Outer Ring Stereochemical Modulation of Cytotoxicity in Cephalostatins

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Supporting Information

Experimental

General Procedures

All reagents purchased were used as received. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Benzene, toluene, and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. Acetonitrile (CH_3CN), chloroform ($CHCl_3$), and methanol (CH_3OH) were spectra-grade. Dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were distilled from calcium hydride. n-BuLi and t-BuLi were titrated prior to use by dropwise addition to a solution of menthol in benzene at room temperature in the presence of 2,2'-dipyridyl (for n-BuLi) and 1,10-phenanthroline (for t-BuLi). Sodium sulfate (Na_2SO_4) and magnesium sulfate ($MgSO_4$) were anhydrous. All recrystallization, chromatographic, and workup solvents were distilled. Powdered 4Å molecular sieves (Lancaster) were oven and/or flame activated under vacuum prior to use.

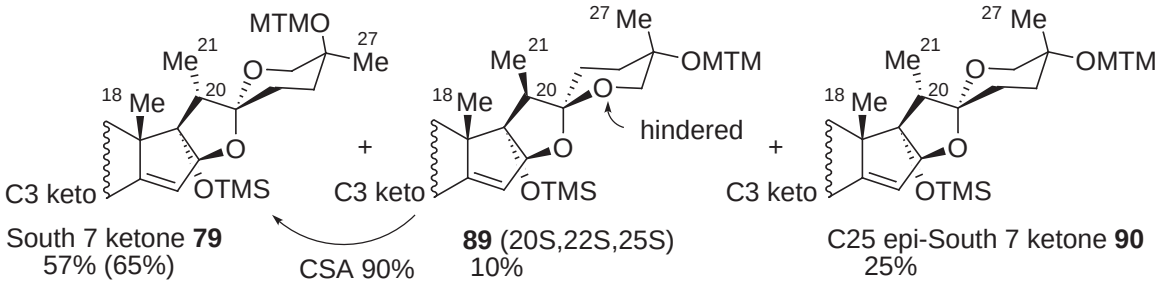
Glasswares were oven dried and/or flame dried. Reactions were carried out under a positive pressure of argon in anhydrous solvents (unless otherwise indicated), and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) in comparision with the starting material(s). TLC was performed on glass-backed silica gel 60 F 254 plates (EM reagents, 0.25 mm) and eluted with (v/v) EtOAc in hexane or the specified solvent solutions. The TLC plates were visualized with a UV lamp (254 nm) and/or with TLC visualizing solutions activated with heat. The two commonly employed TLC visualizing solutions were: (i) p-anisaldehyde solution (1350 mL absolute ethanol, 50 mL concentrated H_2SO_4, 15 mL glacial acetic acid, 37 mL p-anisaldehyde), and (ii) permanganate solution (weight percents of 1% $KMnO_4$ and 2% Na_2CO_3 in water).

Analytical samples were obtained from flash silical gel chromatography (sgc), using silica gel of 60-200 mesh or 230-400 mesh, or from recrystallization of the crude products. Melting points were obtained on a MEL-TEMP capillary melting point apparatus and are uncorrected. Optical rotations were taken on a Rudolph Research Autopol III instrument. ^{1}H-NMR spectra were recorded on General Electric QE-300 (300 MHz), Varian VXR-500S (500 MHz) and Varian UNITY *Plus*-600 (600 MHz) spectrometers. ^{13}C-NMR spectra were recorded on General Electric QE-300 (75 MHz) and Varian UNITY *Plus*-600 (150 MHz) spectrometers. NMR spectra were determined in chloroform-d_1 ($CDCl_3$), benzene-d_6 (C_6D_6) or pyridine-d_5 (C_5D_5N) solution and are reported in parts per million (ppm) from the residual chloroform (7.27 ppm and 77.23 ppm), benzene (7.16 ppm and 128.39 ppm) or pyridine (8.74 ppm and 150.35 ppm) standard, respectively. Peak multiplicities in ^{1}H-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), and/or ap (apparent) and/or br (broad). Peaks in APT spectra were assigned as 'odd' (or starred*) for carbons with one or three attached hydrogen atoms, or 'even' (or unmarked) for carbons with zero or two attached hydrogen atoms. Mass spectra were run by the Purdue University campus wide mass spectrometry facility. The low resolution EI and CI (isobutane) spectra were obtained on a Finnigan 4000 mass spectrometer with a Nova 4 data system with the molecular ion designated as "M^+." The high resolution mass spectra were obtained on a Kratos MS-50 instrument. FAB spectra were also obtained on the Kratos MS-50 instrument with different matrices as noted in the text. Compounds characterized by exact mass were homogeneous by TLC and NMR.

NMR shift assignment were performed by analogy to known compounds and should be regarded as tentative.

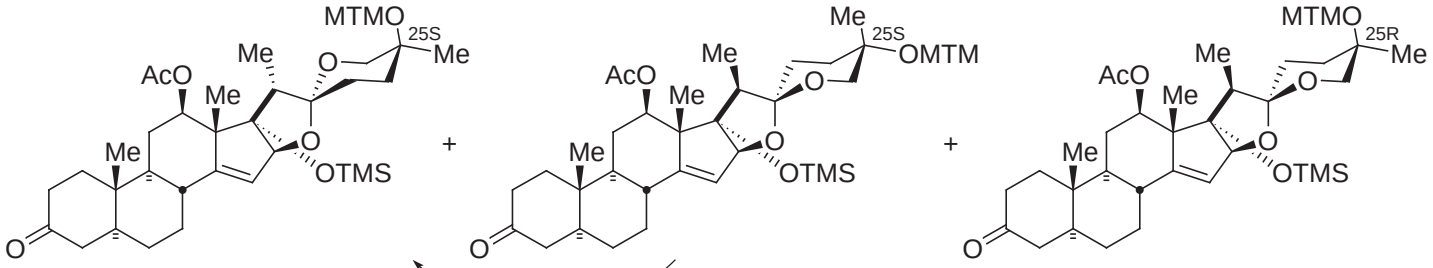
Separation and equilibration of the spiroketals **8a/iso8a/6a** (**79/89/90**, corrected from ref 11b, see NMR tables / comparisons section after the Experimentals for discussion):

Relevant portion of Scheme 20:



South 7 ketone **79** 57% (65%) | **89** (20S,22S,25S) 10% | C25 epi-South 7 ketone **90** 25%

proposed correction to Scheme 20 (note 20βMe = 20R, not 20S):



South 7 ketone **79** (20S,22R,25S) 57% (65%) | **89** (20R,22S,25S) 10% | **90** [20R,22S,25R] 25%

numbering for this work:	**8a** (20S,22R,25S) 20α,22α,25α	**iso-8a** (20R,22S,25S) 20β,22β,25β	**6a** (20R,22S,25R) 20β,22β,25α

The mixture of 6,5-spiroketals **8a/iso-8a/6a** (255 mg, 0.40 mmol) was subjected to column chromatography (CH_2Cl_2/THF: 200:1 to 100:1) to give 90 mg of pure natural spiroketal **8a** and 155 mg of other spiroketals, which were treated with CSA (10 mol %) in CH_2Cl_2 (15 mL) for 1h. The resulting mixture was purified by sgc (CH_2Cl_2/THF: 200:1 to 100:1) to give 56 mg of pure natural spiroketal **8a**, 65 mg of **6a**, and 25 mg of **iso-8a**. Further treatment of **6a** with CSA in CH_2Cl_2 produced no change. Compound **iso-8a** was converted into natural spiroketal **8a** (20 mg) upon another 1 h treatment with CSA in CH_2Cl_2. Overall, the natural spiroketal **8a** (166 mg) and the 25-epimer **6a** (65 mg) were obtained in 65% and 25% yields, respectively.

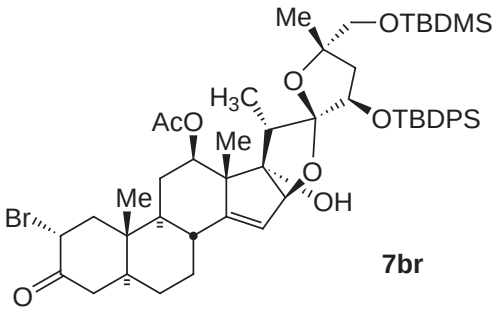
8a: R_f = 0.22 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.34 (1H, t, J=2.3 Hz), 5.14 (1H, dd, J=11.7, 4.6 Hz), 4.78 (1H, d, J=2.3 Hz), 4.39 (1H, d, J=10.5 Hz, H_{MTMa}), 4.31 (1H, d, J=10.5 Hz, H_{MTMb}), 3.58 (1H, dd, J=12.2, 2.2 Hz, H_{26b}), 3.51 (1H, d, J=12.2 Hz, H_{26a}), 2.33 (1H, q, J=7.0 Hz), 2.23 (1H, apdt), 2.05 (3H, s, H_{SMe}), 2.01 (2H, m), 1.75 (3H, s, H_{ac}), 1.12 (3H, s), 1.04 (3H, d, J=7.2 Hz), 0.77 (3H, s), 0.66 (1H, apdt), 0.62 (1H, apbrt), 0.41 (3H, s), 0.29 (9H, s, H_{tms}); ^{13}C NMR (75 MHz, C_6D_6) δ 207.6, 168.9 (C_{ac}), 158.8, 117.5, 107.8, 93.2, 89.8, 73.6, 71.6, 66.9 (C_{mtm}), 64.5, 56.3, 50.2, 46.6, 44.8, 44.0, 37.5 (2C), 35.2, 34.5, 31.3, 29.0, 28.0 (2C), 26.8, 21.2, 20.8, 19.9, 13.9 (C_{mtm}), 10.4, 9.2, 2.3 (3C, C_{tms}); MS (EI): 634 (M^+); MS(CI): 635 (M+H), 545 (M+H-HOTMS); HRMS (EI): calcd for $C_{34}H_{54}O_7SSi$ 634.3360; found 634.3347.

iso-8a: R_f = 0.18 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.25 (1H, s), 5.01 (1H, dd), 4.85 (1H, brs), 4.38 (2H, s, $H_{MTMa,b}$), 4.12 (1H, d, H_{26a}), 3.38 (1H, brd, H_{26b}), 2.82 (1H, q), 2.19 (1H, apdt), 2.03-1.83 (3H, m), 1.91 (3H, s, H_{SMe}), 1.77 (3H, s, H_{ac}), 1.34 (3H, s), 1.22 (3H, s), 0.91 (3H, d), 0.60 (1H, apdt), 0.47 (1H, aptbrt), 0.40 (3H, s), 0.22 (9H, s, H_{tms}); ^{13}C NMR (125 MHz, C_6D_6) δ 207.9, 169.3 (C_{ac}), 155.1, 119.9, 109.2, 95.0, 91.2, 75.2, 72.9, 69.0, 66.9 (C_{mtm}), 56.5, 51.1, 48.5, 45.4, 44.3, 37.8, 35.6, 34.3, 31.2, 30.4, 29.0, 28.6, 28.3, 27.5, 21.2, 20.4 (C_{ac}), 18.0, 14.1 (C_{mtm}), 11.7, 10.7, 2.3 (3C, C_{tms}); MS

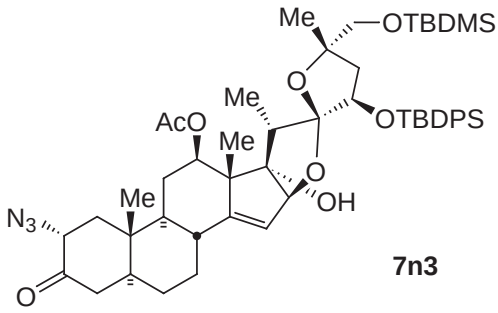
(EI): 634 (M^+); MS(CI): 635 (M+H), 545 (M+H-HOTMS); HRMS (EI): calcd for $C_{34}H_{54}O_7SSi$ 634.3360; found 634.3340.

6a: R_f = 0.20 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.32 (1H, br t), 5.03 (1H, dd), 4.86 (1H, br s), 4.41 (1H, d, J=9.7 Hz, H_{MTMa}), 4.33 (1H, d, J=9.7 Hz, H_{MTMb}), 3.74 (1H, d, H_{26a}), 3.62 (1H, br dd, H_{26b}), 2.88 (1H, q), 2.11 (1H, apdt), 2.00 (3H, s, H_{SMe}), 2.0-1.8 (3H, m), 1.75 (3H, s, H_{ac}), 1.37 (3H, s), 0.96 (3H, d), 0.80 (3H, s), 0.60 (1H, apdt), 0.51 (1H, apbrt), 0.39 (3H, s), 0.22 (9H, s, H_{tms}); ^{13}C NMR (125 MHz, C_6D_6) δ 207.6, 169.1 (C_{ac}), 155.3, 119.5, 109.2, 94.6, 90.5, 74.8, 71.9, 66.9 (C_{mtm}), 66.6, 56.3, 50.8, 48.4, 45.2, 44.1, 37.6, 37.4, 35.4, 34.2, 30.8, 28.8, 28.0, 27.2, 25.8, 21.2, 20.9 (C_{ac}), 17.9, 13.9 (C_{mtm}), 11.1, 10.4, 2.2 (3C, C_{tms}); MS (EI): 634 (M^+); MS(CI): 635 (M+H, base peak), 545 (M+H-HOTMS); HRMS (EI): calcd for $C_{34}H_{54}O_7SSi$ 634.3360; found 634.3353.

