Supplementary Material

1 SUPPLEMENTARY DATA

1.1 General information

Flash chromatography was carried out on handpacked columns of silica gel 60 (230-400 mesh). For thin layer chromatography Merck TLC silica gel 60 F254 aluminum plates were used. HMDSLi was used as a standard commercial solution in toluene from Sigma-Aldrich. Other chemicals were obtained from commercial sources and were used as received. Solvents such as ethyl acetate, acetone, hexane, and dichloromethane, were distilled before being used. Toluene and tetrahydrofuran (THF) were used freshly distilled from metallic sodium. Deuterated solvents were obtained from Cambridge Isotope Laboratories. ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC, NOESY, and anisotropy titrations, of Epo, C4, and C5, data were obtained using Bruker 750 Avance-III, Bruker 400, and Varian 500. TMS was used as an internal reference.

1.2 Synthesis of 5-Iodo-2-methyl-2-pentene, 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile and 6-methyl-2-phenylhept-5-enenitrile

5-Iodo-2-methyl-2-pentene was obtained by means of conditions reported for M. Julia and P. Ward.Julia and Ward (1973)

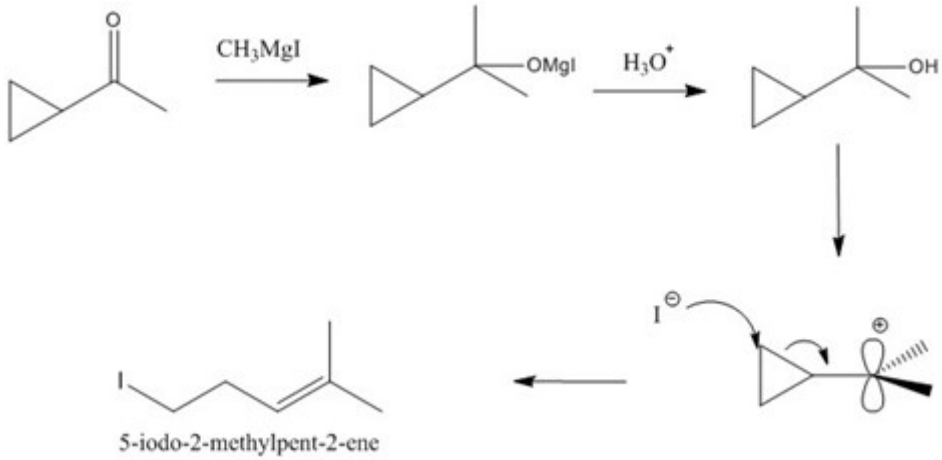

Figure S1. Synthesis of 5-Iodo-2-methyl-2-pentene

^{1}H-NMR (301 MHz, Chloroform-d) δ 5.09 (tdq, J = 7.1, 2.9, 1.5 Hz, 1H), 3.10 (t, J = 7.4 Hz, 2H), 2.57 (tdd, J = 8.2, 5.4, 4.4 Hz, 2H), 1.69 (q, J = 1.3 Hz, 4H), 1.65 – 1.57 (m, 3H).

2-phenyl-6-methylhept-5-enonitrile was obtained using conditions reported for W. G. Kofron. Kofron and Hauser (1970)

^{1}H-NMR (500 MHz, Chloroform-d): δ ppm 7.67 - 7.16 (m, 5H), 5.07 (tdt, J = 5.7, 2.8, 1.4 Hz, 1H), 3.78 (dd, J = 8.8, 6.2 Hz, 1H), 2.28 - 2.08 (m, 2H), 2.08 - 1.78 (m, 2H), 1.71 (q, J = 1.3 Hz, 3H), 1.61 (d, J = 1.3

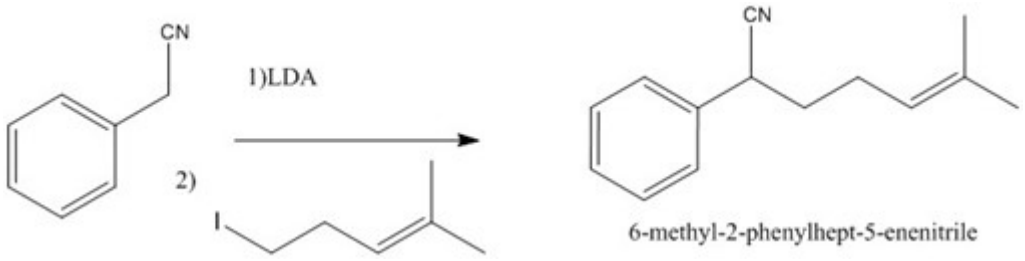

Figure S2. Synthesis of 2-phenyl-6-methylhept-5-enonitrile

Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ ppm 134.96, 133.80, 129.01(2C), 128.22, 127.31 (2C), 122.01, 119.98, 36.98, 36.01, 25.6, 25.78, 16.99.

4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile was obtained by means of conditions reported for L. F. Fieser & M. Fieser. Fieser (1967)

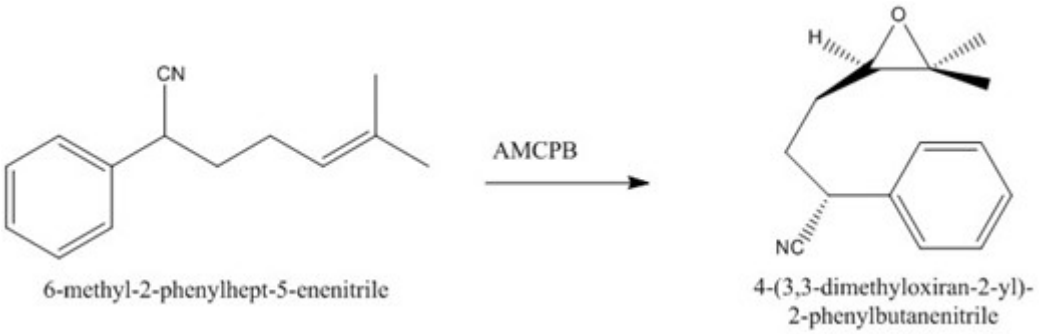

Figure S3. Synthesis of 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

^{1}H-NMR (750 MHz, Chloroform-d) δ 7.33 - 7.24 (m, 10H), 3.86 - 3.80 (m, 2H), 2.66 (ddd, J = 14.7, 7.8, 4.7 Hz, 2H), 2.15 - 1.90 (m, 4H), 1.83 - 1.73 (m, 1H), 1.66 (dddd, J = 14.2, 9.5, 6.1, 4.8 Hz, 1H), 1.62 - 1.54 (m, 1H), 1.54 - 1.45 (m, 1H), 1.23 (s, 6H), 1.20 (s, 3H), 1.15 (s, 3H). ^{13}C-NMR (187.5 MHz, $CDCl_3$) δ 137.00, 136.68, 130.52 (2C), 130.49 (2C), 129.58, 129.55, 128.76 (2C), 128.53(2C), 121.96, 121.84, 64.71, 64.37, 59.78, 59.67, 38.66, 38.05, 34.62, 34.14, 27.94, 27.23, 26.08, 26.06, 20.09, 20.07.

1.3 Synthesis of 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile and u-3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile and 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile were obtained by means of conditions reported for Montelongo et al. Lujan-Montelongo et al. (2009)

^{1}H-NMR (750 MHz, $CDCl_3$): δ ppm 7.61 (dd, J = 7.6, 1.7 Hz, 2H), 7.34 (dt, J = 53.1, 7.6 Hz, 3H), 3.06 (dd, J = 11.0, 8.9 Hz, 1H), 2.73 (ddd, J = 12.4, 10.7, 8.9 Hz, 1H), 2.64 (ddd, J = 12.1, 9.1, 2.6 Hz, 1H), 2.47 (qd, J = 11.0, 9.1 Hz, 1H), 2.12 (dtd, J = 11.5, 8.9, 2.6 Hz, 1H), 1.71 - 1.41 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H). ^{13}C-NMR (187.5 MHz, $CDCl_3$): δ ppm 133.58, 128.07 (2C), 127.52, 126.98 (2C), 123.30, 70.55, 54.66, 41.57, 29.02, 26.24, 26.04, 19.21.

3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

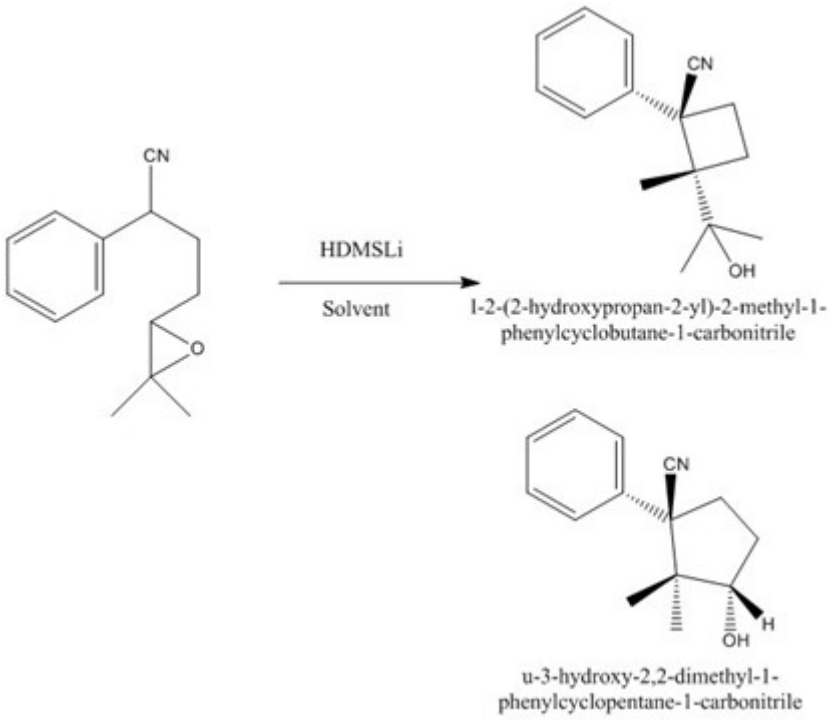

Figure S4. Synthesis of 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile and 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

^{1} H-NMR (750 MHz, $CDCl_3$): δ ppm 7.49 (td, J = 7.2, 1.3 Hz, 1H), 7.43 - 7.36 (m, 4H), 4.30 (t, J = 8.4 Hz, 1H), 2.67 (ddd, J = 13.9, 11.9, 6.5 Hz, 1H), 2.38 (dtd, J = 13.6, 9.3, 6.4 Hz, 1H), 2.21 (ddd, J = 13.9, 9.6, 4.2 Hz, 1H), 1.73 - 1.68 (m, 1H), 1.13 (s, 4H), 0.51 (s, 3H). ^{13}C-NMR (187.5 MHz, $CDCl_3$): δ ppm 134.99, 128.30(2C), 128.28, 127.68(2C), 123.93, 79.56, 54.22, 49.21, 29.71, 28.98, 21.22, 14.61.

