# A concise total synthesis of puberulic acid, potent antimalarial agent

## Electronic Supplementary Information (ESI)

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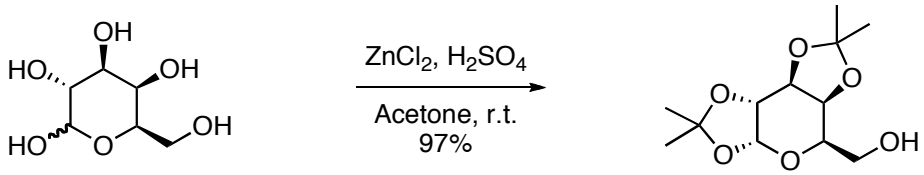
## 1. General Methods and Material

Unless otherwise noted, reagents and solvents were purchased at highest commercial quality and used without further purification. Dry acetone, PhMe, DMF, THF, $CH_2Cl_2$, MeOH, PhH were purchased from Kanto Chemical Co., Inc. Pre-coated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical (0.25 mm) and preparative (0.25 or 0.50 mm) thin layer chromatography. Flash chromatography was carried out with Kanto Chemical silica gel (Kanto Chemical, silica gel 60N, spherical neutral, 0.040–0.050 mm, Cat.-No. 37563–84) or Merck silica gel 230-400 mesh ASTM (60N, 0.040-0.063 mm, Cat.-No. 109385). ODS column chromatography was carried out with Sep-Pak® Plus C18 Short Cartridge (Waters Co. Ltd.) or CHROMATOREX® (Fuji Silysia Chemical Ltd.). $^1$H NMR spectra were recorded on JEOL JNM-ECA-500 (500 MHz) and $^{13}$C NMR spectra were recorded on JEOL JNM-ECA-500 (125 MHz). Chemical shifts are expressed in ppm downfield from the internal solvent peaks for $CDCl_3$ ($^1$H; δ = 7.26 ppm, $^{13}$C; δ = 77.0 ppm), $CD_3OD$ ($^1$H; δ = 3.31 ppm, $^{13}$C; δ = 49.0 ppm), $CD_2Cl_2$ ($^1$H; δ = 5.32 ppm, $^{13}$C; δ = 53.84 ppm), $(CD_3)_2CO$ ($^1$H; δ = 2.05 ppm, $^{13}$C; δ = 29.8, 206.3 ppm) and *J* values are given in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, m = multiplet, br = broad. lnfrared spectra for all compounds were measured on a Horiba FT-210 spectrometer. High- and Low-resolution mass spectra were measured on a JEOL JMS-AX505 HA, JEOL JMS-700 MStation and JEOL JMS-T100LP. Optical rotations were measured by using JASCO P-1010 polarimeter.

## 2. Experimental Procedures and Compounds Characterization

### 2-1. Champion data of total synthesis of puberulic acid

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose: **S1**

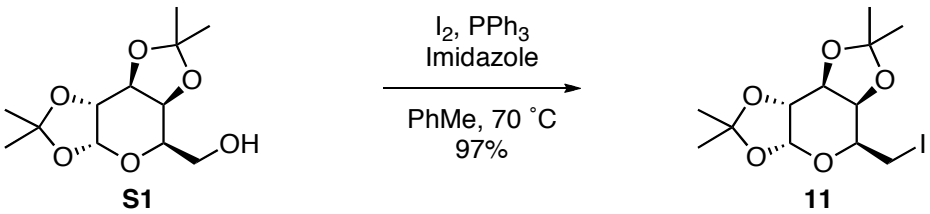



D-(+)-Galactose (**10**) **S1**

To a solution of anhydrous $ZnCl_2$ (28.37 g, 0.21 mol) in acetone (0.28 L) was added $H_2SO_4$ (0.96 mL, 18.09 mmol) and D-(+)-galactose (25.00 g, 0.14 mol) at room temperature. The mixture was stirred at room temperature for 16 h, and then quenched with sat. aq. $NaHCO_3$ (300 mL). The resulted suspension was filtrated through a pad of Celite®, then the Celite® pad was washed with acetone. The filtrate was concentrated under reduced pressure to remove excess acetone and extracted with ether (300 mL × 3). The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **S1** (35.03 g, 97%) as a colorless oil:

R*f* = 0.38 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.57 (d, *J* = 4.6 Hz, 1H), 4.61 (dd, *J* = 7.7, 2.3 Hz, 1H), 4.34 (dd, *J* = 4.6, 2.3 Hz, 1H), 4.28 (dd, *J* = 7.7, 1.7 Hz, 1H), 3.88 (ddd, *J* = 8.0, 6.9, 1.7 Hz, 1H), 3.87 (dd, *J* = 14.9, 6.9 Hz, 1H), 3.75 (dd, *J* = 14.9, 8.0 Hz, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H); identical with the reported data.[1)]

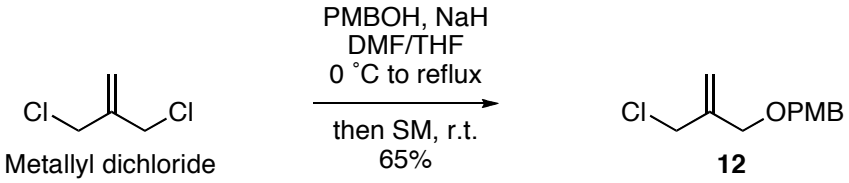
1,2:3,4-Di-*O*-isopropylidene-6-iodo-D-galactopyranose: **11**




To a solution of **S1** (12.00 g, 46.10 mmol) in toluene (0.23 L) was added $I_2$ (8.20 g, 64.62 mmol), $Ph_3P$ (18.00 g, 68.63 mmol) and imidazole (9.53 g, 0.14 mol) at room temperature. The mixture was stirred at 70 ˚C for 15 h. After the reaction was completed, the resulted suspension was filtrated through a pad of Celite®, then the Celite® pad was washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 15/1) to afford **11** (16.55 g, 97%) as a white solid:

R*f* = 0.75 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.55 (d, *J* = 4.6 Hz, 1H), 4.62 (dd, *J* = 7.7, 2.3 Hz, 1H), 4.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 4.30 (dd, *J* = 4.6, 2.3 Hz, 1H), 3.95 (ddd, *J* = 6.9, 6.9, 1.7 Hz, 1H), 3.32 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.21 (dd, *J* = 10.3, 6.9 Hz, 1H), 1.54 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); identical with the reported data.[1)]

2-Chloromethyl-3-(*p*-methoxybenzyloxy)-prop-1-ene: **12**

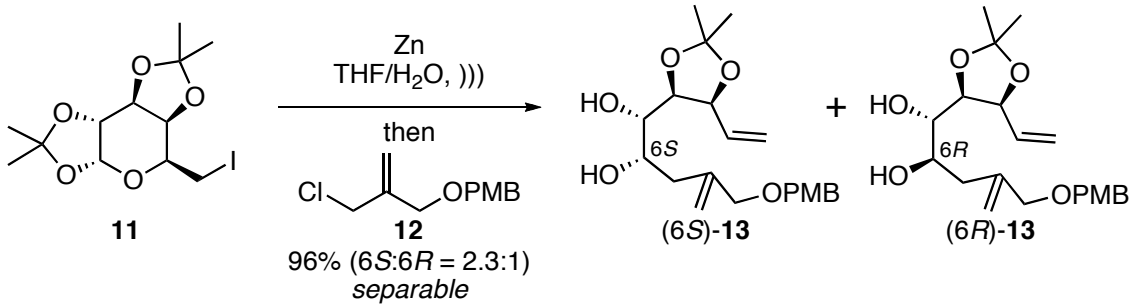



To a solution of PMBOH (24.88 mL, 0.20 mol) in THF (0.13 L) and DMF (0.04 L) was added NaH (10.40 g, 0.26 mol) at 0 ˚C. The mixture was refluxed for 4 h, then cooled to room temperature, and added to a solution of metallyl dichloride (25.00 g, 0.20 mol) in THF (0.13 L) dropwise by additional funnel over 1 h. After being stirred at room temperature for 5 min, the resulted mixture was quenched with sat. aq. $NH_4Cl$ (350 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (350 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford **12** (29.60 g, 65%) as a pale yellow oil:

R*f* = 0.50 (hexane/EtOAc = 3/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.31 (s, 1H), 5.25 (s, 1H), 4.46 (s, 2H), 4.13 (s, 2H), 4.09 (s, 2H), 3.81 (s, 3H); identical with the reported data.[2)]

(*3S,4S,5S*,6*S*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-8-(*p*-methoxybenzyloxy)methyl-1,8-nonadiene: **(6*S*)-13**

(*3S,4S,5S*,6*R*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-(8-*p*-methoxybenzyloxy)methyl-1,8-nonadiene: **(6*R*)-13**




**11** **12** (6*S*)-**13** (6*R*)-**13**

96% (6*S*:6*R* = 2.3:1)
*separable*

To a solution of **11** (4.00 g, 10.81 mmol) in THF (86.48 mL) and $H_2O$ (17.30 mL) was added Zn powder (mesh 75~150 μm; 7.19 g, 0.11 mol) at room temperature, and the mixture was sonicated for 4 h. After consumption of all the starting material, **12** (4.90 g, 21.62 mmol) was added, and then the mixture was stirred vigorously at room temperature for 2 d. The suspension was filtrated by Celite® and the filtrate was extracted with $CHCl_3$ (100 mL), and washed with brine (100 mL). The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 2/1) to afford (6*S*)-**13** (2.74 g, 67%) and (6*R*)-**13** (1.19 g, 29%), respectively as both colorless oils:

(6*S*)-**13:** R*f* = 0.42 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, 8.6 Hz, 2H), 6.12-6.05 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.9, 1H), 5.17 (s, 1H), 5.10 (s, 1H), 4.66 (dd, *J* = 8.0, 7.5 Hz, 1H), 4.54 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.46 (d, *J* = 4.6 Hz, 2H), 3.96 (d, *J* = 2.9 Hz, 2H), 3.80 (s, 3H), 3.64-3.60 (m, 1H), 3.36 (dd, *J* = 8.0, 1.7 Hz, 1H), 2.71 (d, *J* = 14.3, 1.7 Hz, 1H), 2.17 (d, *J* = 14.3, 9.74 Hz, 1H), 1.53 (s, 3H), 1.40 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.5, 142.9, 134.8, 129.7, 119.6, 117.3, 114.0, 108.6, 79.5, 76.5, 73.7, 72.3, 72.0, 71.6, 55.4, 55.4, 38.9, 27.0, 25.0; IR (KBr) $\nu_{max}$ 3462, 2987, 2935, 2838, 1736, 1612, 1585, 1514, 1464, 1373, 1302, 1248, 1213, 1173, 1039, 893, 847, 820 cm$^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{21}H_{30}O_6Na$ 401.1912, found 401.1931; $[\alpha]_D^{27}$ +53.1 (*c* 1.0, $CHCl_3$)

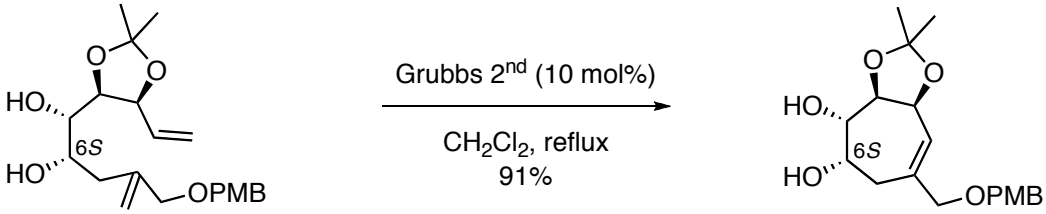
(6*R*)-**13:** R*f* = 0.28 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.03-5.96 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.27

(d, $J$ = 10.3 Hz, 1H), 5.15 (s, 1H), 5.05 (s, 1H), 4.61 (dd, $J$ = 8.0, 7.5 Hz, 1H), 4.44 (s, 2H), 4.28 (dd, $J$ = 6.9, 4.6 Hz, 1H), 3.96 (d, $J$ = 7.5 Hz, 2H), 3.81 (s, 3H), 3.80-3.77 (m, 1H), 3.50 (dd, $J$ = 4.6, 2.3 Hz, 1H), 2.40-2.32 (m, 2H), 1.53 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.4, 142.8, 134.2, 130.1, 129.6, 119.9, 116.1, 114.0, 109.1, 79.5, 79.0, 73.3, 72.1, 71.1, 70.8, 55.4, 38.3, 27.4, 25.2; IR (KBr) $\nu_{max}$ 3369, 3066, 2970, 2904, 1645, 1610, 1512, 1464, 1387, 1302, 1250, 1217, 1165, 1115, 1030, 926, 899, 847, 810, 698, 646 $cm^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{21}H_{30}O_6Na$ 401.1912, found 401.1913; $[\alpha]_D^{26}$ –49.8 (*c* 1.0 $CHCl_3$)

(*3S,4S,5S*,6*S*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-1-(*p*-methoxybenzyloxy)methyl-cyclohept-1-ene: **(6*S*)-14**

(*3S,4S,5S*,6*R*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-1-(*p*-methoxybenzyloxy)methyl-cyclohept-1-ene: **(6*R*)-14**

**Synthesis of single diastereomer (6*S*)-14**

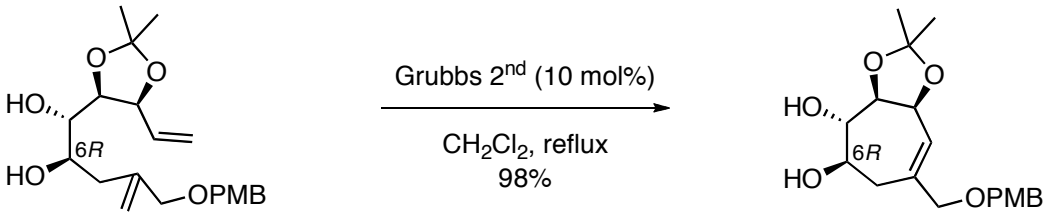



(6*S*)-**13** (6*S*)-**14**

To a solution of (6*S*)-**13** (2.50 g, 6.61 mmol) in $CH_2Cl_2$ (0.66 L) was added Grubbs 2nd generation catalyst (0.56 g, 0.66 mmol) at room temperature. The mixture was refluxed for 4 h, and then filtrated through a pad of Celite® to remove reacted catalyst. After concentration of the filtrate under reduced pressure, the residue was purified by silica gel flash column chromatography (hexane/EtOAc = 1/1) to afford (6*S*)-**14** (2.10 g, 91%) as a colorless oil.

R*f* = 0.48 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.68 (d, *J* = 1.5 Hz, 1H), 5.00 (br-dd, *J* = 7.5, 1.5 Hz, 1H), 4.42 (d, *J* = 1.7 Hz, 2H), 4.32 (dd, *J* = 10.3, 7.5 Hz, 1H), 4.10 (ddd, *J* = 10.9, 6.9, 4.6 Hz, 1H), 3.89 (d, *J* = 4.6 Hz, 2H), 3.80 (s, 3H), 3.67 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.53 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.08 (br-dd, *J* = 13.5, 10.9 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.3, 132.7, 130.2, 129.4, 126.1, 113.9, 108.1, 75.6, 73.8, 73.6, 72.1, 71.3, 66.2, 55.4, 32.2, 27.4, 24.6; IR (KBr) $\nu_{max}$ 3473, 3078, 2987, 2935, 2839, 1612, 1514, 1464, 1381, 1302, 1250, 1213, 1174, 1036, 926, 876, 820, 675 cm$^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{19}H_{26}O_6Na$ 373.1614, found 373.1632; $[\alpha]_D^{26}$ +44.1 (*c* 1.0 $CHCl_3$)

**Synthesis of single diastereomer (6*R*)-14**

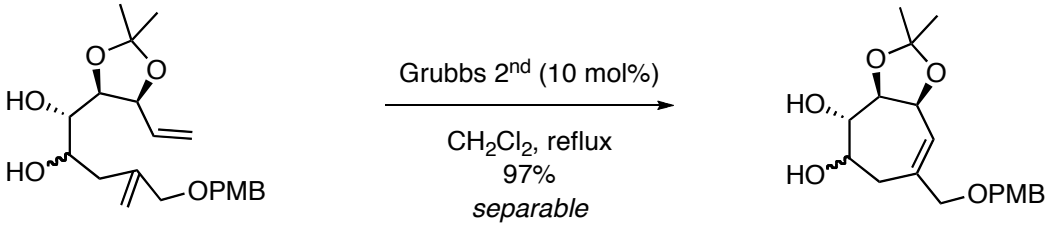



(6*R*)-**13** (6*R*)-**14**

According to the procedure for preparation of (6*S*)-**14**, ring-closing metathesis of (6*R*)-**13** (2.80 g, 7.40 mmol) afforded (6*R*)-**14** (2.54 g, 98%) as a white solid:

R*f* = 0.30 (hexane/EtOAc = 1/1); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.71 (s, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 4.49 (d, *J* = 7.5 Hz, 2H), 3.99 (dd, *J* = 7.5, 10.3 Hz, 1H), 3.86 (d, *J* = 4.6 Hz, 2H), 3.80 (s, 3H), 3.63 (ddd, *J* = 6.9, 4.6, 2.3 Hz, 1H), 3.48 (dd, *J* = 10.3, 6.9 Hz, 1H), 2.38 (dd, *J* = 14.9, 4.6 Hz, 1H), 2.24 (dd, *J* = 14.9, 2.3 1H), 1.48 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.5, 132.7, 129.7, 129.5, 127.8, 114.0, 108.3, 76.7, 76.4, 75.0, 73.7, 72.9, 71.3, 55.4, 33.5, 27.3, 24.3; IR (KBr) $\nu_{max}$ 3460, 2987, 2935, 2839, 1736, 1612, 1514, 1464, 1373, 1302, 1248, 1211, 1174, 1043, 897, 874, 820, 723 $cm^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{11}H_{18}O_5Na$ 253.1052, found 253.1051; $[\alpha]_D^{25}$ –43.0 (*c* 1.0 $CHCl_3$); mp 115 ˚C

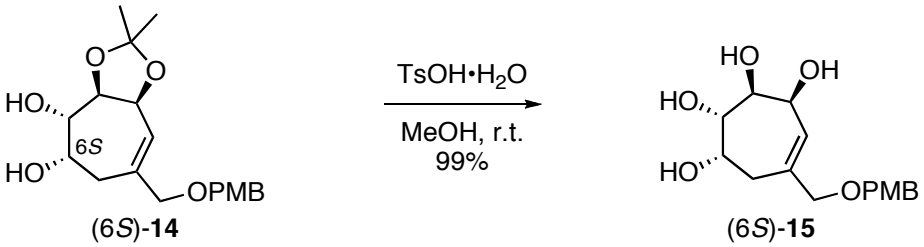
**Synthesis using diastereomixture of 13**




**13** **14**

According to the procedure for preparation of (6*S*)-**14**, ring-closing metathesis of two diastereomixtures (d.r. = 1:1) of **13** (0.12 g, 0.31 mmol) afforded **14** (0.11 g, 97%) as colorless oil.

(*3S,4S,5S*,6*S*)-3,4,5,6-Tetrahydroxy-1-(*p*-methoxybenzyloxy)methyl-cyclohept-1-ene: (6*S*)-**15**




(6*S*)-**14** (6*S*)-**15**

To a solution of (6*S*)-**14** (0.51 g, 1.46 mmol) in MeOH (48.67 mL) was added TsOH•$H_2O$ (13.8 mg, 72.54 μmol) at room temperature. The mixture was stirred at room temperature for 22 h, then the resulted suspension was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 4/1) to afford (6*S*)-**15** (0.45 g, 99%) as a white amorphous:

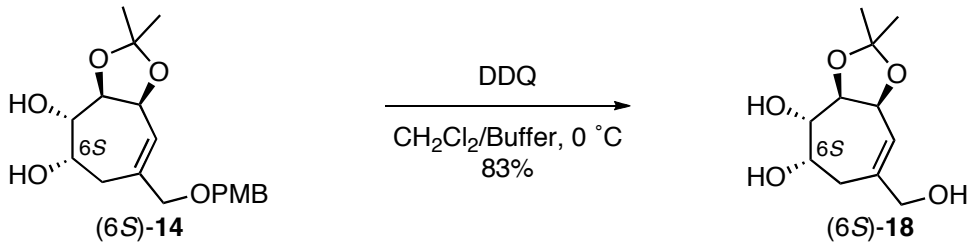
R*f* = 0.26 ($CHCl_3$/MeOH = 10/1); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.59 (s, 1H), 4.72 (br-d, *J* = 2.9 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.95 (br-dd, *J* = 5.2, 2.9 Hz, 1H), 3.90 (s, 2H), 3.86 (d, *J* = 5.2 Hz, 1H), 3.82 (d, *J* = 10.9 Hz, 1H), 3.78 (s, 3H), 2.76 (dd, *J* = 14.3, 10.9 Hz, 1H), 2.00 (d, *J* = 14.3 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 160.6, 135.1, 132.7, 131.4, 130.6, 114.5, 77.5, 75.9, 75.5, 72.3, 69.3, 67.6, 55.5, 31.9; IR (KBr) $\nu_{max}$ 3373, 2908, 2839, 1614, 1587, 1514, 1464, 1362, 1302, 1250, 1174, 1113, 1059, 1036, 941, 852, 818, 759, 687 cm$^{-1}$; HRMS-FAB (*m/z*) $[M+Na]^+$ calcd for $C_{16}H_{22}O_6Na$ 333.1314, found 333.1326

※ Optical rotations could not be measured due to low solubility of the pure amorphous.

(*3S,4S,5S*,6*S*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-1-hydroxymethyl-cyclohept-1-ene: **(6*S*)-18**

(*3S,4S,5S*,6*R*)-3,4-*O*-Isopropylidene-5,6-dihydroxy-1-hydroxymethyl-cyclohept-1-ene: **(6*R*)-18**

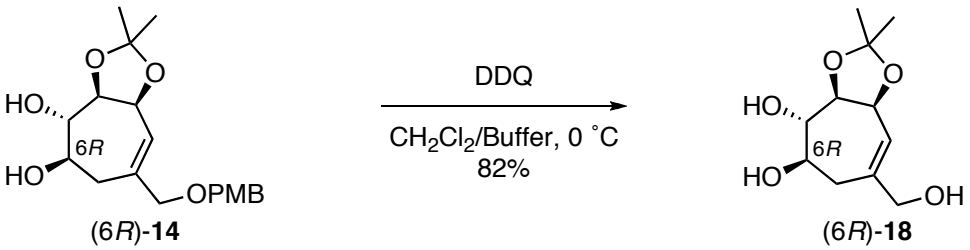
**Synthesis of single diastereomer (6*S*)-18**




To a solution of (6*S*)-**14** (0.40 g, 1.14 mmol) in $CH_2Cl_2$ (10.26 mL) and pH 7 buffer (1.14 mL) was added DDQ (0.39 g, 1.71 mmol) at 0 ˚C. The mixture was stirred at 0 ˚C for 5 h. After the reaction was completed, to the resulted suspension was added Celite® and $H_2O$ (30 mL), then filtrated through a pad of Celite®, and the Celite® pad was washed with $H_2O$ (300 mL). The filtrate was extracted with $CHCl_3$ (300 mL), and the aqueous phase was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 10/1) to afford (6*S*)-**18** (0.22 g, 83%) as a colorless oil:

R*f* = 0.36 ($CHCl_3$/MeOH = 10/1); $^1$H NMR (500 MHz, $CD_3OD$) δ 5.56 (br-s, 1H), 4.97 (br-d, *J* = 7.5 Hz, 1H), 4.28 (dd, *J* = 9.2, 7.5 Hz, 1H), 4.01 (ddd, *J* = 8.6, 6.3, 3.4 Hz, 1H), 3.94 (s, 2H), 3.66 (dd, *J* = 9.2, 3.4, 1H), 2.43 (dd, *J* = 14.9, 6.3 Hz, 1H), 2.15 (dd, *J* = 14.9, 8.6 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 136.5, 126.1, 108.8, 77.7, 76.1, 73.8, 69.0, 66.8, 34.6, 27.5, 24.6; IR (Diamond prism) $\nu_{max}$ 3379, 2989, 2931, 2893, 2877, 2854, 1454, 1373, 1261, 1211, 1161, 1088, 1038, 887, 864, 845, 791, 752, 667, 633 cm$^{-1}$; HRMS-FAB (*m/z*) $[M+Na]^+$ calcd for $C_{11}H_{18}O_5Na$ 253.1052, found 253.1050; $[\alpha]_D^{24}$ +61.6 (*c* 0.1 MeOH)

**Synthesis of single diastereomer (6*R*)-18**

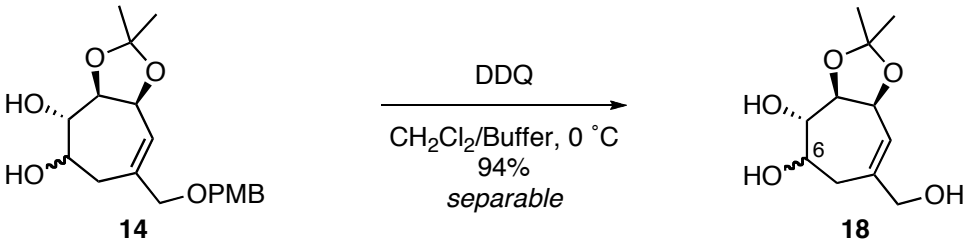



(6*R*)-**14** (6*R*)-**18**

According to the procedure for preparation of (6*S*)-**18**, deprotection of (6*R*)-**14** (0.10 g, 0.29 mmol) afforded (6*R*)-**18** (54.7 mg, 82%) as a white solid:

R*f* = 0.33 ($CHCl_3$/MeOH = 10/1); $^1$H NMR (500 MHz, $CD_3OD$) δ 5.64 (d, *J* = 1.7 Hz, 1H), 4.97 (br-d, *J* = 7.5 Hz, 1H), 4.04 (dd, *J* = 10.3, 7.5 Hz, 1H), 4.03 (d, *J* = 13.8 Hz, 1H), 3.95 (d, *J* =13.8 Hz, 1H), 3.62 (ddd, *J* = 6.9, 4.6, 2.9 Hz, 1H), 3.38 (dd, *J* = 10.3, 6.9 Hz, 1H), 2.37 (dd, *J* = 14.9, 4.6 Hz, 1H), 2.10 (br-d, *J* = 14.9 Hz, 1H), 1.46 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 137.0, 124.3, 108.7, 78.1, 76.8, 76.3, 72.8, 66.5, 33.7, 27.3, 24.2; IR (Diamond prism) $\nu_{max}$ 3448, 3367, 2993, 2931, 2854, 1450, 1373, 1331, 1250, 1219, 1176, 1153, 1095, 1072, 1041, 1007, 910, 879, 845, 822, 802, 694, 648 cm$^{-1}$; HRMS-FAB (*m/z*) $[M+Na]^+$ calcd for $C_{11}H_{18}O_5Na$, found; $[\alpha]_D^{23}$ –54.5 (*c* 0.1 MeOH); mp 110 ˚C

**Synthesis using diastereomixture of 14**

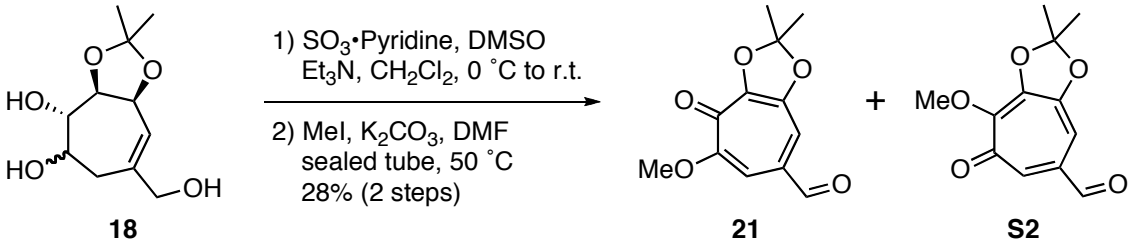



**14** **18**

According to the procedure for preparation of (6*S*)-**18**, deprotection of two diastereomixtures of **14** (0.10 g, 0.28 mmol) afforded **18** (60.3 mg, 94%) as colorless oil.