North 1 α-bromoketone **7br** and α-azidoketone **7n3**:



7br



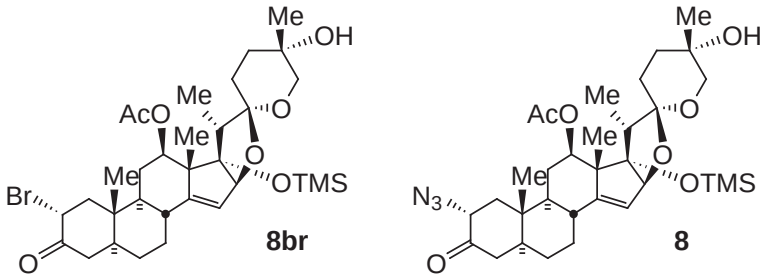
7n3

To a magnetically stirred THF solution (4.9 mL) of north ketone **7a** (84 mg, 0.097 mmol), phenyltrimethylammonium tribromide (PTAB) (38 mg, 0.10 mmol) was added in one portion at 0°C followed by addition of HOAc in THF (10 μg, 1%v/v). The reaction was quenched with concentrated aqueous $Na_2S_2O_3$ at the point when the color of the suspension changed from orange to pale yellow. The mixture was extracted with Et_2O (3x20 mL) and the combined organic extracts were washed with brine (1x25 mL) and dried ($MgSO_4$). Silica gel chromatography (15% EtOAc/hexane) afforded 78.5 mg (86%) of α-bromoketone **7br** and 6 mg (7%) of starting material **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (2H, m), 7.73 (2H, m), 7.42 (6H, m), 5.56 (1H, br s), 5.03 (1H, dd, J =11.0, 5.1 Hz), 4.93 (1H, br s), 4.71 (1H, dd, J=13.0, 6.2 Hz), 4.31 (1H, dd, J=10.0, 8.0 Hz), 3.99 (1H, s), 3.10 (1H, d, J=10 Hz), 2.97 (1H, d, J=10 Hz), 2.55 (1H, dd, J = 13, 6.3 Hz), 2.46-2.42 (2H, m), 1.99 (3H, s), 1.23 (3H, s), 1.13 (3H, s), 1.11 (3H, d, J = 7.1 Hz), 1.10 (3H, s), 1.00 (9H, s), 0.74 (9H, s), -0.15 (3H, s), -0.16 (3H, s), 2.2-0.8 (remaining H's, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5, 170.2, 150.6, 135.9, 135.5, 133.6, 132.6, 130.2, 129.8, 128.0, 127.6, 122.7, 116.4, 93.1, 89.2, 81.9, 74.2, 73.9, 69.1, 53.7, 53.3, 52.2, 50.9, 46.9, 44.2, 43.6, 39.2, 37.5, 33.1, 28.1, 27.8, 27.4, 26.6, 25.9, 25.6, 21.3, 19.2, 18.2, 13.6, 11.9, 8.7, -5.6, -5.8; MS (FAB, NBA): 949 (M^++H); HRMS (FAB, NBA): calcd for $C_{51}H_{74}BrO_8Si_2$ 949.4106; found 949.4125. $[\alpha]_D^{23}$ = + 45° in CH_2Cl_2 (c = 1.0).

Tetramethylguanidinium azide (17 mg, 0.11 mmol) was dissolved in CH_3NO_2 (0.8 mL) and added to a solution of **7br** (26 mg, 0.027 mmol) in CH_3NO_2 (2 mL). The reaction was allowed to stir for 6h. The CH_3NO_2 was removed in vacuo and the product was filtered through a 2 inch pad of silica gel eluting with 15% EtOAc in hexane to afford 25 mg (100%) of **7n3** as a white film. ^{1}H NMR ($CDCl_3$): δ -0.16 (s, 3H), -0.15 (s, 3H), 0.74 (s, 9H), 1.00 (s, 9H), 1.10 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 1.13 (s, 3H), 1.23 (s, 3H), 1.99 (s, 3H), 2.45 (q, J = 7.1 Hz, 1H), 2.97 (d, J = 10 Hz, 1H), 3.10 (d, J = 10 Hz, 1H), 3.96 (dd, J = 13, 6.3 Hz, 1H), 3.99 (s, 1H), 4.31 (dd, J = 10, 8.0 Hz, 1H), 4.93 (br s, 1H), 5.03 (dd, J = 11, 5.1 Hz, 1H), 5.56 (br s, 1H), 7.36-7.46 (m, 6H), 7.72-7.75 (m, 2H), 7.83-7.86 (m, 2H), 0.8-2.4 (remaining H, m); ^{13}C NMR ($CDCl_3$): δ -5.8, -5.6, 8.7, 12.3, 13.6, 18.2, 19.2, 21.3, 25.6, 25.9 (3C), 26.6 (3C), 27.5, 27.9, 28.2, 33.1, 37.2, 37.5, 43.5, 44.2, 44.9, 47.1, 52.3, 53.3, 63.7, 69.1, 73.9, 74.2, 81.9, 89.2, 93.1, 116.4, 122.7, 127.6 (2C), 128.0 (2C), 129.8, 130.2, 132.6, 133.6, 135.5 (2C), 135.9 (2C), 150.6, 170.2, 204.5; MS (FAB,

NBA): 912 (M^++H); HRMS (FAB, NBA): calcd for $C_{51}H_{74}N_3O_8Si_2$ 912.5015; found 912.4987. $[\alpha]_D^{22}$: +64.3º in CH_2Cl_2 (c = 1).

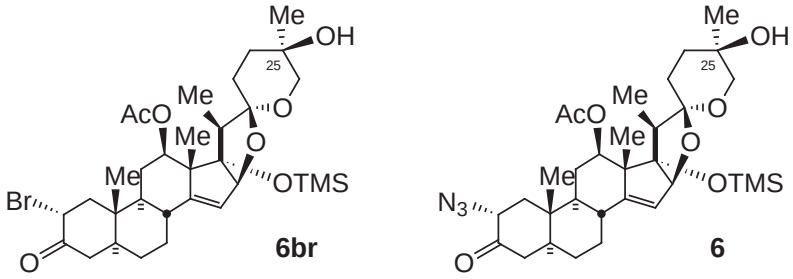
South 7 bromoketone **8br** and azidoketone **8**:



32 mg **8a** gave 25 mg (82%) of **8br**: R_f = 0.16 (1:3 EtOAc/Hex); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.31 (s, 9H), 0.31 (s, 3H), 0.98 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.10 (s, 3H), 1.80 (s, 3H), 1.83-2.1 (4H, m), 2.23 (dd, J = 12.6, 6.2 Hz, 1H), 2.33 (q, J = 7.1 Hz, 1H), 3.24 (dd, J = 11.3, 2.6 Hz, 1H), 3.74 (d, J = 11.3 Hz, 1H), 4.10 (dd, J = 13.4, 6.2 Hz, 1H), 4.77 (d, J = 2.4 Hz, 1H), 5.15 (dd, J = 11.6, 4.6 Hz, 1H), 5.32 (t, J = 2.3 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3 (o), 9.1 (o), 10.8 (o), 19.8 (o), 20.7 (o), 25.1 (o), 26.8 (e), 27.4 (e), 28.2 (e), 28.6 (e), 32.6 (e), 34.0 (o), 38.3 (e), 43.2 (e), 45.0 (o), 46.7 (o), 49.5 (o), 50.0 (e), 53.6 (o), 56.2 (e), 65.9 (e), 68.9 (e), 73.2 (o), 89.9 (o), 93.1 (e), 107.7 (e), 117.8 (o), 158.2 (e), 168.8 (e), 197.9 (e); MS (EI): 652/654 $(M)^+$; HRMS (EI): calculated for $C_{32}H_{49}BrO_7Si$ 652.2431, found 652.2464.

25 mg **8br** gave 23 mg (96%) of **8**: R_f = 0.16 (1:3 EA/Hex); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.31 (s, 9H), 0.32 (s, 3H), 0.98 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.12 (s, 3H), 1.80 (s, 3H), 1.83-2.1 (4H, m), 3.22 (dd, J = 13, 6 Hz, 1H), 3.26 (dd, J = 11.1, 2.5 Hz, 1H), 3.75 (d, J = 11.1, 1H), 4.78 (d, J = 2.2 Hz, 1H), 5.16 (dd, J = 11.7, 4.6 Hz, 1H), 5.33 (t, J = 2.3 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3 (o), 9.1 (o), 11.3 (o), 19.8 (o), 20.7 (o), 25.1 (o), 26.9 (e), 27.4 (e), 28.2(e), 28.7 (e), 32.6 (e), 33.9 (o), 36.2 (e), 43.0 (e), 44.2 (e), 44.9 (o), 46.7 (o), 49.5 (o), 56.3 (e), 63.0 (o), 65.9 (e), 68.9(e), 73.3 (o), 89.9 (o), 93.2 (e), 107.7 (e), 117.6 (o), 158.2 (e), 168.9 (e), 202.8 (e); MS (EI): 615 $(M)^+$; HRMS (EI): calcd for $C_{32}H_{49}N_3O_7Si$ 615.3340, found 615.3321.

25'epi-South 7 bromoketone **6br** and azidoketone **6**:

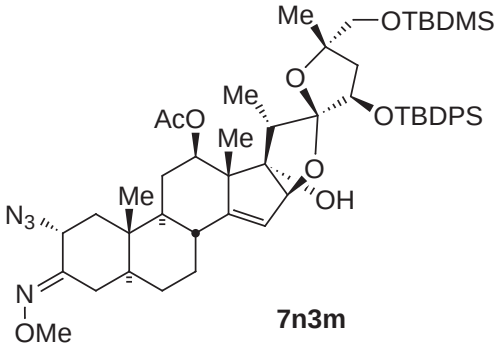


15 mg of **6a** gave 5 mg (33%) of mixed 2-bromo-3-keto-5,6- and 5,5-spiroketals and 8 mg (52%) of **6br:** ^{1}H NMR (300 MHz, C_6D_6): δ 5.26 (1H, br s), 5.10 (1H, dd, J=11.5, 4.5 Hz, H_{12}), 4.72 (1H, brs, H_{16}), 4.05 (dd, J = 13.4, 6.2 Hz, 1H), 3.72 (1H, d, J=11 Hz, H_{26a}), 3.18 (1H, dd, J=11, 2 Hz, H_{26b}), 2.30 (1H, q, J=7.0 Hz, H_{20}), 2.18 (dd, J = 12.6, 6.2 Hz, 1H, H_{1a}), 2.08-1.85 (3H, m), 1.75 (3H, s, H_{Ac}), 1.14 (3H, s, H_{27}), 1.07 (3H, s, H_{18}), 0.99 (3H, d, J=7 Hz, H_{21}), 0.27 (3H, s, H_{19}), 0.25 (9H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 197.9 (C_3), 168.8 (C_{ac}), 158.0 (C_{14}), 117.8 (C_{15}), 107.4 (C_{22}), 93.1 (C_{16}), 89.7 (C_{17}), 73.2 (C_{12}), 68.8 (C_{26}), 66.5 (C_{25}), 56.2 (C_{13}), 53.5 (C_2), 50.0 (C_4), 49.4 (C_9), 46.2 (C_{20}), 44.9 (C_5), 43.2 (C_1), 38.3 (C_{10}), 34.4, 34.0 (C_8), 30.8 (C_{24}), 28.6 (C_7), 27.4 (C_{23}), 26.8 (C_{11}), 24.2 (C_{27}), 20.7 (C_{ac}), 19.8 (C_{18}), 10.9 (C_{19}), 9.1 (C_{21}), 2.3 (C_{tms}). MS (FAB): 653/655 $(M+H)^+$; HRMS (FAB): calculated for M+H $C_{33}H_{49}BrO_7Si$ 653.2509, found 653.2522.

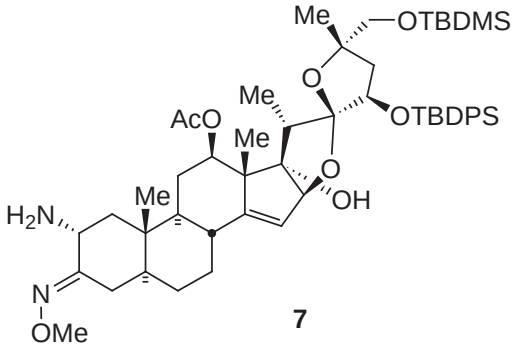
7 mg of **6br** gave 4 mg (61%) of **6** containing 15% **6br:** ^{1}H NMR (300 MHz, C_6D_6): δ 5.26 (1H, br s), 5.10 (1H, dd, J=11.5, 4.5 Hz, H_{12}), 4.72 (1H, brs, H_{16}), 3.72 (1H, d, J=11 Hz, H_{26a}), 3.18 (1H, dd, J=11,2

Hz, H_{26b}), 3.14 (1H, dd, J=13, 7 Hz, H_2), 2.28 (1H, q, J=7.0 Hz, H_{20}), 2.03-1.87 (3H, m), 1.75 (3H, s, H_{Ac}), 1.15 (3H, s, H_{18}), 1.09 (3H, s, H_{19}), 0.99 (3H, d, J=7 Hz, H_{21}), 0.24 (9H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 202.4 (C_3), 168.5 (C_{ac}), 158.0 (C_{14}), 117.8 (C_{15}), 107.4 (C_{22}), 93.1 (C_{16}), 89.8 (C_{17}), 73.3 (C_{12}), 68.8 (C_{26}), 66.5 (C_{25}), 63.0 (C_2), 56.2 (C_{13}), 49.5 (C_9), 46.2 (C_{20}), 44.9 (C_4), 44.1 (C_5), 43.0 (C_1), 36.5 (C_{10}), 33.9 (C_8), 30.8 (C_{24}), 30.1 (C_7), 28.6 (C_6), 27.4 (C_{23}), 26.9 (C_{11}), 24.2 (C_{27}), 20.7 (C_{ac}), 19.8 (C_{18}), 11.2 (C_{19}), 9.0 (C_{21}), 2.3 (C_{tms}).

North α-azido methoxime **7n3m** and α-aminomethoxime **7**:



7n3m

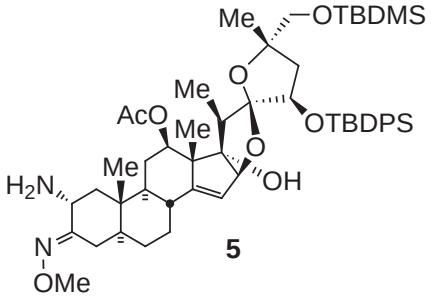


7

To a CH_2Cl_2 solution (3 mL) of α-azido ketone **7n3** (11 mg, 0.012 mmol) was added pyridine (0.2 mL) and methoxyamine hydrochloride (2.9 mg, 0.035 mmol). The resulted mixture was stirred at R.T. for 2h. After concentration, residue was purified by flash column chromatography on silica gel (1:10 EtOAc/Hex) to provide 11 mg (98%) of α-azido methoxime **7n3m**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (2H, d, J=7.8 Hz), 7.76 (2H, d, J=7.6 Hz), 7.42 (6H, m), 5.53 (1H, s), 5.03 (1H, dd, J=11.7, 4.9 Hz), 4.93 (1H, s), 4.29 (1H, dd, J=10.0, 8.0 Hz), 3.99 (1H, s), 3.96 (3H, s), 3.09 (1H, d, J=10 Hz), 2.96 (1H, d, J=10 Hz), 2.43 (1H, q, 7.1 Hz), 1.99 (3H, s), 1.22 (3H, s), 1.11 (3H, d, J=7.1 Hz), 1.09 (3H, s), 1.00 (9H, s), 0.97 (3H, s), 0.76 (9H, s), -0.16 (3H, s), -0.17 (3H, s), 2.2-0.8 (remaining H's, m). ^{13}C NMR (75 MHz, $CDCl_3$): d 170.4, 155.2, 151.1, 136.1, 135.6, 133.7, 132.7, 130.3, 129.9, 128.1, 127.7, 122.6, 116.5, 93.3, 89.4, 82.0, 74.5, 74.0, 69.3, 62.1, 57.7, 53.4, 52.7, 44.5, 44.4, 37.6, 37.0, 33.3, 28.3, 27.7, 27.4, 26.7, 26.0, 25.7, 21.5, 19.3, 18.3, 13.7, 12.3, 8.9, -5.5, -5.7.; MS(FAB, DTT/DTE): 913 (M^+-N_2+H); HRMS (FAB, DTT/DTE): calcd for $C_{52}H_{75}N_2O_8Si_2$ 913.5219 found 913.5227; $[\alpha]_D$ = + 69° (c=1.0, CH_2Cl_2).

