Total Synthesis of Vinigrol

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SUPPORTING INFORMATION

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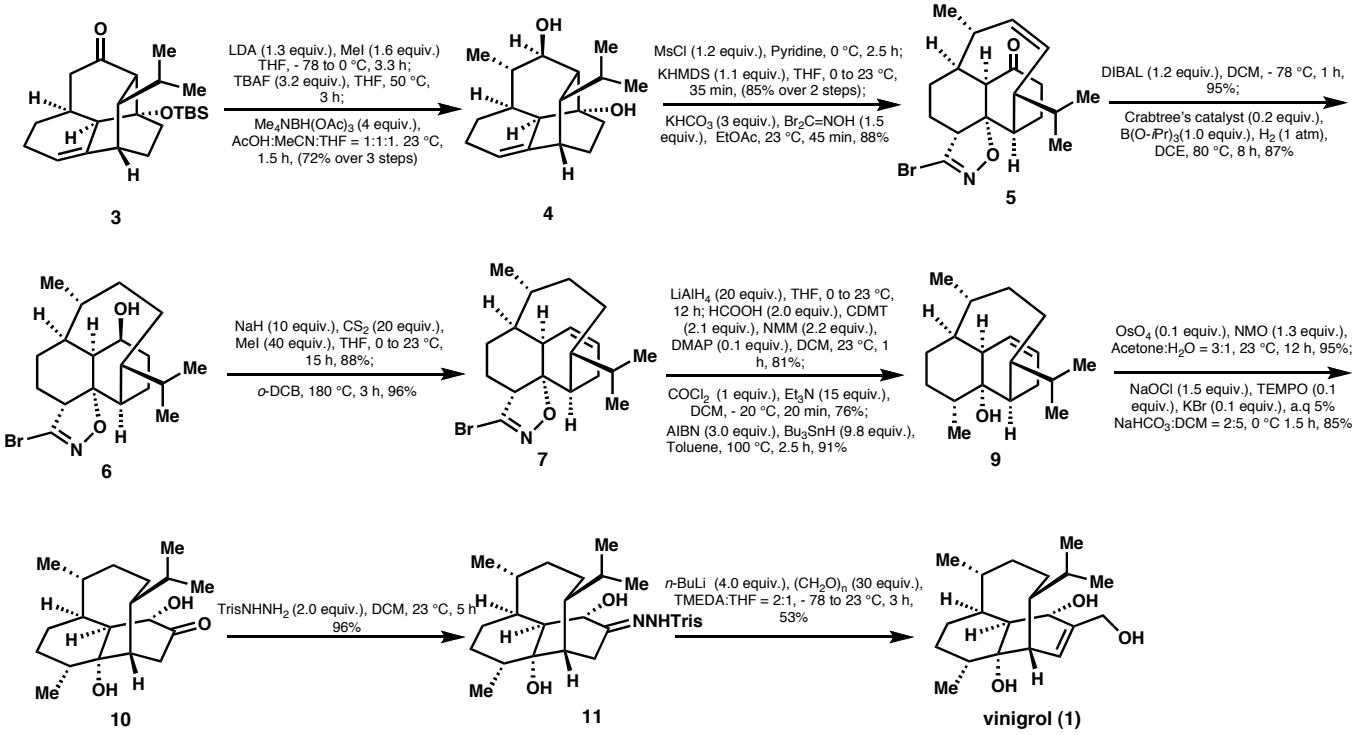
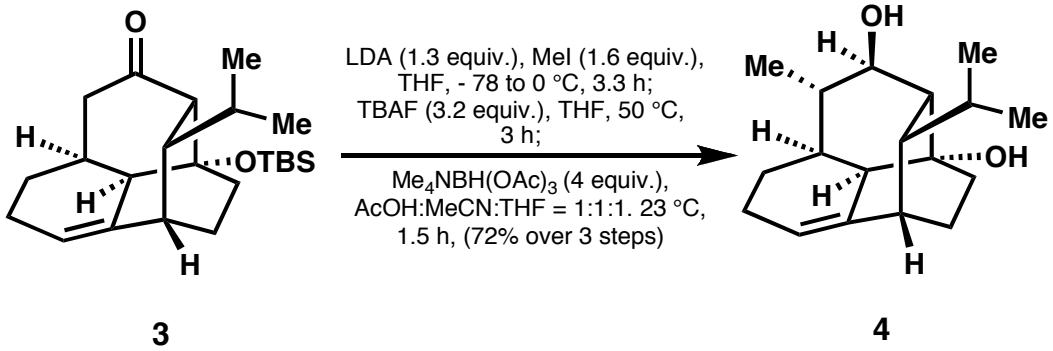
General procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH_2Cl_2), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), *N,N*-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.

Scheme S1. Total Synthesis of Vinigrol (1)



Experimental

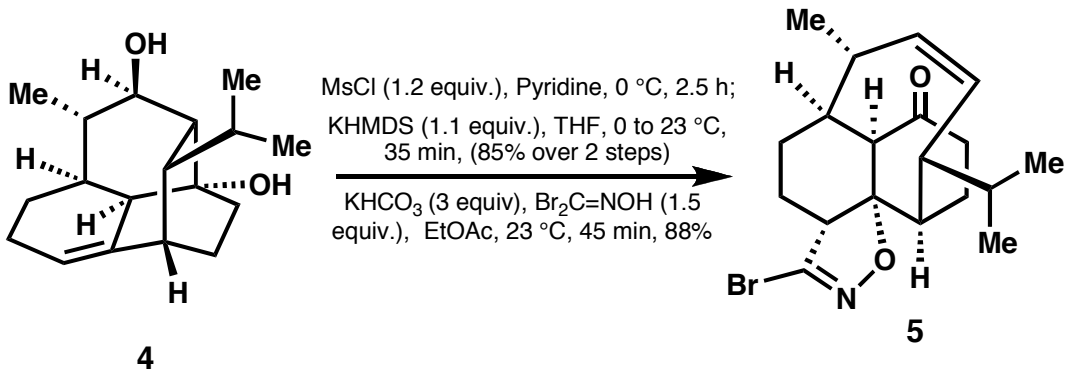


Compound 4: *i.* To a flame dried flask was added compound **3** (5.85 g, 15.6 mmol, 1 equiv.) and THF (150 mL) under Argon. The solution was cooled to –78 °C and LDA (1.0 M in THF, 20.0 mL, 20.0 mmol, 1.3 equiv.) was added dropwise over 10 minutes. The mixture was stirred for 15 minutes at –78 °C, warmed to 0 °C and stirred for 10 minutes, then cooled back to –78 °C and stirred for 5 minutes. MeI (1.6 mL, 25.6 mmol, 1.6 equiv.) was added dropwise at –78 °C and the solution stirred for 30 minutes at

–78 °C. The mixture was then slowly warmed to 0 °C and stirring continued for 2.5 hours at this temperature. The reaction was partitioned between saturated aqueous NH_4Cl (250 mL) and Et_2O (200 mL) and the aqueous layer extracted with Et_2O (200 mL, 2X). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$), and the volatiles removed *in vacuo* to yield the crude α-methyl ketone (6.1 g) as a single diastereomer.

ii. The aforementioned crude α-methyl ketone (6.1 g, 15.7 mmol, 1 equiv.) was dissolved in THF (125 mL) and TBAF (1.0 M solution in THF, 25 mL, 25 mmol, 1.6 equiv.) was added. The mixture was heated at 50 °C for 1 hour at which point additional TBAF (25 mL) was added, and heating continued for 2 hours. Upon cooling, the reaction mixture was partitioned between saturated aqueous NH_4Cl (150 mL) and Et_2O (150 mL) and the aqueous layer extracted with Et_2O (150 mL, 3X). The combined organic layers were washed with 1N HCl (500 mL), water (500 mL), brine (500 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a yellow solid which was re-dissolved in AcOH:MeCN:THF (1:1:1 v/v/v, 150 mL). $Me_4NBH(OAc)_3$ (16.5 g, 62.7 mmol, 4 equiv.) was added portion-wise to the rapidly stirring solution. The reaction mixture was stirred for 1.5 hours then carefully poured into saturated aqueous $NaHCO_3$ (250 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (200 mL, 3X) and the combined organic layers carefully washed with saturated aqueous $NaHCO_3$ (250 mL, 5X), brine (250 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (gradient from 2:1 to 1:1 hexanes:Et_2O) to afford compound **4** (3.1 g, 72% over 3 steps) as a white solid; m.p.: 165 °C (Et_2O); TLC (Et_2O:hexanes, 5:1 v/v): R_f = 0.13; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.28 (dd, J = 4.5, 2.5 Hz, 1 H), 3.79 (dd, J = 10.4, 5.0 Hz, 1 H), 2.20 (s, 1 H), 2.15 – 2.10 (m, 1 H), 2.03 – 1.97 (m, 2 H), 1.86 – 1.77 (m, 3 H), 1.72 – 1.71 (m, 1 H), 1.67 – 1.58 (m, 5 H), 1.45 – 1.36 (m, 2 H), 1.15 – 1.13 (m, 2 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.93 (J = 6.5 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5, 117.0, 74.3, 73.1, 50.3, 46.7, 45.1, 36.3, 34.8,

34.7, 32.6, 32.1, 23.8, 21.9, 21.9, 21.5, 20.5, 15.3; IR (film) ν_{max} 3371, 2929, 1638, 1469, 1368, 1326, 1227, 1034, 988 cm^{-1}. HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{18}H_{28}O_2Na$, 299. 1981; found, 299.1969.