5-hydroxy-5-methyl-1-phenylhexan-1-one

^{1}H-NMR (750 MHz, Chloroform-d) δ 7.97 (dd, J = 8.2, 1.4 Hz, 2H), 7.52 - 7.47 (m, 1H), 7.32 (t, J = 7.8 Hz, 2H), 2.72 (dt, J = 8.1, 4.5 Hz, 1H), 1.72 (dddd, J = 13.4, 9.1, 7.4, 4.3 Hz, 2H), 1.32 (ddd, J = 8.8, 4.8, 3.6 Hz, 1H), 1.25 (d, J = 5.7 Hz, 6H), 1.21 - 1.16 (m, 1H), 1.13 (tddd, J = 15.0, 14.3, 6.0, 3.6, 0.0 Hz, 0H). ^{13}C-NMR (189 MHz, $CDCl_3$) δ 200.37, 138.04, 134.99, 127.68, 123.93, 79.56, 77.39, 77.22, 77.05, 68.97, 36.93, 30.64, 29.98, 29.89, 22.48, 15.99.

1.4 NMR Spectra

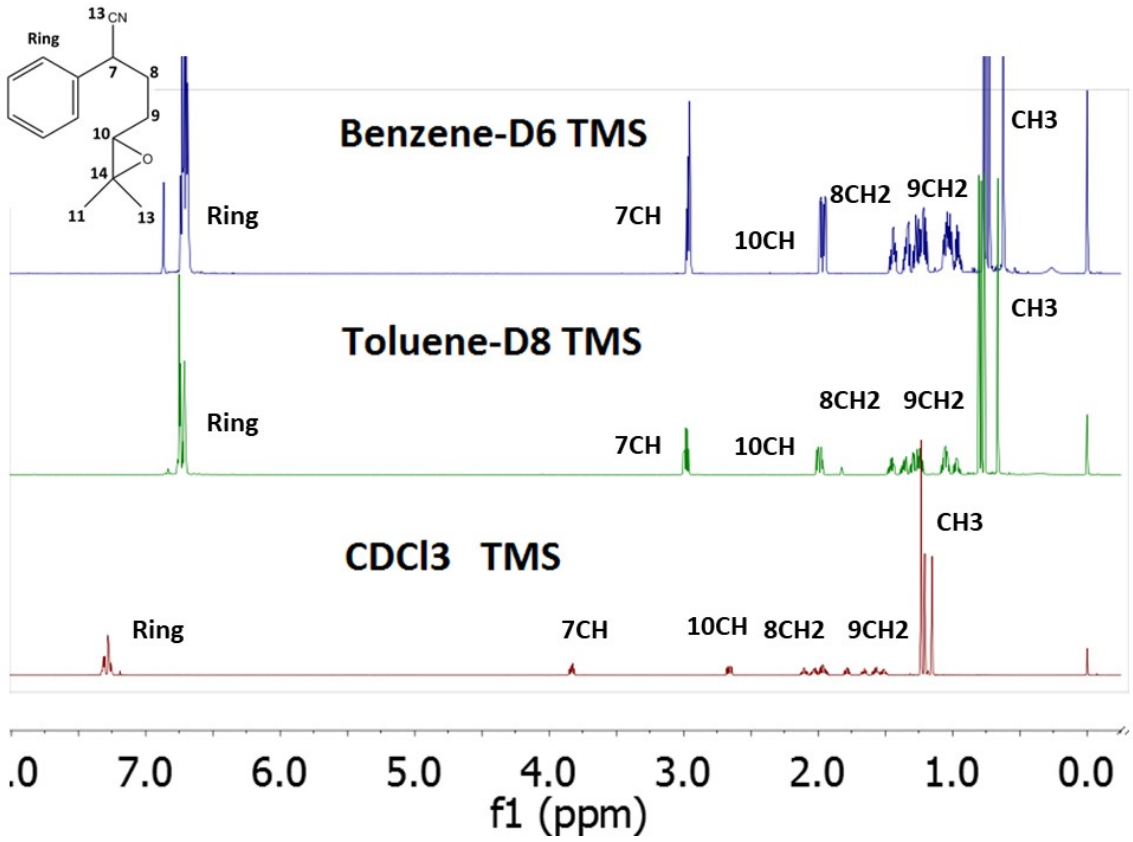

Figure S5. ^{1}H-NMR 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

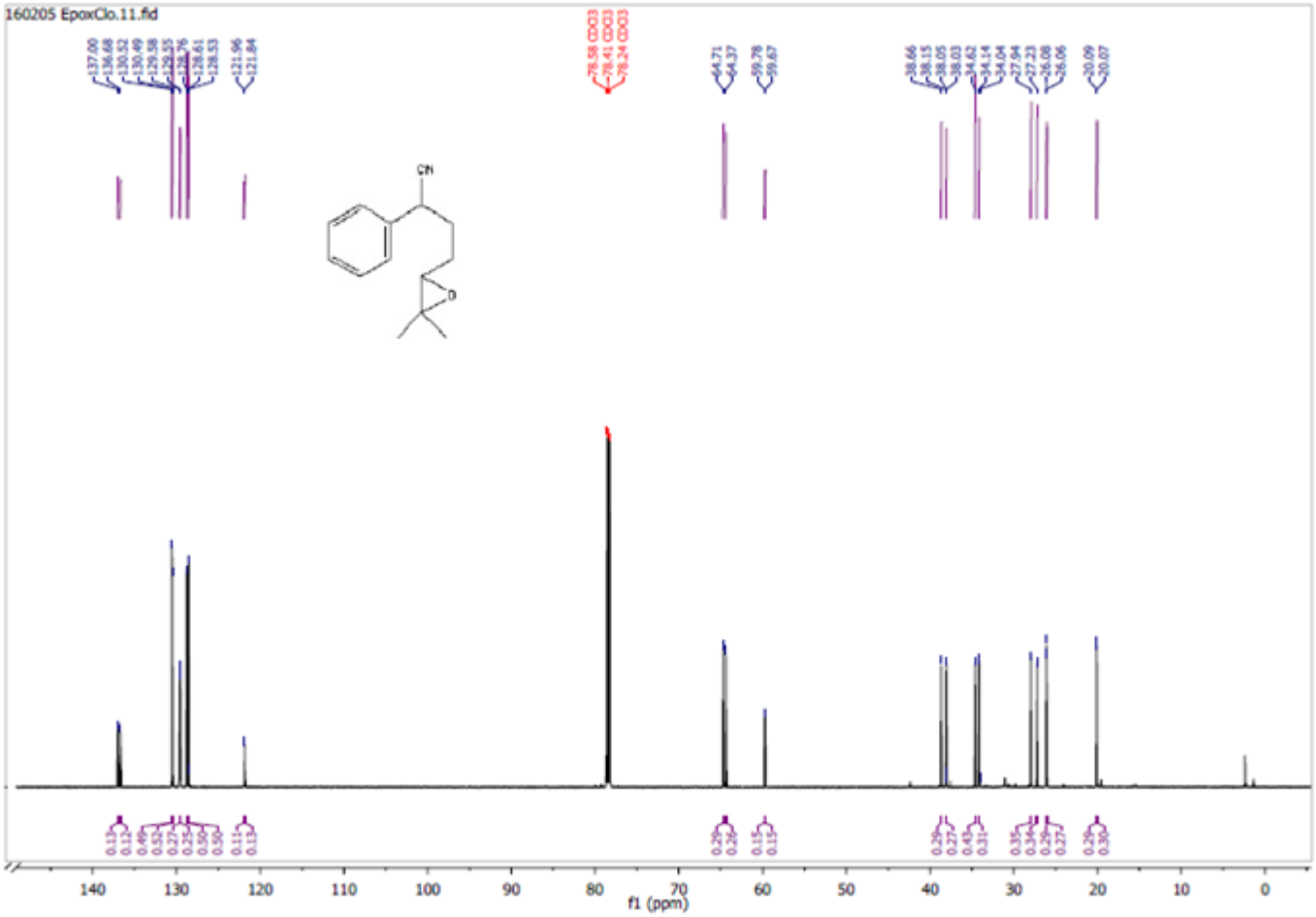

Figure S6. ^{13}C-NMR 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

