

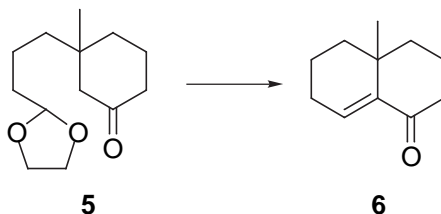
Supporting Information

Efficient One-Step Conversion of Primary Aliphatic Amines into Primary Alcohols: Application to a Successful Model Study for the Total Synthesis of (±)-Scopadulin

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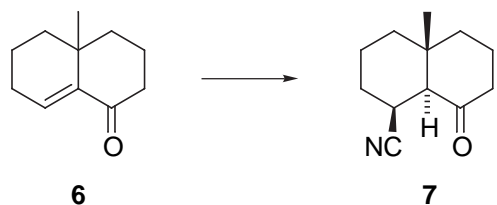
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General Methods. Melting points are uncorrected. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. ¹H- and ¹³C-NMR spectra were recorded in CDCl₃. Chemical shifts are reported in parts per million downfield from internal Me₄Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, m = multiplet).

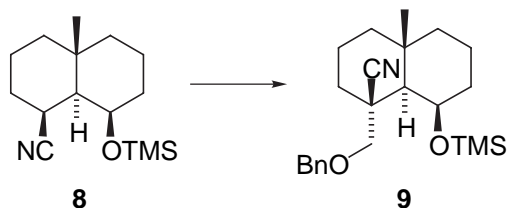


6-Methylbicyclo[4.4.0]dec-1(10)-en-2-one (6): Aqueous HCl (10%; 2.7 ml) was added to a solution of the ketone **5** (392 mg, 1.73 mmol) in MeOH (5 ml) and the resulting mixture was heated at 65 °C for 4 h. The reaction was neutralized by saturated NaHCO₃, and MeOH was evaporated out. The aqueous layer was then extracted with EtOAc, washed with water and brine, dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography (3:7 → 3:2 EtOAc/hexane) to give 230 mg (73%) of bicyclic alcohol (6-methylbicyclo[4.4.0]dec-2-one-10-ol) along with 54 mg (19%) of the title compound **6** as an oil. ¹To a stirred solution of the bicyclic alcohol (250 mg, 1.37 mmol) in benzene (25 ml) was added *p*-toluenesulphonic acid monohydrate (38 mg, 0.2 mmol). The resulting mixture was refluxed (dean-stark device) at 110 °C for 1.5 h. The mixture was then washed with saturated NaHCO₃ and water, dried (MgSO₄), filtered and concentrated. Purification of the concentrate by column chromatography (2:1 hexane/EtOAc) yielded the enone **6** (181 mg, 81%, combined yield 78% in two steps) as an oil. IR (KBr) cm⁻¹: 1682, 1620. ¹H-NMR (CDCl₃, 500 MHz) δ: 1.02 (s, 3H), 1.40 (td, *J* = 12.5, 4.5 Hz, 1H), 1.51-1.61 (m, 2H), 1.64-1.70 (m, 3H), 1.83-1.88 (m, 1H), 1.93-2.02 (m, 1H), 2.08-2.20 (m, 2H), 2.26 (ddd, *J* = 16.5, 12.5, 7.5 Hz, 1H), 2.50-2.55 (m, 1H), 6.36 (dd, *J* = 4.5, 3.0 Hz, 1H). ¹³C-NMR (CDCl₃, 125 MHz): 17.8, 19.3, 25.5, 25.9, 35.6, 37.8, 38.9, 40.4, 133.2, 144.6, 202.9. MS (EI) *m/z* (%): 164 (M⁺, 100). HRMS (EI) Calcd for C₁₁H₁₆O: 164.1201. Found: 164.1211.

(1) One-step conversion using an acid produced a complex mixture of unidentified products with low yield of the desired enone **6**. For one-step conversion, see ref 2b and 4.

