A flexible asymmetric synthesis of the tetracyclic core of berkelic acid using a Horner-Wadsworth-Emmons/oxa-Michael cascade –Electronic supporting information

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Index

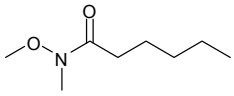
Experimental Procedures

General details

All reactions were carried out in flame or oven-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran and diethyl ether were dried over sodium wire and dichloromethane was dried over calcium hydride. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063-0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualised using UV irradiation at 365 nM and / or staining with: vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulphate in aqueous sulfuric acid or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Preparatory TLC was carried out on 500 μm Uniplate™ (Analtech) silica gel (20 x 20 cm) thin layer chromatography plates. Infrared spectra were obtained as indicated using a Perkin-Elmer Spectrum 1000 series Fourier Transform IR (FTIR) spectrometer as a thin film between sodium chloride plates or Perkin-Elmer Spectrum One FTIR spectrometer on a diamond ATR sampling accessory. Absorption maxima are expressed in wave numbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10^{-1} deg cm^2 g^{-1}.

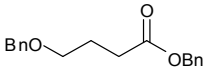
Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded as indicated on either the Bruker Avance 300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using the Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei and 162 MHz for ^{31}P nuclei. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (^{1}H) or $CDCl_3$ (^{1}H and ^{13}C). ^{1}H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets, coupling constant (*J* Hz) and assignment. Assignments were made with the aid of DEPT 135, COSY, NOESY and HSQC experiments where required. High resolution mass spectra were recorded on a VG-70SE at a nominal accelerating voltage of 70 eV.

Synthesis of *N*-methoxy-*N*-methylhexamide, 10



Oxalyl chloride (12.2 mL, 143.4 mmol) was added to a stirred solution of hexanoic acid (3.00 mL, 23.9 mmol) in dichloromethane (50 mL). DMF (2 drops) was added resulting in vigorous gaseous evolution for 30 minutes after which the reaction mixture was stirred at rt for a further 30 min then the solvent and residual oxalyl chloride were removed *in vacuo*. Chloroform (200 mL) and the hydrochloric acid salt of *N*,*O*-dimethylhydroxylamine (5.13 g, 52.6 mmol) were added to the crude yellow oil before cooling to 0 ^{o}C. Pyridine (4.33 mL, 52.6 mmol) was added and the reaction mixture warmed to rt for 1 h then the solvent was removed *in vacuo*. Saturated sodium chloride (50 mL), diethyl ether (25 mL) and dichloromethane (25 mL) were added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) then diethyl ether (2 x 50 mL) and the combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo*. Purification *via* flash chromatgraphy eluting with hexanes-ethyl acetate (4:1, R_F = 0.17) gave the *title compound* **10** (3.78 g, 99%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 0.85 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3$), 1.23-1.30 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 1.53-1.63 (2H, m, $C\underline{H}_2CH_2CO$), 2.36 (2H, t, *J* = 7.6 Hz, $C\underline{H}_2CO$), 3.12 (3H, s, $NC\underline{H}_3$), 3.63 (3H, s, $OC\underline{H}_3$). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[1]

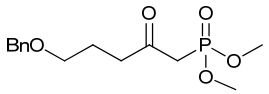
Synthesis of benzyl 4-(benzyloxy)butanoate, 14



A mixture of γ-butyrolactone (2.29 mL, 30.0 mmol), benzyl bromide (17.4 mL, 147.0 mmol) and potassium hydroxide (5.89 g, 105.0 mmol) in toluene (60 mL) was heated to reflux under Dean-Stark conditions for 50 h. The reaction mixture was cooled to rt, water (50 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated sodium bicarbonate (50 mL) and saturated sodium chloride (50 mL) before drying over magnesium sulfate and concentration *in vacuo*. The resultant crude oil was purified *via* flash chromatography using hexanes-ethyl acetate as eluent (19:1, R_F = 0.17) to afford the *title compound* **14** (7.14 g, 88%) as a pale yellow oil; ν_{max} (diamond/cm^{-1}) 3032 (C-H Ar str.), 2932 (C-H str.), 2859 (C-H (CH_2O) str.), 1732 (C=O str.), 1495, 1454, 1162 (C-O str.), 1083; δ_H (300 MHz, $CDCl_3$) 1.93-1.98 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.48 (2H, t, *J* = 7.5 Hz, $C\underline{H}_2COOBn$), 3.49 (2H, t, *J* = 6.15 Hz, $BnOC\underline{H}_2$), 4.46 (2H, s, $C_6H_5C\underline{H}_2OCH_2$), 5.09 (2H, s, $COOC\underline{H}_2C_6H_5$), 7.28-7.34 (10H, m, $C_6\underline{H}_5$ x 2); δ_C (75 MHz; $CDCl_3$) 25.1 (CH_2, $CH_2\underline{C}H_2CH_2$), 31.07 (CH_2, $\underline{C}H_2COOBn$), 66.1 (CH_2, $COO\underline{C}H_2C_6H_5$), 69.1 ($CH_2$, $BnO\underline{C}H_2$), 72.8

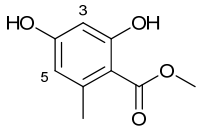
(CH_2, $C_6H_5\underline{C}H_2OCH_2$, 127.5, 127.5, 128.1, 128.3, 128.5 (10 x CH, ArH from 2 x C_6H_5), 136.0 (quat., from $CH_2COO\underline{Bn}$), 138.4 (quat., from $\underline{Bn}OCH_2$), 173.2 (quat., C=O); *m/z* (ESi+, %) 284 (MH^+, 4), 181 (100), 166 (8), 91 (20); Found MH^+, 285.1477. $C_{18}H_{21}O_3$ requires 285.1485.

Synthesis of dimethyl 5-(benzyloxy)-2-oxopentylphosphonate, 5



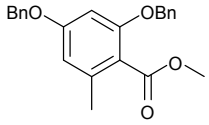
n-Butyllithium (3.47 mL, 1.6 M in hexane, 5.6 mmol) was added dropwise to a solution of dimethyl methylphosphonate (0.60 mL, 5.6 mmol) in THF (20 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min before addition of **14** (0.5 g, 1.9 mmol). After 1 h at -78 °C saturated ammonium chloride (20 mL) was added and the reaction mixture warmed to rt then extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (20 mL), saturated sodium chloride (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified *via* flash chromatography using ethyl acetate as eluent (R_F = 0.18) to afford the *title compound* **5** (0.49 g, 88%) as a colourless oil; ν_{max} (NaCl/cm^{-1}) 3029 (ArCH str.), 2956 (CH str.), 2856 (CH str.), 1715 (C=O str.), 1454 (Ar C-C str.), 1253 (P=O str.), 1096 (C-O-C str.), 1029 (P-O str.), 813 (P-O-Cal str.), 741 (P-C str.); δ_H (400 MHz, $CDCl_3$) 1.90 (2H, q, *J* = 6.6 Hz, $CH_2C\underline{H}_2CH_2$), 2.72 (2H, t, *J* = 7.1 Hz, $COC\underline{H}_2CH_2$), 3.08 (2H, d, *J* = 22.6 Hz, $POC\underline{H}_2CO$), 3.48 (2H, t, *J* = 6.1 Hz, $C\underline{H}_2OBn$), 3.74, 3.77 (2 x CH_3, s, 2 x $C\underline{H}_3$), 4.46 (2H, s, $C\underline{H}_2C_6H_5$), 7.36-7.23 (5H, m, $C_6\underline{H}_5$); δ_C (100 MHz; $CDCl_3$) 23.5 (CH_2, $CH_2\underline{C}H_2CH_2$) 40.6 (CH_2, $CO\underline{C}H_2CH_2$), 41.1 (CH_2, *J* = 127.5 Hz, $PO\underline{C}H_2CO$), 52.7, 52.8 (2 x CH_3, 2 x $O\underline{C}H_3$), 68.8 (CH_2, $\underline{C}H_2OBn$), 72.6 (CH_2, $C\underline{H}_2C_6H_5$), 127.3, 127.4, 128.1 (5 x ArCH, Bn), 138.1 (quat., from $\underline{Bn}O$), 201.4 (quat., *J* = 6.1 Hz, C=O); δ_P (162 MHz) 22.760; *m/z* (FAB+, %) 301 (MH^+, 2), 282 (3), 209 (5), 194 (30), 191 (25), 179 (10), 166 (100, MH^+-$C_9H_{11}O$), 151 (50), 124 (50), 109 (26), 94 (10), 91 (100, C_7H_7), 81 (17), 65 (16); Found MH^+, 301.12049. $C_{14}H_{22}O_5P$ requires 301.12049.

Synthesis of methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate), 8



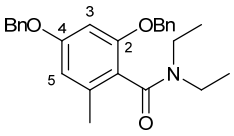
8 was synthesized according to the procedure of Chiarello and Joullié.[2] Methyl acetoacetate (18.6 mL, 0.17 mol) was added dropwise over 15 min to a suspension of sodium hydride (10.3 g, 60% in paraffin, 0.24 mol) in THF (100 mL) at 0 °C. The reaction mixture was cooled to -78 °C and *n*-butyllithium (100 mL, 1.6 M in hexane, 0.16 mol) added dropwise over 15 min. The reaction mixture was warmed to rt for 17 h, heated at reflux for a further 24 h before cooling to 0 °C and acidifying to pH 1 using concentrated hydrochloric acid (30 mL, 36%). After 2 h at rt, water (50 mL) was added and the mixture extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to afford a brown oil which was purified *via* flash chromatography using hexanes-ethyl acetate as eluent (3:1, R_F = 0.38) to afford the *title compound* **8** (11.36 g, 72%) as a pale yellow solid, m.p. = 137-138.5 °C (lit 136-138 °C[2]). δ_H (400 MHz, $CDCl_3$) 2.49 (3H, s, $C\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$), 5.41 (1H, br. s, C4O$\underline{H}$) 6.23 (1H, d, *J* = 2.5 Hz, C3$\underline{H}$), 6.28 (1H, d, *J* = 2.5 Hz, C5$\underline{H}$), 11.74 (1H, s, (1H, s, C2O$\underline{H}$). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[2]

Synthesis of methyl 2,4-dibenzyloxy-6-methylbenzoate, 15



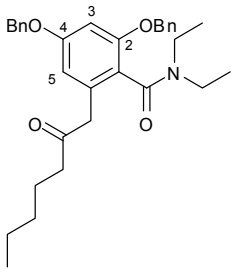
A solution of benzyl bromide (3.26 mL, 27.4 mmol), **8** (2.00 g, 10.8 mmol) and potassium carbonate (6.00 g, 43.2 mmol) in acetone (50 mL) was heated to reflux for 17 h. The solvent was removed *in vacuo* and water (50 mL) added. The resulting mixture was extracted with diethyl ether (3 x 70 mL), the combined organic layers dried over magnesium sulfate and the solvent removed *in vacuo*. The crude oil was purified *via* flash chromatography using hexanes-ethyl acetate as eluent (4:1, R_F = 0.41) to afford the *title compound* **15** (3.78 g, 96%) as a pale yellow solid, m.p. = 66 - 67.5 °C (lit 67-68 °C[3]). δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, C$\underline{H}_3$), 3.89 (3H, s, OC$\underline{H}_3$), 5.03, 5.07 (2 x 2H, s, 2 x C$\underline{H}_2C_6H_5$), 6.45 (2H, s, 2 x Ar$\underline{H}$), 7.20-7.42 (10H, m, $C_6\underline{H}_5CH_2$). The ^{1}H NMR data obtained was in agreement with that reported in the literature.[3]

Synthesis of 2,4-bis(benzyloxy)-*N*,*N*-diethyl-6-methylbenzamide, 9



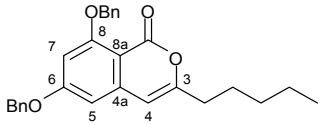
A solution of trimethylaluminium (9.3 mL, 2.0 M in hexanes, 18.6 mmol) in toluene (20 mL) was cooled to -6 °C, diethylamine (1.9 mL, 18.7 mmol) added, and the reaction mixture stirred for 10 min at -6 °C before warming to rt for 25 min. A solution of **15** (1.68 g, 4.6 mmol) in toluene (6 mL) was added and the resulting reaction mixture heated to reflux for 16 h before cooling to 0 °C and addition of aqueous hydrochloric acid (20 mL, 10%). The layers were separated and the organic layer was washed with aqueous hydrochloric acid (40 mL, 10%). The combined aqueous layers were extracted with ethyl acetate (2 x 60 mL), the combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo*. The resultant crude oil was purified *via* flash chromatography utilizing hexane-ethyl acetate as eluent (3:2, R_F = 0.32) to afford the *title compound* **9** (1.75 g, 94%) as a pale yellow solid, m.p. = 83.8 - 84.0 °C. ν_{max} (NaCl/cm^{-1}) 2973 (C-H str.), 2934, 1602 (C=O str.), 1151, 733, 696; δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$CH$_2$), 1.19 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$CH$_2$), 2.27 (3H, s, C$\underline{H}_3$), 3.10 – 3.24 (2H, m, C$\underline{H}_2$CH$_3$), 3.49 (1H, qd, *J* = 14.2, 7.1 Hz, C$\underline{H}$HCH$_3$), 3.66 (1H, qd, *J* = 14.2, 7.1 Hz, CH$\underline{H}$CH$_3$), 4.98-5.05 (4H, m, 2 x C$\underline{H}_2C_6H_5$), 6.47 (2H, s, 2 x Ar$\underline{H}$), 7.26-7.44 (10H, m, 2 x $C_5\underline{H}_6$); δ_C (100 MHz; $CDCl_3$) 12.5, 13.8 (2 x CH$_3$, 2 x CH$_2\underline{C}$H$_3$), 19.0 (CH$_3$, Ar$\underline{C}$H$_3$), 38.5, 42.4 (2 x CH$_2$, 2 x $\underline{C}$H$_2$CH$_3$), 69.8, 69.9 (2 x CH$_2$, 2 x $\underline{C}$H$_2$C$_6$H$_5$), 97.9 (CH, C3), 107.8 (CH, C5), 119.9 (quat., $\underline{C}$1), 126.8, 127.3, 127.5, 127.8, 128.1, 128.4 (10 x CH, from 2 x OBn), 136.5 (quat., from 2 x OBn), 136.6 (quat., $\underline{C}$6), 155.4 (quat., $\underline{C}$2), 159.3 (quat., $\underline{C}$4), 168.1 (quat., $\underline{C}$=O); *m/z* (EI+, %) 403 (M+, 24), 331 (22), 241 (8), 181 (9), 151 (5), 100 (4), 91 ($C_5H_6CH_2$, 100), 72 (N(CH$_2$CH$_3$)$_2$, 12), 65 (9), 58 (4), 39 (4); Found M+, 403.21487. $C_{26}H_{29}NO_3$ requires 403.21474.

Synthesis of 2,4-bis(benzyloxy)-*N*,*N*-diethyl-6-(2-oxoheptyl)benzamide, 11



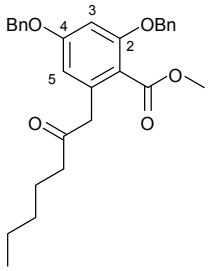
tert-Butyllithium (3.00 mL, 1.5 M in pentane, 4.5 mmol) and *N*,*N*-tetramethylenediamine (0.75 mL, 4.46 mmol) were added dropwise simultaneously to a stirred solution of **9** (1.5 g, 3.72 mmol) in THF (60 mL) at -78 °C and the mixture stirred for 15 min. **10** (1.24 g, 7.81 mmol) was then added dropwise and the resultant mixture stirred at -78 °C for 1 h. Aqueous hydrochloric acid (60 mL, 10%) was added and the reaction mixture allowed to warm to rt. Ethyl acetate (50 mL) was added, the layers separated and the aqueous layer extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo*. The resulting crude oil was purified *via* flash chromatography using hexanes-ethyl acetate as eluent (4:1, R_F = 0.09) to afford the *title compound* **11** (1.70 g, 91%) as a viscous colourless oil. ν_{max} (diamond/cm^{-1}) 2931 (C-H str.), 1713 (C=O str. ketone), 1602 (C=O str. amide), 1432, 1154, 698; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* = 7.0, $CH_2CH_2C\underline{H}_3$), 0.97 (3H, t, *J* = 7.1 Hz, $C\underline{H}_3CH_2N$), 1.11 (3H, t, *J* = 7.1 Hz, $C\underline{H}_3CH_2N$), 1.19-1.33 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.54 (2H, quint., *J* = 7.4 Hz, $COCH_2C\underline{H}_2$), 2.46 (2H, t, *J* = 7.4 Hz, $COC\underline{H}_2CH_2$), 3.14 (2H, q, *J* = 7.1 Hz, $NC\underline{H}_2CH_3$), 3.37-3.45 (1H, m, $NC\underline{H}HCH_3$), 3.74-3.55 (3H, m, $NCH\underline{H}CH_3$ and $ArC\underline{H}_2CO$), 4.96-5.07 (4H, m, 2 x $C\underline{H}_2C_6H_5$), 6.44 (1H, d, *J* = 2.1 Hz, C3$\underline{H}$), 6.52 (1H, d, *J* = 2.1 Hz, C5$\underline{H}$), 7.26-7.41 (10H, m, 2 x $C_6\underline{H}_5$); δ_C (100 MHz; $CDCl_3$) 12.5, 13.6 (2 x CH_3, 2 x $\underline{C}H_3CH_2N$), 13.8 (CH_3, $CH_2CH_2\underline{C}H_3$), 22.4 (CH_2, $CH_2\underline{C}H_2CH_3$), 23.3 (CH_2, $COCH_2\underline{C}H_2$), 31.2 (CH_2, $\underline{C}H_2CH_2CH_3$), 38.5 (CH_2, $CO\underline{C}H_2CH_2$), 42.3, 42.8 (2 x CH_2, 2 x $CH_3\underline{C}H_2N$), 46.9 (CH_2, $Ar\underline{C}H_2CO$), 70.1, 70.2 (2 x CH_2, 2 x $\underline{C}H_2C_6H_5$), 99.2 (CH, $\underline{C}$3), 108.1 (CH, $\underline{C}$5), 120.3 (quat., $\underline{C}$1), 128.50, 128.29, 127.99, 127.76, 127.49, 127.06 (10 x CH, from 2 x OBn), 133.9 (quat., $\underline{C}$6), 136.3, 136.4 (2 x quat., from 2 x OBn), 155.7 (quat., $\underline{C}$2), 157.6 (quat., $\underline{C}$4), 167.7 (quat., $\underline{C}ONEt_2$), 208.1 (quat., $CH_2\underline{C}OCH_2$); *m/z* (EI+, %) 501 (M+, 9), 429 (6), 388 (14), 256 (5), 122 (13), 105 (41), 91 ($C_5H_6CH_2$, 100), 77 (39), 58 (32), 44 (64); Found M^+, 501.28603. $C_{32}H_{39}NO_4$ requires 501.28791.

Synthesis of 6,8-bis(benzyloxy)-3-pentyl-1*H*-isochromen-1-one, 12



A solution of **11** (0.3 g, 0.6 mmol) in acetic acid (3 mL) was heated to 170 °C in a sealed tube for 49 h. Silica (~0.5 g) was added, the acetic acid removed *in vacuo*, and the resultant pre-loaded silica purified by flash chromatography using hexanes-ethyl acetate as eluent (4:1, R_F = 0.34) to afford the *title compound* **12** (0.206 g, 80%) as a white solid, m.p. = 83.9 °C. ν_{max} (diamond/cm^{-1}) 3061 (=C-H str.), 2956 (C-H str.), 2857 (C-H (CH_2O) str.), 1708 (C=O str.), 1596 (C=C-O str.), 1564, 1166 (C-O str.), 739, 694; δ_H (300 MHz, $CDCl_3$) 0.89-0.94 (3H, m, $CH_2C\underline{H}_3$), 1.32-1.37 (4H, $C\underline{H}_2C\underline{H}_2CH_2CH_3$), 1.64-1.74 (2H, m, $C\underline{H}_2CH_3$), 2.45 (2H, t, *J* = Hz, $COC\underline{H}_2CH_2$), 5.08, 5.23 (2 x 2H, s, 2 x $C\underline{H}_2C_6H_5$), 6.06 (1H, s, C4H), 6.40 (1H, d, *J* = 2.1 Hz, C7H), 6.54 (1H, d, *J* = 2.1 Hz, C5H), 7.26-7.59 (10H, m, 2 x $CH_2C_6\underline{H}_5$); δ_C (75 MHz; $CDCl_3$) 13.9 (CH_3, $CH_2\underline{C}H_3$), 22.3 (CH_2, $\underline{C}H_2CH_3$), 26.4 (CH_2, $COCH_2\underline{C}H_2$), 31.1 (CH_2, $\underline{C}H_2CH_2CH_3$), 33.2 (CH_2, $CO\underline{C}H_2CH_2$), 70.2, 70.4 (2 x CH_2, 2 x $\underline{C}H_2C_6H_5$), 100.3 (CH, C7), 100.8 (CH, C5), 102.8 (CH, C4), 103.6 (quat., C8a), 126.5, 127.5, 127.6, 128.3, 128.5, 128.6 (10 x CH, from 2 x OBn), 135.7, 136.2 (2 x quat., from 2 x OBn), 142.3 (quat., C4a), 159.2 (quat., C8), 159.3 (quat., $CH\underline{C}OCH_2$), 162.0 (quat., C6), 164.2 (quat., C=O); *m/z* (ESi+, %) 429 (MH^+, 15), 337 (7), 261 (22), 249 (12), 181 (100), 91 (75); Found MH^+, 429.2063 $C_{28}H_{29}O_4$ requires 429.2060.