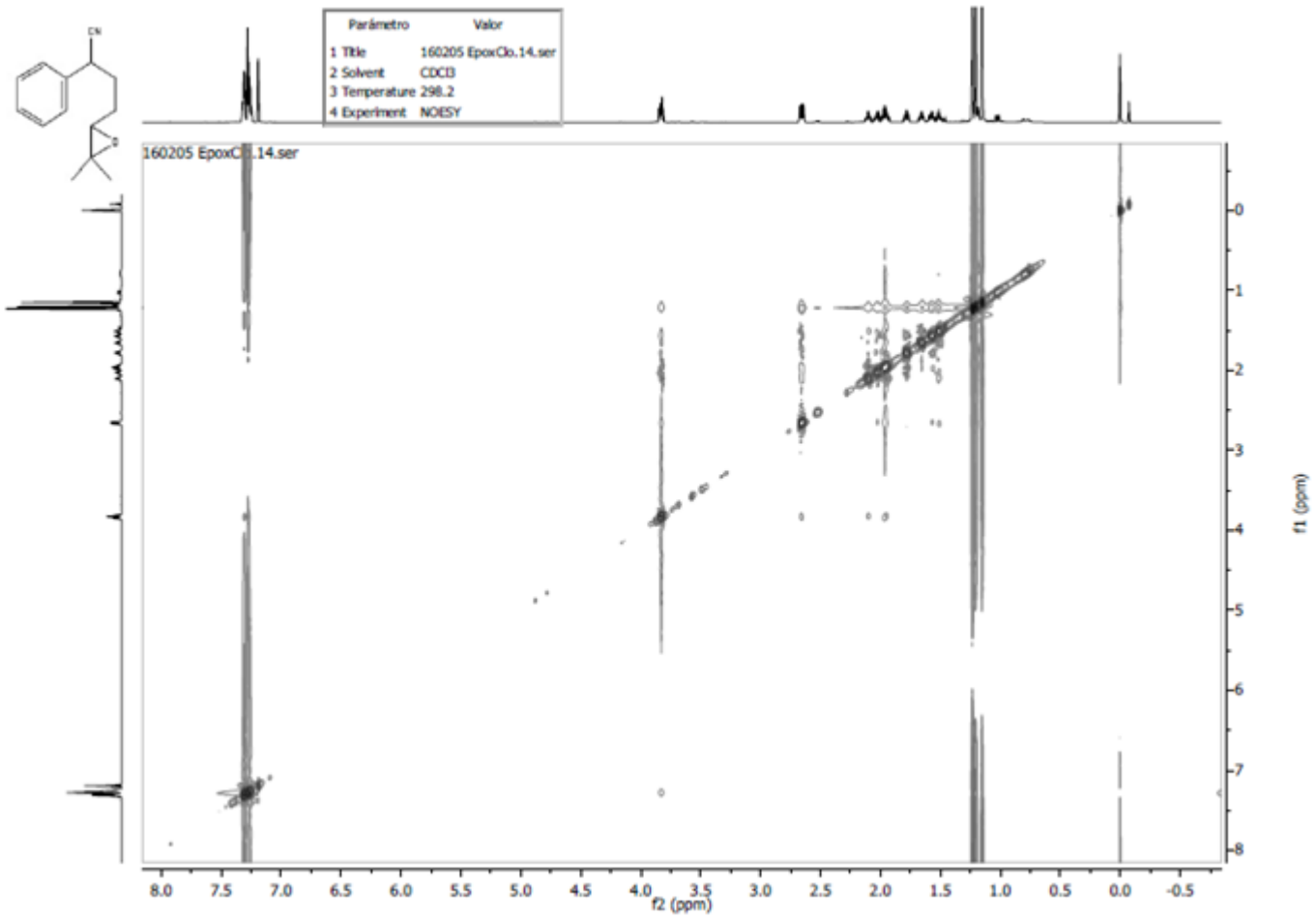

Figure S7. NOESY 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

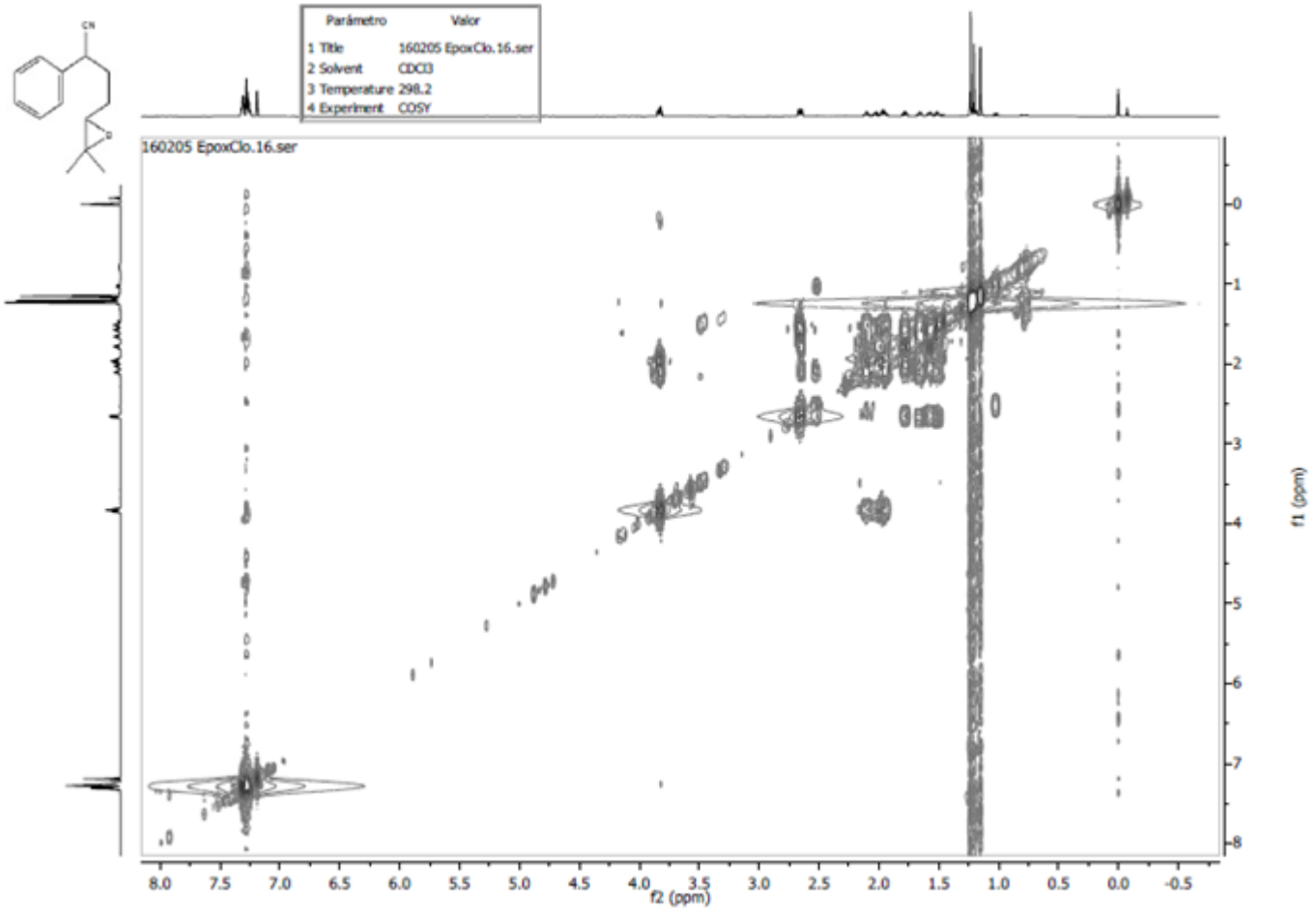

Figure S8. COSY 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

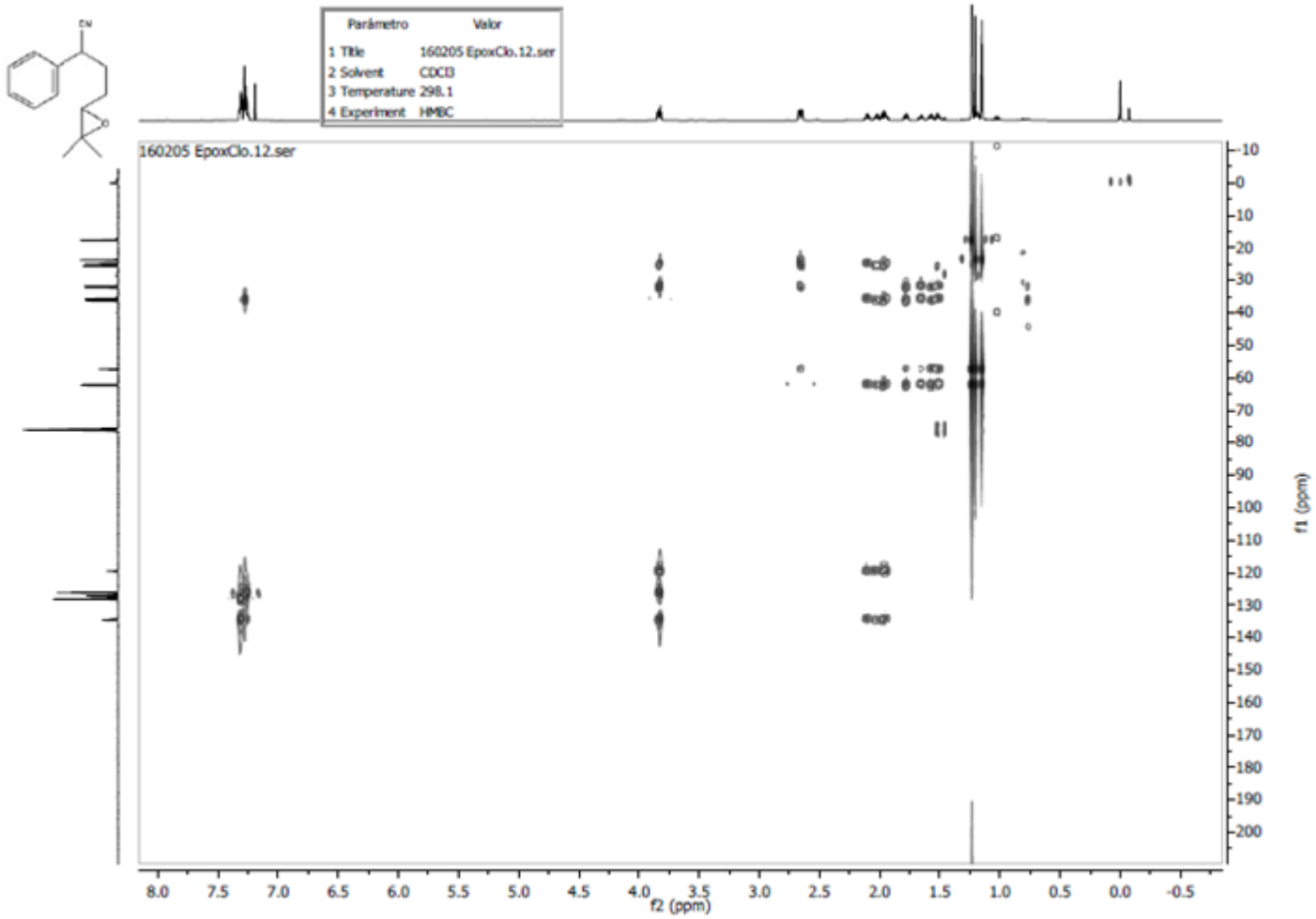

Figure S9. HMBC 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

