.8 (CH_3), 28.5 (CH_2), 28.4 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 22.2 (CH_2), 13.7 (CH_3); LRMS m/z 395.40 ($M+H^+$), calcd $C_{20}H_{30}N_2O_6$ 394.2104; Anal. calcd for $C_{20}H_{30}N_2O_6$ (394.2104): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.61; N, 7.22%.



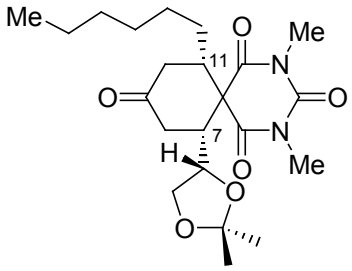
***cis*-1ncb**

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,4-dimethyl-11-pentyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1ocb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_{D}$ = –13.0 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2924, 1677 (C=O), 1421, 1376, 1132, 1056, 880 and 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91-3.84 (2H, m), 3.60 (1H, dd, *J* = 8.4, 5.6 Hz), 3.37 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 3.00 (1H, t, *J* = 14.4 Hz), 2.82-2.68 (2H, m), 2.63-2.52 (2H, m), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz), 1.27 (3H, s, CH_3), 1.28-1.10 (8H, m), 1.17 (3H, s, CH_3), 0.82 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, C=O), 172.1 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 66.0 (CH_2, OCH_2), 56.1 (C), 47.7 (CH), 44.7 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 28.8 (CH_3), 28.4 (CH_3), 26.1 (CH_2), 25.6 (CH_3), 24.6 (CH_3), 22.3 (CH_2), 13.8 (CH_3); LRMS m/z 409.00 ($M+H^+$), calcd $C_{21}H_{32}N_2O_6$ 408.2260; Anal. calcd for $C_{21}H_{32}N_2O_6$ (408.2260): C, 61.75; H, 7.90; N, 6.86. Found: C, 61.82; H, 7.82; N, 6.75%.



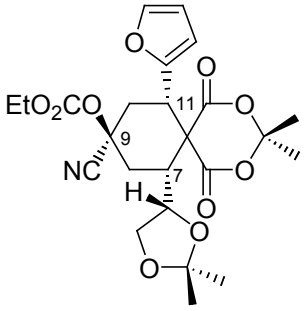
***cis*-1ocb**

(4'*S*,7*R*,11*S*)-7-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-11-hexyl-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone (*cis*-1pcb): Prepared following procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 88 °C; **$[\alpha]^{25}_{D}$ = –13.8 (*c* 1.0, $CHCl_3$);** IR (neat): ν_{max} 2988, 2361, 1675 (C=O), 1451, 1421, 1378, 1274, 1209,, 1056, 878, 755 and 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89-3.88 (1H, m), 3.84 (1H, t, *J* = 8.4 Hz), 3.59 (1H, dd, *J* = 8.4, 5.6 Hz), 3.36 (3H, s, NCH_3), 3.26 (3H, s, NCH_3), 2.98 (1H, t, *J* = 14.8 Hz), 2.77 (1H, t, *J* = 14.4 Hz), 2.68 (1H, br dd, *J* = 14.0, 2.0 Hz), 2.61-2.56 (1H, m), 2.51 (1H, dd, *J* = 15.2, 4.8 Hz), 2.31 (1H, dd, *J* = 15.6, 3.6 Hz), 1.26 (3H, s, CH_3), 1.22-1.08 (10H, m), 1.16 (3H, s, CH_3), 0.82 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, C=O), 172.0 (C, O=C-N), 168.8 (C, O=C-N), 151.0 (C), 109.8 (C, O-C-O), 74.3 (CH, OCH), 65.9 (CH_2, OCH_2), 56.1 (C), 47.6 (CH), 44.7 (CH), 42.0 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 28.85 (CH_2), 28.83 (CH_3), 28.4 (CH_3), 26.4 (CH_2), 25.6 (CH_3), 24.6 (CH_3), 22.4 (CH_2), 13.9 (CH_3); LRMS m/z 423.00 ($M+H^+$), calcd $C_{22}H_{34}N_2O_6$ 422.2417; Anal. calcd for $C_{22}H_{34}N_2O_6$ (422.2417): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.23; N, 6.55%.