To a THF solution (5 mL) of α-azido methoxime **7n3m** (160 mg, 0.17 mmol) was added PPh_3 (134 mg, 0.51 mmol) and water (0.14 mL). The resulted solution was stirred at R.T. for 24h and then concentrated. Small amout of water was removed by azeotropic distillation over toluene (20 mL). The resulted residue was purified by flash column chromatography on silica gel (1:1 EtOAc/Hex to 1:20 MeOH/CH_2Cl_2) to give 133 mg (86%) of the north α-amino methoxime **7**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (2H, d, J=7.8 Hz), 7.76 (2H, d, J=11.7 Hz), 7.42 (6H, m), 5.52 (1H, s), 5.00 (1H, dd, J=11.7, 4.9 Hz), 4.92 (1H, s), 4.29 (1H, dd, J=10.0, 8.0 Hz), 3.97 (1H, s), 3.84 (3H, s), 3.09 (1H, d, J=10 Hz), 2.96 (1H, d, J=10 Hz), 2.42 (1H, q, 7.0 Hz), 2.04 (2H, br s), 2.00 (3H, s), 1.22 (3H, s), 1.09 (3H, d, J=7.1 Hz), 1.08 (3H, s), 1.00 (9H, s), 0.99 (3H, s), 0.77 (9H, s), -0.17 (3H, s), -0.18 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 160.5, 151.5, 136.1, 135.6, 133.7, 132.7, 130.3, 129.9, 128.1, 127.7, 122.3, 116.5, 93.4, 89.4, 81.9, 74.7, 74.0, 69.3, 61.6, 53.5, 52.8, 49.7, 48.6, 45.6, 44.4, 37.6, 37.0, 33.3, 29.8, 28.5, 27.8, 27.4, 27.3, 26.7, 26.0, 25.7, 21.5, 19.3, 18.3, 13.7, 12.4, 8.9, -5.5, -5.7.; MS(FAB, DTT/DTE): 915 (M^++H); HRMS (FAB, DTT/DTE): calcd for $C_{52}H_{79}N_2O_8Si_2$ 915.5375 found 915.5384; $[\alpha]_D$ = + 54° (c=2.0, CH_2Cl_2).

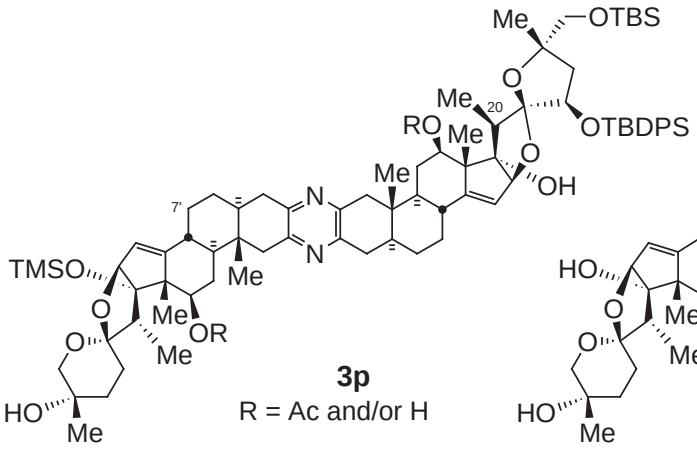
20epi-North 1 aminomethoxime **5**:



5

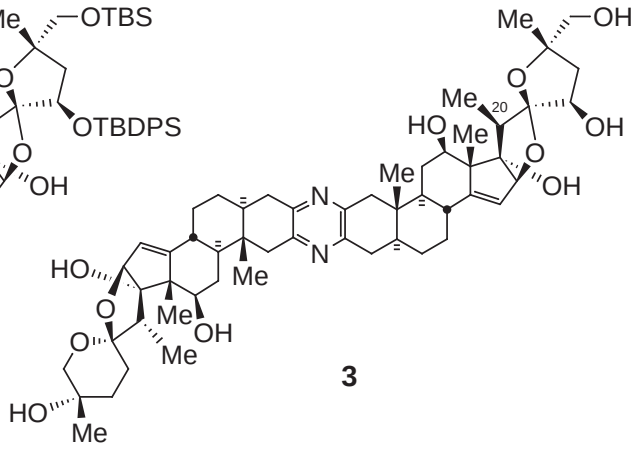
By the same procedures, 10 mg of ketone **5a** gave 8.4 mg (80% for 4 steps, 95 x 99 x 92 x 91) of **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.8-7.6 (2H, m), 7.43-7.3 (3H, m), 5.52 (1H, br s), 5.27 (1H, dd, J=11.4, 5.4 Hz), 4.49 (1H, br s), 3.97 (1H, m), 3.84 (3H, s), 3.2-2.96 (3H, m), 2.42 (1H, q, 7.0 Hz), 2.04 (3H, s), 1.39 (3H, s), 1.18 (3H, s), 1.09 (9H, s), 0.97 (3H, s), 0.77 (9H, s), 0.69 (3H, d, J=7 Hz), -0.18 (3H, s), -0.19 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 159.2, 136.1, 134.1, 133.7, 129.9, 129.7, 127.9, 127.6, 125.7, 119.2, 119.1, 114.1, 109.5, 91.4, 90.5, 81.8, 75.2, 74.5, 69.6, 61.6, 60.5, 56.6, 49.6, 48.1, 45.1, 38.5, 36.6, 33.4, 29.8, 29.1, 27.8, 27.2, 26.1, 26.0, 25.9, 21.9, 19.4, 18.3, 16.4, 14.3, 12.2, 7.8, -5.5, -5.6. MS(FAB, DTT/DTE): 914 (M^+); HRMS(FAB, DTT/DTE): Calcd for $C_{52}H_{78}N_2O_8Si_2$ 915.5375, found 915.5346.

Protected 20epi-cephalostatin 7 **3p** and 20epi-Cephalostatin 7 **3:**



3p

R = Ac and/or H



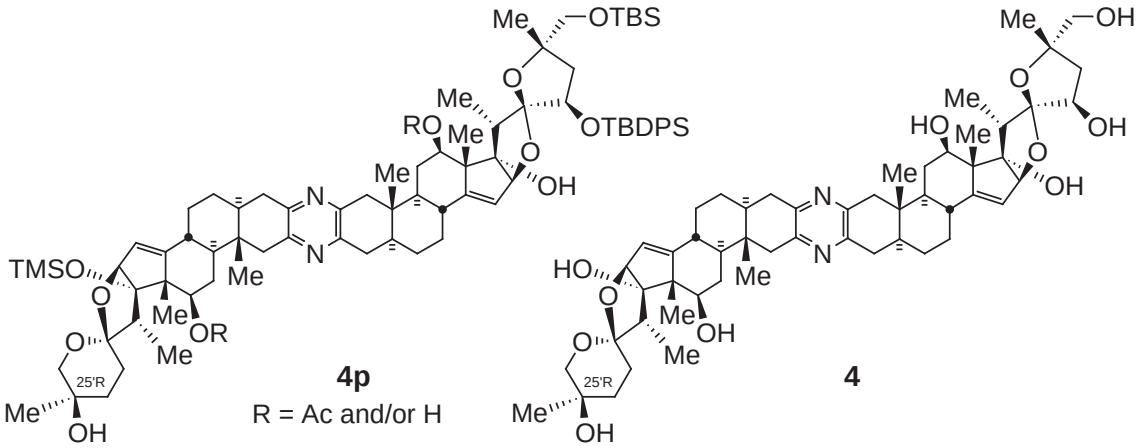
3

To a solution of α-azidoketone **8** (3.5 mg, 0.568 μmol) and α-amino methoxime **5** (5.7 mg, 0.625 μmol) in benzene (3 mL) was added dibutyltindichloride (0.3 mg, 10 mol%), 4Å molecular sieves (9 mg, 100 wt%) and polyvinylpyridine (9 mg, 100 wt%). The reaction flask was equipped with a Dean-Stark trap and the mixture was heated at reflux, with azeotropic removal of water, for 2.5 hours (2-4 mL of fresh benzene was added twice to maintain the solvent level in the reaction vessel) at which time TLC (25% EtOAc in hexane) indicated complete consumption of the α-azidoketone **8**. The mixture was cooled, filtered through celite and the solids were washed with methylene chloride. Evaporation of the filtrates and sgc gave 2 mg recovered **5** (quant.) and 6.1 mg of **3p** (76%, 99% based on recovered **5**) containing ~20% 12- and/or 12'-alcohols. The mixture was deprotected without further purification. For the mixture **3p**, ^{1}H NMR (300 MHz, $CDCl_3$) (selected): δ 8.0 (4H, m), 7.3 (3H, m), 5.09 and 4.81 (1H, br s, H16), 4.41 (1H, t, H23), 3.9 (1H, br s, 17-OH).

To a solution of **3p** (6.1 mg, 0.43 μmol) in THF (2 mL) was added 20 μL of a 1.0M solution of TBAF in THF (2 μmol, 4.5 eq) and the mixture was heated at reflux for 2 hours. The reaction mixture was cooled and the solvent was evaporated. The residue was dissolved in an 8:1 mixture of MeOH/H_2O (2 mL) and K_2CO_3 (7.5 mg, 0.054 mmol) was added. The resulting suspension was heated at reflux for 0.5 hours, cooled, and the volatile components were removed on a rotary evaporator. The residue was dissolved in EtOAc, washed with water, and dried over sodium sulfate. Evaporation of the solvent followed by sgc (3-5% MeOH in chloroform) of the residue gave 2.8 mg of **3** (71%). ^{1}H NMR (600 MHz, C_5D_5N): δ 6.60 (1H, s), 6.40 (1H, d, J=10 Hz), 6.30 (1H, t, J=5.5 Hz), 5.72 (1H, s), 5.62 (1H, s, H_{15}), 5.60 (1H, s, $H_{15'}$), 5.50 (1H, d, J=4.1 Hz), 5.18 (1H, s, $H_{16'}$), 5.12 (1H, s), 5.10 (1H, s), 4.72 (1H, s, H_{16}), 4.68-4.58 (2H, m, H_{12}, H_{23}), 4.19 (1H, m, $H_{12'}$), 4.01 (1H, d, J=11.5 Hz, $H_{26'a}$), 3.80 (1H, dd, J=11, 5.9 Hz, H_{26a}), 3.70 (1H, dd, J=11, 5.9 Hz, H_{26b}), 3.61 (1H, d, J=11.3 Hz, $H_{26'b}$), 3.46 (1H, q, J=7.5 Hz, H_{20}), 3.13 (1H, d), 3.10 (1H, d), 2.90 (2H, m), 2.83

(1H, dd), 2.7-2.5 (5H, m), 2.28-2.04 (8H, m [1H unassigned]), 1.95 (1H, s), 1.91 (3H, s, H_{18}), 1.66 (3H, d, J=7.5 Hz, H_{21}), 1.62 (3H, s, H_{27}), 1.32 (3H, s, $H_{18'}$), 1.29 (3H, d, J=6.9 Hz, $H_{21'}$), 1.23 (3H, s, $H_{27'}$), 1.04 (1H, apdt), 0.95 (1H, apdt), 0.86 (1H, apt), 0.75 (6H, brs, $H_{19\ \&\ 19'}$). ^{13}C NMR (150 MHz, C_5D_5N): 158.9 (C_{14}), 154.8 ($C_{14'}$), 148.9 (C_2), 148.8 ($C_{2'}$), 148.6 ($C_{3'}$), 148.5 (C_3), 120.0 ($C_{15'}$), 119.6 (C_{15}), 114.8 (C_{22}), 107.9 ($C_{22'}$), 93.7 ($C_{16'}$), 93.3 ($C_{17'}$), 93.2 (C_{16}), 92.8 (C_{17}), 81.9 (C_{25}), 75.7 ($C_{12'}$), 74.6 (C_{12}), 73.0 (C_{23}), 70.2 ($C_{26'}$), 69.4 (C_{26}), 65.8 ($C_{25'}$), 58.4 (C_{13}), 56.0 ($C_{13'}$), 52.9 ($C_{9'}$), 51.6 (C_9), 50.9 (C_{20}), 48.5 ($C_{20'}$), 46.3 ($C_{1'}$), 46.0 (C_1), 41.7 ($C_{5'}$), 41.6 (C_5), 40.6 (C_{24}), 36.3 (2C, $C_{10\&10'}$), 36.0 (C_4), 35.8 ($C_{4'}$), 34.0 ($C_{8'}$), 33.9 (C_8), 33.3 ($C_{24'}$), 29.9 (C_{11}), 29.5 (C_7), 29.2 ($C_{11'}$), 29.0 ($C_{7'}$), 28.4 (C_6), 28.3 ($C_{6'}$), 27.7 ($C_{23'}$), 27.0 ($C_{27'}$), 26.9 (C_{27}), 15.0 (C_{18}), 13.0 ($C_{18'}$), 11.8 (C_{19}), 11.7 ($C_{19'}$), 10.1 (C_{21}), 8.2 ($C_{21'}$). MS (FAB, DTT/DTE): 929 (M^++H); HRMS(FAB, DTT/DTE): Calcd for $C_{54}H_{77}N_2O_{11}$ 929.5527, found 929.5498.

Protected 25'epi-cephalostatin 7 (**4p**) and 25'epi-cephalostatin 7 (**4**):



Using the same procedure as for **3p**, 3 mg of **6** (85% pure, 0.414 μmol) and 4.9 mg of **7** (0.536 μmol) afforded 2.9 mg of **4p** (50%, contained ~25% 12- and/or 12'-alcohols). **4p**: ^{1}H NMR (300 MHz, $CDCl_3$) (selected): δ 5.52 (1H, br s, H15), 4.79 and 4.72 (1H, br s, H16), 4.60 (1H, t, H23), 4.33 (1H, br s, 17-OH).