2,3-*O*-Isopropylidene-7-methoxy-5-formyl-tropone: **21**

3,4-*O*-Isopropylidene-2-methoxy-6-formyl-tropone: **S2**




**18** **21** **S2**

To a solution of two diastereomixtures of **18** (21.7 mg, 94.24 μmol) in $CH_2Cl_2$ (0.94 mL) was added DMSO (0.10 mL, 1.41 mmol), $Et_3N$ (0.39 mL, 2.83 mmol), and $SO_3$•Pyridine (0.15 g, 0.94 mmol) at 0 ˚C. The mixture was stirred at room temperature for 20 h, monitored by LC-UV analysis, then quenched with 1M aq. HCl (10 mL), and extracted with $CHCl_3$ (10 mL ×3). The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure to yield crude product as a dark brown amorphous. This crude product was used in subsequent reaction without further purification.

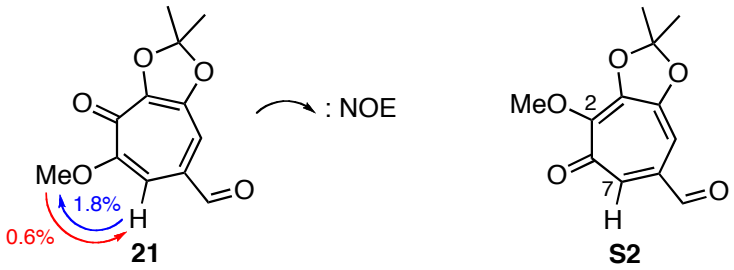
To a stirred solution of crude product in DMF (0.94 mL) in sealed tube was added $K_2CO_3$ (0.13 g, 0.94 mmol) and MeI (58.52 μL, 0.94 mmol) at room temperature. The mixture was stirred at 50 ˚C for 2 h, then quenched with 1M aq. HCl (10 mL), and extracted with $CHCl_3$ (10 mL ×3). The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc) to afford **21** (3.2 mg, 14% over 2 steps) as a yellow solid and **S2** (3.1 mg, 14% over 2 steps) as a yellow solid:

**21:** R*f* = 0.18 (EtOAc); $^1$H NMR (500 MHz, $CD_2Cl_2$) δ 9.75 (s, 1H), 7.32 (d, *J* = 1.2 Hz, 1H), 7.29 (br-d, 1H), 4.01 (s, 3H), 1.78 (s, 6H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 191.3, 167.1, 164.7, 151.1, 149.7, 133.8, 122.1, 119.4, 105.3, 56.9, 26.2; IR (Diamond prism) $\nu_{max}$ 1685, 1597, 1577, 1469, 1442, 1369, 1288, 1219, 1142, 1084, 1049, 1007, 980, 937, 868, 802, 779, 729 cm$^{-1}$; HRMS-EI (*m/z*) $[M+Na]^+$ calcd for $C_{12}H_{12}O_5$ 236.0685, found 236.0688; mp 232 ˚C

**S2:** R*f* = 0.57 (EtOAc); $^1$H NMR (500 MHz, $CD_2Cl_2$) δ 9.65 (s, 1H), 7.17 (d, *J* = 1.2 Hz, 1H), 6.83 (d, *J* = 1.2 Hz, 1H), 3.95 (s, 3H), 1.75 (s, 6H); $^{13}$C NMR (125 MHz, $CD_3OD$)

δ 193.8, 179.6, 155.8, 152.0, 148.8, 140.5, 138.8, 118.8, 99.8, 60.0, 26.3; IR (Diamond prism) $\nu_{max}$ 1705, 1635, 1566, 1442, 1385, 1350, 1254, 1211, 1161, 1119, 1041, 964, 941, 856, 798, 779, 706, 648 $cm^{-1}$; HRMS-EI (*m/z*) $[M+Na]^+$ calcd for $C_{12}H_{12}O_5$ 236.0685, found 236.0688; mp 87 ˚C

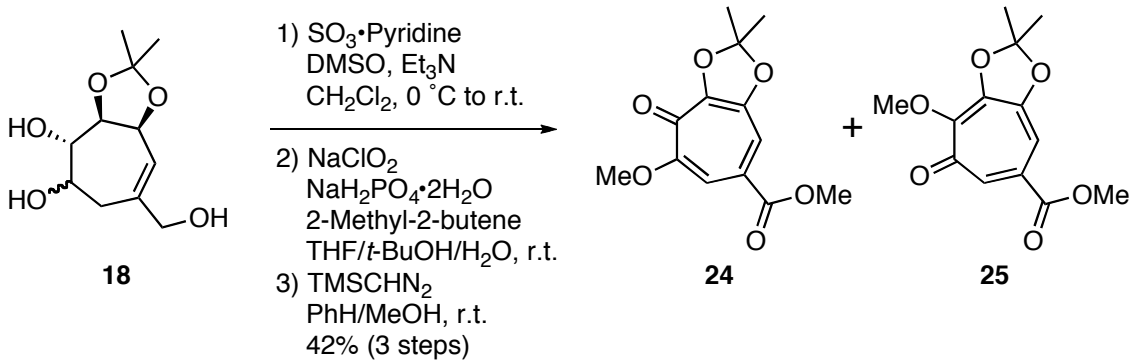
**NOE observation of 21 and S2:**




※ NOE correlation between methoxy group at C2 position and 7-H of **S2** was not observed.

2,3-*O*-Isopropylidene-7-methoxy-5-methoxycarbonyl-tropone: **24**

3,4-*O*-Isopropylidene-2-methoxy-6-methoxycarbonyl-tropone: **25**




According to the procedure for preparation of **21**, Parikh-Doering oxidation of two diastereomixtures of **18** (42.2 mg, 0.18 mmol) afforded crude product as a dark brown amorphous. This crude material was used in subsequent reaction without further purification.

To a stirred solution of crude product and 2-methyl-2-butene (0.39 mL, 3.66 mmol) in THF (1.83 mL) and *t*-BuOH (1.83 mL) was added the mixture of $NaClO_2$ (33.1 mg, 0.37 mmol) and $NaH_2PO_4$ (0.11 g, 0.73 mmol) in $H_2O$ (1.83 mL) dropwise by Pasteur pipette. The mixture was stirred at room temperature for 5 min, monitored by UC-UV analysis, then quenched with 1M aq. HCl (20 mL), and extracted with $CHCl_3$ (30 mL ×3). The combined organic layers were dried over sodium sulfate, and concentrated under reduced pressure to yield crude product as a dark brown amorphous. This crude material was used in subsequent reaction without further purification.

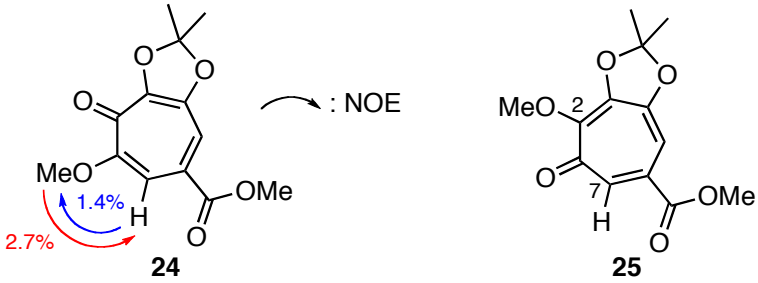
To a stirred solution of crude product in PhH (1.65 mL) and MeOH (0.18 mL) was added $TMSCHN_2$ (0.6M in hexane; 0.64 mL, 0.38 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, and then concentrated under reduced pressure at 20 ˚C. The residue was purified by preparative TLC (EtOAc) to afford **24** (10.0 mg, 21% over 3 steps) as a yellow solid and **25** (9.9 mg, 21% over 3 steps) as a yellow solid:

**24:** R*f* = 0.08 (hexane/EtOAc = 1/1); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.84 (s, 1H), 7.73 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 1.79 (s, 6H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 167.4, 167.3, 165.1, 152.5, 152.0, 130.9, 120.5, 118.2, 111.3, 56.8, 53.9, 25.8; IR (Diamond

prism) $\nu_{max}$ 1712, 1577, 1500, 1423, 1381, 1342, 1296, 1214, 1111, 1076, 1003, 876, 768, 652 $cm^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{13}H_{14}O_6Na$ 289.0688, found 289.0689; mp 187 ˚C

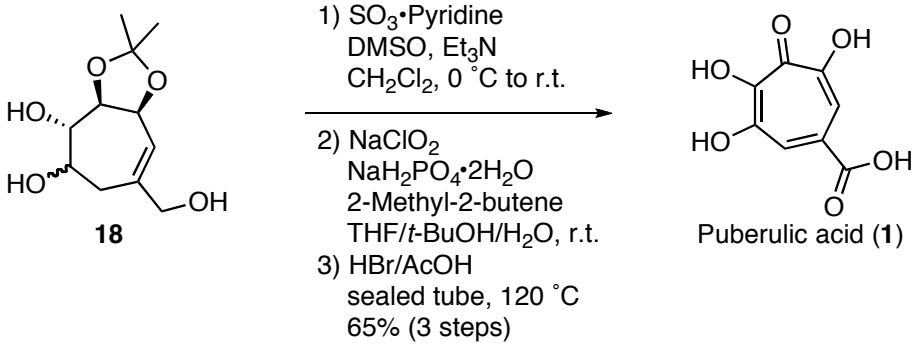
**25:** R*f* = 0.36 (hexane/EtOAc = 1/1); $^1H$ NMR (500 MHz, $CD_3OD$) δ 7.62 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 1.79 (s, 6H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 181.0, 167.7, 156.7, 153.5, 149.9, 136.4, 134.3, 120.5, 106.0, 60.5, 54.0, 26.0; IR (Diamond prism) $\nu_{max}$ 2954, 1724, 1562, 1427, 1385, 1350, 1250, 1207, 1157, 1065, 1018, 941, 860, 779, 737, 675 $cm^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{13}H_{14}O_6Na$ 289.0688, found 289.0689; mp 113 ˚C

**NOE observation of 21 and S2:**




※ NOE correlation between methoxy group at C2 positionand 7-H of **25** was not observed.

Puberulic acid: **1**




According to the procedure for preparations of **24** and **25**, Parikh-Doering oxidation of two diastereomixtures of **18** (20.5 mg, 89.03 μmol) and subsequent Pinnick oxidation afforded crude product as a dark brown amorphous. This crude material was used in subsequent reaction without further purification.

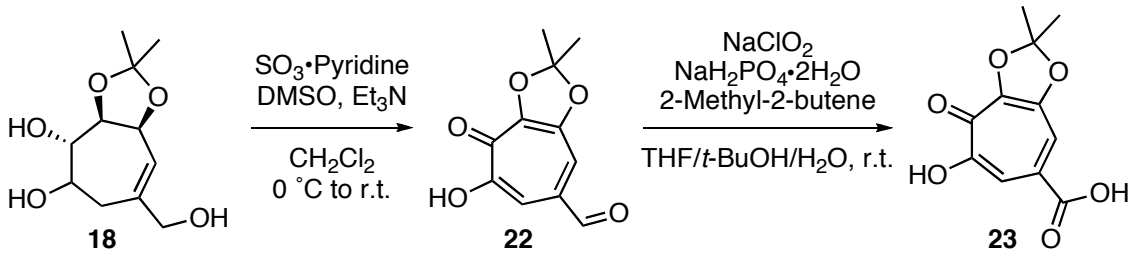
The solution of crude product in 33% HBr/AcOH (0.89 mL) was refluxed for 16 h and monitored by LC-UV analysis. After the reaction was completed, the resulted mixture was concentrated under reduced pressure. The residue was purified by Sep-pak® Plus C18 Short Cartridge to afford puberulic acid (11.5 mg, 65% over 3 steps) as a yellow solid:

$^1$H NMR (500 MHz, $(CD_3)_2CO$) δ 7.94 (s, 2H); (500 MHz, $CD_3OD$) δ 7.90 (s, 2H); $^{13}$C NMR (125 MHz, $(CD_3)_2CO$) δ 167.5, 159.5, 155.5, 128.3, 119.3; (125 MHz, $CD_3OD$) δ 168.6, 159.7, 156.0, 128.5, 119.2; IR (Diamond prism) $\nu_{max}$ 3502, 3259, 3143, 3051, 2808, 2511, 1697, 1593, 1535, 1389, 1342, 1284, 1180, 1053, 1014, 903, 775, 733, 687 $cm^{-1}$; HRMS-EI (*m/z*) $[M]^+$ calcd for $C_8H_6O_6$ 198.0164 , found 198.0154; mp 258 ˚C

※ $CD_3OD$ solvent of NMR analysis is better due to low-solubility in $(CD_3)_2CO$.

2,3-*O*-Isopropylidene-5-formyl-tropolone: **22**

2,3-*O*-Isopropylidene-5-carboxy-tropolone: **23**




The synthetic intermediates of puberulic acid, which are troponoids **22** and **23**, were purified by Sep-pak® Plus C18 Short Cartridge for the measurement of spectra data. The experimental procedures are according to preparation of **24** and **25**:

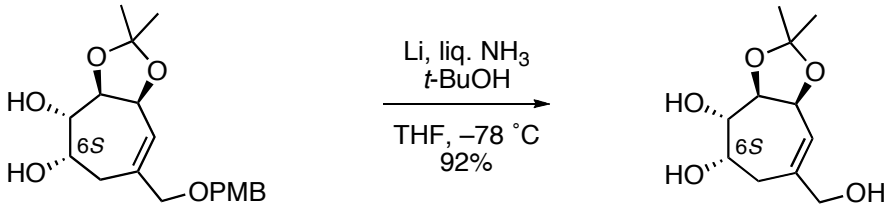
**22:** a yellow solid; $^{1}$H NMR (500 MHz, $(CD_3)_2CO$) δ 9.89 (s, 1H), 7.54 (d, $J$ = 1.2 Hz, 1H), 7.49 (d, $J$ = 1.2 Hz, 1H), 1.81 (s, 6H); $^{13}$C NMR (125 MHz, $(CD_3)_2CO$) δ 192.9, 166.6, 163.1, 154.0, 149.4, 137.4, 120.6, 116.7, 112.7, 26.2; IR (Diamond prism) $\nu_{max}$ 3209, 2931, 2823, 2723, 1701, 1581, 1550, 1500, 1392, 1350, 1315, 1184, 1119, 1038, 960, 837, 771, 687 cm$^{-1}$;HRMS-FAB (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{11}O_5$ 223.0606, found 223.0606; mp 196 ˚C

**23:** a yellow solid; $^{1}$H NMR (500 MHz, $CD_3OD$) δ 7.89 (d, $J$ = 1.7 Hz, 1H), 7.74 (br-d, $J$ = 1.7 Hz, 1H), 1.80 (s, 6H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 168.3, 166.8, 163.4, 154.6, 150.3, 134.5, 120.7, 116.2, 115.4, 26.0; IR (Diamond prism) $\nu_{max}$ 3155, 2850, 2592, 1697, 1628, 1581, 1504, 1462, 1408, 1365, 1315, 1211, 1103, 1026, 872, 764, 702, 629 cm$^{-1}$; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{11}O_6$ 239.0556, found 239.0547; mp 261 ˚C

## 2-2. For large-scale synthesis of puberulic acid

In gram-scale synthesis of puberulic acid, the deprotection of PMB group with DDQ was inefficient and irreproducibility, probably because the concentration of huge amount of the aqueous phase with residual hydroquinone caused the decomposition of the product. So Birch reduction was applied in this step, although the yield was inferior to the deprotection using DDQ.

**Large-scale synthesis of (6*S*)-18**



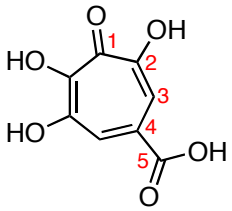

(6*S*)-**14** (6*S*)-**18**

To a solution of Li (0.15 g, 22.26 mmol) in liq. $NH_3$ (34.25 mL) was added the mixture of (6*S*)-**14** (1.20 g, 3.42 mmol) in THF (34.25 mL) and *t*-BuOH (0.71 mL) dropwise under Ar atmosphere. The mixture was stirred at –78 ˚C for 5 min, then quenched with isoprene (3 mL), and warmed to room temperature to remove liq. $NH_3$. To the resulted suspension was added MeOH (20 mL) and silica gel (100 cc), and the mixture was concentrated under reduced pressure. The dried silica gel was eluted with MeOH, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) to afford (6*S*)-**18** (0.73 g, 92%) as a colorless oil.

**Purification of large-scale puberulic acid (1)**

According to the procedure for preparations of puberulic acid (**1**), Parikh-Doering oxidation of (6*S*)-**18** (1.03 g, 4.47 mmol), subsequent Pinnick oxidation and deprotection of the acetonide group afforded crude product as a dark brown amorphous. This crude material was dissolved in 1% MeOH/0.1% TFA aq. (1.5 L) and applied on reverse-phase column chromatography (50 ϕ × 130 mm, CHROMATOREX®). After washing 5% and 10% MeOH/0.1% TFA aq. (400 mL each), **1** was eluted with 15, 20, 25 and 30% MeOH/0.1% TFA aq. (400 mL each), followed by concentration under reduced pressure to afford **1** (0.40 g, 45%) as a yellow solid.

## 2-3. Comparison of the NMR data of synthetic and natural puberulic acid



Puberulic acid

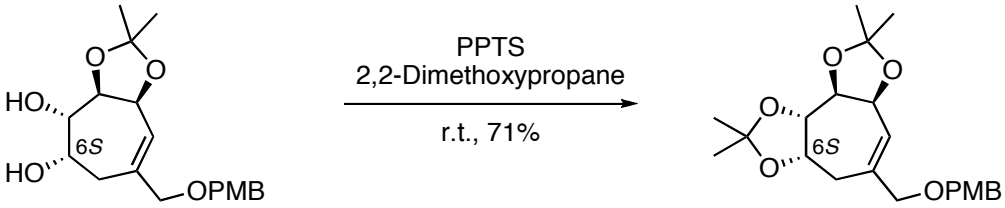
| | Synthetic puberulic acid[a] | | Reported one[b,3)] | |
|---|---|---|---|---|
| | $^{13}$C NMR | $^{1}$H NMR | $^{13}$C NMR | $^{1}$H NMR |
| Position | $\delta_C$ (ppm) | $\delta_H$ (ppm), [mult., Int.] | $\delta_C$ (ppm) | $\delta_H$ (ppm), [mult., Int.] |
| 1 | 159.5 | | 159.4 | |
| 2 | 155.5 | | 155.5 | |
| 3 | 119.3 | 7.94 (s, 2H) | 119.4 | 7.94 (s, 2H) |
| 4 | 128.3 | | 128.5 | |
| 5 | 167.5 | | 167.3 | |

[a]exp. $^{13}$C NMR: 125 MHz, $^{1}$H NMR: 500 MHz in $(CD_3)_2CO$

[b]exp. $^{13}$C NMR: 75 MHz, $^{1}$H NMR: 300 MHz in $(CD_3)_2CO$

## 2-4. Determination of stereochemistry at C6 position

(*3S,4S,5S,*6*S*)-3,4:5,6-*O*-Isopropylidene-1-(*p*-methoxybenzyloxy)methyl-cyclohept-1-en e: **S3**

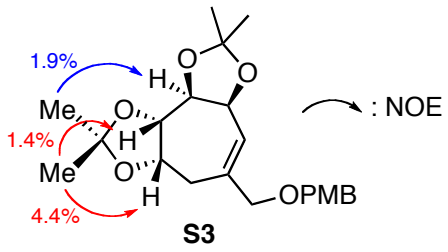



(6*S*)-**14** **S3**

To a solution of (6*S*)-**14** (20.0 mg, 57.08 μmol) in 2,2-dimethoxypropane (0.57 mL) was added PPTS (0.14 mg, 5.71 μmol) at room temperature. The mixture was stirred at room temperature for 24 h, then quenched with sat. aq. $NaHCO_3$ (3 mL), and extracted with EtOAc (5 mL). The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc = 1/2) to afford **S3** (15.8 mg, 71%) as a colorless oil:

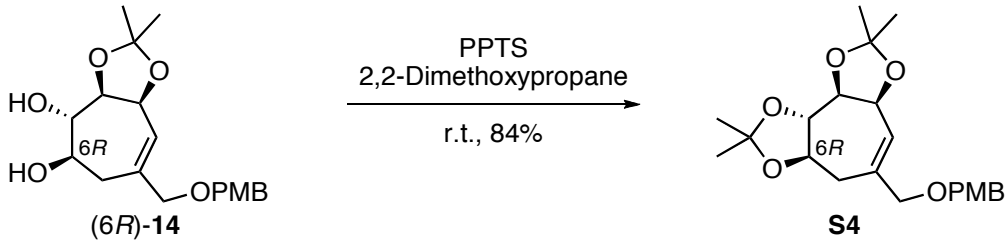
R*f* = 0.55 (hexane/EtOAc = 1/2); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 1H), 4.93 (d, *J* = 7.5 Hz, 1H), 4.45 (s, 2H), 4.35 (ddd, *J* = 12.6, 6.9, 4.6 Hz, 1H), 4.28 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.99 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.92 (s, 2H), 3.81 (s, 3H), 2.48 (dd, *J* = 13.2, 4.6 Hz, 1H), 2.23 (dd, *J* = 13.2, 12.6 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.4, 133.1, 130.1, 129.4, 125.8, 114.0, 109.3, 107.8, 78.3, 74.5, 73.9, 73.5, 72.2, 55.4, 29.1, 28.3, 27.8, 25.3, 24.7; IR (KBr) $\nu_{max}$ 2989, 2937, 2844, 1738, 1612, 1583, 1514, 1462, 1381, 1302, 1248, 1215, 1161, 1065, 1038, 970, 906, 852, 820, 756 cm$^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{22}H_{30}O_6Na$ 413.1916, found 413.1915; $[\alpha]_D^{25}$ +18.5 (*c* 1.0 $CHCl_3$)

**NOE observations of S3:**




**S3**

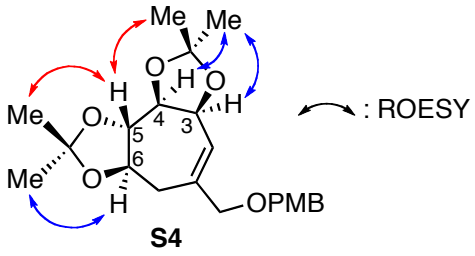
(*3S,4S,5S,6R*)-3,4:5,6-*O*-Isopropylidene-1-(*p*-methoxybenzyloxy)methyl-cyclohept-1-ene: **S4**




According to the procedure for preparation of **S3**, protection of (6*R*)-**14** (16.2 mg, 46.23 μmol) afforded **S4** (15.2 mg, 84%) as a colorless oil:

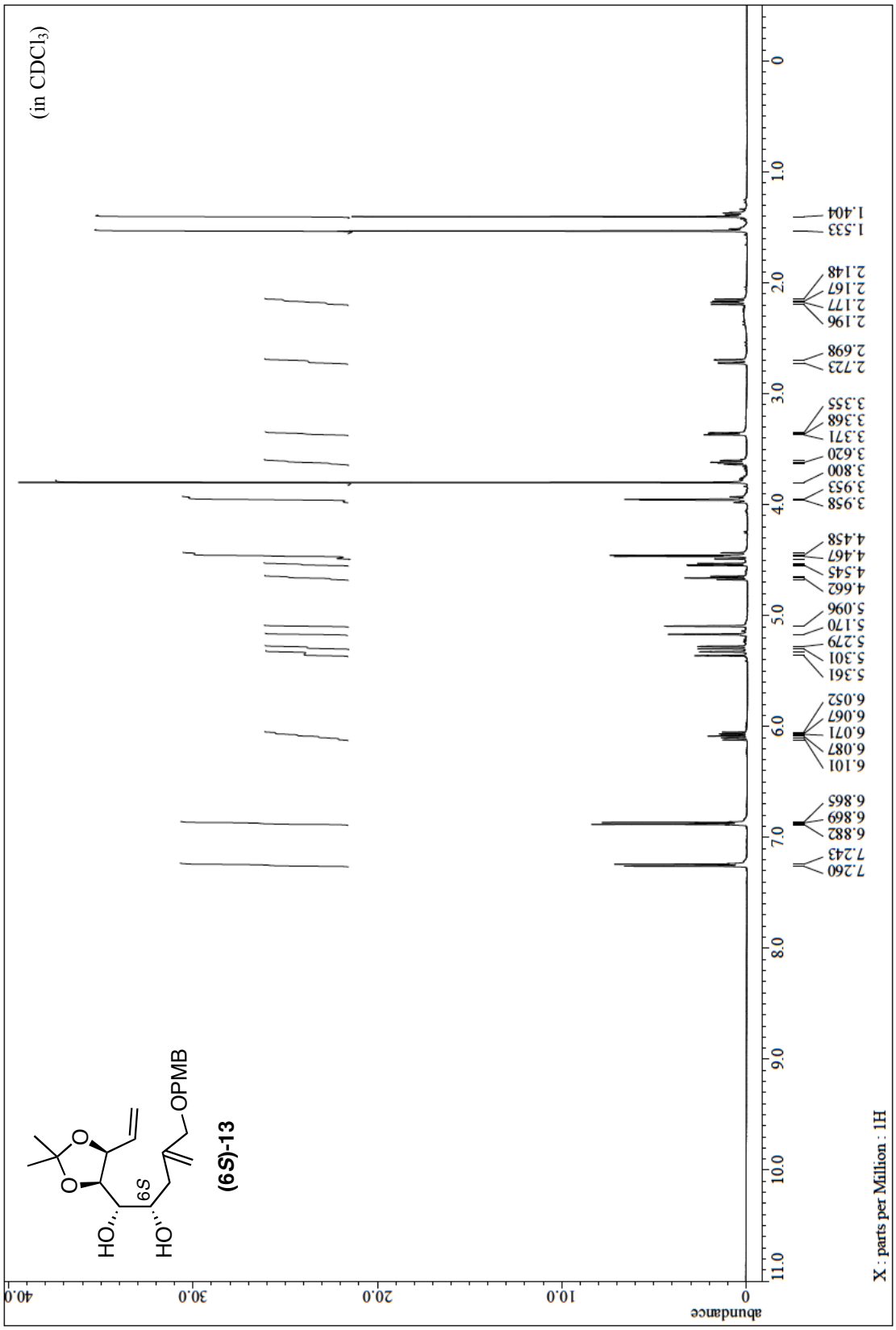
R*f* = 0.58 (hexane/EtOAc = 1/2); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.67 (s, 1H), 4.83 (br-d, *J* = 6.9 Hz, 1H), 4.41 (s, 2H), 4.29 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.95 (ddd, *J* = 9.8, 9.2, 5.2 Hz, 1H), 3.92 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.87 (s, 2H), 3.81 (s, 3H), 2.84 (dd, *J* = 17.8, 5.2 Hz, 1H), 2.52 (dd, *J* = 17.8, 9.8 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.4, 132.2, 130.1, 129.5, 126.2, 113.9, 110.8, 109.4, 81.6, 80.3, 75.9, 73.6, 73.5, 71.9, 55.4, 35.3, 27.7, 27.3, 27.2, 25.3; IR (KBr) $\nu_{max}$ 2987, 2935, 2900, 2841, 1728, 1614, 1514, 1462, 1371, 1248, 1217, 1173, 1105, 1051, 899, 852, 814, 758 cm$^{-1}$; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{22}H_{30}O_6Na$ 413.1916, found 413.1918; $[\alpha]_D^{26}$ –14.4 (*c* 1.0 $CHCl_3$)

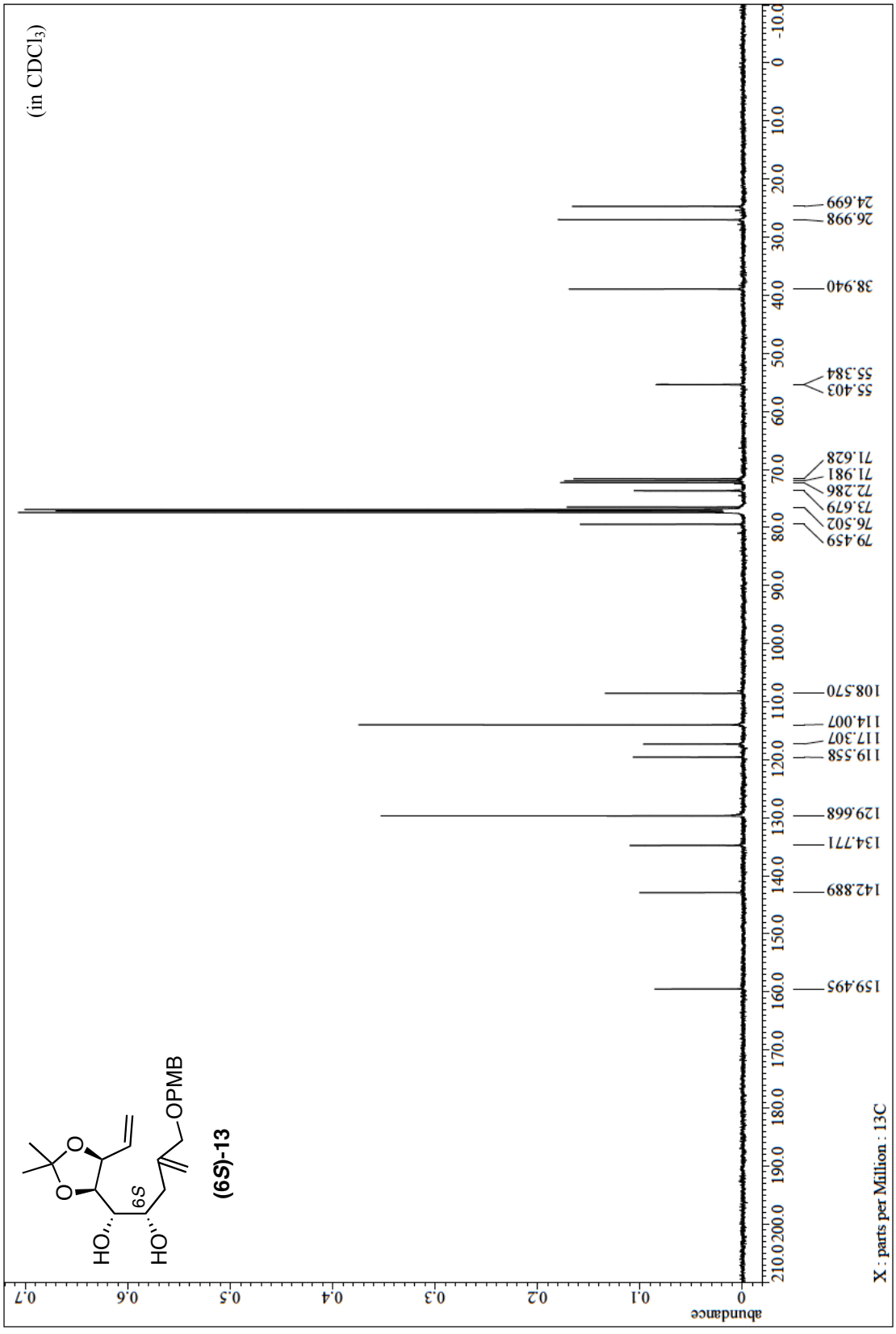
**ROESY observations of S4:**

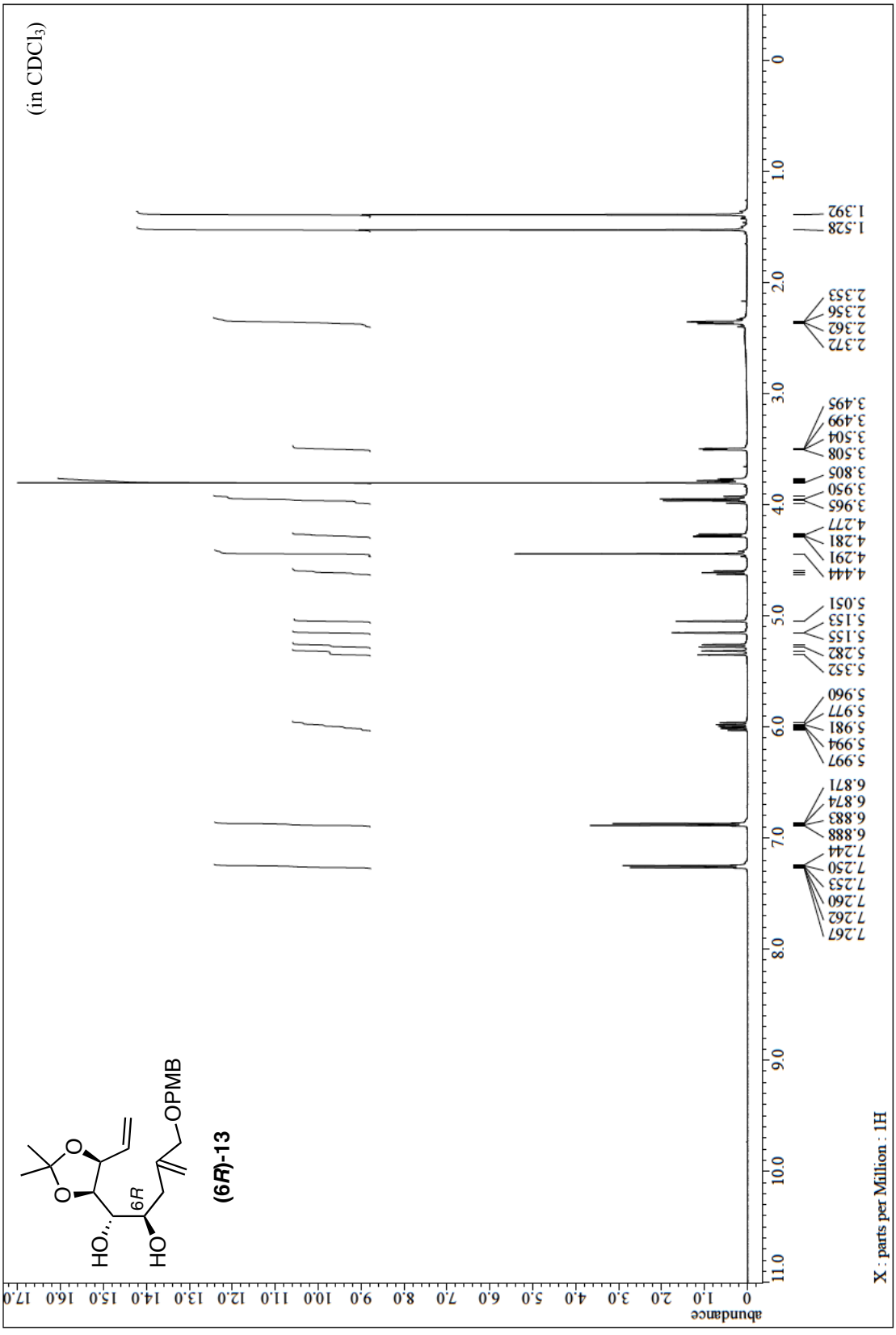


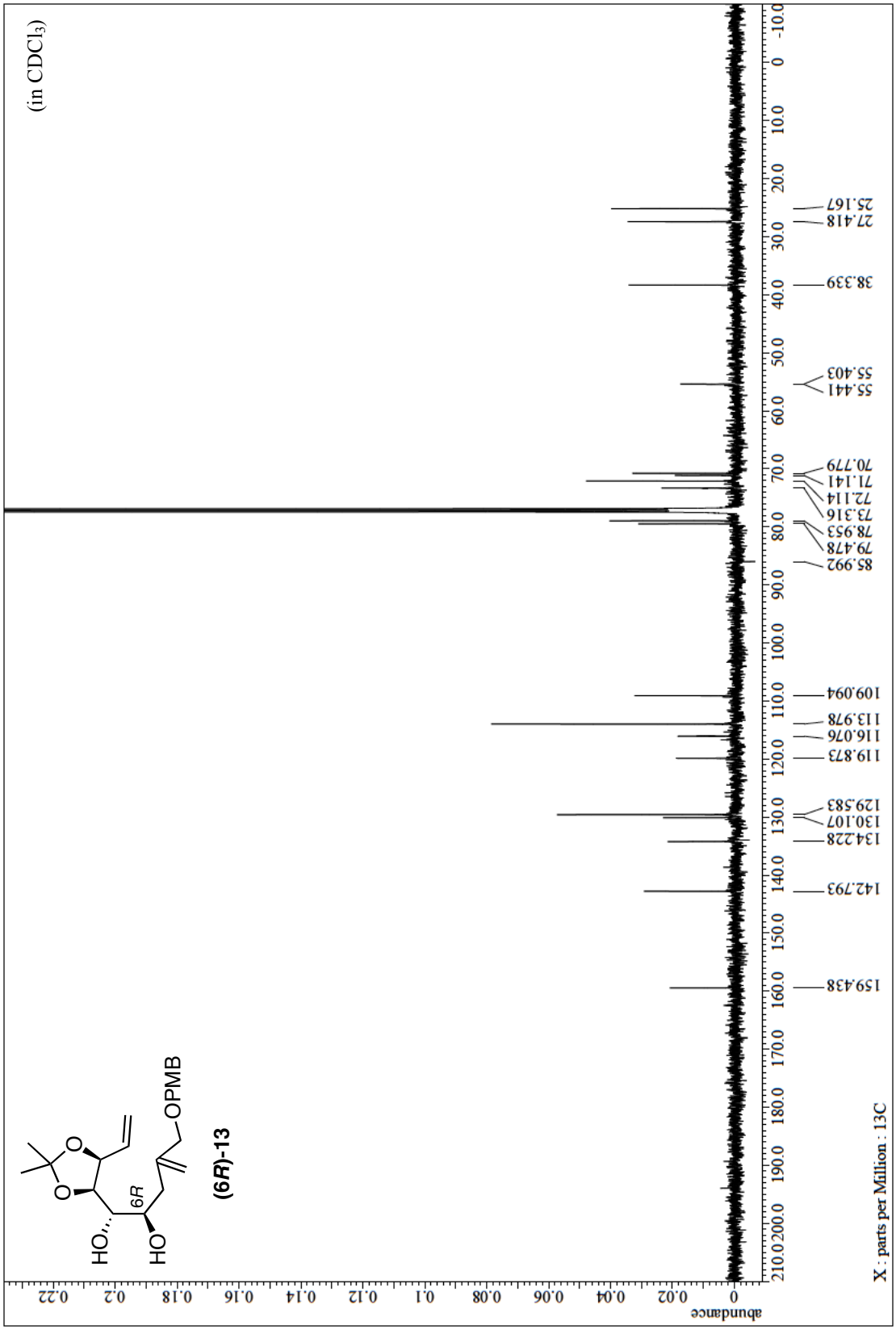
# 3. Spectra Charts

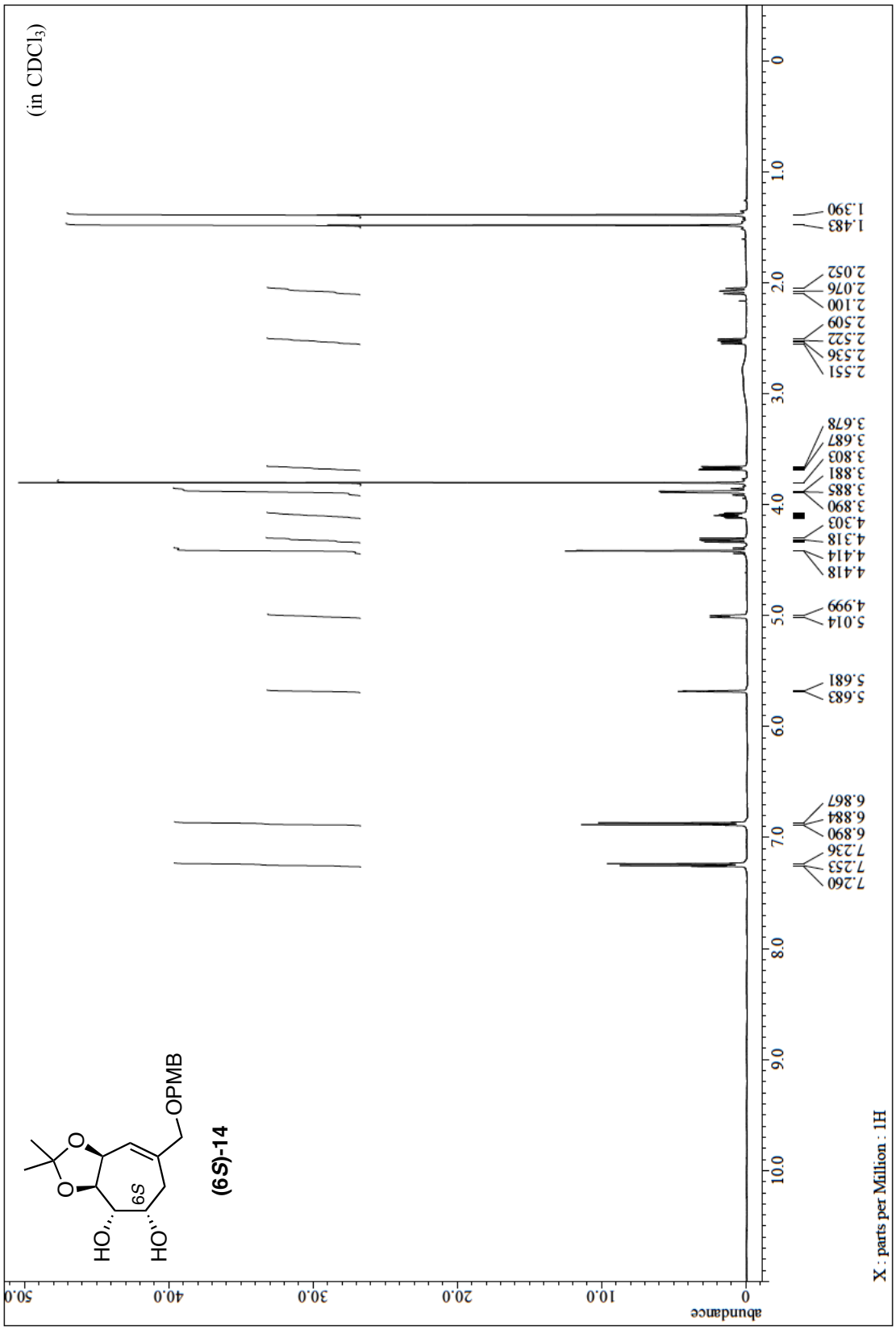
## 3-1. $^{1}$H NMR and $^{13}$C NMR charts

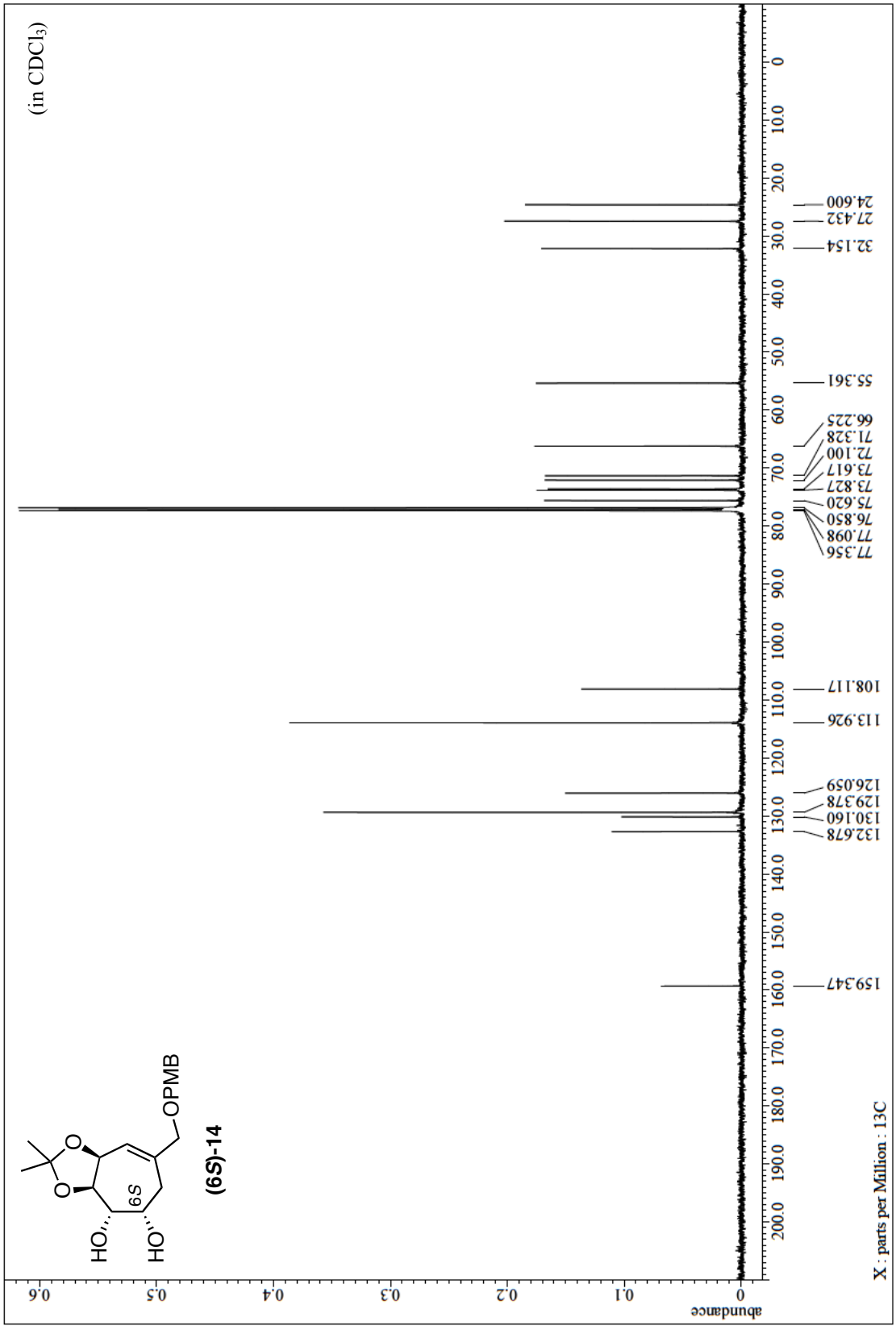


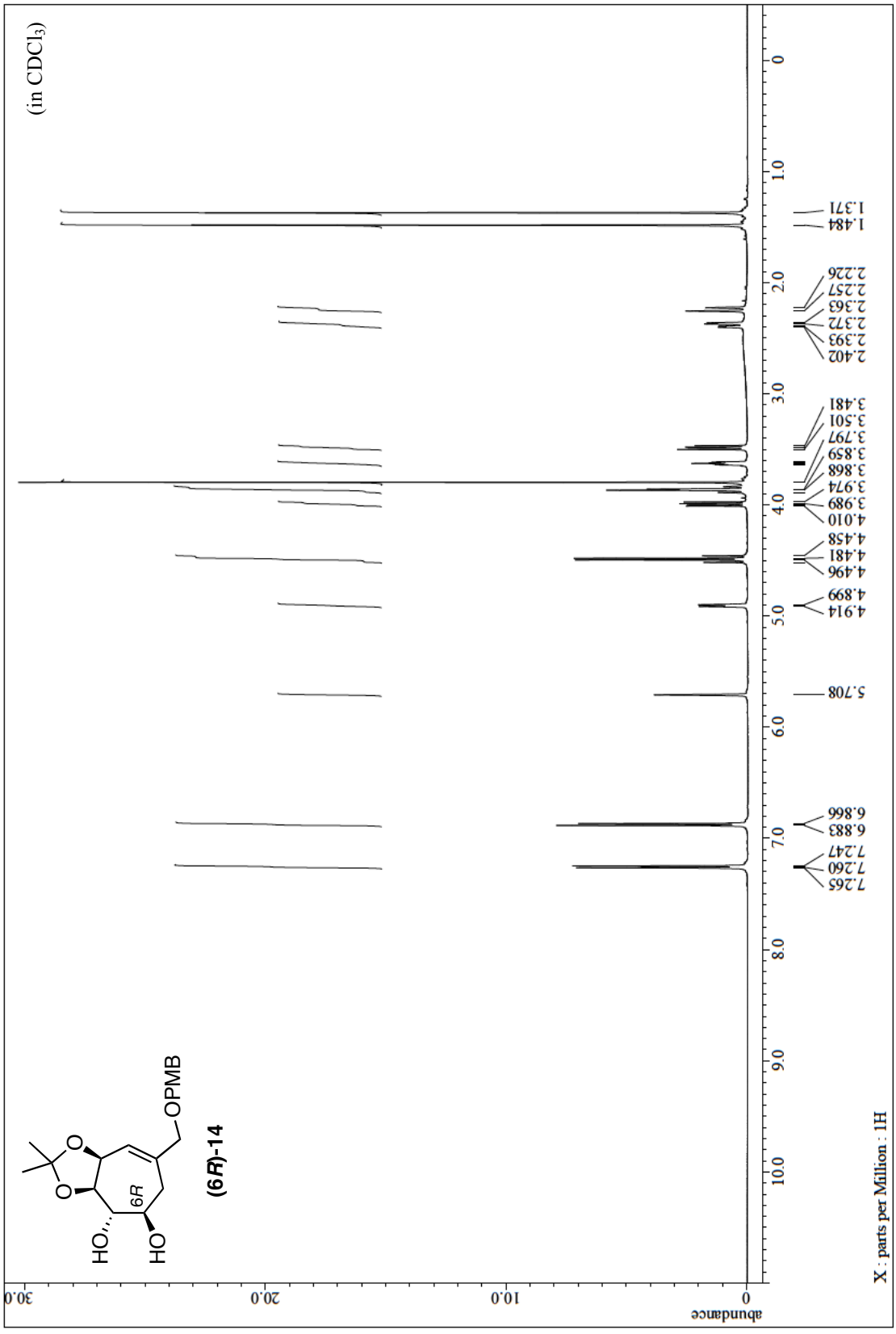

(in $CDCl_3$)
OPMB
HO
HO
6S
(6S)-13
159.495
142.889
134.771
129.668
119.558
117.307
114.007
108.570
79.459
76.502
73.679
72.286
71.981
71.628
55.403
55.384
38.940
26.998
24.699
abundance
X : parts per Million : 13C