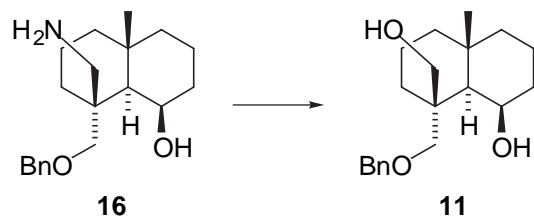


(6*R,10*S**)-6-Methyl-2-oxobicyclo[4.4.0]decane-10-carbonitrile (7)**: A solution of the enone **6** (315 mg, 1.92 mmol) in benzene (5 ml) was added dropwise to a stirred solution of diethylaluminum cyanide (1.0 M in toluene, 5.7 ml) at 0 °C. After being stirred for 2 h at 0 °C, a viscous solution of Et₃N (2.60 ml, 18.7 mmol) and TMSCl (1.20 ml, 9.53 mmol) in benzene (1.5 ml) was added using a canula. The resulting mixture was warmed to rt, and Et₂O (80 ml) and saturated aqueous NaHCO₃ (35 ml) were added carefully. The phases were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, dried (K₂CO₃), filtered and concentrated to give the crude silyl enol ether. The concentrate was then dissolved in 10:1 THF-H₂O (17 ml) and 1 M HCl (0.17 ml) was added and the mixture was stirred at rt for 15 min. The resulting mixture was diluted with ether (40 ml), and K₂CO₃ (533 mg) was added. The mixture was stirred for 10 min, dried (Na₂SO₄), filtered, and concentrated. Purification of the residue by flash chromatography (3:1 hexane/EtOAc) gave 330 mg (90%) of the title compound **7** as a colorless solid. Recrystallization (hexane/Et₂O) provided analytically pure coarse powder: mp 95-96 °C. IR (KBr) cm⁻¹: 2235, 1712. ¹H-NMR (CDCl₃, 500 MHz): 1.10 (s, 3H), 1.31 (td, *J* = 14.0, 4.5 Hz, 1H), 1.50 (tt, *J* = 14.0, 4.5 Hz, 1H), 1.56-1.64 (m, 4H), 1.80-1.90 (m, 1H), 1.92-2.01 (m, 2H), 2.10 (d, *J* = 14.6 Hz, 1H), 2.23-2.30 (m, 2H), 2.45 (dt, *J* = 14.6, 3.3 Hz, 1H), 2.97 (br s, 1H). ¹³C-NMR (CDCl₃, 125 MHz): 18.1, 18.7, 21.4, 23.4, 29.4, 39.4, 39.8, 40.5, 41.9, 57.3, 121.6, 208.0. MS (EI) *m/z* (%): 191 (M⁺, 32), 111 (100). HRMS (EI) Calcd for C₁₂H₁₇NO: 191.1310. Found: 191.1334.



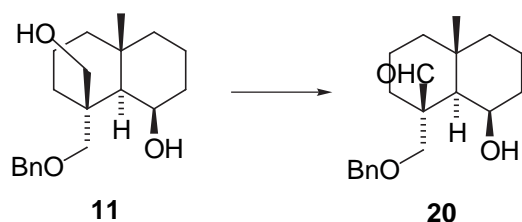
(2*R,6*R**,10*R**)-2-(Benzyloxymethyl)-6-methyl-10-trimethylsilyloxybicyclo[4.4.0]decane-2-carbonitrile (9)**: To a stirred solution of diisopropylamine (0.105 ml, 0.749 mmol) in THF (0.85 ml), *n*-butyllithium (1.6 M in hexane, 0.46 ml, 0.736 mmol) was added dropwise at -78 °C, and the mixture was warmed to 0 °C for 30 min. Then a solution of the nitrile **8** (85 mg, 0.32 mmol) in THF (0.85 ml) was added dropwise and the resulting solution was stirred for 20 min. The yellow solution obtained was cooled to -78 °C and freshly distilled benzyloxymethyl chloride (0.085 ml, 0.61 mmol) was added rapidly. The reaction mixture was warmed to 0 °C. After stirring for 1.5 h at 0 °C, the reaction mixture was quenched with saturated aqueous NaHCO₃ (excess). The mixture was then extracted with EtOAc,

