# Supporting Information:

# Asymmetric Total Synthesis and Stereochemical Elucidation of the Antitumor Agent PM-94128

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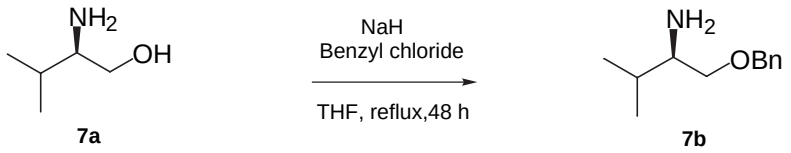
**General Procedures :**

All non-aqueous reactions were performed under a positive pressure of dry argon in oven-dried, or flame-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Toluene was freshly distilled over sodium. All reagents were purchased from either Aldrich or Accros chemical companies and used without purification. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates (Merck, Kieselgel 60 $F_{254}$). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a *p*-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). Product purification by gravity or forced-flow column chromatography were performed using Macherey-Nagel Silica Gel 60 (70-230 or 230-400 mesh, respectively). Melting points were determined with a Büchi B-545 apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane or ether solution of the compound on sodium chloride discs. All IR spectra were recorded on a Nicolet Impact-400 Fourier transform infrared spectrometer (FTIR) and the data are reported in reciprocal centimeters ($cm^{-1}$). $^{1}H$ NMR (300 MHz), and $^{13}C$ NMR (75 MHz) spectra were run on an Advance300 spectrometer. All shifts for $^{1}H$ spectra are values downfield from tetramethylsilane and are reported as follows: chemical shift (ppm), multiplicity, coupling constants (Hz) and integration. If not otherwise mentioned, all nuclear magnetic resonance (NMR) spectra were obtained from deuterochloroform ($CDCl_3$). Mass spectra (LRMS) were recorded on a ThermoFinnigan PolarisQ ion-trap spectrometer using DCI (ammonia/isobutane 63/37). Elemental analyses were performed at the Service Central d'Analyse du CNRS, Vernaison, France.

**(*R*)-1-Benzyloxymethyl-2-methyl-propylamine (7b)**




**7a** **7b**

To a stirred solution of (*R*)-valinol **7a** (5.0 g, 48.5 mmol ) in THF (50 mL) was added sodium hydride (60% dispersion, 1.94 g, 48.5 mmol) in one portion and the resultant suspension was refluxed for 30 minutes. Benzyl chloride (6.1 g, 48 mmol) was then added and the reaction mixture was refluxed for further 48 hours. On cooling, water (10 mL) was added and the solvent was removed *in vacuo*. The residue was treated with 6N KOH until pH 12 was reached and then extracted with dichloromethane. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil which upon column chromatography over silica gel yielded compound **7b** (8.554 g, 91%).

$[\alpha]^{20}_{D}$ –14.2 (*c* 1.58, $CHCl_3$).

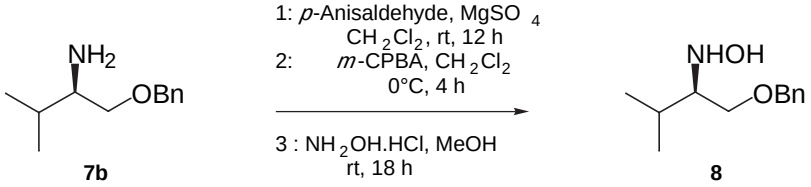
$^1$H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J*=7 Hz, 6H), 1.35 (bs, 2H), 1.64 (m, 1H), 2.77 (m, 1H), 3.29 (t, *J* = 9 Hz, 1H), 3.51 (dd, $J_1$ = 9 Hz, $J_2$ = 4 Hz, 1H), 4.52 (s, 2H), 7.27-7.34 (m, 5H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.06, 19.40, 30.92, 56.32, 73.22, 74.08, 127.55, 127.60, 128.42 138.42.

IR ($CH_2Cl_2$) 3383, 3067, 3037, 2960, 2895, 2865, 1585, 1496, 1468, 1453, 1386, 1364, 1209, 1102, 1032, 912, 854, 741, 702 $cm^{-1}$.

MS (DCI) *m/z* (%) 194 ($MH^+$, 100).

**(*R*)-*N*-(1-Benzyloxymethyl-2-methyl-propyl)-hydroxylamine (8).**




**7b** **8**

To a solution of (*R*)-1-benzyloxymethyl-2-methyl-propylamine **7b** (8.0 g, 41.4 mmol) in dichloromethane (50 mL) were added *p*-anisaldehyde (5.52 g, 40.5 mmoles) and anhydrous $MgSO_4$ (7.5 g). The reaction was stirred 15 h at room temperature, then the mixture was filtered through celite and concentrated *in vacuo* to give the crude corresponding imine. This imine was dissolved in dichloromethane (50 mL), and to the solution was added dropwise a solution of *m*-chloroperbenzoic acid (75% purity, 14.3 g, 62.3 mmol) in dichloromethane (100 mL) at 0°C over 1.5 hour. After further stirring for 2 hours, precipitated *m*-chlorobenzoic acid was filtered off, and the filtrate was washed with 10% aqueous solution of potassium carbonate and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* to give a residue which was dissolved in methanol (50 mL). To this solution was added dropwise hydroxylamine hydrochloride (8.63 g, 124.2 mmol) in methanol (100 mL) at 0°C. The reaction mixture was allowed to come to room temperature and was further

stirred for 18 hour. The methanol was removed *in vacuo* and the residue, after treatment with 6N KOH was extracted with dichloromethane. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product, which upon column chromatography over silica gel yielded compound **8** ( 5.924 g, 68%) as a yellow oil.