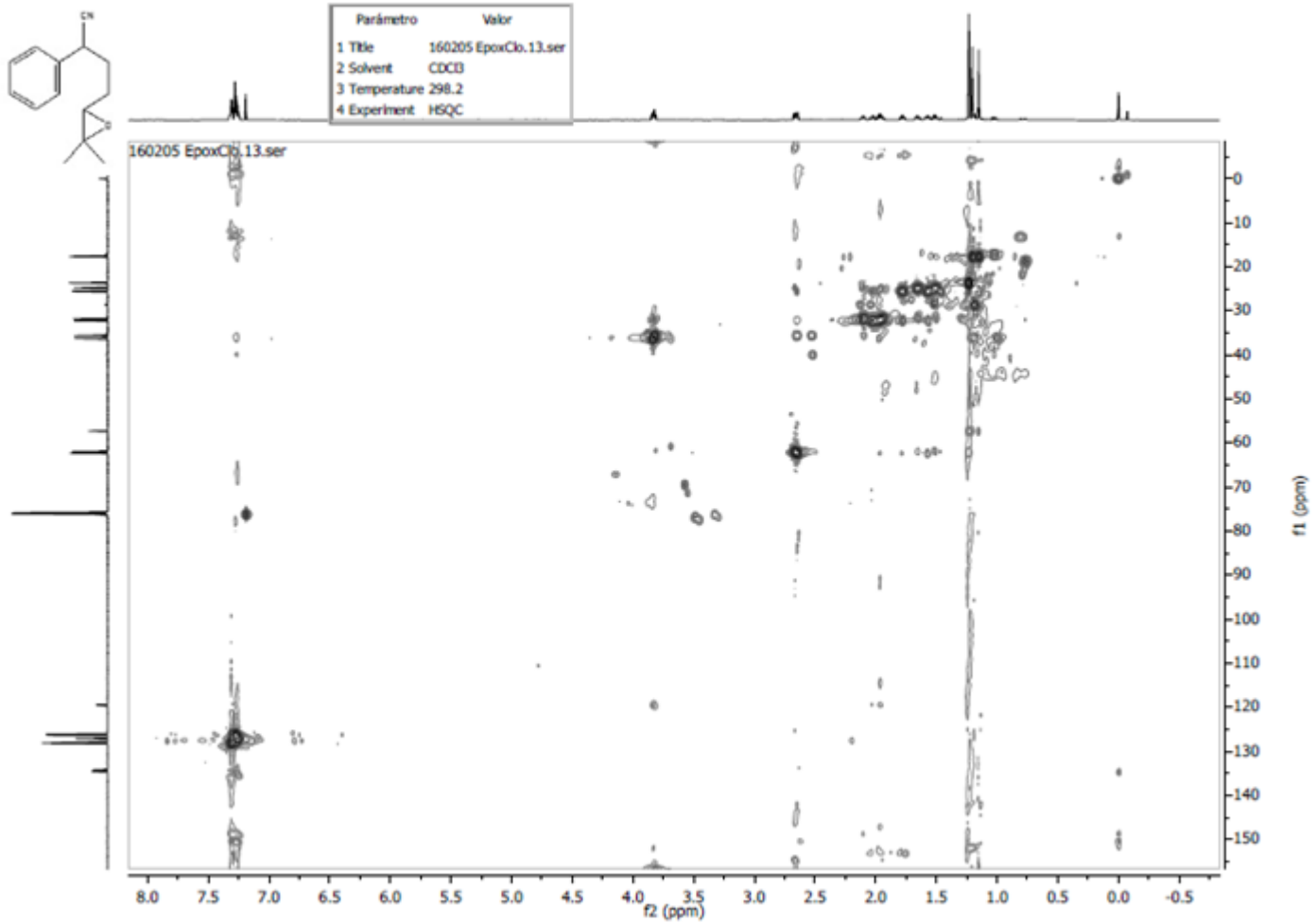

Figure S10. HSQC 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

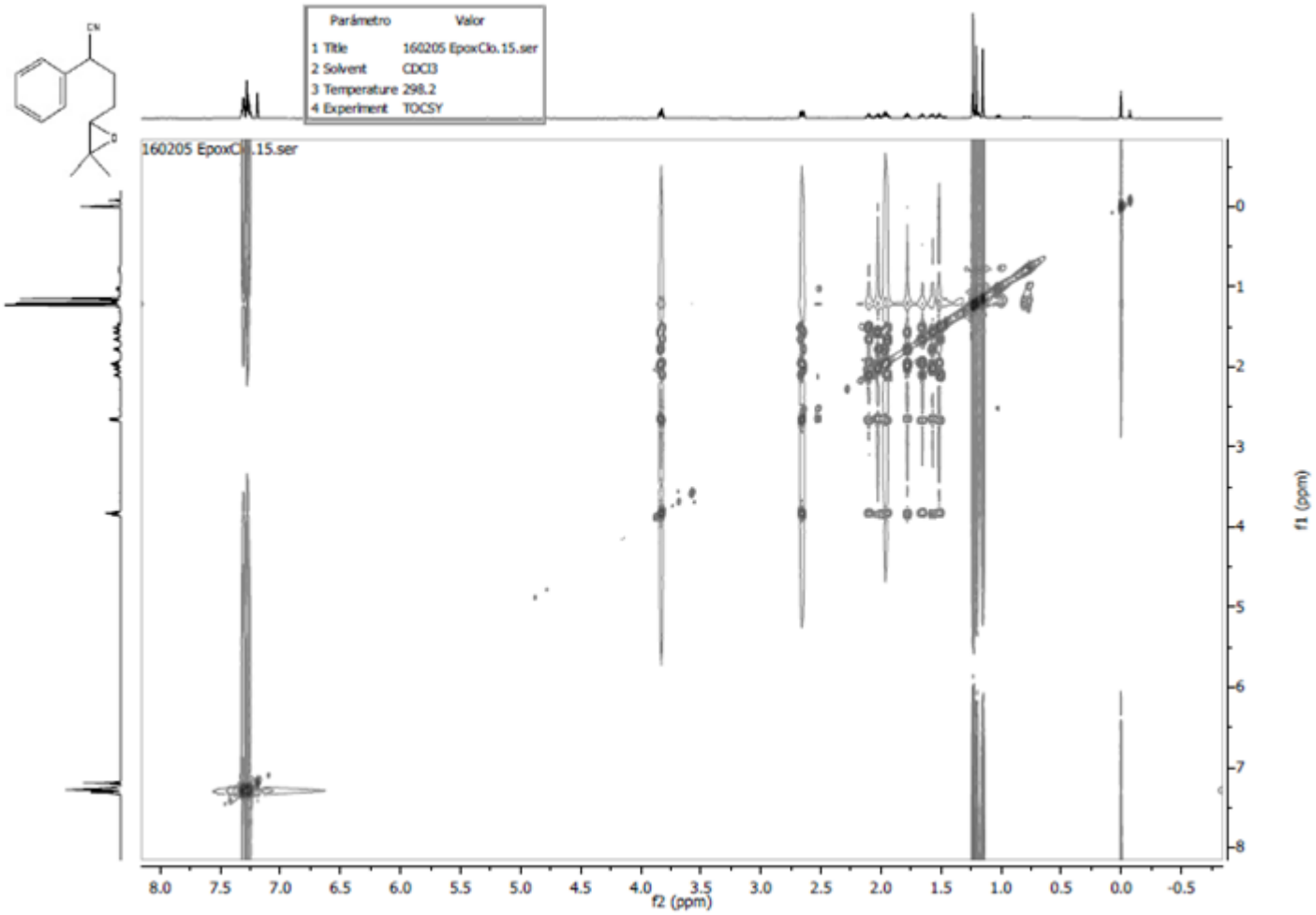

Figure S11. TOCSY 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

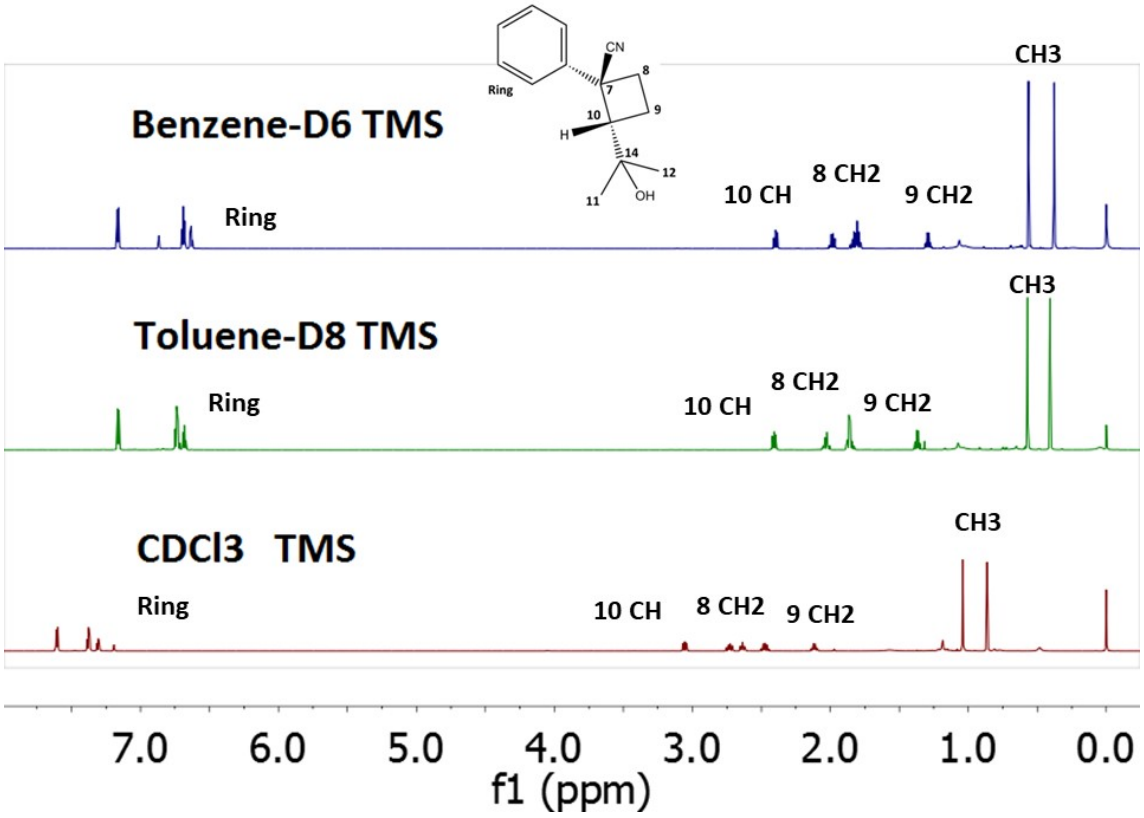

Figure S12. ^{1}H-NMR 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

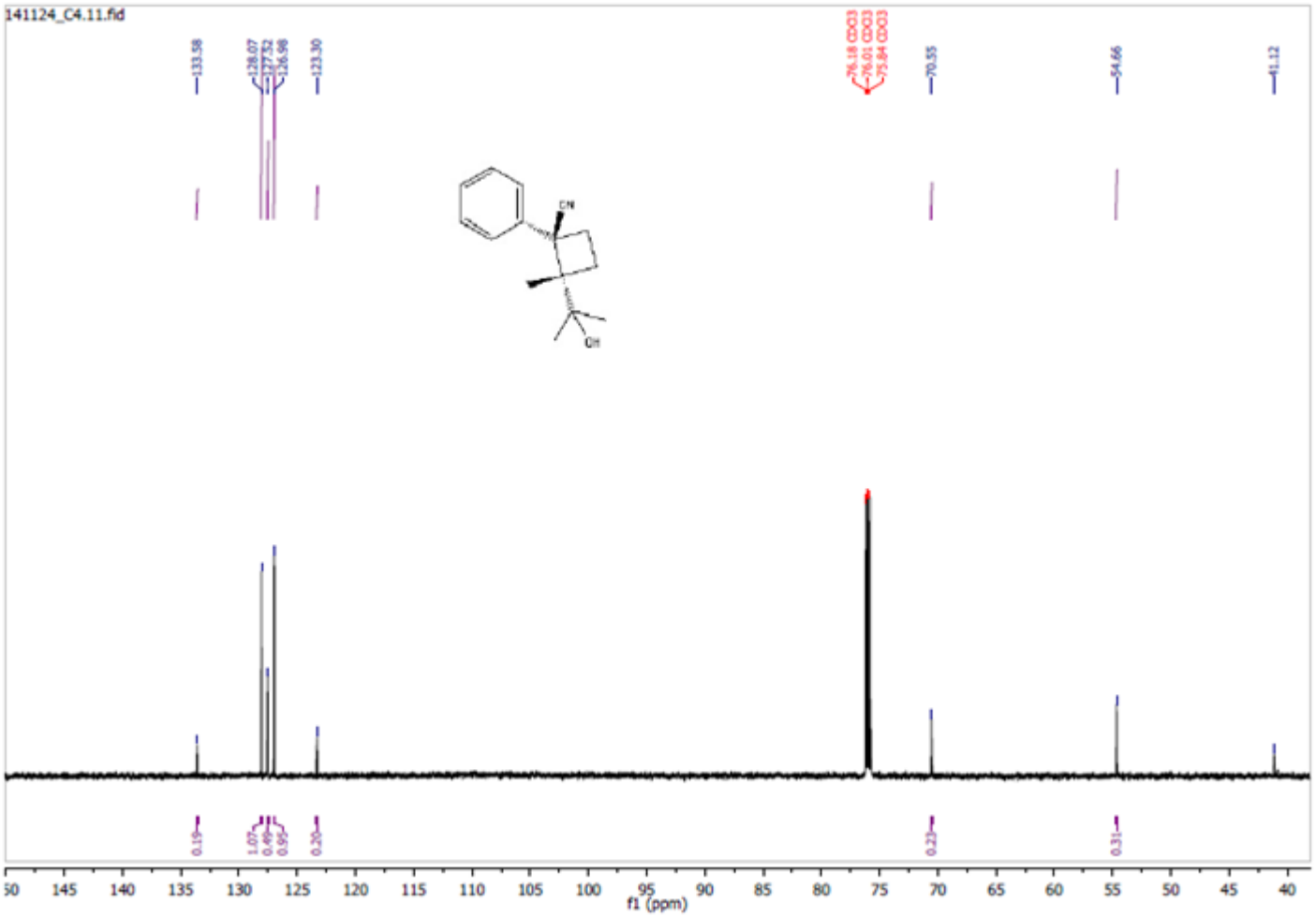