washed with brine, dried over MgSO_4 , filtered and concentrated. Purification of the concentrate by flash chromatography (60:1 hexane/EtOAc) yielded 112 mg (91%) of the title compound **9** as a colorless oil. IR (KBr) cm^{-1} : 2231. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): 0.07 (s, 9H), 1.07 (t, $J = 12.8$ Hz, 2H), 1.40 (s, 3H), 1.32-1.42 (m, 4H), 1.58 (m, 1H), 1.72-2.02 (m, 6H) 3.42 (d, $J = 9.0$ Hz, 1H), 3.57 (d, $J = 9.0$ Hz, 1H), 4.00 (m, 1H), 4.46 (d, $J = 12.3$ Hz, 1H), 4.60 (d, $J = 12.3$ Hz, 1H), 7.30-7.38 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): 0.34, 16.5, 19.1, 20.5, 34.6, 34.7, 36.1, 38.2, 43.1, 44.2, 49.2, 66.4, 72.7, 73.5, 123.3, 127.9, 128.0, 128.5, 137.5. MS (FAB) m/z (%): 386 (MH^+ , 37), 91 (100). HRMS (FAB) Calcd for $\text{C}_{23}\text{H}_{35}\text{NO}_2\text{Si}$ (MH^+): 386.2515. Found: 386.2502.



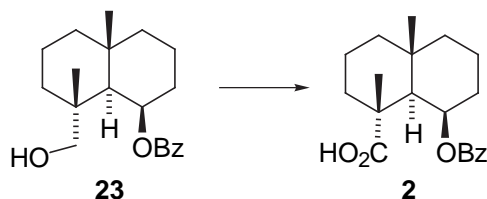
General procedure for one-step conversion of primary aliphatic amines into alcohols: (2*R,6*R**,10*R**)-10-(Benzyloxymethyl)-10-(hydroxymethyl)-6-methylbicyclo[4.4.0]decan-2-ol**

(11): The amine **16** (10 mg, 0.0315 mmol), KOH (100 mg, 1.75 mmol, excess) and diethylene glycol (0.6 ml) were placed in a round bottom flask equipped with a refluxing condenser and the mixture was heated at 210 °C for 3 h. The black solution was then cooled to rt, Et_2O (2 ml) and H_2O (1.5 ml) were added. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were then washed with brine, dried (MgSO_4), filtered and concentrated. Purification of the residue by column chromatography (5:1 hexane/EtOAc) gave 6.5 mg (65%) of the title compound **11**. Recrystallization from hexane/ Et_2O provided analytically pure white solid: mp 139 °C. IR (KBr) cm^{-1} : 3236 (br). $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): 1.33 (s, 3H), 1.06-1.59 (m, 11H), 1.84-1.87 (m, 1H), 1.90-1.99 (m, 1H), 3.39 (d, $J = 9.0$ Hz, 1H), 3.47 (d, $J = 12.5$ Hz, 1H), 3.48 (d, $J = 9.0$ Hz, 1H), 4.14 (br s, 2H), 4.20 (s, 1H), 4.21 (d, $J = 12.5$ Hz, 1H), 4.47 (d, $J = 12.0$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 7.27-7.37 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): 16.9, 18.4, 22.3, 34.6, 35.4, 35.6, 42.7, 44.5, 46.2, 52.2, 66.2, 66.3, 73.5, 78.2, 127.5, 127.6, 128.4, 138.3. MS (FAB) m/z (%): 319 (MH^+ , 25), 91 (100). HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3$ (MH^+): 319.2273. Found: 319.2269.