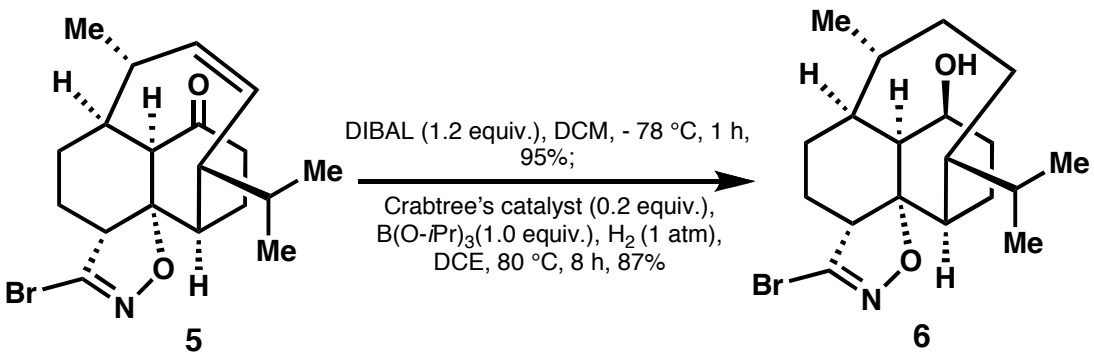


Compound 5: *i*. Diol **4** (3.1 g, 11.2 mmol, 1 equiv.) was dissolved in anhydrous pyridine (100 mL) and cooled to 0 °C. MsCl (1.05 mL, 13.6 mmol, 1.2 equiv.) was added dropwise to the solution at 0 °C, and stirring was continued for 2.5 hours at this temperature. The reaction was partitioned between 1N HCl (150 mL) and Et_2O (150 mL). The aqueous layer extracted with Et_2O (100 mL, 3X). The combined organic layers were washed with 1N HCl (500 mL, 4X), water (500 mL), brine (500 mL), and dried ($MgSO_4$). Volatiles were removed *in vacuo* to yield the crude mesylate

ii. The aforementioned crude mesylate (4.8 g, 13.5 mmol, 1 equiv.) was azeotropically dried with benzene and the residual solvent removed under high vacuum. Dry THF (110 mL) was added and the reaction cooled to 0 °C under an atmosphere of argon. KHMDS (0.5 M solution in THF, 30 mL, 15 mmol, 1.1 equiv.) was added dropwise over 15 minutes to the solution at 0°C. The reaction mixture was stirred at 0 °C for 20 minutes, then warmed to room temperature and quenched (while under argon) by the dropwise addition of AcOH (10 mL). The reaction mixture was partitioned between saturated aqueous NH_4Cl (100 mL) and Et_2O (100 mL) and the aqueous layer extracted with Et_2O (100 mL, 3X). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (250 mL, 3X), water (250 mL), brine (250 mL), and dried ($MgSO_4$). Volatiles were removed *in vacuo* and the crude material

purified by silica gel flash chromatography (gradient from 10:1 → 5:1 hexanes:Et_2O) to afford the Grob product (2.5 g, 85% over 2 steps) as a colorless oil.

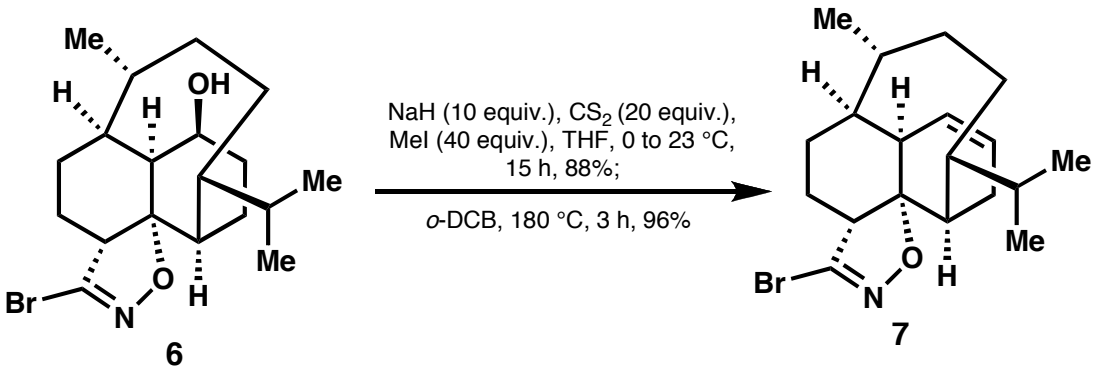
iii. The aforementioned Grob product (3.03 g, 11.7 mmol, 1 equiv.) was dissolved in EtOAc (100 mL) and $KHCO_3$ (3.5 g, 35 mmol, 3 equiv.) was added in one portion. To the rapidly stirring mixture was added dibromoformaldoxime (3.6 g, 17.6 mmol, 1.5 equiv.). Stirring continued until TLC analysis indicated complete consumption of starting material [Note: sometimes additional portions of $KHCO_3$ and dibromoformaldoxime are required to drive the reaction to completion]. The reaction was partitioned between saturated aqueous NH_4Cl (150 mL) and DCM (100 mL) and the aqueous layer extracted with DCM (100 mL, 2X). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), and the volatiles removed *in vacuo*. The crude material was purified by silica gel flash chromatography (gradient from 20:1 → 10:1 → 5:1 hexanes:Et_2O) to afford bromoisoxazole **5** (3.9 g, 88%) as a white crystalline solid; m.p.: 115°C (Et_2O); TLC (Et_2O:hexanes, 5:1 v/v): R_f = 0.54; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.31 – 5.23 (m, 2 H), 3.2 (dd, *J* = 6.4, 3.6 Hz, 1 H), 2.67 – 2.63 (m, 1 H), 2.58 – 2.52 (m, 1 H), 2.50 – 2.42 (m, 1 H), 2.40 – 2.33 (m, 2 H), 2.31 – 2.18 (m, 3 H), 2.09 – 2.01 (m, 2 H), 2.09 – 1.81 (m, 1 H), 1.76 – 1.72 (m, 1 H), 1.67 – 1.62 (m, 1 H), 1.55 – 1.51 (m, 1 H), 1.07 (d, *J* = 6.4 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.6, 145.3, 141.9, 131.2, 92.0, 53.8, 53.7, 44.0, 43.5, 42.0, 36.3, 32.7, 30.2, 24.6, 21.5, 21.4, 21.0, 20.6, 18.1; IR (film) ν_{max} 2957, 1698, 1460, 1387, 1327, 1262, 1093, 840, 817 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{19}H_{27}BrNO_2$, 380. 1220; found, 380.1223.



Compound 6: *i.* Bromoisoxazole **5** (1.0 g, 2.6 mmol, 1 equiv.) was dissolved in DCM (20 mL) and cooled to –78 °C. DIBAL (1.2 M solution in toluene, 2.6 mL, 3.1 mmol, 1.2 equiv.) was added dropwise to the cooled solution and the reaction mixture stirred for 1 hour at –78 °C. EtOAc (25 mL) and saturated aqueous Rochelle's salt solution (50 mL) were added and the mixture warmed to room temperature and vigorously stirred for 8 hours. The reaction mixture was partitioned and the aqueous layer extracted with EtOAc (25 mL, 3X). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude material was purified by silica gel flash chromatography (2:1 hexanes:Et_2O) to afford the corresponding alcohol (955 mg, 95%) as white foam.

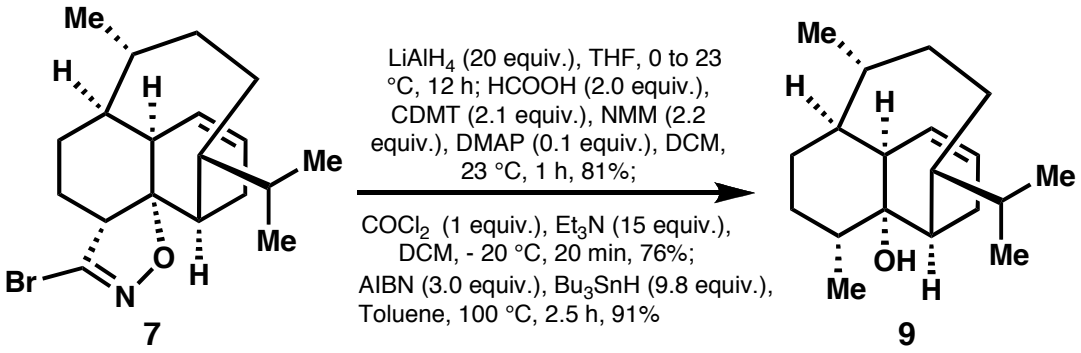
ii. To a flame dried flask was added the aforementioned alcohol (2.7 g, 7.03 mmol, 1 equiv.) followed by Crabtree's catalyst (1.13 g, 1.43 mmol, 0.2 equiv.) and the flask was evacuated, then backfilled with argon. Degassed DCE (140 mL) was added followed by B(O-*i*Pr)$_3$ (1.7 mL, 7.03 mmol, 1.0 equiv.). Hydrogen was bubbled through the solution for 10 minutes, then the flask was placed in an 80 °C oil bath and heated under an atmosphere of H_2 (non-bubbling) for 8 hours. Upon cooling, the reaction was partitioned between 1N HCl (25 mL) and DCM (25 mL), and the aqueous layer extracted with DCM (20 mL, 3X). The combined organic layers were washed with 1N HCl (50 mL, 3X), brine (50 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (3:1 hexanes: Et_2O) to afford title compound **55** (2.3 g, 87%) as a white foam; TLC (Et_2O:hexanes, 1:1 v/v): $R_f = 0.38$; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (m, 1 H), 3.02 (t, $J = 4.7$ Hz, 1 H),

2.38 – 2.32 (m, 1 H), 2.11 – 2.07 (m, 1 H), 2.04 – 1.99 (m, 1 H), 1.95 – 1.94 (m, 1 H), 1.93 – 1.85 (m, 3 H), 1.81 – 1.77 (m, 1 H), 1.75 – 1.69 (m, 3 H), 1.64 – 1.59 (m, 1 H), 1.56 – 1.37 (m, 7 H), 0.99 (d, J = 6 .2 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 94.3, 67.2, 54.1, 45.7, 39.2, 39.0, 38.9, 37.4, 31.7, 30.5, 21.8, 28.7, 27.3, 25.8, 22.1, 21.4, 19.6; IR (film) ν_{max} 3443, 2952, 1459, 1362, 1289, 1063, 1033, 900, 753 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{19}H_{31}BrNO_2$, 384.1533; found, 384.1529.



Compound 7: *i.* To a flame dried flask was added NaH (60% dispersion in mineral oil, 1.28 g, 32mmol, 10 equiv.) and THF (25mL). The mixture was cooled to 0 °C and alcohol **6** (1.24 g, 3.2 mmol, 1 equiv.) in THF (7 mL) was added dropwise over 5 minutes. The reaction mixture was stirred for 5 minutes at 0°C, then warmed to room temperature and stirred for 1 hour. CS_2 (3.9 mL, 65 mmol, 20 equiv.) was added and stirring continued for 3 hours, followed by the addition of MeI (7.9 mL, 127 mmol, 40 equiv.) and an additional 12 hours of stirring. The reaction mixture was partitioned between 1N HCl (100 mL) and Et_2O (50 mL), and the aqueous layer extracted with Et_2O (50 mL, 3X). The combined organic layers were washed with 1N HCl (250 mL), brine (250 mL), and dried ($MgSO_4$). Volatiles were removed *in vacuo* in a well-ventilated fume hood [Caution: MeI may still be present] and the crude material purified by silica gel flash chromatography (5:1 hexanes:Et_2O) to afford the corresponding xanthate (1.35 g, 88%) as a yellow oil.

ii. The aforementioned xanthate (1.35 g, 2.84 mmol, 1 equiv.) was dissolved in degassed *o*-DCB (55 mL) under an atmosphere of argon. The mixture was heated to 180 °C for 3 hours. Upon cooling, the reaction mixture was passed through a short plug of silica gel, eluting with hexanes (to remove *o*-DCB), followed by 1:1 hexanes:Et_2O to afford title compound **7** (1.0 g, 96%) as a slightly yellow oil; TLC (Et_2O:hexanes, 1:1 v/v): R_f = 0.81; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 – 5.66 (m, 2 H), 3.03 (t, *J* = 4.7 Hz, 1 H), 2.52 – 2.48 (m, 1 H), 2.36 (s, 1 H), 2.16 – 2.04 (m, 5 H), 1.66 – 1.48 (m, 7 H), 1.41 – 1.34 (m, 1 H), 1.29 – 1.26 (m, 1 H), 1.00 – 0.96 (m, 6 H), 0.85 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 129.1, 124.8, 91.6, 54.0, 43.0, 41.6, 39.9, 39.0, 37.2, 32. 6, 30.9, 27.7, 26.1, 25.5, 25.4, 22.0, 21.5, 19.6; IR (film) ν_{max} 2953, 1575, 1462, 1386, 1367, 1099, 1059, 899, 864, 810, 740 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{19}H_{29}BrNO$, 366.1427; found, 366.1430.