$[\alpha]^{20}_D$ –11.2 (*c* 1.29, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* =7 Hz, 3H), 0.97 (d, *J* =7 Hz, 3H), 1.95 (m, 1H), 2.81 (td, $J_1$ = 7 Hz, $J_2$ = 4 Hz 1H), 3.46 (dd, $J_1$ = 10 Hz, $J_2$ = 7 Hz, 1H),), 3.64 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 4.49 (d, *J*=12 Hz, 1H), 4.56 (d, *J* =12 Hz, 1H), 7.29-7.33 (m, 5H).

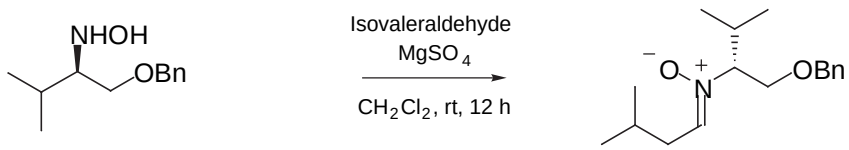
$^{13}$C NMR (75MHz, $CDCl_3$) δ 18.00, 19.33, 30.83, 56.23, 73.13, 73.96, 127.47, 127.52, 128.27, 138.33.

IR ($CH_2Cl_2$) 3267, 2959, 2874,1502,1456,1374,1371,1101,738, 700 $cm^{-1}$.

MS (DCI) *m/z* (%) 210 ($MH^+$, 100).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87%; H, 9.15%; N, 6.69%. Found : C, 68.92%; H, 9.12%; N, 6.69%.

**(*R*)-(1-Benzyloxy-3-methyl-2-butyl)-(3-methyl-butylidene)-amine *N*-oxide (9).**




**8** **9**

To a solution of (*R*)-*N*-(1-Benzyloxymethyl-2-methyl-propyl)-hydroxylamine **8** (5.8 g, 27.7 mmol) in dichloromethane (60 mL) were added isovaleraldehyde (2.63 g, 30.5 mmoles) and anhydrous $MgSO_4$ (5 g). The reaction mixture was stirred for 12 h at room temperature, then it was filtered through celite and dichloromethane was evaporated under reduced pressure to give a residue, which upon column chromatography over silica gel yielded nitrone **9** (6.124 g, 79%) as a white solid.

mp 41-42 °C.

$[\alpha]^{20}_D$ +2.2 (*c* 1.38, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 3H), 0.97 (d, *J* = 7 Hz, 6H), 1.92 (m, 1H), 2.18 (m, 1H), 2.43 (dd, $J_1$ = 7 Hz, $J_2$ = 6 Hz, 2H), 3.46 (td, $J_1$ = 9 Hz, $J_2$ = 3 Hz, 1H), 3.65 (dd, $J_1$ = 10 Hz, $J_2$ = 3 Hz, 1H), 4.01 (dd, $J_1$ = 10 Hz, $J_2$ = 9 Hz, 1H), 4.46 (d, *J* = 12 Hz, 1H), 4.58 (d, *J* = 12 Hz, 1H), 6.69 (t, *J* = 6 Hz, 1H), 7.26-7.35 (m, 5H).

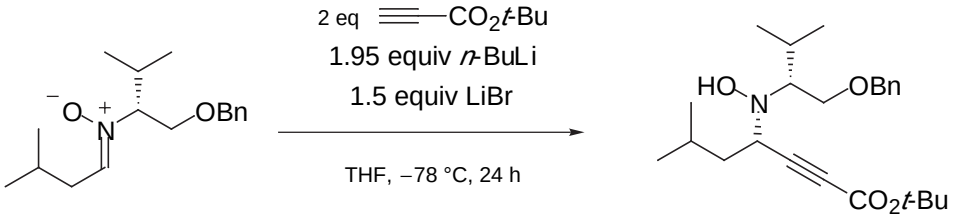
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.27, 19.67, 22.58, 22.60, 26.00, 27.40, 35.17, 68.39, 73.36, 81.70, 127.53, 127.58, 128.29, 138.08, 139.38.

IR ($CH_2Cl_2$) 3414, 3077, 3052, 3022, 2968, 2877, 1585, 1494, 1464, 1453, 1423, 1386, 1367, 1326, 1272, 1173, 1119, 1075, 1035, 736, 701 $cm^{-1}$.

