Eur. J. Org. Chem. **2007** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2007 · ISSN 1434–193X

SUPPORTING INFORMATION

Title: Formation of a Tetracyclic Isoquinoline Derivative by Rearrangement of a [(Bromophenyl)butyryl]oxazolidinone
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Ref. No.: O200600918

General Methods. ^{1}H NMR spectra were recorded on a Bruker Avance 300, a Bruker Avance 500 (499.9 MHz) or a Varian Gemini 2000 spectrometer, using $CDCl_3$ solvent (or other indicated solvent) as reference and/or internal deuterium lock. ^{13}C NMR spectra, were recorded on a Bruker Avance 300 (75.5 MHz) or a Bruker Avance 500 (125.7 MHz) spectrometer using the PENDANT sequence and internal deuterium lock. All other ^{13}C spectra were recorded on a Varian Gemini 2000 (75.5 MHz) spectrometer using composite pulse ^{1}H decoupling. Two-dimensional NMR spectroscopy such as ^{1}H-^{1}H COSY spectra, ^{1}H-^{13}C COSY spectra (HSQC) and long-range ^{1}H-^{13}C COSY spectra (HMBC), were carried out to determine the correlation between ^{1}H and ^{13}C. The chemical shifts for all NMR spectra are expressed in parts per million to high frequency of TMS reference. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz.

The IR spectra were obtained on a Perkin Elmer FT-IR Paragon 1000 spectrometer. Solids were run as nujol mulls and liquids were run as thin films on NaCl plates. Low resolution and high-resolution (HR) mass spectral analysis (EI and CI) were recorded using a VG AUTOSPEC mass spectrometer or a Micromass GCT (Time-of-Flight), high performance, orthogonal acceleration spectrometer coupled to an Agilent Technologies 6890N GC system. Electrospray mass spectrometry (ESMS) was recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only major peaks are reported and intensities are quoted as percentages of the base peak. TLC was carried out using either Polygram silica plates (0.2mm with 254 nm fluorescent dye) or Fluka alumina plates (0.2 mm with 254 nm fluorescent dye). The components were observed under ultraviolet light (254 nm/365 nm) and stained with ninhydrin (1–2 % in EtOH) or $KMnO_4$ aqueous solution. Column chromatography was performed using silica gel (40–63 μm, Fluorochem). Diethyl ether and THF were freshly distilled from sodium benzophenone ketyl. Dry hexane was obtained by distillation from sodium. Where dry DCM was used, it was distilled over CaH_2. DMSO was dried, distilled from CaH_2 and stored over 4 Å molecular sieves. Nitrogen gas was dried (NaOH, $CaCl_2$, 4 Å molecular sieves) prior to use. Glassware was oven dried for at least 2 h for all oxygen/water free reactions.

EPR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 KHz modulation. Irradiation of samples was carried out in the resonant cavity by unfiltered light from a 500 W super pressure Hg arc. Samples were contained in ~ 1 mm od quartz tubes. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker Simfonia software package and/or Winsim 2002 beta suite. For concentration measurements, signals were double integrated using the Bruker WinEPR software and radical concentrations were calculated by reference to a known concentration of DPPH.

Computational Methods. Quantum chemical calculations were carried out with the Gaussian 03W package.[1] Density functional theory, UB3LYP variant, was employed. The equilibrium geometries were fully optimised with respect to all geometric variables, no symmetry being assumed, with the B3LYP/6-31G* basis set. For the calculation of total energies the B3LYP/6-311++G(d,p)//B3LYP/6-31G* level was utilised. Computed $<S^2>$ values for all types of radicals were 0.7500 after annihilation of higher multiplicity spin states. Isotropic EPR hfs were derived from computed Fermi contact integrals evaluated at the H-nuclei. The hfs were taken directly from the Gaussian output files.

[1] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr.,, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.;. Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision A.1, Gaussian, Inc., Pittsburgh PA, 2003.