Figure S13. ^{13}C-NMR 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

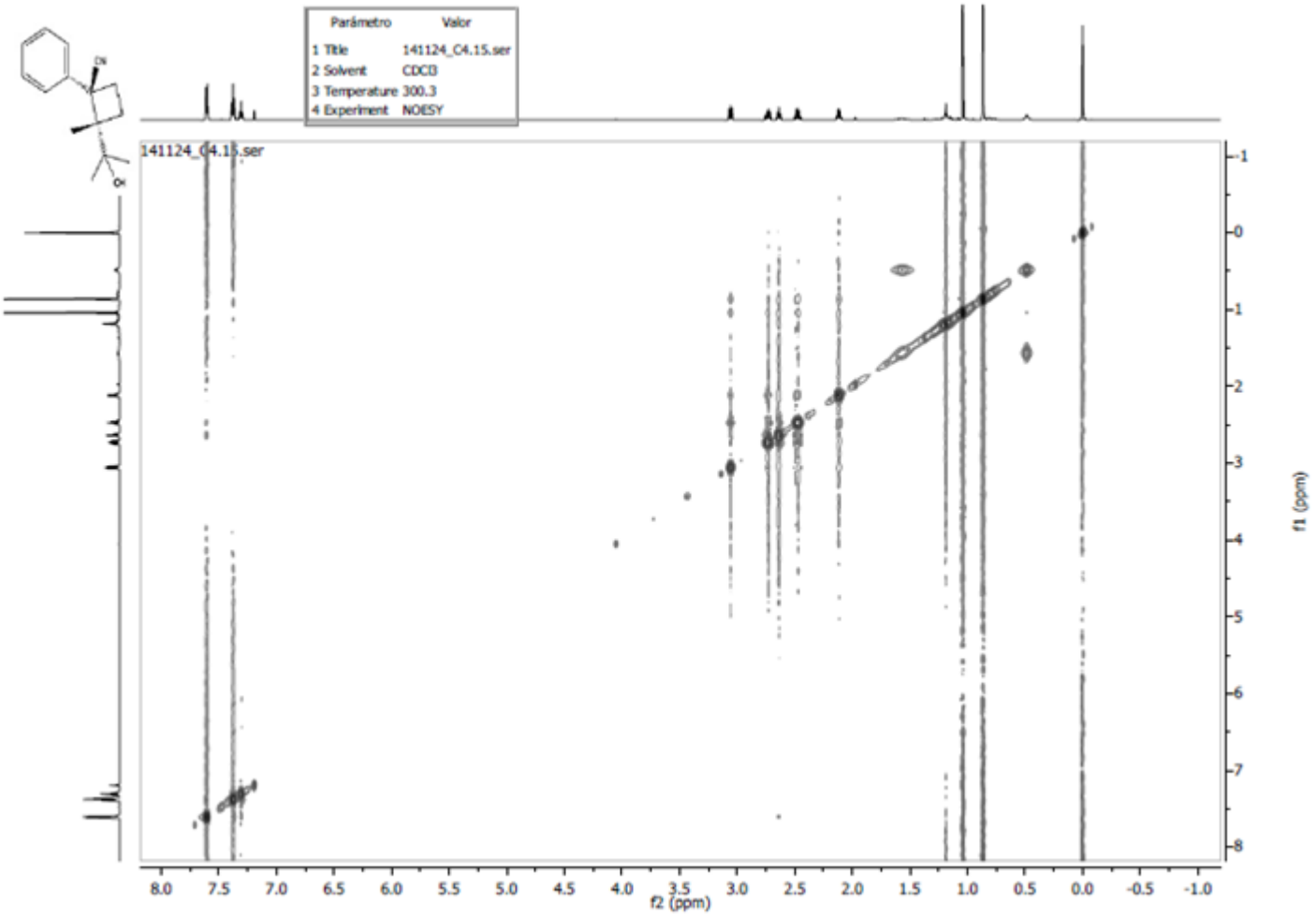

Figure S14. NOESY 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

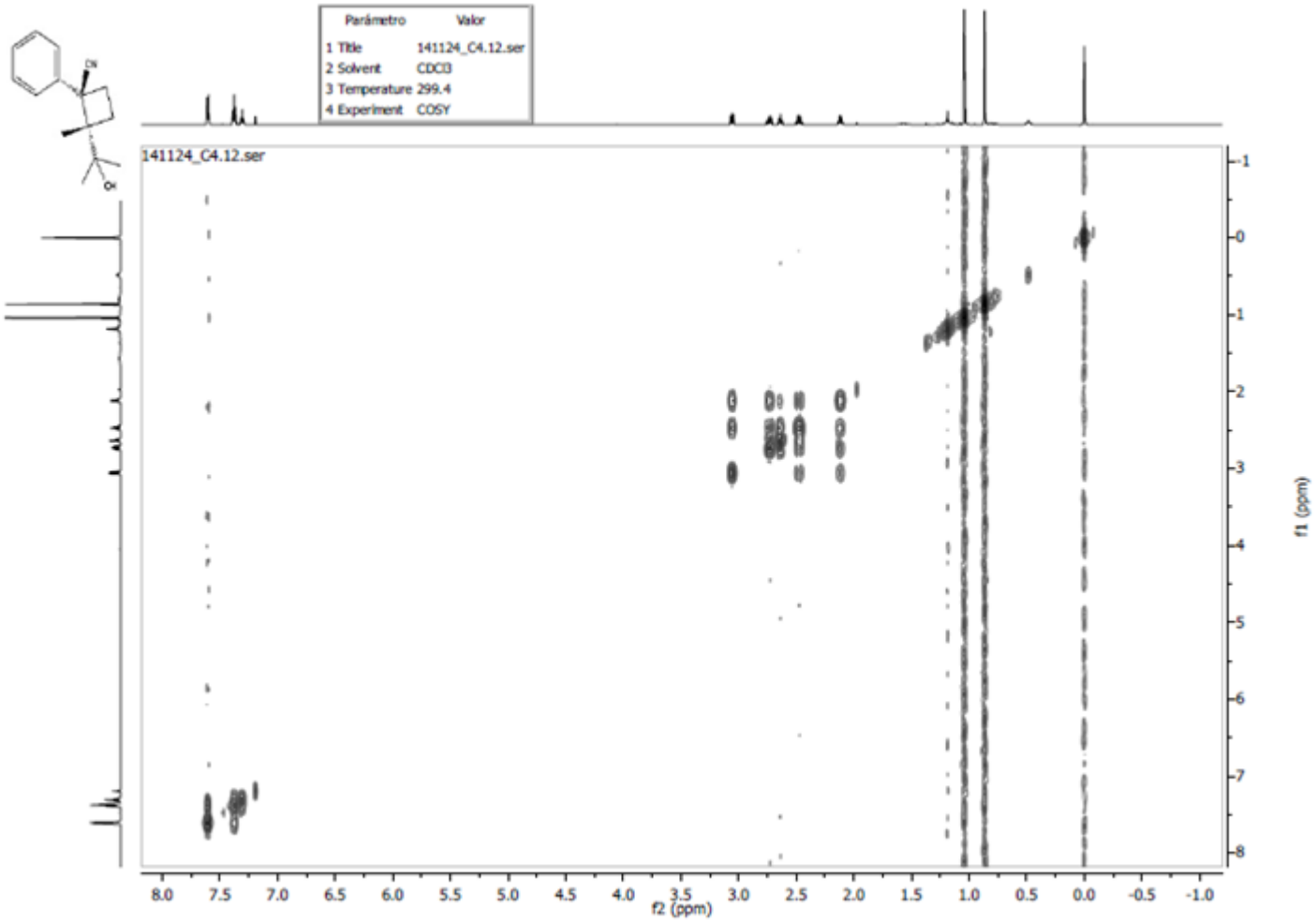

Figure S15. COSY 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

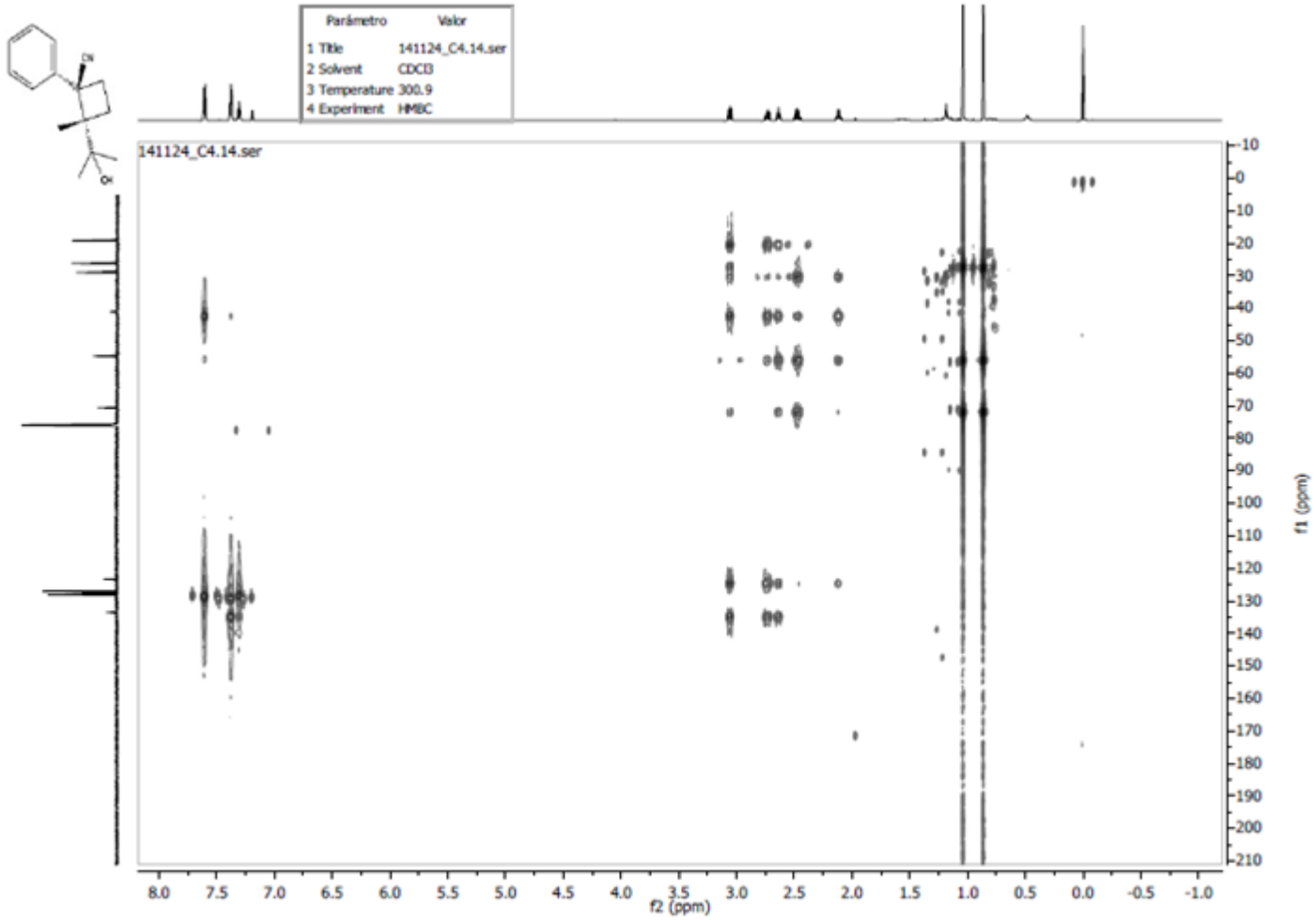