MS (DCI) *m/z* (%) 278 ($MH^+$, 100).

Anal. Calcd for $C_{17}H_{27}NO_2$ : C, 73.61%; H, 9.81%; N, 5.05%. Found : C, 73.65%; H, 9.88%; N, 5.01%.

**4-[(1-Benzyloxymethyl-2-methyl-propyl)-hydroxy-amino]-6-methyl-hept-2-ynoic acid *tert*-butyl ester (10).**




**9** **10**

To a stirred solution of *t*-butylpropiolate (5.05 g, 40 mmol) in THF (250 mL) placed under argon atmosphere was added dropwise *n*-BuLi (27 mL, 1.44 M solution in hexanes, 39 mmol) at –78 °C. The solution was stirred for 30 minutes at –78 °C, then a solution of nitrone **9** (5.55 g, 20 mmol) and LiBr (2.6 g, 30 mmol) in THF (150 mL) was added dropwise at –78 °C. The reaction mixture was stirred for 24 h at the same temperature, and then was quenched with water and extracted with ethylacetate (3 * 25 mL). The organic phase, after washing with brine (20 mL) was dried over $MgSO_4$, filtered and concentrated to give a residue which upon column chromatography over silica gel yielded the hydroxylamine **10** (6.314 g, 78%) as a yellow oil.

$[\alpha]^{20}_D$ –11.5 (*c* 1.23, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.89 (d, $J$ = 7 Hz, 3H), 0.90 (d, $J$ = 7 Hz, 3H), 0.91 (d, $J$ = 7 Hz, 3H), 1.00 (d, $J$ = 7 Hz, 3H), 1.49 (s, 9H), 1.65 (m, 1H), 1.78 (m, 1H), 1.91 (m, 1H), 2.04 (m, 1H), 2.68 (td, $J_1$ = 6 Hz, $J_2$ = 4 Hz, 1H), 3.79 (t, $J$ = 7 Hz, 1H), 3.84 (d, $J$ = 4 Hz, 2H), 4.49 (d, $J$ = 12 Hz, 1H), 4.59 (d, $J$ = 12 Hz, 1H), 7.26-7.35 (m, 5H).

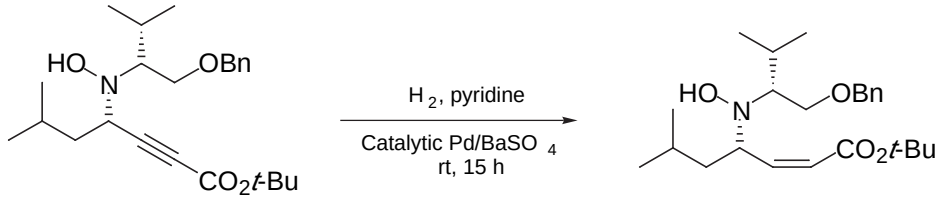
$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.32, 20.24, 22.30, 22.38, 24.62, 27.91, 28.25, 41.94, 55.81, 68.31, 69.87, 73.05, 78.97, 83.15, 84.20, 127.60, 127.68, 128.31, 137.91, 152.53.

IR ($CH_2Cl_2$) 3396, 2955, 2865, 2220, 1706, 1485, 1460, 1387, 1371, 1265, 1159, 1101, 1077, 1019, 840, 742, 726, 693 $cm^{-1}$.

MS (DCI) *m/z* (%) 403 ($MH^+$, 100), 388 ($MH^+$-$H_2O$, 70).

Anal. Calcd for $C_{24}H_{37}NO_4$ : C, 71.43%; H, 9.24%; N, 3.47%. Found : C, 71.48%; H, 9.20 %; N, 3.42%.

**4-[(1-Benzyloxymethyl-2-methyl-propyl)-hydroxy-amino]-6-methyl-hept-2-enoic acid *tert*-butyl ester (11a).**




**10** **11a**

To a solution of **10** (5.9 g, 14.6 mmol) in pyridine (90 mL) was added $Pd/BaSO_4$ (1.46 g) and the resulting suspension was stirred under $H_2$ atmosphere at room temperature for 15 h. The suspension was then filtered through celite and concentrated *in vacuo* to give a residue which upon column chromatography over silica gel yielded **11a** (4.112 g, 69%).

$[\alpha]^{20}_D$ +84.7 (*c* 1.15, $CHCl_3$).