4-(2-Bromophenyl)-2-phenylbutyric acid: To a solution of phenyl acetic acid (1 g, 7.3 mmol) in THF (30 mL), under N_2 at –78 °C was added carefully dropwise 2 equiv. *n*-BuLi (5.9 mL of a 2.5 M soln in hexanes, 14.7 mmol). After stirring for 20 min 2-(2-bromophenyl)ethyl iodide (2.3 g, 7.3 mmol) in THF (5 mL) was added dropwise over 5 min. The mixture was allowed to warm to room temperature over 2 h and stirred overnight. The mixture was quenched by addition of solid

ammonium chloride and the solvent removed. The residue was dissolved in 2M HCl (100 mL), and the cloudy mixture extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude acid (1.8 g, 77 %) which was used without further purification; ν_{max}(nujol)/cm^{-1} 1705 (C=O) & 3060 (OH); ^{1}H NMR δ 2.05-2.18 (m, 1H), 2.33-2.46 (m, 1H), 2.62-2.78 (m, 2H), 3.61 (t, *J* = 7.6, 1H), 7.00-7.05 (m, 1H), 7.13-7.35 (m, 7H) and 7.48-7.51 (m, 1H), CO_2H not observed; ^{13}C NMR δ 32.8 (CH_2), 34.0 (CH_2), 51.0 (CH), 124.4 (C), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.8 (CH), 130.5 (CH), 132.9 (CH), 137.9 (C), 140.5 (C) and 179.5 (C); *m/z* (CI) 319 [100 %, ($M+H^+$)]. Calcd for $C_{16}H_{15}O_2{}^{79}Br$ $(MH)^+$: 319.0334. Found: 319.0326.

4-(2-Bromophenyl)-2-phenylbutyryl chloride: Distilled thionyl chloride (1.2 mL, 17 mmol) was added slowly via syringe to 4-(2-bromophenyl)-2-phenylbutyric acid (1.8 g, 5.6 mmol). The solution was then refluxed at 75 °C for 1.5 h and left to stand overnight at room temperature. The excess thionyl chloride was evaporated to afford the acid chloride (1.89 g, 99 %) which was used immediately without further purification; ^{1}H NMR δ 2.10-2.22 (m, 1H), 2.42-2.54 (m, 1H), 2.62-2.79 (m, 2H), 4.01 (t, *J* = 7.5, 1H), 7.03-7.41 (m, 8H) and 7.51 (d, *J* = 7.9, 1H); ^{13}C NMR δ 33.0 (CH_2), 33.6 (CH_2), 62.8 (CH), 124.3 (C), 127.6 (CH), 128.0 (CH), 128.4 (CH), 128.43 (CH), 129.1 (CH), 130.4 (CH), 133.0 (CH), 135.4 (C), 139.8 (C) and 174.6 (C).

Incomplete reaction of 1b with LDA. A solution of **1b** (156 mg, 0.39 mmol) in THF (4 mL) was treated with LDA as described above. After 3 h at rt the reaction was quenched with a solution of ammonium chloride (2 mL) and worked up as before to give product (100 mg). The ^{1}H and ^{13}C NMR spectra showed this to be a mixture of unreacted **1b** and tetracycle **2b** in a 1:3 ratio, together with minor by-products. The ^{13}C signal of unreacted **1b** at 174.5 ppm was strongly enhanced whereas no enhancement was observed for the oxazoldinone ring C=O signal at 153.6 ppm. From integration of the two sets of multiplets at 3.42 ppm in the ^{1}H NMR spectrum of tetracycle **2b** the proportions of ^{13}C to ^{12}C at C(9) were found to be 51% to 49 %.

EPR spectroscopic experiments: To a solution of 0.48 M LDA in THF (0.75 mL) at –78 °C under nitrogen was added a solution of oxazolidinone **1a** (0.05 g, 0.12 mmol) in THF (0.35 mL). After stirring for 10 min the solution was allowed to warm to room temperature over 30 min, at which time more THF (2.1 mL) was added. The mixture was then stirred at rt and aliquots of ca. 0.1 mL were removed under N_2 and transferred to quartz capillary tubes (ca. 1 mm i.d.). These solutions were photolysed in the resonant cavity of the 9 GHz EPR spectrometer with light from a 500 W super pressure Hg arc at temperatures in the range 270 to 195 K. Broad EPR signals were

observable at higher temperatures but the well-resolved spectra developed on photolysis in the range 195 < T < 240 K.