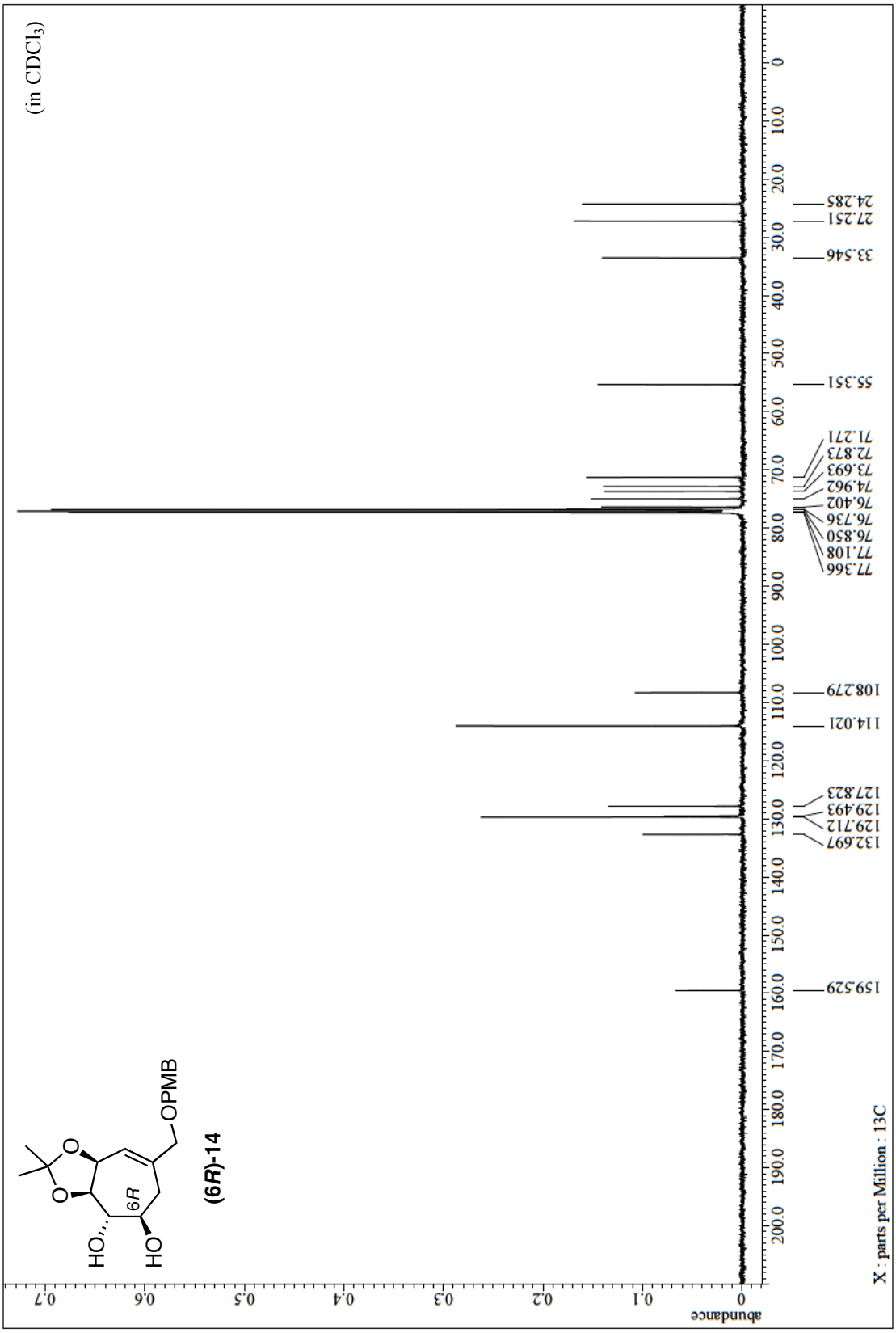

(in CDCl3)
(6R)-13
OPMB
HO
HO
6R
abundance
X : parts per Million : 1H
7.267
7.262
7.260
7.253
7.250
7.244
6.888
6.883
6.874
6.871
5.997
5.994
5.981
5.977
5.960
5.352
5.282
5.155
5.153
5.051
4.444
4.291
4.281
4.277
3.965
3.950
3.805
3.508
3.504
3.499
3.495
2.372
2.362
2.356
2.353
1.528
1.392

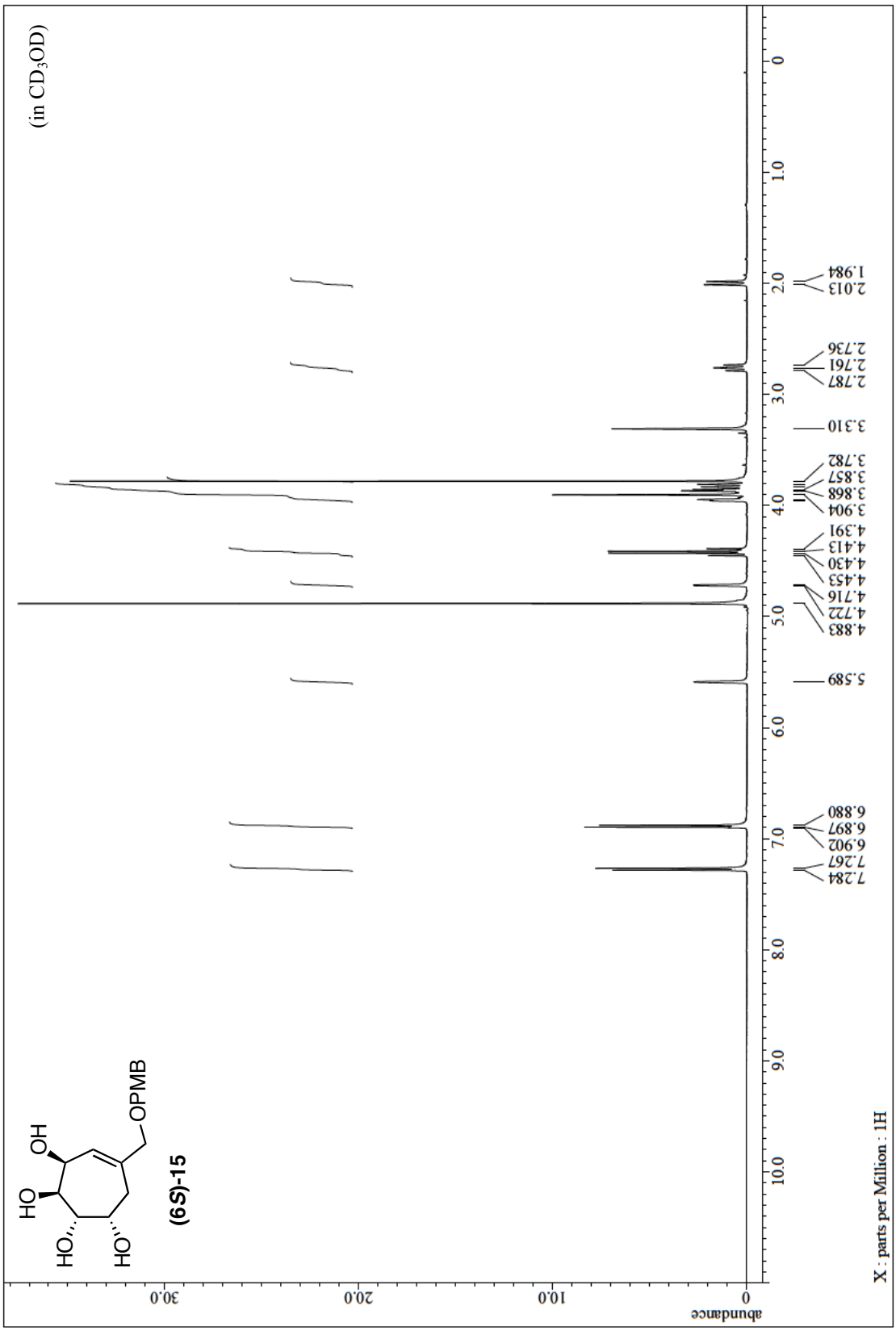

(in $CDCl_3$)
(6R)-13
OPMB
HO
HO
6R
abundance
X : parts per Million : 13C
159.438
142.793
134.228
130.107
129.583
119.873
116.076
113.978
109.094
85.992
79.478
78.953
73.316
72.114
71.141
70.779
55.441
55.403
38.339
27.418
25.167

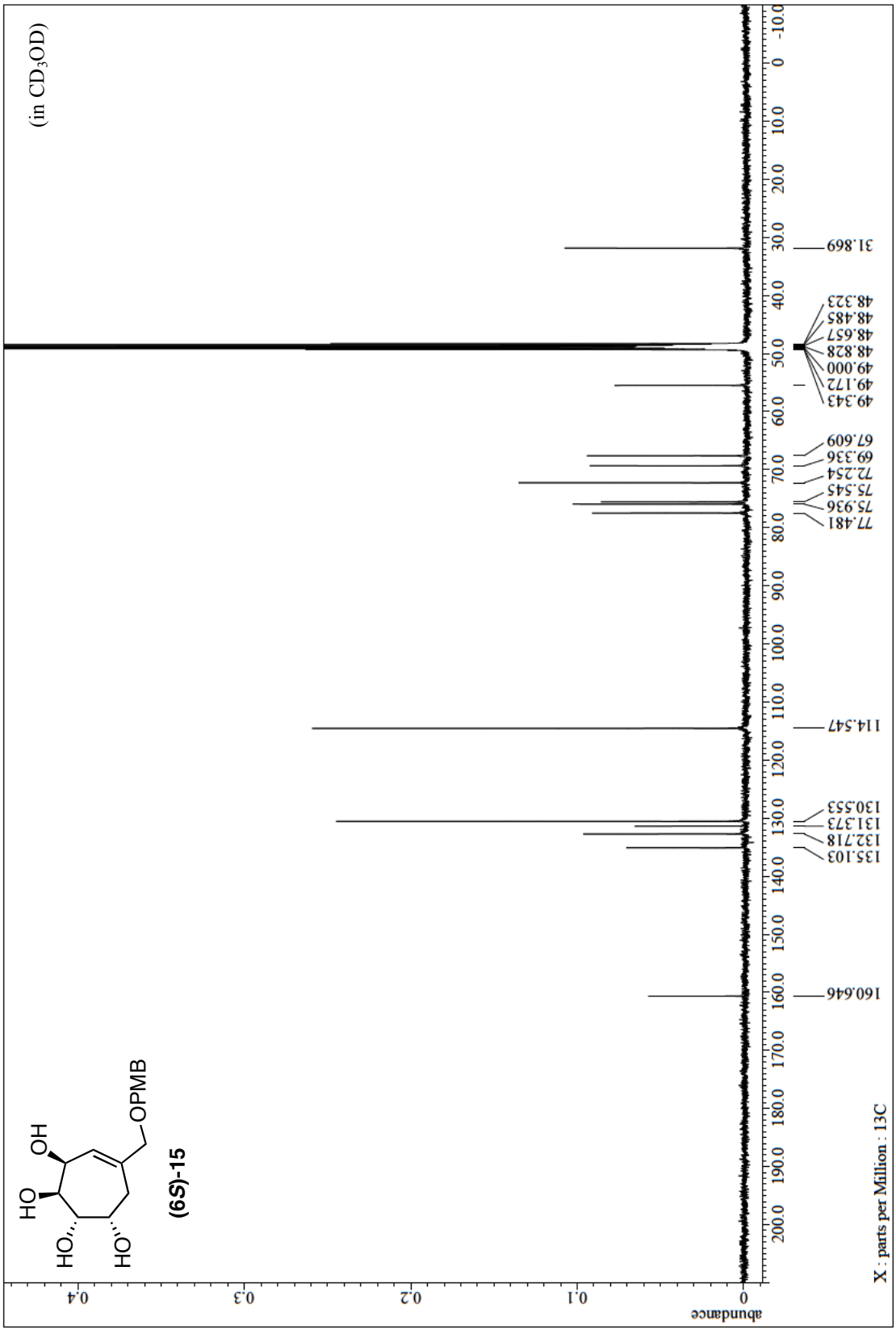

(in $CDCl_3$)
OPMB
HO
HO
6S
(6S)-14
abundance
X : parts per Million : 1H
7.260
7.253
7.236
6.890
6.884
6.867
5.683
5.681
5.014
4.999
4.418
4.414
4.318
4.303
3.890
3.885
3.881
3.803
3.687
3.678
2.551
2.536
2.522
2.509
2.100
2.076
2.052
1.483
1.390

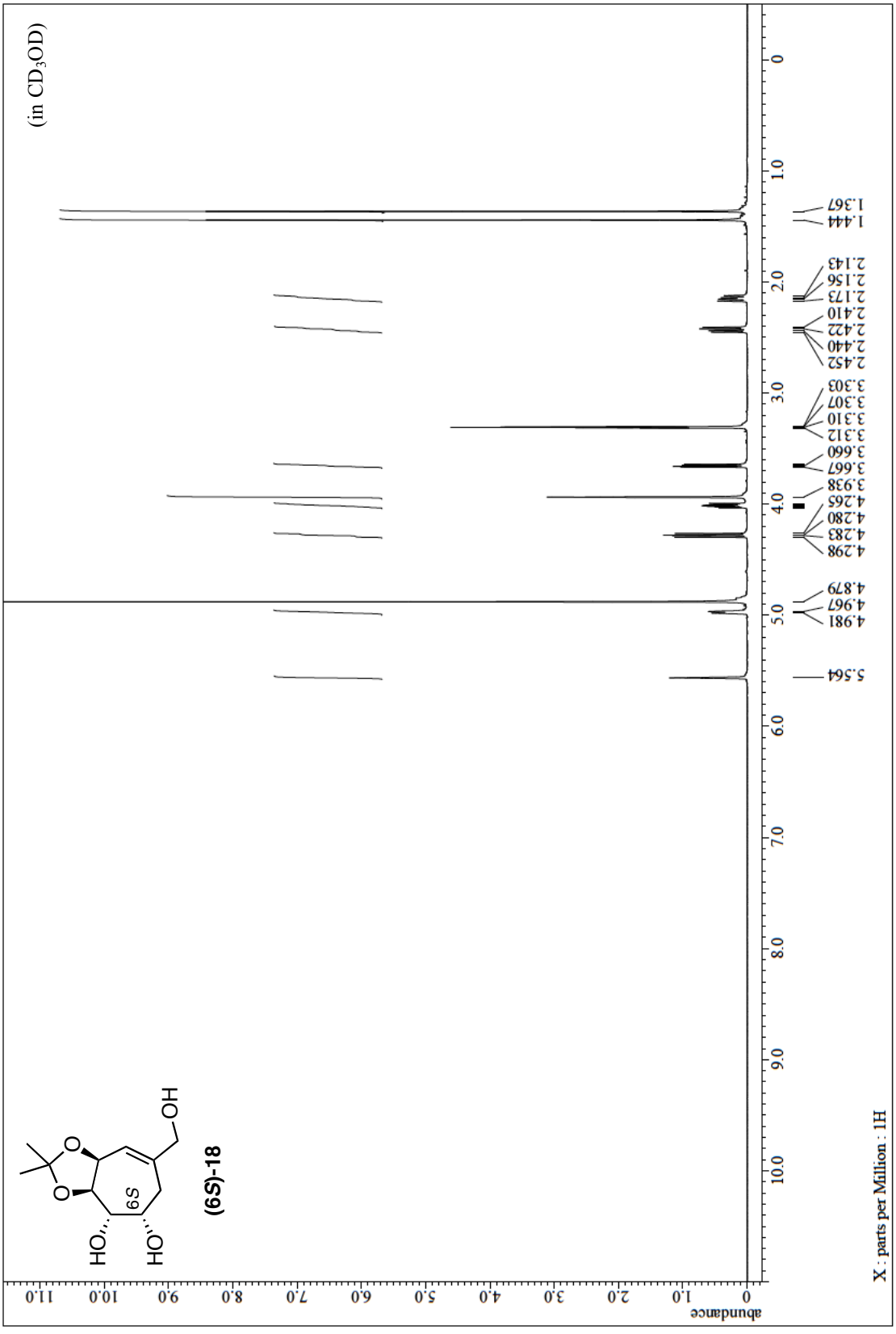

(in $CDCl_3$)
(6S)-14
OPMB
HO
HO
6S
159.347
132.678
130.160
129.378
126.059
113.926
108.117
77.356
77.098
76.850
75.620
73.827
73.617
72.100
71.328
66.225
55.361
32.154
27.432
24.600
abundance
X : parts per Million : 13C

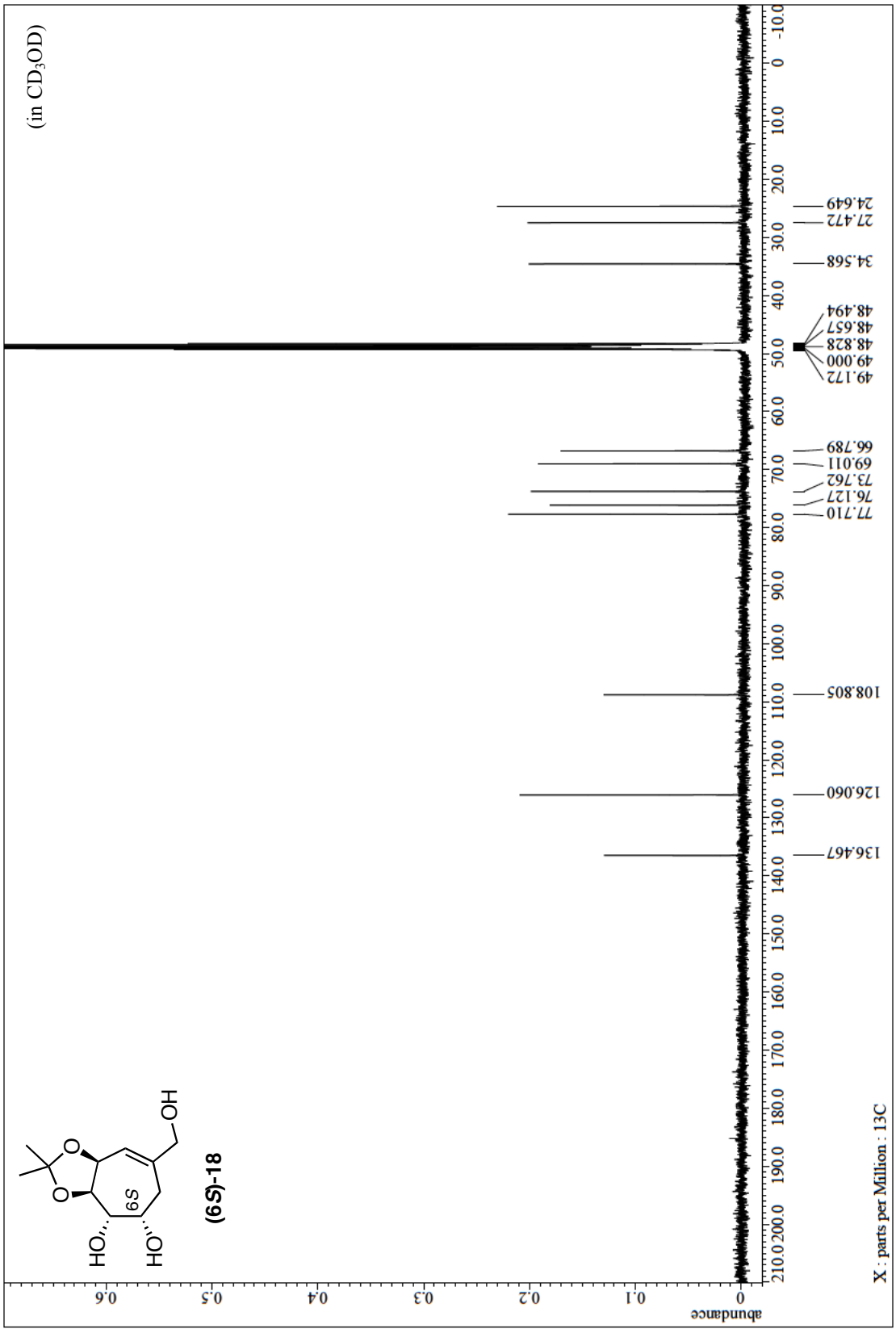

(in CDCl3)
OPMB
HO
HO
6R
(6R)-14
abundance
X : parts per Million : 1H
7.265
7.260
7.247
6.883
6.866
5.708
4.914
4.899
4.496
4.481
4.458
4.010
3.989
3.974
3.868
3.859
3.797
3.501
3.481
2.402
2.393
2.372
2.363
2.257
2.226
1.484
1.371

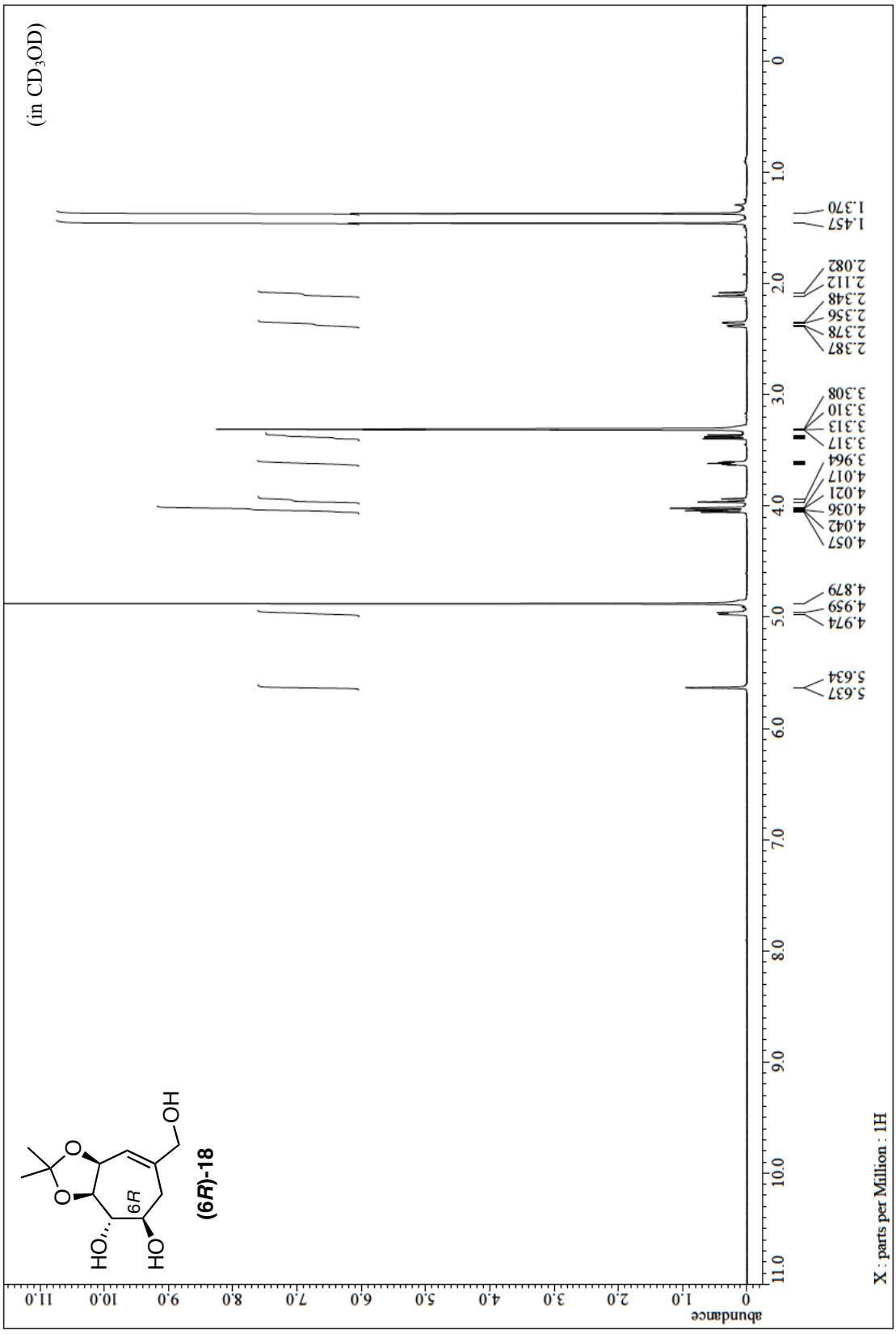

(in $CDCl_3$)
OPMB
HO
HO
6R
(6R)-14
abundance
X : parts per Million : 13C
159.529
132.697
129.712
129.493
127.823
114.021
108.279
77.366
77.108
76.850
76.736
76.402
74.962
73.693
72.873
71.271
55.351
33.546
27.251
24.285