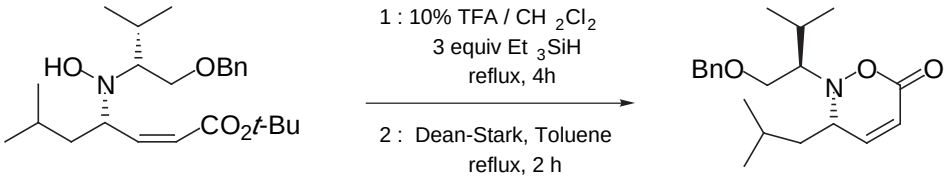
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (d, $J$ = 7 Hz, 3H), 0.91 (d, $J$ = 7 Hz, 3H), 0.92 (d, $J$ = 7 Hz, 3H), 0.94 (d, $J$ = 7 Hz, 3H), 1.23 (m, 1H), 1.47 (s, 9H), 1.60-1.77 (m, 2H), 2.07 (m, 1H), 2.69 (td, $J_1$ = 5 Hz, $J_2$ = 4 Hz, 1H), 3.67 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 3.76 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 4.50 (s, 2H), 4.73 (dt, $J_1$ = 10 Hz, $J_2$ = 5 Hz, 1H), 4.86 (bs, 1H), 5.78 (dd, $J_1$ = 12 Hz, $J_2$ = 1 Hz, 1H), 6.35 (dd, $J_1$ = 12 Hz, $J_2$ = 10 Hz, 1H), 7.23-7.35 (m, 5H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.26, 20.07, 22.91, 24.57, 28.00, 41.82, 58.90, 68.34, 68.94, 73.07, 80.16, 122.51, 127.50, 127.64, 128.26, 138.12, 146.65, 165.63.

IR ($CH_2Cl_2$) 3358, 2951, 2923, 2872, 1709, 1642, 1611, 1553, 1464, 1462, 1404, 1391, 1366, 1226, 1156, 832, 736, 698 $cm^{-1}$.

MS (DCI) *m/z* (%) 403 ($MH^+$, 100).

**2-(1-Benzyloxymethyl-2-methyl-propyl)-3-isobutyl-2,3-dihydro-[1,2]oxazine-6-one (12).**




**11a** **12**

A solution of **11a** (4.0 g, 9.86 mmol), trifluoroacetic acid (9.9 mL, 128.2 mmol) and triethylsilane (3.44 g, 29.6 mmol) in dichloromethane (100 mL) was refluxed for 4 h. The reaction mixture was then concentrated *in vacuo*. The obtained crude residue **11b** was dissolved in toluene (50 mL) and heated at reflux temperture with a Dean-Stark trap for 2 h. After cooling, the reaction mixture was washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated to give a residue which upon column chromatogaphy over silica gel yielded **12** (2.143 g, 66%) as a yellow oil.

$[\alpha]^{20}_{D}$ +72.5 (*c* 0.94, $CHCl_3$).
$^1$H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H), 0.93 (d, *J* = 7 Hz, 3H), 0.98 (d, *J* = 7 Hz, 3H), 1.46 (m, 1H), 1.61-1.77 (m, 2H), 2.03 (m, 1H), 3.01 (td, $J_1$ = 7 Hz, $J_2$ = 3 Hz, 1H), 3.55 (dd, $J_1$ = 10 Hz, $J_2$ = 3 Hz, 1H), 3.78 (dd, $J_1$ = 10 Hz, $J_2$ = 7 Hz, 1H), 3.98 (m, 1H), 4.41 (d, *J* = 12 Hz, 1H), 4.47 (d, *J* = 12 Hz, 1H), 5.96 (dd, $J_1$ = 10 Hz, $J_2$ = 1.6 Hz, 1H), 6.90 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 7.25-7.36 (m, 5H).

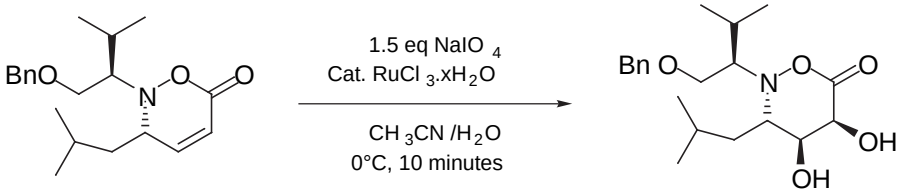
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.73, 19.95, 21.87, 23.46, 24.69, 28.57, 38.67, 56.94, 67.26, 67.75, 73.16, 118.27, 127.65, 127.79, 128.31, 137.83, 149.59, 165.40.

IR ($CH_2Cl_2$) 3062, 3026, 2966, 2936, 2864, 1733, 1497, 1470, 1452, 1385, 1370, 1246, 1113, 1025, 804, 737, 701 $cm^{-1}$.

MS (DCI) *m/z* (%) 331 ($MH^+$, 100).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47%; H, 8.82%; N, 4.23%. Found : C, 72.74%; H, 8.99%; N, 4.16%.

**2-(1-Benzyloxymethyl-2-methyl-propyl)-3-isobutyl-4.5-dihydroxy-2,3-dihydro-[1,2]oxazine-6-one (13).**




**12** **13**

To a vigorously stirred solution of the **12** (2.0 g, 6.03 mmol) in acetonitrile (72 mL) at 0°C was added a solution of $RuCl_3.3H_2O$ (0.42 mmol) and $NaIO_4$ (1.93 g, 9.04 mmol) in distilled water (12 mL). The reaction mixture was stirred vigorously for 10 minutes at 0°C and quenched with an aqueous solution of sodium bisulfite. The reaction mixture was filtered, extracted with ethylacetate, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by chromatography over silica gel afforded the diol **13** (1.836 g, 83%) as white solid.

mp 88-89 °C.