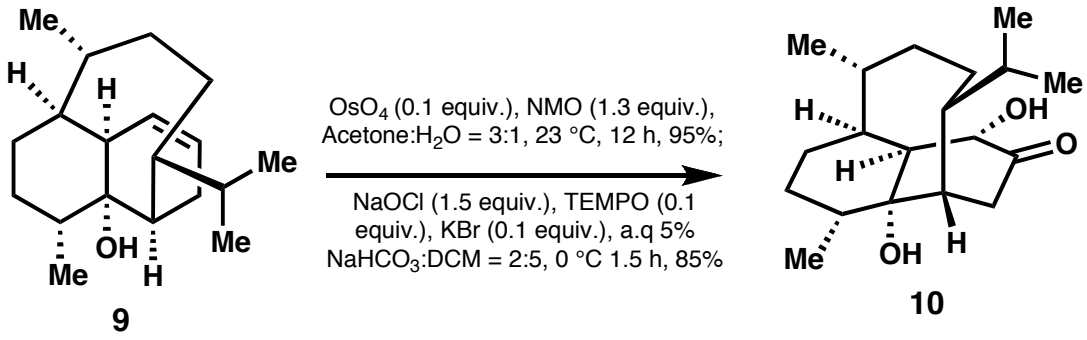
Compound 9: Olefin **7** (1.90 g, 4.96 mmol, 1 equiv.) was azeotropically dried with benzene and the residual solvent removed under high vacuum. THF (5 mL) was added and the solution cooled to 0 °C. $LiAlH_4$ (1.0 M solution in THF, 99.2 mL, 99.2 mmol, 20 equiv.) was added drop-wise at 0 °C over 15 minutes, and the mixture warmed to room temperature and stirred for 12 hours. The reaction mixture was cooled to 0 °C, the septum removed, and 1N HCl (10 mL) was added very slowly dropwise [Caution: gas evolution occurs]. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (75 mL) and

EtOAc (25 mL) and the aqueous layer thoroughly extracted with EtOAc (25 mL, 3X) and then DCM (25 mL, 3X). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the crude amine (1.44 g) as a yellow foam.

The aforementioned crude amine (1.99 g, 6.83 mmol, 1 equiv.) was dissolved in DCM (68 mL). To this solution was added formic acid (515 μl, 13.68 mmol, 2.0 equiv.), CDMT (2.52 g, 14.34 mmol, 2.1 equiv.), NMM (1.65 mL, 15.03 mmol, 2.2 equiv.) and DMAP (83 mg, 0.68 mmol, 0.1 equiv.) in that order. The mixture was stirred for 1 hour then partitioned between 1N HCl (25 mL) and DCM (15 mL). The aqueous layer was extracted with DCM (15 mL, 3X), and the combined organic layers washed with 1N HCl (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL), and dried (Na_2SO_4). Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (gradient from 1:1 → 2:1 EtOAc:Hexanes → pure EtOAc) to afford the corresponding formamide (1.81 g, 81% from bromoisoxazole **7**) as a white foam.

iii. The aforementioned formamide (1.20 g, 3.76 mmol, 1 equiv.) was dissolved in DCM (37.6 mL) and Et_3N (7.78 mL, 56.4 mmol, 15 equiv.) and cooled to – 20 °C. Phosgene (20 wt% solution in toluene, 1.84 mL, 3.76 mmol, 1 equiv.) was added very slowly dropwise over 5 minutes to the cooled solution. The reaction mixture was stirred for 20 minutes at –20 °C, then quenched at this temperature by the dropwise addition of saturated aqueous $NaHCO_3$ (25 mL). The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and DCM (50 mL), and the aqueous layer extracted with DCM (50 mL, 2X). The combined organic layers were washed with 1N HCl (50 mL, 2X), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$). Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et_2O) to afford isonitrile (0.86 g, 76%) as a colorless solid.

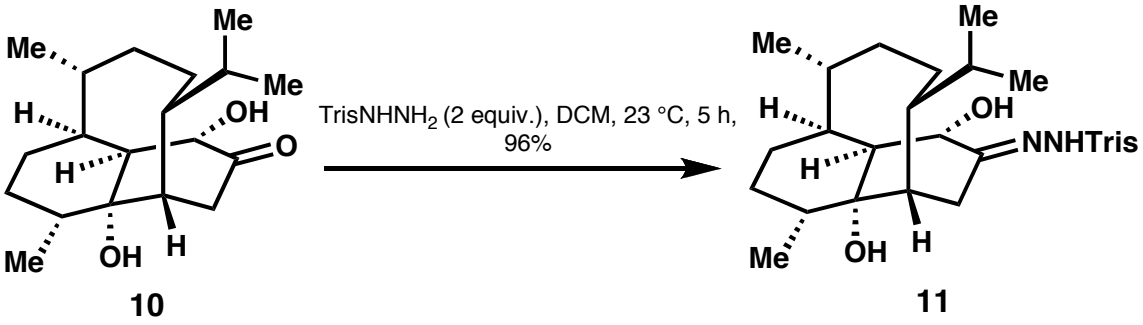
To a re-sealable vial was added isonitrile (1.03 g, 3.42 mmol, 1 equiv.) and AIBN (1.68 g, 10.3 mmol, 3.0 equiv.) and the flask was evacuated then back-filled with argon. Degassed toluene (68.4 mL) was added followed by Bu_3SnH (8.88 mL, 33.51 mmol, 9.8 equiv.). The sealed vial was placed into a 100 °C oil bath for 2.5 hours. After cooling, all volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (gradient from 10:1 → 5:1 hexanes:Et_2O) to afford the corresponding olefin **9** (858 mg, 91%) as a colorless oil: TLC (pure CH_2Cl_2): R_f = 0.57; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.66 (s, 2 H), 2.38 – 2.33 (m, 1 H), 2.18 (bs, 1 H), 2.08 – 2.03 (m, 2 H), 1.97 – 1.92 (m, 2 H), 1.73 – 1.66 (m, 1 H), 1.57 – 1.49 (m, 4 H), 1.45 –1.29 (m, 7 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.6, 1.5 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.9, 123.7, 75.3, 45.7, 42.0, 40.6, 37.3, 37.0, 35.8, 32.2, 31.6, 29.2, 25.8, 25.6, 24.0, 23.7, 22.2, 21.3, 20.7, 13.9; IR (film) ν_{max} 3467, 2953, 1456, 1372, 1055, 1033, 1012, 958, 759 cm^{-1}; HRMS (*m*/*z*): [M+Na]$^+$ calcd. for $C_{19}H_{32}NaO$, 299.2345; found, 299.2349.



Compound 10: Olefin **9** (59 mg, 0.21 mmol, 1 equiv.) was dissolved in Acetone:H_2O = 3:1 (4 mL), OsO_4 (218 μL, 0.02 mmol, 0.1 equiv.) and NMO (32 mg, 0.27 mmol, 1.3 equiv.) were added. The reaction mixture was stirred for 12 hours at room temperature and then quenched at this temperature by the dropwise addition of saturated aqueous $NaHCO_3$ (25 mL). The reaction mixture was partitioned between

saturated aqueous $Na_2S_2O_3$ (10 mL) and DCM (15 mL), and the aqueous layer extracted with DCM (10 mL, 2X). The combined organic layers were washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et_2O) to afford triol (61 mg, 95%) as a colorless solid.

The aforementioned triol (45 mg, 0.145 mmol, 1 equiv.) was dissolved in DCM (5 mL) followed by the addition of 5% aqueous $NaHCO_3$ (2.0 mL), KBr (1.7 mg, 0.014 mmol, 0.10 equiv.) and TEMPO (2.2 mg, 0.014, 0.10 equiv.). The biphasic mixture was cooled to 0 °C and bleach (commercial bleach solution, 6% NaOCl, 0.27 mL, 0.22 mmol, 1.5 equiv.) was added dropwise to the rapidly stirring mixture. The reaction mixture was stirred for 1.5 hours at 0 °C and then partitioned between saturated aqueous $Na_2S_2O_3$ (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (10 mL, 2X) and the combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et_2O) to afford to yield ketone **10** (37 mg, 85%) as a white foam: TLC (EtOAc:hexanes, 1:1 v/v): R_f = 0.5; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.35 (d, J = 3.9 Hz, 1 H), 3.86 (bs, 1 H), 2.75 (dd, J = 17.7, 9.8 Hz, 1 H), 2.44 (d, J = 9.6 Hz, 1 H), 2.22 (d, J = 17.8 Hz, 1 H), 2.15 (bs, 1 H), 1.96 (s, 2 H), 1.73 – 1.66 (m, 4 H), 1.67 – 1.60 (m, 2 H), 1.57 – 1.41 (m, 4 H), 1.45 –1.34 (m, 2 H), 1.00 (d, J = 4.3 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.9, 76.6, 73.4, 58.6, 42.4, 40.5, 38.7, 37.5, 36.1, 35.4, 31.6, 31.5, 29.0, 25.5, 24.7, 24.0, 21.5, 20.4, 14.2; IR (film) ν_{max} 3438, 2955, 1711, 1465, 1374, 1235, 1099, 941 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{19}H_{32}NaO_3$, 331.2244; found, 331.2245.