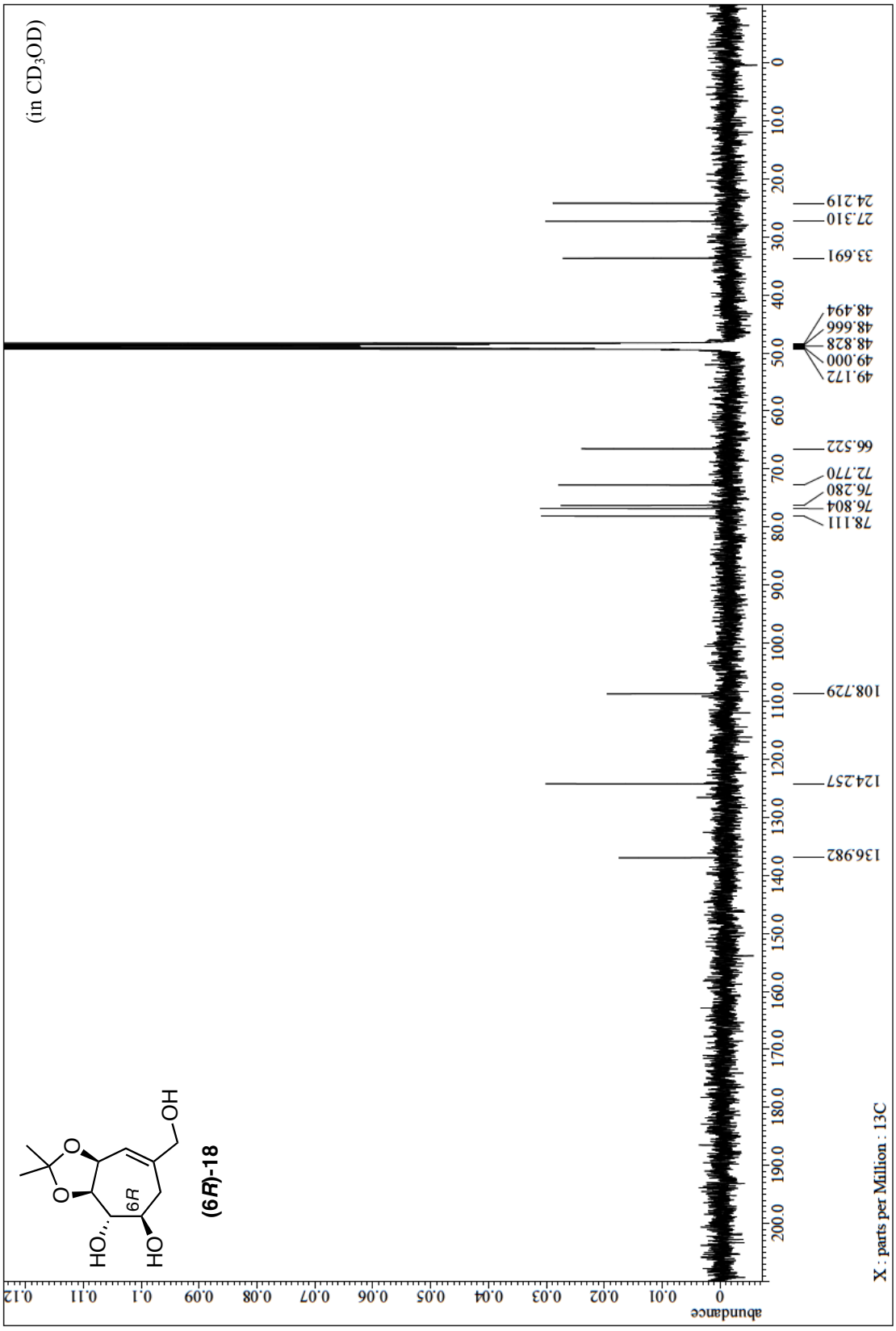

(in $CD_3OD$)
OPMB
OH
HO
HO
HO
(6S)-15
7.284
7.267
6.902
6.897
6.880
5.589
4.883
4.722
4.716
4.453
4.430
4.413
4.391
3.904
3.868
3.857
3.782
3.310
2.787
2.761
2.736
2.013
1.984
abundance
X : parts per Million : 1H

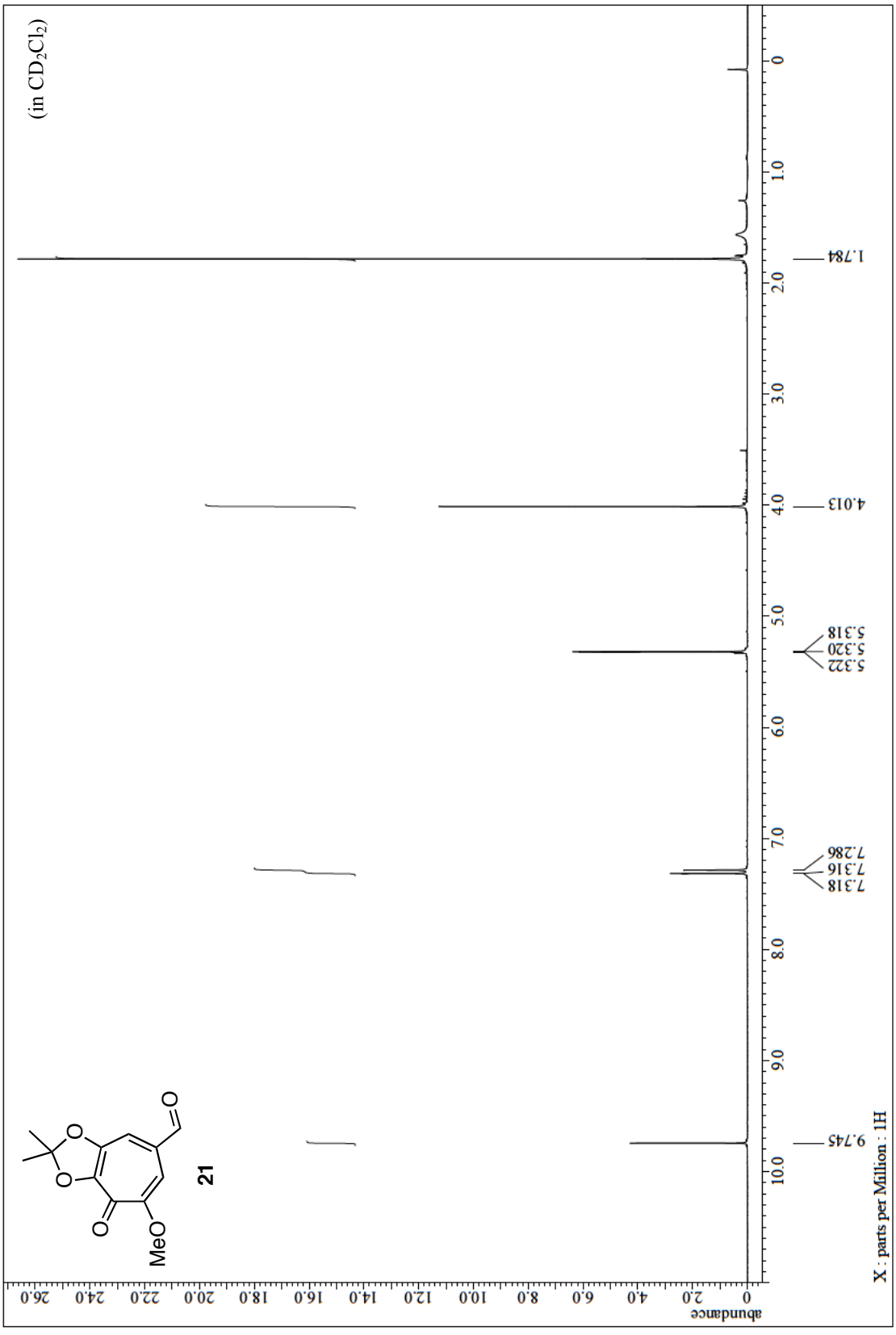

(in $CD_3OD$)
OPMB
OH
HO
HO
HO
(6S)-15
X : parts per Million : 13C
abundance
160.646
135.103
132.718
131.373
130.553
114.547
77.481
75.936
75.545
72.254
69.336
67.609
49.343
49.172
49.000
48.828
48.657
48.485
48.323
31.869

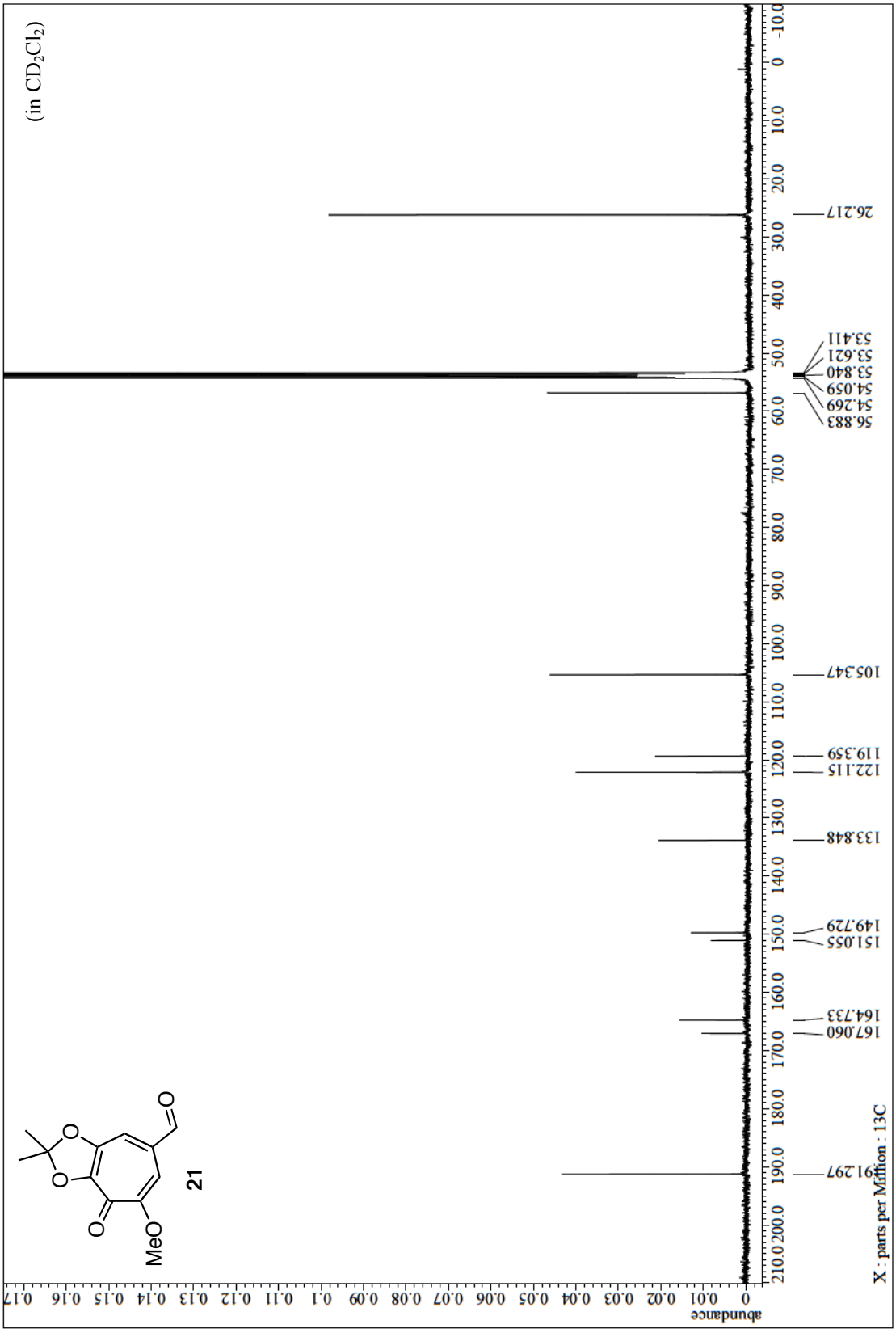

(in $CD_3OD$)
(6S)-18
6S
HO
HO
OH
O
O
abundance
X : parts per Million : 1H
1.444
1.367
2.452
2.440
2.422
2.410
2.173
2.156
2.143
3.312
3.310
3.307
3.303
3.667
3.660
3.938
4.265
4.298
4.283
4.280
4.981
4.967
4.879
5.564

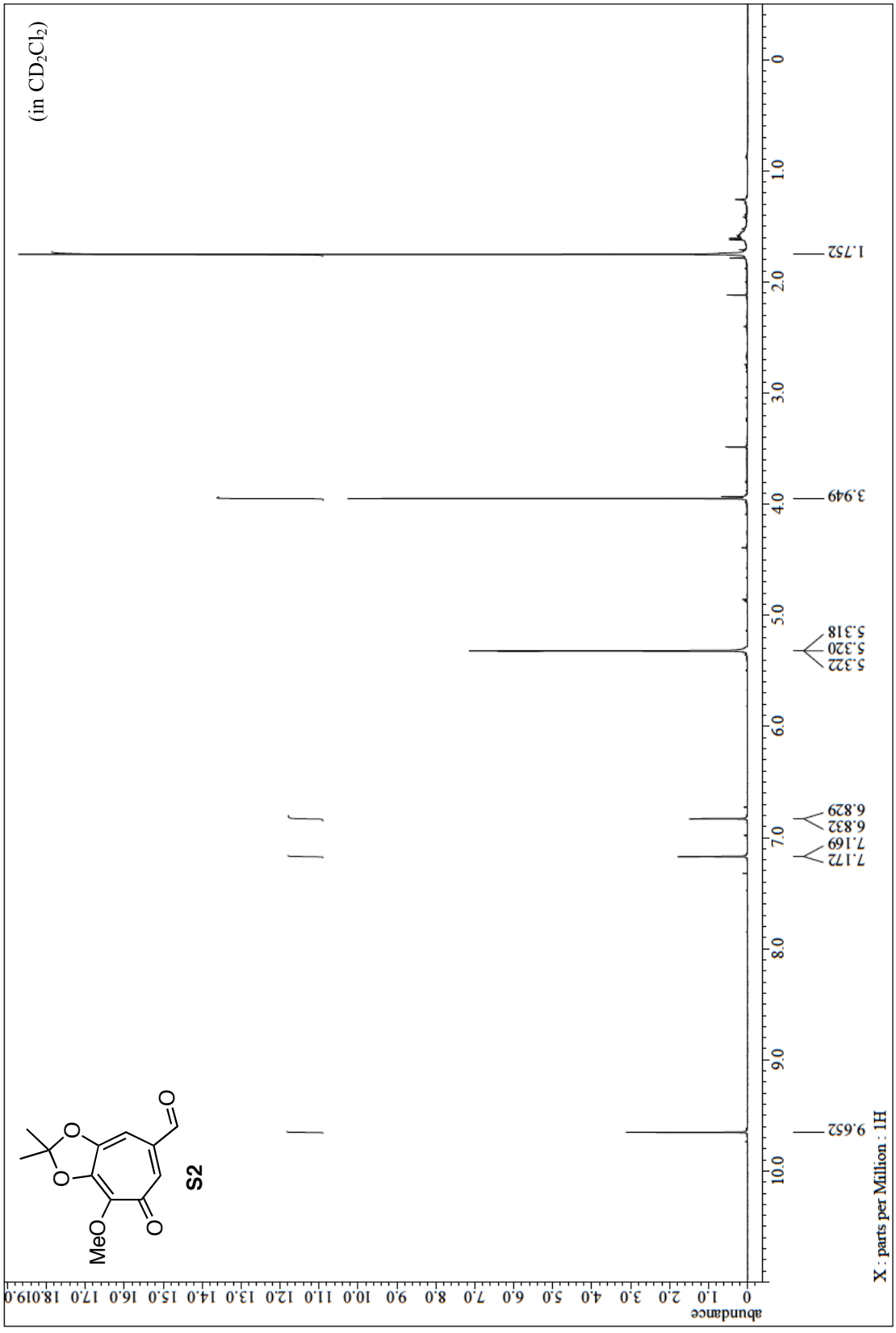

(in $CD_3OD$)
(6S)-18
X : parts per Million : 13C
abundance
24.649
27.472
34.568
48.494
48.657
48.828
49.000
49.172
66.789
69.011
73.762
76.127
77.710
108.805
126.060
136.467

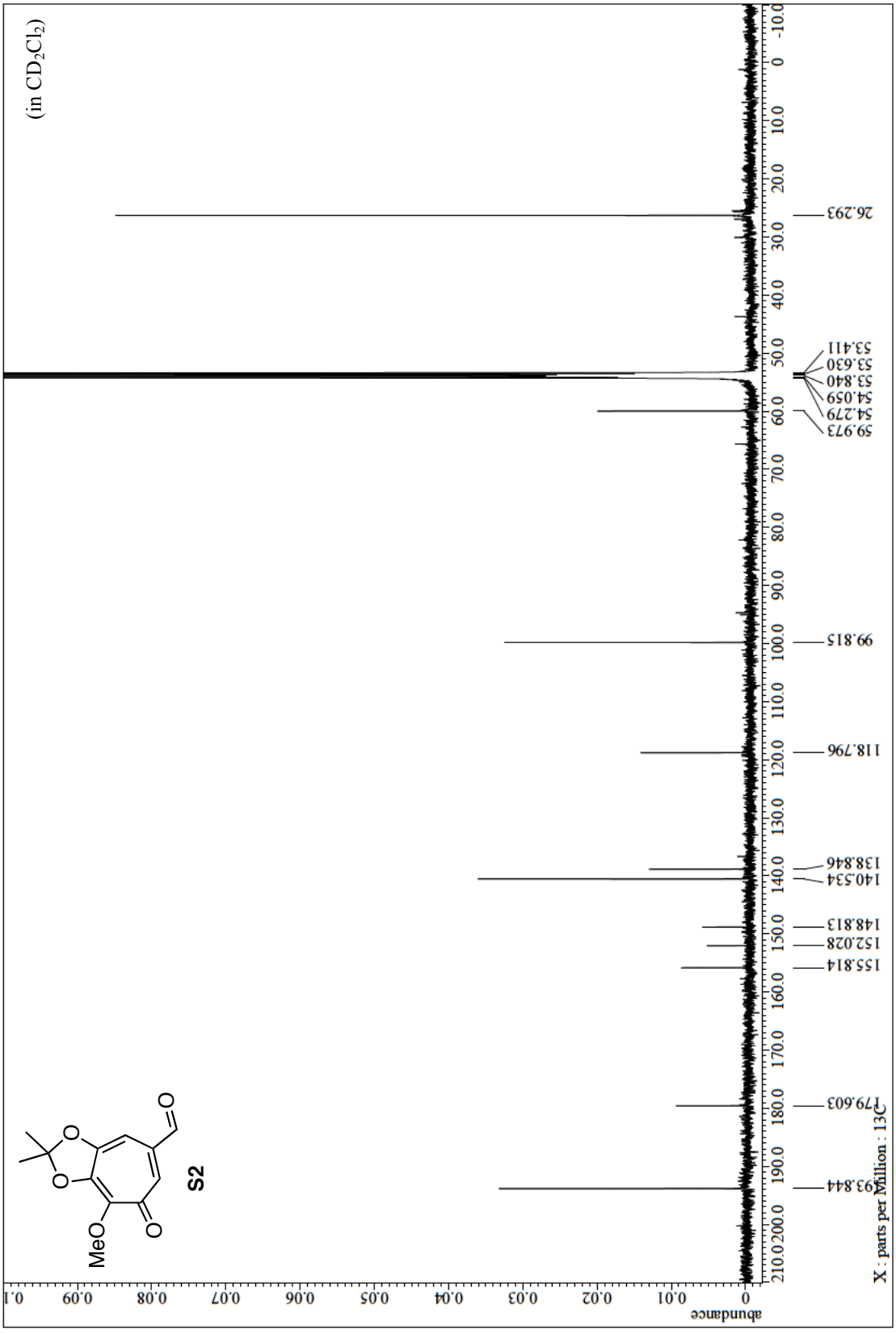

(in $CD_3OD$)
(6R)-18
6R
HO
HO
OH
O
O
abundance
X : parts per Million : 1H
5.637
5.634
4.974
4.959
4.879
4.057
4.042
4.036
4.021
4.017
3.964
3.317
3.313
3.310
3.308
2.387
2.378
2.356
2.348
2.112
2.082
1.457
1.370

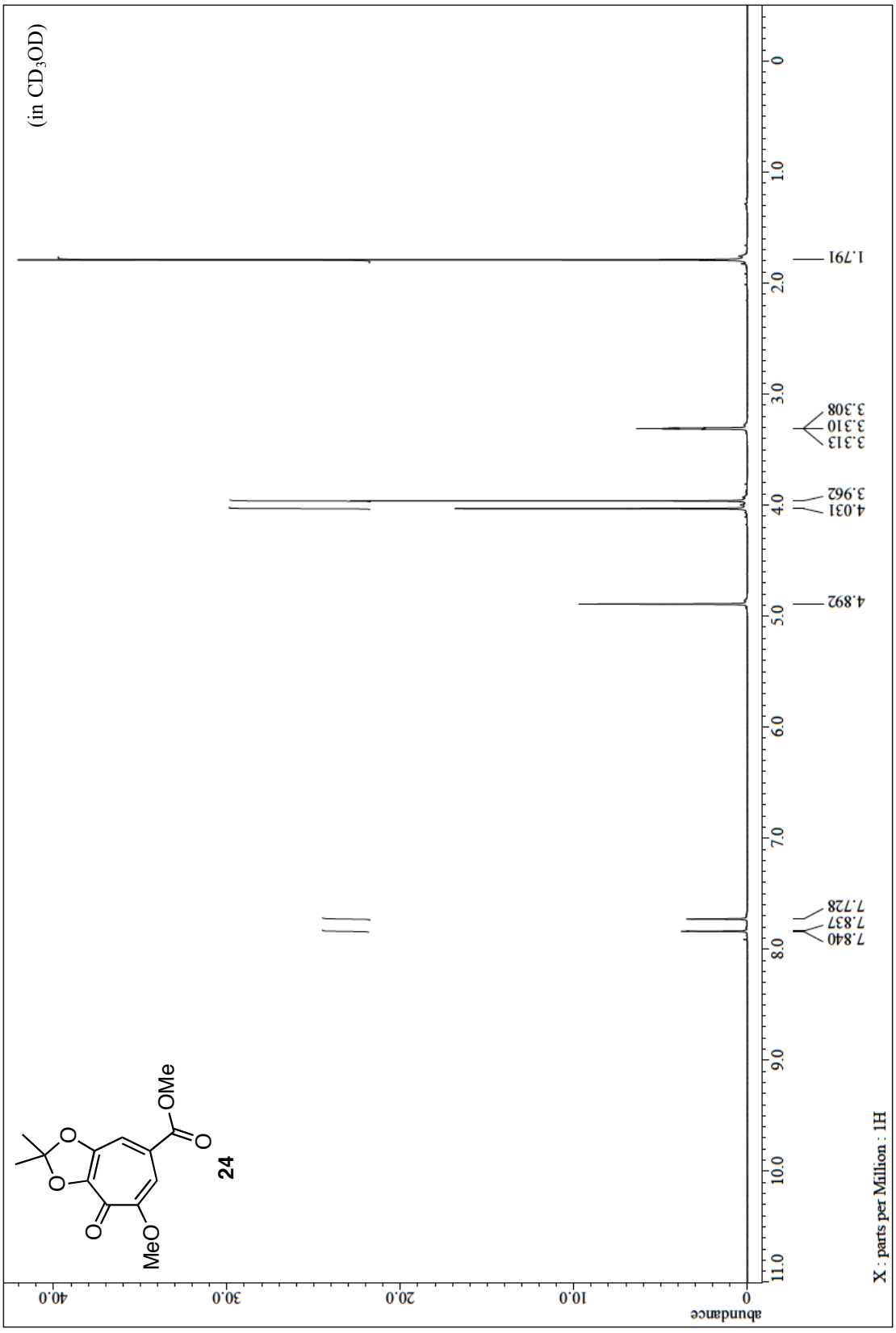

(in $CD_3OD$)
(6R)-18
6R
HO
HO
OH
O
O
abundance
X : parts per Million : 13C
24.219
27.310
33.691
48.494
48.666
48.828
49.000
49.172
66.522
72.770
76.280
76.804
78.111
108.729
124.257
136.982