When even traces of oxygen were present the spectrum of a nitroxide (aminoxyl) radical (g = 2.0064) was obtained. Comparison of the hyperfine splittings (hfs) a(N) = 14.6, a(2H) = 4.2 G at 290 K with the literature showed that this was due to the di-isopropyl nitroxide. Minor signals from other nitroxides accompanied this spectrum. The detection of di-isopropyl nitroxide in the presence of oxygen is evidence in favor of the radical-mediated chain. The nitroxide was probably derived from the di-isopropylaminyl radical generated from LDA. The nitroxide will also inhibit the $S_{RN}1$ chain, and this is consistent with the observed sensitivity of the reactions to oxygen.

Crystal data and structure refinement for 2b: Empirical formula $C_{21}H_{21}NO_3$, Formula weight 335.39, Temperature 93(2) K, Wavelength 0.71073 Å, Crystal system Monoclinic, Space group P2(1)/c, Unit cell dimensions, a = 9.173(2) Å, b = 6.7359(18) Å, c = 26.879(7) Å, α= 90°, β= 94.218(7)°, γ = 90°, Volume 1656.4(8) $Å^3$, Z 4, Density (calculated) 1.345 Mg/m^3, Absorption coefficient 0.090 mm^{-1}, F(000) 712, Crystal size 0.1000 × 0.1000 × 0.1000 mm^3, Theta range for data collection 2.60 to 25.31°, Index ranges –10<=h<=10, –6<=k<=8, –32<=l<=31, Reflections collected 8795, Independent reflections 2820 [R(int) = 0.0239], Completeness to theta = 25.31° 93.2 %, Absorption correction Multiscan, Max. and min. transmission 1.0000 and 0.3059, Refinement method Full-matrix least-squares on F^2, Data / restraints / parameters 2820 / 1 / 231, Goodness-of-fit on F^2 1.047, Final R indices [I>2sigma(I)] R1 = 0.0356, wR2 = 0.0851, R indices (all data) R1 = 0.0426, wR2 = 0.0897, Largest diff. peak and hole 0.181 and –0.193 $e.Å^{-3}$. CIF deposited at CCDC no.:606950.