Figure S16. HMBC 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

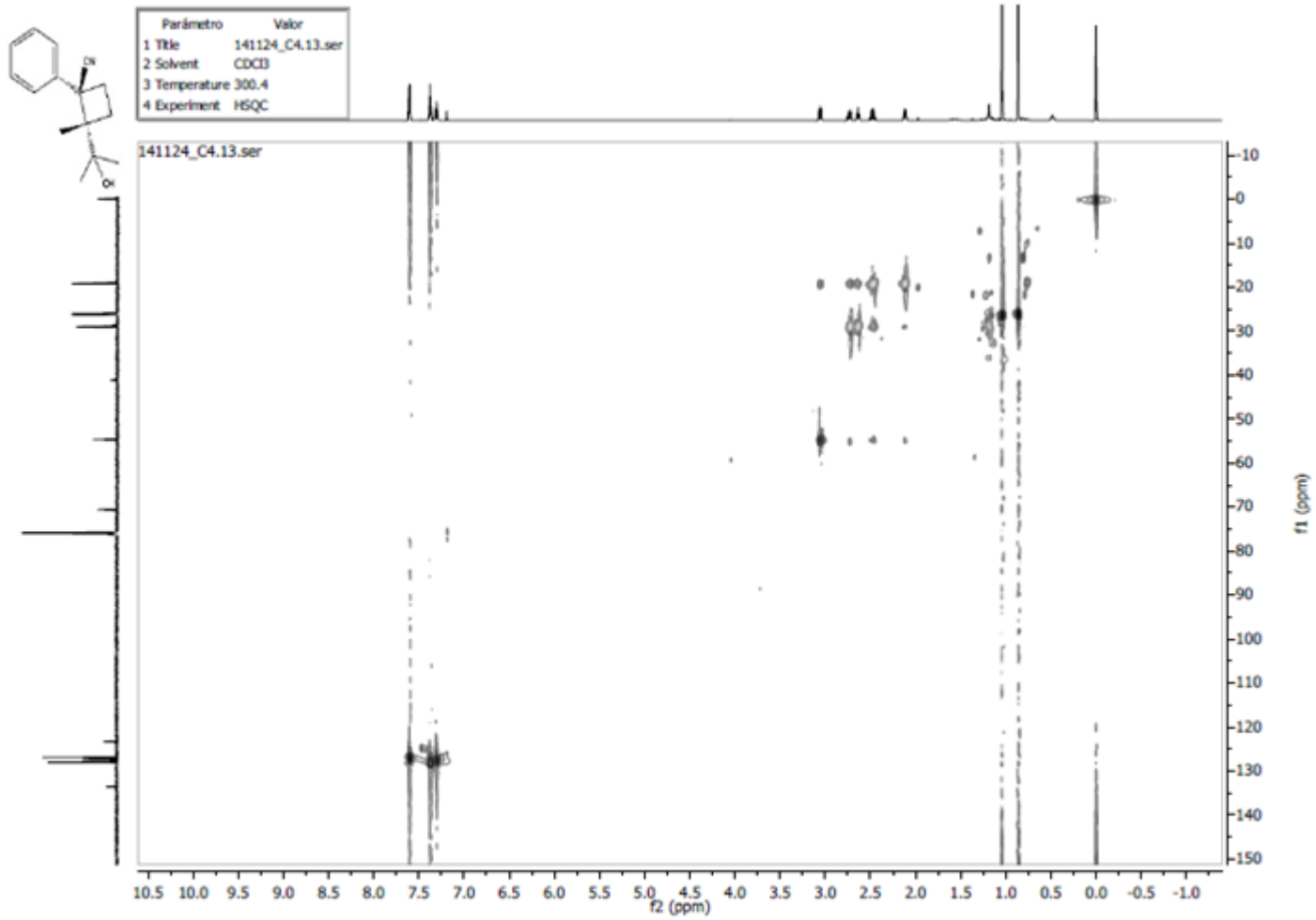

Figure S17. HSQC 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

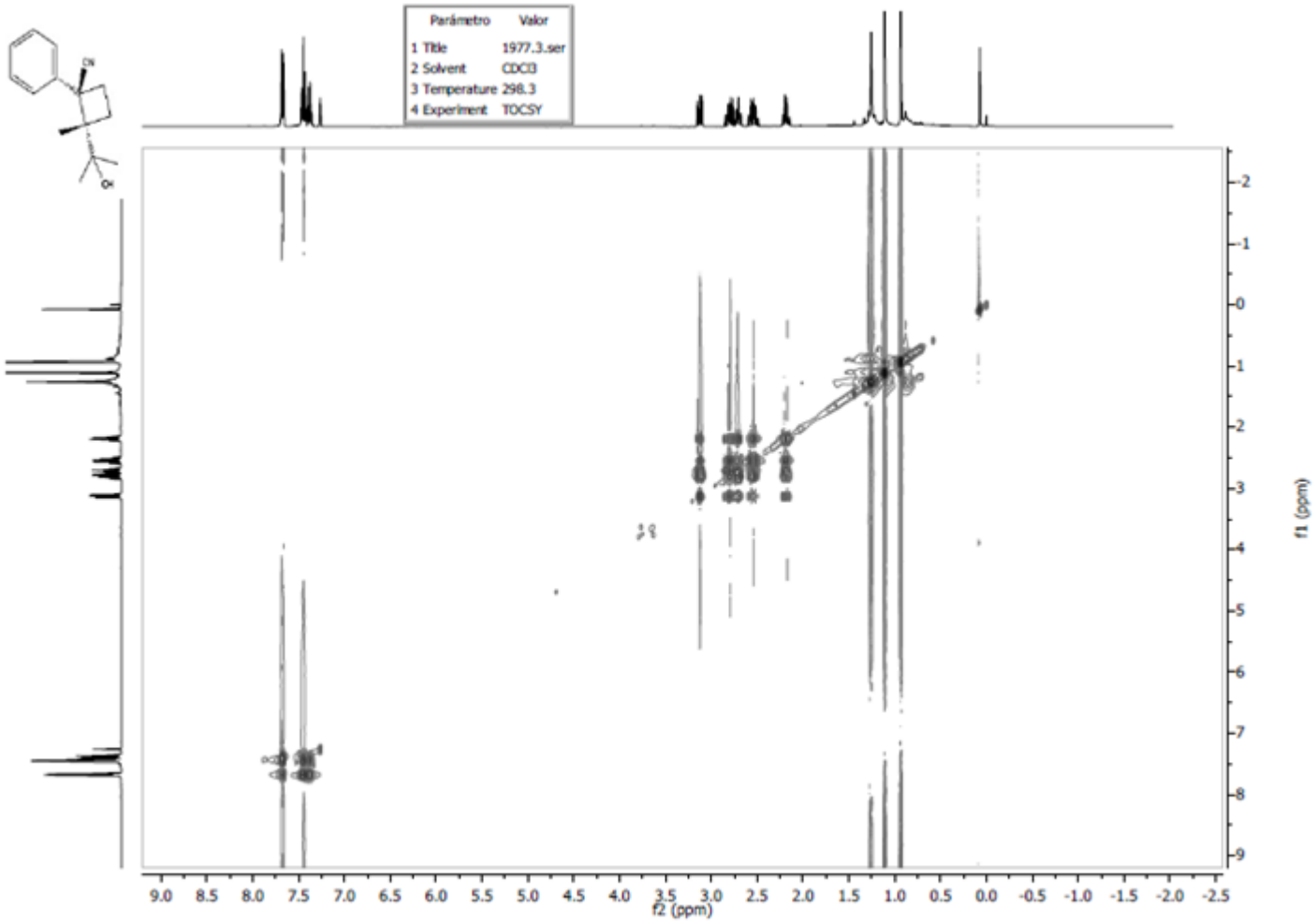

Figure S18. TOCSY 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

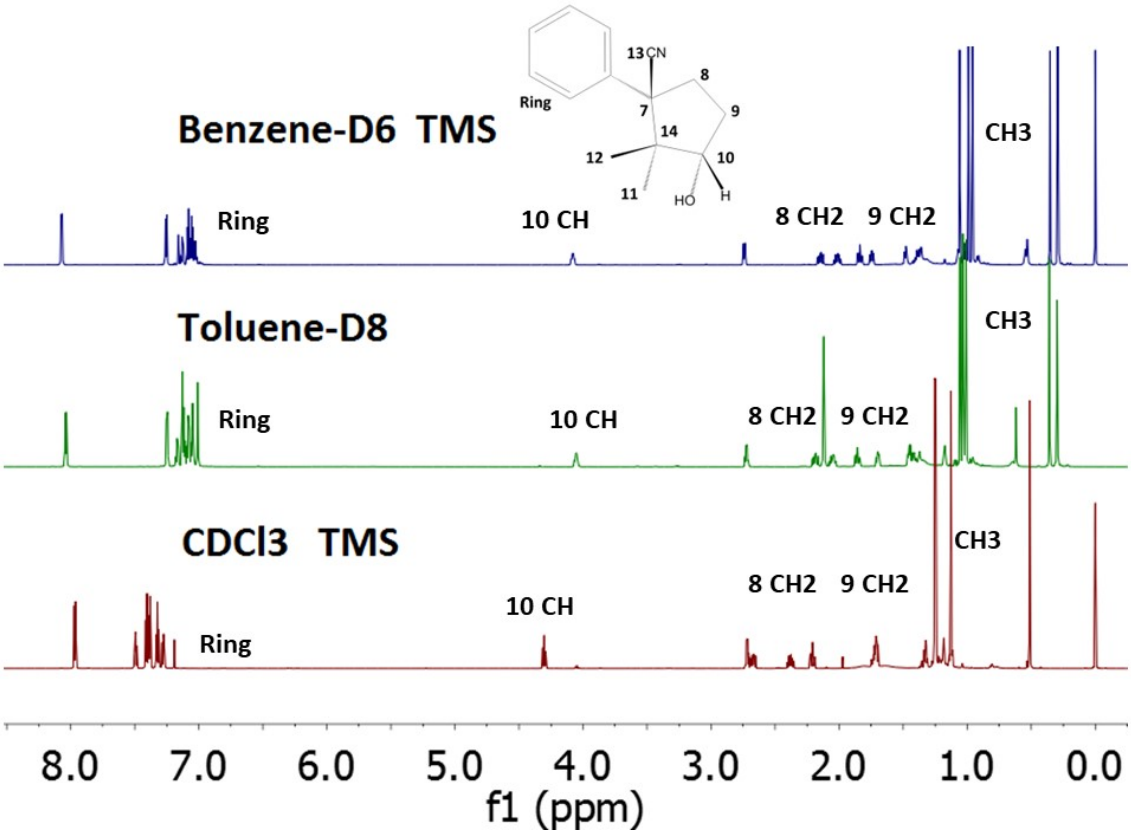

Figure S19. ^{1}H-NMR 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