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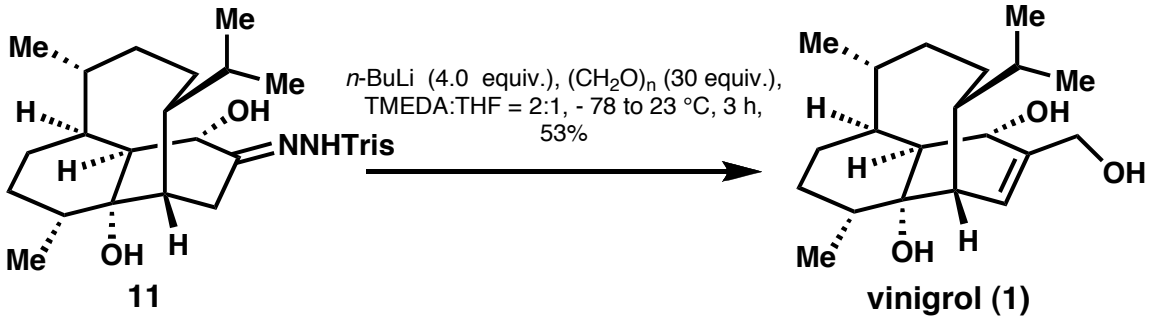
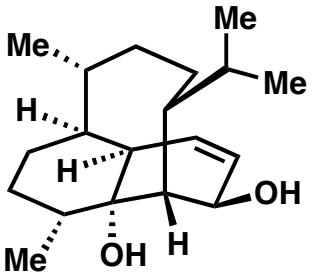
Compound 11: Ketone **10** (35 mg, 0.11 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (1 mL) and 2,4,6-Triisopropylbenzenesulfonyl hydrazide (68 mg, 0.22 mmol, 2 equiv.) was added. The reaction mixture was stirred for 5 hours at room temperature. Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography (1:1 hexanes:Et_2O) to afford hydrazone **11** as inseperable mixture of Z - and E - isomers (32 mg, 96%) as a white foam: TLC (EtOAc:hexanes, 1:1 v/v): $R_f = 0.7$; Both Z and E isomers of **11** are observed, here reported the major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (brs, 1 H), 7.15 (s, 2 H), 4.34 (brs, 1 H), 4.27 (brs, 2 H), 2.91 – 2.76 (m, 1 H), 2.39 – 2.32 (m, 1 H), 2.10 – 1.88 (m, 4 H), 1.61 – 1.45 (m, 4 H), 1.45 – 1.34 (m, 7 H), 1.27 –1.22 (m, 21 H), 0.93 – 0.88 (m, 12 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.2, 153.3, 151.5, 131.0, 123.7, 71.2, 55.4, 40.2, 39.9, 37.1, 35.3, 29.9, 29.7, 28.9, 25.5, 24.8, 24.0, 23.6, 23.1, 21.7, 20.6, 14.3; IR (film) ν_{max} 3484, 3173, 2957, 2871, 1600, 1462, 1426, 1383, 1320, 1164, 1153, 1037, 940, 882, 732 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{34}H_{56}N_2O_4S$, 589.4033; found, 589.4037.

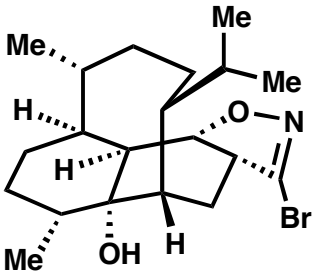


Compound 1: To a flame dried tube was added hydrazone **11** (25.0 mg, 0.043 mmol, 1.0 equiv.) and THF:TMEDA = 1:2 (2.1 mL) under Argon. The solution was cooled to –78 °C and *n*-BuLi (2.49 M in Hexanes, 72 μL, 0.17 mmol, 4.0 equiv.) was added dropwise. The mixture was stirred for 1 hour at –78 °C, warmed to 0 °C and stirred for 20 minutes, then room temperature and stirred for 10 minutes, finally cooled back to 0 °C and stirred for 5 minutes. Paraformaldehyde (39 mg, 1.29 mmol, 30 equiv., in 0.1 mL THF) was added dropwise at 0 °C and the solution stirred for 5 minutes at 0 °C. The mixture was then slowly warmed to room temperature and stirring continued for 20 minutes at this temperature. The reaction was partitioned between saturated aqueous NH_4Cl (5 mL) and DCM (5 mL) and the aqueous layer extracted with DCM (5 mL, 2X). The combined organic layers were washed with 1 N HCl (10 mL, 2X), brine (10 mL), dried ($MgSO_4$), and the volatiles removed *in vacuo*. The crude material was purified by PTLC (pure Et_2O) to afford vinigrol **1** (7.5 mg, 53%) as a colorless film: TLC (pure Et_2O): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 (d, *J* = 5.5 Hz, 1 H), 4.30 (AB q, *J* = 12.0 Hz, 2 H), 4.20 (s, 1 H), 3.40 (bs, 1 H), 2.65 (bs, 1 H), 2.30 (d, *J* = 5.4 Hz, 1 H), 2.25 (d, *J* = 3.7 Hz, 1 H), 2.15 – 2.09 (m, 1 H), 1.99 – 1.93 (m, 2 H), 1.80 – 1.70 (m, 5 H), 1.65 – 1.50 (m, 4 H), 1.40 – 1.05 (m, 6 H), 1.00 – 0.95 (m, 9 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 128.4, 75.5, 72.8, 67.9, 51.1, 45.5, 44.2, 40.2, 35.8, 34.5, 33.0, 29.6, 28.9, 28.6, 27.2, 24.8, 21.5, 20.5, 15.3; IR (film) ν_{max} 3393, 2955, 2928, 2851, 1469, 1385, 1262, 1138, 1109, 966, 904 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{20}H_{34}NaO_3$, 345.2400; found, 345.2407.



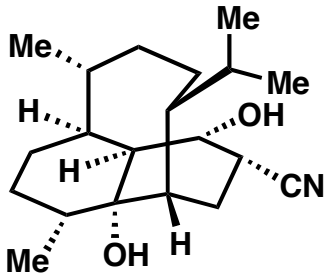
13

Compound 13: white solid: m.p. = 160 °C (Et_2O); TLC (Et_2O:hexanes, 2:1 v/v): R_f = 0.18; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.66 (m, 2 H), 4.91 (s, 1 H), 2.45 (d, J = 6.4 Hz, 1 H), 2.10 (m, 2 H), 1.94 – 1.89 (m, 1 H), 1.75 – 1.70 (m, 2 H), 1.56 – 1.51 (m, 1 H), 1.48 – 1.35 (m, 5 H), 1.31 – 1.22 (m, 4 H), 1.11 – 1.09 (m, 1 H), 1.1 (d, J = 6.3 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.89 – 0.75 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.1, 129.1, 76.8, 69.4, 46.0, 42.6, 42.5, 36.7, 34.6, 32.6, 31.5, 30.5, 28.7, 26.6, 25.1, 24.3, 23.9, 23.3, 13.7; IR (film) ν_{max} = 3476, 3300, 2957, 1706, 1459, 1372, 1296, 1274, 1225, 1145, 1052, 1033, 935, 867, 761; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{19}H_{32}O_2Na$, 315.2294; found, 315.2292.



14

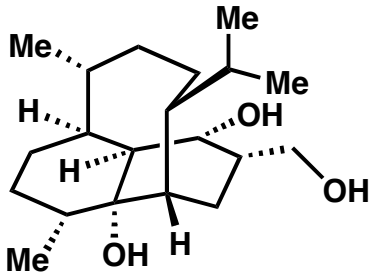
Compound 14: white solid: m.p.: 123–125°C (Et_2O); TLC (Et_2O:hexanes, 2:1 v/v): R_f = 0.73; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.79 (d, J = 8.8 Hz, 1 H), 3.15 (dd, J = 20.0, 9.0 Hz, 1 H), 2.26 (s, 1 H), 2.10 – 2.05 (m, 2 H), 2.02 – 1.97 (m, 2 H), 1.94 – 1.85 (m, 2 H), 1.70 – 1.52 (m, 4 H), 1.45 – 1.36 (m, 4 H), 1.34 – 1.27 (m, 2 H), 1.08 – 1.01 (m, 1 H), 0.98 – 0.91 (m, 6 H), 0.90 – 0.85 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.8, 87.4, 74.7, 47.4, 44.3, 44.2, 40.3, 37.6, 36.1, 35.1, 32.6, 30.7, 29.5, 27.8, 25.8, 24.5, 22.1, 21.5, 14.2; IR (film) ν_{max} 3574, 2957, 1573, 1456, 1374, 1264, 1238, 1096, 959, 870, 847, 724 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{20}H_{33}BrNO_2$, 398.1689; found, 398.1696.



15

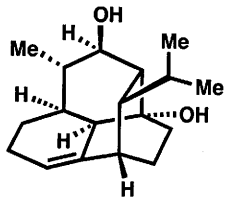
Compound 15: an oil which slowly solidified to white solid: TLC (Et_2O:hexanes, 2:1 v/v): R_f = 0.29; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.05 (d, J = 3.1 Hz, 1 H), 3.75 (bs, 1 H), 3.43 (m, 1 H), 2.41 (dt, J = 13.6, 6.2 Hz, 1 H),

2.27 (d, J = 4.9 Hz, 1 H), 2.13 – 2.10 (m, 1 H), 2.05 – 2.01 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.80 (bs, 1 H), 1.74 – 1.50 (m, 7 H), 1.45 – 1.40 (m, 1 H), 1.36 – 1.25 (m, 4 H), 1.02 – 0.91 (m, 9 H), 0.84 (d, J = 6.8 Hz, 3 H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 121.7, 76.9, 70.2, 49. 3, 42.6, 39.1, 37.3, 34.7, 32.5, 31.4, 31.2, 30.4, 25.9, 25.3, 23.5, 22.3, 21.5, 20.8, 13.2; IR (film) ν_{max} 3423, 2956, 2242, 1726, 1456, 1373, 1058, 952, 738 cm^{-1}; HRMS (*m*/*z*): [M+H]$^+$ calcd. for $C_{20}H_{34}NO_2$, 320.2584; found, 320.2589.