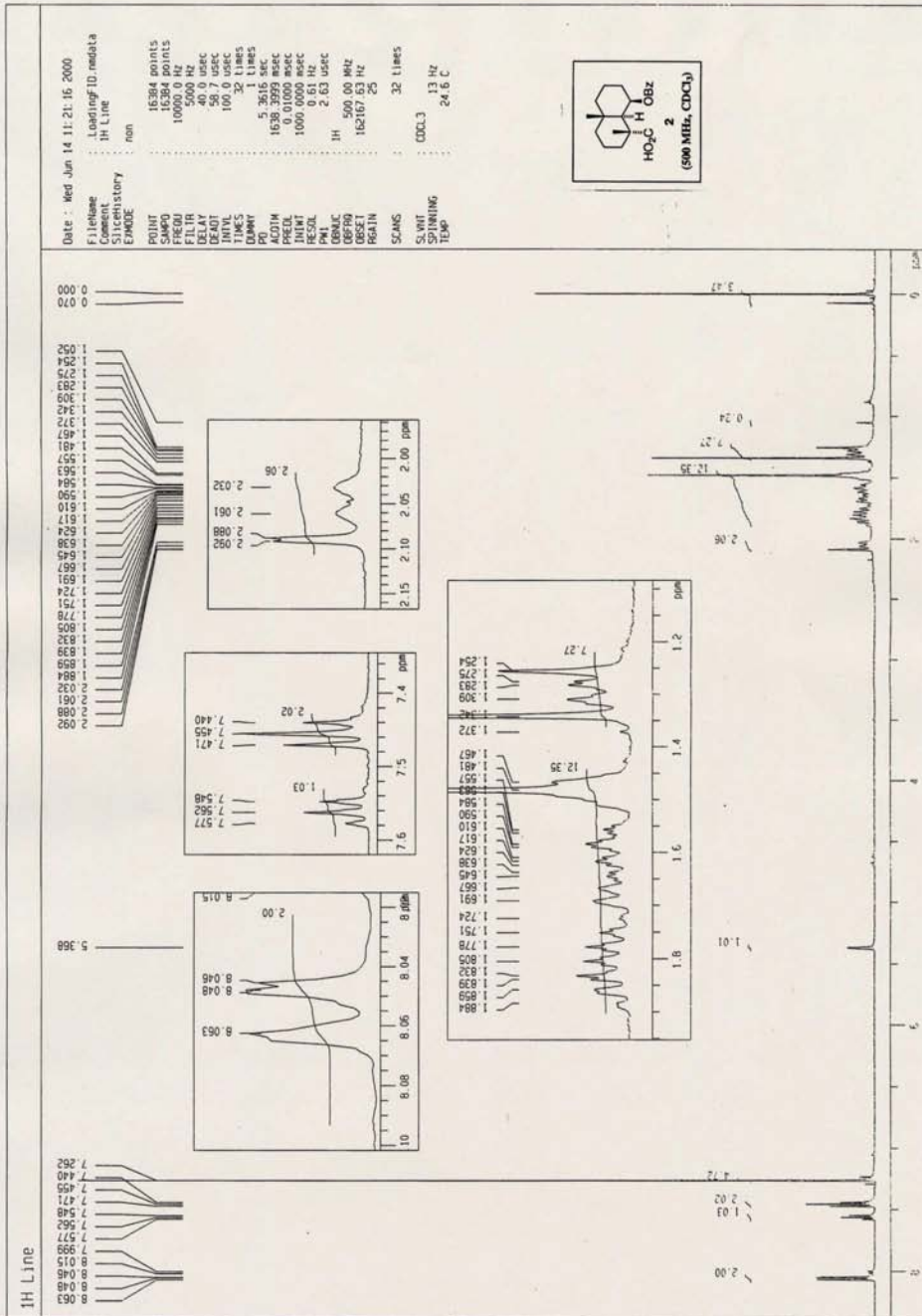


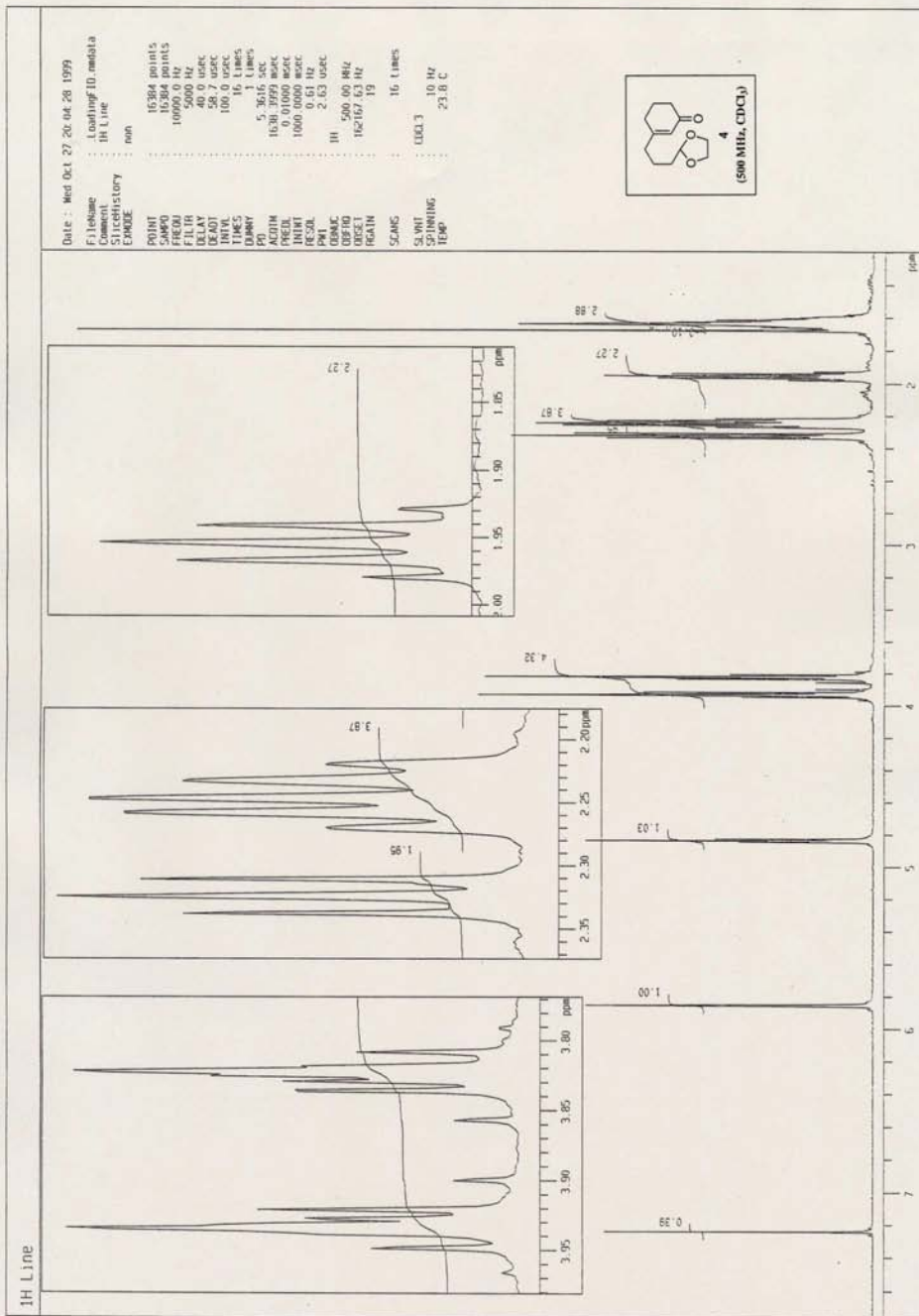
(2*R,6*R**,10*S**)-10-(Benzyloxymethyl)-2-hydroxy-6-methylbicyclo[4.4.0]decane-2-carbaldehyde** (**20**): $\text{RuCl}_2(\text{PPh}_3)_3$ (30 mg, 0.031 mmol) was added to a solution of the diol **11** (12 mg, 0.0377 mmol) in benzene (0.9 ml), and the resulting mixture was stirred at rt for 24 h. The black solution obtained, was concentrated and the residue was chromatographed on silica gel (3:1 hexane/EtOAc) to afford the