$[\alpha]^{20}_{D}$ +78.4 (*c* 1.00, $CHCl_3$).

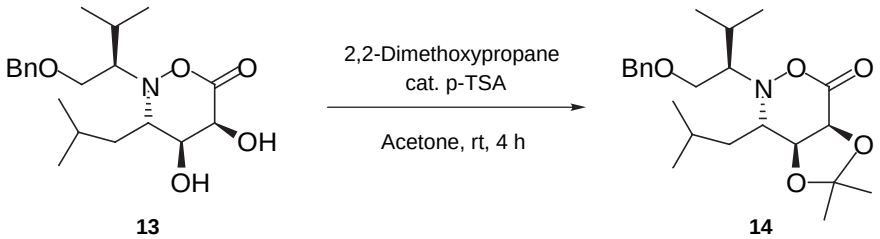
$^1$H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 7 Hz, 3H), 0.89 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 6H), 1.32-1.45 (m, 2H), 1.79-1.90 (m, 2H), 2.89 (m, 1H), 3.53 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 3.62 (ddd, $J_1$ = 11 Hz, $J_2$ = 4 Hz, $J_3$ = 3 Hz, 1H), 3.97 (dd, $J_1$ = 10 Hz, $J_2$ = 6 Hz, 1H), 4.23 (dd, $J_1$ = 4 Hz, $J_2$ = 3 Hz, 1H), 4.43 (d, *J* = 12 Hz, 1H), 4.52 (d, *J* = 12 Hz, 1H), 4.68 (d, *J* = 4 Hz, 1H) , 7.23-7.44 (m, 5H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.14, 20.46, 21.36, 24.18, 24.73, 29.51, 39.55, 66.06, 66.39, 67.57, 68.72, 73.25, 74.06, 127.64, 127.84, 128.31, 137.92, 175.50.

IR ($CH_2Cl_2$) 3438, 3020, 2967, 2929, 2853, 1754, 1465, 1389, 1365, 1218, 1111, 1073, 763 $cm^{-1}$.

MS (DCI) *m/z* (%) 366 ($MH^+$, 100).

**6-(1-Benzyloxymethyl-2-methyl-propyl)-7-isobutyl-2,2-dimethyl-tetrahydro-1,3,5-trioxa-6-aza-inden-4-one (14).**




**13** **14**

To a solution of diol **13** (1.7 g, 4.65 mmol) in acetone (17 mL), were added 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulphonic acid. The reaction mixture was stirred at room temperature for 4 h. Then $NaHCO_3$ was added to the reaction mixture, the suspension was filtered and concentrated *in vacuo;* the obtained residue, upon chromatography over silica gel, yielded **14** (1.564 g, 83%) as a white solid, which was crystallised in ethylacetate/pentane.

mp 85-86 °C.

$[\alpha]^{20}_D$ +113.2 (*c* 1.20, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, *J* = 7 Hz, 3H), 0.88 (d, *J* = 7 Hz, 3H), 0.94 (d, *J* = 7 Hz, 3H), 0.97 (d, *J* = 7 Hz, 3H), 1.22 (m, 1H), 1.39 (s, 3H), 1.50 (s, 3H), 1.61-1.92 (m, 3H), 2.84 (m, 1H), 3.48 (m, 1H), 3.52 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 3.94 (dd, $J_1$ = 10 Hz, $J_2$ = 6 Hz, 1H), 4.40 (t, *J* = 7 Hz, 1H), 4.45 (d, *J* = 12 Hz, 1H), 4.50 (d, *J* = 12 Hz, 1H), 4.69 (d, *J* = 7 Hz, 1H) , 7.23-7.42 (m, 5H).

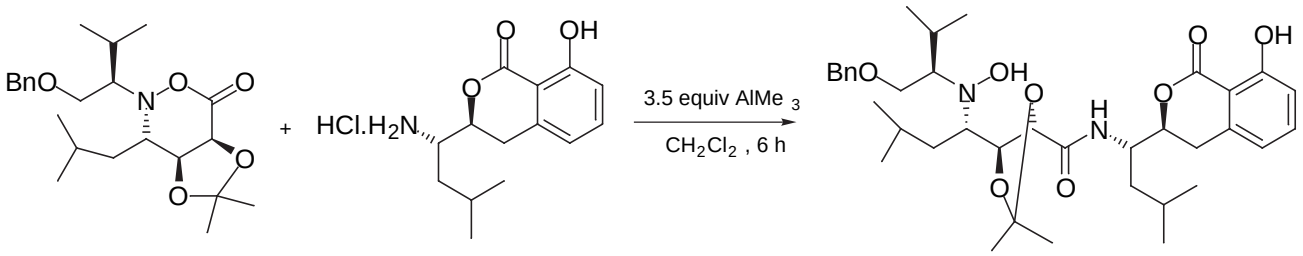
$^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.31, 20.35, 20.98, 24.37, 24.42, 25.86, 27.15, 29.53, 40.23, 65.12, 65.27, 67.39, 73.08, 73.43, 80.59, 112.48, 127.71, 127.92, 128.34, 137.91, 172.16.