16

Compound 16: a white cystalline solid: m.p.: 164 –172 °C (EtOAc); TLC (pure Et_2O): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 (bs, 1 H), 4.07 (s, 1 H), 3.87 (dd, J = 12.0, 4.2 Hz, 1 H), 3.72 (dd, J = 12.1, 4.3 Hz, 1 H), 2.30 – 2.27 (m, 1 H), 2.17 – 2.16 (m, 1 H), 2.15 – 2.11 (m, 1 H), 2.09 – 2.04 (m, 2 H), 1.96 – 1.94 (m, 1 H), 1.67 – 1.42 (m, 8 H), 1.33 – 1.25 (m, 5 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.96 – 0.92 (m, 6 H), 0.84 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 77.7, 75.3, 67.0, 50.2, 40.2, 38.9, 36.3, 34.4, 32.7, 31.9, 30.9, 29.7, 29.4, 25.5, 22.7, 22.3, 21.6, 18.9, 14.1, 13.3; IR (film) ν_{max} 3366, 2955, 2927, 2872, 1459, 1375, 1260, 1160, 949, 907, 734 cm^{-1}; HRMS (*m*/*z*): [M+Na]$^+$ calcd. for $C_{20}H_{36}O_3Na$, 347.2556; found, 347.2554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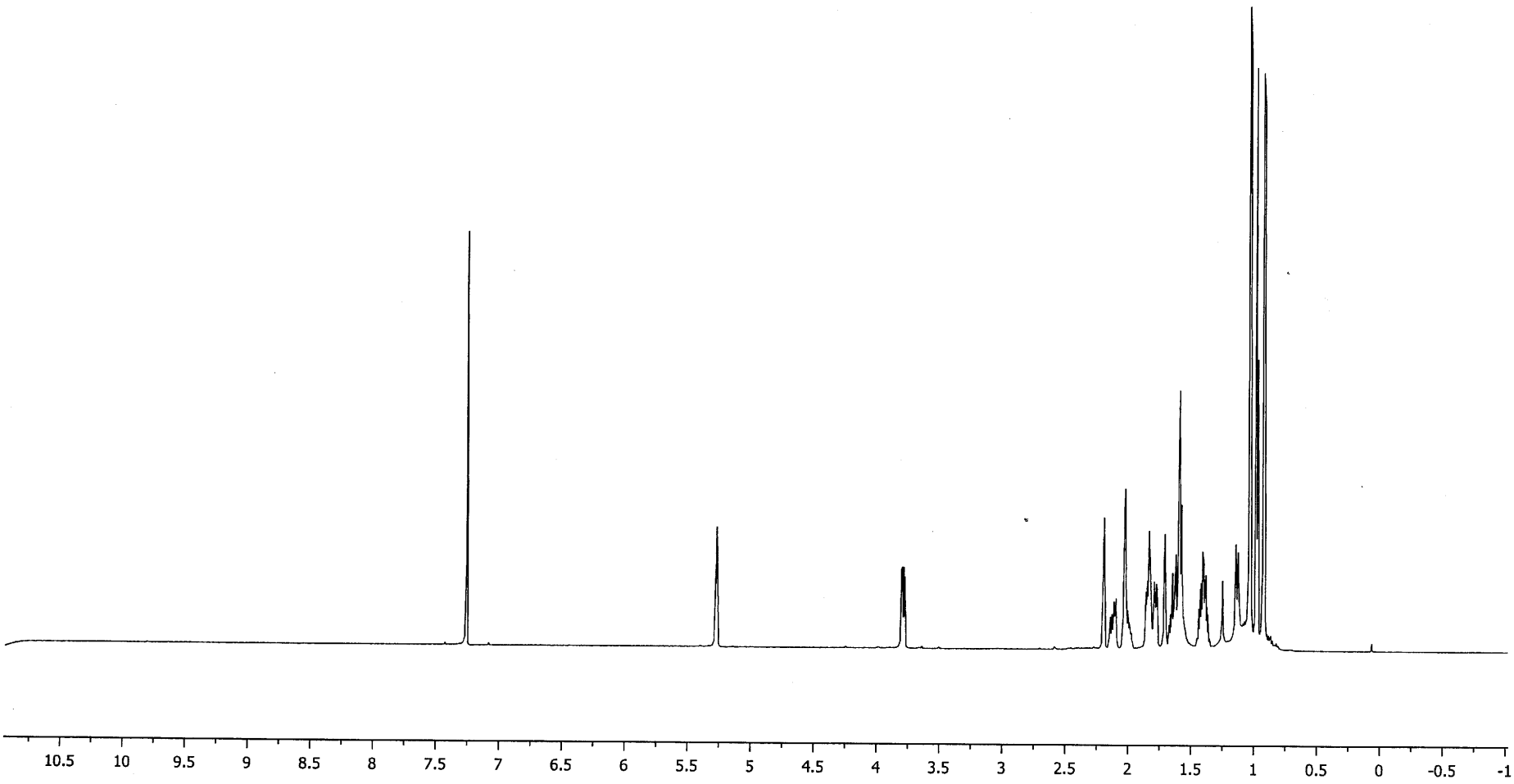
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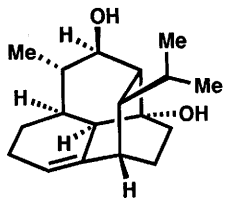
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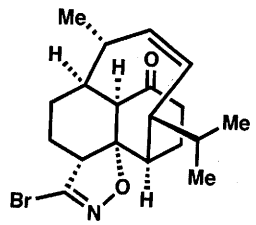
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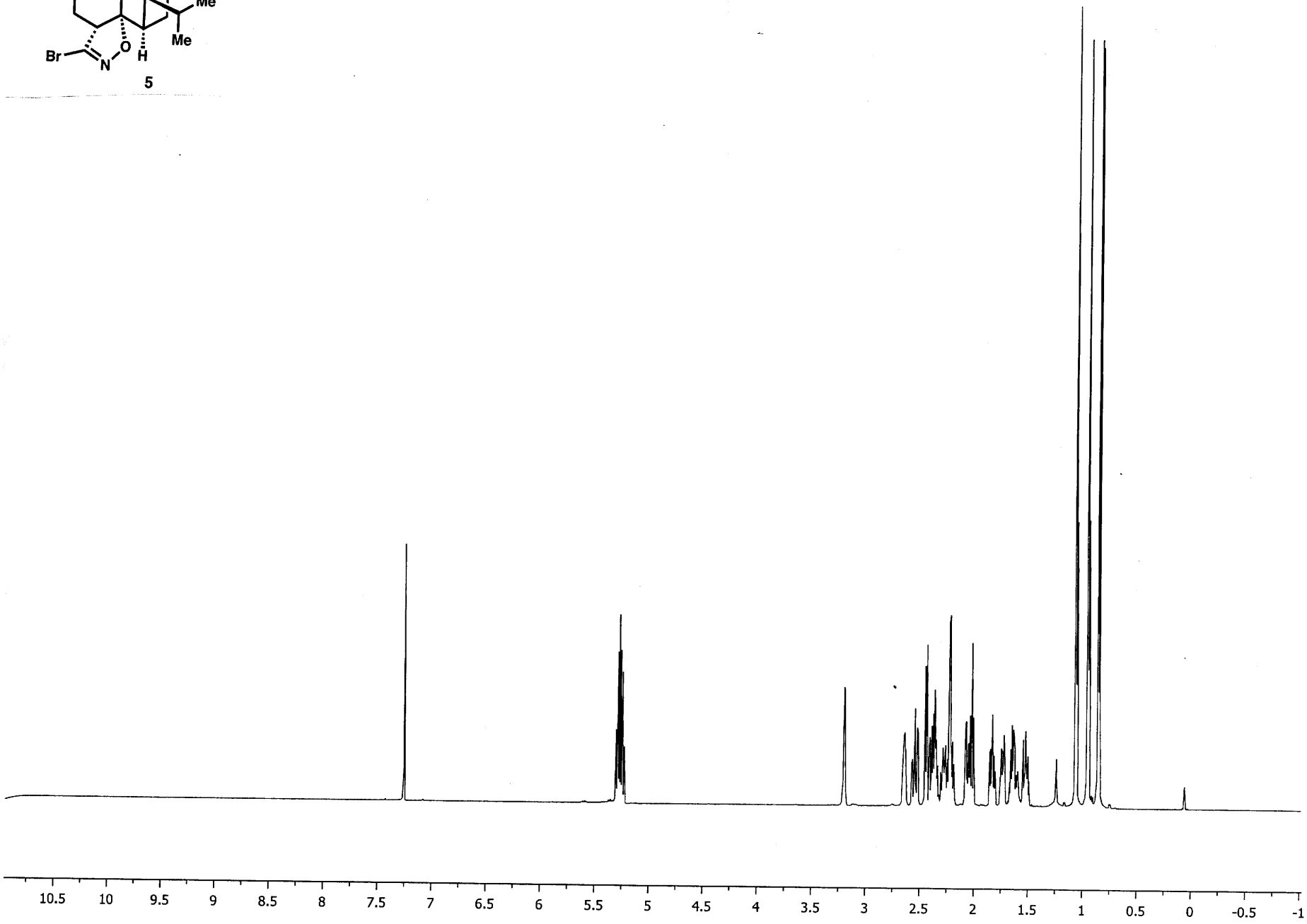
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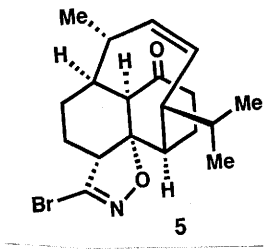
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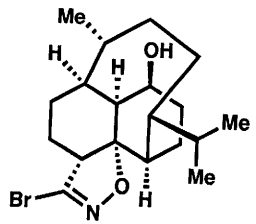
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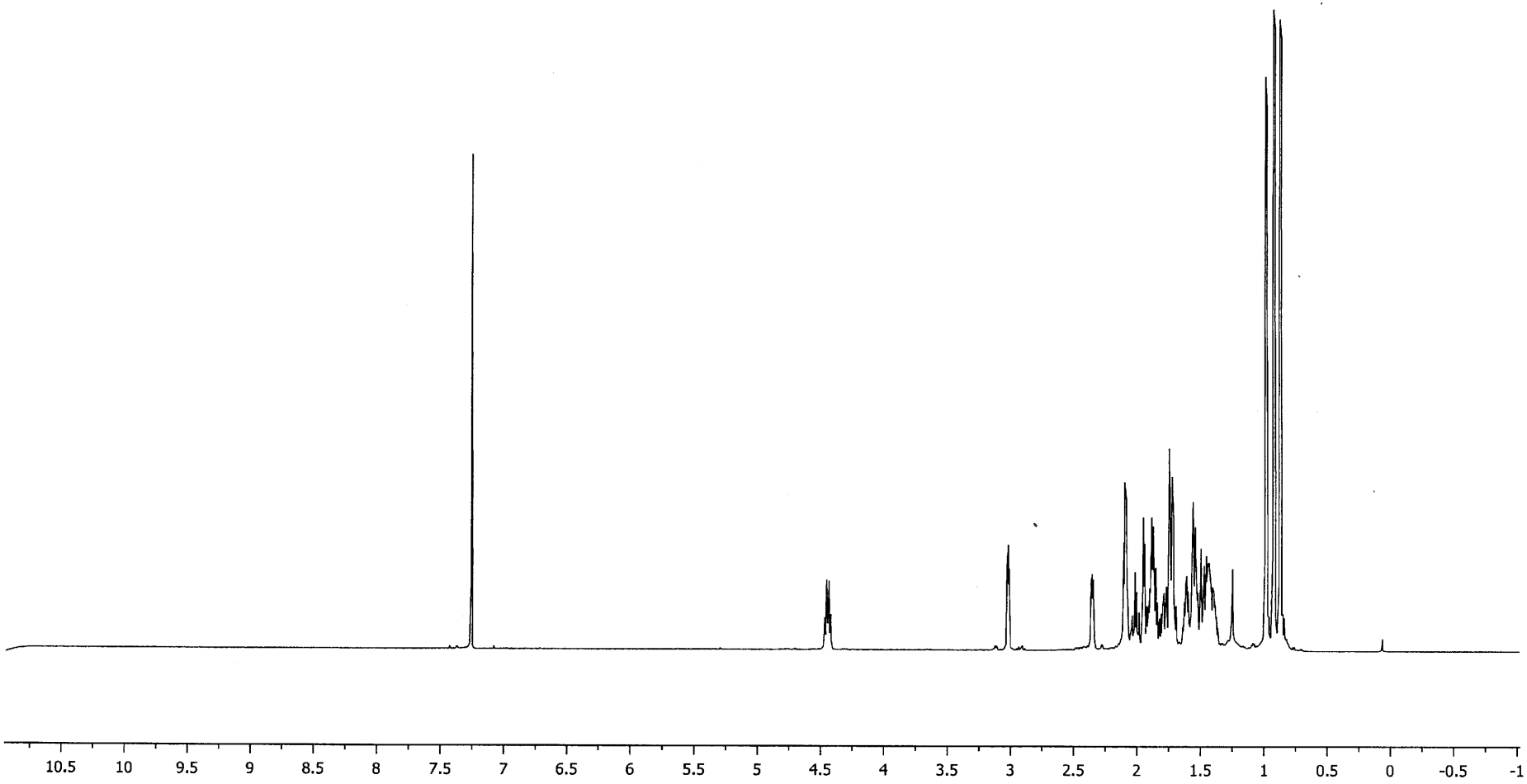
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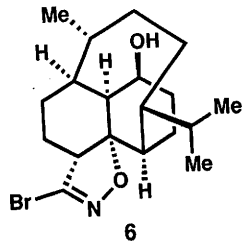
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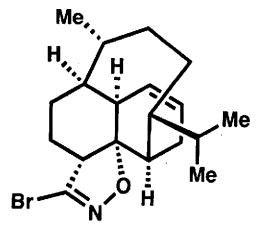
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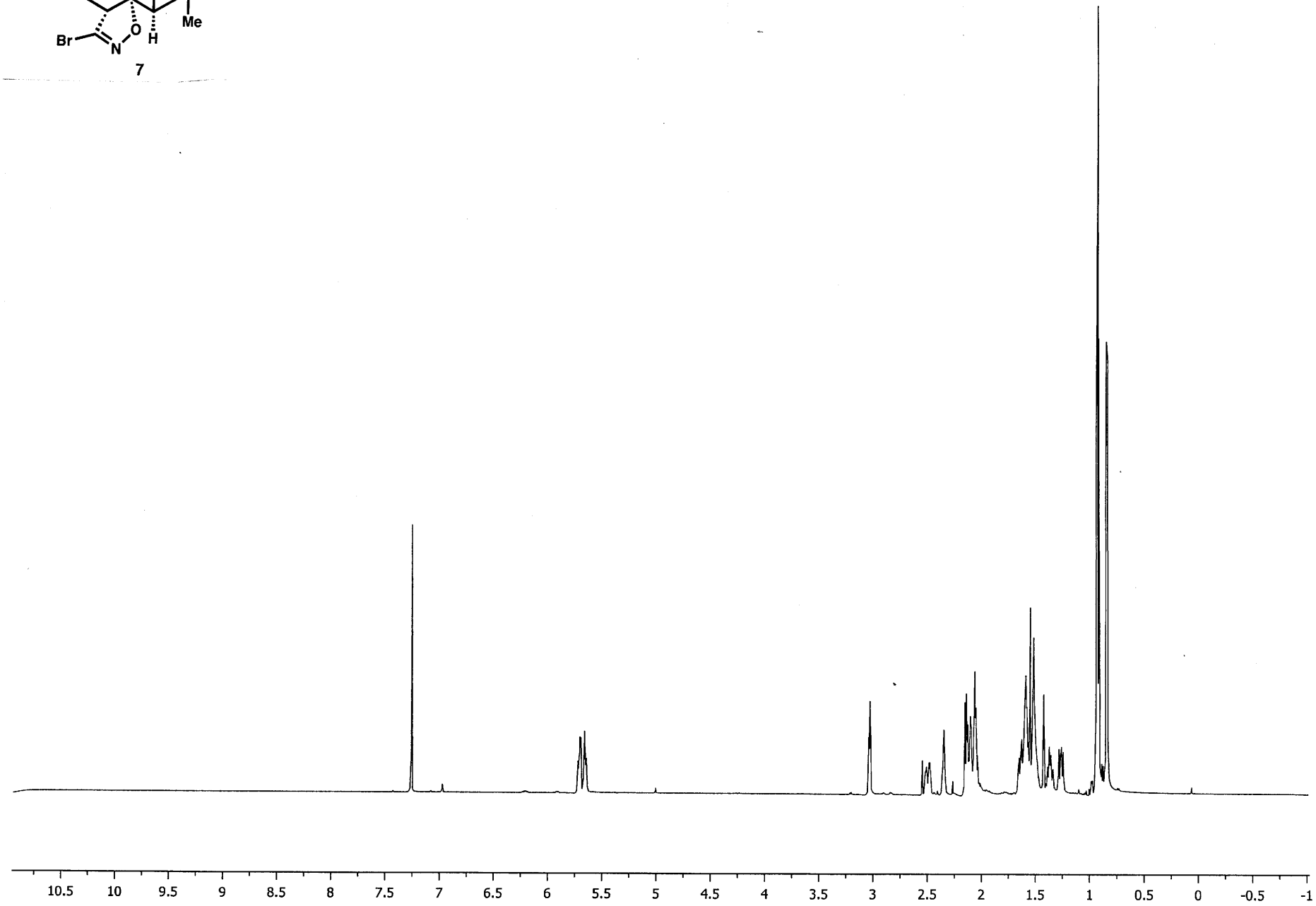
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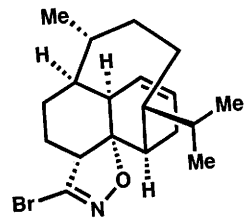
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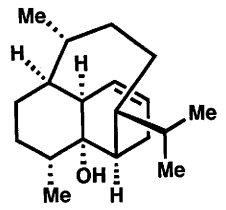