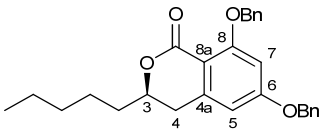
Synthesis of methyl 2,4-bis(benzyloxy)-6-(2-oxoheptyl)benzoate, 13



A solution of potassium hydroxide (1.00 g, 17.8 mmol) and **12** (0.62 g, 1.4 mmol) in ethanol (20 mL) and water (20 mL) was heated to reflux for 14 h. The solvent was removed *in vacuo* and the reaction mixture acidified using aqueous hydrochloric acid (~ 5 mL, 10%) before extracting with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo*. The resulting crude oil was dissolved in acetone (40 mL) and anhydrous potassium carbonate (0.774 g, 5.6 mmol) and methyl iodide (0.26 mL, 4.2 mmol) were added. The resulting mixture was heated to reflux for 2 h at which point the warm reaction mixture was filtered through a plug of basic alumina, washed with warm acetone (100 mL) and the solvent removed *in vacuo*. The resultant crude oil was dry loaded onto basic alumina and purified *via* flash chromatography, utilizing hexanes-ethyl acetate as eluent (4:1, R_F = 0.47) to afford the *title compound* **11** (0.583 g, 87%) as a white solid, m.p. = 62.7 – 63.0 °C. ν_{max} (diamond/cm^{-1}) 2931 (C-H str.), 1707 (C=O str.), 1601, 1433, 1275, 1164 (C-O str.), 1029, 733; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* = 6.9 Hz, $CH_2C\underline{H}_3$), 1.24-1.36 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.54-1.64 (2H, m, $COCH_2C\underline{H}_2$), 2.46 (2H, t, *J* = 7.4 Hz, $COC\underline{H}_2$), 3.73 (2H, s, $ArC\underline{H}_2CO$), 3.85 (3H, s, $OC\underline{H}_3$), 5.04 and 5.07 (2 x 2H, s, 2 x $C\underline{H}_2C_6H_5$), 6.46 (1H, d, *J* = 2.1 Hz, C3H), 6.56 (1H, d, *J* = 2.1 Hz, C5H), 7.26-7.40 (10H, m, 2 x $CH_2C_6\underline{H}_5$); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3, $CH_2\underline{C}H_3$), 22.3 (CH_2, $\underline{C}H_2CH_3$), 23.1 (CH_2,

$COCH_2\underline{C}H_2$), 31.1 (CH_2, $\underline{C}H_2CH_2CH_3$), 41.8 (CH_2, $CO\underline{C}H_2CH_2$), 48.0 (CH_2, $Ar\underline{C}H_2CO$), 51.8 (CH_3, OCH_3), 70.0, 70.5 (2 x CH_2, 2 x $\underline{C}H_2C_6H_5$), 99.8 (CH, $\underline{C}$5), 108.8 (CH, $\underline{C}$3), 116.6 (quat., $\underline{C}$1), 126.8, 127.4, 127.7, 128.0, 128.3, 128.5 (10 x CH, from 2 x $CH_2C_6\underline{H}_5$), 135.8, 136.1, 136.4 (3 x quat., $\underline{C}$6 and from 2 x BnO), 158.0 (quat., $\underline{C}$2), 160.6 (quat., $\underline{C}$4), 167.9 (quat., $\underline{C}OOCH_3$), 207.3 (quat., $CH_2\underline{C}OCH_2$); *m/z* (ESi+, %) 461 (MH^+, 2), 429 (82), 337 (9), 261 (100), 181 (8), 91 (12); Found MH^+, 461.2331 $C_{29}H_{33}O_5$ requires 461.2323.

Synthesis of (*R*)-6,8-bis(benzyloxy)-3-pentylisochroman-1-one, 7



METHOD A:

(*S*)-Me-CBS (0.43 mL, 1 M in THF, 0.43 mmol) was added to a solution of **11** (0.72 g, 1.44 mmol) in THF (22 mL) and the mixture stirred for 15 min at rt before BH_3.DMS (0.15 mL, 1.59 mmol) was added. The reaction mixture was stirred for 15 h at rt then methanol (0.5 mL) in diethyl ether (20 mL) was added followed by saturated sodium bicarbonate (20 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 x 60 mL). The combined organics were dried over magnesium sulfate and the solvent removed *in vacuo*. The crude oil was partially purified *via* flash chromatography using hexanes-ethyl acetate as eluent (3:2) and the two rotameric alcohols (R_F = 0.27 and 0.35) were collected. The two combined rotamers (0.72 g) were heated to 90 ^oC for 19 h in a solution of anhydrous hydrochloric acid (40 mL, 2 M in dioxane). The reaction mixture was cooled to rt, diethyl ether (30 mL) and saturated sodium bicarbonate (30 mL) added and the layers separated. The organic layer was washed with water (30 mL) and the combined aqueous layers extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* to afford a crude oil consisting of the partially deprotected desired product **7**. This oil was dissolved in dimethylformamide (20 mL), silver (I) oxide (1.67 g, 7.2 mmol) and benzyl bromide (0.86 mL, 7.2 mmol) were added and the mixture stirred at rt for 6 h. The reaction mixture was filtered through a pad of Celite that was washed with ethyl acetate (50 mL). The filtrate was washed with water (2 x 30 mL) and saturated sodium chloride (30 mL). The combined aqueous layers were extracted with ethyl acetate (3 x 20 mL), and the combined organic layers dried over magnesium sulfate and the solvent removed *in vacuo*. The resulting oil was purified *via* flash chromatography using hexane-ethyl acetate as eluent (4:1, R_F = 0.38) to afford the *title compound* **7** (0.36 g, 57%) as a colourless oil. e.e. = 51% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), v = 0.5 mL.min^{-1}, λ = 254 nm, t_1(*R*) = 29.06 (75.53%), t_2(*S*) = 64.82 (24.47%); $[\alpha]_D^{20}$ = +32.6° (*c* 0.1 in CH_2Cl_2); ν_{max} (diamond/cm^{-1}) 2930 (C-H str.), 1712 (C=O str.), 1600, 1579, 1161 (C-O str.), 733, 695; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* = 6.3 Hz, $C\underline{H}_3$), 1.22-1.37 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.37-1.95 (4H, m, $CHOC\underline{H}_2C\underline{H}_2$), 2.71–2.87 (2H, m, C4$\underline{H}_2$), 4.31-4.35 (1H, m, C3$\underline{H}$), 5.03 (2H, s, $C\underline{H}_2C_6H_5$), 5.16 (2H, q, *J* = 14.0 Hz, $C\underline{H}_2C_6H_5$), 6.37 (1H, s, C7$\underline{H}$), 6.50 (1H, s, C5$\underline{H}$), 7.24-7.39 (8H, m, from 2 x $CH_2C_6\underline{H}_5$), 7.53 (2H, d, *J* = 7.6 Hz, from 2 ArH x $CH_2C_6H_5$); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3, $\underline{C}H_3$), 22.4 (CH_2, $CHOCH_2\underline{C}H_2$), 24.6 (CH_2, $\underline{C}H_2CH_3$), 31.5 (CH_2, $\underline{C}H_2CH_2CH_3$), 34.6 (CH_2, $CHO\underline{C}H_2$), 34.9 (CH_2, $\underline{C}$4), 70.1, 70.4 (2 x CH_2, 2 x $\underline{C}H_2C_6H_5$), 77.1 (CH, $CH_2\underline{C}HOCH_2$), 100.1 (CH, $\underline{C}$7), 105.1 (CH, $\underline{C}$5), 107.8 (quat., $\underline{C}$8a), 126.5, 127.4, 127.5, 128.2, 128.4, 128.6 (10 x CH, 2 x $CH_2C_6\underline{H}_5$), 135.8, 136.3 (2 x quat., from 2 x $\underline{Bn}$O), 143.9 (quat., $\underline{C}$4a), 161.8 (quat., $\underline{C}$8), 162.4 (quat.,

C=O), 163.1 (quat., C6); *m/z* (EI+, %) 430 (M+, 14), 340 (7), 181 (3), 91 ($C_5H_6CH_2$, 100), 69 (3), 65 (5), 55 (4), 43 (4); Found M+ 430.21328. $C_{28}H_{30}O_4$ requires 430.21441.

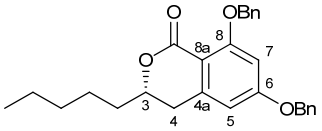
METHOD B:

Freshly prepared[4] (L)-TarB-NO_2 (1.44 mL, 0.5 M in THF) was added to **13** (0.167 g, 0.36 mmol) at rt and the mixture stirred for 10 min. The resulting complex was added to a suspension of sodium borohydride (0.027 g, 0.72 mmol) in THF (0.5 mL) at -78 °C. The reaction mixture was allowed to warm to rt in the dry ice bath for 13.5 h before aqueous hydrochloric acid (5 mL, 10%) was added. After gaseous evolution had ceased, the reaction mixture was basified to pH 12 using aqueous sodium hydroxide (~10 mL, 1 M) before extracting with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo*. The resultant crude oil was dissolved in dichloromethane (5 mL), Amberlyst 15® (0.2 g, Aldrich) was added, and the reaction mixture stirred at rt for 2 h. The resin was removed by filtration, washed with dichloromethane (50 mL) and the solvent removed *in vacuo*. The resultant crude oil was purified *via* flash chromatography utilizing hexanes-ethyl acetate (4:1, R_F = 0.38) as eluent to afford the *title compound* **7** (0.15 g, 97%) as a colourless oil. e.e. = 73% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), v = 0.5 mL.min^{-1}, λ = 254 nm, t_1(*R*) = 24.31 (86.38%), t_2(*S*) = 54.86 (13.62%); $[\alpha]_D^{22}$ = +45.5° (*c* 0.2 in CH_2Cl_2)

Preparatory HPLC separation of desired enantiomer:

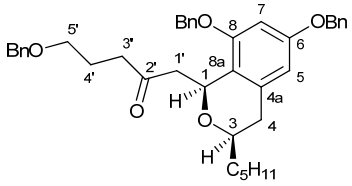
7 (0.094 g, 0.22 mmol, 69% e.e. (HPLC)) was split into 4 batches and run on a Chiralpak® AD-H semiprep column (i.d. 10 mm) using hexanes/isopropanol (13/7), v = 4.7 mL.min^{-1}, λ = 254 nm, t_1(*R*) = 9.0 - 14.0, t_2(*S*) = 21.5 – 32.0, to afford **7** ((*R*), 0.076 g, 0.18 mmol) and ***ent*-7** ((S), 0.014 g, 0.03 mmol) (96% recovery of product) which were determined to have e.e.'s of >99% ($[\alpha]_D^{16.4}$ = +59.4° (*c* 0.05 in CH_2Cl_2)) and 90% ($[\alpha]_D^{19.1}$ = -61.5° (*c* 0.15 in CH_2Cl_2)) respectively by analytical chiral HPLC as above.

Synthesis of (*S*)-6,8-bis(benzyloxy)-3-pentylisochroman-1-one, *ent*-7

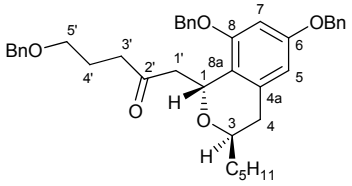


***ent*-7** was synthesized in a similar manner to its enantiomer. (D)-TarB NO_2[4] (1.76 mL, 0.5 M in THF), was added to **13** (0.21 g, 0.44 mmol) and stirred at rt for 10 min. The resulting complex was added to a suspension of sodium borohydride (0.033 g, 0.88 mmol) in THF (0.5 mL) at -78 °C. The reaction mixture was allowed to warm to rt in the dry ice bath over 18 h before work up and Amberlyst 15® catalyzed cyclization as for **7** to afford the *title compound* ***ent*-7** (0.145 g, 77%) as a colourless oil. e.e. = 73% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), v = 0.5 mL.min^{-1}, λ = 254 nm, t_1(*R*) = 25.28 (13.51%), t_2(*S*) = 50.07 (86.49%); $[\alpha]_D^{18}$ = -37.5° (*c* 0.1 in CH_2Cl_2). The ^{1}H NMR data obtained was in agreement with that reported above for **7**.

Synthesis of 5-(benzyloxy)-1-((1*S*,3*R*)-6,8-bis(benzyloxy)-3-pentylisochroman-1-yl)pentan-2-one and 5-(benzyloxy)-1-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-pentylisochroman-1-yl)pentan-2-one, *cis* and *trans*-3



1*S*, 3*R*-**XXX** (cis)



1*R*, 3*R*-**XXX** (trans)

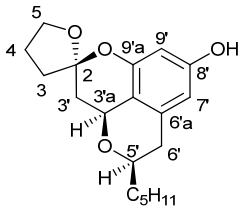
Diisobutylaluminium hydride (0.12 mL, 1 M in toluene, 0.12 mmol) was added to a solution of **7** (0.05 g, 0.12 mmol) in toluene (1 mL) at -78 °C and the reaction mixture was stirred at this temperature for 3 h. Ethyl acetate (1 mL), methanol (0.1 mL) and water (1 mL) were added, the reaction mixture warmed to rt and the layers separated. The aqueous layer was extracted with ethyl acetate (5 mL), the combined organic layers dried over magnesium sulfate and the solvent removed *in vacuo* to afford the crude lactol.

A solution of **5** (0.1081 g, 0.36 mmol) in THF (0.5 mL) was added to a suspension of sodium hydride (0.0144 g, 0.36mmol, 60% in paraffin) in THF (0.5 mL) at 0 ^{o}C and the reaction mixture stirred at rt for 30 min. A solution of the crude lactol in THF (1 mL) was added and the reaction mixture heated to reflux for 15.5 h. The reaction mixture was cooled to rt and water (5 mL) added then extracted with diethyl ether (3 x 5 mL) then dichloromethane (3 x 5 mL). The combined organics were dried over magnesium sulfate and the solvent removed *in vacuo*. The resultant crude oil was purified *via* flash chromatography using hexanes-ethyl acetate as eluent (4:1, R_F = 0.57) to afford the *title compound* **3** (0.0581 g, 80%*) as a colourless solid, m.p. = 93.5-94.5 °C. e.e. > 99% (**3a** and **3b**), d.r. = 1:1.48 (**3a**:**3b**) (HPLC, Chiralpak® IC, hexanes/isopropanol (9/1), v = 0.5 mL.min^{-1}, λ = 210 nm, t_1(1*S*, 3*R*) = 20.44 (40.33%), t_2(1*R*, 3*R*) = 37.56 (59.67%); $[\alpha]_D^{20.6}$ = +41.0° (*c* 0.01 in CH_2Cl_2); ν_{max} (diamond/cm^{-1}) 2928 (C-H str.), 2856 (C-H str.), 1707 (C=O, str.) 1596, 1150, 1092 (C-O-C ring, str.), 1337, 733, 694; δ_H (400 MHz, $CDCl_3$) 0.86-0.90 (3H, m, C$\underline{H}_3$), 1.24-1.51 (8H, m, 4 x C$\underline{H}_2$ from C_5H_{11}), 1.78-1.89 (2H, m, C4′$\underline{H}_2$), 2.46-2.66 (4.6H, m, C3′$\underline{H}_2$, C4$\underline{H}_2$, C1′$\underline{H}H_{CIS}$), 2.84 (0.6H, dd, *J* = 10.4, 14.8 Hz, C1′$\underline{H}H_{TRANS}$), 3.00 (0.59H, dd, *J* = 3.0, 15.4H, C1′H$\underline{H}_{TRANS}$), 3.27 (0.44H, dd, *J* = 2.8, 14.8 Hz, C1′H$\underline{H}_{CIS}$), 3.40-3.50 (2.55H, m, C5′$\underline{H}_2$, C3$\underline{H}_{CIS}$), 3.80-3.86 (0.59H, m, C3$\underline{H}_{TRANS}$), 4.45-4.46 (2H, m, $CH_2OC\underline{H}_2C_6H_5$), 5.00-5.02 (4H, m, 2 x $ArOC\underline{H}_2C_6H_5$), 5.34 (0.43H, br. d, *J* = 6.8 Hz, C1$\underline{H}_{CIS}$), 5.51 (0.57H, dd, *J* = 3.0, 10.6 Hz, C1$\underline{H}_{TRANS}$), 6.33 (1H, d, *J* = 2.0 Hz, C7$\underline{H}$), 6.44 (1H, dd, *J* = 2.4, 4.8 Hz, C5$\underline{H}$), 7.24-7.42 (15H, m, 3 x $CH_2C_6\underline{H}_5$); δ_C (100 MHz; $CDCl_3$) 14.05 (CH_3, $\underline{C}H_3$), 22.6 (CH_2, from C_5H_{11}), 23.65, 23.69 (CH_2, $\underline{C}4'_{CIS}$ and $_{TRANS}$), 25.08, 25.10 (2 x CH_2, from C_5H_{11} $_{CIS}$ and $_{TRANS}$), 31.8, 31.9 (2 x CH_2, from C_5H_{11} $_{CIS}$ and $_{TRANS}$), 34.5 (CH_2, C3′ or C4 $_{CIS}$ or $_{TRANS}$), 35.6 (CH_2, C3′ or C4 $_{CIS}$ or $_{TRANS}$), 35.8, 35.9 (2 x CH_2, from C_5H_{11} $_{CIS}$ and $_{TRANS}$), 38.8 (CH_2, C3′ or C4 $_{CIS}$ or $_{TRANS}$), 39.7 (CH_2, C3′ or C4 $_{CIS}$ or $_{TRANS}$), 46.9 (CH_2, $\underline{C}1'_{TRANS}$), 49.0 (CH_2, $\underline{C}1'_{CIS}$), 67.3 (CH, $\underline{C}3_{TRANS}$), 68.9 (CH, $\underline{C}1_{TRANS}$), 69.5, 69.6 (CH_2, $\underline{C}5'_{CIS}$ and $\underline{C}5'_{TRANS}$), 69.9, 70.0 (2 x CH_2, $ArO\underline{C}H_2C_6H_5$ $_{CIS}$ and $_{TRANS}$), 70.10, 70.12 (2 x CH_2, $ArO\underline{C}H_2C_6H_5$ $_{CIS}$ and $_{TRANS}$), 71.4 (CH, $\underline{C}1_{CIS}$), 72.7, 72.8 (2 x CH_2, $CH_2OC\underline{H}_2C_6H_5$ $_{CIS}$ and $_{TRANS}$), 73.3 (CH, $\underline{C}3_{CIS}$), 98.3, 98.7 (2 x CH, $\underline{C}5_{CIS}$ and $\underline{C}5_{TRANS}$), 105.7, 106.0 (2 x CH, $\underline{C}7_{CIS}$ and $\underline{C}7_{TRANS}$), 118.69 and 119.73 (2 x quat., $\underline{C}8a_{CIS}$ and $\underline{C}8a_{TRANS}$), 127.1, 127.5, 127.6, 127.9, 128.0, 128.3, 128.6 (15 x CH, from 3 x OBn), 135.8 (quat., from CH_2OBn), 136.6 (quat., $\underline{C}4a$), 136.9, 137.7 (2 x quat., from 2 x ArOBn), 155.2, 155.8 (2 x quat., $\underline{C}8_{CIS}$ and $\underline{C}8_{TRANS}$), 158.2, 158.4 (2 x quat., $\underline{C}6_{CIS}$ and $\underline{C}6_{TRANS}$), 208.6, 209.5 (2 x quat., $\underline{C}2'_{CIS}$ and $\underline{C}2'_{TRANS}$);

m/z (FAB+, %) 606 (M^+, 2), 515 (10), 415 (36), 325 (5), 181 (3), 91 (100); Found M^+, 606.3345. $C_{40}H_{46}O_5$ requires 606.33452.

* upon repetition the yield for this step proved to be variable

Synthesis (2*R*,3a′*S*,5′*R*)-5′-pentyl-3′,3a′,4,5,5′,6′-hexahydro-3H-spiro[furan-2,2′-pyrano[2,3,4-de]chromen]-8′-ol, 2



Palladium hydroxide (0.0098 g, 20% in carbon) and hydrochloric acid (2 drops, 4 M in dioxane) was added to a solution of **3** (0.045 g, 0.07 mmol) in tetrahydrofuran (1 mL) and the mixture stirred under a hydrogen atmosphere at rt for 18 h. The reaction mixture was loaded directly onto a preparatory thin layer plate and was eluted with hexanes-ethyl acetate (4:1, R_F = 0.48) to give the *title compound* **2** (0.0147 g, 72%) as a colourless solid, m.p. = 34.4-35.6 °C. e.e. >99%, d.r. = 14:1 (2(*R*):2(*S*)) (HPLC, Chiralpak® IC, hexanes/isopropanol (19/1), v = 0.5 mL.min^{-1}, λ = 210 nm, t_1(2*R*, 3′a*S*, 5′*R*) = 29.69 (93.57%), t_2(2*S*, 3′a*S*, 5′*R*) = 48.74 (6.43%); $[\alpha]_D^{19.9}$ = +72.7° (c 0.045, CH_2Cl_2); ν_{max} (diamond/cm^{-1}) 3346 (O-H str.), 2928 (C-H str.), 2859 (C-H (CH_2O) str.), 1600, 1456, 1316, 1151, 1078, 1016, 838; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* = 6.8 Hz, C$\underline{H}_3$), 1.26-1.41 (6H, m, 3 x C$\underline{H}_2$ from C_5H_{11}), 1.50-1.68 (4, m, 2 x C$\underline{H}_2$ from C_5H_{11}), 1.91-2.06 (3H, m, C3$\underline{H}$H and C4$\underline{H}_2$), 2.23-2.29 (3H, m, C3H$\underline{H}$ and C3′$\underline{H}_2$), 2.59 (1H, dd, *J* = 11.0, 16.8 Hz, C6′$\underline{H}$H), 2.74 (1H, dd, *J* = 4.4, 16.8 Hz, C6′H$\underline{H}$), 3.80-3.87 (1H, m, H5′), 3.98-4.00 (1H, m, C5$\underline{H}$H), 4.02-4.09 (1H, m, C5H$\underline{H}$), 4.68 (1H, s, O$\underline{H}$), 4.81 (1H, dd, *J* = 5.4, 12.2 Hz, C3′a$\underline{H}$), 6.10 (1H, d, *J* = 2.4 Hz, C9′$\underline{H}$), 6.16 (1H, d, *J* = 1.6 Hz, C7′$\underline{H}$); δ_C (75 MHz; $CDCl_3$) 14.1 (CH_3, $\underline{C}H_3$), 22.6 (CH_2, $\underline{C}H_2CH_3$), 23.8 (CH_2, $\underline{C}H_2(CH_2)_2CH_3$), 25.2 ($CH_2$, C4), 31.8 ($CH_2$, C3′), 34.1 ($CH_2$, $\underline{C}H_2CH_2CH_3$), 36.3 (CH_2, $\underline{C}H_2(CH_2)_3CH_3$), 36.5 ($CH_2$, $\underline{C}$6′), 37.8 (CH_2, $\underline{C}$3), 68.3 (CH_2, $\underline{C}$5), 68.6 (CH, $\underline{C}$7′), 75.6 (CH, $\underline{C}$5′), 100.5 (CH, $\underline{C}$9′), 107.1 (CH, $\underline{C}$7′), 108.2 (quat., $\underline{C}$2), 113.9 (quat., central C), 135.0 (quat., $\underline{C}$6a′), 151.9 (quat., $\underline{C}$8′), 115.5 (quat., $\underline{C}$9a′); *m/z* (EI+, %) 318 (M^+, 35), 259 (24), 234 (100), 163 (26), 73 (16); Found M^+, 318.1834 $C_{19}H_{26}O_4$ requires 318.1831.