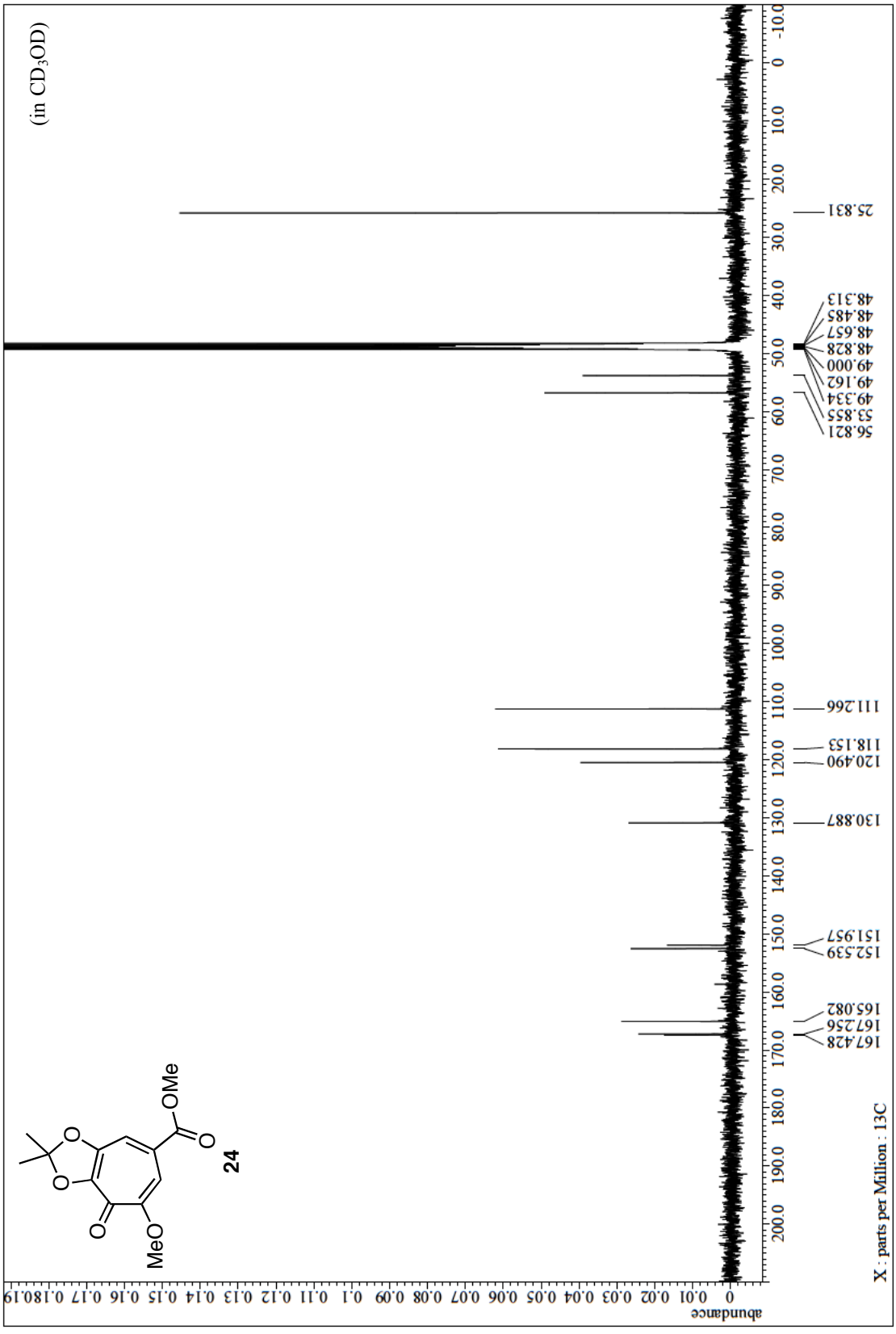

(in $CD_2Cl_2$)
21
MeO
O
O
O
O
9.745
7.318
7.316
7.286
5.322
5.320
5.318
4.013
1.784
abundance
X : parts per Million : 1H

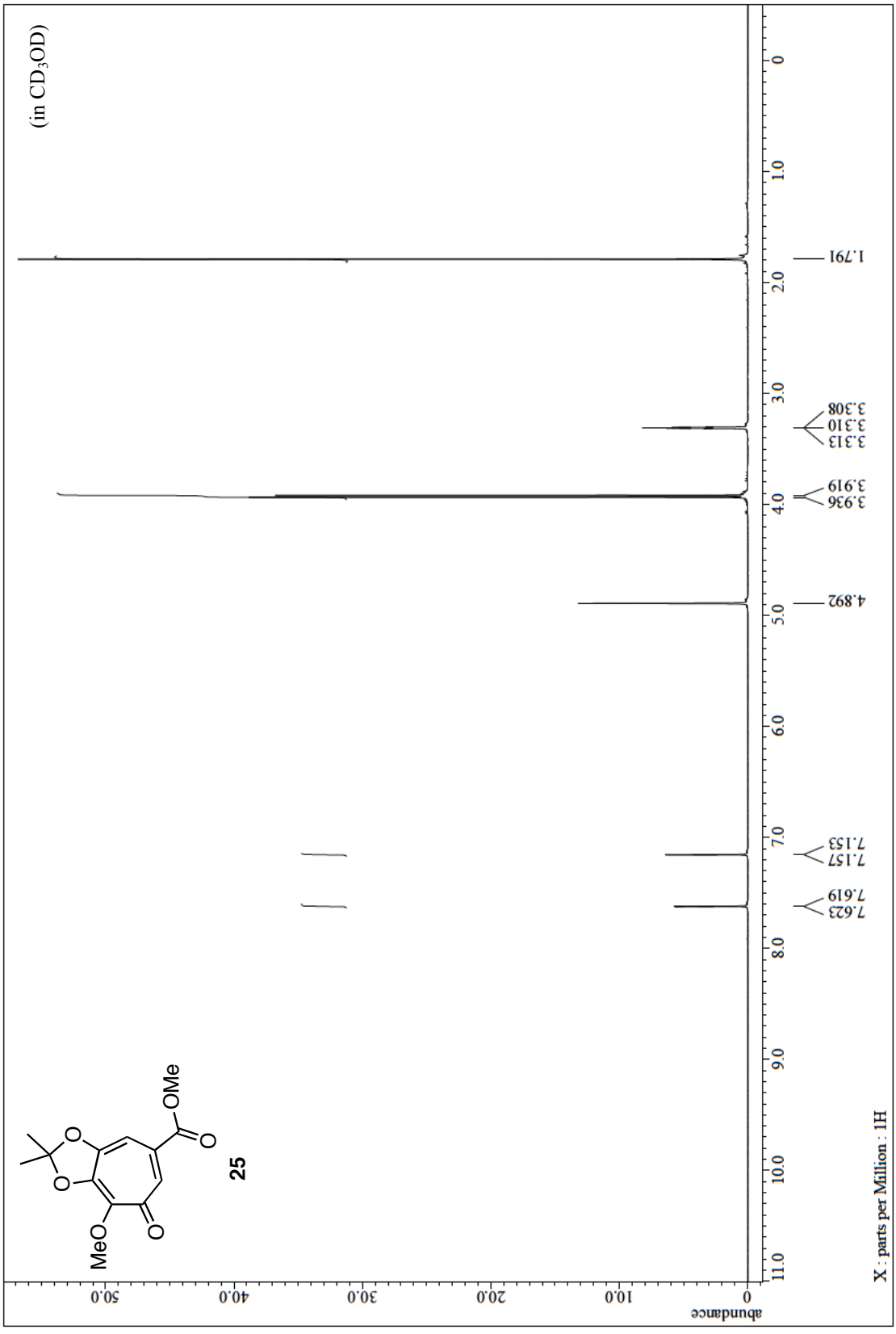

(in $CD_2Cl_2$)
21
MeO
O
O
O
O
26.217
53.411
53.621
53.840
54.059
54.269
56.883
105.347
119.359
122.115
133.848
149.729
151.055
164.733
167.060
191.297
X : parts per Million : 13C
abundance

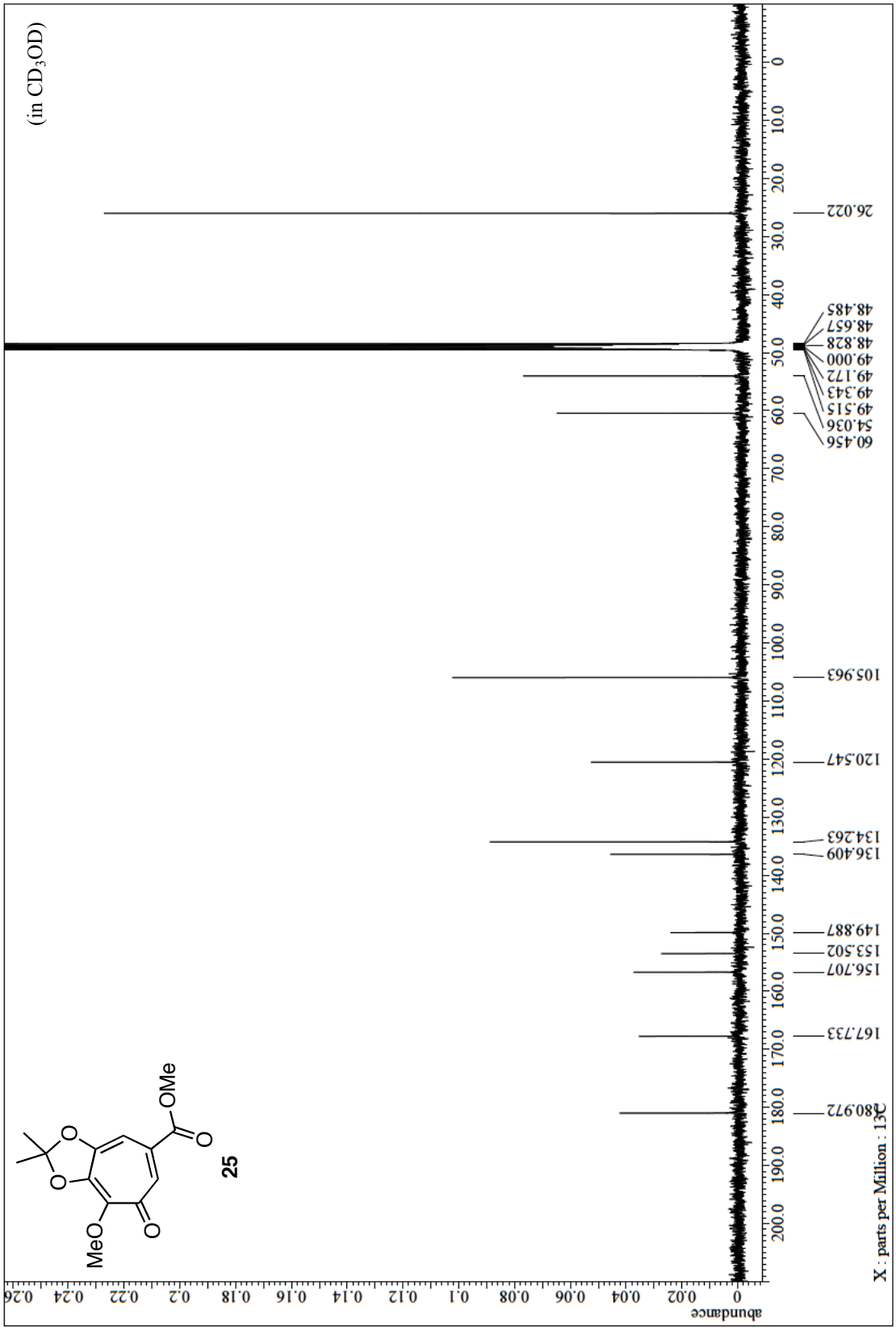

(in $CD_2Cl_2$)
S2
MeO
O
O
O
O
9.652
7.172
7.169
6.832
6.829
5.322
5.320
5.318
3.949
1.752
X : parts per Million : 1H
abundance

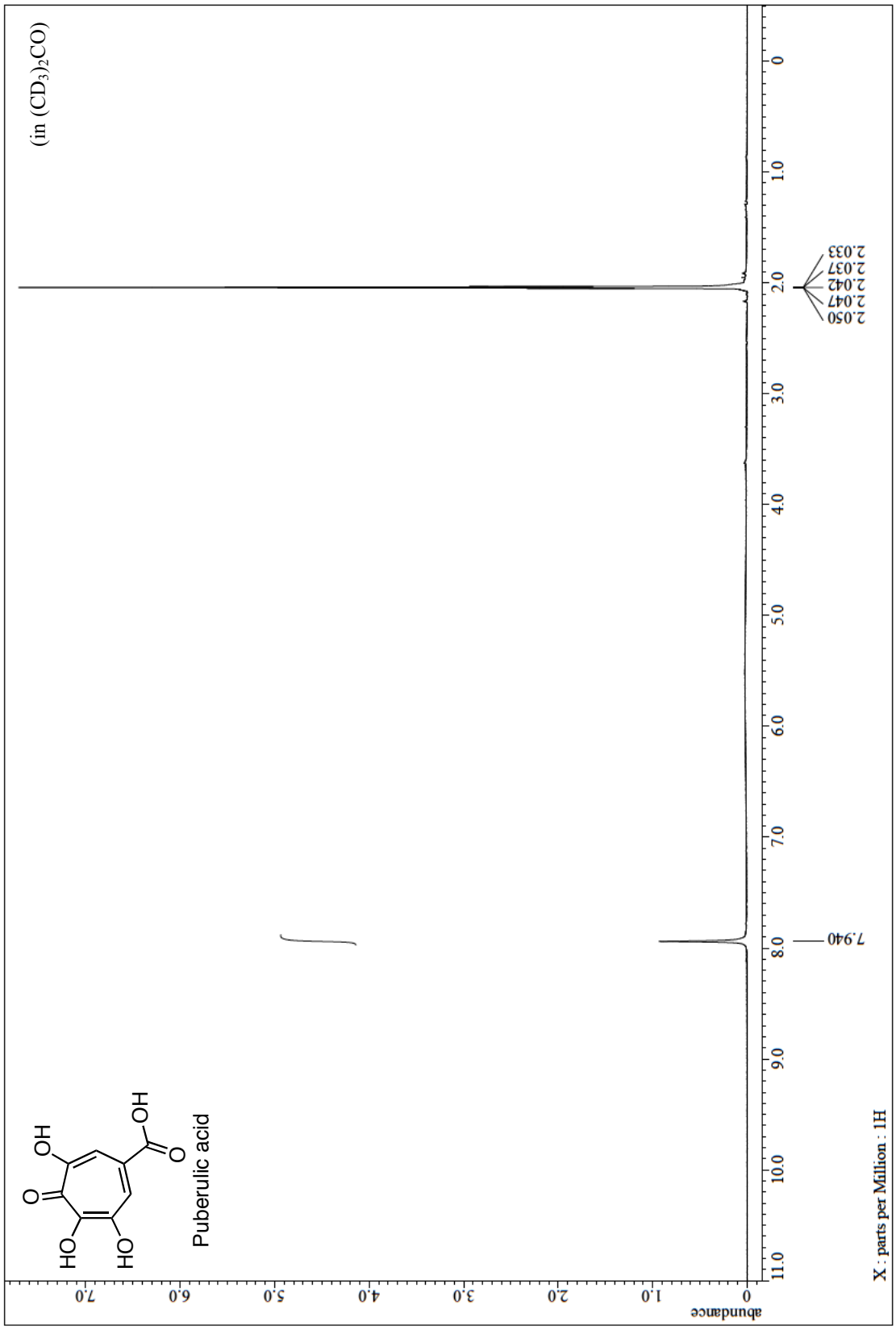

(in $CD_2Cl_2$)
S2
MeO
O
O
O
O
26.293
53.411
53.630
53.840
54.059
54.279
59.973
99.815
118.796
138.846
140.534
148.813
152.028
155.814
179.603
193.844
X : parts per Million : 13C
abundance

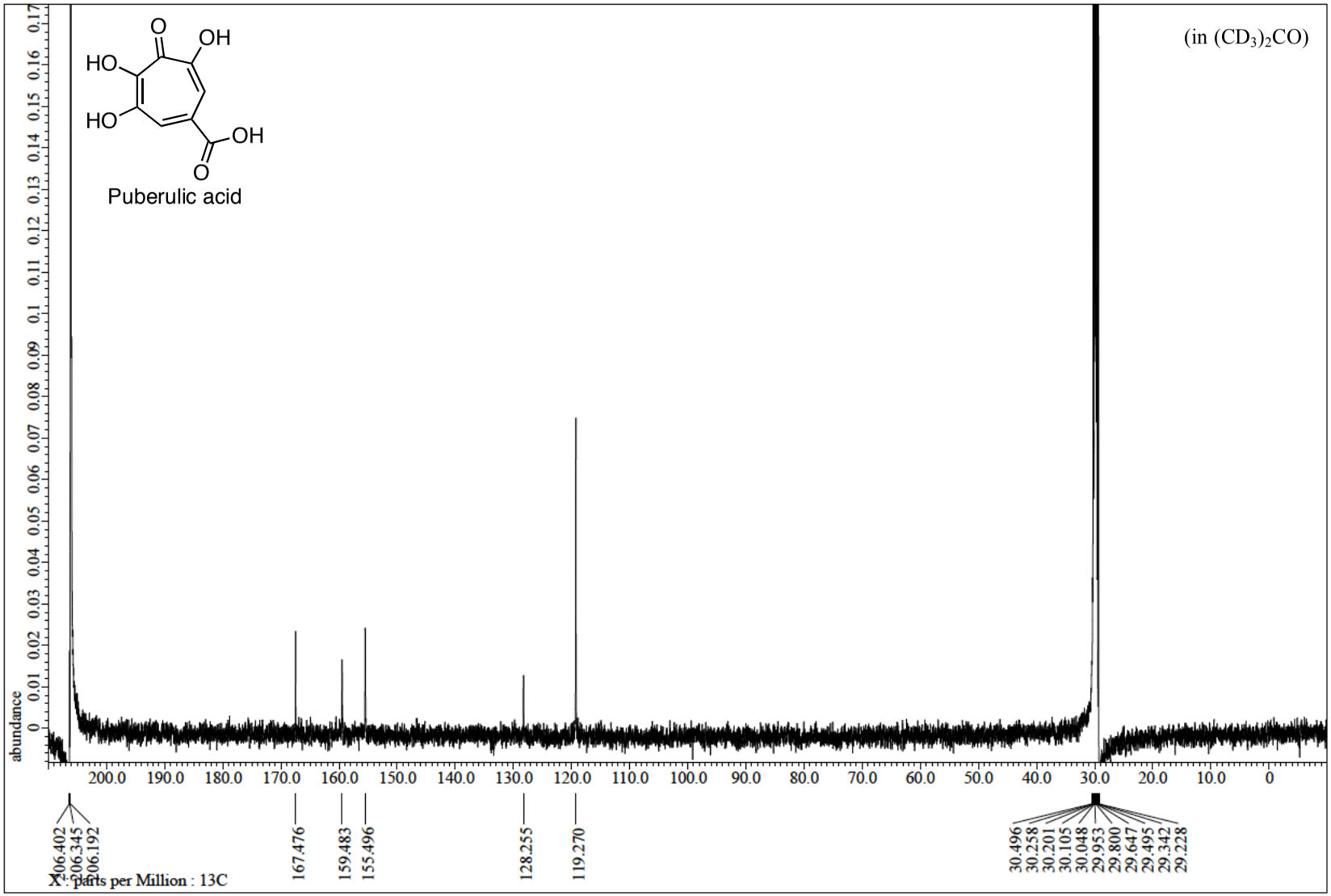

(in $CD_3OD$)
24
MeO
OMe
1.791
3.308
3.310
3.313
3.962
4.031
4.892
7.728
7.837
7.840
abundance
X : parts per Million : 1H

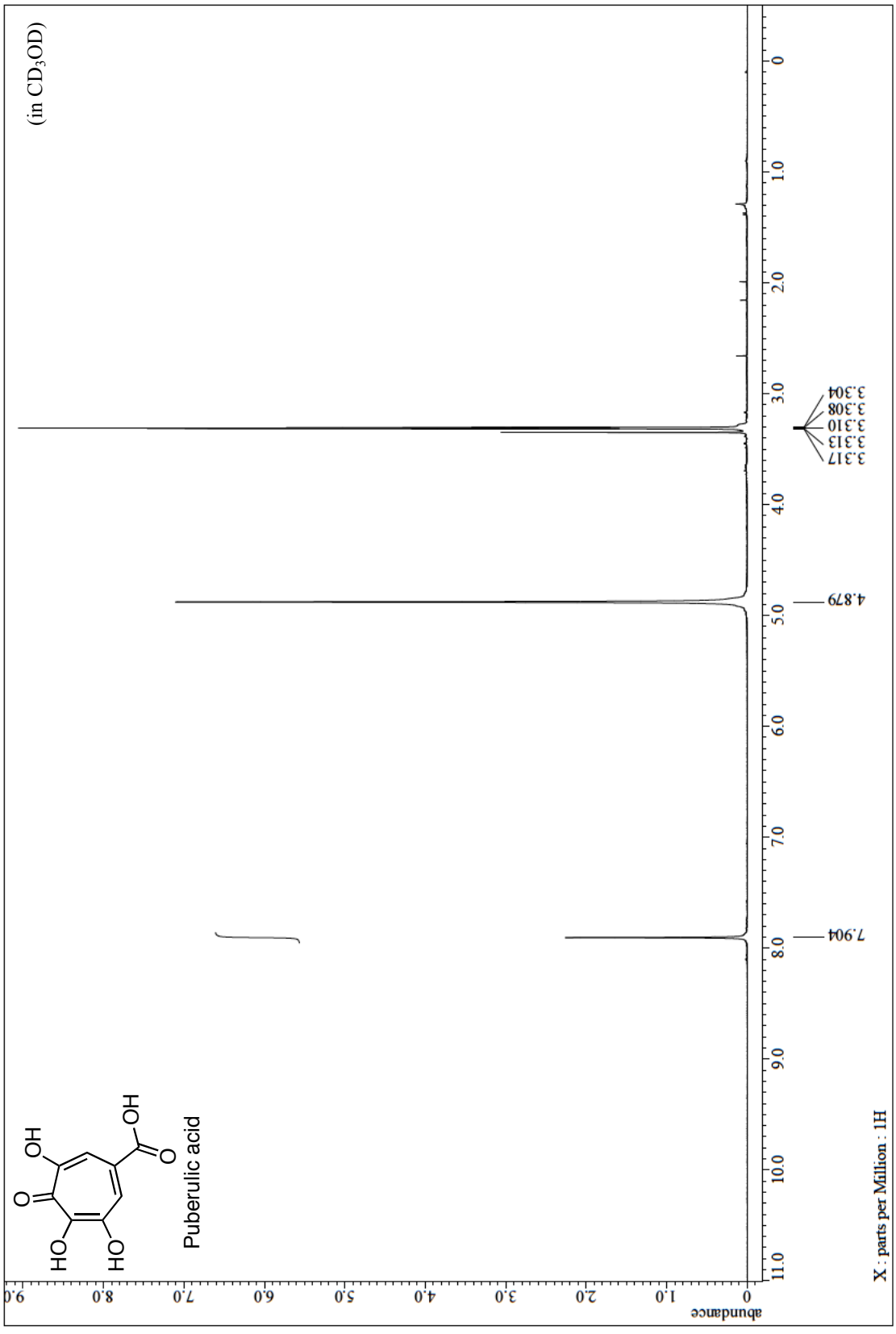

(in $CD_3OD$)
24
OMe
MeO
O
25.831
48.313
48.485
48.657
48.828
49.000
49.162
49.334
53.855
56.821
111.266
118.153
120.490
130.887
151.957
152.539
165.082
167.256
167.428
X : parts per Million : 13C
abundance

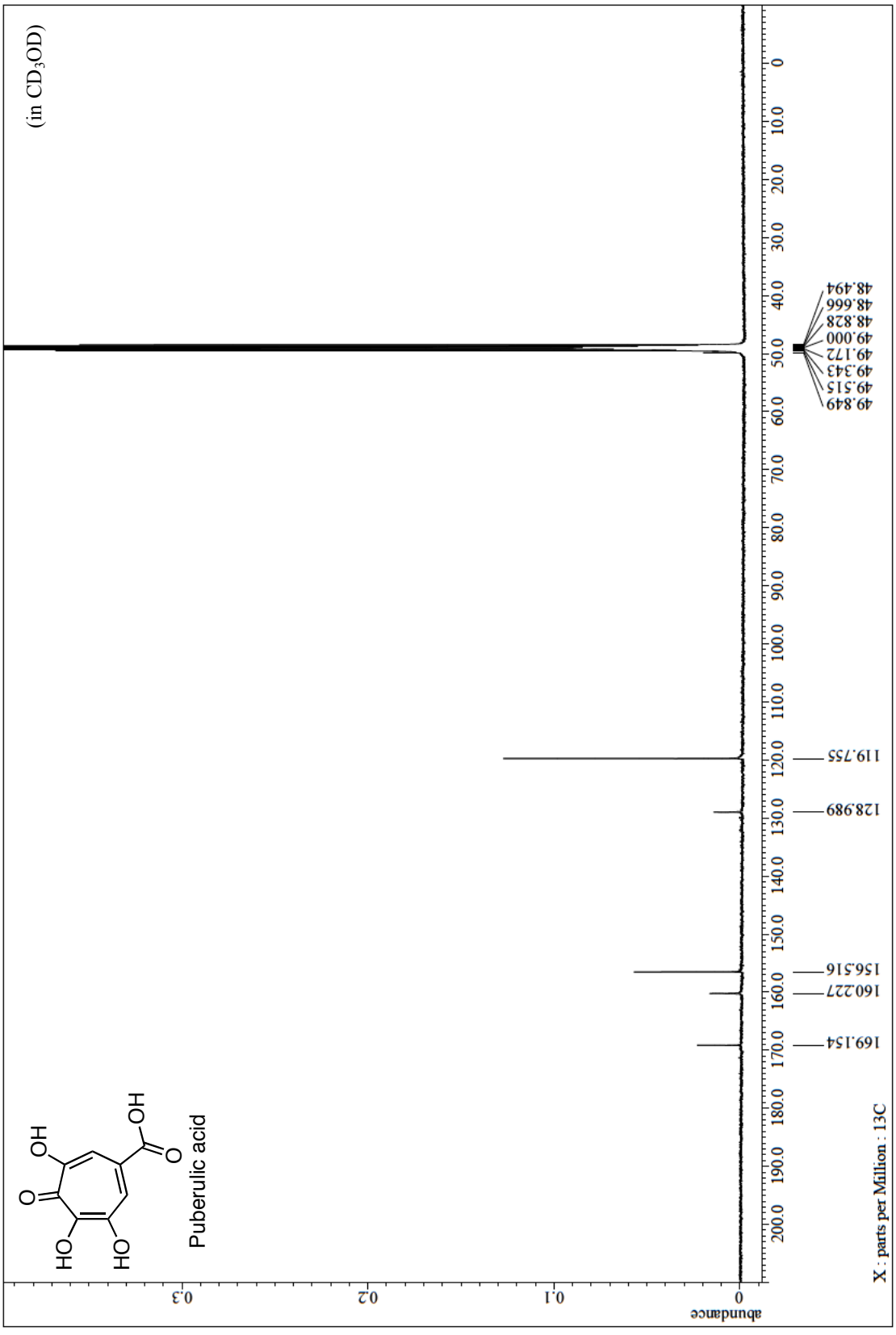

(in $CD_3OD$)
25
MeO
OMe
1.791
3.308
3.310
3.313
3.919
3.936
4.892
7.153
7.157
7.619
7.623
X : parts per Million : 1H
abundance