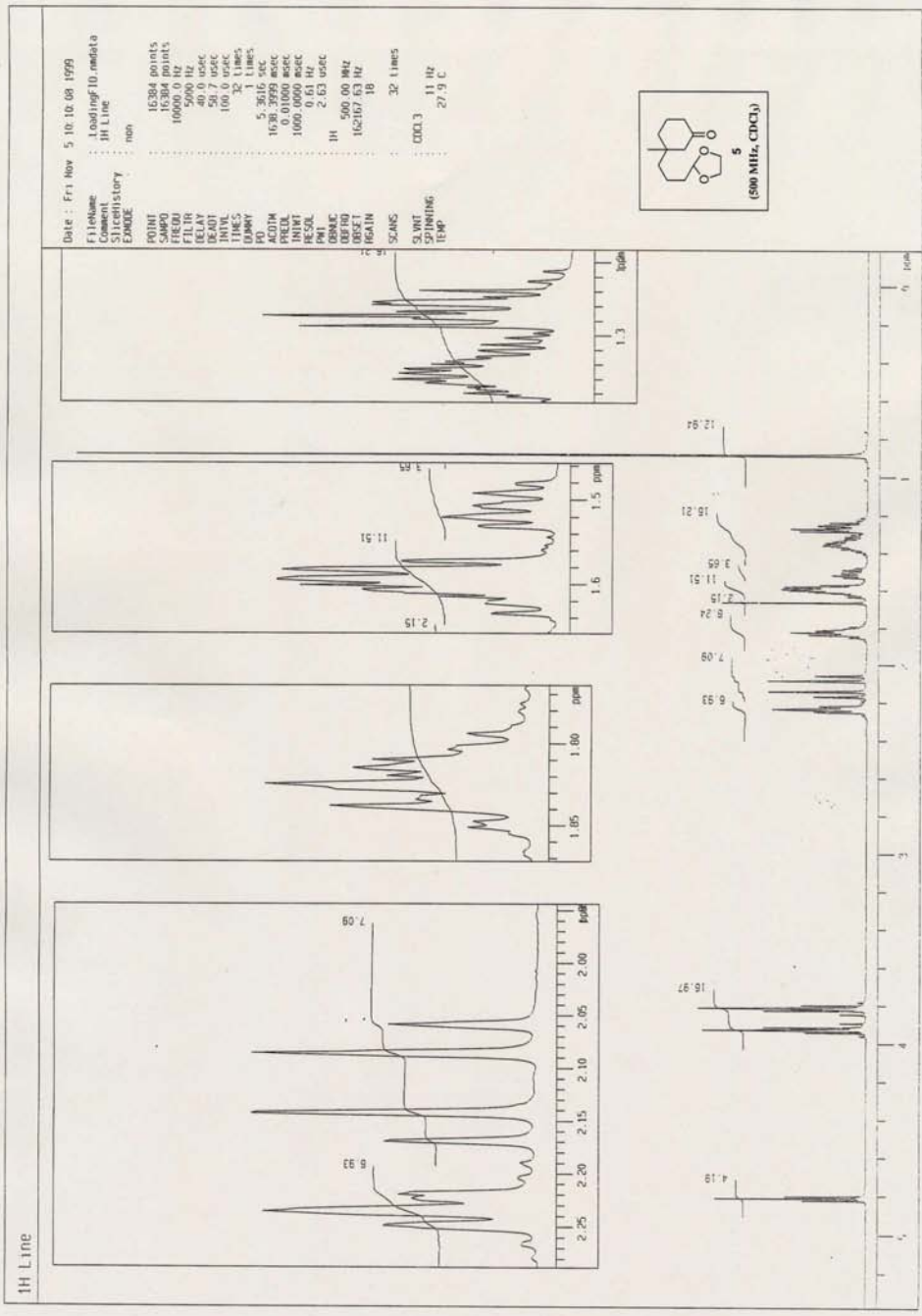
title compound **20** (7.5 mg, 63%) as a thick oil, together with 3.9 mg (33%) of the recovered diol **11**: IR (KBr) cm^{-1} : 3477, 1764. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): 1.03 (s, 3H), 1.10-1.15 (m, 2H), 1.32-1.48 (m, 6H), 1.59-1.70 (m, 2H), 1.87-1.94 (m, 2H), 2.38 (d, $J = 14.5$ Hz, 1H), 3.32 (s, 1H), 3.43 (d, $J = 8.5$ Hz, 1H), 3.59 (d, $J = 8.5$ Hz, 1H), 4.26 (m, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 7.26-7.36 (m, 5H), 10.10 (s, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): 16.5, 18.7, 22.4, 32.9, 34.5, 35.1, 43.5, 44.1, 52.7, 53.7, 66.4, 73.7, 75.6, 127.5, 127.8, 128.4, 137.7, 211.4. MS (FAB) m/z (%): 339 (MNa^+ , 48), 91 (100). HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}_3$ (MNa^+): 339.1936. Found: 339.1958.



(2*R,6*R**,10*R**)-2-(Benzyloxycarbonyl)-6,10-dimethylbicyclo[4.4.0]decane-2-carboxylic acid (2):** A solution of the alcohol **23** (4 mg, 0.0126 mmol) in acetone (0.5 ml) was treated with Jones reagent dropwise until TLC indicated that no starting material was present. The reaction mixture was diluted with CH_2Cl_2 , washed with water and brine sequentially, dried (MgSO_4), filtered and concentrated. Purification of the concentrate by column chromatography (3:1 hexane/EtOAc) gave 3.5 mg (84%) of the title compound **2** as a white solid. Recrystallization (hexane) afforded analytically pure colorless solid: mp 182-183 $^\circ\text{C}$. IR (KBr) cm^{-1} : 2931 (br), 1716. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): 1.28 (m, 4H), 1.34 (s, 3H), 1.48 (s, 3H), 1.56-1.88 (m, 8H), 2.05 (m, 1H), 2.09 (d, $J = 2.0$ Hz, 1H), 5.37 (m, 1H), 7.46 (m, 2H), 7.56 (m, 1H), 8.05 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): 17.5, 18.1, 22.3, 29.7, 32.3, 34.5, 39.8, 43.6, 45.3, 47.1, 49.6, 73.1, 128.2, 128.5, 130.9, 132.8, 166.1, 182.0. MS (FAB) m/z (%): 353 (MNa^+ , 100). HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_4$ (MNa^+): 353.1729. Found: 353.1727.