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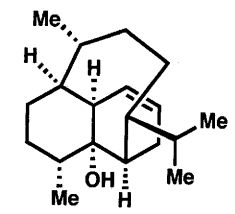
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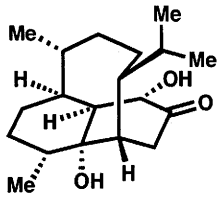
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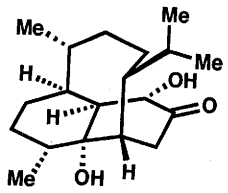
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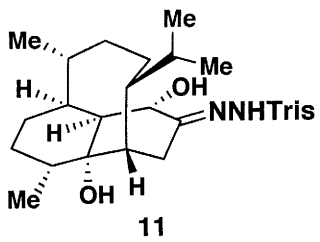

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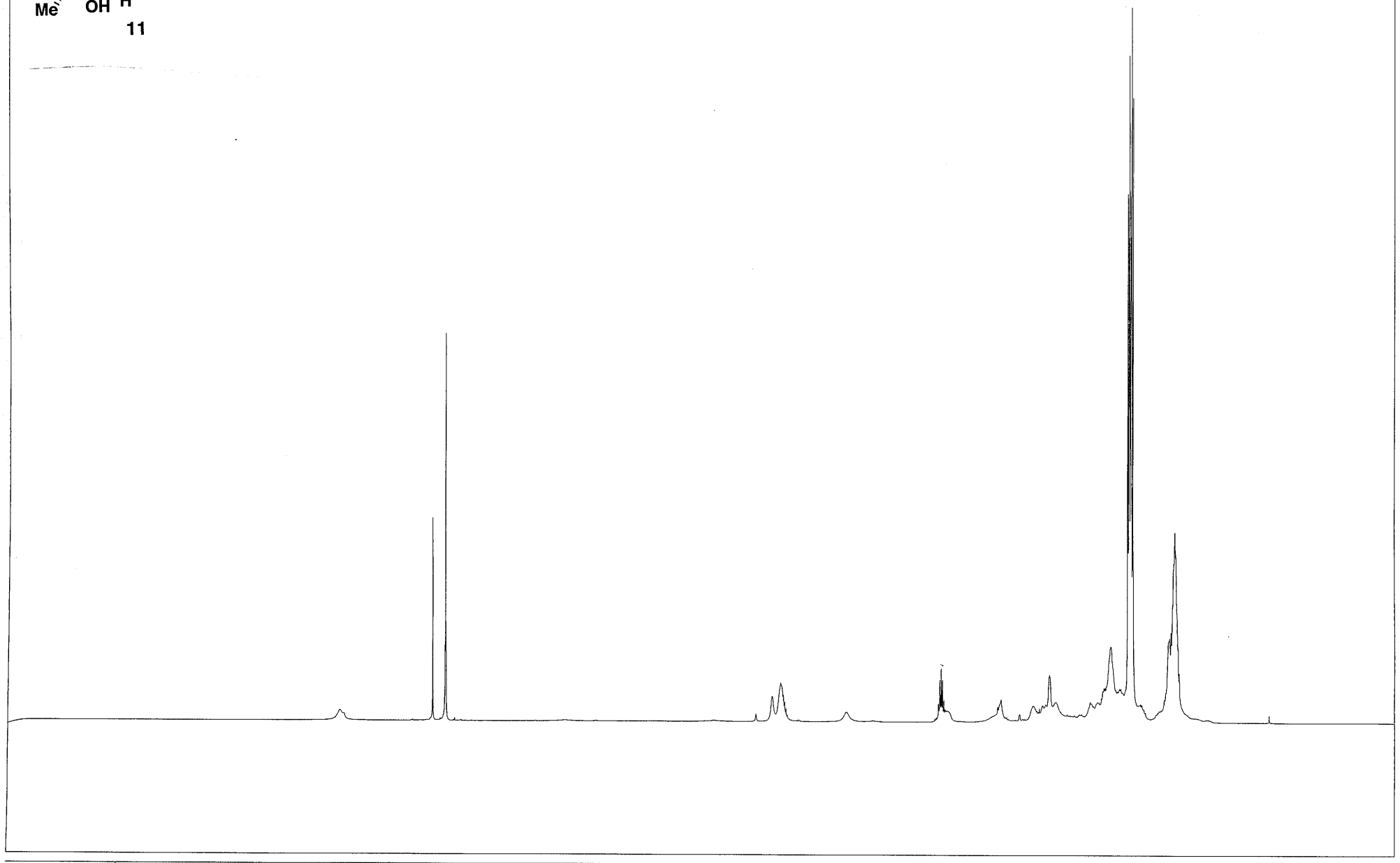