Deprotection of **4p** (2.9 mg) utilizing the same procedure as for **3p** afforded 1.4 mg of **4** (73%): ^{1}H NMR (300 MHz, C_5D_5N) **[many peaks -0.05 from cstat 7]**: δ 8.13 (1H, d, J=11.3 Hz), 6.60 (1H, br t, J=6 Hz), 6.23 (1H, s), 6.21 (1H, s), 5.59 (1H, brs, H_{15}), 5.49 (1H, s, $H_{15'}$), 5.20 (1H, s, H_{16}), 5.11 (1H, s, $H_{16'}$), 4.78 (1H, dd, H_{23}), 4.77 (1H, s), 4.66 (1H, s), 4.14 (1H, d, J=11.2 Hz, $H_{26'a}$), 4.12 (1H, ddd, 11.9, 5.0, 1.0 $H_{12'}$), 4.01 (1H, dd, H_{12}), 3.75 (1H, dd, J=11.0, 5.9 Hz, H_{26a}), 3.65 (1H, dd, J=11, 5.9 Hz, H_{26b}), 3.55 (1H, m), 3.41 (1H, d, J=11.2 Hz, $H_{26'b}$), 3.05 (1H, d), 3.03 (1H, d), 2.97-2.77 (3H, m), 2.75-2.5 (4H, m), 2.42 (1H, apdt), 2.30 (1H, t), 2.16 (1H, q), 2.1-1.9 (5H, m), 1.96 (1H, s), 1.58 (3H, s, H_{27}), 1.44 (3H, s $H_{27'}$), 1.29 (3H, d, J=7 Hz, H_{21}), 1.28 (3H, s, H_{18}), 1.24 (3H, d, J=7 Hz, $H_{21'}$), 0.90 (1H, apbrt, H_9), 0.86 (1H, apbrt, $H_{9'}$), 0.70 (3H, s, H_{19}), 0.68 (3H, s, $H_{19'}$). ^{13}C NMR (125 MHz, $CDCl_3$): 154.9 ($C_{14'}$), 152.8 (C_{14}), 148.9 (C_2), 148.8 ($C_{2'}$), 148.6 (2C, $C_{3\ \&\ 3'}$), 121.4 (C_{15}), 119.3 ($C_{15'}$), 116.7 (C_{22}), 107.5 ($C_{22'}$), 93.6 (2C, $C_{16'\&17'}$), 93.2 (C_{16}), 91.7 (C_{17}), 82.4 (C_{25}), 75.4 (C_{12}), 75.3 ($C_{12'}$), 71.6 (C_{23}), 69.8 ($C_{26'}$), 69.6 (C_{26}), 67.5 ($C_{25'}$), 55.3 ($C_{13'}$), 55.2 (C_{13}), 53.4 (C_9), 53.0 ($C_{9'}$), 47.1 ($C_{20'}$), 45.8 (C_1), 43.9 (C_{20}), 41.9 (C_5), 41.8 ($C_{5'}$), 40.4 (C_{24}), 36.4 (2C, $C_{10\&10'}$), 35.5 (2C, $C_{4\&4'}$), 34.4 ($C_{24'}$), 34.0 ($C_{8'}$), 33.9 (C_8), 30.0 ($C_{23'}$), 29.1 (C_{11}), 28.7 ($C_{11'}$), 28.5 (2C, $C_{7\&7'}$), 28.4 ($C_{6'}$), 28.3 (C_6), 25.6 (C_{27}), 24.3 ($C_{27'}$), 12.5 (C_{18}), 12.2 ($C_{18'}$), 12.0 (2C, $C_{19\&19'}$), 9.1 (C_{21}), 7.6 ($C_{21'}$). MS (FAB, DTT/DTE): 929 (M^++H); HRMS(FAB, DTT/DTE): Calcd for $C_{54}H_{77}N_2O_{11}$ 929.5527, found 929.5497.

Comparison of the analogues **3** and **4** to natural cephalostatin 7 (**2**) shows the expected NMR relationships. For **3**, substantial shielding changes characteristic of 20βMe steroids occur throughout the C-F rings in both carbon and proton spectra (see also the following Tables 3si and 6si). As these patterns held true throughout the synthesis, and this series' stereochemistry was unambiguously determined by X-ray,[11a] the identity of the product rests secure. For **4**, shielding changes due to the altered C25 stereochemistry are restricted to the F-ring as is typical for other known steroids (see also the following Tables 2si, 4si and 5si). In keeping with the greater shielding effect of oxygen vs carbon,[17] exchanging an axial OH for an axial Me results in significant deshielding of C23–25 (the reverse occurs when exchanging an H for an Me) and shielding of the C27.

Table 1si. ^{13}C NMR and ^{1}H NMR comparison of cephalostatin 7 (**2**),[19] 20*epi*-cephalostatin 7 (**3**), and 25'*epi*-cephalostatin 7 (**4**). Substantial variations[a] from **2** are in bold.

nucleus			^{13}C					^{1}H					
cpd	**2**	**3**	**4**	**2**	**3**	**4**		**2**	**3**	**4**	**2**	**3**	**4**
subunit	south	south	south	north	north	north		south	south	south	north	north	north
solvent	P	P	C	P	P	C		P	P	P	P	P	P
1	46.0	46.0	45.8	46.0	46.3	45.8	1α	2.61	2.62	2.6	2.61	2.58	2.6
							1β	3.08	3.13	3.03	3.08	3.10	3.05
2	148.9	148.8	148.8	148.9	148.9	148.9	2						
3	148.6	148.6	148.6	148.6	148.5	148.6	3						
4	35.8	35.8	35.5	35.8	36.4	35.5	4α	2.89	2.90	2.83	2.89	2.90	2.83
							4β	2.60	2.65	2.6	2.66	2.65	2.6
5	41.8	41.6	41.8	41.8	41.7	41.9	5	1.56			1.56		
6	28.3	28.3	28.4	28.3	28.4	28.3	6α	1.48			1.48		
							6β	1.20			1.20		
7	29.0	29.0	28.5	29.0	29.5	28.5	7α	1.31			1.63		
							7β	1.55			1.42		
8	34.0	34.0	34.0	33.8	33.9	33.9	8	2.06	2.1	~2	2.04	2.1	~2
9	52.9	52.9	53.0	53.2	**51.6**	53.4	9	0.85	0.86	0.82	0.88	**1.04**	0.90
10	36.3	36.3	36.4	36.3	36.3	36.4	10						
11	29.2	29.2	28.7	29.0	29.9	29.1	11α	2.08	2.1	~2	2.04	2.1	~2
							11β	1.75			1.72		
12	75.7	75.7	75.3	75.6	**74.6**	75.4	12	4.17	4.19	4.12	4.05	**4.63**	4.01
13	56.0	56.0	55.3	55.4	**58.4**	55.2	13						
14	154.9	154.8	154.9	152.7	**158.9**	152.8	14						
15	120.0	119.6	119.3	122.3	**120.0**	121.4	15	5.60	5.60	5.49	5.64	5.62	5.59
16	93.7	93.7	93.6	93.2	**92.8**	93.2	16	5.17	5.18	5.11	5.24	**4.72**	5.20
17	93.3	93.3	93.6	91.7	**93.2**	91.7	17						
18	13.0	13.0	12.5	12.6	**15.0**	12.2	18	1.31	1.32	1.28	1.31	**1.91**	1.28
19	11.7	11.7	12.0	11.7	11.8	12.0	19	0.76	0.75	0.70	0.75	0.75	0.68
20	48.5	48.5	**47.1**	44.5	**50.9**	43.9	20	2.19	2.2	2.16	2.83	**3.46**	2.85
21	8.1	8.2	7.6	9.0	**10.1**	9.1	21	1.26	1.29	1.24	1.33	**1.66**	1.29
22	107.9	107.9	107.5	117.2	**114.8**	116.7	22						
23	27.7	27.7	**30.0**	71.5	**73.0**	71.6	23α	2.53	2.56	**2.42**	4.79	**4.63**	4.78
							23β	1.52					
24	33.3	33.3	**34.4**	39.5	**40.6**	40.4	24α	1.85			2.71	**2.83**	2.71
							24β	2.11	2.1	~2	2.34	**2.2**	2.30
25	65.8	65.8	**67.5**	82.8	**81.9**	82.4	25						
26	70.2	70.2	69.8	69.3	69.4	69.6	26α	3.57	3.61	**3.41**	3.79	3.80	3.75
							26β	3.98	4.01	**4.14**	3.70	3.70	3.65
27	27.0	27.0	**24.3**	26.4	26.9	25.6	27	1.23	1.23	**1.44**	1.61	1.62	1.58

[a]Defined generally as >0.5 ppm changes in CNMR shifts and >0.05 ppm changes in HNMR shifts. Since much of the CNMR spectrum of **4** is shifted upfield by ~0.2–0.5 ppm, upfield changes >0.7 ppm and downfield changes >0.3 ppm are here considered substantial. The HNMR spectrum of **4** is also shifted upfield ~0.05 ppm, so similar considerations apply. The upfield shifts in the CNMR spectrum of **4** evident for C15,15',20, and 20' are ascribed to the use of CDCl3 solvent.

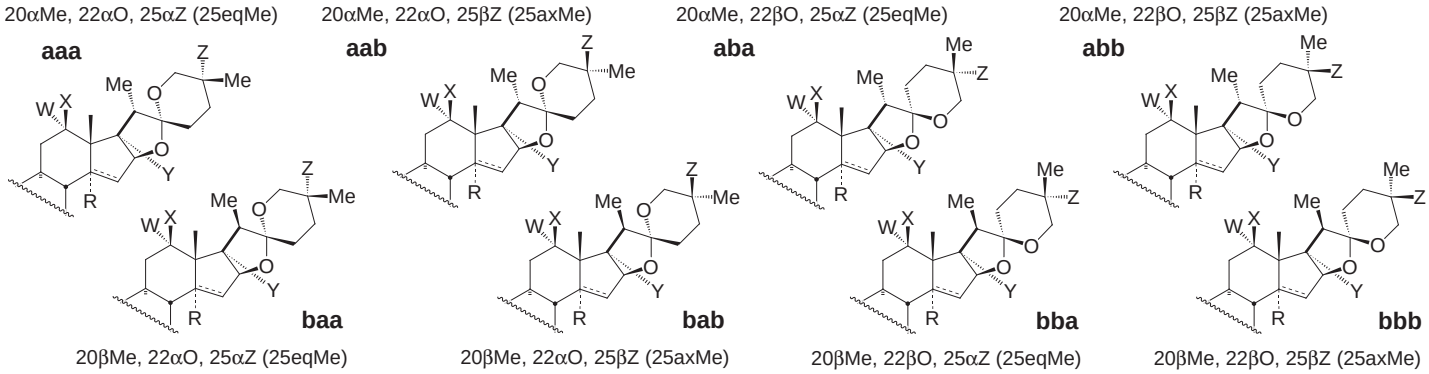


Table 2si. Brief overview of HNMR of [5,6]-spiroketals as a function of 20,22,25 stereochemistry.

[ref] A-ring substituent	**code, #**[a]	W / X	R	Y[a]	Z[a]	sol.[a]	12	16	18	19	20	21	26a/b	27
[18] 3Ac	**aaa** (tig)	H / H	αH	H	H	C		4.39	0.76	0.84	<2	0.95	3.47 /3.37	0.79
[18] 3Ac	**baa** (tig)	H / H	αH	H	H	C		4.42	**0.93**	0.83	**2.41**	**1.23**	**3.47 m**	0.78
[18] 3Ac	**aab** (tig)	H / H	αH	H	H	C		4.39	0.77	0.84	<2	0.87	**3.96 / 3.28**	**1.08**
[18] 3Ac	**aaa** (hec)	O	αH	H	H	C		4.36	1.05	0.92	~2	1.06	3.43 / 3.30	0.79
[18] 3Ac	**baa** (hec)	O	αH	H	H	C		4.40	1.23	0.92	**2.58**	**1.25**	**3.45 m**	0.78
[11b] 3Ac	**aaa** (**51**)	H/OAc	ene	OT	OH	B	5.22	4.80	1.14	0.52	2.35	1.05	3.76 / 3.25	0.99
[11b] 3Ac	**aab** (**72**)	H/OAc	ene	OT	OH	B	5.17	4.77	1.12	0.48	2.32	1.00	3.72 / **3.19**	**1.15**
[11b] 3keto	**aaa** (**79**) **8a**	H/OAc	ene	OT	OM	B	5.14	4.77	1.12	0.41	2.33	1.04	3.58 / 3.51	0.77
[11b] 3keto	**bbb** (**89**)	H/OAc	ene	OT	OM	B	**5.01**	4.85	**1.34**	0.40	**2.82**	**0.91**	**4.12 / 3.38**	**1.22**
[11b] 3keto	**bba** (**90**) **6a**	H/OAc	ene	OT	OM	B	**5.03**	4.86	**1.37**	0.39	**2.88**	**0.96**	**3.63 / 3.75**	0.80
[11b] 3keto	**aaa** (**78**)	H/OAc	ene	OT	OH	B	5.18	4.78	1.14	0.46	2.36	1.04	3.75 / 3.24	0.98
2Br,3keto	**aaa 8br**	H/OAc	ene	OT	OH	B	5.15	4.77	1.10	0.31	2.33	1.03	3.74 / 3.24	0.98
2Br,3keto	**aab 6br**	H/OAc	ene	OT	OH	B	5.10	4.72	1.07	0.27	2.30	0.99	**3.72 / 3.18**	**1.14**
[11b] $2N_3$,3keto	**aaa** (**6**) **8n3**	H/OAc	ene	OT	OH	B	5.16	4.78	1.12	0.32	2.33	1.03	3.75 / 3.26	0.98
$2N_3$,3keto	**aab 6n3**	H/OAc	ene	OT	OH	B	5.10	4.72	1.15	0.29	2.30	0.99	**3.72 / 3.18**	**1.14**
[19] pyraz.	**aaa 2**	H/OH	ene	OH	OH	P	4.17	5.17	1.31	0.76	2.19	1.26	3.98 / 3.57	1.23
[20] pyraz.	**?abb** (**2**)	H/OH	ene	OH	OH	P	4.20	5.18	1.35	0.78	2.22	1.27	4.01 / 3.61	1.23
[21] pyraz.	**?abb** (**13**)	H/OH	ene	H	OH	P	4.19	5.19	1.33	0.77	2.21	1.29	4.02 / 3.62	1.23
pyraz	**aaa 3**	H/OH	ene	OH	OH	P	4.19	5.18	1.32	0.75	2.20	1.29	4.01 / 3.61	1.23
pyraz	**aab 4**	H/OH	ene	OH	OH	P	4.12	5.11	1.28	0.70	2.16	1.24	**4.14 / 3.41**	**1.44**

[a] Compound numbers used in the present work; those in parentheses are the numbers used in the reference given. T = TMS, M = MTM. Spectral solvents: C = CDCl3, B = C6D6, P = C5D5N.