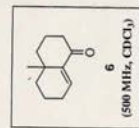
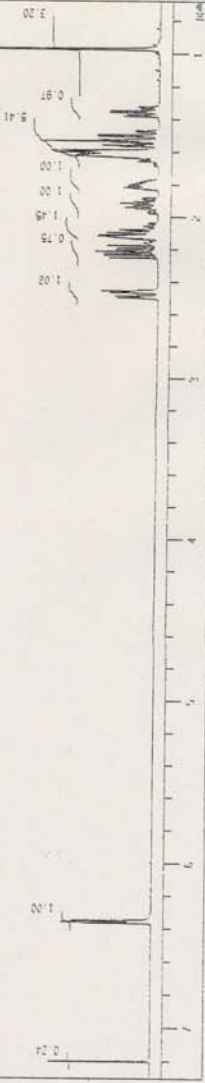




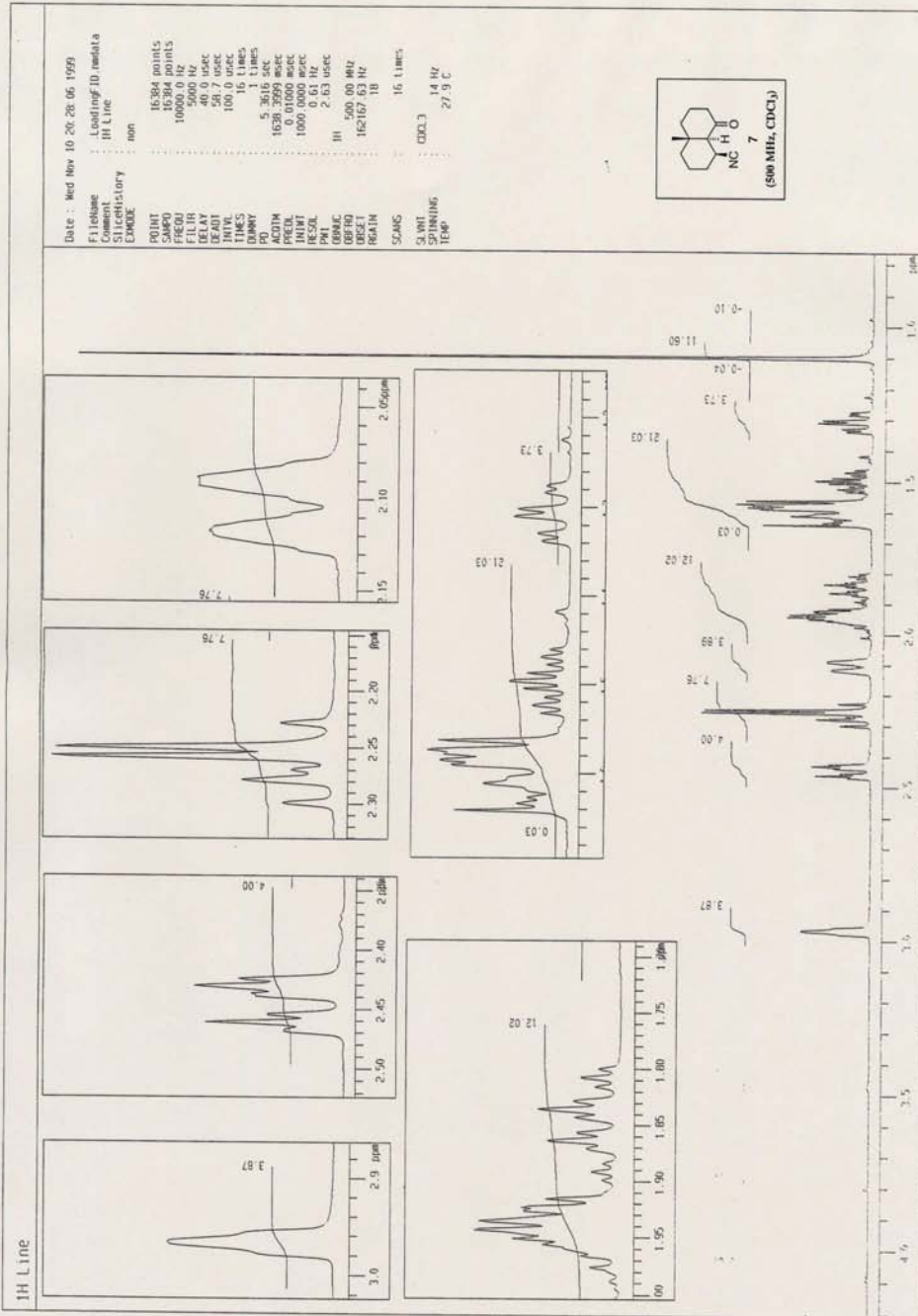
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