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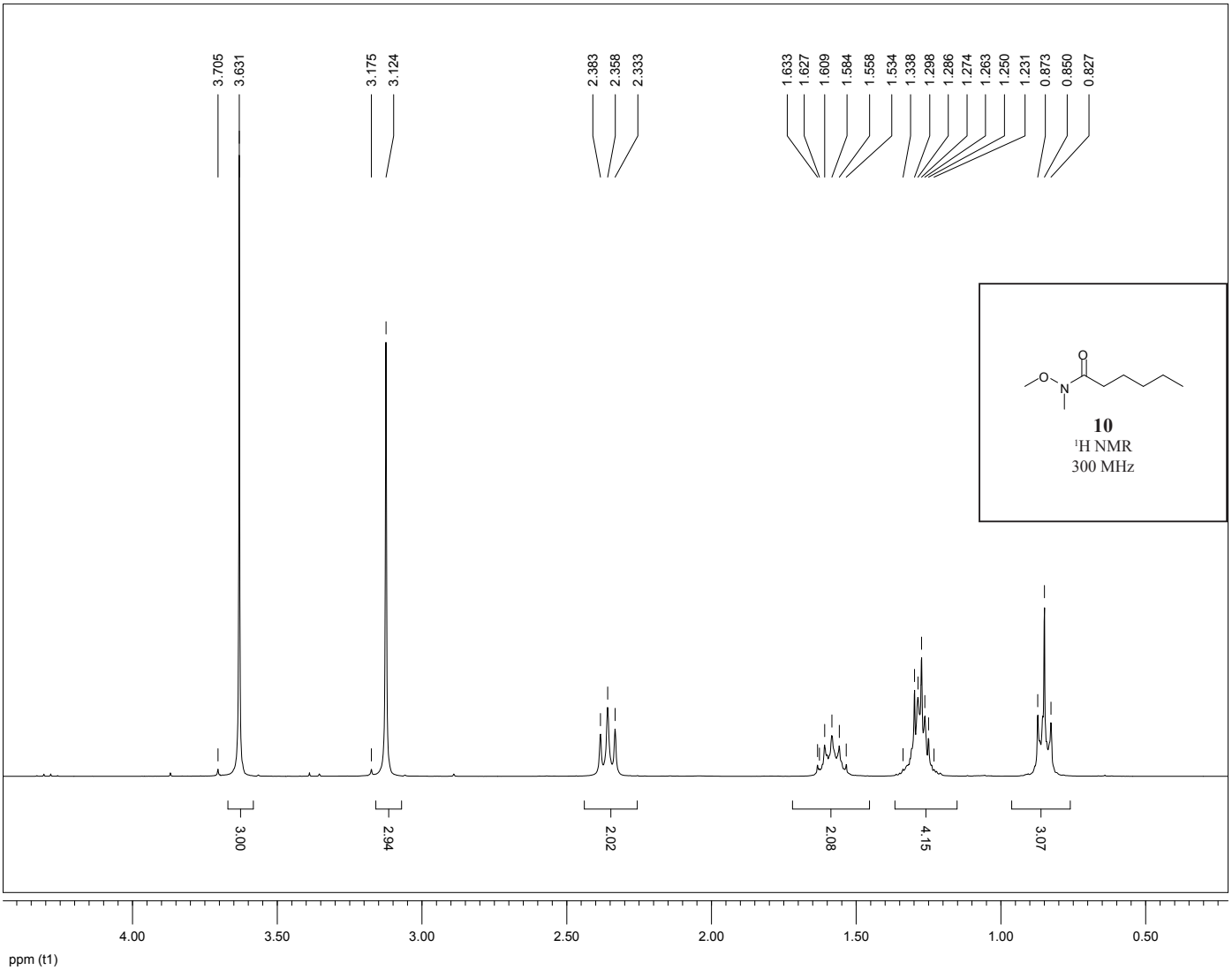
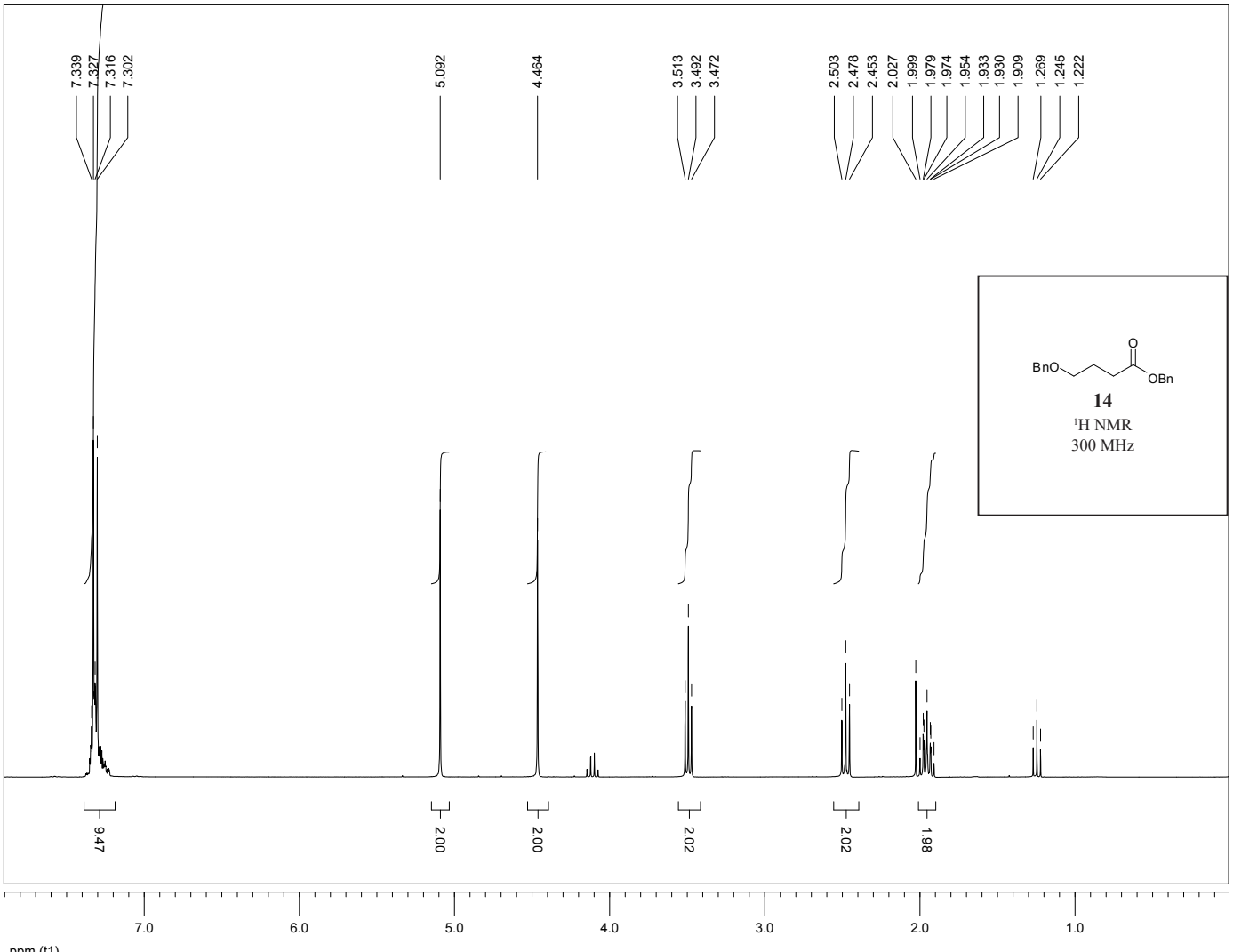
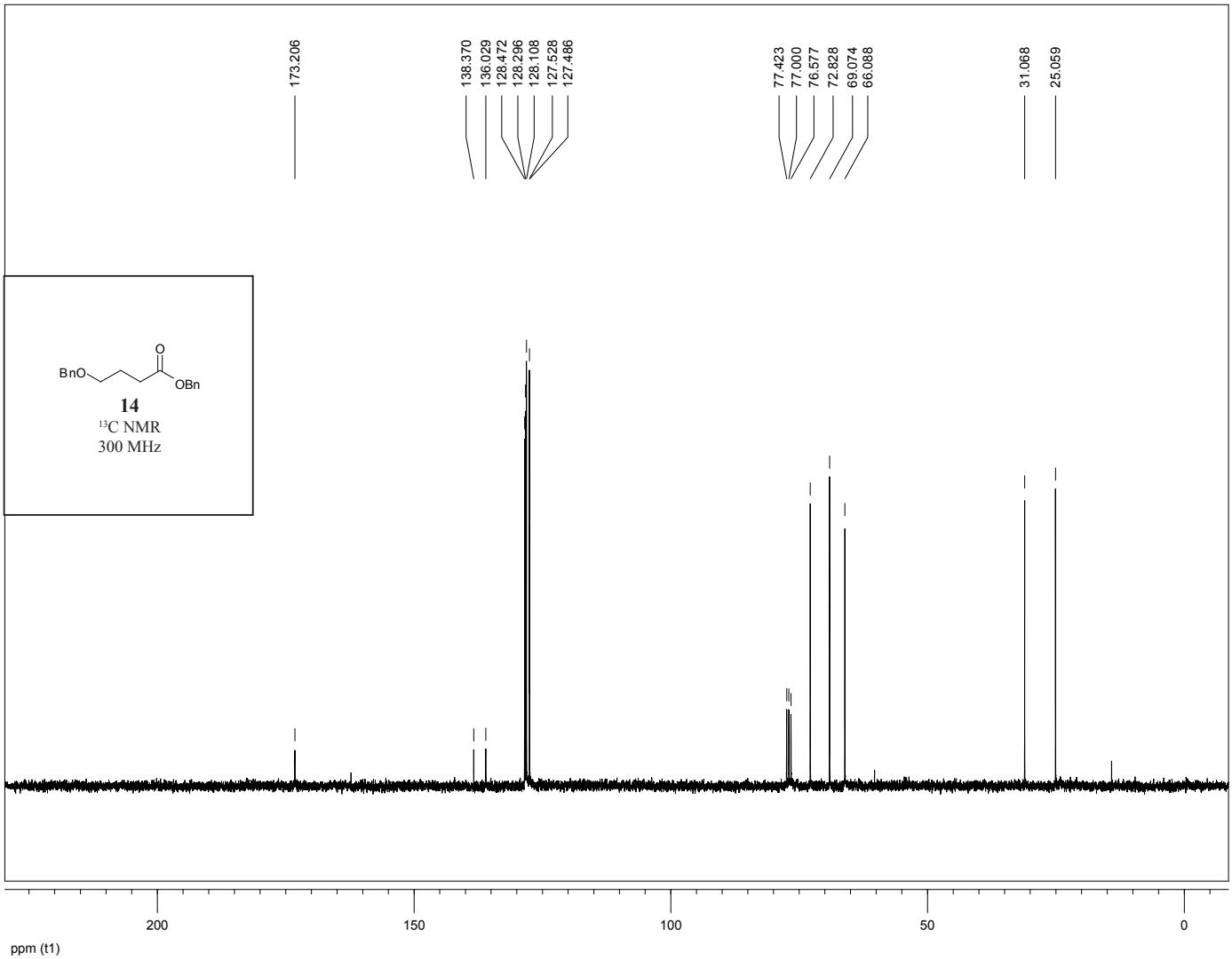
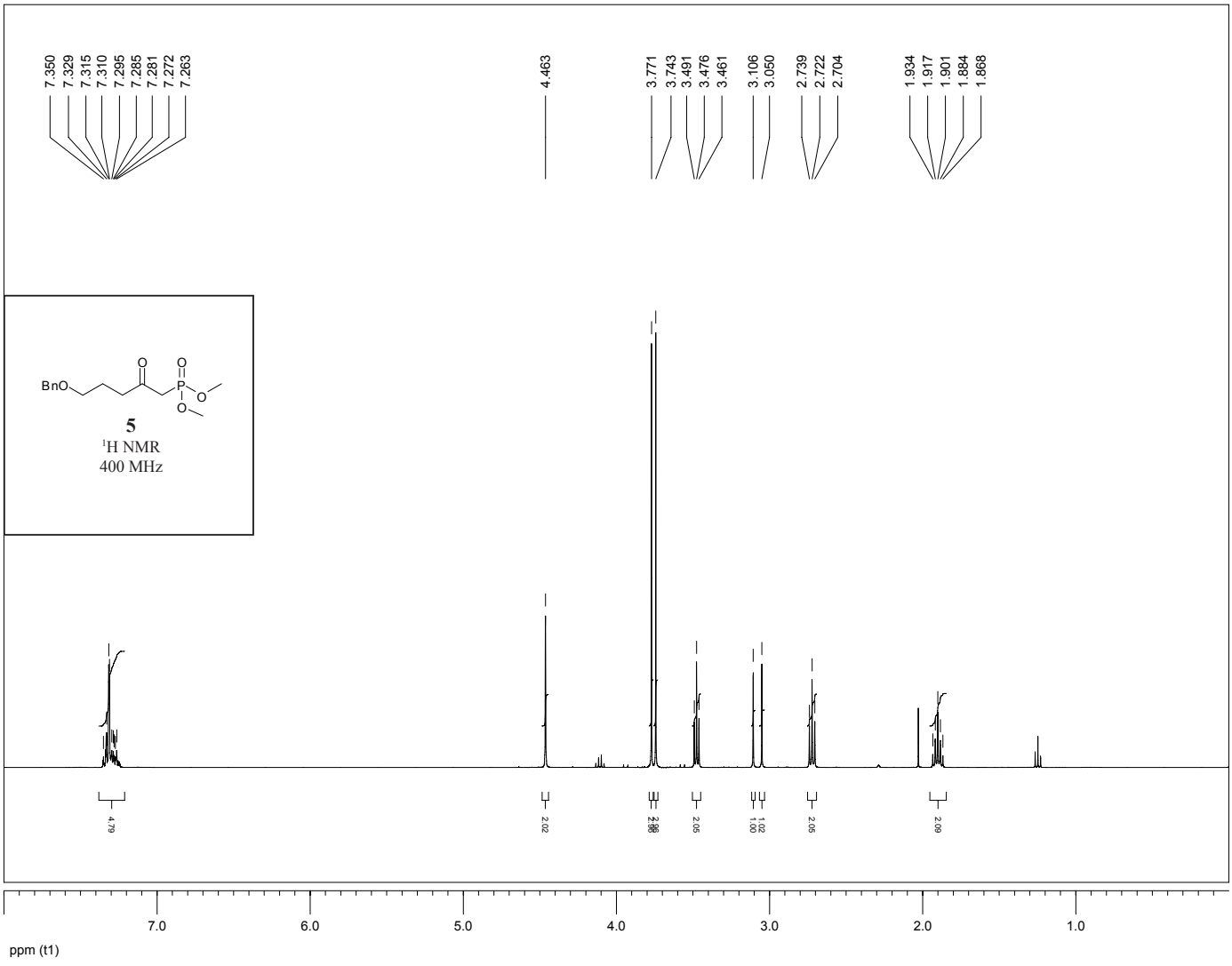