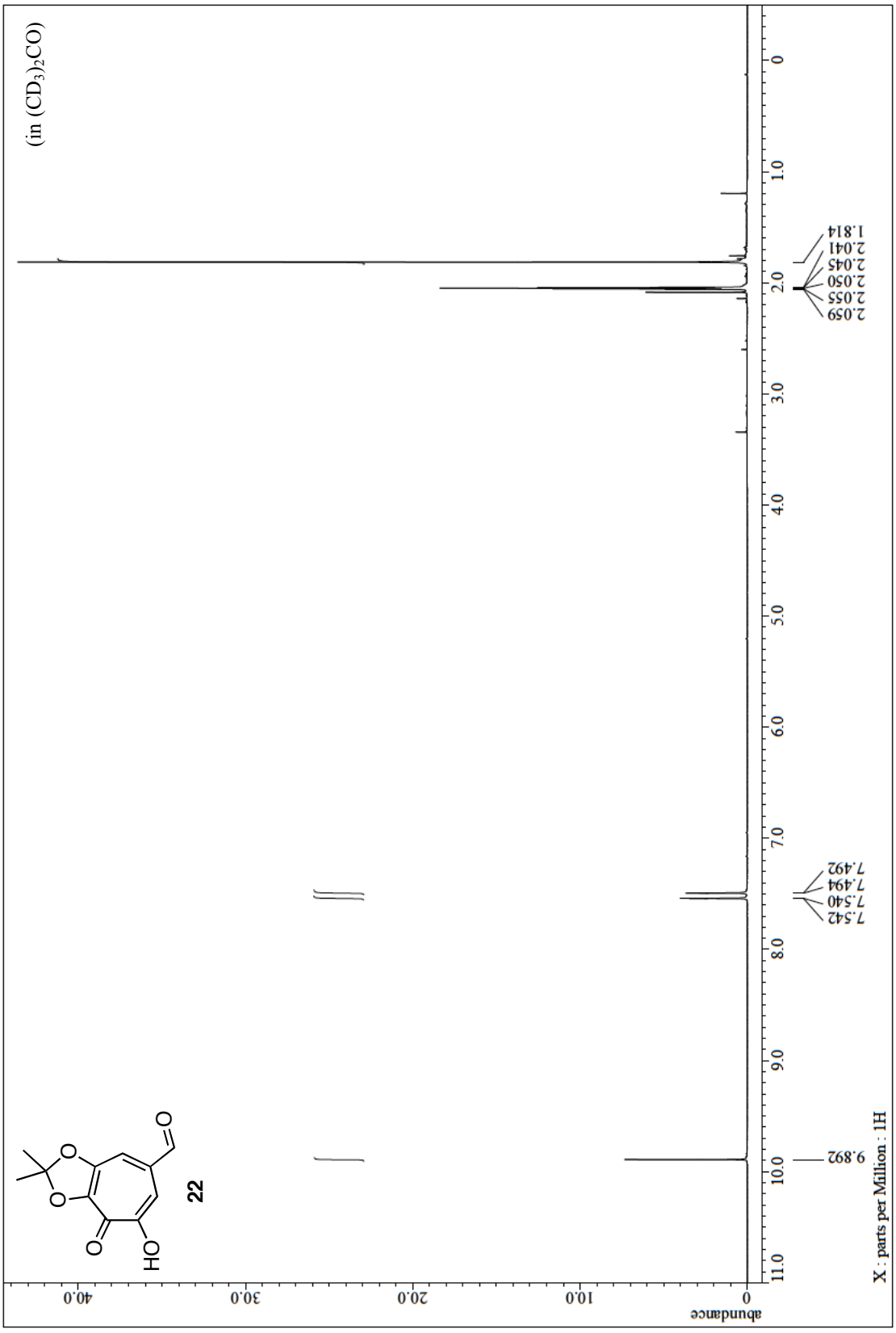

(in $CD_3OD$)
OMe
O
O
O
O
MeO
25
26.022
48.485
48.657
48.828
49.000
49.172
49.343
49.515
54.036
60.456
105.963
120.547
134.263
136.409
149.887
153.502
156.707
167.733
180.972
X : parts per Million : 13C
abundance

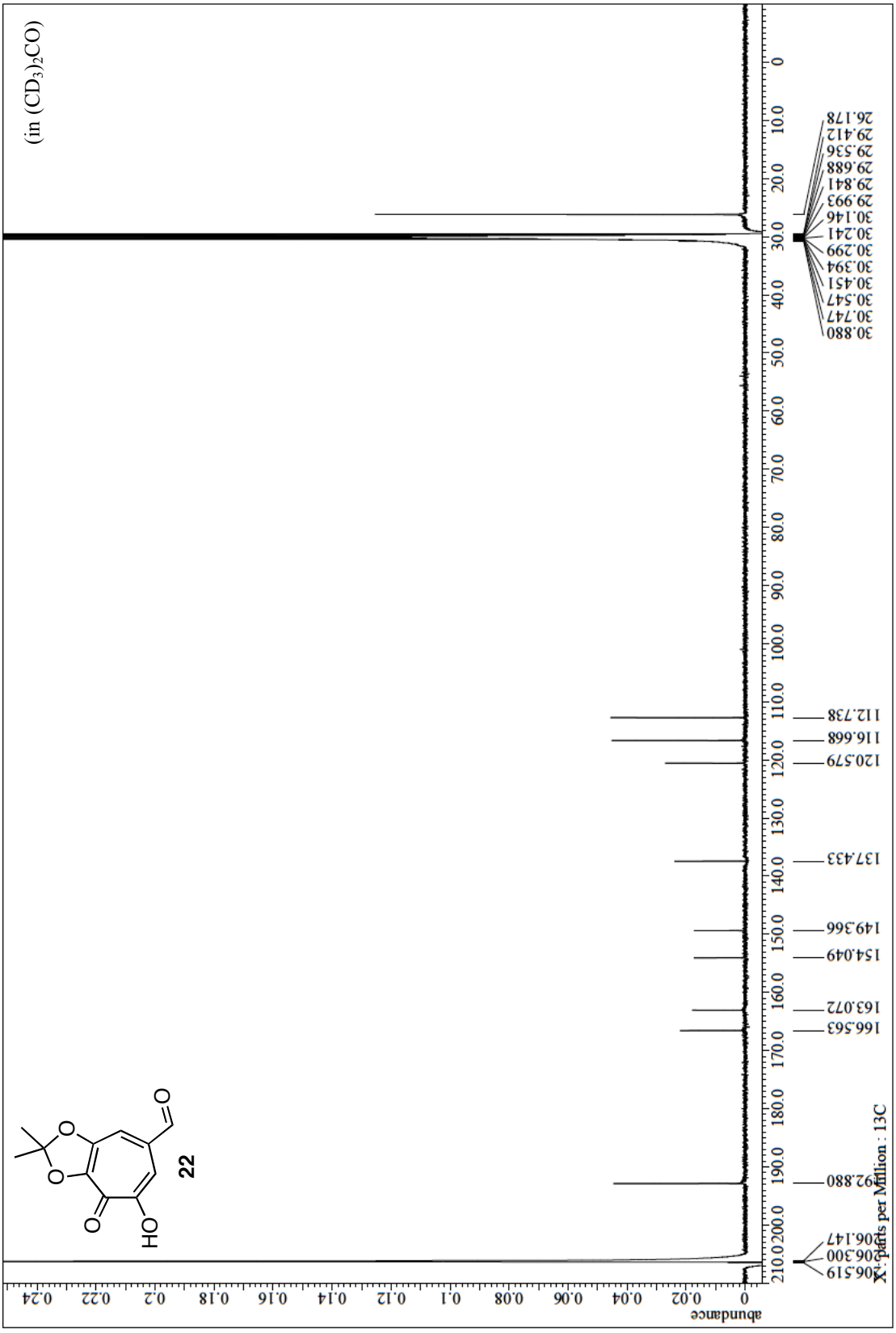

(in $(CD_3)_2CO$)
Puberulic acid
OH
O
HO
HO
OH
O
abundance
X : parts per Million : 1H
7.940
2.050
2.047
2.042
2.037
2.033

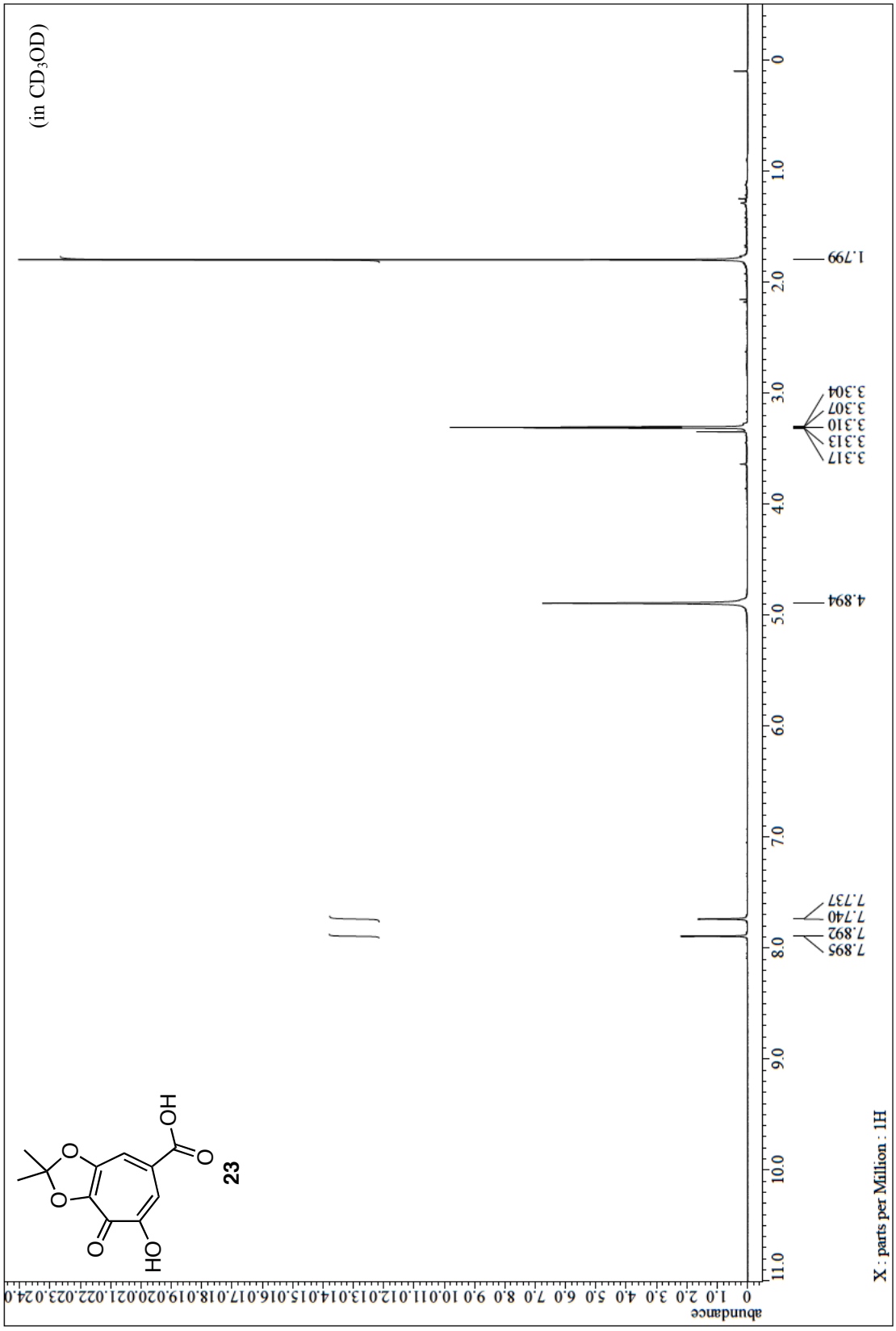

Puberulic acid
(in $(CD_3)_2CO$)
abundance
X : parts per Million : 13C
206.402
206.345
206.192
167.476
159.483
155.496
128.255
119.270
30.496
30.258
30.201
30.105
30.048
29.953
29.800
29.647
29.495
29.342
29.228

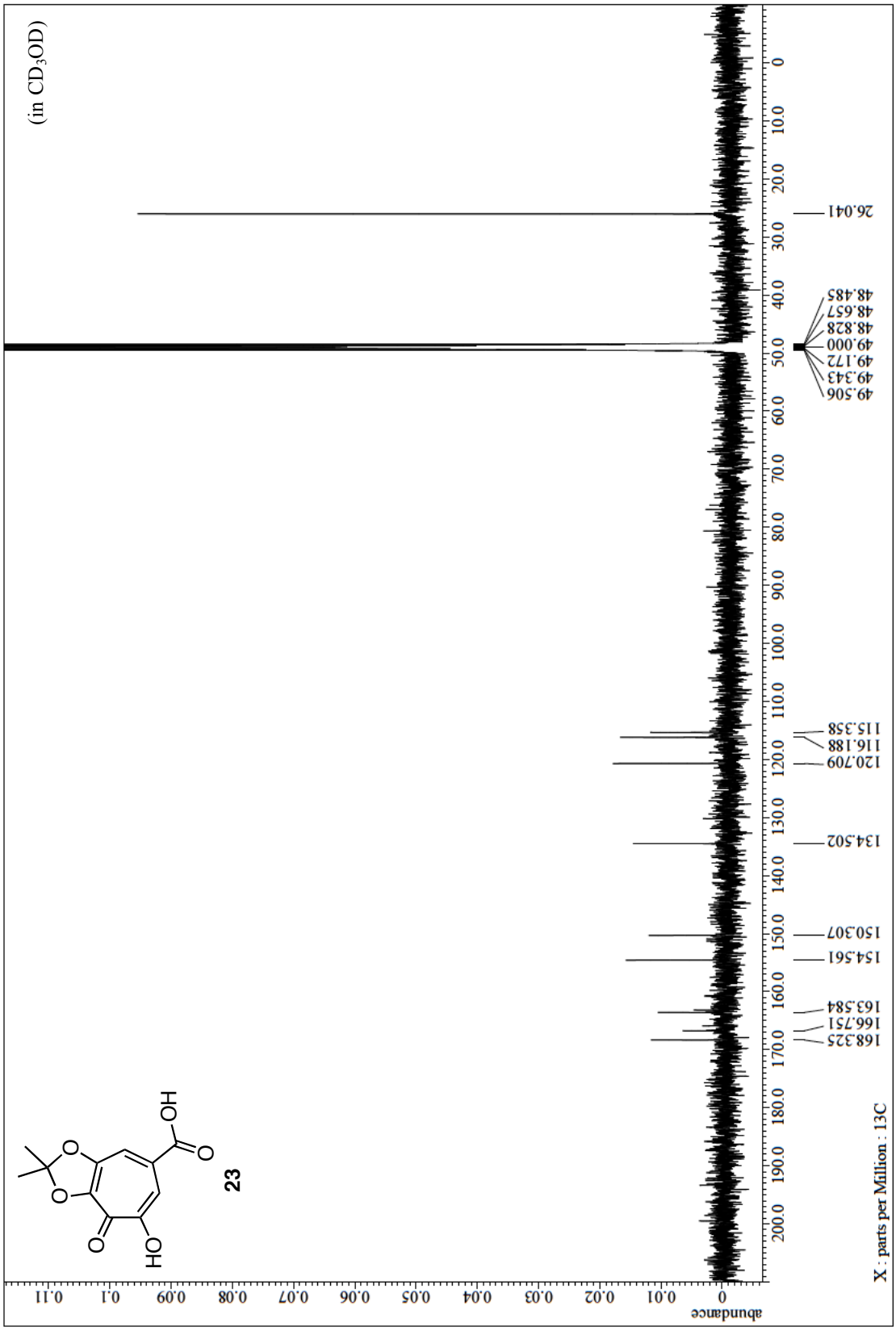

(in $CD_3OD$)
Puberulic acid
OH
O
HO
HO
OH
O
7.904
4.879
3.317
3.313
3.310
3.308
3.304
abundance
X : parts per Million : 1H

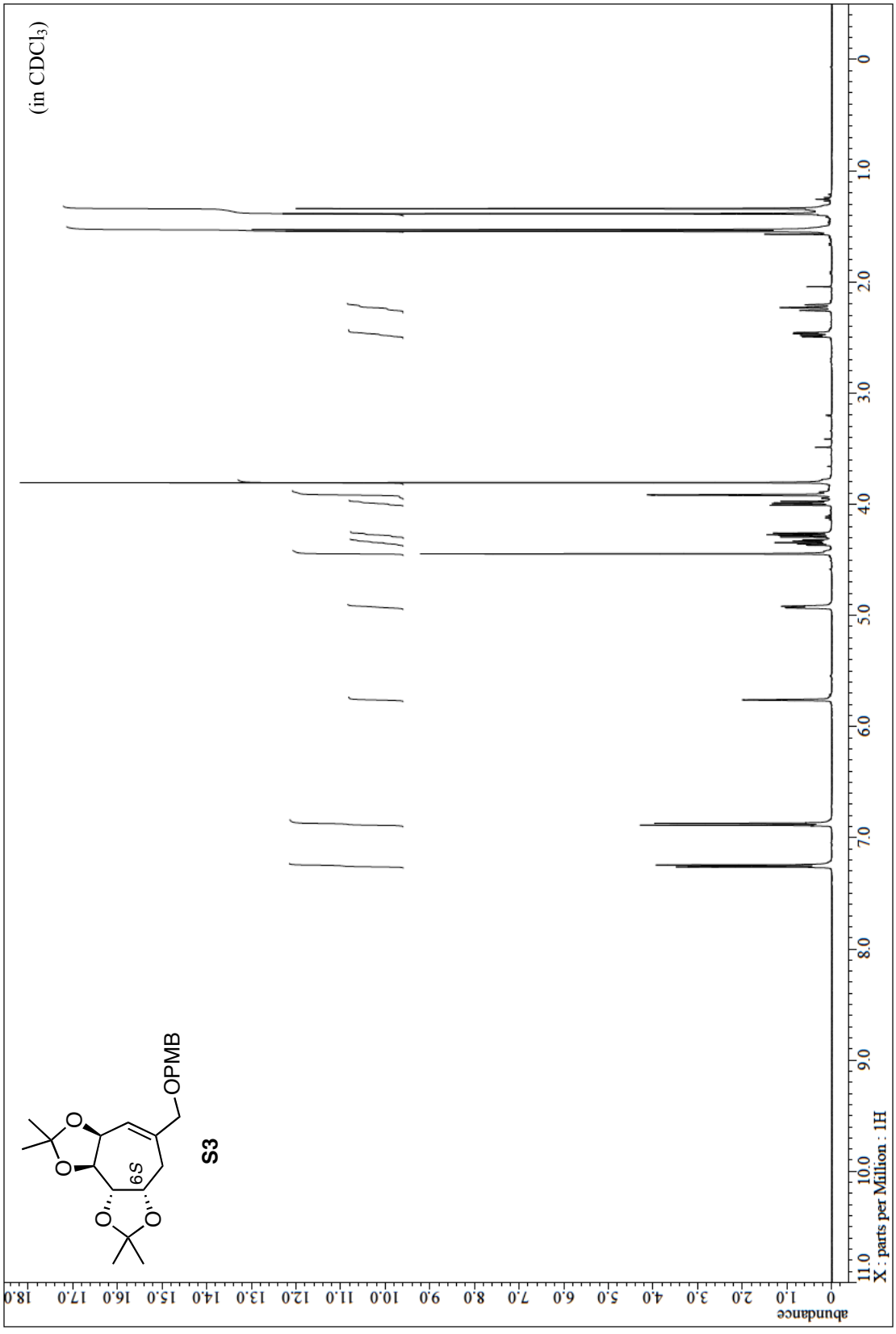

(in $CD_3OD$)
Puberulic acid
X : parts per Million : 13C
abundance
169.154
160.227
156.516
128.989
119.755
49.849
49.515
49.343
49.172
49.000
48.828
48.666
48.494

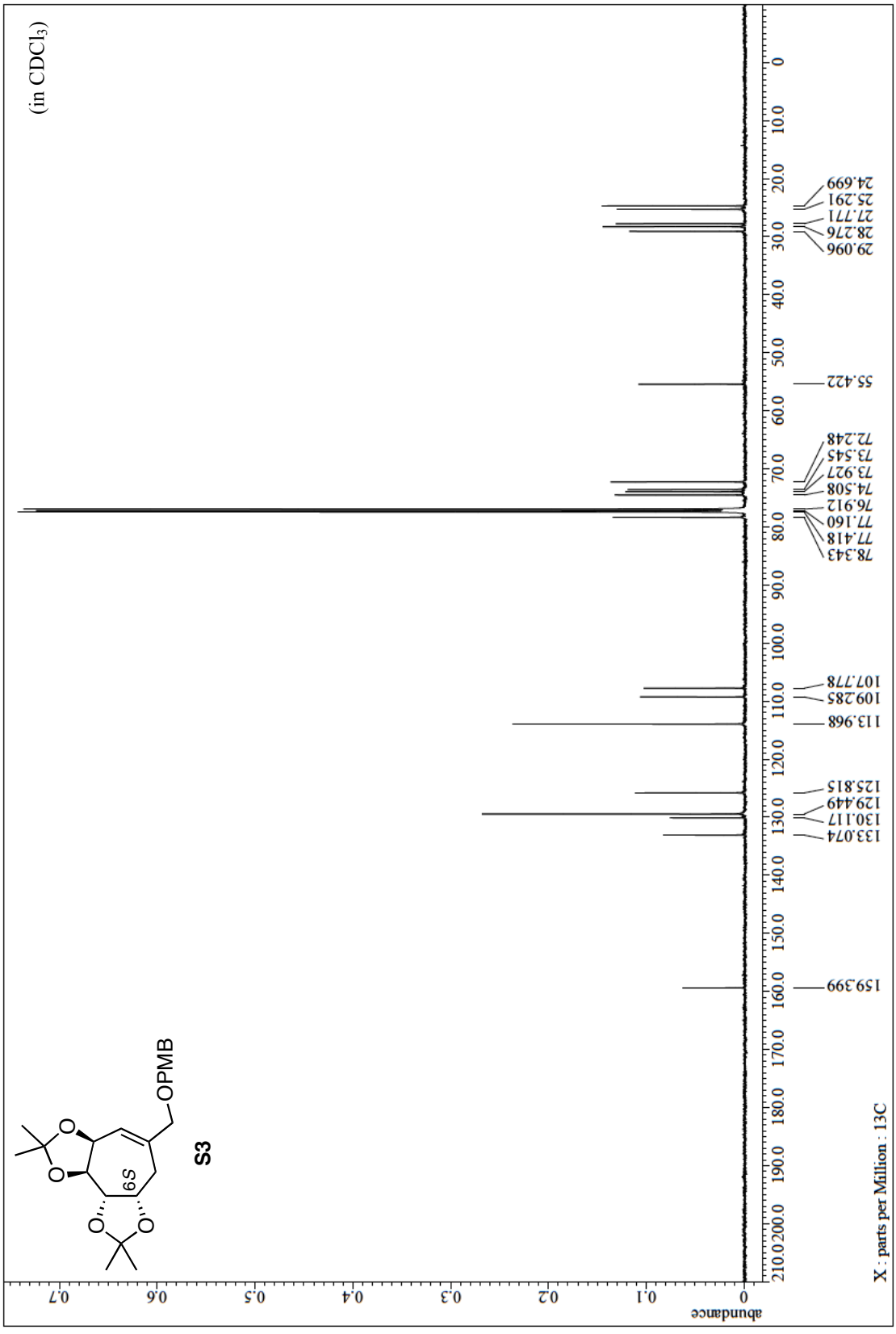

(in $(CD_3)_2CO$)
22
9.892
7.542
7.540
7.494
7.492
2.059
2.055
2.050
2.045
2.041
1.814
X : parts per Million : 1H
abundance