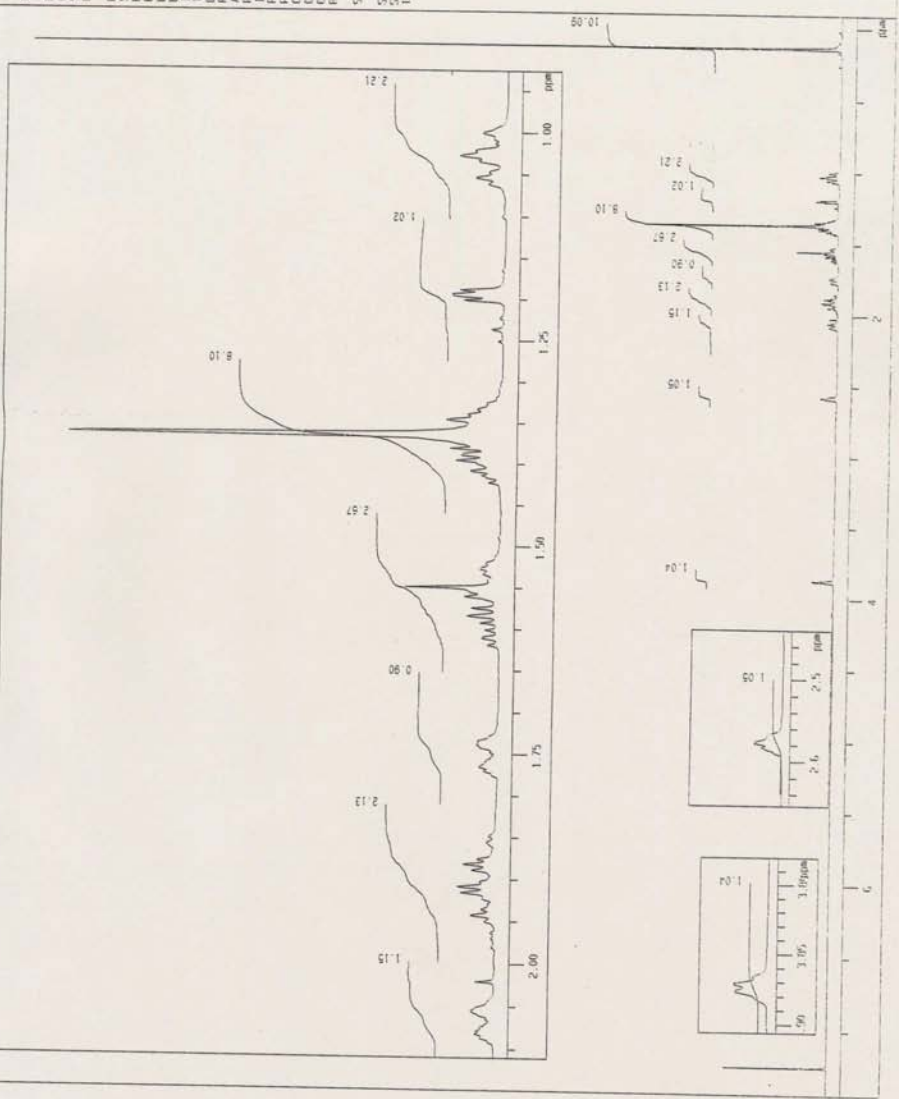
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No. 2-88



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