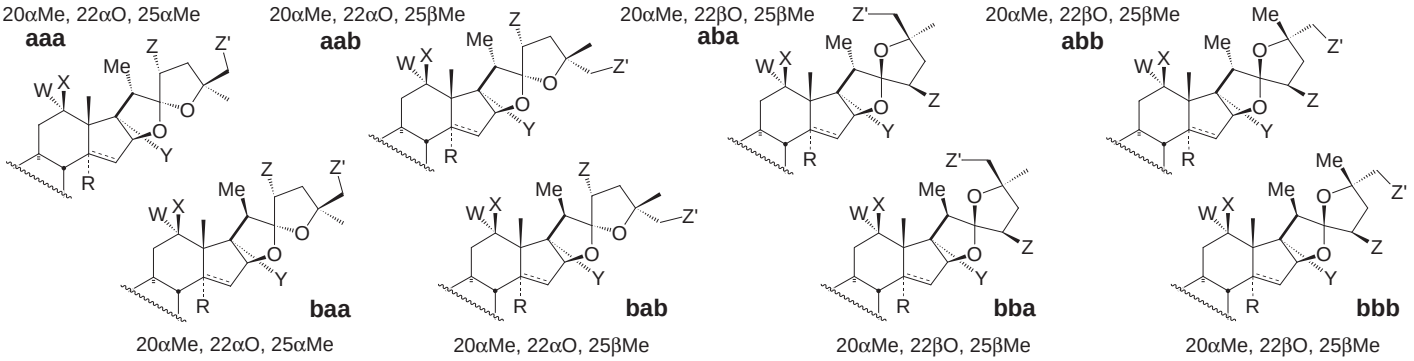


Table 3si. HNMR of [5,5]-spiroketals as a function of 20,22,25 stereochemistry

[ref] A-ring	**code, #**[a]	W / X	R	Y	Z	Z'	sol.	12 /Ac	16	18	19	20	21	26a/b	27
[11b]	**aaa** (**75*S***)	H/OAc	ene	OH	H	OH	B	3.93 /1.75	4.84	1.18	0.59	2.01?	0.89	3.37 / 3.51	0.83
[11b]	**aab** (**75*R***)	H/OAc	ene	OH	H	OH	B	4.04 /1.74	4.97	1.21	0.60	2.05?	0.98	3.15-3.23	1.31
[11a] 3OAc	**bbb** (**64**β)	H/OAc	ene	OT	OP	OH	C	5.05 /2.05	4.7	1.41	0.97	2.74	0.83	3.13 / 3.01	1.15
[11a] 3keto	**abb** (**90**α)	H/OAc	ene	OH	OP	OH	C	5.04 /1.99	4.94	1.25	1.06	2.48	1.08	3.06 / 2.93	1.16
[11a] 3keto	**bba** (**90**β)	H/OAc	ene	OH	OP	OH	C	5.27	4.54	1.37			0.66		
[11a] 3keto	**aba** (**93**α)	H/OAc	ene	OH	OP	OH	C	5.02	4.93	1.25*	1.07	2.46	1.07	3.24 / 3.06	1.24*
[11a] 3keto	**bba** (**93**α)	H/OAc	ene	OH	OP	OH	C	5.28	4.54	1.35			0.71		
[11a] 3keto	**abb** (**91**α) **7a**	H/OAc	ene	OH	OP	OD	C	5.03 /1.99	4.94	1.24	1.06	2.46	1.11	3.10 / 2.97	1.10
[11a] 3keto	**bbb** (**91**β) **5a**	H/OAc	ene	OH	OP	OD	C	5.28 /2.07	4.50	1.38	1.04	2.45	0.69	3.15 / 3.09	1.16
[11a] 3OAc	**abb** (**92**α)	H/OAc	ene	OH	OP	OD	C	5.00 /1.97	4.93	1.20	0.87	2.46	1.09	3.09 / 2.96	1.09
[11a] 3OAc	**bbb** (**92**β)	H/OAc	ene	OH	OP	OD	C	5.27 /2.06	4.50	1.39	0.86	2.48	0.69	3.15 / 3.09	1.18
[11a] 2NH2, 3NOMe	**abb** (**6**) 7	H/OH	ene	OH	OP	OD	C	5.00	4.92	1.22	0.99	2.42	1.09	3.09 / 2.96	1.08
2NH2, 3NOMe	**bbb 5**	H/OH	ene	OH	OP	OD	C	5.27	4.49	1.39	0.97	2.42	0.69	3.08 / 3.05	1.18
[11a] 3OH	**abb** (**94**α)	H/OH	ene	OH	OH	OH	P	4.03	5.23	1.34	0.79	2.85	1.36	3.80 / 3.70	1.64
[11a] 3OH	**bbb** (**94**β)	H/OH	ene	OH	OH	OH	P	4.59	5.10	1.88	0.79	3.44	1.64	3.79 / 3.70	1.60
[19]	**abb 2**	H/OH	ene	OH	OH	OH	P	4.05	5.24	1.31	0.75	2.83	1.33	3.79 / 3.70	1.65
pyraz	**bbb 3**	H/OH	ene	OH	OH	OH	P	~4.62	5.12	1.91	0.75	3.46	1.66	3.80 / 3.70	1.62
pyraz	**abb 4**	H/OH	ene	OH	OH	OH	P	4.01	5.20	1.28	0.70	2.85	1.29	3.75 / 3.65	1.58

[a] Compound numbers used in the present work; those in parentheses are the numbers used in the reference given. T = TMS, D = TBS, P = TBDPS. Spectral solvents: C = CDCl3, B = C6D6, P = C5D5N. *Assignments may be interchanged.

The NMR shielding patterns for "25'*epi*-South 7 ketone" **6a** (**90**) do not match those expected for a steroid differing only at C25 from a related steroid. Tables 4si and 5si present the NMR of related compounds which should make clear that, although the starting spiroketal apparently did not possess an axial methyl at C25, the bromoketone intermediate **6br** displayed all of the expected NMR shifts for the requisite 20α,22α,22β (20*S*,22*R*,25*R*) stereochemistry, as did the coupling partner **6** and the final product **4.**

Table 4si. ^{13}C NMR[a] Comparison of **South 7** type units isolated or in cephalostatins, ritterazines or analogues: 20Me, 22O$_F$, 25Me α **vs** β (25βMe = axial for natural 22α "prone" F-ring chair)

ref	11b,21	11b,19	11b,21	11b	11b	11b	11b	11b	11b		11b			
cpd	ritt K (**11**)	cstat 7 (**10**)	ritt K (**11**)	South 7 (**77**)	South 7 (**78**)	South 7 (**79**)	20β,22β South 7 (**89**)	20β,25β South 7 (**90**)	South 7 (**80**)	25β-South 7	South 7 (**6**)	25β-South 7	20β-cstat 7	25'β-cstat 7
#		**2**				**8a**	**iso-8a**	**6a**	**8br**	**6br**	**8**	**6**	**3**	**4**
P[b]				3OH, 12Ac, 17OT	3keto, 12Ac, 17OT	3keto, 12Ac, 17OT, 25OM	3keto, 12Ac, 17OT, 25OM	3keto, 12Ac, 17OT, 25OM	2αBr, 3keto, 12Ac, 17OT	2αBr, 3keto, 12Ac, 17OT	2αN_3, 3keto, 12Ac, 17OT	2αN_3, 3keto, 12Ac, 17OT		
	ααα	ααα	ααα	ααα	ααα	ααα	βββ	βαβ	ααα	ααβ	ααα	ααβ	ααα	ααβ
sol	P	P	B	B	B	B	B	B	B	B	B	B	P	**C**
1	46.0	46.0	46.0	35.5	35.2	35.2	35.6	35.4	43.2	43.2	43.0	43.0	46.0	45.8
2	148.7	148.9	148.6	31.5	37.5	37.5	37.8	37.4	53.6	53.5	63.0	63.0	148.8	148.8
3	148.6	148.6	148.9	70.3	208.2	207.6	207.9	207.6	197.9	197.9	202.8	202.9	148.6	148.6
4	35.8	35.8	35.8	38.0	44.0	44.0	44.3	44.1	50.0	50.0	44.2	44.1	35.8	35.5
5	41.7	41.8	41.8	44.0	44.8	44.8	45.4	45.2	45.0	44.9	44.9	44.9	41.6	41.8
6	28.2	28.3	28.3	29.6	28.2	28.0	28.3	28.0	28.2	27.4	28.2	27.4	28.3	28.4
7	28.9	29.0	29.0	35.5	29.0	29.0	29.0	28.8	28.6	28.6	28.7	28.6	29.0	28.5
8	34.0	34.0	34.0	34.8	34.5	34.5	34.3	34.2	34.0	34.0	33.9	33.9	34.0	34.0
9	52.9	52.9	52.9	50.9	50.1	50.2	**51.1**	**50.8**	49.5	49.4	49.5	49.5	52.9	53.0
10	36.3	36.3	36.3	36.7	37.5	37.5	37.8	37.6	38.3	38.3	36.2	36.5	36.3	36.4
11	29.2	29.2	29.2	26.7	26.8	26.8	**27.5**	**27.2**	26.8	26.8	26.9	26.9	29.2	28.7
12	75.6	75.7	75.7	74.0	73.6	73.6	**75.2**	**74.8**	73.2	73.2	73.3	73.3	75.7	75.3
13	56.0	56.0	56.0	56.3	56.3	56.3	56.5	56.3	56.2	56.2	56.3	56.2	56.0	55.3
14	154.8	154.9	154.8	159.5	158.8	158.8	**155.1**	**155.3**	158.2	158.0	158.2	158.0	154.8	154.9
15	120.0	120.0	120.0	117.1	117.4	117.5	**119.9**	**119.5**	117.8	117.8	117.6	117.8	119.6	119.3
16	93.7	93.7	93.7	93.2	93.1	93.2	**95.0**	**94.6**	93.2	93.1	93.2	93.1	93.7	93.6
17	93.3	93.3	93.3	89.9	89.9	89.8	**91.2**	**90.5**	89.9	89.7	89.9	89.8	93.3	93.6
18	13.0	13.0	13.0	19.9	19.9	19.9	**18.0**	**17.9**	19.8	19.8	19.8	19.8	13.0	12.5
19	11.7	11.7	11.8	11.7	10.4	10.4	10.7	10.7	10.8	10.8	11.3	11.2	11.7	12.0
20	48.4	48.5	48.5	46.6	46.6	46.6	**48.5**	**48.4**	46.7	46.2	46.7	46.2	48.5	**47.1**
21	8.2	8.1	8.2	9.2	9.2	9.2	**11.7**	**11.1**	9.1	9.1	9.1	9.0	8.2	7.6
22	107.9	107.9	107.9	107.8	107.8	107.8	**109.2**	**109.2**	107.7	107.4	107.7	107.4	107.9	107.5
23	27.7	27.7	27.7	28.2	28.0	28.0	**28.6**	**25.8**	27.4	**30.8**	27.4	**30.8**	27.7	**30.0**
24	33.3	33.3	33.3	32.6	32.6	31.3	**30.4**	**30.8**	32.6	**34.4**	32.6	**34.4**	33.3	**34.4**
25	65.7	65.8	65.8	66.1	66.0	71.6	**72.9**	71.9	65.9	**66.4**	65.9	**66.5**	65.8	**67.5**
26	70.2	70.2	70.2	68.8	68.8	64.5	**69.0**	**66.6**	68.9	68.8	68.9	68.8	70.2	69.8
27	27.0	27.0	27.0	25.4	25.3	21.2	21.2	21.2	25.1	**24.2**	25.1	**24.2**	27.0	**24.3**
Ac					169.0	168.9	169.3	169.1	168.8	168.8	168.9	168.5		
Ac					20.8	20.8	20.4	20.9	20.7	20.7	20.7	20.7		
T					2.3	2.3	2.3	2.2	2.3	2.3	2.3	2.3		
M						13.9	14.1	13.9						
M						66.9	66.9	66.9						

[a] Spectra in C_5D_5N solvent = P, C_6D_6 = B, $CDCl_3$ = C. [b]OT = OTMS, OM = OMTM, Br = equatorial bromide, N_3 = equatorial azide.