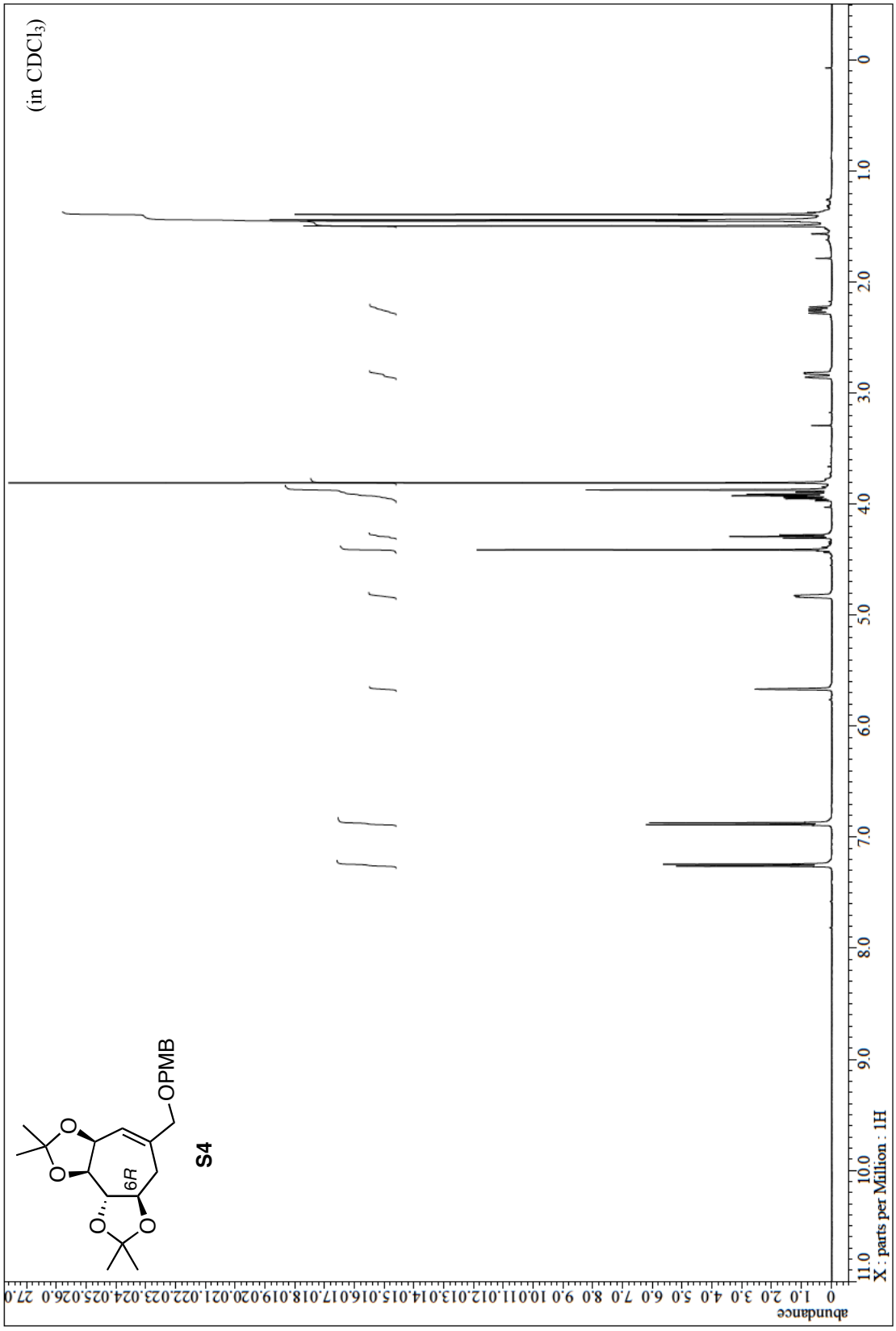

(in (CD3)2CO)
22
O
HO
O
O
O
X : parts per Million : 13C
abundance
206.519
206.300
206.147
192.880
166.563
163.072
154.049
149.366
137.433
120.579
116.668
112.738
30.880
30.747
30.547
30.451
30.394
30.299
30.241
30.146
29.993
29.841
29.688
29.536
29.412
26.178

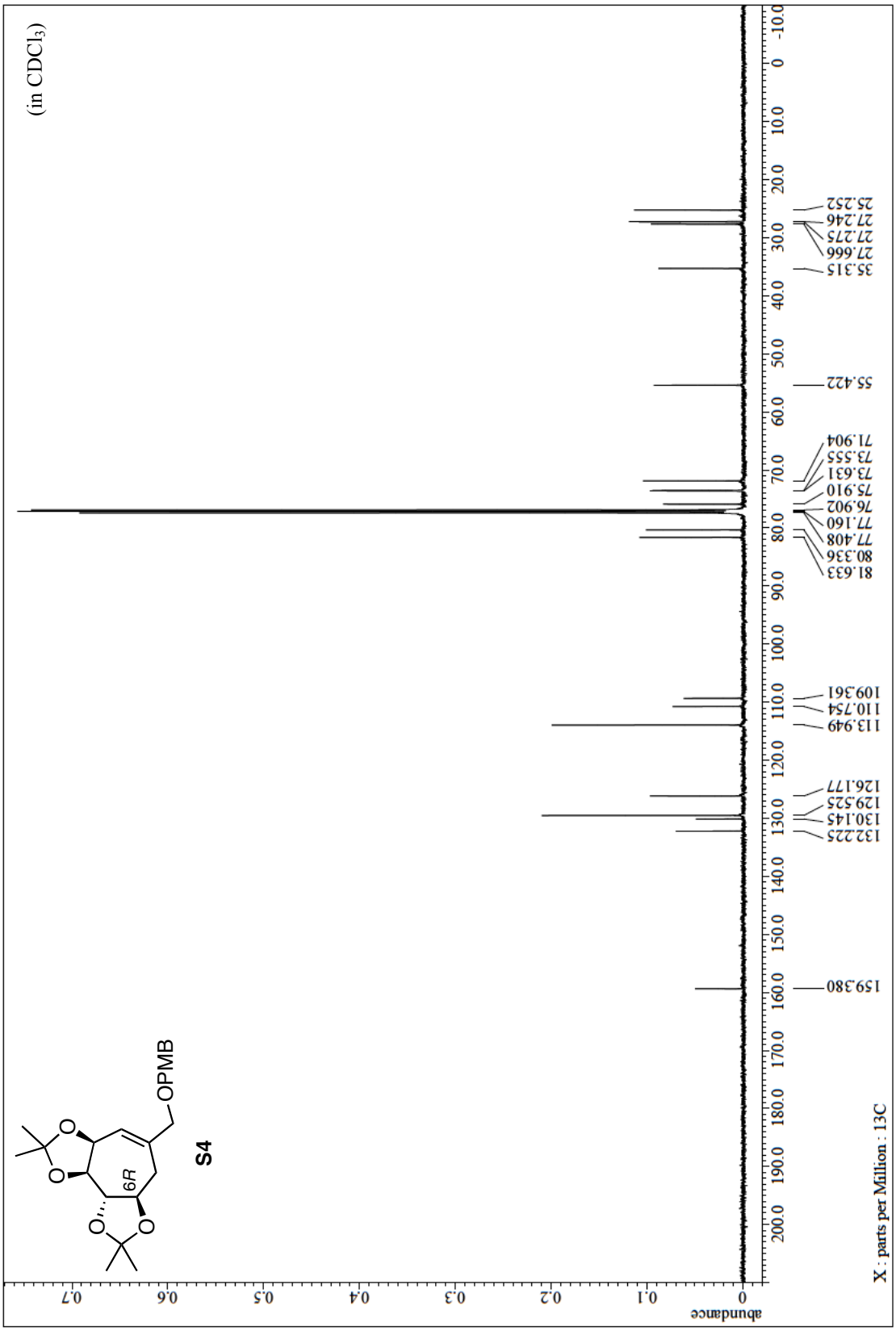

(in $CD_3OD$)
23
1.799
3.304
3.307
3.310
3.313
3.317
4.894
7.737
7.740
7.892
7.895
X : parts per Million : 1H
abundance


(in $CD_3OD$)
23
abundance
X : parts per Million : 13C
26.041
48.485
48.657
48.828
49.000
49.172
49.343
49.506
115.358
116.188
120.709
134.502
150.307
154.561
163.584
166.751
168.325


(in $CDCl_3$)
OPMB
6S
S3
abundance
X : parts per Million : 1H


(in $CDCl_3$)
OPMB
6S
S3
159.399
133.074
130.117
129.449
125.815
113.968
109.285
107.778
78.343
77.418
77.160
76.912
74.508
73.927
73.545
72.248
55.422
29.096
28.276
27.771
25.291
24.699
abundance
X : parts per Million : 13C


(in $CDCl_3$)
OPMB
6R
S4
abundance
X : parts per Million : 1H


(in CDCl3)
OPMB
6R
S4
159.380
132.225
130.145
129.525
126.177
113.949
110.754
109.361
81.633
80.336
77.408
77.160
76.902
75.910
73.631
73.555
71.904
55.422
35.315
27.666
27.275
27.246
25.252
X : parts per Million : 13C
abundance

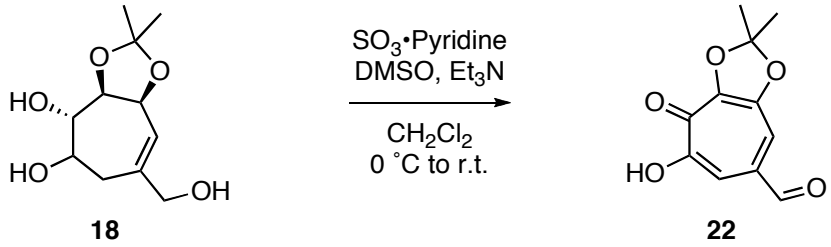
## 3-2. LC-UV analytical conditions and chromatograms

LC-UV analysis was carried out with LC-UV Agilent 1100 Series (Agilent Technology Inc.) under following conditions.

Column: Symmetry C18 (Waters Co. Ltd., 2.1 ϕ × 150 mm)
Mobile phase: 5-100% $CH_3CN$/0.05% $H_3PO_4$ (linear gradient over 20 min)
Flow rate: 0.2 mL/min
Detection: photodiode array (190-600 nm)
Column temperature: 40 ˚C

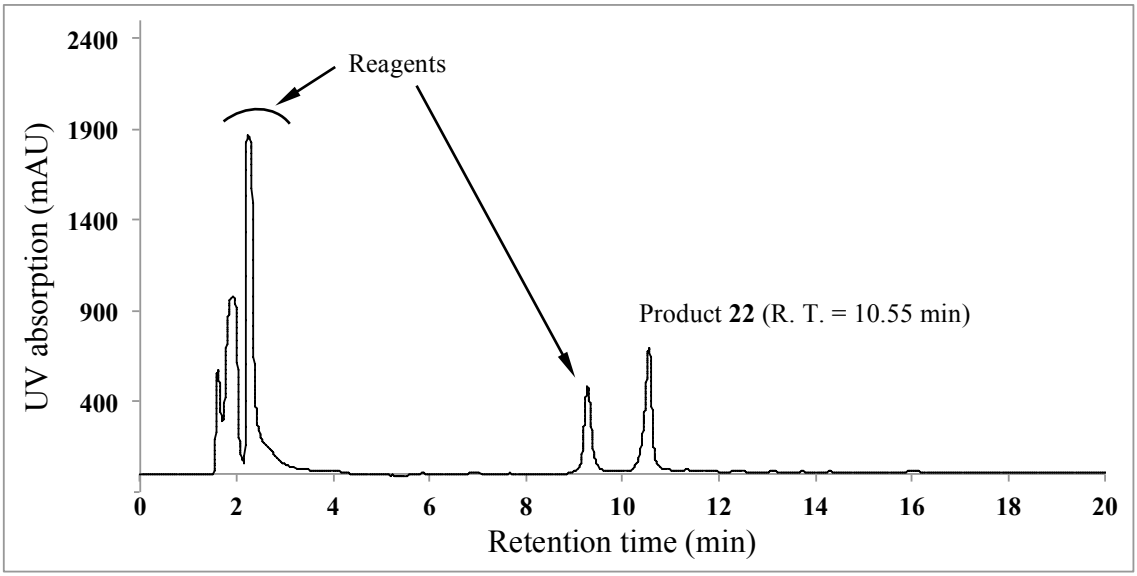
The reactions to form the tropolone skeleton were monitored with LC-UV analysis. Its chromatograms and UV spectra are shown below (Retention Time: R. T.).

• Synthesis of aldehyde **22** (Parikh-Doering oxidation)

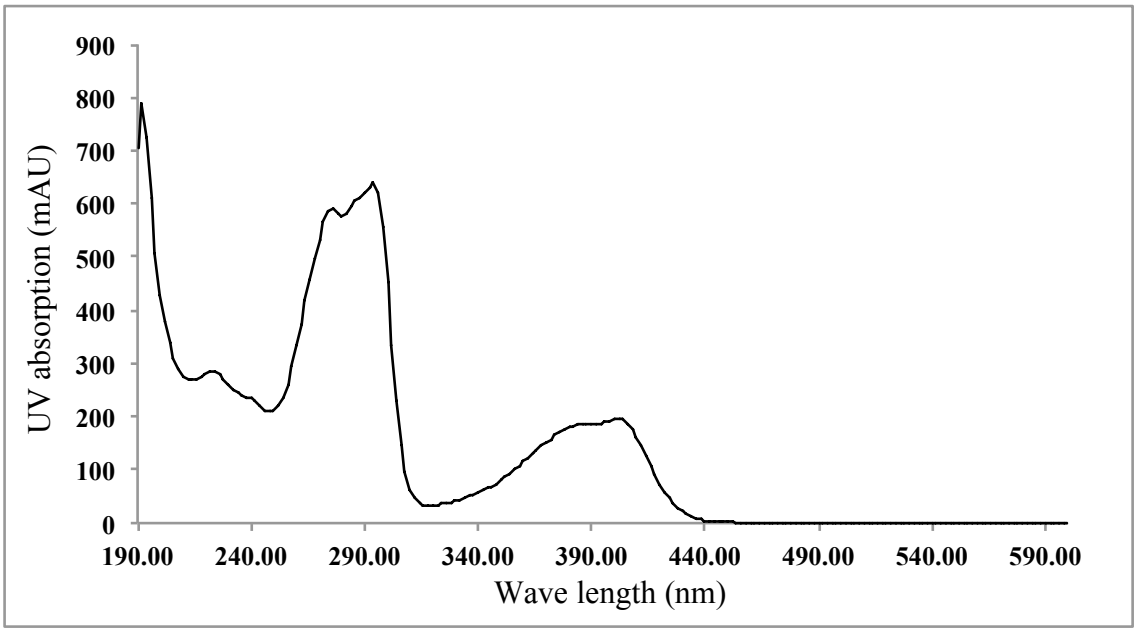



**18** **22**

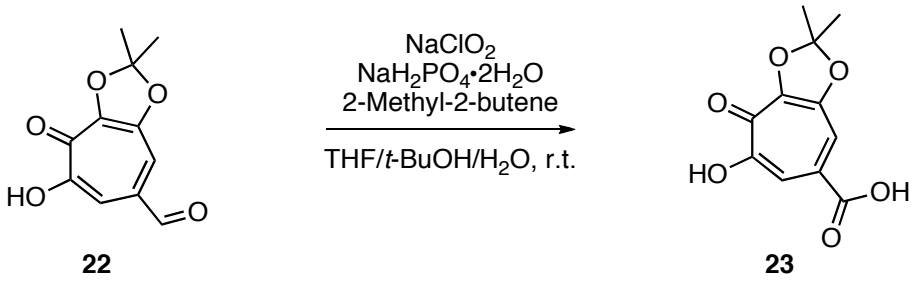
LC-UV chart (210 nm)



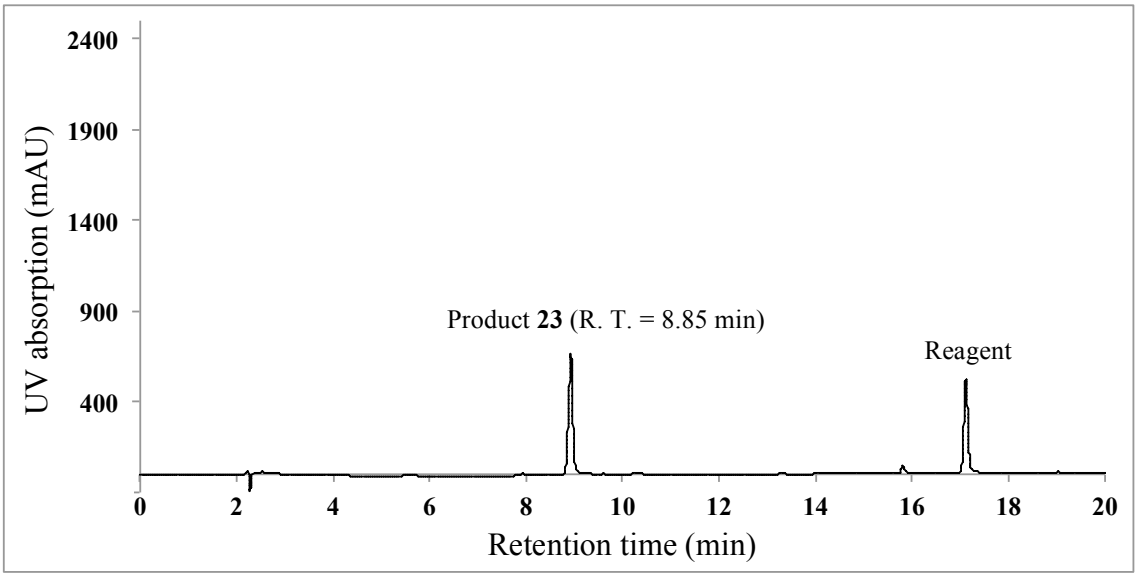

UV spectrum (R. T. = 10.55 min)



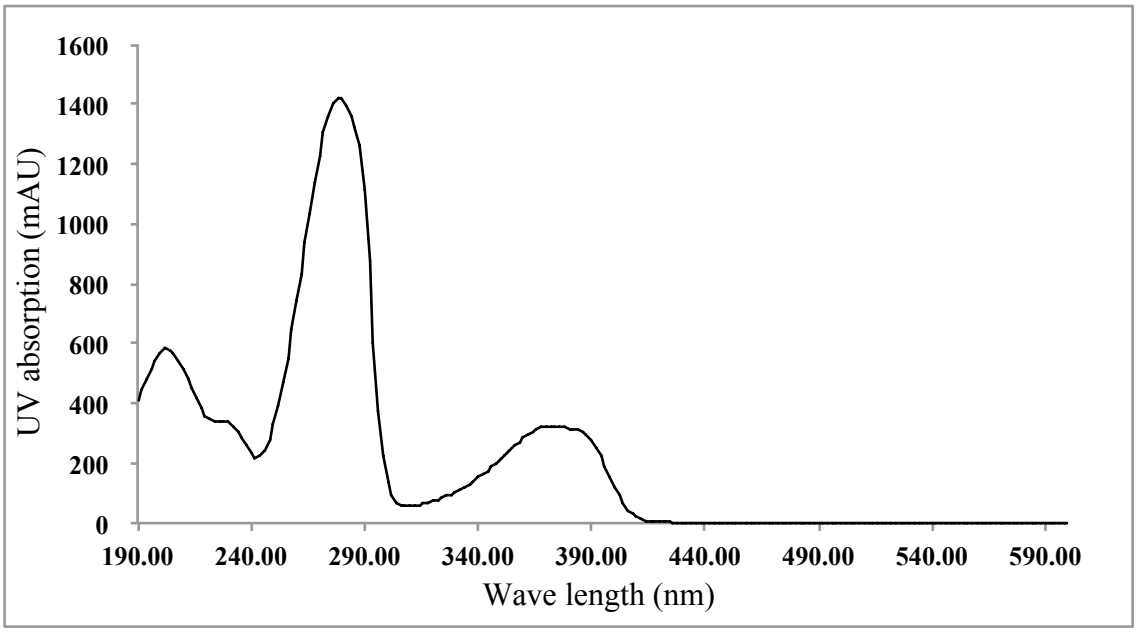
• Synthesis of carboxylic acid **23** (Pinnick oxidation)



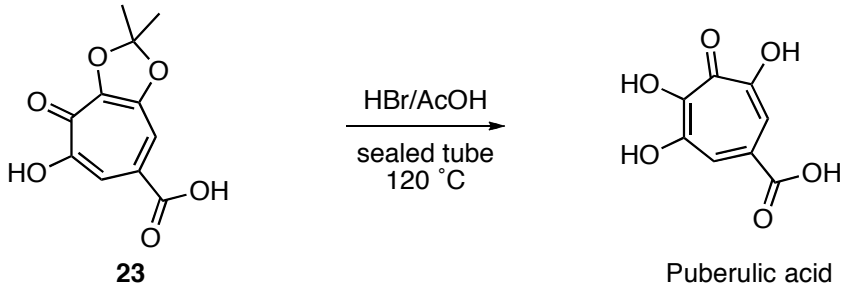

LC-UV chart (210 nm) over 2 steps




UV spectrum (R. T. = 8.85 min)

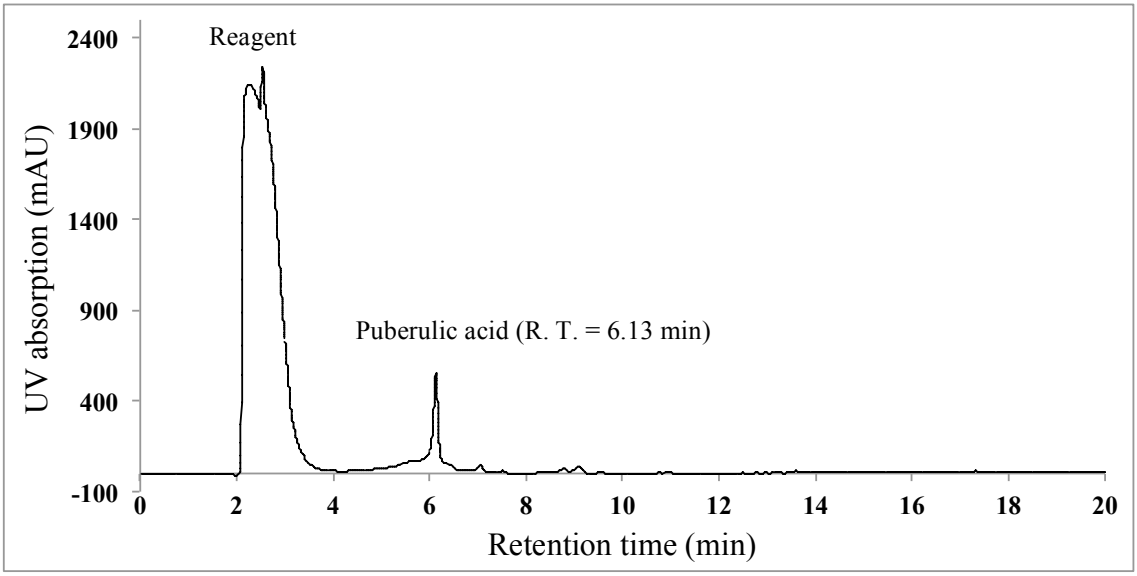


• Synthesis of Puberulic acid

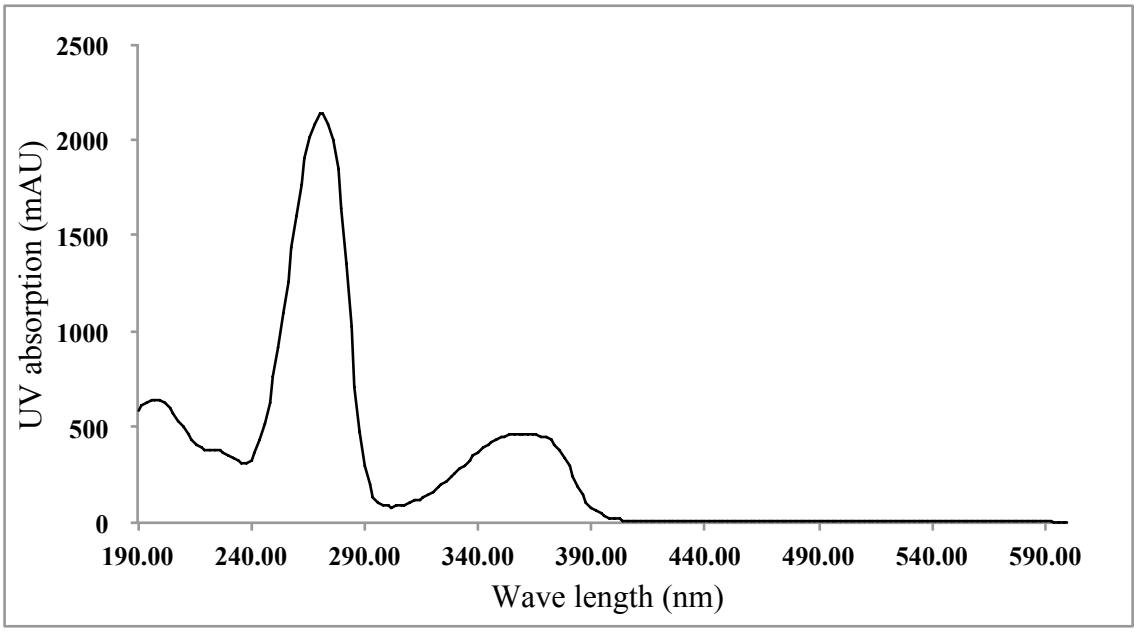



**23** Puberulic acid

LC-UV chart (210 nm) over 3 steps




UV spectrum (R. T. = 6.13 min)



## 4. Refferences


1) Z. Yu, L. Ya-Peng and Z. Li, *J. Carbohydr. Chem.*, 2008, **27**, 113.
2) Z. Kałuża, A. Kazimierski, K. Lewandowski, K. Suwińska, B. Szczęsna and M. Chmielewski, *Tetrahedron*, 2003, **59**, 5893.
3) M. G. Banwell, M. P. Collis, M. F. Mackay and S. L. Richards, *J. Chem. Soc. Perkin Trans. 1*, 1993, 1913.