IR ($CH_2Cl_2$) 3057, 3027, 2967, 2866, 1769, 1470, 1453, 1385, 1373, 1267, 1224, 1204, 1158, 1100, 994, 854, 738, 702 $cm^{-1}$.

MS (DCI) *m/z* (%) 406 ($MH^+$, 100).

Anal. Calcd for $C_{23}H_{35}NO_5$ : C, 68.12%; H, 8.70%; N, 3.45%. Found : C, 68.05%; H, 8.65%; N, 3.42%.

**5-[1-((1-Benzyloxymethyl-2-methyl-propyl)-hydroxyamino)-3-methyl-butyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid [1-(8-hydroxy-1-oxo-isochroman-3-yl)-3-methyl-butyl]-amide (16a).**




**14** **15** **16a**

A mixture of **14** (405 mg, 1 mmol) and aminodihydroisocoumarin hydrochloride **15** (997 mg, 3.5 mmol) in dichloromethane (5 mL) was stirred at room temperature for 30 min, and a solution of trimethylaluminium (1.75 mL, 2 M solution in heptane, 3.5 mmol) was then added. The resulting solution was stirred at room temperature for 6 h. The reaction was quenched with pH7 phosphate buffer, extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated to give a residue which upon chromatography over silica gel afforded **16a** (408 mg, 62%) as a white solid.

mp 42-43 °C.

$[\alpha]^{20}_D$ -31 (*c* 1.00, $CHCl_3$).

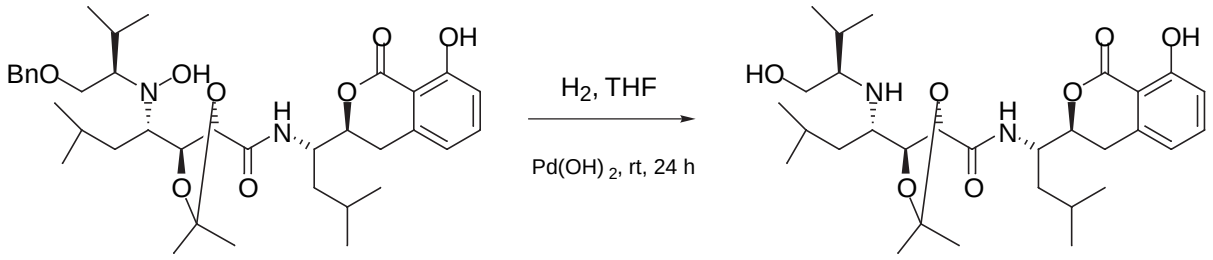
$^1$H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 7 Hz, 3H), 0.89 (d, *J* = 7 Hz, 3H), 0.94 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 3H), 0.96 (d, *J* = 7 Hz, 3H), 1.03 (d, *J* = 7 Hz, 3H), 1.36 (s, 3H), 1.38-1.54 (m, 3H), 1.56 (s, 3H), 1.61-1.86 (m, 3H), 2.08 (m, 1H), 2.71 (m, 1H), 2.77 (dd, $J_1$ = 16 Hz, $J_2$ = 3 Hz, 1H), 3.01 (dd, $J_1$ = 16 Hz, $J_2$ = 13 Hz, 1H), 3.42 (td, $J_1$ = 6 Hz, $J_2$ = 5 Hz, 1H), 3.67 (dd, $J_1$ = 10 Hz, $J_2$ = 4 Hz, 1H), 3.85 (dd, $J_1$ = 10 Hz, $J_2$ = 5 Hz, 1H), 4.34 (m, 1H), 4.43-4.70 (m, 5H), 6.56 (bs, 1H), 6.67 (d, *J* = 7 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 9 Hz, 1H), 7.24-7.36 (m, 5H), 7.40 (dd, $J_1$ = 8 Hz, $J_2$ = 7 Hz, 1H), 10.81 (s, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.42, 20.12, 21.97, 22.67, 22.92, 22.94, 24.14, 24.53, 25.19, 26.79, 29.00, 30.16, 38.50, 40.47, 48.67, 60.93, 66.24, 67.15, 73.07, 77.66, 79.49, 80.61, 107.87, 108.19, 116.05, 117.99, 127.25, 127.45, 128.07, 136.30, 138.35, 139.15, 162.04, 169.27, 171.75.

IR ($CH_2Cl_2$) 3405, 3210, 2960, 2871, 1674, 1620, 1583, 1518, 1464, 1384, 1369, 1233, 1215, 1163, 1109, 1062, 914, 882, 869, 807, 755, 697, 664 $cm^{-1}$.

MS (DCI) *m/z* (%) 655 ($MH^+$, 9), 406 ($MH^+$-$C_{14}H_{19}O_3N$, 100).