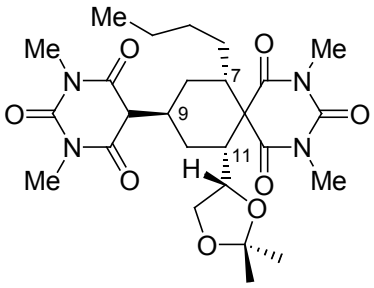
***cis*-1pcb**

Ethyl (4'*S*,7*R*,9*R*,11*S*)-9-cyano-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-11-furan-2-yl-3,3-dimethyl-1,5-dioxo-2,4-dioxa-spiro[5.5]undec-9-yl carbonate [(–)-8jca]: Prepared following procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid. **$[\alpha]^{25}_{D}$ = –33.5 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2990, 1757 (O-C=O), 1736 (C=O), 1374, 1257, 1067, 1014, 735 and 627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, d, *J* = 0.8 Hz), 6.30 (1H, dd, *J* = 3.2, 1.6 Hz), 6.18 (1H, d, *J* = 3.2 Hz), 4.28 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.21-4.19 (1H, m), 4.07 (1H, dd, *J* = 9.2, 7.6 Hz), 3.96 (1H, dd, *J* = 13.6, 3.2 Hz), 3.78 (1H, dd, *J* = 9.2, 4.8 Hz), 3.03 (1H, t, *J* = 13.2 Hz), 2.78-2.73 (3H, m), 2.46 (1H, d, *J* = 10.8 Hz), 1.68 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.34 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.24 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.5 (C,O-C=O), 163.7 (C, O=C-O), 152.3 (C, O-(O=*C*)-O), 150.4 (C), 142.7 (CH), 117.5 (C, CN), 110.9 (CH), 110.6 (C, O-C-O), 109.2 (CH), 106.6 (C, O-C-O), 74.3 (C), 73.8 (CH, OCH), 66.7 (CH_2, OCH_2), 65.2 (CH_2, OCH_2CH_3), 54.8 (C), 45.8 (CH), 41.8 (CH), 34.0 (CH_2), 29.1 (CH_2), 28.9 (CH_3), 28.8 (CH_3), 25.6 (CH_3), 24.2 (CH_3), 14.1 (CH_3, OCH_2CH_3); LRMS m/z 490.25 ($M-H^+$), calcd $C_{24}H_{29}NO_{10}$ 491.1791; Anal. calcd for $C_{24}H_{29}NO_{10}$ (491.1791): C, 58.65; H, 5.95; N, 2.85. Found: C, 58.47; H, 5.89; N, 2.90%.



(–)-8jca

(4'*S*,7*S*,9*S*,11*R*)-7-Butyl-11-(2,2-dimethyl-[1,3]dioxolan-4-yl)-9-(1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5-trione [(–)-9ncb]:



(–)-9ncb

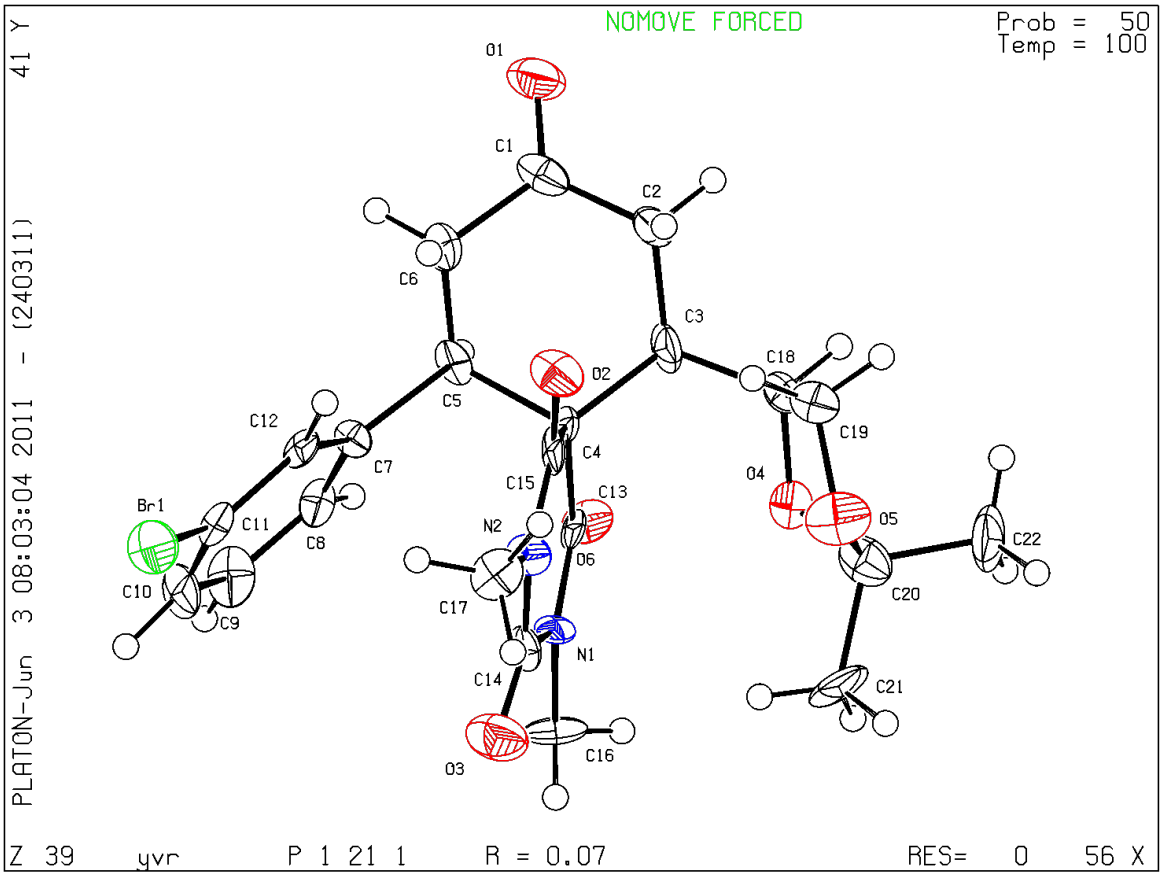
Prepared following procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as colorless solid. mp.: 96 °C; **$[\alpha]^{25}_{D}$ = –31.6 (*c* 0.5, $CHCl_3$);** IR (neat): ν_{max} 2958, 2926, 2360, 1675 (N-C=O), 1445, 1373, 1261, 1131, 1062, 758 and 641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88-3.78 (3H, m), 3.37 (3H, s, NCH_3), 3.28 (6H, s, 2 x NCH_3), 3.24 (3H, s, NCH_3), 2.69 (1H, d, *J* = 12.4 Hz), 2.53-2.48 (1H, m), 2.31-2.17 (3H, m), 1.85 (1H, d, *J* = 13.2 Hz), 1.52 (1H, d, *J* = 13.6 Hz), 1.26 (3H, s, CH_3), 1.26-1.18 (5H, m), 1.18 (3H, s, CH_3), 0.95-0.84 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.0 (C, O=C-N), 169.3 (C, O=C-N), 168.8 (C, O=C-N), 168.6 (C, O=C-N), 151.9 (C), 151.4 (C), 109.4 (C, O-C-O), 75.0 (CH, OCH), 66.0 (CH_2, OCH_2), 57.0 (C), 51.5 (CH), 42.9 (CH), 39.7 (CH), 37.2 (CH), 31.3 (CH_2), 28.77 (CH_3), 28.75 (CH_3), 28.72 (CH_3) 28.4 (CH_3), 27.2 (2 x CH_2), 25.7 (CH_3), 24.5 (CH_3), 22.5 (CH_2), 22.2 (CH_2), 13.8 (CH_3); LRMS m/z 535.25 ($M+H^+$), calcd $C_{26}H_{38}N_4O_8$ 534.2690; Anal. calcd for $C_{26}H_{38}N_4O_8$ (534.2690): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.29; H, 7.22; N, 10.55%.