Table 5si. ^{1}H NMR[a] Comparison of **South 7** type units alone or in cephalostatins, ritterazines and analogues: 20Me, 22O_F, 25Me α vs β (25βMe = axial for normal "prone" F-ring chair)

ref	21	11b,19	11b,21		11b	11b	11b	11b	11b	11b	11b	11b		11b	
cpd	ritt K (**11**)	cstat 7 (**10**)	20*R*-cstat 7	25'*R*-cstat 7	South 7 (**76**)	ritt K (**11**)	cstat 7 (**10**)	South 7 (**51**)	25*R*-South 7 (**72**)	South 7 (**79**)	20*R*,22 *R*-South 7 (**89**)	20*R*,25 *R*-South 7 (**90**)	South 7 (**80**)	25*R*-South 7	South 7 (**6**)	25*R*-South 7
#		**2**	**3**	**4**			**2**			**8a**	**iso-8a**	**6a**	**8br**	**6br**	**8**	**6**
P[b]					3OAc			3,12-diAc, 17OT	3,12-diAc, 17OT	3keto, 12Ac, 17OT, 25OM	3keto, 12Ac, 17OT, 25OM	3keto, 12Ac, 17OT, 25OM	2αBr, 3keto, 12Ac, 17OT	2αBr, 3keto, 12Ac, 17OT	2αN_3, 3keto, 12Ac, 17OT	2αN_3, 3keto, 12Ac, 17OT
	ααα	ααα	ααα	αaβ	ααα	ααα	ααα	ααα	αaβ	ααα	βββ	βαβ	ααβ	ααβ	ααβ	ααβ
sol	P	P	P	P	P	B	B	B	B	B	B	B	B	B	B	B
1α	2.67	2.61	2.62	2.6		2.53	2.50									
1β	3.13	3.08	3.13	3.03		3.17	3.15						2.23	2.18		
2													4.10	4.05	3.22	3.14
3					4.79			4.67	4.66							
4α	2.92	2.89	2.90	2.83		2.92	2.90									
4β	2.67	2.60	2.65	2.6		2.62	2.61									
5	1.63	1.56														
6α	1.55	1.48														
6β	1.27	1.20														
7α	1.35	1.31														
7β	1.75	1.55														
8	2.09	2.06	2.1	~2	2.08	2.10	2.05	2.10	2.07	2.03	2.00	2.00	2.03	1.98	2.04	1.98
9	0.99	0.85	0.86	0.82	0.85	0.77	0.68	0.70	0.65	065	0.61	0.61	0.61	0.56	0.62	0.57
10																
11	2.13	2.08	2.1	~2	2.11	2.10	2.10									
α 11β	1.82	1.75			1.80											
12	4.19	4.17	4.19	4.12	4.15	4.07	4.08	5.22	5.17	5.14	**5.01**	**5.03**	5.15	5.10	5.16	5.10
13																
14																
15	5.60	5.60	5.60	**5.49**	5.58	5.40	5.39	5.40	5.32	5.34	**5.25**	5.32	5.32	5.26	5.33	5.26
16	5.18	5.17	5.18	5.11	5.15	4.91	4.89	4.79	4.77	4.77	**4.85**	**4.86**	4.77	4.72	4.78	4.72
17																
18	1.33	1.31	1.32	1.28	1.30	1.19	1.18	1.14	1.12	1.12	**1.34**	**1.37**	1.10	1.07	1.12	1.07
19	0.78	0.76	0.75	0.70	0.75	0.61	0.61	0.52	0.48	0.41	0.40	0.39	0.31	0.27	0.32	0.29
20	2.21	2.19	2.2	2.16	2.20	2.10	2.11	2.35	2.32	2.33	**2.82**	**2.88**	2.33	2.30	2.33	2.30
21	1.29	1.26	1.29	1.24	1.27	1.02	1.00	1.04	1.00	1.04	**0.91**	**0.96**	1.03	0.99	1.03	0.99
22																
23	2.50	2.53	2.56	**2.42**	2.54			2.01	1.98	2.23	**2.19**	**2.11**	1.95	1.93	1.92	1.93
α 23β	1.58	1.52														
24	1.88	1.85			1.88											
α 24β	2.18	2.11	2.1	~2	2.18											
25																
26	3.62	3.57	3.61	**3.41**	3.61	3.03	3.00	3.25	**3.19**	3.51	**3.38**	**3.75**	3.24	**3.18**	3.26	**3.18**
α 26β	4.02	3.98	4.01	**4.14**	4.00	3.72	3.69	3.76	**3.72**	3.58	**4.12**	**3.63**	3.74	**3.72**	3.75	**3.72**
27	1.22	1.23	1.23	**1.44**	1.22	0.93	0.90	0.99	**1.15**	0.77	**1.22**	**0.80**	0.98	**1.14**	0.98	**1.14**
Ac								1.75	1.75	1.75	**1.77**	1.75	1.80	1.75	1.80	1.75
T								0.33	0.28	0.33	**0.22**	**0.22**	0.31	0.25	0.31	0.24
M_{Me}										2.05	**1.91**	2.05				
M_a										4.39	**4.38**	4.41				

M_b			4.31	**4.38**	4.33		

[a] Spectra in C_5D_5N solvent = P, C_6D_6 = B. [b]OT = OTMS, OM = OMTM, Br = equatorial bromide, N_3 = equatorial azide.

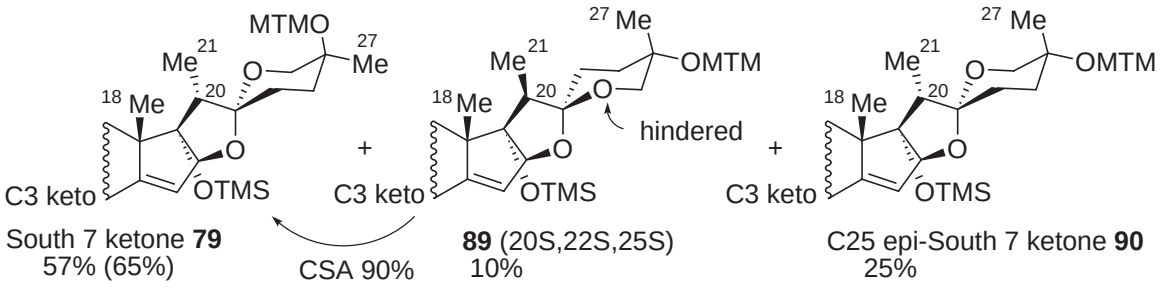
Table 6si. NMR comparison of 20Me and 22O$_F$ epimeric steroids in cephalostatins, ritterazines, analogues and sapogenins: α vs β in 5,6- and 5,5-spiroketals.

^{13}C											^{1}H							
19	20	21	21	21	22	23	lab	19		ref	19	20	21	21	21			
22α	**?22β**	22α	**?22β**	22α	**22β**	22α	**20β**	20α	**20β**		22α	**?22β**	22α	**?22β**	22α	**22β**	20α	**20β**
5,6	5,6	5,6	5,6	5,5	5,5	5,6	5,6	5,5	5,5	type	5,6	5,6	5,6	5,6	5,6	5,6	5,6	5,6
2				**10**	**9**			**2**	**3**	**cpd**	**2**				**10**	**9**	**2**	**3**
cstat 7	cstat 16	ritt L	ritt M	ritt F	ritt B	hec Ac	cyclo-pseudo hecAc	cstat 7	20epi-7		cstat 7	cstat 16	ritt L	ritt M	ritt F	ritt B	cstat 7	20epi-7
south 17OH	north 17OH	north 17H	north 17H	north 17H	north 17H	17H	17H	north 17OH	north 17OH		south 17OH	north 17OH	north 17H	north 17H	north 17H	north 17H	north 17OH	north 17OH
P	P	P	P	P	P	C	C	P	P	sol	P	P	P	P	P	P	P	P
46.0	46.0	45.8	45.9	46.1	46.3	36.2	36.2	46.0	46.3	1α	2.61	2.61	2.67	2.64	2.72	2.71	2.61	2.58
										1β	3.08	3.12	3.13	3.10	3.17	3.17	3.08	3.10
148.9	149.7	148.9	148.9	149.3	149.3	27.2	27.1	148.9	148.9	2								
148.6	148.3	149.0	148.9	149.0	149.0	72.8	73.0	148.6	148.5	3								
35.8	35.8	35.5	35.6	35.6	35.9	33.8	33.6	35.8	36.4	4α	2.89	2.90	2.91	2.91	2.95	2.94	2.89	2.90
										4β	2.60	2.68	2.66	2.65	2.68	2.68	2.66	2.65
41.8	41.8	41.5	41.5	41.4	41.5	44.6	44.3	41.8	41.7	5	1.56	1.62	1.64	1.64	1.56	1.57	1.56	
28.3	28.3	28.0	28.1	28.7	29.0	28.2	28.1	28.3	28.4	6α	1.48		1.55	1.55	1.46	1.48	1.48	
										6β	1.20		1.28	1.28	1.21	1.28	1.20	
29.0	29.0	29.4	**29.8**	31.4	31.7	31.4	31.3	29.0	29.5	7α	1.31	1.36	1.38	**1.55**	1.05	1.10	1.63	
										7β	1.55	1.74	1.85	**1.86**	1.40	1.49	1.42	
34.0	34.0	33.7	**34.5**	32.4	32.6	34.4	34.1	33.8	33.9	8	2.06	2.08	2.14	**2.23**	1.61	1.68	2.04	2.1
52.9	52.9	52.6	**49.5**	45.6	45.5	55.3	**53.2**	53.2	**51.6**	9	0.85	0.85	1.00	**1.77**	1.34	1.36	0.88	**1.04**
36.3	36.3	36.5	36.8	35.9	35.9	36.0	36.0	36.3	36.3	10								
29.2	29.0	30.7	**29.3**	30.6	30.7	37.6	37.4	29.0	29.9	11α	2.08	**1.36**	2.13	**1.91**	2.07	2.04	2.04	2.1
										11β	1.75	**1.74**	1.90	**1.77**	1.67	1.67	1.72	
75.7	75.7	78.9	**76.3**	72.0	71.8	211.7	**213.6**	75.6	**74.6**	12	4.17	4.20	3.52	**4.03**	3.60	3.64	4.05	**4.63**
56.0	55.8	53.7	**52.9**	49.0	48.6	54.9	**55.7**	55.4	**58.4**	13								
154.9	154.8	157.9	**154.0**	47.3	**47.8**	55.6	**56.1**	152.7	**158.9**	14					2.28	**2.08**		
120.0	119.9	120.0	**119.0**	33.2	**32.8**	31.5	**31.0**	122.3	**120.0**	15	5.60	5.59	5.63	5.61	1.84	**1.80**	5.64	5.62
															2.01	**1.83**		
93.7	93.7	85.4	**86.9**	78.4	**80.0**	78.9	**79.3**	93.2	**92.8**	16	5.17	5.18	5.25	**5.46**	4.48	**4.78**	5.24	**4.72**
93.3	**91.3**	56.6	**54.4**	56.9	**57.5**	53.6	**57.5**	91.7	**93.2**	17			3.18	**3.32**	2.84	**3.15**		
13.0	13.0	13.8	**18.8**	14.0	13.7	15.9	**12.0**	12.6	**15.0**	18	1.31	1.35	1.32	**1.23**	1.26	1.26	1.31	**1.91**
11.7	11.8	11.7	11.5	11.7	11.9	11.8	11.7	11.7	11.8	19	0.76	0.78	0.77	0.80	0.69	0.75	0.75	0.75
48.5	48.5	44.9	45.0	40.7	**42.0**	42.2	**44.5**	44.5	**50.9**	20	2.19	2.22	2.11	2.08	2.29	**2.01**	2.83	**3.46**
8.1	8.2	14.2	14.5	16.3	**14.7**	13.2	**15.8**	9.0	**10.1**	21	1.26	1.27	1.38	**1.23**	1.08	**1.18**	1.33	**1.66**
107.9	107.9	107.3	107.1	117.8	**117.0**	108.7	**108.0**	117.2	**114.8**	22								
27.7	27.7	27.5	27.5	30.1	**33.2**	31.1	**30.5**	71.5	**73.0**	23α	2.53	2.55	2.57	2.56	1.75	**1.85**	4.79	**4.63**
										23β	1.52	1.57	1.64	1.64	1.87	**2.12**		
33.3	33.3	33.1	33.4	37.0	37.3	28.9	**28.4**	39.5	**40.6**	24α	1.85	1.87	1.86	1.90	1.67	1.68	2.71	**2.83**
										24β	2.11	2.16	2.18	2.20	2.05	2.04	2.34	**2.2**
65.8	65.8	66.2	66.0	81.0	81.4	30.2	30.4	82.8	**81.9**	25								

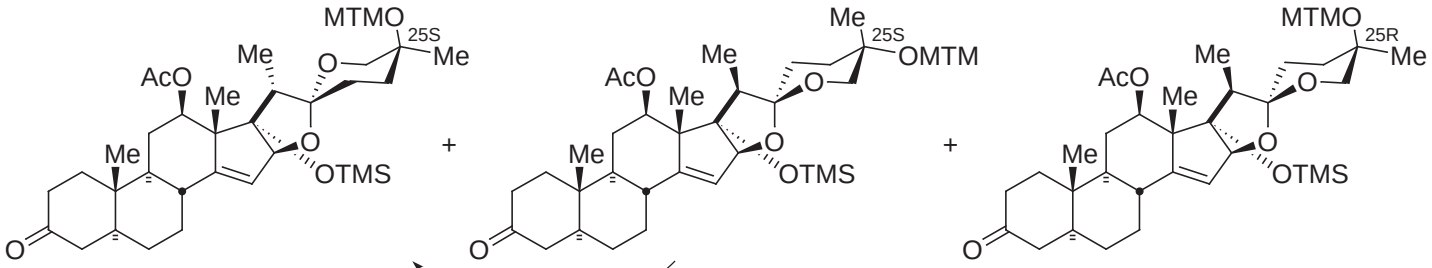
70.2	70.2	70.0	70.2	29.7	**28.8**	66.8	**68.0**	69.3	69.4	26α 26 β	3.57 3.98	3.61 4.01	3.75 4.08	3.72 4.05	1.44	**1.18**	3.79 3.70	3.80 3.70
27.0	27.0	26.8	26.8	28.4	**30.3**	17.1	17.1	26.4	26.9	27	1.23	1.23	1.26	1.24	1.20	**1.43**	1.61	1.62

Rationale for stereochemical and/or conformational correction to ref. 11b for **6a** (**90**):

Relevant portion of Scheme 20:



proposed correction to Scheme 20 (note 20βMe = 20R, not 20S):



numbering for this work:

8a (20S,22R,25S) 20α,22α,25α

iso-8a (20R,22S,25S) 20β,22β,25β

6a (20R,22S,25R) 20β,22β,25α

(published) **Table 4.** Proton NMR resonances in C_6D_6 (ppm)

Compound	C-18 (s)	C-21 (d)	C-27 (s)
MTM ether **79** (20S,22R,25S)	0.77	1.11	1.12
MTM ether **90** (20S,22R,25R)	0.80	0.97	1.36
MTM ether **89** (20R,22S,25S)	1.22	0.91	1.33
alcohol **51** (20S,22R,25S)	1.14	1.05	1.00
alcohol **72** (20S,22R,25R)	1.11	1.00	1.13

(revised) **Table 4.** Proton NMR resonances in C_6D_6 (ppm)

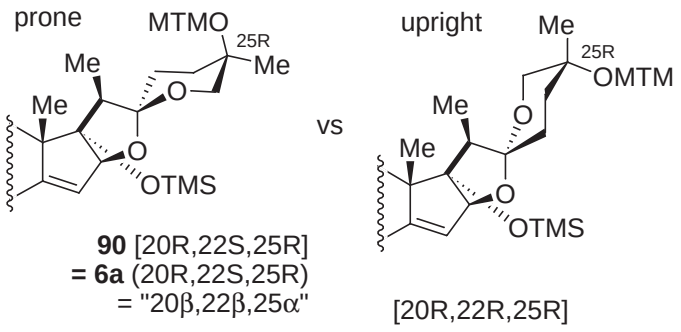
Compound	C-18 (s)	C-21 (d)	C-27 (s)
MTM ether **79** (20S,22R,25S)	1.12	1.04	0.77
MTM ether **90** (20R,22S,25R)	1.37	0.96	0.80
MTM ether **89** (20R,22S,25S)	1.34	0.91	1.22
alcohol **51** (20S,22R,25S)	1.14	1.05	0.99
alcohol **72** (20S,22R,25R)	1.12	1.00	1.15