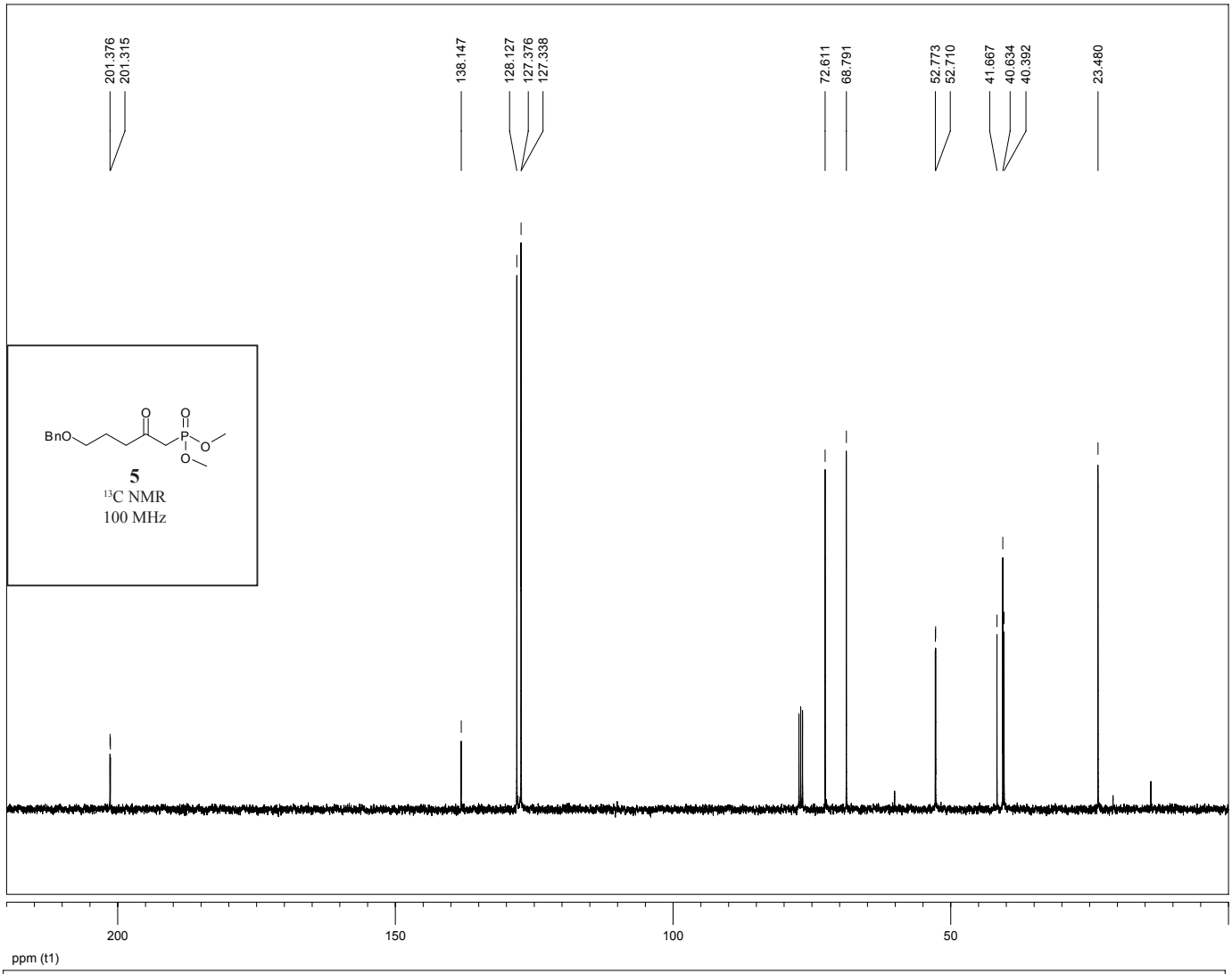
10
^{1}H NMR
300 MHz

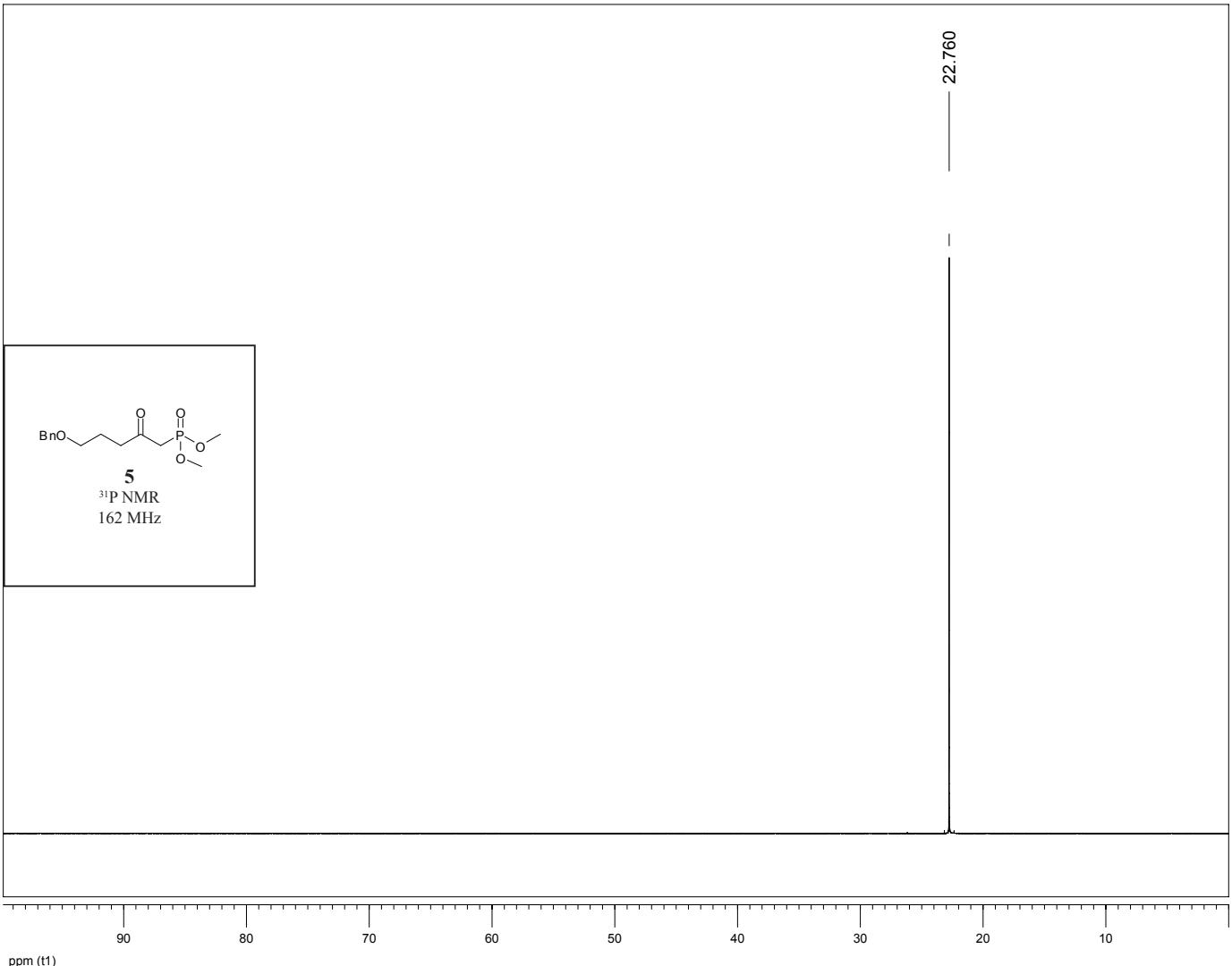


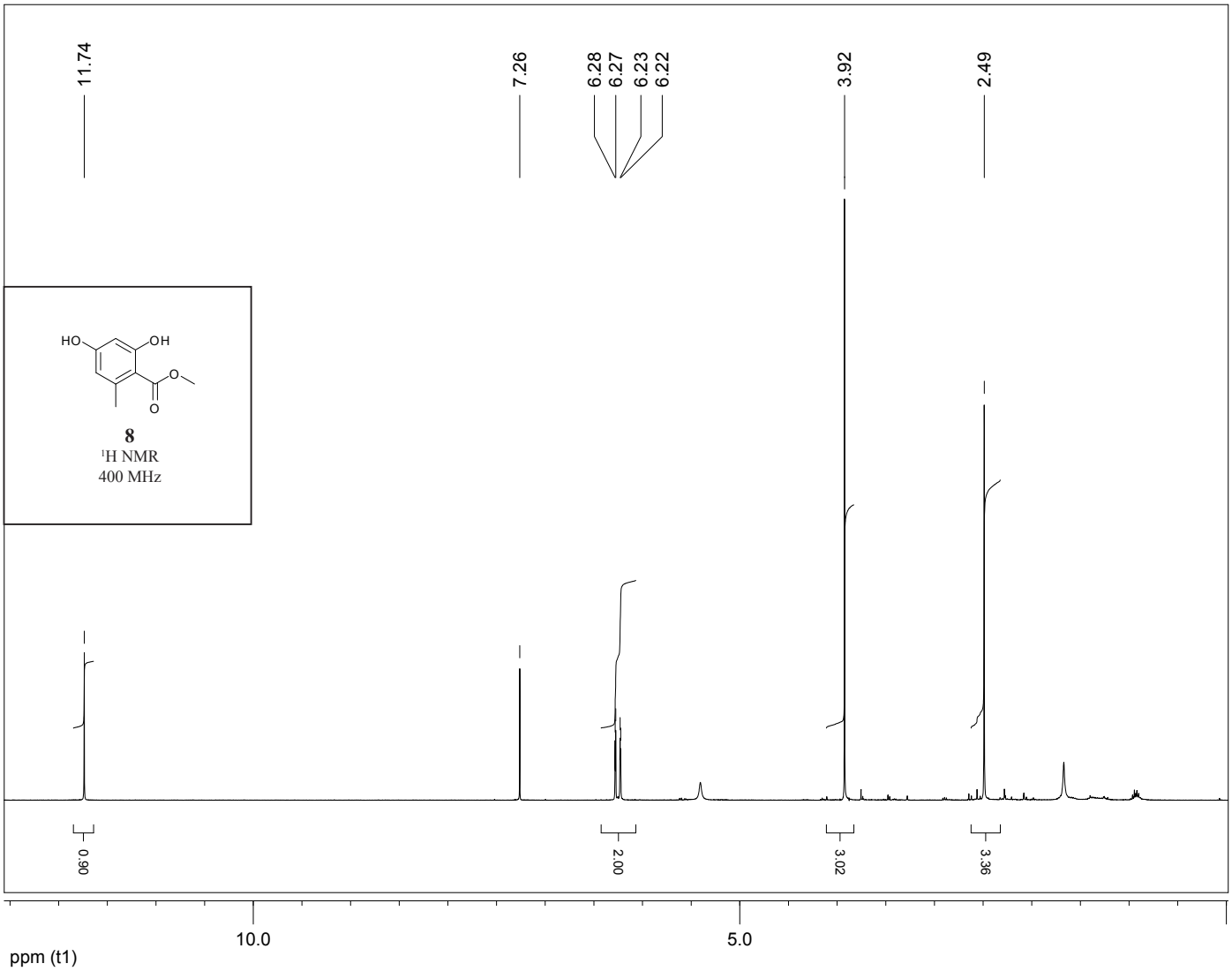
14
^{1}H NMR
300 MHz

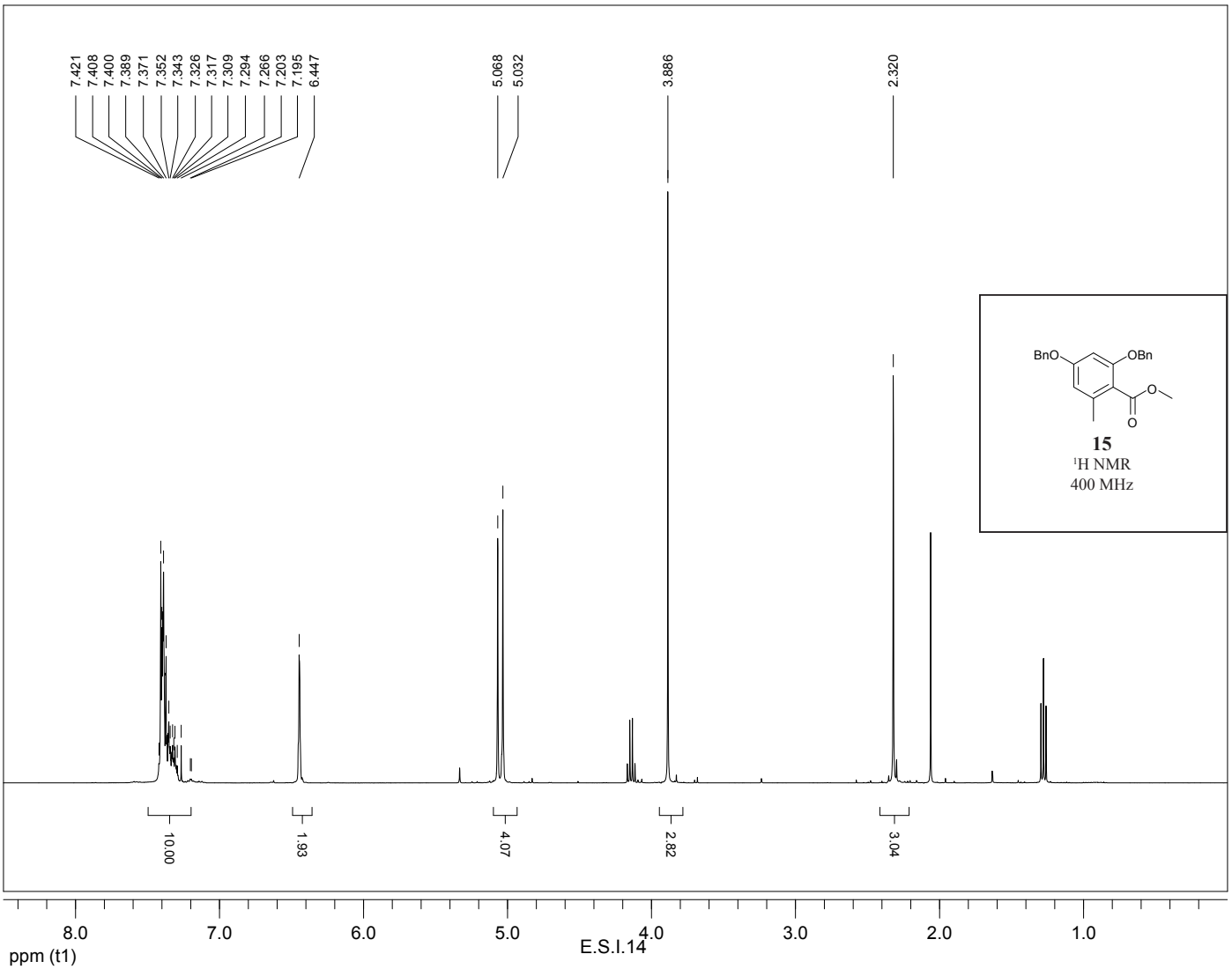

173.206
138.370
136.029
128.472
128.296
128.108
127.528
127.486
77.423
77.000
76.577
72.828
69.074
66.088
31.068
25.059
BnO
OBn
14
13C NMR
300 MHz
200
150
100
50
0
ppm (t1)

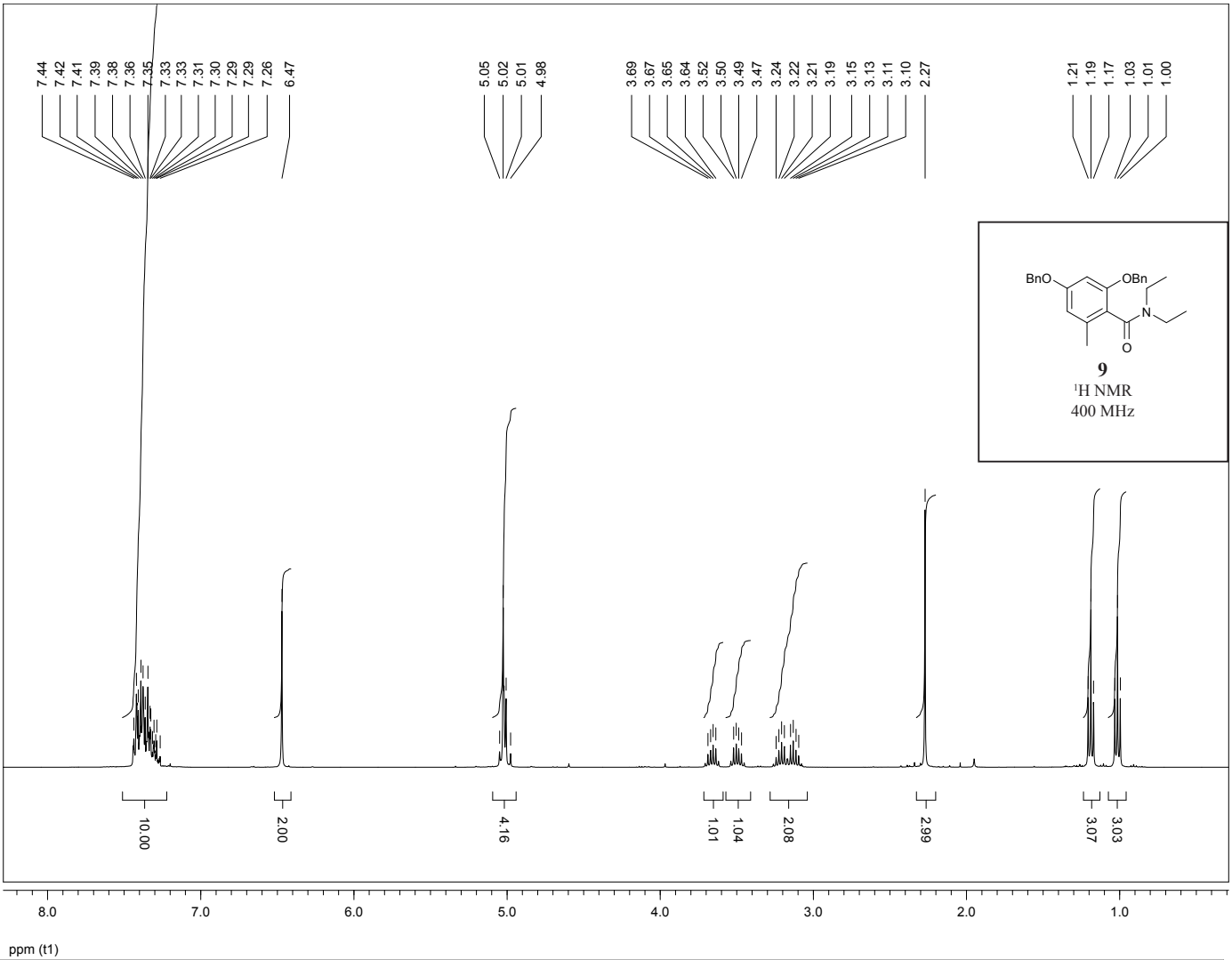

7.350
7.329
7.315
7.310
7.295
7.285
7.281
7.272
7.263
4.463
3.771
3.743
3.491
3.476
3.461
3.106
3.050
2.739
2.722
2.704
1.934
1.917
1.901
1.884
1.868
BnO
5
1H NMR
400 MHz
4.79
2.02
2.05
1.00
1.02
2.05
2.09
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

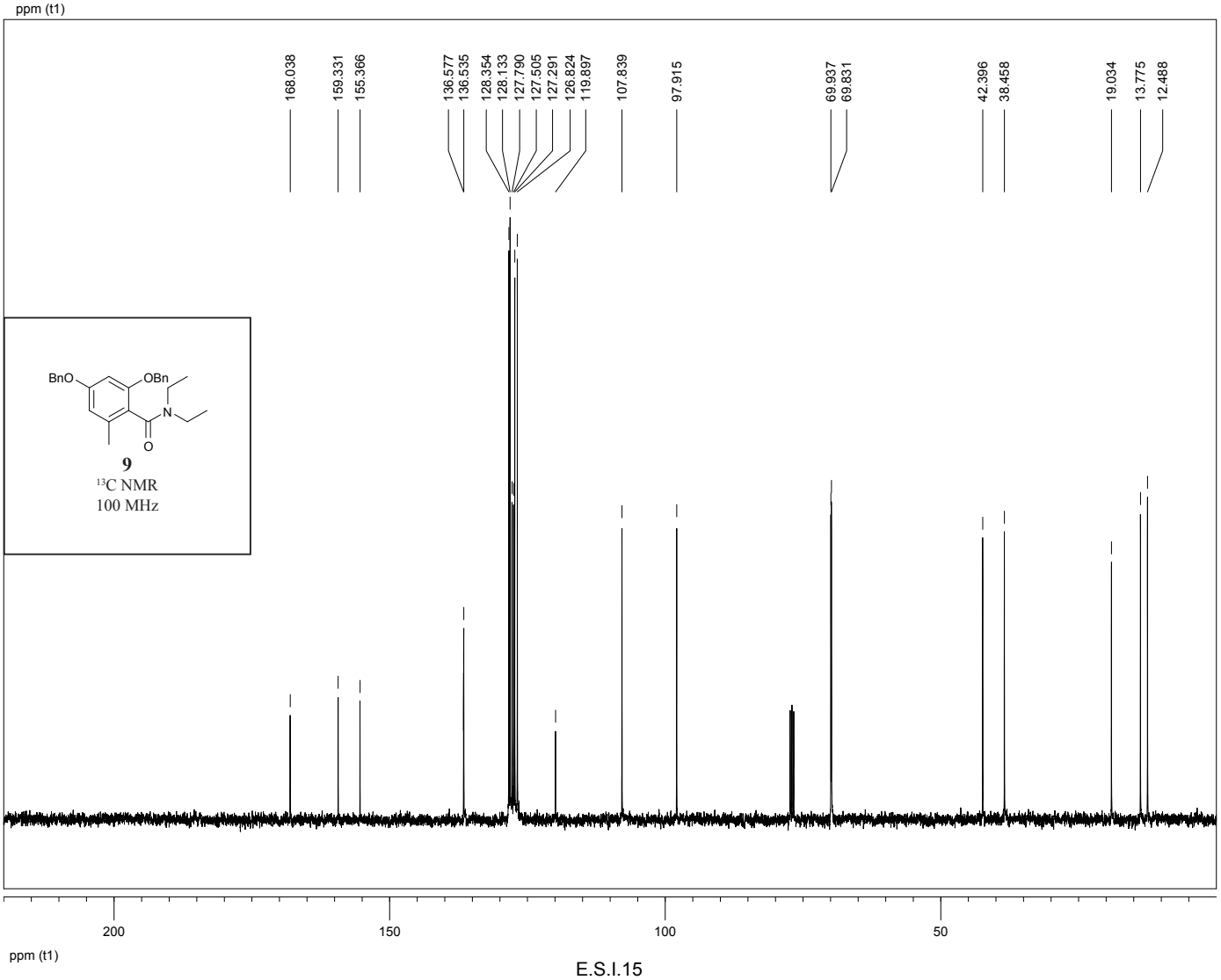

201.376
201.315
138.147
128.127
127.376
127.338
72.611
68.791
52.773
52.710
41.667
40.634
40.392
23.480
BnO
5
13C NMR
100 MHz
200
150
100
50
ppm (t1)

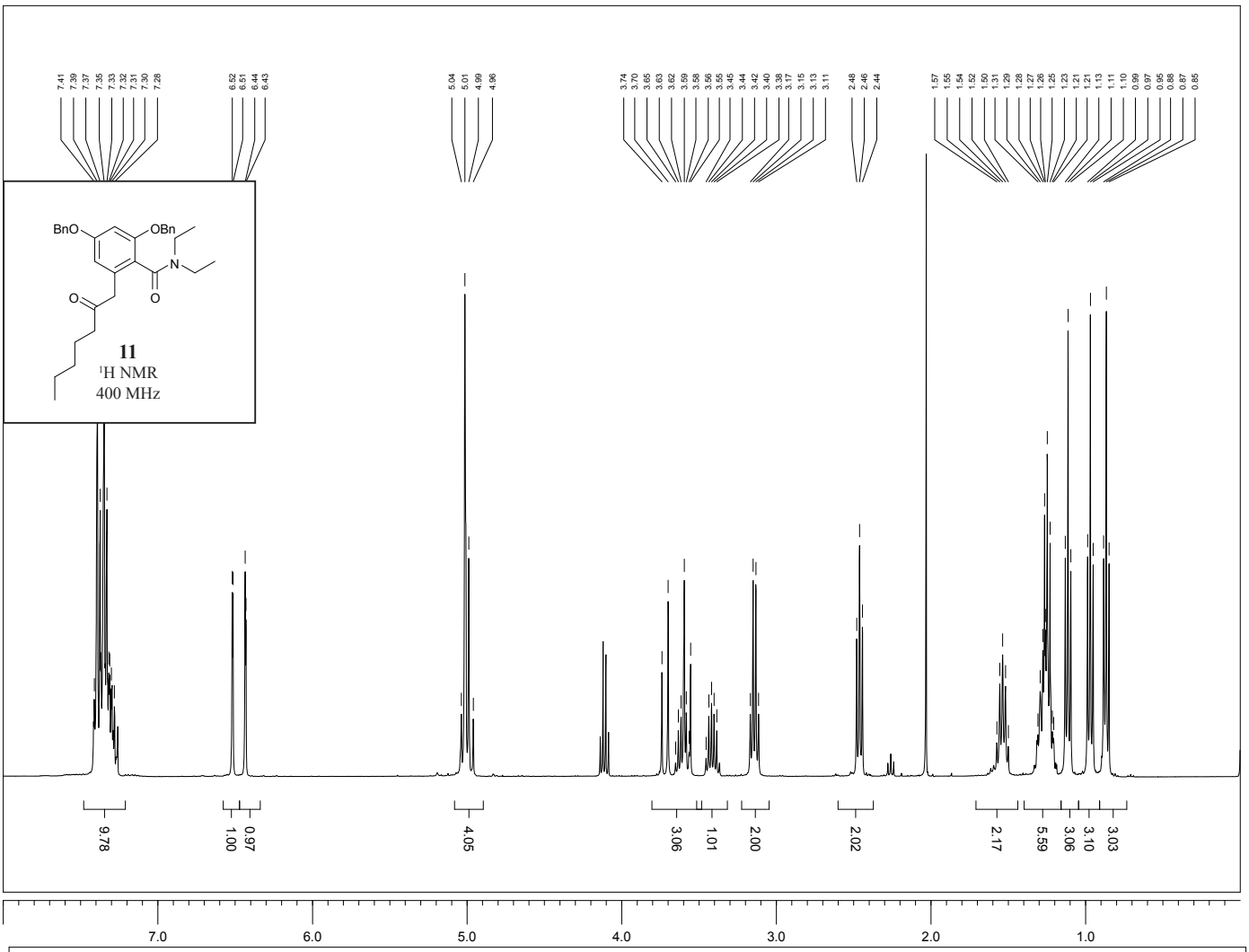

22.760
BnO
5
31P NMR
162 MHz
90
80
70
60
50
40
30
20
10
ppm (t1)

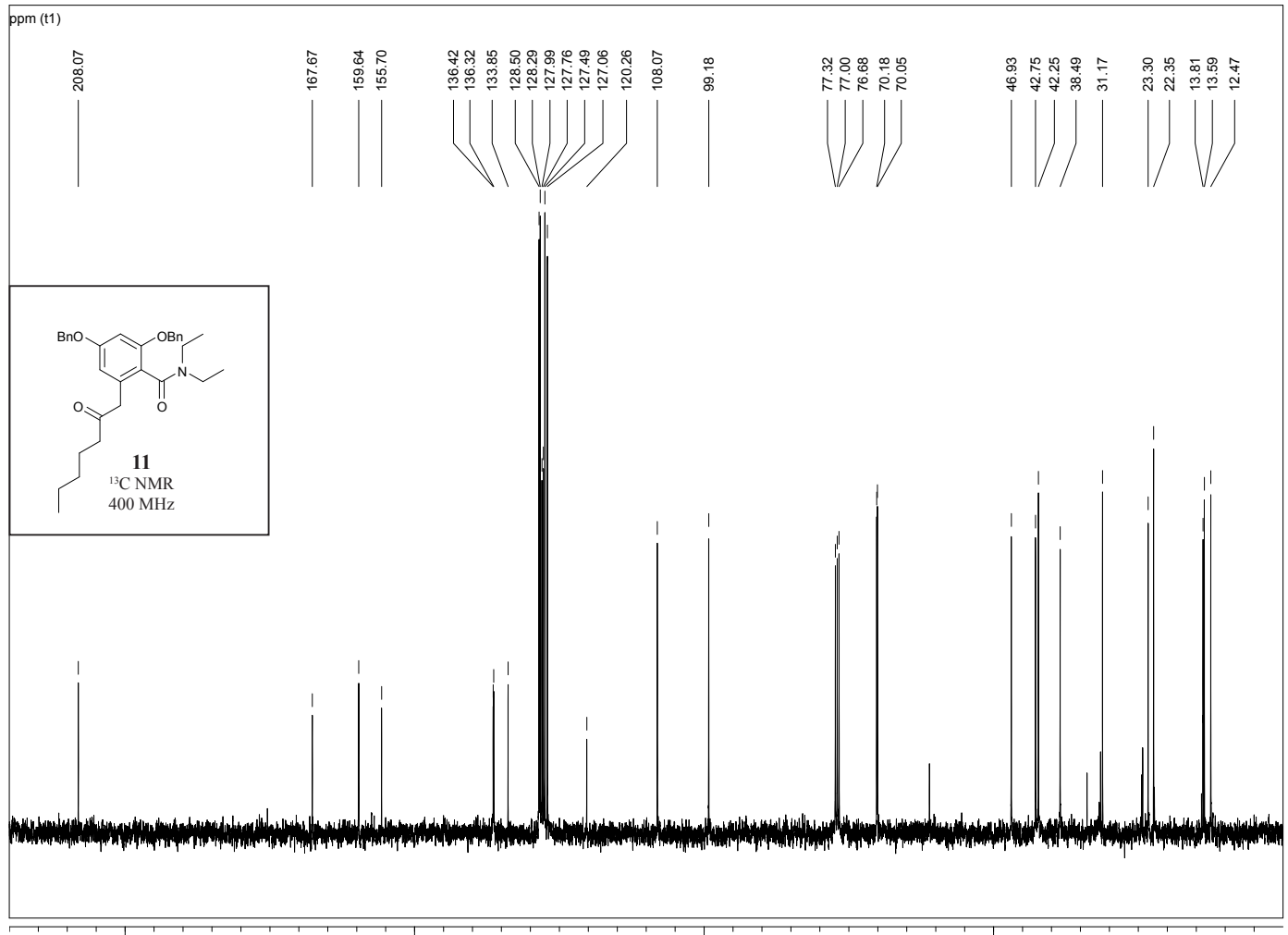

11.74
7.26
6.28
6.27
6.23
6.22
3.92
2.49
HO
OH
O
O
8
1H NMR
400 MHz
0.90
2.00
3.02
3.36
10.0
5.0
ppm (t1)