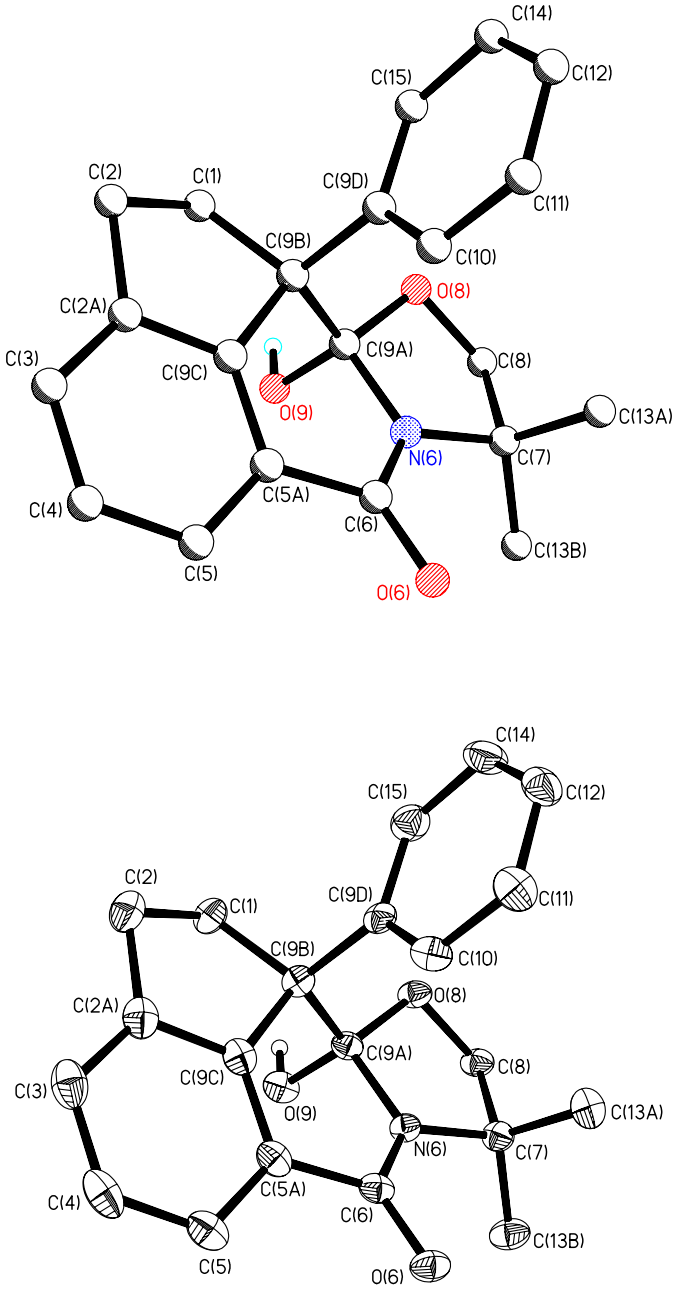


Figure S1. X-Ray crystal structures of **2b:** 50% probability thermal ellipsoids with hydrogen atoms omitted for clarity**.**

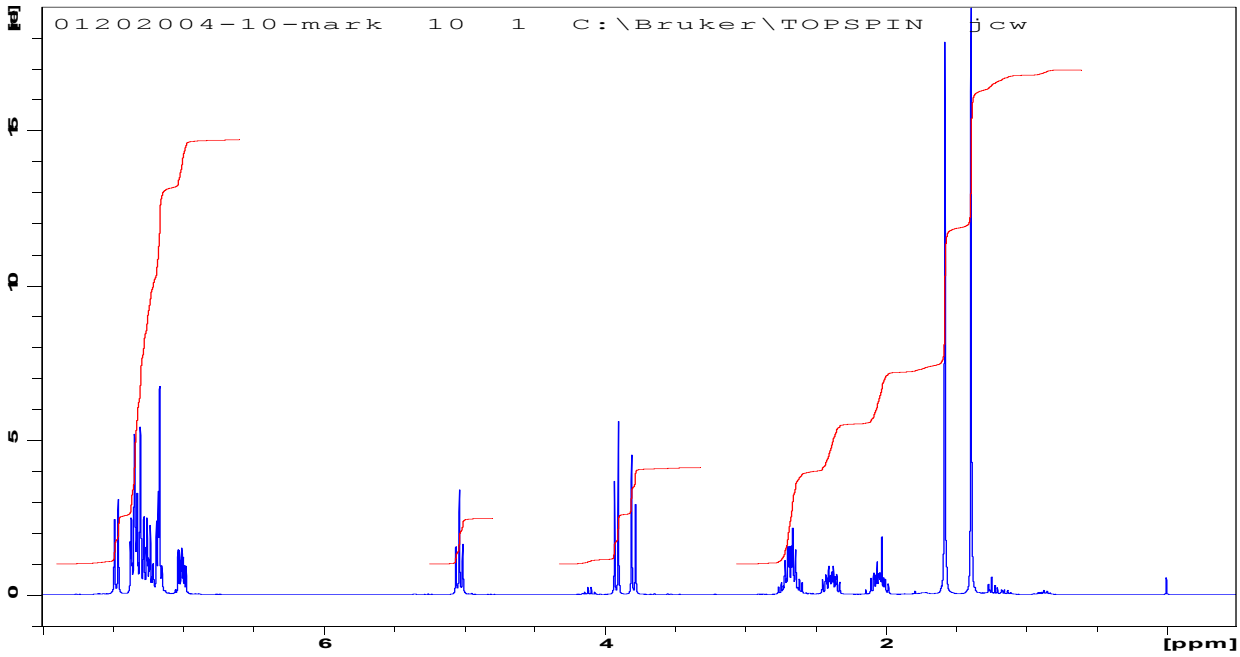


Figure S2. ^{1}H NMR spectrum of 3-[4-(2-Bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one (**1a**)