1. The published table entries do not appear internally consistent.
   a. The shift assignments appear unreasonable. No precedent for the large H18 upfield shift upon derivation at C25 is known to this author. For the published structure of **6a** (**90**), H18 should absorb at ~1.12 as in **79, 51** and **72** no matter the stereochemistry or substitution at C25. See point #2 and Tables 2si and 5si.
   b. Some published chemical shift table entries do not agree with experimental shift lists, and some errors were also found in those lists when the actual spectra were reexamined. Corrected values are shown in the revised table and are included in the experimental for this article and/or in the foregoing Tables 1–5si.
2. Steroids epimeric at C25 show characteristic NMR shielding differences which are restricted mainly to the F-ring.[18,23] By contrast, **6a** (**90**) shows substantial changes throughout the C-F rings.
   a. Downfield HNMR shifts for H27 in 5,6-spiroketals of sapogenins with an axial methyl (C27) at C25, relative to equatorial Me sapogenins, are substantial (+0.2–0.5 ppm, solvent dependent) and diagnostic. The gap between the signals for 26α (axial) and 26β (equatorial) protons is magnified and the splitting patterns change in a characteristic manner. Smaller shifts for H23 and H24 are also evident. Similar changes have been recorded for authentic 17,25-hydroxylated steroids: **51** and **72** are especially relevant, as they were prepared by an independent route which did not permit any opportunity for spiroketal equilibration (addition of methyllithium to the corresponding 25-ketone).[11b] See Table 5si.

b. Carbon NMR is even more diagnostic, as most positions are relatively insensitive to solvent changes.[23] Table 4si clearly shows the match between the isolated South 7 intermediates in ref 11b and cephalostatin 7 (**2**) and ritterazine K. Spiroketal **6a** matches neither these nor the **6br/6** intermediates nor **4**, but **6br** and **6** appear to match the chemical shifts in **4** and differ from **2** in an entirely rational way.

3. The published structure for **iso-8a (89)** is consistent with NMR data and with its equilibration to **8a (79)**.
   a. An axial methyl is evident from both HNMR and CNMR shifts of positions 23, 24, 26 and 27. The coincidental identity of the CNMR shifts for C27 (21.2 ppm = –4 ppm from 25.3 ppm in alcohol **78**) in the three MTM ethers is consistent with CNMR conformational analysis[17] of the MTM sidechain.
      i. In **8a** and **6a**, the MTM methylene avoids lying over the ring and exerts an enforced γ-gauche shielding effect (–3.8 ppm)[17] on the equatorial methyl (C27), which would otherwise lie downfield (+1 ppm)[23] of an axial methyl. Prediction [25.1 – 3.8 = 21.3 ppm] and experiment are in excellent agreement.
      ii. In **iso-8a**, the MTM can adopt an anti relationship to C27 (–0.6 ppm γ-effect).[17] A "quick and dirty" estimate of the shielding contributions from the populations of the two main gauche and one anti MTM conformers (rel. ΔE's = +0.1, +0.6, 0 kcal/mol, relative pop. 0.85/2.2=0.39, 0.36/2.2=0.17, 1.0/2.2 =0.44) gives [(0.39)(–3.8) + (0.17)(–3.8) + (0.44)(–0.6)] = –2.4 ppm. When added to an already upfield (–1 ppm) axial C27, prediction (24.1 – 2.4 = 21.7 ppm) agrees with experiment within the normal variation (0.5 ppm) and little difference in shift for C27 in the three MTM ethers is expected. Full treatment utilizing all 27 MTM conformers predicts (24.1 – 2.9 = 21.2), an exact match.
   b. The 25S axial methyl requires either 22β stereochemistry or a 22α orientation with the F-ring in the "upright" conformation. The latter has been explicitly treated and dismissed for 22α and 22β sapogenins with a 20αMe.[18,24] Calculations indicate a >5 kcal/mol preference in such steroids for the normal "prone" chair form and similar preferences in **iso-8a** forms, which all lie >5 kcal/mol above the 20α,22α natural isomer, so a 22β form appears most viable. However, the 22β orientation alone is expected to account for only a portion of the extent and direction of the changes noted. Table 6si presents values for the 22-epimeric ritterazines F **10** and B **9**, and similar shielding patterns for 22-epimers occur in sapogenins.[23]
   c. A 20βMe rationalizes most of both the extent and direction of the shielding effects in the C-F rings in **iso-8a**. The changes from 20αMe "parent" hecogenin acetate (hecAc) evident in "analogue" 20β-hecAc (cyclopseudo-hecAc) and in **3** relative to **2** are persuasive.

4. Compound **6a (90)** is most likely in the **20β,22β form.**
   a. An equatorial Me at C25 is evident in both HNMR and CNMR shifts for position 27 as for **8a** (**79**), which requires either 22β stereochemistry or a 22α orientation with the F-ring in the "upright" conformation.
   b. A 20βMe accounts for changes parallel to those for **iso-8a (89)** in the D/C rings.
   c. The simplest explanation is the **20β,22β form**, since the NMR data are so similar to that for **iso-8a**. Shielding effects in the F-ring of **6a** differ from both **8a** and **iso-8a** and are entirely consistent with a prone 20β,22β chair with attendant increased shielding by axial oxygen as opposed to axial carbon.
   d. This form is most consistent with the failure of **6a** to equilibrate under conditions (25 °C, CSA/CH_2Cl_2) which deliver **8a** from **iso-8a**. Notwithstanding the axial Me driving force in **iso-8a**, equilibration is slow. Cyclopseudo-hecAc (20β,22α, equatorial Me) is a more easily protonated and opened spiroketal (no electron-withdrawing OH group at C17), yet it equilibrates even more slowly to hecAc (20α,22α) in identical chlorocarbon solvent (~20% conversion in 1 h with CSA or HCl), not at all with mild acid (8 h with PPTs), but rapidly in polar solvent (<30 min, PPTs in CH_3CN). **6a** in the 20β,22β "prone" chair likewise lacks the axial Me driving force, the 17OH renders it more resistant to oxonium/oxacarbenium ion formation than *c*.pseudohecAc, and the 25R stereochemistry provides an extra barrier to C22 equilibration.



90 [20R,22S,25R]
= 6a (20R,22S,25R)
= "20β,22β,25α"

[20R,22R,25R]

e. In this 25*R* case, the "upright" 20α,22β chair of the MTM ether lies only 0.3 kcal/mol above the "prone" form and the NMR signals would be broad and/or averaged between axial and equatorial Me shifts.

5. Two 5,6-isomers lie close to the 20α,22α isomer (20α,22β: +1 kcal/mol; 20β,22β: +1.9 kcal/mol). The corresponding 25-alcohol suffers further and rapid equilibration to more stable 5,5-spiroketals.[11b] Not surprisingly, during bromination in THF (HBr coproduct and loss of MTM in oxygenated solvent, permitting greater effective acidity than CH_2Cl_2), a substantial portion of the material converts to the 20α,22α,25β isomer **6br** (52%) but is also diverted to a variety of other 5,6- and 5,5-spiroketals. Further loss of material during azidation with imminium salt TMGA in the highly polar solvent CH_3NO_2 (60% yield) can be likewise rationalized.

Table 7si. Raw and benchmark-normalized cytotoxicities (log GI_{50} and "average" GI_{50}) of steroidal antineoplastics in the NCI-60 panel.[25]

	tumor line	**cstat 1** orig[26]	**cstat 1** 8/97	corr. 8/97	**cstat 7**[a] 8/97	corr. 8/97	**20*epi*-cstat 7**[a]	corr. 8/97	**25'epi-cstat 7**[a]	corr. 8/97	**rstat G_N1_N**[a]	corr. 8/97
leukemia	CCRF-CEM [c]	-9.7	-9.33	-9.7	-7.52	-7.82	-6.24	-6.49	-6.39	-6.64	-8.20	-8.53
	HL -60 [c]	-9.7	-9.49	-9.7	-7.53	-7.70	-6.35	-6.49	-7.18	-7.34	-8.77	-8.96
	K-562 [c]	-9.5	-7.94	-9.5	-6.90	-8.26	-6	-7.18	-6	-7.18	-7.88	-9.43
	MOLT-4 [c]	-9.8	-9.60	-9.8	-7.62	-7.78	-6.57	-6.71	-6.62	-6.76	-8.65	-8.83
	RPMI-8226 [c]	< -10	-9.96	-10	-8.15	-8.18	-6.7	-6.73	-7.07	-7.10	-8.96	-9.00
	SR [c]	-9.85	-9.16	-9.85	-7.45	-7.89	-6.41	-6.79	-6.64	-7.03	-7.97	-8.44
lung	A549 [d]	-9.4	-9.13	-9.4	**-7.13**	-7.34	**-6.1**	-6.28	**-6.1**	-6.28	**-8.16**	-8.40
	EKVX	-8.1	-8.49	-8.1	-7.03	-6.71	-6.15	-5.87	-6.08	-5.80	-7.24	-6.91
	HOP-62	-9.8	-8.91	-9.8	-7.00	-7.70	-6.1	-6.71	-6.26	-6.89	-7.73	-8.50
	HOP-92	-9.3	-8.75	-9.3	-6.82	-7.25	-6.29	-6.69	-6.24	-6.63	-7.70	-8.18
	NCI-H226	-9.3	-7.85	-9.3	-6.12	-7.25	-6	-6	-6	-6	-6.83	-8.09
	NCI-H23	-8.9	-8.45	-8.9	-7.30	-7.69	-6.05	-6.37	-6.06	-6.38	-7.05	-7.43
	NCI-H322M	-7.5	-7.79	-7.5	-6.74	-6.49	-6	-5.78	-6.11	-5.88	-6.72	-6.47
	NCI-H460	-9.6	-9.31	-9.6	-7.25	-7.48	-6.14	-6.33	-6.12	-6.31	-8.16	-8.41
	NCI-H522	-9	-8.08	-9	-6.98	-7.77	-6	-6.68	-6.02	-6.71	-7.01	-7.81
colon	COLO-205	-8.9	-8.52	-8.9	-6.77	-7.07	-6	-6	-6	-6.27	-7.50	-7.83
	HCC-2998	-7.5	-7.35	-7.5	-6	-6.12	-6	-6	-6	-6	-6.56	-6.69
	HCT-116	-9.2	-9.14	-9.2	-7.56	-7.61	-6.33	-6.37	-6.38	-6.42	-8.40	-8.46
	HCT-15	-8.8	-7.95	-8.8	-6.60	-7.31	-6	-6.64	-6	-6.64	-7.07	-7.83
	HT-29 [d]	-8.6	-8.37	-8.6	**-6.57**	-6.75	**-6.95**	-7.14	**-6**	-6.16	**-7.07**	-7.26
	KM12	-9	-8.86	-9	-6.62	-6.72	-6.51	-6.61	-6.15	-6.25	-7.80	-7.92
	SW-620	-9.4	-8.93	-9.4	-7.09	-7.46	-6.03	-6.35	-6.1	-6.42	-7.59	-7.99
CNS	SF-268	-9.2	-8.20	-9.2	-6.30	-7.07	-6	-6.73	-6	-6.73	-7.38	-8.28
	SF-295 [c]	< -10	-10.00	-10	-7.97	-7.97	-6.6	-6.60	-7.03	-7.03	-9.09	-9.09
	SF-539	< -10	-9.78	-10	-7.74	-7.91	-6.55	-6.70	-6.77	-6.92	-8.74	-8.94
	SNB-19	-8.5	-8.80	-8.5	-7.86	-7.59	-6.09	-5.88	-6.25	-6.04	-8.11	-7.83
	SNB-75	< -10	-9.73	-10	-6.09	-6.26	-7.1	-7.30	-6.87	-7.06	-8.72	-8.96
	U251	-9.7	-9.58	-9.7	-7.93	-8.03	-6.12	-6.20	-6.36	-6.44	-8.40	-8.51
melanoma	LOX IMVI	-9.4	-9.14	-9.4	-7.30	-7.51	-6.03	-6.20	-6.19	-6.37	-7.95	-8.18
	MALME-3M	-8	-8.37	-8	-7.26	-6.94	-6.1	-5.83	-6	-5.73	-7.05	-6.74
	M14	-9.5	-9.06	-9.5	-6.97	-7.31	-6	-6.29	-6	-6.29	-7.93	-8.32
	SK-MEL-2	-8.9	-9.20	-8.9	-7.15	-6.92	-6.06	-5.86	-6	-5.80	-8.04	-7.78
	SK-MEL-28	-9.1	-8.89	-9.1	-7.02	-7.19	-6.04	-6.18	-6	-6.14	-7.94	-8.13
	SK-MEL-5	-8.5	-7.91	-8.5	-6.80	-7.31	-6	-6.45	-6.01	-6.46	-6.92	-7.44
	UACC-257	-8.5	-8.12	-8.5	-6.91	-7.23	-6	-6.28	-6	-6	-7.28	-7.62
	UACC-62	-9.5	-9.22	-9.5	-7.44	-7.67	-6	-6.18	-6.17	-6.36	-8.10	-8.35
ovarian	IGROV1	-8	-8.30	-8	-6.57	-6.33	-6	-5.78	-6	-5.78	-7.01	-6.76
	OVCAR-3	-7.1	-7.31	-7.1	-6	-6	-6	-6	-6	-6	-6.06	-5.89
	OVCAR-4	-7.2	-7.48	-7.2	-6	-6	-6	-6	-6	-6	-6.72	-6.47
	OVCAR-5	-8.3	-7.43	-8.3	-6	-6.70	-6	-6	-6	-6	-6.70	-7.48