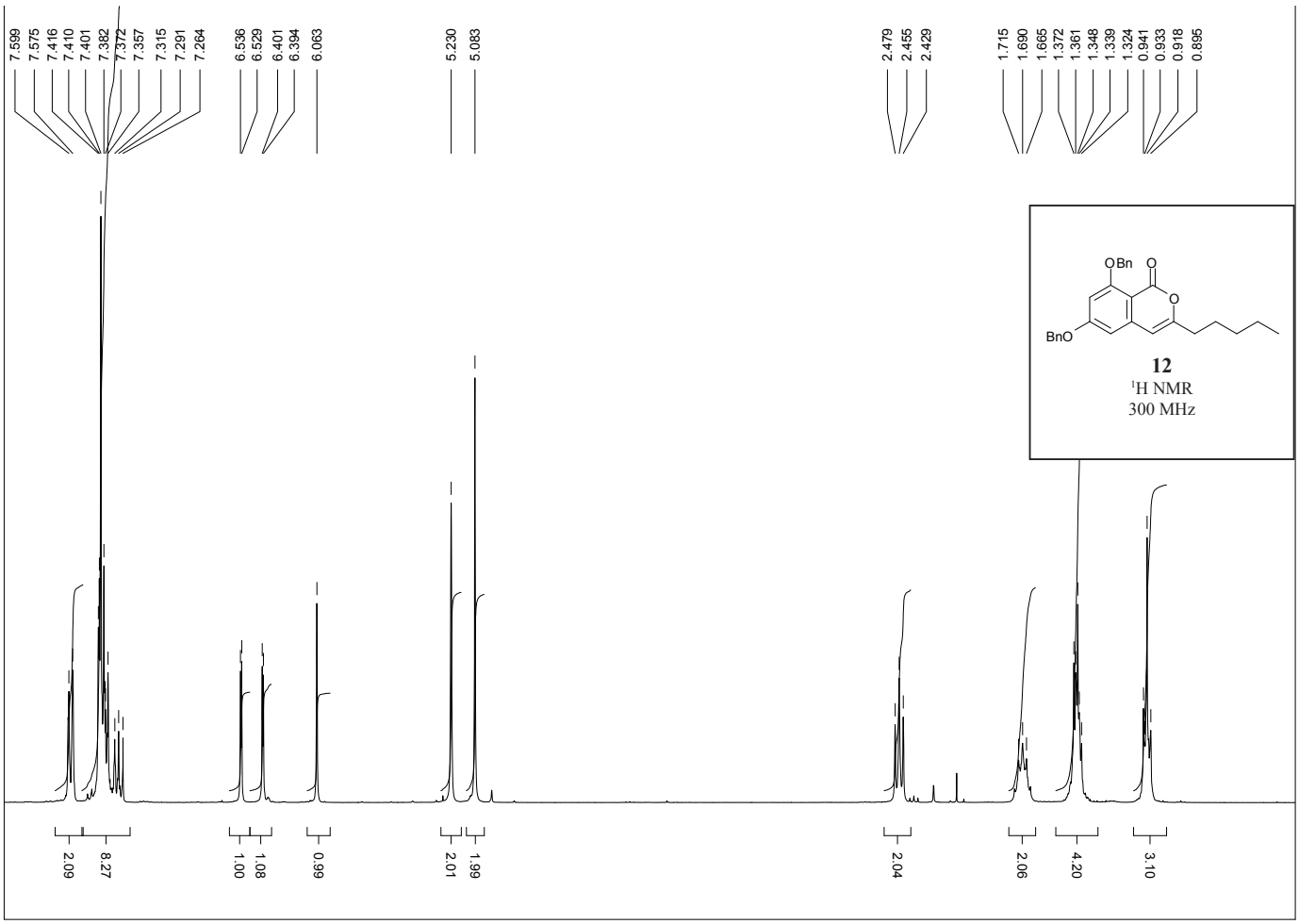

7.421
7.408
7.400
7.389
7.371
7.352
7.343
7.326
7.317
7.309
7.294
7.266
7.203
7.195
6.447
5.068
5.032
3.886
2.320
BnO
OBn
O
O
15
1H NMR
400 MHz
10.00
1.93
4.07
2.82
3.04
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

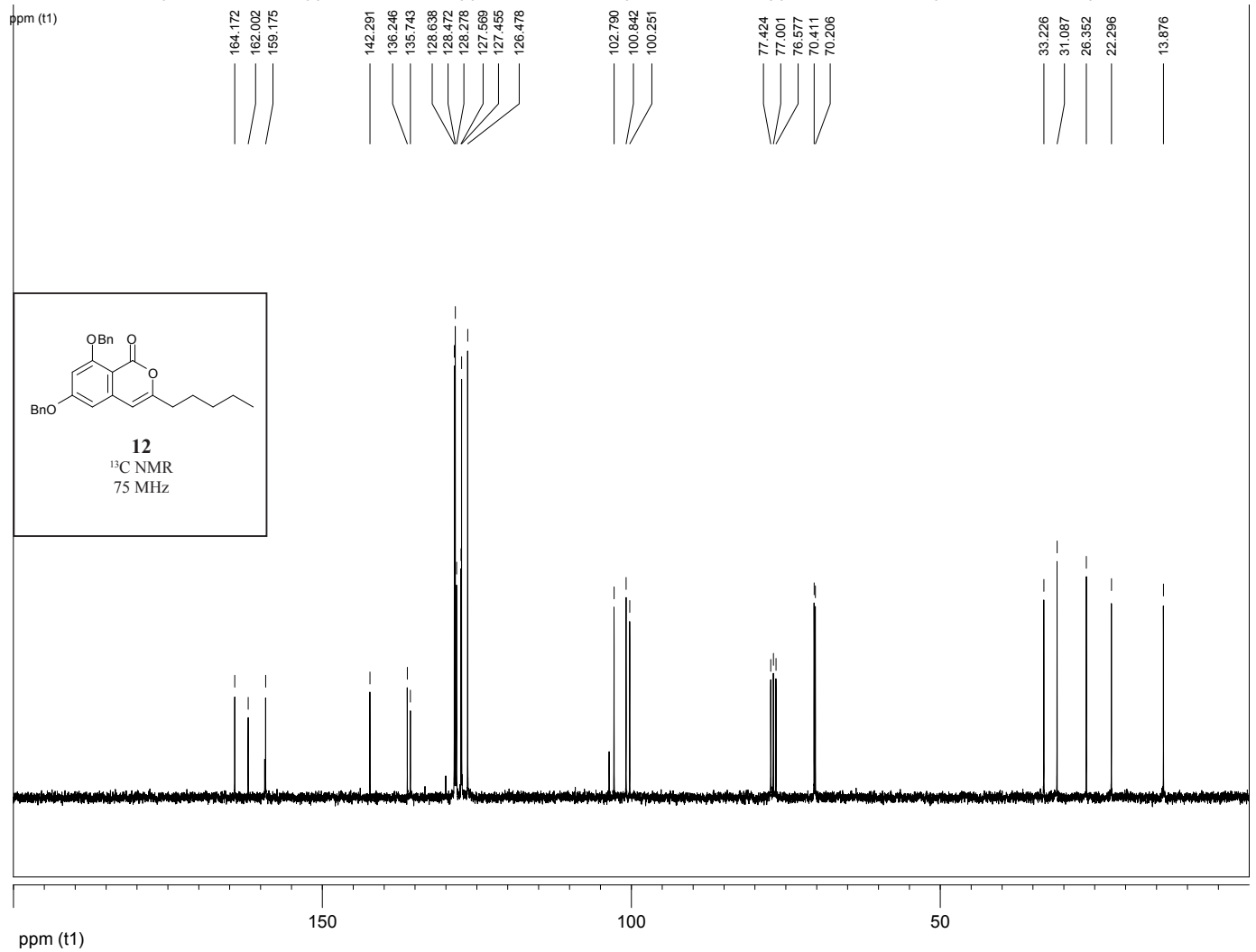

7.44
7.42
7.41
7.39
7.38
7.36
7.35
7.33
7.33
7.31
7.30
7.29
7.29
7.26
6.47
5.05
5.02
5.01
4.98
3.69
3.67
3.65
3.64
3.52
3.50
3.49
3.47
3.24
3.22
3.21
3.19
3.15
3.13
3.11
3.10
2.27
1.21
1.19
1.17
1.03
1.01
1.00
10.00
2.00
4.16
1.01
1.04
2.08
2.69
3.07
3.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
BnO
OBn
N
O
9
1H NMR
400 MHz

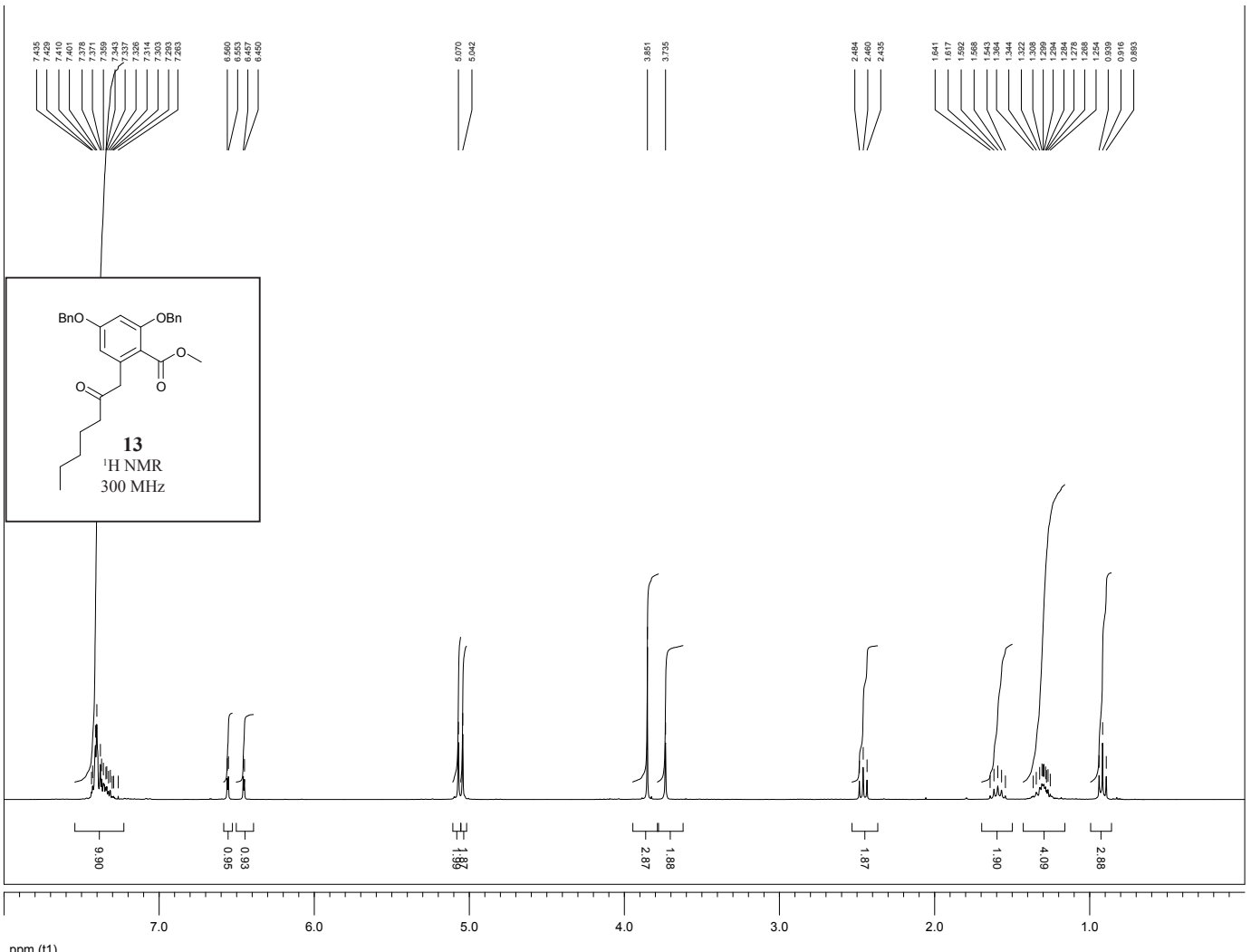

168.038
159.331
155.366
136.577
136.535
128.354
128.133
127.790
127.505
127.291
126.824
119.897
107.839
97.915
69.937
69.831
42.396
38.458
19.034
13.775
12.488
200
150
100
50
ppm (t1)
BnO
OBn
N
O
9
13C NMR
100 MHz

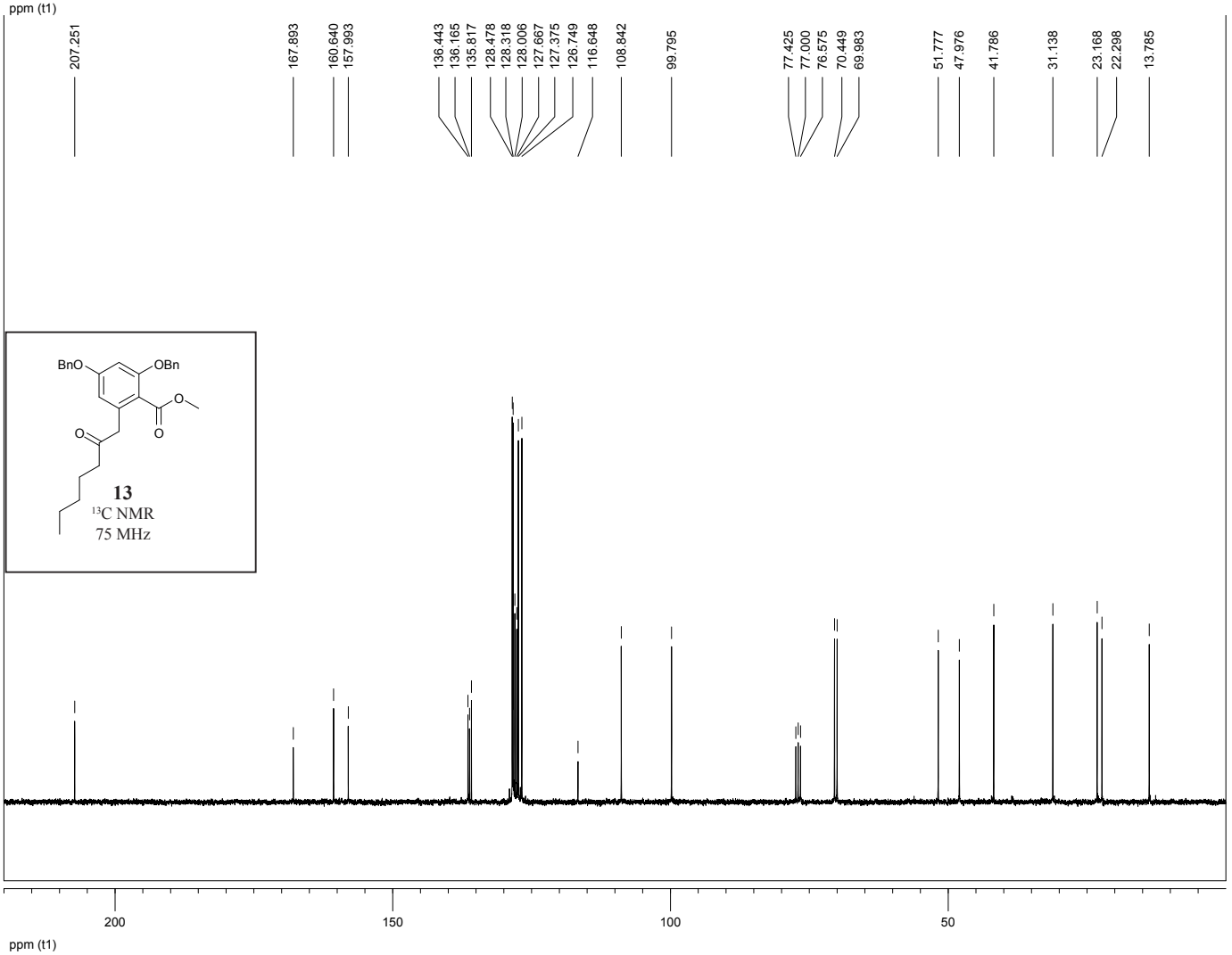

BnO
OBn
N
O
O
11
1H NMR
400 MHz

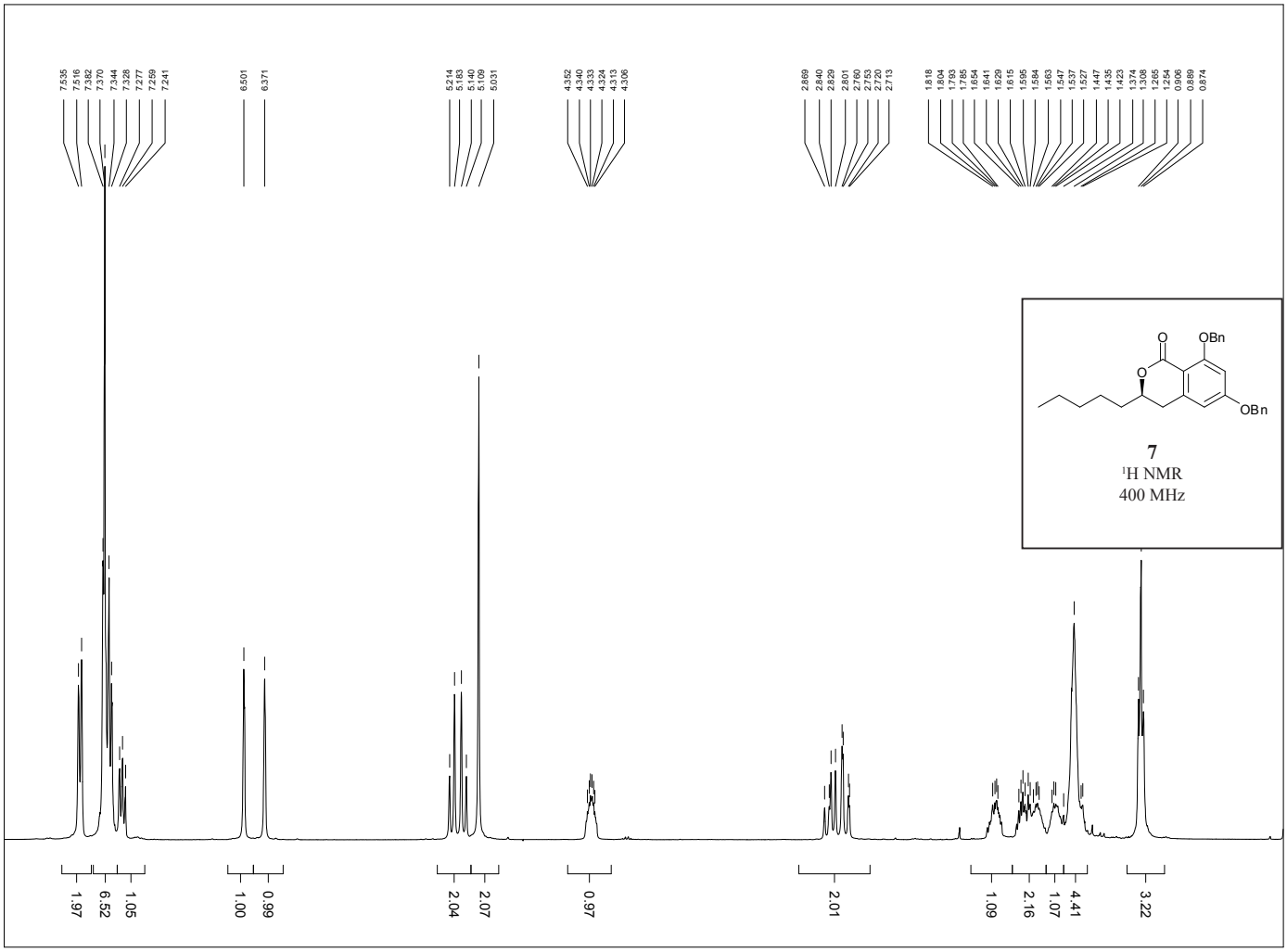

ppm (t1)
BnO
OBn
N
O
O
11
13C NMR
400 MHz

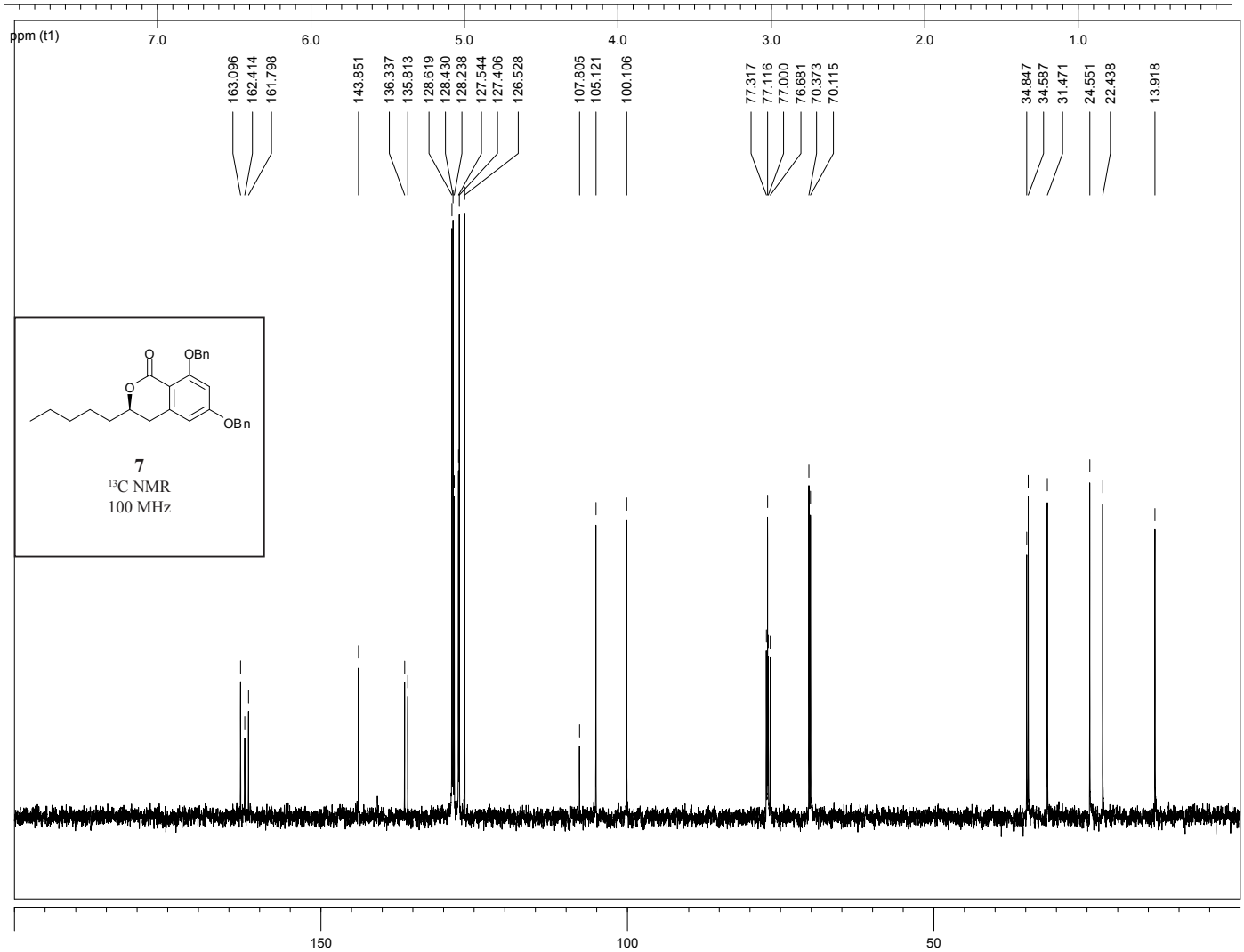

7.599
7.575
7.416
7.410
7.401
7.382
7.372
7.357
7.315
7.291
7.264
6.536
6.529
6.401
6.394
6.063
5.230
5.083
2.479
2.455
2.429
1.715
1.690
1.665
1.372
1.361
1.348
1.339
1.324
0.941
0.933
0.918
0.895
OBn
O
O
BnO
12
1H NMR
300 MHz
2.09
8.27
1.00
1.08
0.99
2.01
1.99
2.04
2.06
4.20
3.10
7.0
6.0
5.0
4.0
3.0
2.0
1.0