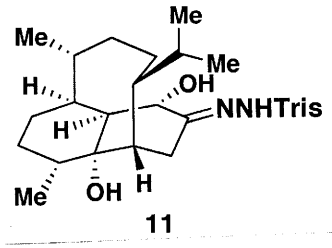

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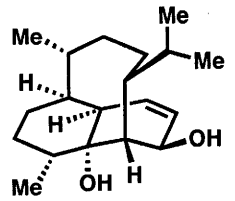
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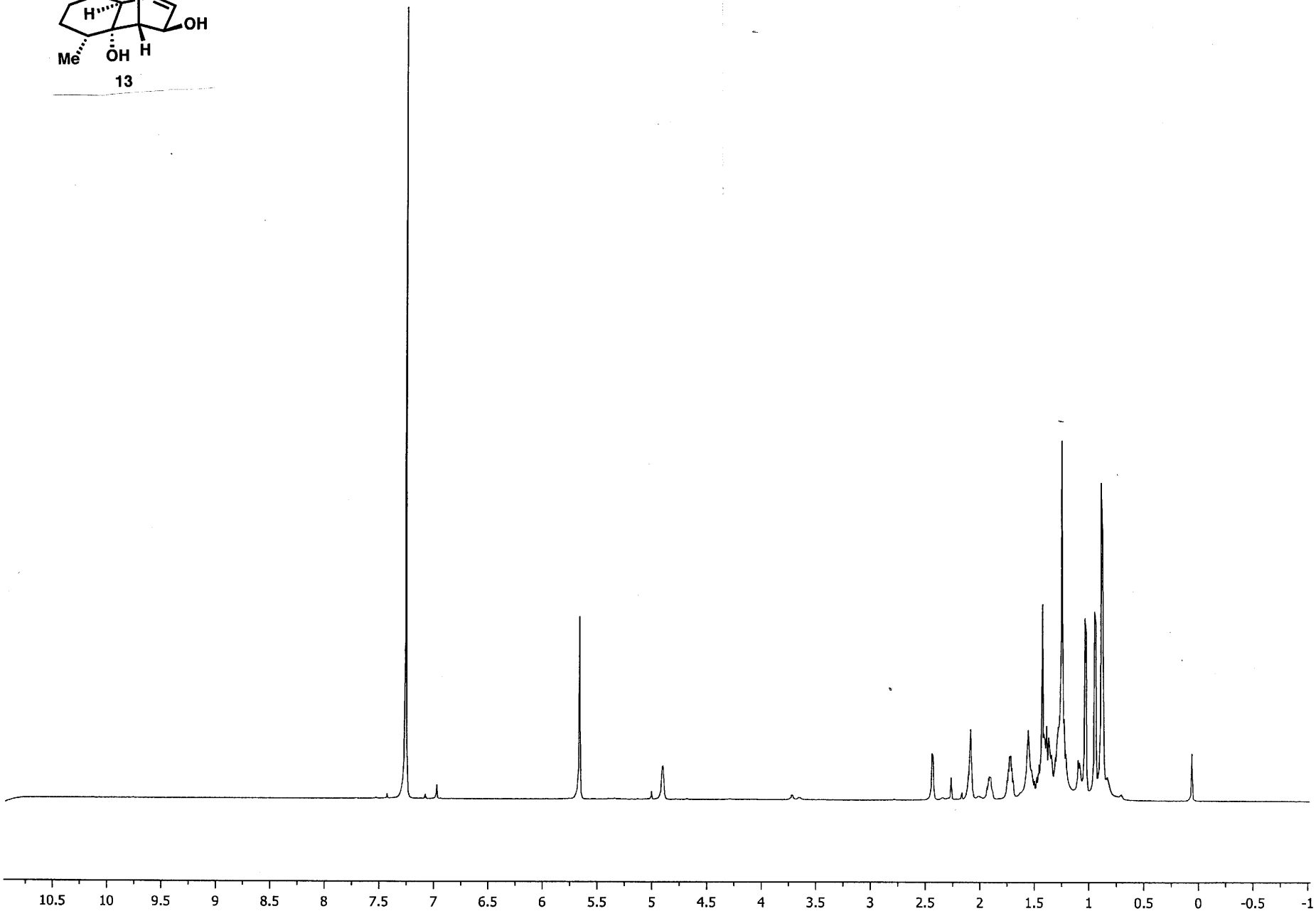
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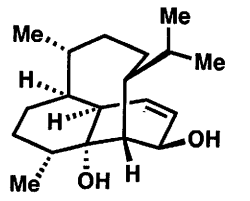
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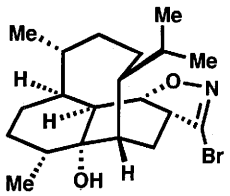
40
30
20
10
0
-10
-20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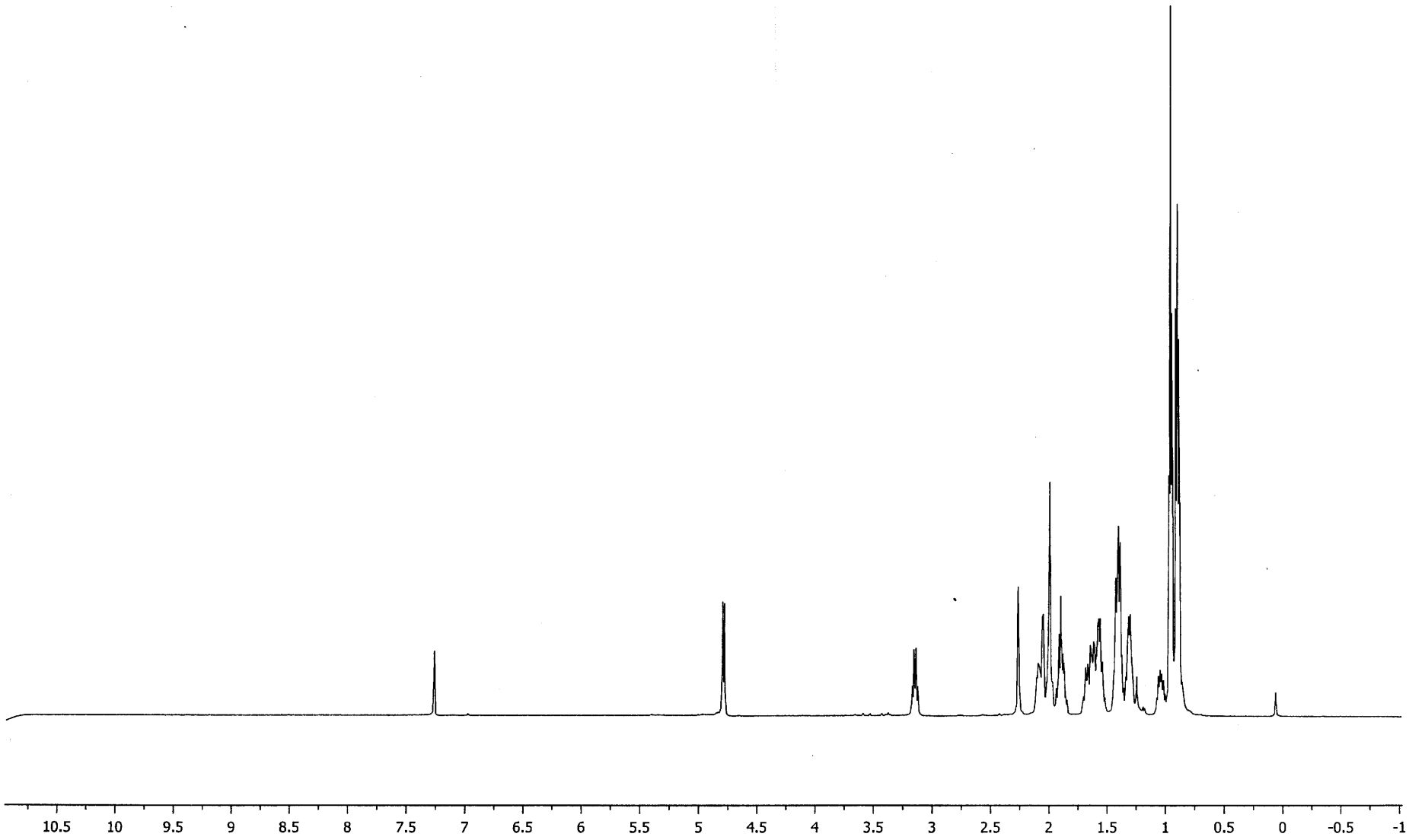
Me
Me
H
O
N
H
Br
Me
OH
H

14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7.5
7
6.5
6
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4.5
4
3.5
3
2.5
2
1.5
1
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0
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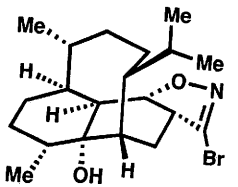
-1


Me
Me
Me
H
O
N
H
Br
Me
OH
H

14

220
210
200
190
180
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150
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100
90
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50
40
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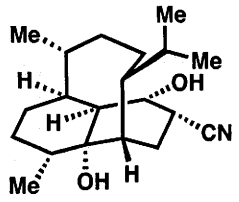
0
-10
-20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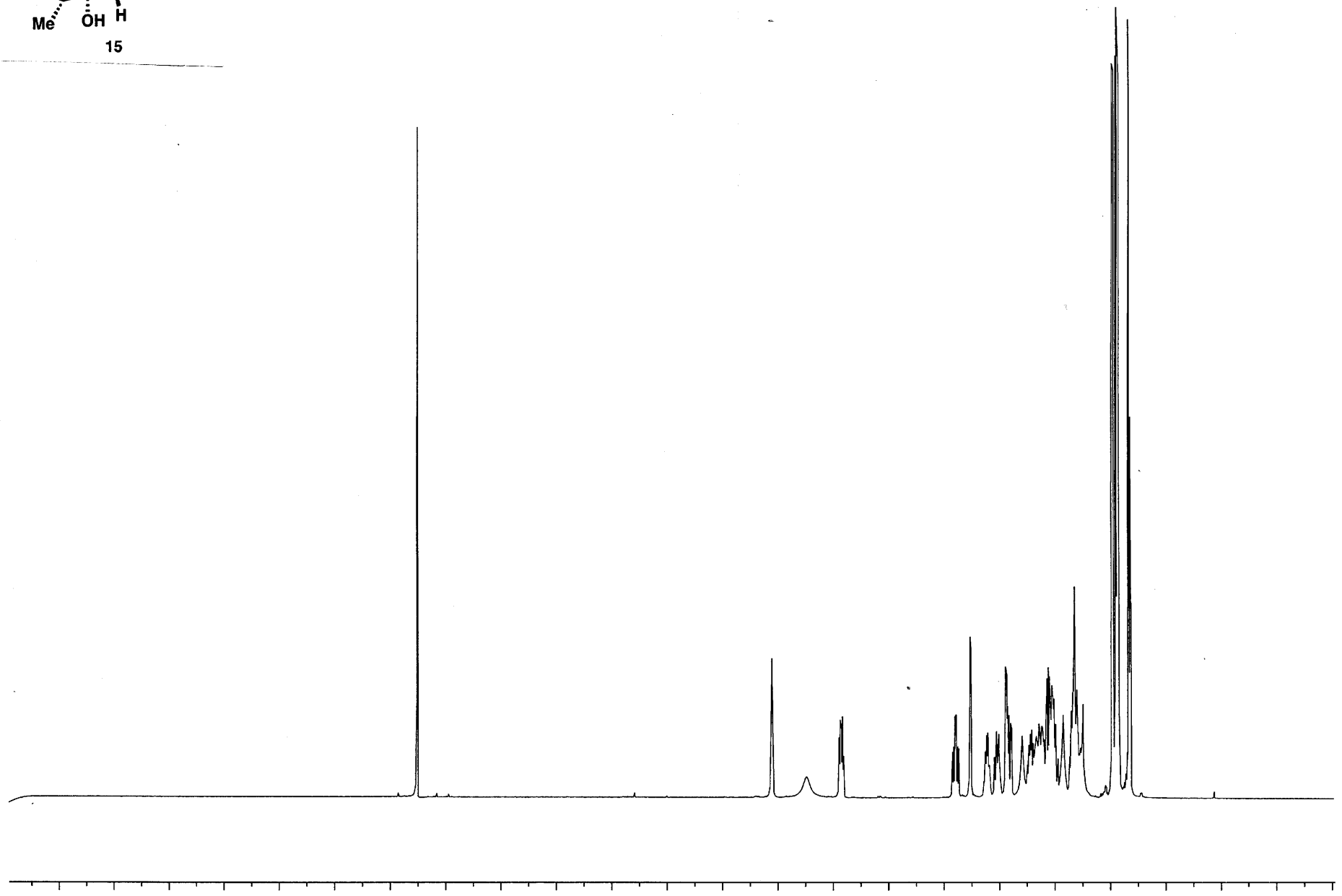
Me
Me
H
OH
H
CN
Me
OH
H