**5-[1-(1-Hydroxymethyl-2-methyl-propylamino)-3-methyl-butyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid [1-(8-hydroxy-1-oxo-isochroman-3-yl)-3-methyl-butyl]-amide (16b).**




**16a** **16b**

To a solution of **16a** (295mg, 0.45 mmol) in THF (10 mL) was added $Pd(OH)_2$ (300 mg) and the resulting suspension was stirred under $H_2$ atmosphere at room temperature for 24 h. The suspension was then filtered through celite and concentrated *in vacuo* to give a residue which upon column chromatography over silica gel yielded **16b** (203 mg, 82%).

mp 47-48°C.

$[\alpha]^{20}_D$ -74.3 (*c* 0.98, $CHCl_3$).

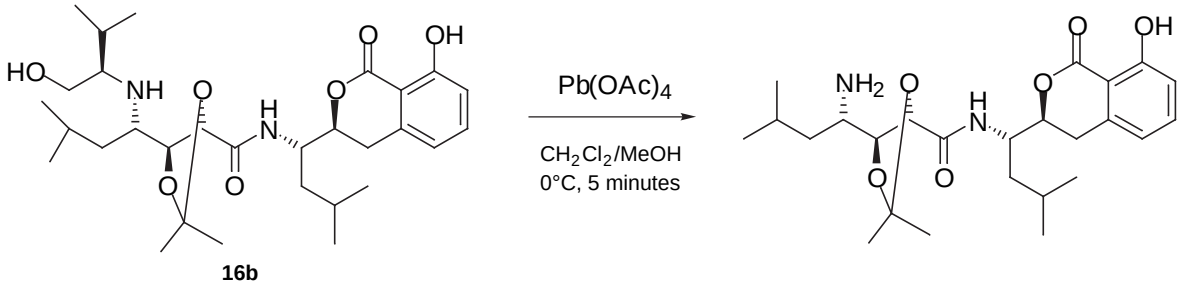
$^1$H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, $J$ = 7 Hz, 3H), 0.85 (d, $J$ = 7 Hz, 3H), 0.86 (d, $J$ = 7 Hz, 3H), 0.89 (d, $J$ = 7 Hz, 3H), 0.90 (d, $J$ = 7 Hz, 3H), 0.91 (d, $J$ = 7 Hz, 3H), 1.31 (s, 3H), 1.43 (m, 2H), 1.52 (s, 3H), 1.55-1.73 (m, 4H), 2.28 (m, 1H), 2.74 (dd, $J_1$ = 17 Hz, $J_2$ = 3 Hz, 1H), 2.90-2.99 (m, 2H), 3.32 (dd, $J_1$ = 11 Hz, $J_2$ = 5 Hz, 1H), 3.53 (dd, $J_1$ = 11 Hz, $J_2$ = 3 Hz, 1H), 4.21-4.31 (m, 2H), 4.45 (d, $J$ = 7 Hz, 1H), 4.56 (ddd, $J_1$ = 13 Hz,$J_2$ = 3 Hz,$J_3$ = 2 Hz, 1H), 6.61 (d, $J$ = 7 Hz, 1H), 6.79 (d, $J$ = 8 Hz, 1H), 6.86 (d, $J$ = 10 Hz, 1H), 7.33 (dd, $J_1$ = 8 Hz, $J_2$ = 7 Hz, 1H), 10.8 (bs, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.97, 20.17, 22.41, 22.66, 22.89, 23.14, 24.39, 24.68, 25.28, 26.82, 30.16, 30.39, 40.58, 41.21, 48.78, 53.43, 60.64, 62.32, 76.17, 80.52, 81.24, 108.05, 108.94, 116.18, 118.15, 136.44, 139.39, 162.18, 169.47, 171.32.

IR ($CH_2Cl_2$) 3485, 3410, 3151, 3062, 2980, 2919, 2871, 1667, 1621, 1586, 1523, 1463, 1385, 1370, 1270, 1228, 1215, 1165, 1111, 1066, 976, 919, 877, 811, 742, 709 $cm^{-1}$.

MS (DCI neg) *m/z* (%) 548 ($M^{-\cdot}$, 100).

**5-(1-Amino-3-methyl-butyl)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid [1-(8-hydroxy-1-oxo-isochroman-3-yl)-3-methyl-butyl]-amide.**




**16b**

To a stirred solution of **16b** (192mg, 0.35 mmol) in a 2:1 mixture of $CH_2Cl_2$/MeOH (6 mL) was added $Pb(OAc)_4$ (95% purity, 192 mg, 0.35 mmol) in one portion at 0°C. The resulting reaction mixture was stirred at same temperature for 5 minutes then quenched with 5% $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (2 * 3 mL), and the combined organic layer were dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* to give a crude residue, which upon column chromatography over silica gel yielded the pure free amine (135 mg, 83%) as a white solid.

mp 53-54 °C.