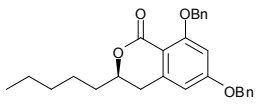

ppm (t1)
164.172
162.002
159.175
142.291
136.246
135.743
128.638
128.472
128.278
127.569
127.455
126.478
102.790
100.842
100.251
77.424
77.001
76.577
70.411
70.206
33.226
31.087
26.352
22.296
13.876
OBn
O
O
BnO
12
13C NMR
75 MHz
150
100
50
ppm (t1)


7.435
7.429
7.410
7.401
7.378
7.371
7.359
7.343
7.337
7.326
7.314
7.303
7.283
7.263
6.560
6.553
6.457
6.450
5.070
5.042
3.851
3.735
2.484
2.460
2.435
1.641
1.617
1.592
1.568
1.543
1.364
1.344
1.322
1.308
1.299
1.284
1.278
1.268
1.254
0.939
0.916
0.893
BnO
OBn
O
O
O
13
1H NMR
300 MHz
9.90
0.96
0.93
1.99
1.87
2.87
1.88
1.87
1.90
4.09
2.88
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


207.251
167.893
160.640
157.993
136.443
136.165
135.817
128.478
128.318
128.006
127.667
127.375
126.749
116.648
108.842
99.795
77.425
77.000
76.575
70.449
69.983
51.777
47.976
41.786
31.138
23.168
22.298
13.785
BnO
OBn
O
O
O
13
13C NMR
75 MHz
200
150
100
50
ppm (t1)


7.535
7.516
7.382
7.370
7.344
7.328
7.277
7.259
7.241
6.501
6.371
5.214
5.165
5.140
5.109
5.031
4.352
4.340
4.333
4.324
4.313
4.306
2.869
2.840
2.829
2.801
2.760
2.753
2.720
2.713
1.818
1.804
1.793
1.785
1.654
1.641
1.629
1.615
1.595
1.584
1.563
1.547
1.537
1.527
1.447
1.435
1.423
1.374
1.308
1.265
1.254
0.906
0.889
0.874
1.97
6.52
1.05
1.00
0.99
2.04
2.07
0.97
2.01
1.09
2.16
1.07
4.41
3.22
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
O
OBn
O
OBn
7
1H NMR
400 MHz

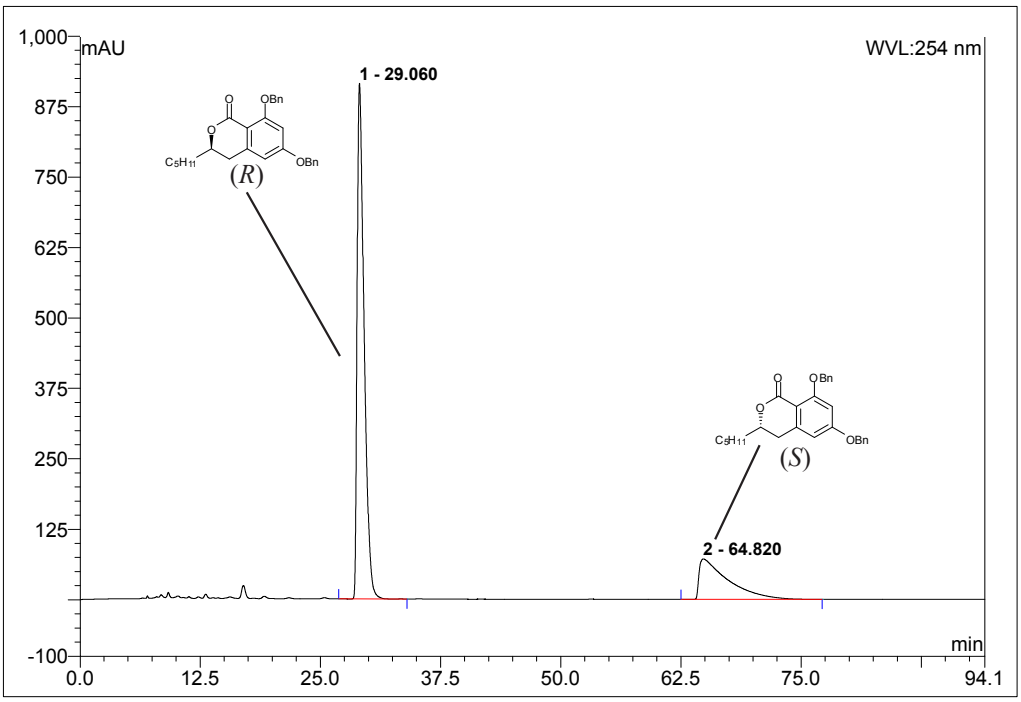

163.096
162.414
161.798
143.851
136.337
135.813
128.619
128.430
128.238
127.544
127.406
126.528
107.805
105.121
100.106
77.317
77.116
77.000
76.681
70.373
70.115
34.847
34.587
31.471
24.551
22.438
13.918
150
100
50
ppm (t1)
O
OBn
O
OBn
7
13C NMR
100 MHz



7

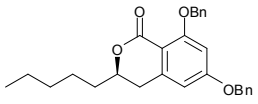
METHOD A:

Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 254 nM



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.06	n.a.	914.650	767.396	75.53	n.a.	BMB*
2	64.82	n.a.	71.726	248.646	24.47	n.a.	BMB*
Total:			986.376	1016.042	100.00	0.000	

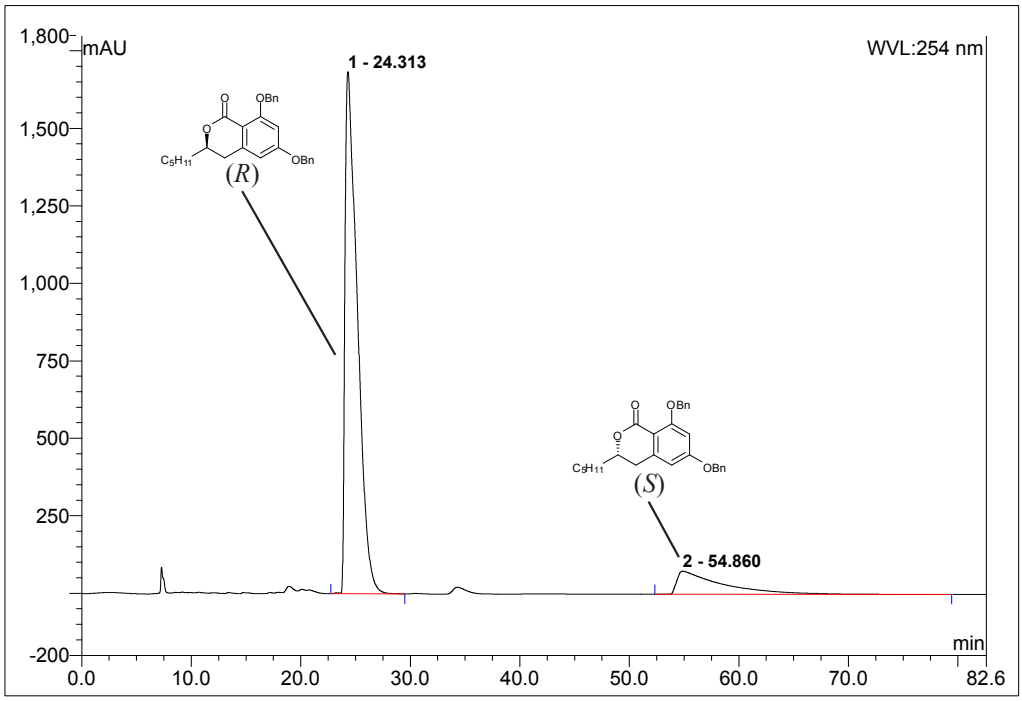
e. e. = 75.53 - 24.47 = 51% (*R*)



7

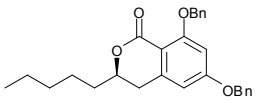
METHOD B:

Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 254 nM



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.31	n.a.	1683.966	2210.467	86.38	n.a.	BMB*
2	54.86	n.a.	74.620	348.679	13.62	n.a.	BMB*
Total:			1758.586	2559.146	100.00	0.000	

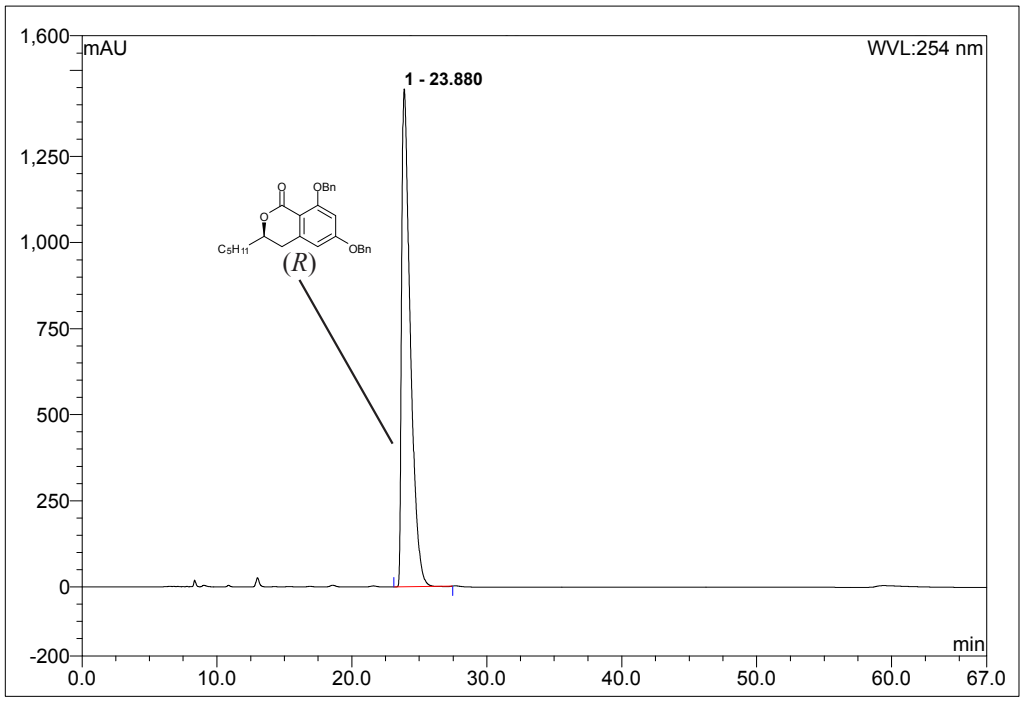
e. e. = 86.38 - 13.62 = 73% (*R*)



7

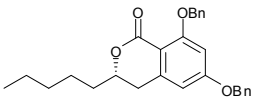
AFTER SEMI-PREP

Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 254 nM



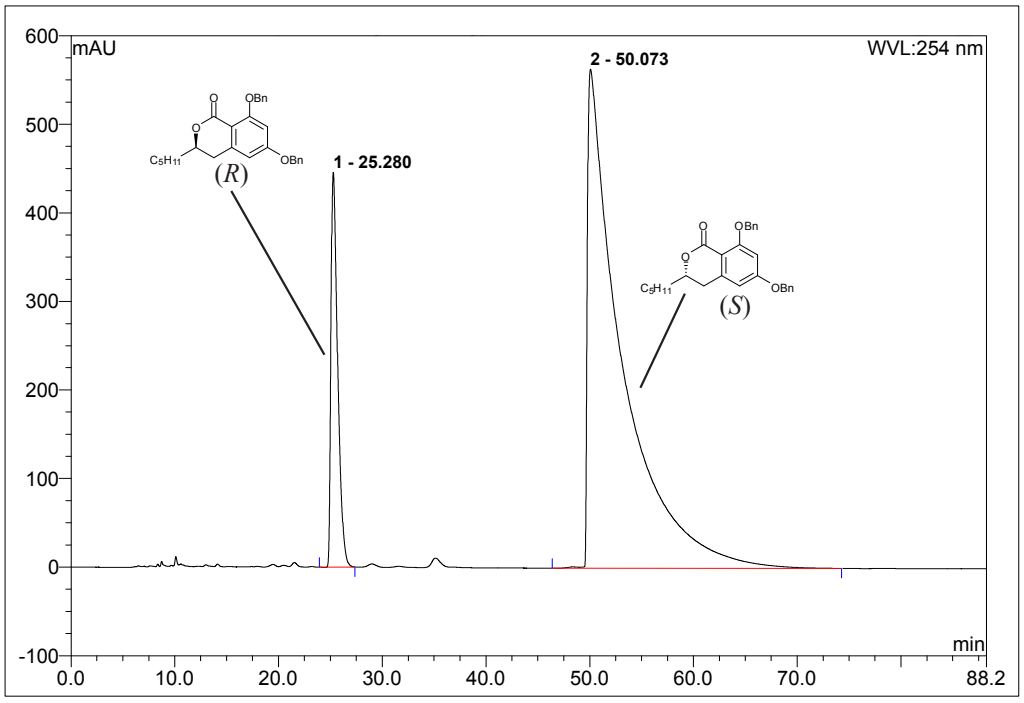
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.88	n.a.	1445.857	1080.213	100.00	n.a.	BMB*
Total:			1445.857	1080.213	100.00	0.000	

e. e. > 99% (*R*)



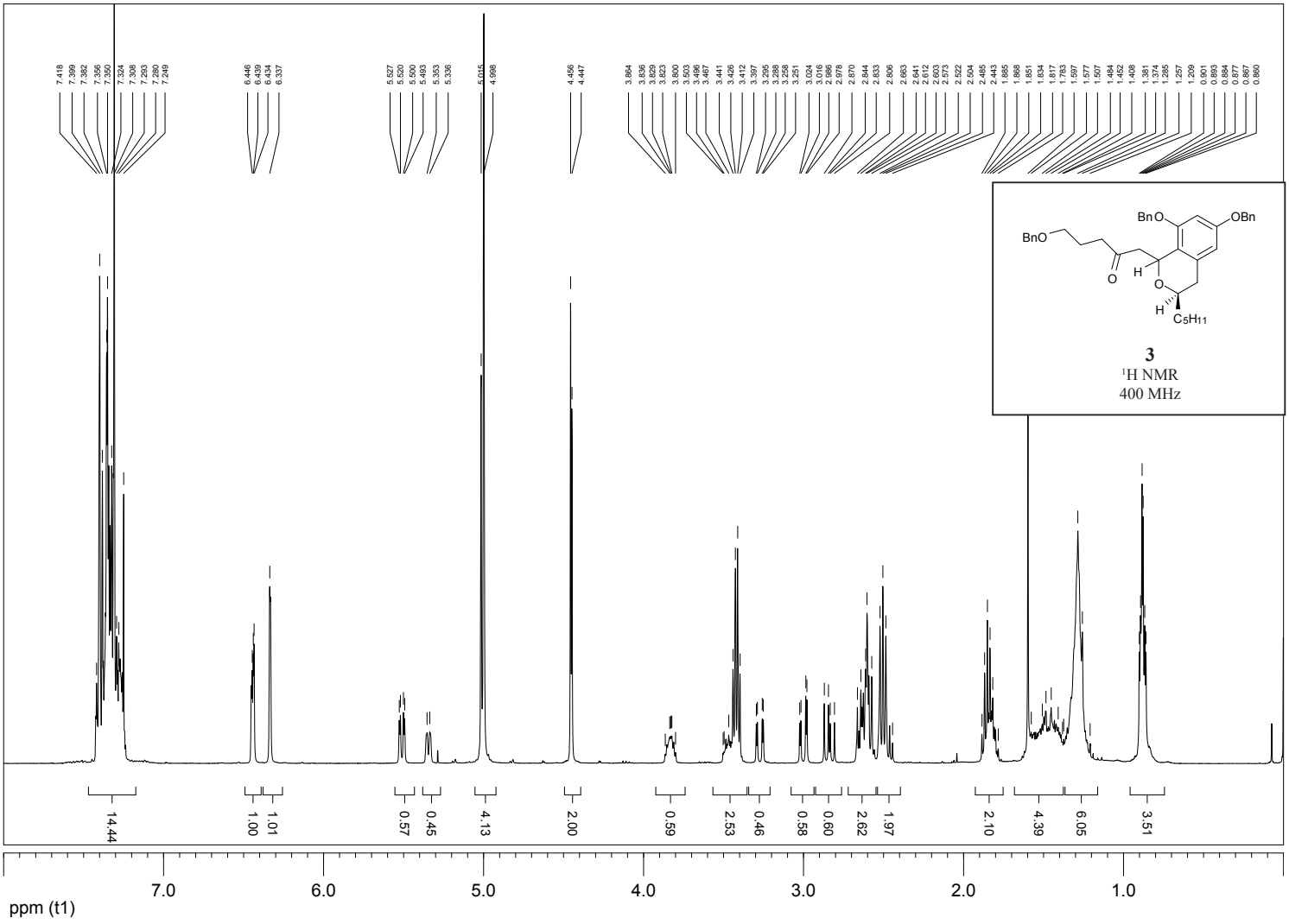
***ent*-7**

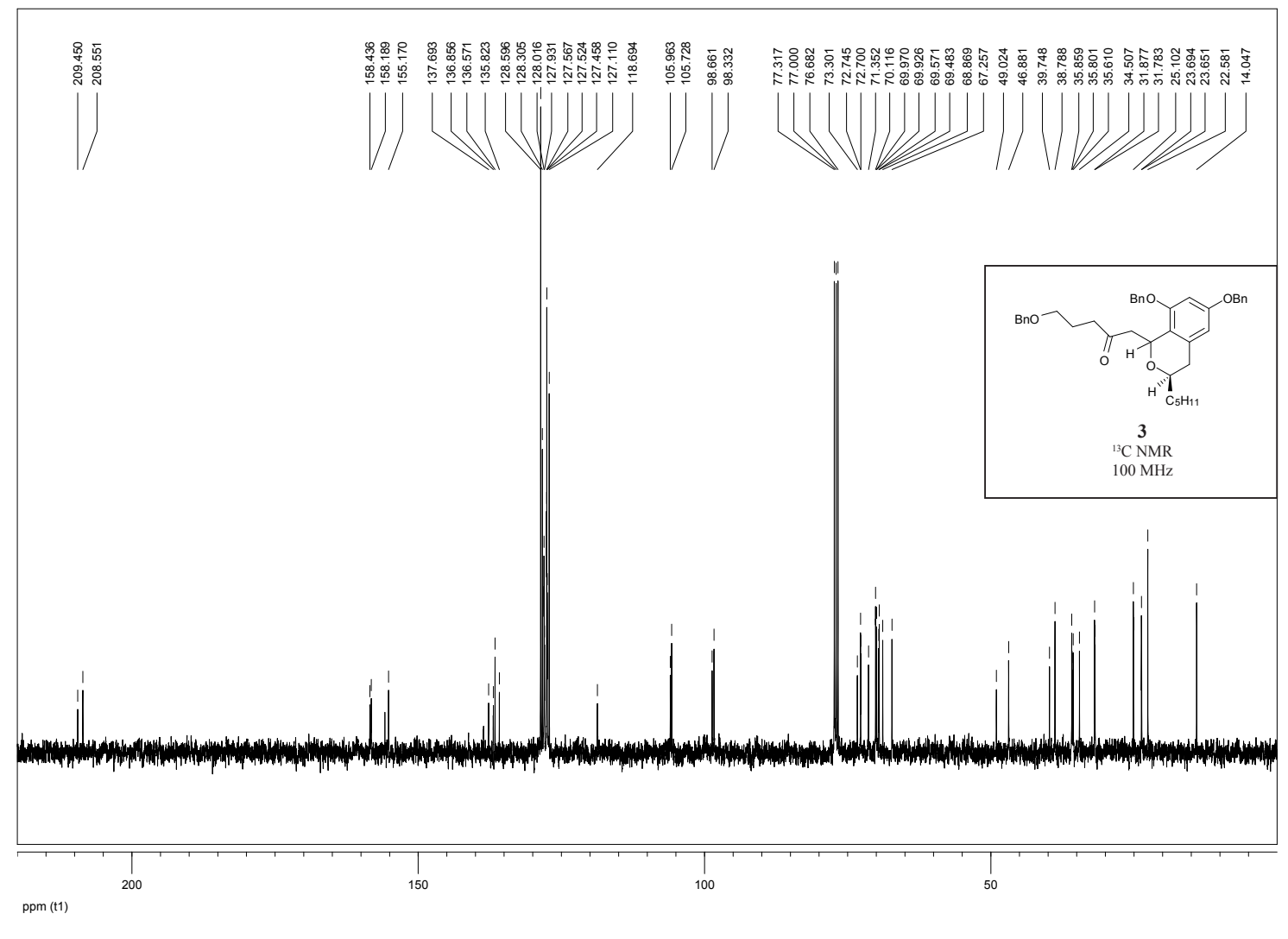
Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 254 nM