15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3
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1
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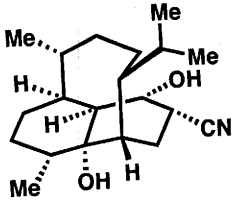
Me
Me
Me
H
OH
H
CN
Me
OH
H

15

220
210
200
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180
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130
120
110
100
90
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40
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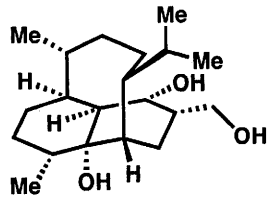
Me
Me
Me
H
OH
H
OH
Me
OH
H

16

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9
8.5
8
7.5
7
6.5
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4
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3
2.5
2
1.5
1
0.5
0
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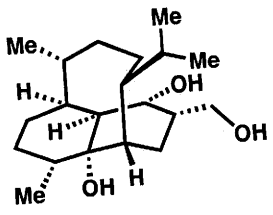
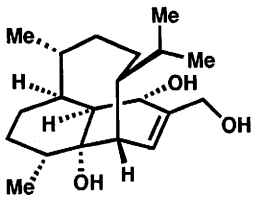
-1

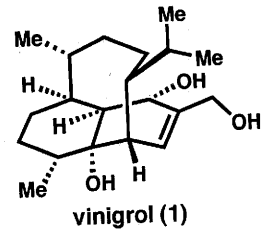


16


Me
Me
Me
H
OH
H
OH
Me
OH
H

vinigrol (1)

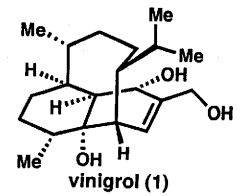
10.5
10
9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1

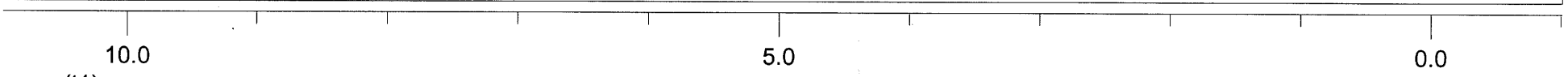

Me
Me
Me
H
OH
H
OH
Me
OH
H

vinigrol (1)

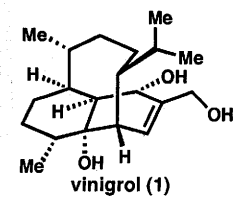
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

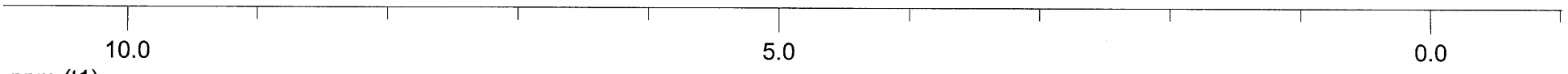
synthetic vinigrol (1)



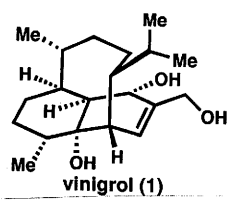


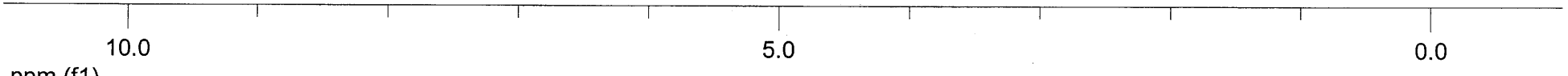
natural vinigrol



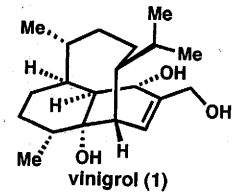


synthetic vinigrol mixed with natural vinigrol

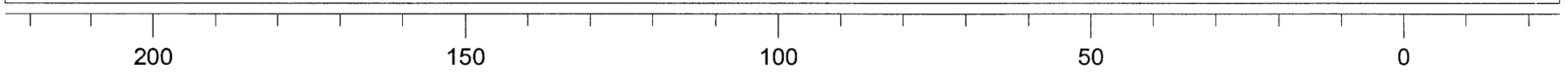




synthetic vinigrol (1)

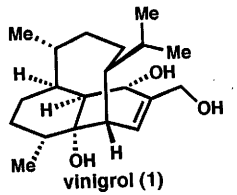


vinigrol (1)

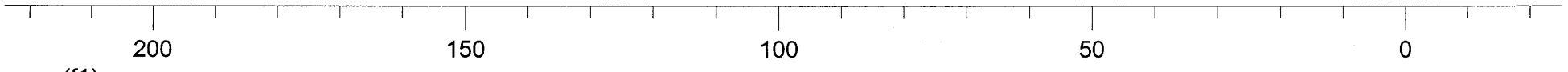


ppm (f1)

natural vinigrol



vinigrol (1)



ppm (f1)

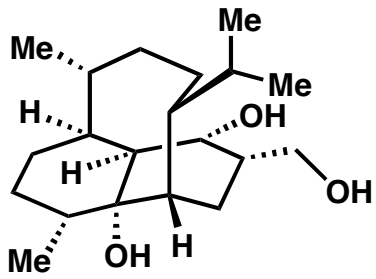
Table 1. ^{1}H NMR data comparison between synthetic vinigrol (**1**), natural vinigrol (natural sample provided by Astellas Pharma Inc. (Japan)) and natural vinigrol reported data[1].

Synthetic Vinigrol (**1**) ^{1}H NMR (CDCl3, 600 MHz) (δ, multiplicity, coupling constant (Hz))	Natural Vinigrol ^{1}H NMR (CDCl3, 600 MHz, sample provided by Astellas Pharma Inc.) (δ, multiplicity, coupling constant (Hz))	Natural Vinigrol ^{1}H NMR (CDCl3, 400 MHz, reported by ref. 1) (δ, multiplicity, coupling constant (Hz))
5.83, d, 5.5	5.83, d, 5.5	5.81, d, 5.6
4.30, AB q, 12.0	4.30, AB q, 12.0	4.25, AB q, 12.0
4.20, s	4.19, bs	4.20, s
3.40, bs	3.40, bs	–
2.65, bs	2.65, bs	–
2.30, d, 5.4	2.30, d, 5.4	2.32, d, 5.6
2.25, d, 3.7	2.25, d, 3.7	2.23, d, 3.6
2.15 – 2.09, m	2.15 – 2.09, m	2.12, m
1.99 – 1.93, m	1.99 – 1.93, m	1.96, m
1.80 – 1.70, m	1.80 – 1.70, m	1.8 – 1.5, m
1.65 – 1.50, m	1.65 – 1.50, m	–
1.40 – 1.05, m	1.40 – 1.05, m	1.4 – 1.0, m
1.00 – 0.95, m	1.00 – 0.95, m	1.0 – 0.8, m
0.9, d, 6.8	0.9, d, 6.8	–

Table 2. ^{1}C NMR data comparison between synthetic vinigrol (**1**), natural vinigrol (natural sample provided by Astellas Pharma Inc. (Japan)) and natural vinigrol reported data[1].

Synthetic Vinigrol (1) ^{13}C NMR (CDCl3, 150 MHz) (δ)	Natural Vinigrol (1) ^{13}C NMR (CDCl3, 150 MHz, sample provided by Astellas Pharma Inc.) (δ)	Natural Vinigrol (1) ^{13}C NMR (CDCl3, 100 MHz, reported by ref. 1) (δ)
136.5	136.4	136.5
128.4	128.5	128.5
75.5	75.5	75.5
72.8	72.8	72.7
67.9	67.9	67.6
51.1	51.1	51.3
45.5	45.3	45.1
44.2	44.2	44.3
40.2	40.2	40.3
35.8	35.8	35.9
34.5	34.5	34.6
33.0	33.0	33.1
29.6	29.6	29.7
28.9	28.9	28.9
28.6	28.6	28.6
27.2	27.2	27.3
24.8	24.8	24.8
21.5	21.5	21.5
20.5	20.5	20.6
15.3	15.3	15.5

X-Ray Crystallography:



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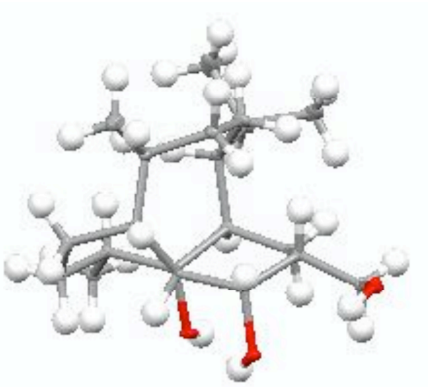
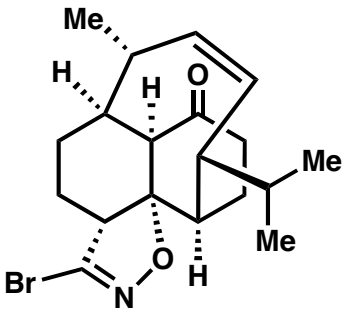
X-ray





5

X-ray