	tumor line	**cstat 1** orig[26]	**cstat 1** 8/97	corr. 8/97	**cstat 7**[a] 8/97	corr. 8/97	**20*epi*-cstat 7**[a]	corr. 8/97	**25'epi-cstat 7**[a]	corr. 8/97	**rstat** G_N1_N[a]	corr. 8/97
	OVCAR-8	-7.2	-6.61	-7.2	-6	-6.54	-6	-6	-6	-6	-6.00	-6.54
	SK-OV-3	-9	-7.77	-9	-6	-6.95	-6	-6	-6	-6	-6.28	-7.27
renal	786-0 [c]	-9.9	-9.59	-9.9	-7.85	-8.10	-6.52	-6.73	-6.70	-6.92	-8.61	-8.89
	A498 [d]	-9.2	-7.43	-9.2	**-6.00**	-7.43	**-6**	-6	**-6**	-6	**-6.69**	-8.28
	ACHN	-8.1	-8.27	-8.1	-7.32	-7.17	-6.02	-5.90	-6.02	-5.90	-6.96	-6.82
	CAKI-1	-8.7	-8.14	-8.7	-7.04	-7.52	-6	-6.41	-6.03	-6.44	-7.18	-7.67
	RXF-393 [c]	< -10	-10.22	-10	-7.95	-7.78	-7.05	-6.90	-7.3	-7.14	-9.47	-9.27
	SN12C	-6.8	-6.00	-6.8	-6.00	-6.80	-6	-6	-6	-6	-6	-6
	TK-10	-7.5	-8.36	-7.5	-7.18	-6.44	-6.02	-5.40	-6	-5.38	-7.6	-6.82
	UO-31	-8.9	-8.77	-8.9	-7.28	-7.39	-6.16	-6.25	-6.18	-6.27	-7.76	-7.88
prostate	PC-3 [d]	< -10	-9.29	-10	**-7.18**	-7.73	**-6.17**	-6.64	**-6.01**	-6.47	**-8.22**	-8.85
	DU-145	-7.6	-7.39	-7.6	-6.04	-6.21	-6	-6.17	-6.07	-6.24	-6.8	-6.99
breast	MCF-7 [d]	< -10	-8.93	-10	**-7.35**	-8.23	**-6.21**	-6.95	**-6.26**	-7.01	**-7.55**	-8.45
	MCF7/ADR [d]	-7.7	-6.72	-7.7	-6.43	-7.37	-6	-6.88	-6	-6	-6.23	-7.14
	MDA-MB-231	< -10	-7.07	-10	-6.06	-8.57	-6	-6	-6	-6	-6.00	-8.49
	HS-578T [c]	< -10	-9.70	-10	-7.28	-7.51	-6.77	-6.98	-7.14	-7.36	-8.9	-9.18
	MDA-MB-435	< -10	-8.51	-10	-7.01	-8.24	-6	-7.05	-6	-7.05	-7.28	-8.55
	MDA-N	< -10	-8.72	-10	-7.02	-8.05	-6	-6.88	-6	-6.88	-7.62	-8.74
	BT-549	-9.8	-9.07	-9.8	-7.45	-8.05	-6.28	-6.79	-6.32	-6.83	-8.23	-8.89
	T-47D	-8	-7.82	-8	-6.26	-6.40	-6	-6	-6	-6	-7.06	-7.22
# lines tested		60	60	60	60	60	60	60	60	60	60	60
# affected		60	59	60	53	58	33	48	34	47	58	59
activity fraction		**1.00**	0.98	**1.00**	0.88	**0.97**	0.55	**0.80**	0.57	**0.78**	0.97	**0.98**
avg log		-8.98	-8.54	-8.98	-6.95	-7.31	-6.18	-6.38	-6.22	-6.40	-7.56	-7.93
avg nM		**1.1**	2.90	**1.1**	≥113[e]	**49**	>660 [e]	**>420** [e]	>603 [e]	**>395** [e]	27.5	**11.6**

[a]8/97 test. [b]6/99 test (4-8 run avg). [c]Used for NCI-10. [d]Cell line used in PCCL through 11/98. [e]Lower limit only; too few cell lines affected for a true average.

Table 7si continued.

	tumor line	**rstat** G_N1_S[a]	corr. 8/97	**rstat** G_N7_S[a]	corr. 8/97	**rstat 14-** *epi*B_N7_S[a]	corr. 8/97	**cstat 1** 6/99	corr. 6/99	**ritt B**	corr. 6/99	**ritt C**	corr. 6/99
leukemia	CCRF-CEM [c]	-6	-6.20	-7.71	-8.02	-6.58	-6.84	-8.71	-9.7	-8.45	-9.41	-6.50	-7.24
	HL -60 [c]	-6	-6.11	-8.51	-8.70	-6.32	-6.46	-8.51	-9.7	-8.63	-9.84	-6.88	-7.84
	K-562 [c]	-6	-7.61	-7.12	-8.52	-6.12	-7.32	-8.43	-9.5	-8.00	-9.02	-6.40	-7.21
	MOLT-4 [c]	-6	-6.02	-8.15	-8.32	-7.59	-7.75	-8.96	-9.8	-8.80	-9.63	-8.15	-8.91
	RPMI-8226 [c]	-6.22	-6.22	-8.47	-8.50	-8.06	-8.09	-9.5	-10	-9.56	-10.06	-7.40	-7.79
	SR [c]	-6.1	-6.41	-7.82	-8.28	-6.55	-6.94	-9.13	-9.85	-9.10	-9.67	-6.61	-7.02
lung	A549 [d]	-6	-6.08	-7.41	-7.63	-7.02	-7.23	**-8.15**	-9.4	-7.55	-8.71	-6.12	-7.06
	EKVX	-6.52	-6.18	-7.24	-6.91	-6.09	-5.81	-7.41	-8.1	-7.70	-8.42	-6.96	-7.61
	HOP-62	-6	-6	-7.11	-7.82	-7.10	-7.81	-8.73	-9.8	-8.48	-9.52	-6.36	-7.14
	HOP-92	-6	-6.63	-7.82	-8.31	-6.66	-7.08	-7	-9.3	-6.55	-8.70	-6	-6
	NCI-H226	-6	-6	-6	-6	-6	-6	-7.2	-9.3	-6.75	-8.72	-6.48	-8.37
	NCI-H23	-6	-6	-6.87	-7.24	-6.11	-6.44	-7.64	-8.9	-6.98	-8.13	-6.04	-7.04
	NCI-H322M	-6	-6	-6.00	-5.78	-6.97	-6.71	-6.75	-7.5	-6	-6.67	-6	-6
	NCI-H460	-6	-6	-7.65	-7.89	-6.93	-7.15	-8.99	-9.6	-8.63	-9.22	-6.24	-6.66
	NCI-H522	-6	-6.84	-6.60	-7.35	-6.60	-7.35	-7.58	-9	-7.06	-8.38	-6	-6
colon	COLO-205	-6	-6	-6	-6.27	-6	-6.27	-8	-8.9	-6.93	-7.71	-7.04	-7.83
	HCC-2998	-6	-6	-6	-6.12	-6.50	-6.63						
	HCT-116	-6	-6	-7.95	-8.00	-7.37	-7.42	-8.4	-9.2	-7.80	-8.54	-6.08	-6.66
	HCT-15	-6	-6	-6.05	-6.70	-6.29	-6.96	-7.32	-8.8	-6.22	-7.48	-6	-7.21
	HT-29 [d]	**-6**	-6.14	-6	-6.16	-6	-6.16	-7.63	-8.6	-6.67	-7.52	-6.30	-7.10
	KM12	-6	-6	-7.13	-7.24	-6.82	-6.93	**-7.78**	-9	-6.23	-7.21	-6	-6.94
	SW-620	-6	-6	-7.00	-7.37	-6.27	-6.60	-8.47	-9.4	-8.13	-9.02		
CNS	SF-268	-6	-6	-6	-6.73	-6	-6.73	-7.83	-9.2	-7.34	-8.62	-6.31	-7.41
	SF-295 [c]	-6.14	-6.21	-8.57	-8.57	-7.87	-7.87	-9.43	-10	-9.50	-10.07	-6.71	-7.12
	SF-539	-6.04	-6.15	-8.14	-8.32	-7.43	-7.60	-8.64	-10	-8.41	-9.73	-7.08	-8.19
	SNB-19	-6	-5.78	-7.40	-7.15	-6.81	-6.58	-8.29	-8.5	-6.95	-7.13	-6.03	-6.18
	SNB-75	-6.19	-6.34	-8.41	-8.64	-7.93	-8.15	-8.72	-10	-8.96	-10.28	-6.74	-7.73
	U251	-6	-6.01	-8.22	-8.32	-6.95	-7.04	-9.06	-9.7	-9.10	-9.74	-6.66	-7.13
melanoma	LOX IMVI	-6	-6	-7.81	-8.03	-7.17	-7.37	-8.67	-9.4	-8.42	-9.13	-6.19	-6.71
	MALME-3M	-6	-5.73	-7.20	-6.88	-6	-5.73	-7.74	-8	-7.43	-7.68	-6.17	-6.38
	M14	-6	-6	-7.14	-7.49	-6.25	-6.55	-8.54	-9.5	-7.99	-8.89	-6.15	-6.84
	SK-MEL-2	-6	-6	-6.96	-6.73	-6.59	-6.38	-8.03	-8.9	-8.02	-8.89	-6.27	-6.95
	SK-MEL-28	-6	-6.09	-6.73	-6.89	-6.04	-6.18	-7.6	-9.1	-6	-7.18	-6.01	-7.20
	SK-MEL-5	-6	-6	-6.31	-6.78	-6.11	-6.57	-8.65	-8.5	-8.75	-8.60	-7.13	-7.01
	UACC-257	-6	-6	-6	-6	-6	-6.28	-7.83	-8.5	-6.63	-7.20	-6	-6
	UACC-62	-6	-6	-7.63	-7.86	-7.14	-7.36	-8.57	-9.5	-8.43	-9.34		
ovarian	IGROV1	-6	-6	-6	-5.78	-6	-5.78	-7.45	-8	-6	-6.44	-6	-6.44
	OVCAR-3	-6	-6	-6	-6	-6	-6	-6.34	-7.1	-6.72	-7.53	-6	-6
	OVCAR-4	-6	-6	-6	-6	-6.36	-6.12	-7.04	-7.2	-6	-6.14	-6	-6.14
	OVCAR-5	-6	-6	-6	-6.70	-6	-6.70	-7.47	-8.3	-7.00	-7.78	-6	-6

	tumor line	**rstat G_N1_S**[a]	corr. 8/97	**rstat G_N7_S**[a]	corr. 8/97	**rstat 14-*epi*B_N7_S**[a]	corr. 8/97	**cstat 1** 6/99	corr. 6/99	**ritt B**	corr. 6/99	**ritt C**	corr. 6/99
	OVCAR-8	-6	-6	-6	-6.54	-6	-6	-6.47	-7.2	-6	-6	-6	-6
	SK-OV-3	-6	-6	-6	-6.95	-6	-6	-7.11	-9	-6.77	-8.57	-6	-6
renal	786-0 [c]	-6.05	-6.17	-8.48	-8.75	-7.49	-7.73	-9.42	-9.9	-9.61	-10.10	-6.84	-7.19
	A498 [d]	**-6**	-6	-7.39	-9.15	-6	-7.43	**-8.78**	-9.2	-8.75	-9.17	-6.52	-6.83
	ACHN	-6	-6	-6.76	-6.62	-6.35	-6.22	-7.62	-8.1	-6.98	-7.42	-6.08	-6.46
	CAKI-1	-6	-6	-6.64	-7.10	-6.12	-6.54	-8.39	-8.7	-7.99	-8.29	-6.17	-6.40
	RXF-393 [c]	-6.21	-6.21	-9.02	-8.83	-8.22	-8.04	-9.48	-10	-10.04	-10.59	-7.36	-7.76
	SN12C	-6	-6	-6	-6	-6	-6	-6.23	-6.8	-6	-6.55	-6	-6
	TK-10	-6	-6	-6.71	-6.02	-6.41	-5.75	-7.11	-7.5	-6	-6.33	-6	-6
	UO-31	-6.04	-6.15	-7.59	-7.70	-7.00	-7.10	-8.72	-8.9	-8.57	-8.75	-6.45	-6.58
prostate	PC-3 [d]	**-6**	-6	-7.47	-8.04	-6.86	-7.38	**-7.89**	-10	-7.64	-9.68	-6	-7.60
	DU-145	-6	-6	-7.42	-7.63	-6	-6.17	-7.33	-7.6	-8.44	-8.75	-6	-6
breast	MCF-7 [d]	**-6**	-6	-6.76	-7.57	-6.33	-7.09	**-8.11**	-10	-7.76	-9.57	-6	-7.40
	MCF7/ADR [d]	-6.19	-6	-6	-6.88	-6	-6	-6	-7.7	-6	-6	-6	-6
	MDA-MB-231	-6	-6	-6	-6	-6	-6	-7.64	-10	-6.40	-8.38	-6	-7.85
	HS-578T [c]	-6.16	-6.29	-8.65	-8.92	-8.12	-8.37	-9.54	-10	-9.68	-10.15	-7.34	-7.69
	MDA-MB-435	-6	-7.04	-6.05	-7.11	-6	-7.05	-7.95	-10	-6.62	-8.33	-6	-7.55
	MDA-N	-6	-6	-7.07	-8.11	-6.27	-7.19	-8.23	-10	-7.46	-9.06	-6.04	-7.34
	BT-549	-6	-6.28	-7.30	-7.89	-7.16	-7.74	-7.93	-9.8	-7.95	-9.82	-6.18	-7.64
	T-47D	-6	-6	-6.14	-6.28	-6	-6.14	-7.96	-8	-7.49	-7.53	-6	-6
# lines tested		60	60	60	60	60	60	59	59	59	59	57	57
# affected		11	21	45	54	43	53	58	59	52	58	36	44
activity fraction		0.18	**0.35**	0.75	**0.90**	0.72	**0.88**	0.98	**1.00**	0.88	**0.98**	0.63	**0.77**
avg log		-6.03	-6.11	-7.04	-7.33	-6.58	-6.81	-8.04	-8.98	-7.63	-8.49	-6.35	-6.94
avg nM		>931[e]	**>768**[e]	>90.6[e]	**≥46.3**[e]	>262[e]	**≥153**[e]	9.21	**1.1**	≥23.6[e]	**3.23**	>446[e]	**>116**[e]

[a]8/97 test. [b]6/99 test (4-8 run avg). [c]Used for NCI-10. [d]Cell line used in PCCL through 11/98. [e]Lower limit only; too few cell lines affected for a true average.

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(25) For compounds lacking a raw GI_{50} (i.e. an entry of "-6") for a given cell line, normalization was applied to that line only if a steep enough dose-response curve indicated achievement of a GI_{33} or better which might reasonably indicate that a GI_{50} would be achieved at slightly higher concentration.
(26) Full NCI-60 results for cephalostatins 1-9 (NSC# 363979-81, 378727-36), some at more than one concentration, are at http://dtp.nci.nih.gov.