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.28	n.a.	445.747	335.602	13.51	n.a.	BMB*
2	50.07	n.a.	563.511	2148.017	86.49	n.a.	BMB*
Total:			1009.258	2483.619	100.00	0.000	

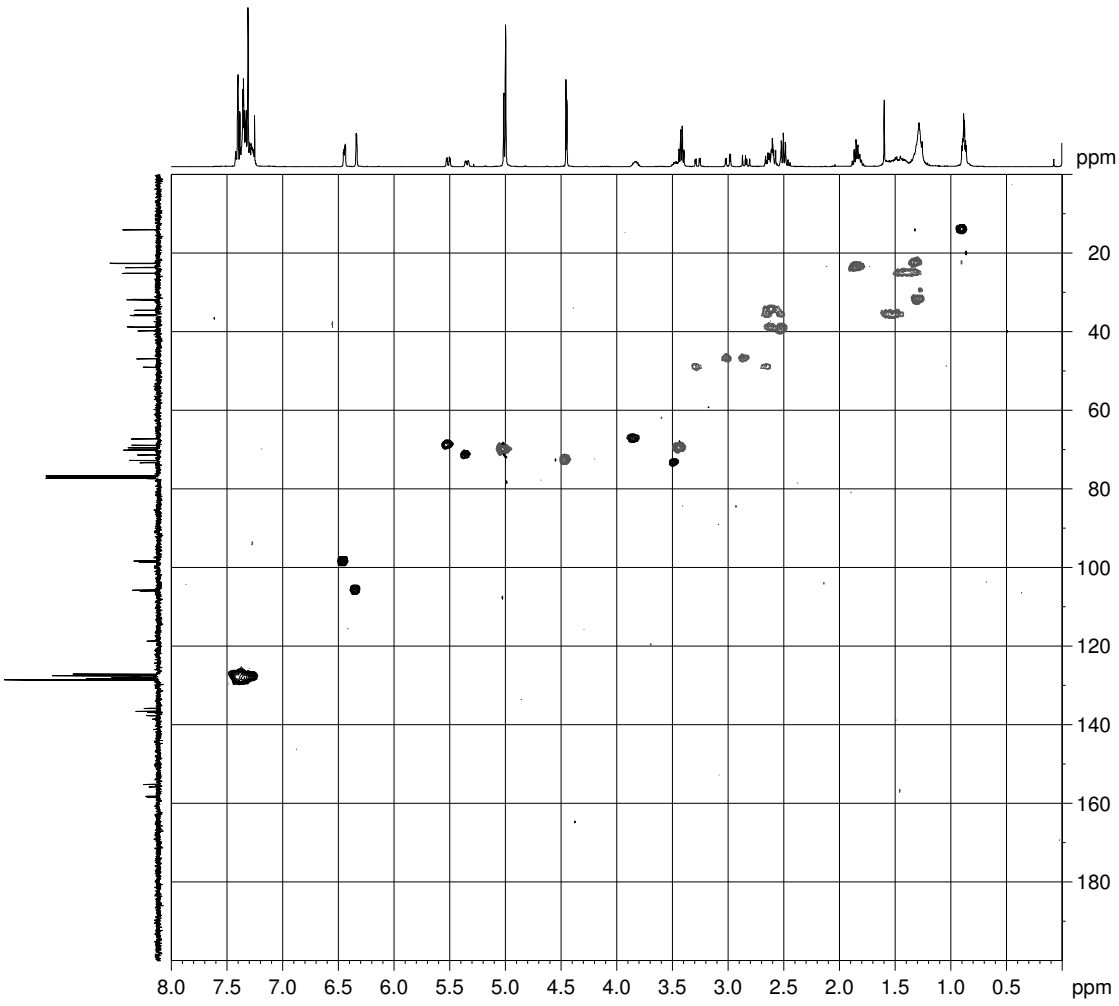
e. e. = 86.49 - 13.51 = 73% (*S*)

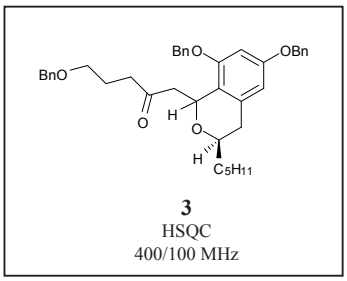

BnO
OBn
BnO
O
H
O
H
C5H11
3
1H NMR
400 MHz


ppm (t1)

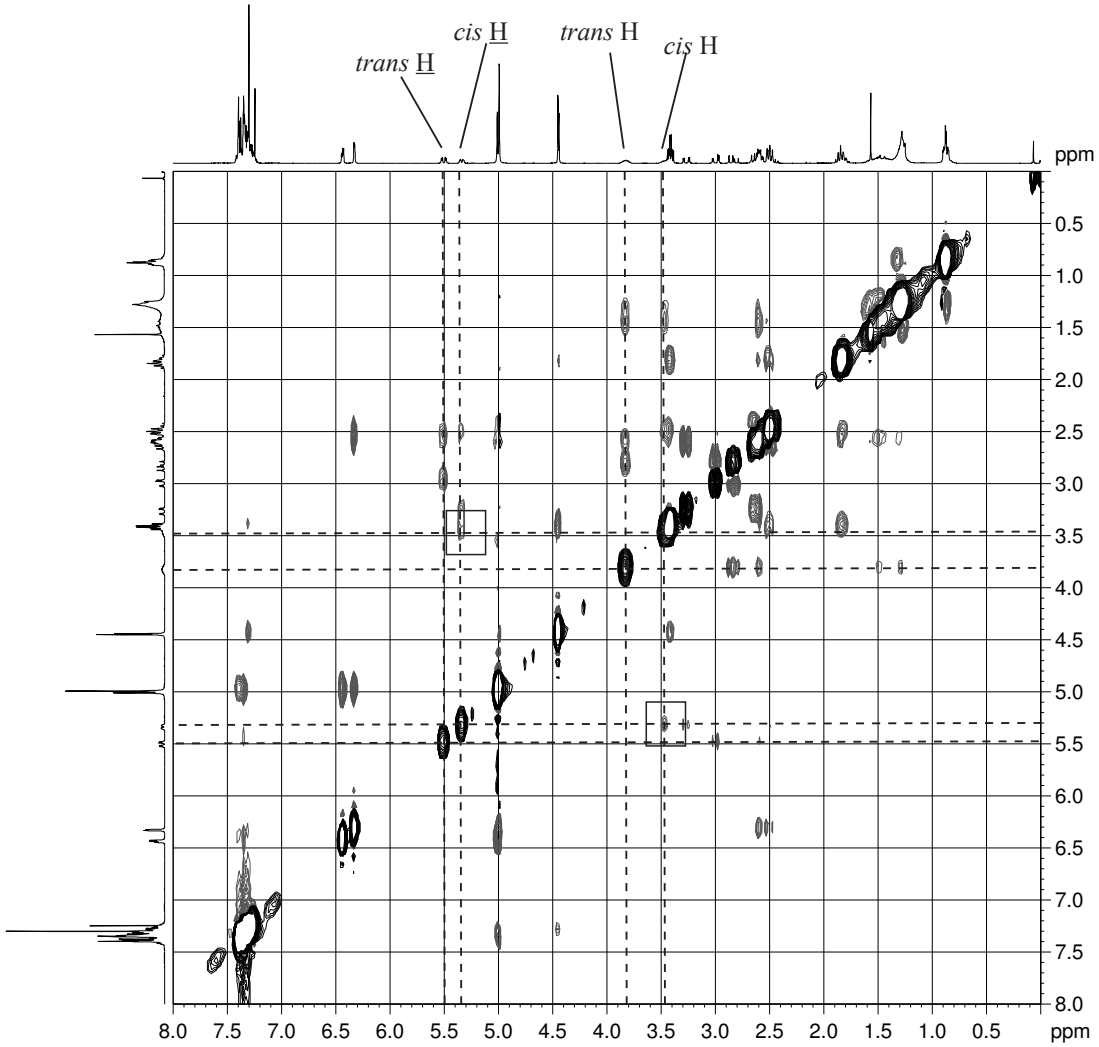
BnO
OBn
BnO
O
H
O
H
C5H11
3
13C NMR
100 MHz

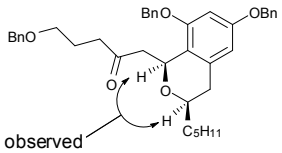
ppm (t1)



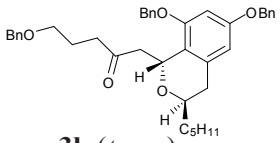


3
HSQC
400/100 MHz



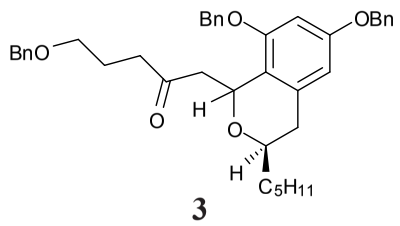


3a (*cis*)



3b (*trans*)

NOESY
300 MHz

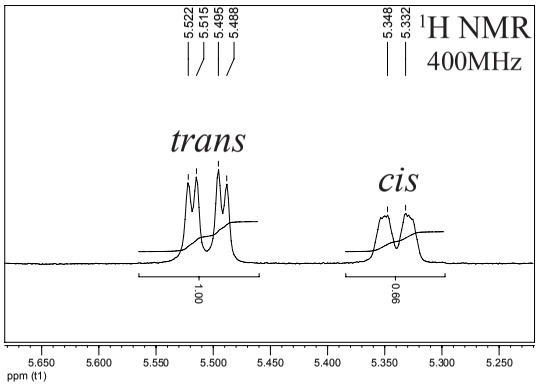


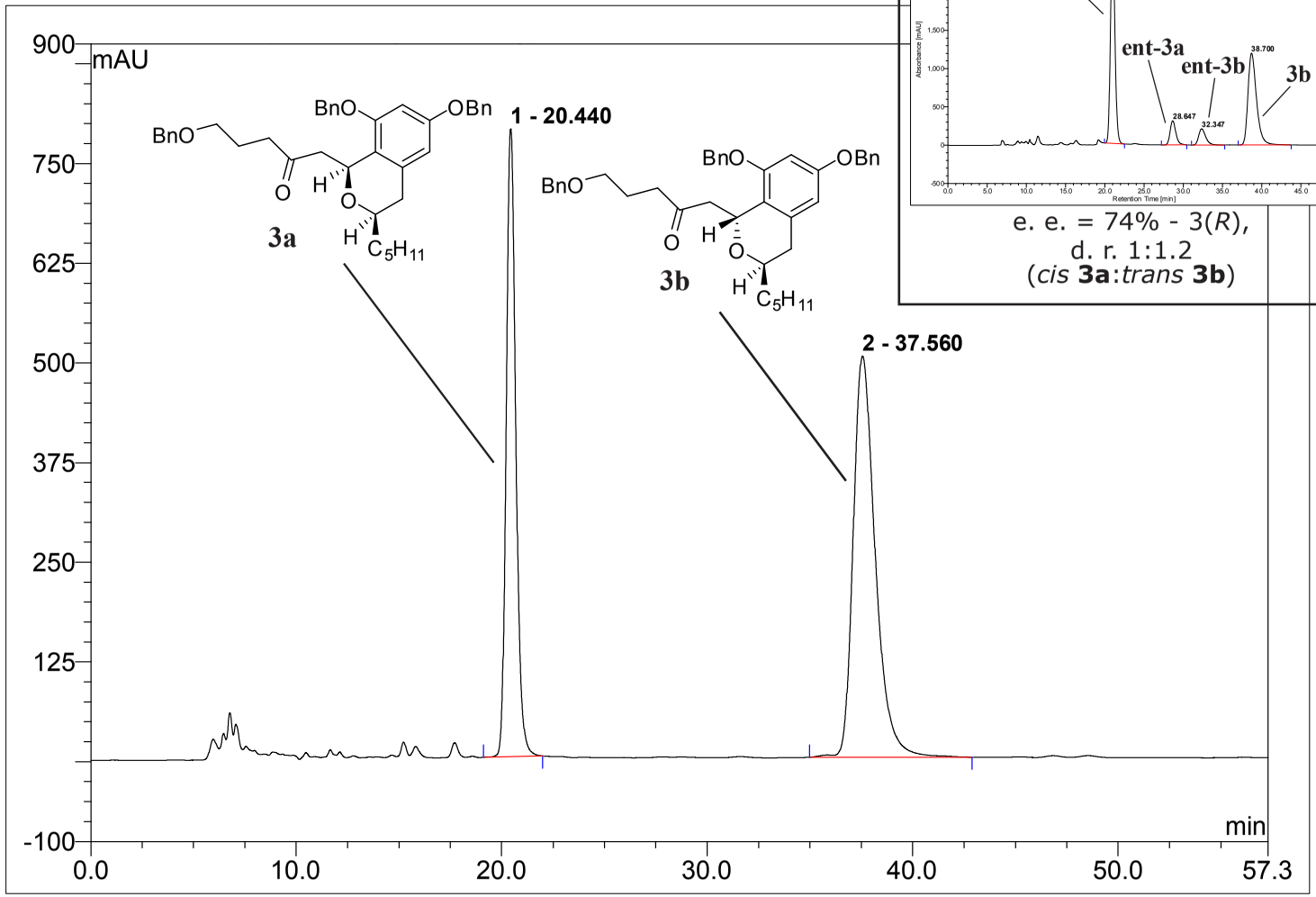
3

Eluent = Hexanes-isopropanol (90:10)
Column = Chiralpak® IC, 4.6 mm i.d. x 250 mm
Packing = cellulose tris(3,5-dichloro phenylcarbamate) immobilised on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 210 nM

E.S.I.24

e. e. > 99% (**3a** and **3b**)
d. r. (HPLC) = 1:1.48
d.r. (NMR) = 1:1.51
(*cis* **3a**:*trans* **3b**)

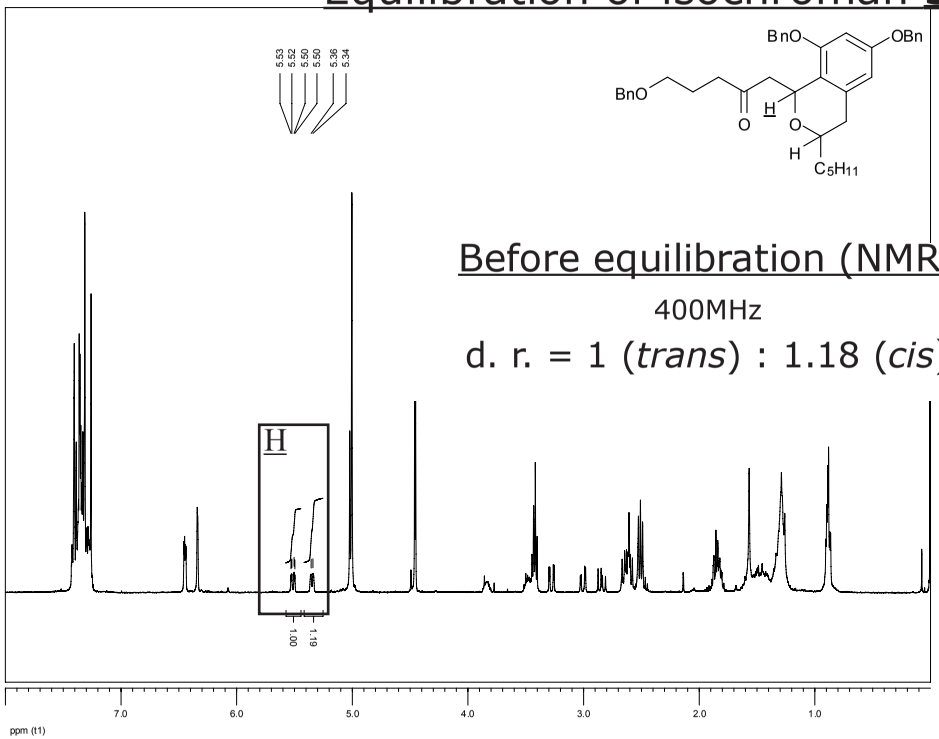




e. e. = 74% - 3(*R*),
d. r. 1:1.2
(*cis* **3a**:*trans* **3b**)

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.44	n.a.	787.334	424.137	40.33	n.a.	BMB*
2	37.56	n.a.	503.068	627.489	59.67	n.a.	BMB*
Total:			1290.402	1051.626	100.00	0.000	

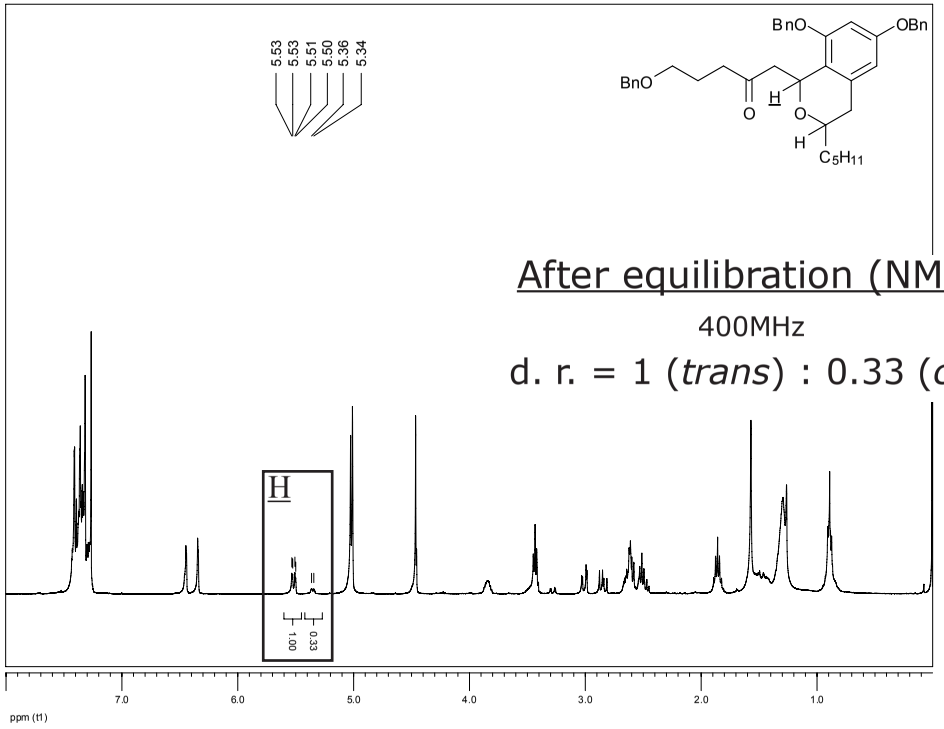
Equilibration of isochroman **3** using anhydrous HCl in THF (50% e.e.)