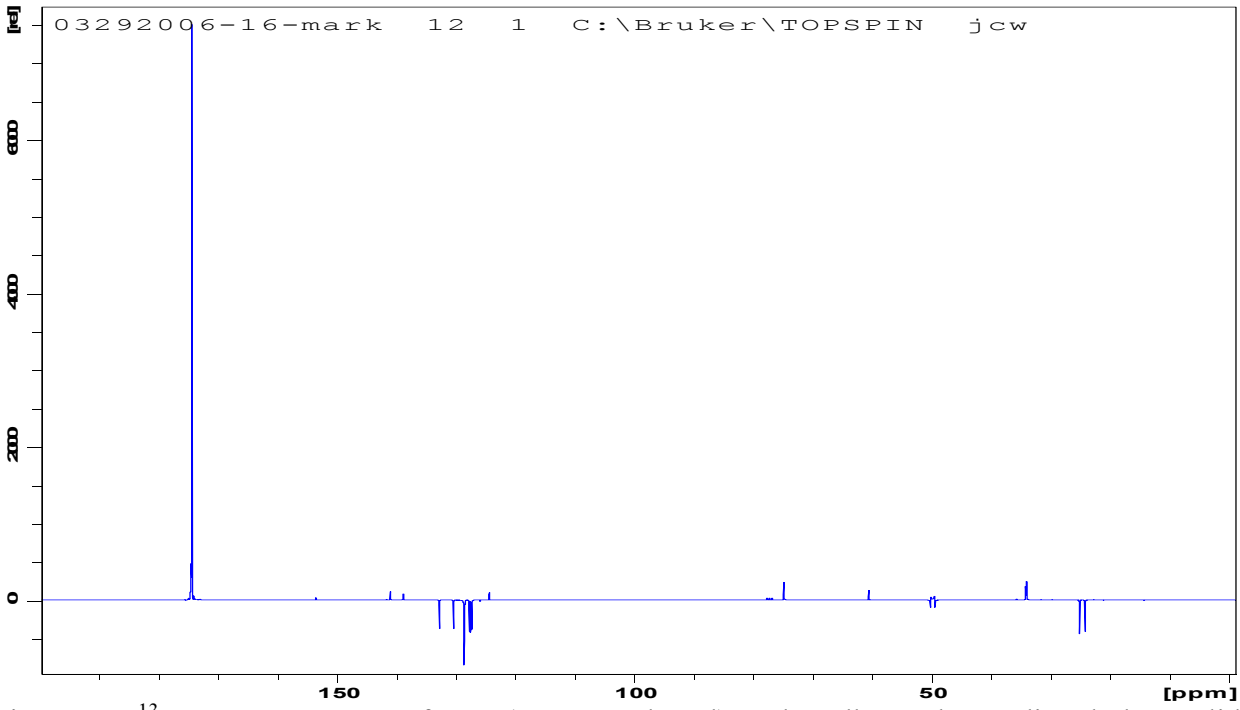


Figure S3. ^{13}C NMR spectrum of 3-[4-(2-Bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one (^{13}C *CON*) **(1b).**