$[\alpha]^{20}_D$ -82.5 (*c* 1.00, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.79 (d, $J$ = 7 Hz, 3H), 0.87 (d, $J$ = 7 Hz, 3H), 0.89 (d, $J$ = 7 Hz, 3H), 0.90 (d, $J$ = 7 Hz, 3H), 1.19 (m, 1H), 1.29 (s, 3H), 1.33-1.46 (m, 2H), 1.50 (s, 3H), 1.54-1.83 (m, 4H), 2.71-2.81 (m, 2H), 2.97 (dd, $J_1$ = 16 Hz, $J_2$ = 13 Hz, 1H), 3.97 (dd, $J_1$ = 9 Hz, $J_2$ = 7 Hz, 1H), 4.29 (dt, $J_1$ = 10 Hz, $J_2$ = 3 Hz, 1H), 4.50-4.55 (m, 2H), 6.61 (d, $J$ = 8 Hz, 1H), 6.79 (d, $J$ = 8 Hz, 2H), 7.32 (dd, $J$ = 8 Hz, 1H).

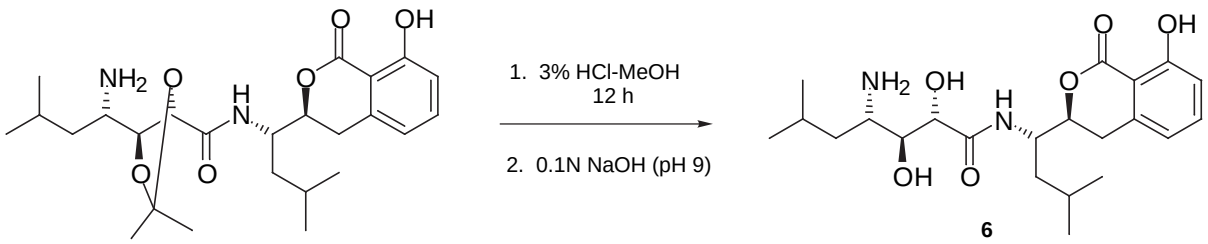
$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.99, 21.63, 23.13, 23.92, 24.44, 24.72, 27.07 30.32, 40.80, 43.09, 48.70, 49.21, 77.32, 81.26, 83.67, 107.96, 109.37, 116.10, 118.10, 136.36, 139.30, 162.11, 169.38, 170.81.

IR ($CH_2Cl_2$) $cm^{-1}$ 3413, 2967, 2922, 2871, 1680, 1618, 1589, 1518, 1390, 1460, 1371, 1267, 1230, 1217, 1162, 1109, 1073, 917, 879, 813, 737, 705.

MS (DCI neg.) *m/z* (%) 462 ($M^{-\cdot}$, 100).

Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91%; H, 8.28%; N, 6.06%. Found : C, 64.70%; H, 8.19%; N, 5.89%.

**4-Amino-2.3-dihydroxy-6-methyl-heptanoic acid [1-(8-hydroxy-1-oxo-isochroman-3-yl)-3-methyl-butyl]-amide (6).**




The acetonide protected PM-94128 (130 mg, 0.28 mmol) was treated with 3% HCl-MeOH (5 mL) and stirred at room temperature for 12 h. After removing the MeOH *in vacuo*, the obtained white solid was dissolved in $H_2O$ (2 mL), 0.1 M aq. NaOH was added dropwise until pH 9 was reached. The white suspension was extracted with dichloromethane (2 * 5 mL), the organic layer was washed with brine, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* to give a white solid, which was crystallized with ethyl acetate to yield pure PM-94128 (**6**)(110 mg, 93%).

mp 170-171 °C.

$[\alpha]^{20}_D$ –90.1 (*c* 2.00, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, $J$ = 6 Hz, 3H), 0.88 (d, $J$ = 6 Hz, 3H), 0.89 (d, $J$ = 7 Hz, 3H), 0.90 (d, $J$ = 7 Hz, 3H), 1.08 (m, 1H), 1.42 (m, 1H), 1.53-1.83 (m, 4H), 2.74 (dd, $J_1$ = 17 Hz, $J_2$ = 3 Hz, 1H), 2.87 (td, $J_1$ = 8 Hz, $J_2$ = 2 Hz, 1H), 3.01 (dd, $J_1$ = 17 Hz, $J_2$ = 13 Hz, 1H), 3.19 (t, $J$ = 8 Hz, 1H), 4.01 (d, $J$ = 8 Hz, 1H), 4.29 (td, $J_1$ = 10 Hz, $J_2$ = 3 Hz, 1H), 4.54 (bd, $J$ = 10 Hz, 1H), 6.62 (d, $J$ = 8 Hz, 1H), 6.79 (d, $J$ = 8 Hz, 1H), 7.33 ((t, $J$ = 8 Hz, 1H), 7.37 ((bd, $J$ = 11 Hz, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.97, 21.82, 22.99, 23.58, 23.98, 24.78, 30.22, 40.43, 44.15, 48.57, 54.94, 73.67, 74.78, 80.98, 108.04, 116.09, 118.15, 136.37, 139.38, 162.08, 169.46, 175.13.

MS (DCI) *m/z* (%) 423 ($MH^+$, 100).