CheckCIF/PLATON report for the compound cis-(-)-1gcb

Datablock: YVR-V-151

```
Bond precision:      C-C = 0.0113 A              Wavelength=1.54184
Cell:        a=7.6547(9)    b=10.4150(9)   c=13.3157(14)
             alpha=90       beta=90.1000   gamma=90
Temperature: 100 K
                    Calculated                    Reported
Volume              1061.58(19)                   1061.58(19)
Space group         P 21                          P 1 21 1
Hall group          P 2yb                         ?
Moiety formula      C22 H25 Br N2 O6              ?
Sum formula         C22 H25 Br N2 O6              C22 H25 Br N2 O6
Mr                  493.34                        493.35
Dx,g cm-3           1.543                         1.543
Z                   2                             2
Mu (mm-1)           3.008                         3.008
F000                508.0                         508.0
F000'               508.09
h,k,lmax            9,12,15                       8,12,15
Nref                1914[ 3608]                   3117
Tmin,Tmax           0.362,0.718                   0.379,0.733
Tmin'               0.261
Correction method= MULTI-SCAN
Data completeness= 1.63/0.86   Theta(max)= 65.050
R(reflections)= 0.0729( 3010)     wR2(reflections)= 0.1709( 3117)
                 S = 1.020            Npar= 285
```

Datablock: YVR-V-151- ellipsoid plot



CheckCIF/PLATON report for the compound cis-(-)-1gab

Datablock: YVR-V-106

Bond precision: C-C = 0.0051 A Wavelength=1.54184

Cell: a=10.5256(2) b=12.1392(2) c=20.3601(3)
alpha=90 beta=90 gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	2601.46(8)	2601.46(8)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	?
Moiety formula	C25 H31 Br N2 O8	C25 H31 Br N2 O8
Sum formula	C25 H31 Br N2 O8	C25 H31 Br N2 O8
Mr	567.42	567.43
Dx,g cm-3	1.449	1.449
Z	4	4

Mu (mm-1)	2.590	2.590
F000	1176.0	1176.0
F000'	1176.77	
h,k,lmax	11,13,22	11,13,22
Nref	2143[3738]	2927
Tmin,Tmax	0.408,0.537	0.505,1.000
Tmin'	0.309	