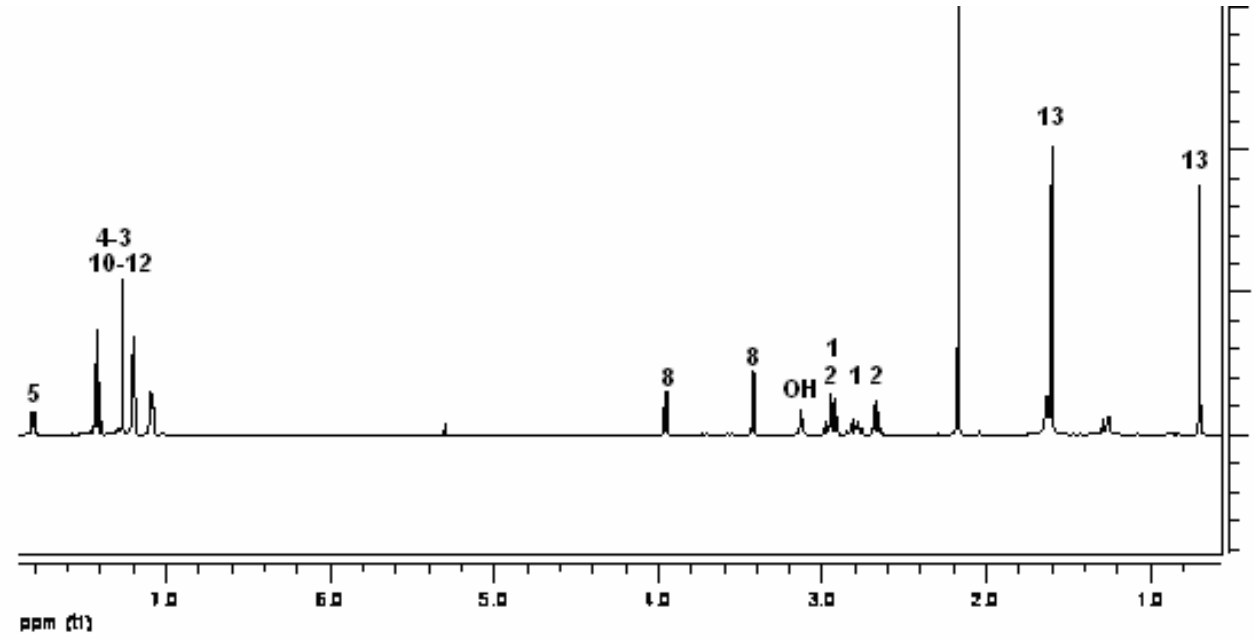


Figure S4. 500 MHz ^{1}H NMR spectrum of tetracycle **2a** in $CDCl_3$

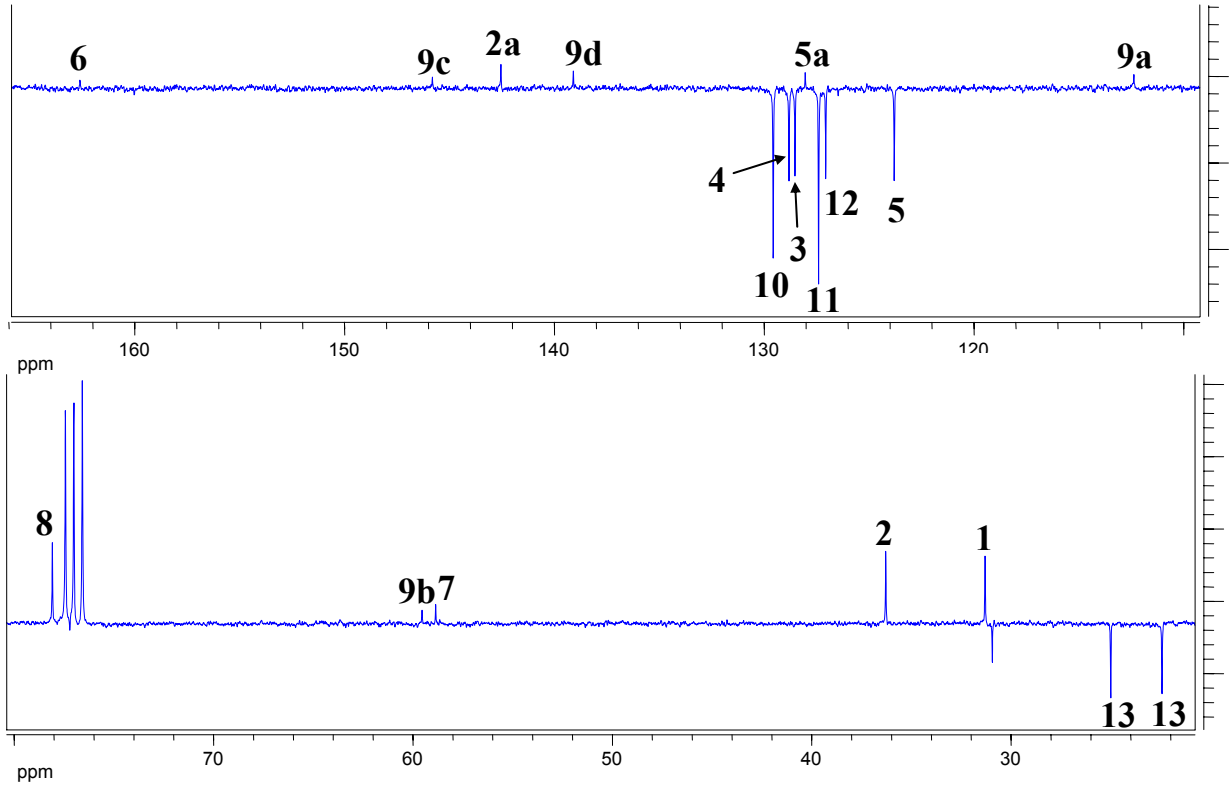
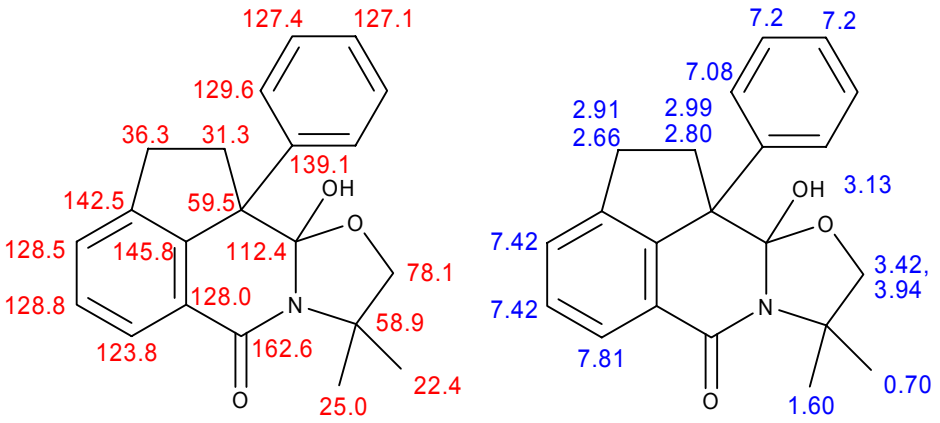