Before equilibration (NMR)

400MHz

d. r. = 1 (*trans*) : 1.18 (*cis*)

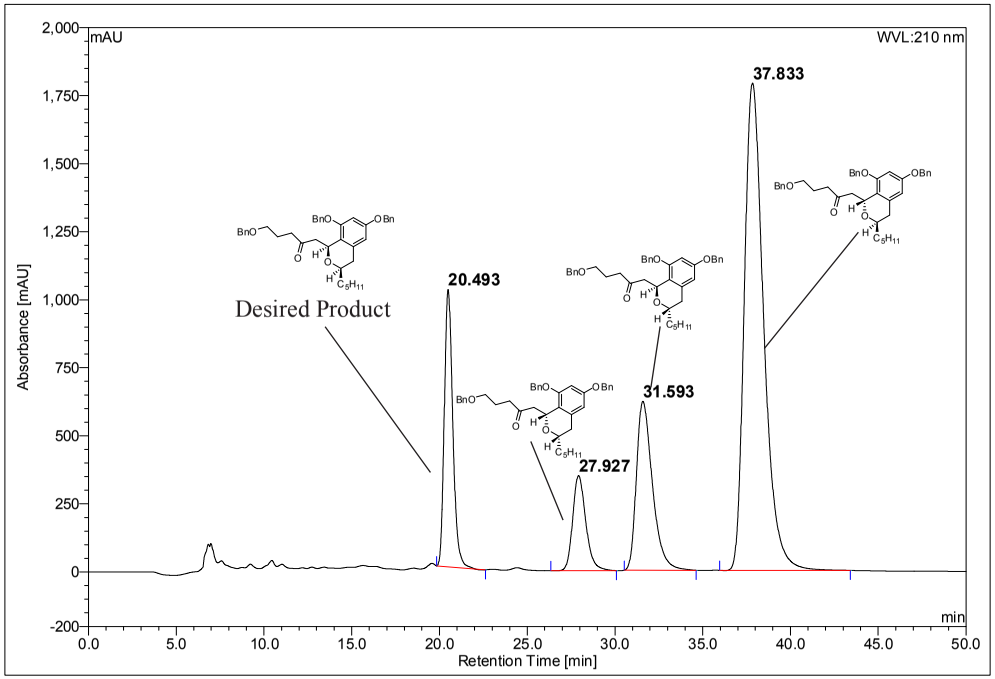


After equilibration (NMR)

400MHz

d. r. = 1 (*trans*) : 0.33 (*cis*)

Eluent = Hexanes-isopropanol (90:10)
Column = Chiralpak® IC, 4.6 mm i.d. x 250 mm
Packing = cellulose tris(3,5-dichloro phenylcarbamate) immobilised on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 210 nM



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.49	n.a.	1019.074	570.276	14.93	n.a.	BMB*
2	27.93	n.a.	348.859	301.409	7.89	n.a.	BMB*
3	31.59	n.a.	620.132	655.817	17.17	n.a.	BMB*
4	37.83	n.a.	1790.116	2292.054	60.01	n.a.	BMB*
Total:			3778.182	3819.557	100.00	0.000	

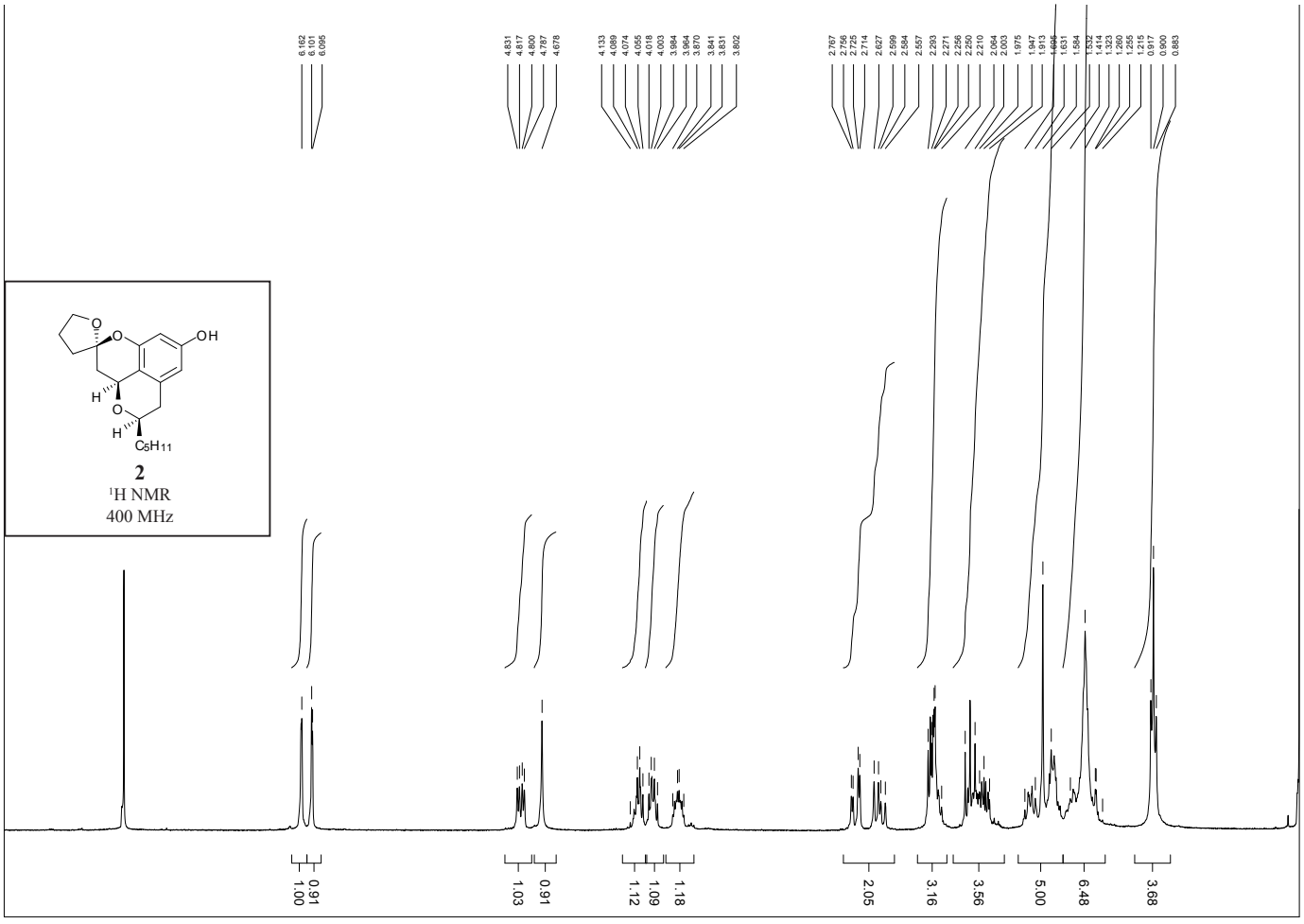
After equilibration (HPLC)

d. r. = 1 (*trans*) : 0.30 (*cis*)

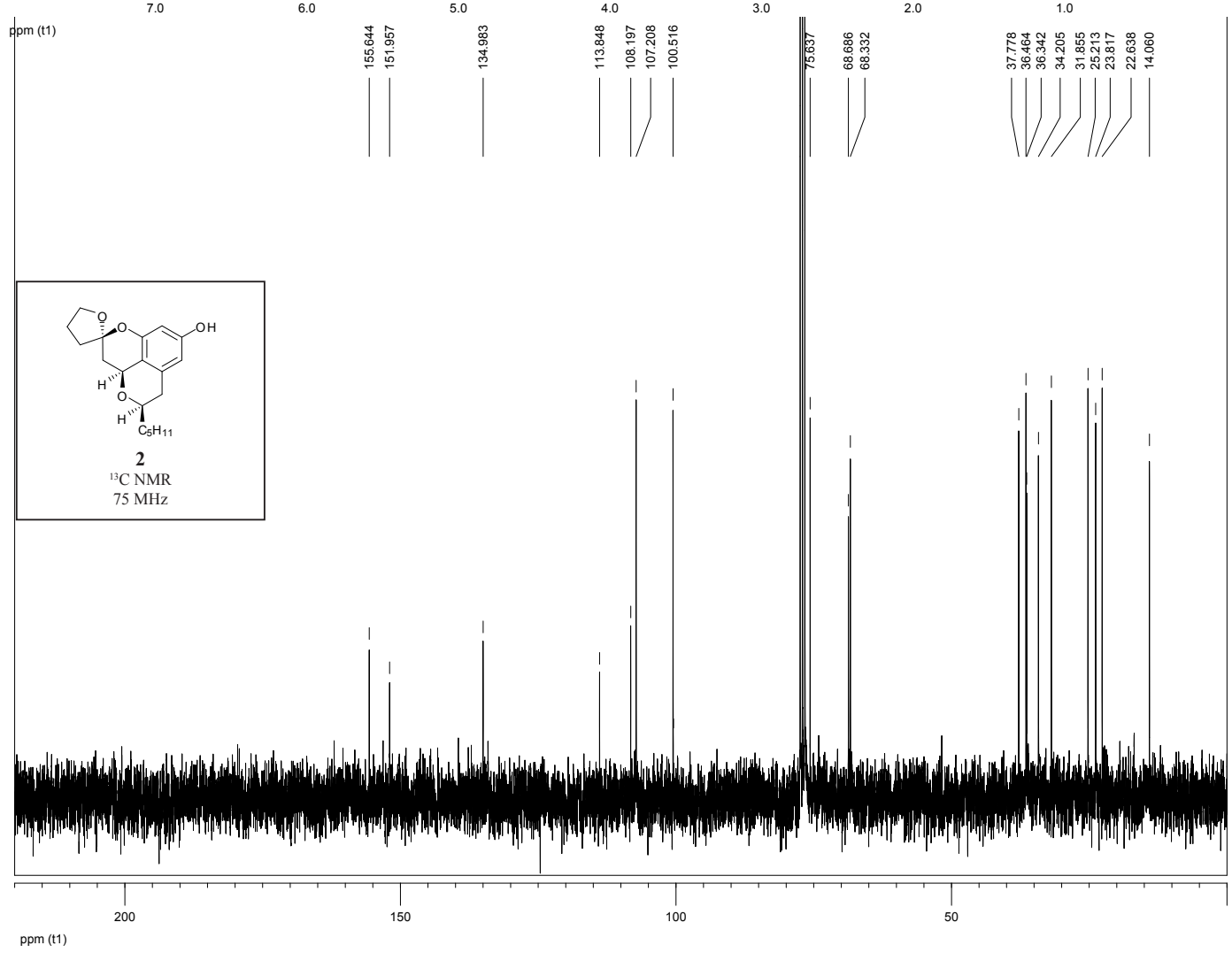
d. e. = (17.17 + 60.01) - (14.93 + 7.89) = 50%

In THF in the presence of HCl overnight the *cis* isochroman equilibrates to the *trans*

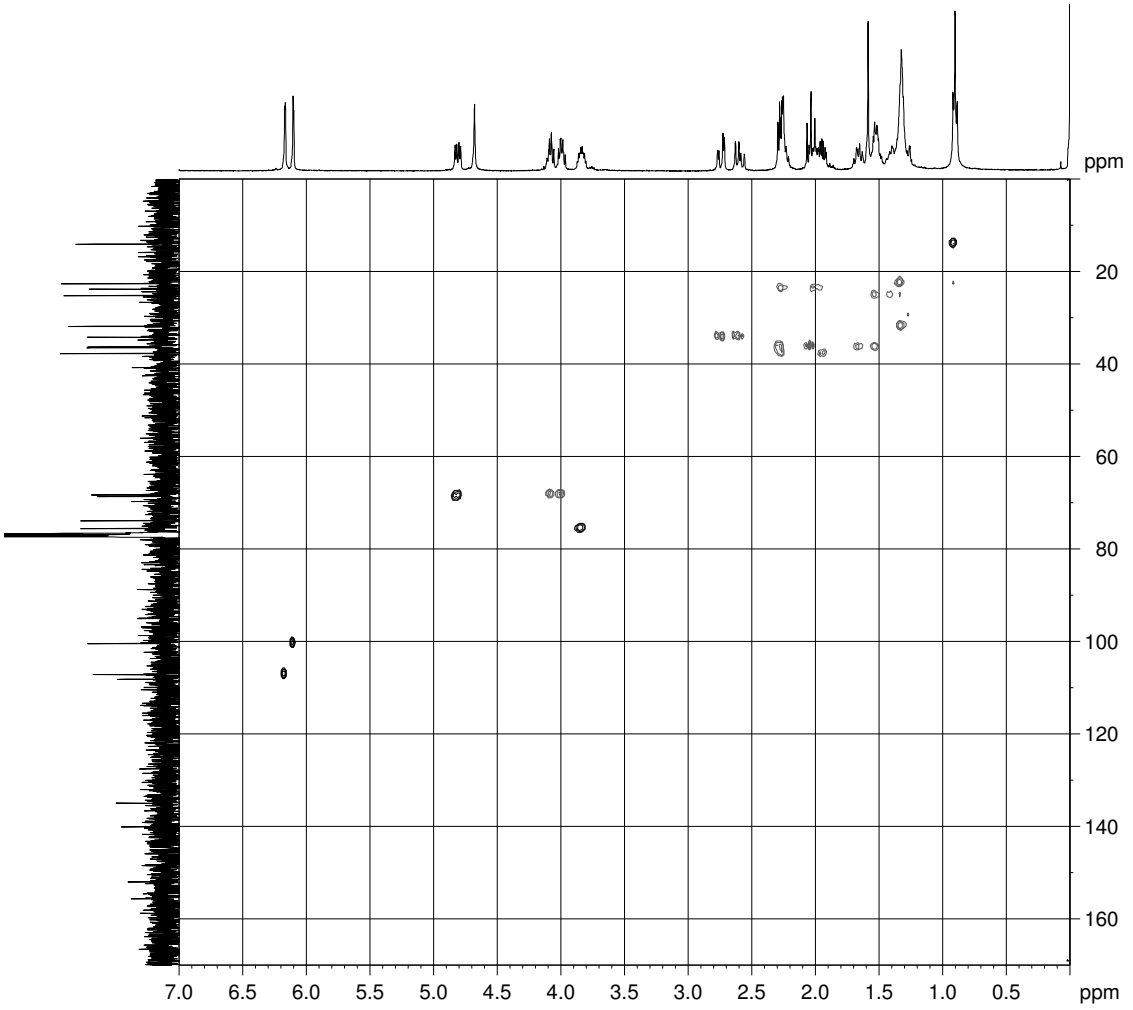
E.S.I.25

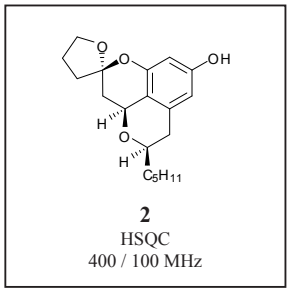


2
^{1}H NMR
400 MHz

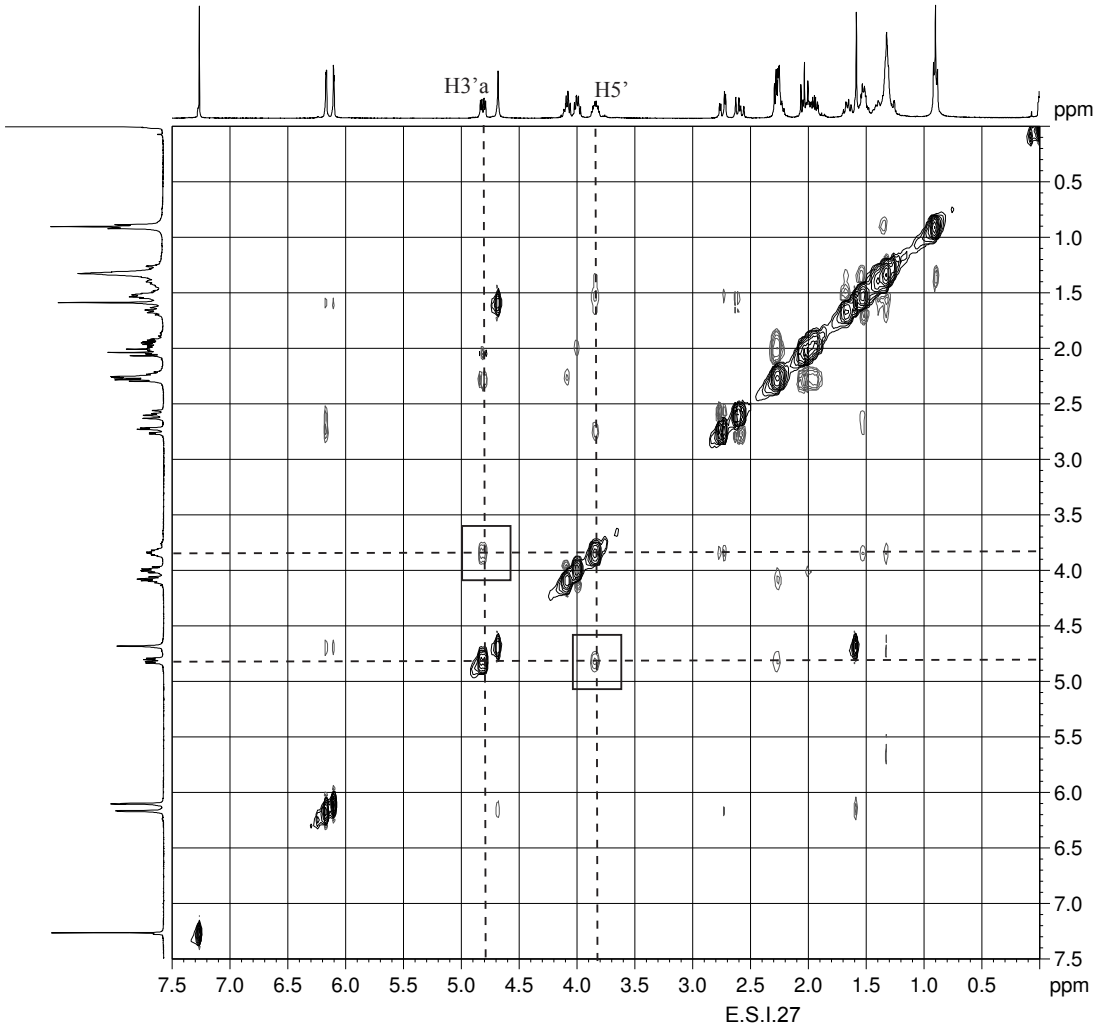


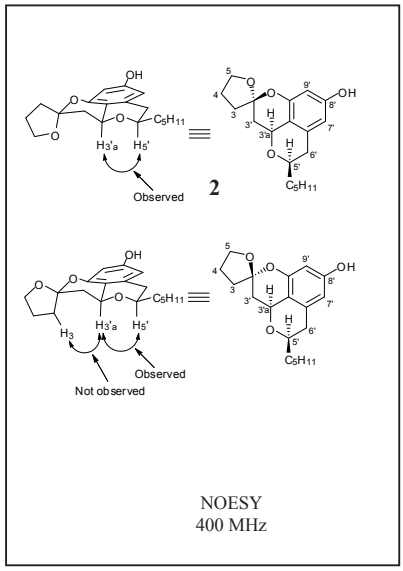
2
^{13}C NMR
75 MHz

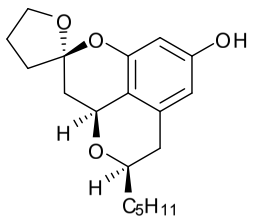




2
HSQC
400 / 100 MHz



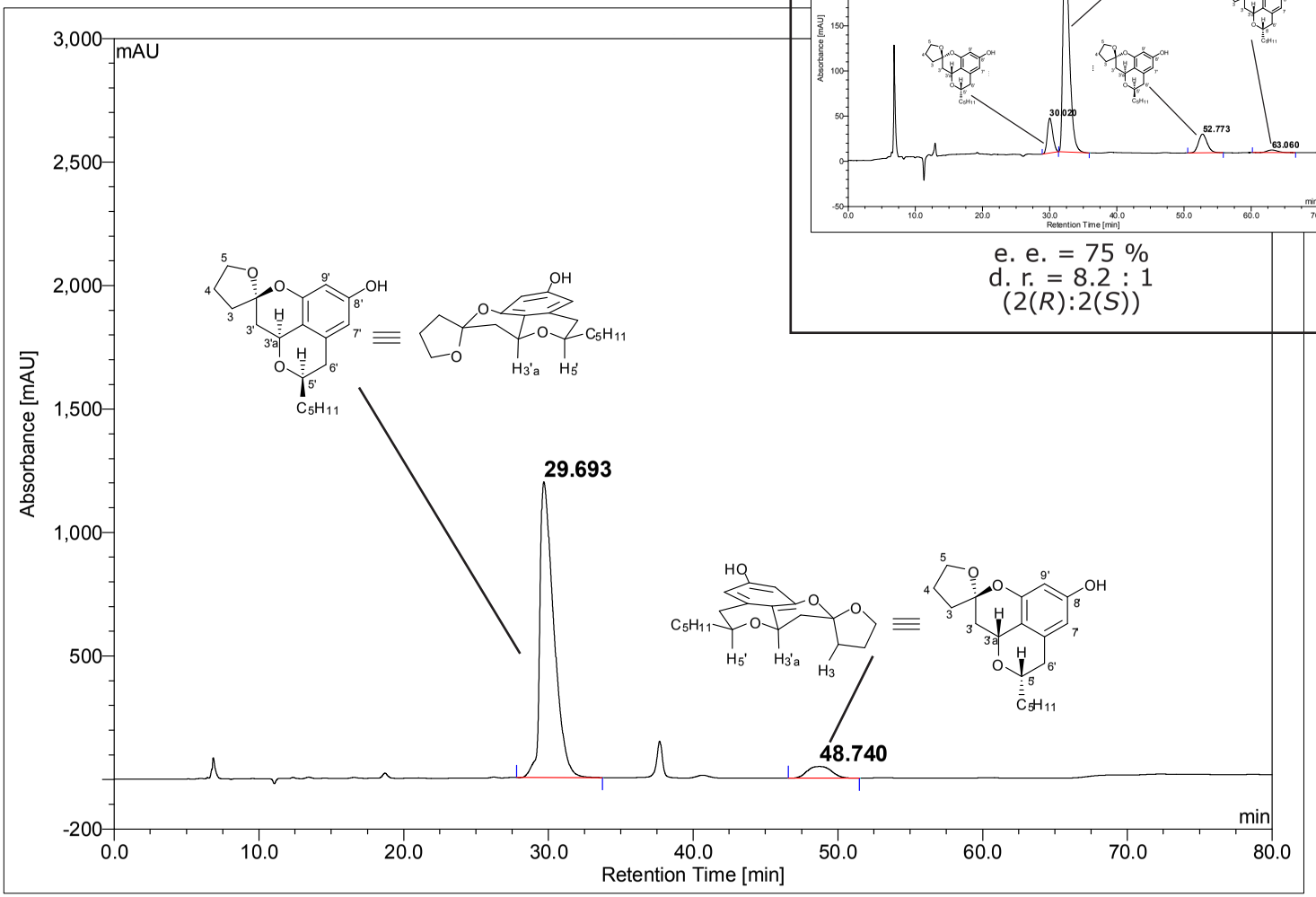




2

Eluent = Hexanes-isopropanol (95:5)
Column = Chiralpak® IC, 4.6 mm i.d. x 250 mm
Packing = cellulose tris(3,5-dichloro phenylcarbamate) immobilised on silica gel
Particle size = 5 µm
Flow rate = 0.5 mL/min
Wavelength = 210 nM

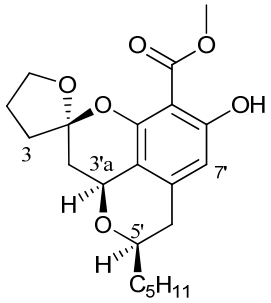
e. e. >99%
d. r. = 14 : 1
(2(*R*):2(*S*))



e. e. = 75 %
d. r. = 8.2 : 1
(2(*R*):2(*S*))

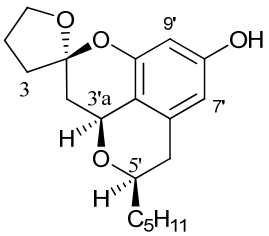
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.69	n.a.	1196.067	1335.372	93.57	n.a.	BMB*
2	48.74	n.a.	47.258	91.790	6.43	n.a.	BMB*
Total:			1243.325	1427.162	100.00	0.000	

^{1}H NMR comparison of **2** with Zhou and Snider's related spiroketal



J. Y. Zhou and B. B. Snider,

Org Lett, 2007, **9**, 2071-2074.



2

assignment	shift	multiplicity / *J* (Hz)	# H	shift	multiplicity / *J* (Hz)	# H
	0.90	t / 6.8	3	0.90	t / 6.8	3
	1.27-1.75	m	8	1.26-1.68	m	8
	1.87-1.97	m	1	1.91-2.06	m	3
	2.05	dd / 12.0, 12.2	1			
	2.01-2.10	m	1			
	2.31	dd / 5.4, 12.0	1	2.23-2.29	m	3
	2.25-2.35	m	2			
	2.61	dd / 10.7, 17.4	1	2.59	dd / 11.0, 16.8	1
	2.77	dd / 4.2, 17.4	1	2.74	dd / 4.4, 16.8	1
	3.77-3.85	m	1	3.80-3.87	m	1
OC<u>H</u>$_3$	3.90	s	3			
	3.99-4.07	m	1	3.98-4.00	m	1
	4.08-4.15	m	1	4.02-4.09	m	1
O<u>H</u>				4.68	br. s	1
<u>H</u>3'a	4.77	dd / 5.4, 12.2	1	4.81	dd / 5.4, 12.2	1
C9'<u>H</u>				6.10	d / 2.4	1
C7'<u>H</u>	6.31	s	1	6.16	d / 1.6	1
O<u>H</u>	11.35	s	1			