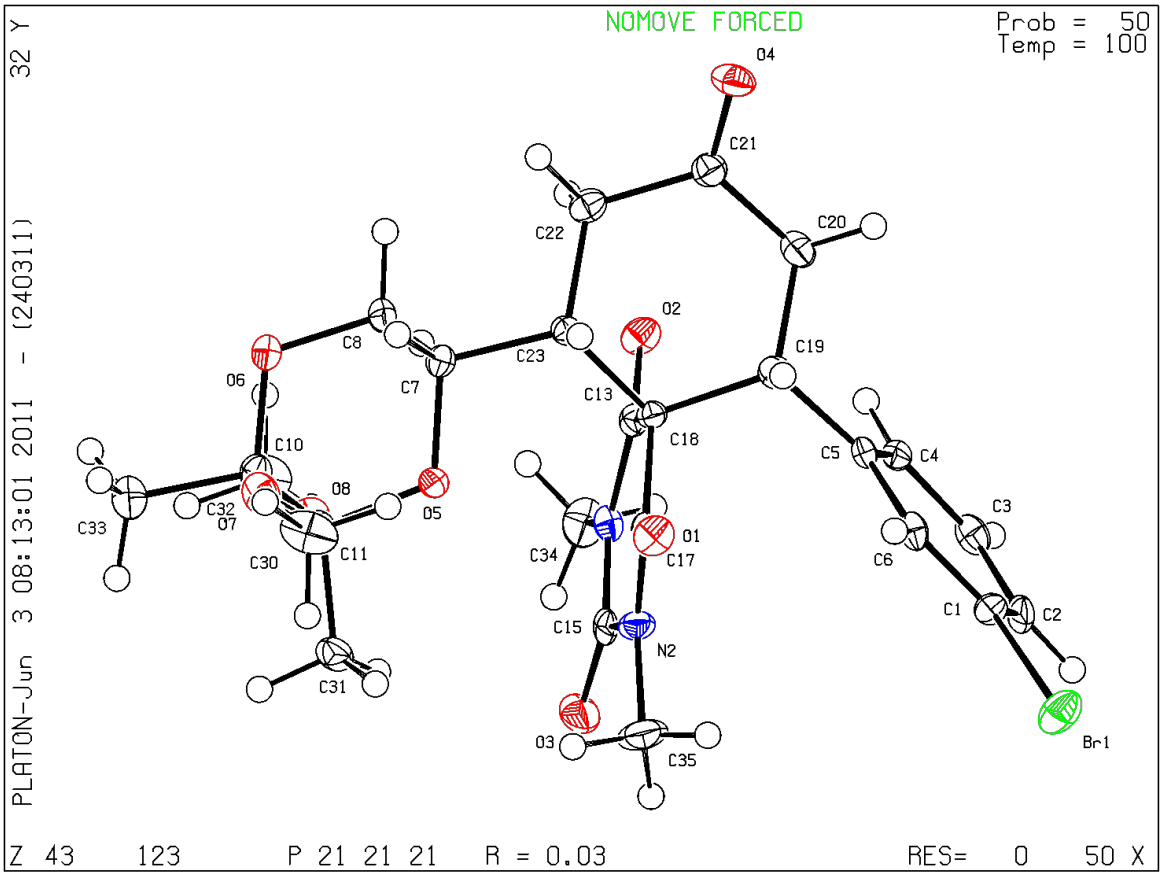
Correction method= MULTI-SCAN

Data completeness= 1.37/0.78 Theta(max)= 58.900

R(reflections)= 0.0295(2922) wR2(reflections)= 0.0791(2927)

S = 1.111 Npar= 332

Datablock –YVR-V-106 - ellipsoid plot



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1) (a) Michel, P.; Ley, S. V.; *Angew. Chem. Int. Ed.,* **2002**, *41*, 3898-3901. (b) Michel, P.; Ley, S. V.; *Synthesis,* **2003**, 1598-1602. (c) Ley, S. V.; Michel, P.; *Synthesis,* **2004**, 147-150. (d) Baer, E.; Fischer, H. O. L.; *J. Biol. Chem.,* **1939**, 463-473. (e) Leyes, A. E.; Poulter, C. D.; *Org. Lett.,* **1999**, *1*, 1067-1070. (f) Garner, P.; Park, J. M.; *Organic Synthesis*, **1998**, *9*, 300. (g) Reetz, T.; Drewes, M. W.; Schwickardi, R.; *Organic Synthesis*, **2004**, *10*, 256.

2) 1. D'Andrea, G., F. Brisdelli, et al. (**2008**). "AZT: an old drug with new perspectives." Curr Clin Pharmacol **3**(1): 20-37.

3) 2. Kutner, R. H., X. Y. Zhang, et al. (**2009**). "Production, concentration and titration of pseudotyped HIV-1-based lentiviral vectors." Nat Protoc **4**(4): 495-505.

4) 3. Ahmed, N., K. G. Brahmbhatt, et al. (**2010**). "Synthesis and anti-HIV activity of alkylated quinoline 2,4-diols." Bioorg Med Chem **18**(8): 2872-2879.

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