Figure S5. 125 MHz ^{13}C NMR spectrum of tetracycle **2a** in $CDCl_3$

The final assignments of ^{13}C and ^{1}H NMR resonances to specific atoms of tetracycle **2a** are shown below. The assignments were deduced from the 500 MHz ^{1}H-^{1}H-COSY, HSQC and HMBC spectra.



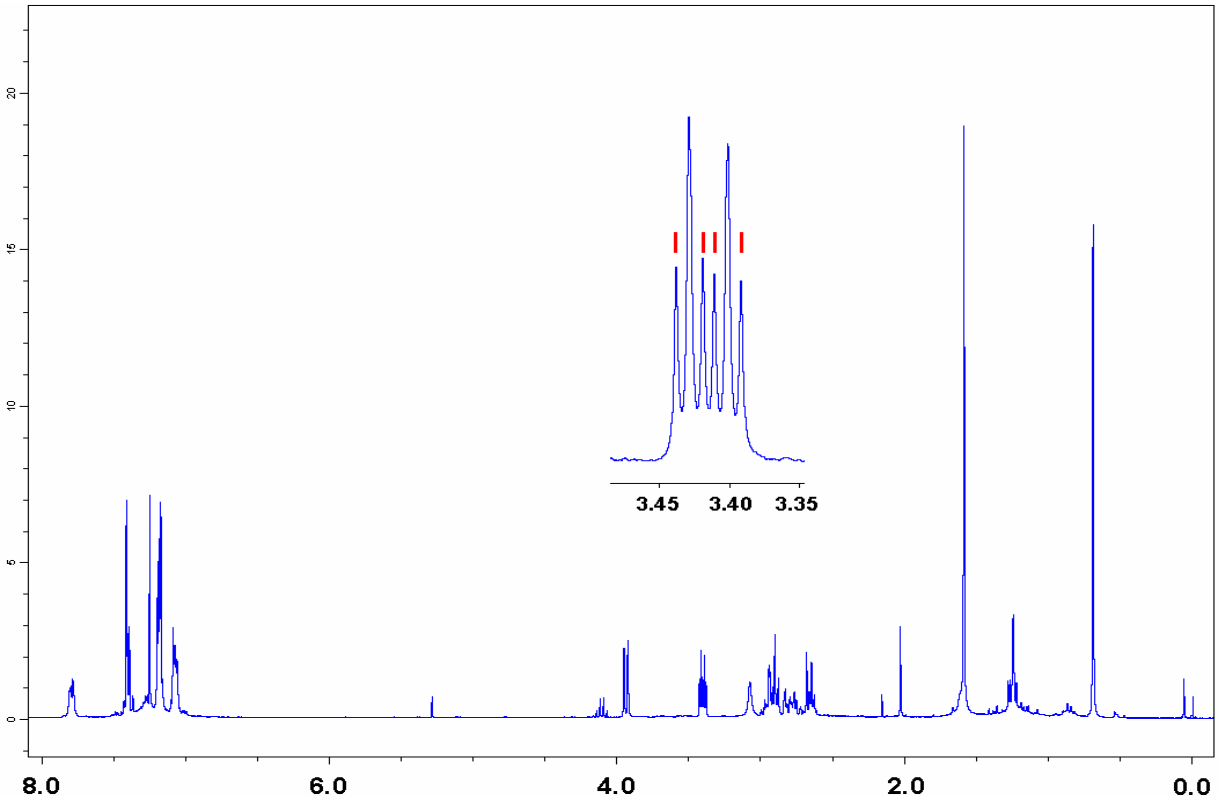


Figure S6. ^{1}H NMR spectrum of ^{13}C labelled tetracycle **2b**. The insert shows the multiplet for CH_{E}H$_{F}$O with an expanded scale. The signals of the ^{13}C labelled isotopomer are marked with red lines and the ^{12}C isotopomer appears as a doublet.

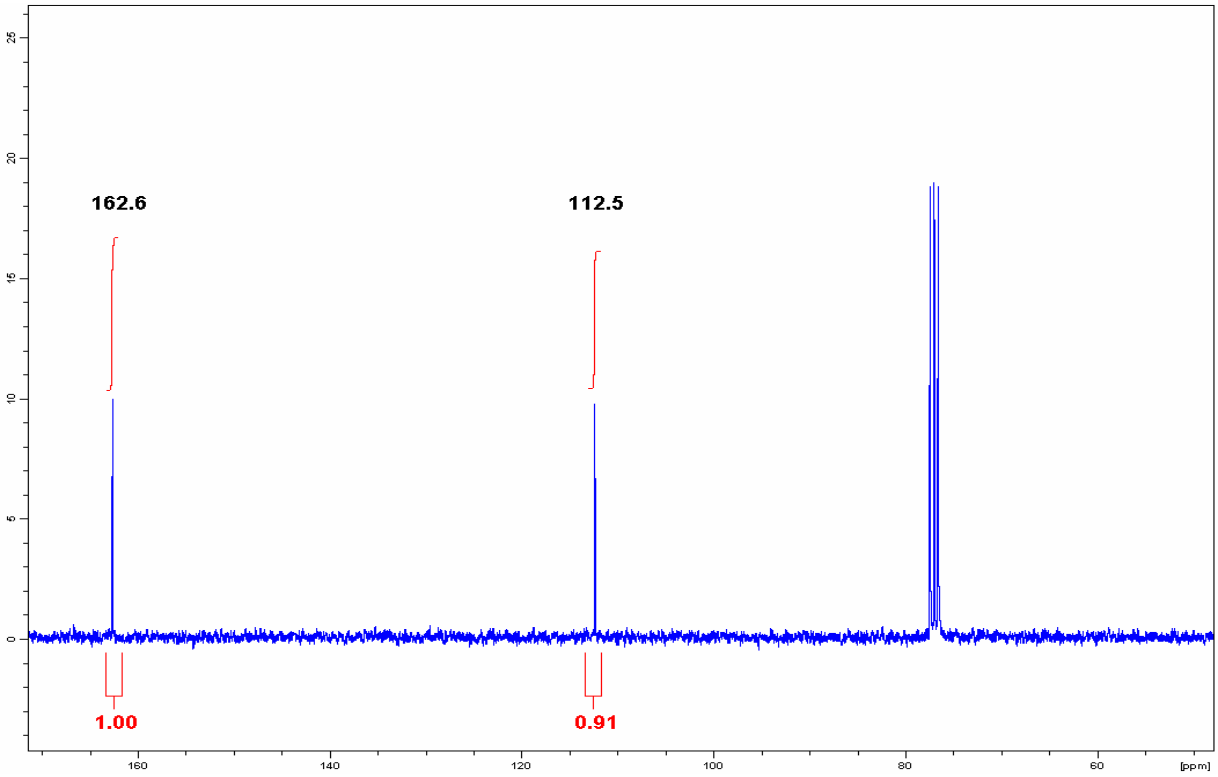


Figure S7. Partial ^{13}C NMR spectrum of ^{13}C labelled tetracycle **2b** observed with inverse gated decoupling so as to provide valid integral values.