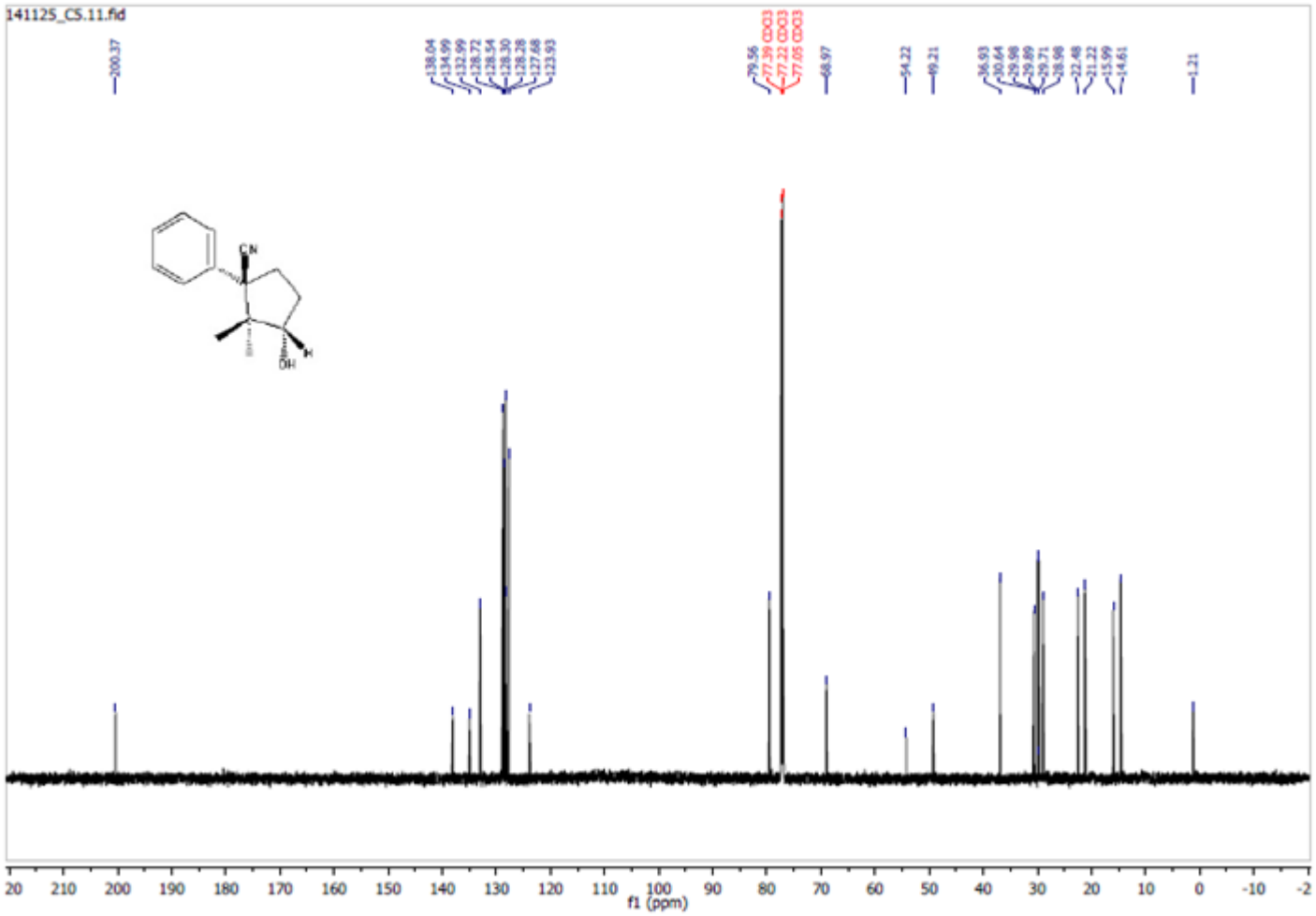

Figure S20. ^{13}C-NMR 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

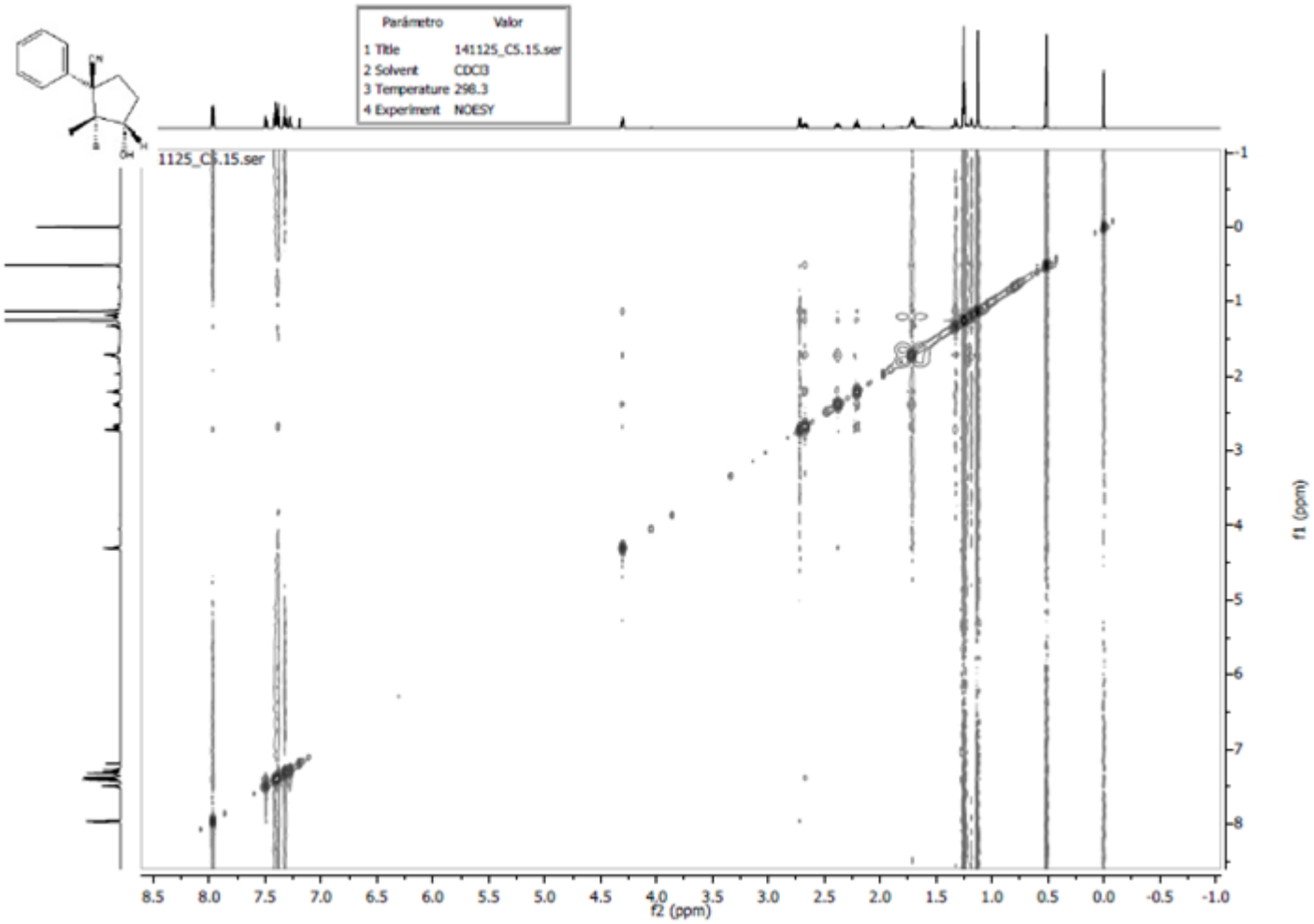

Figure S21. NOESY 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

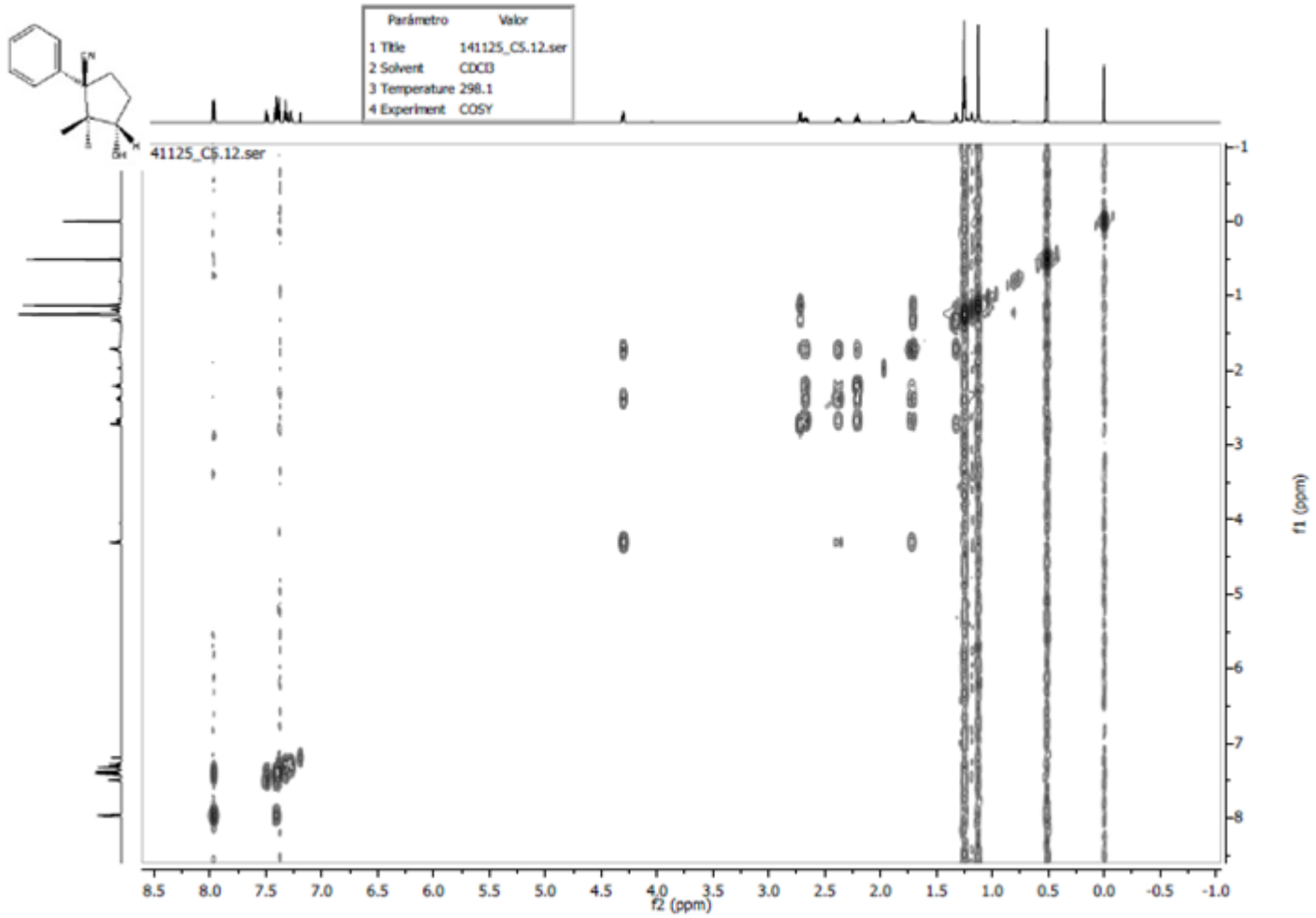

Figure S22. COSY 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

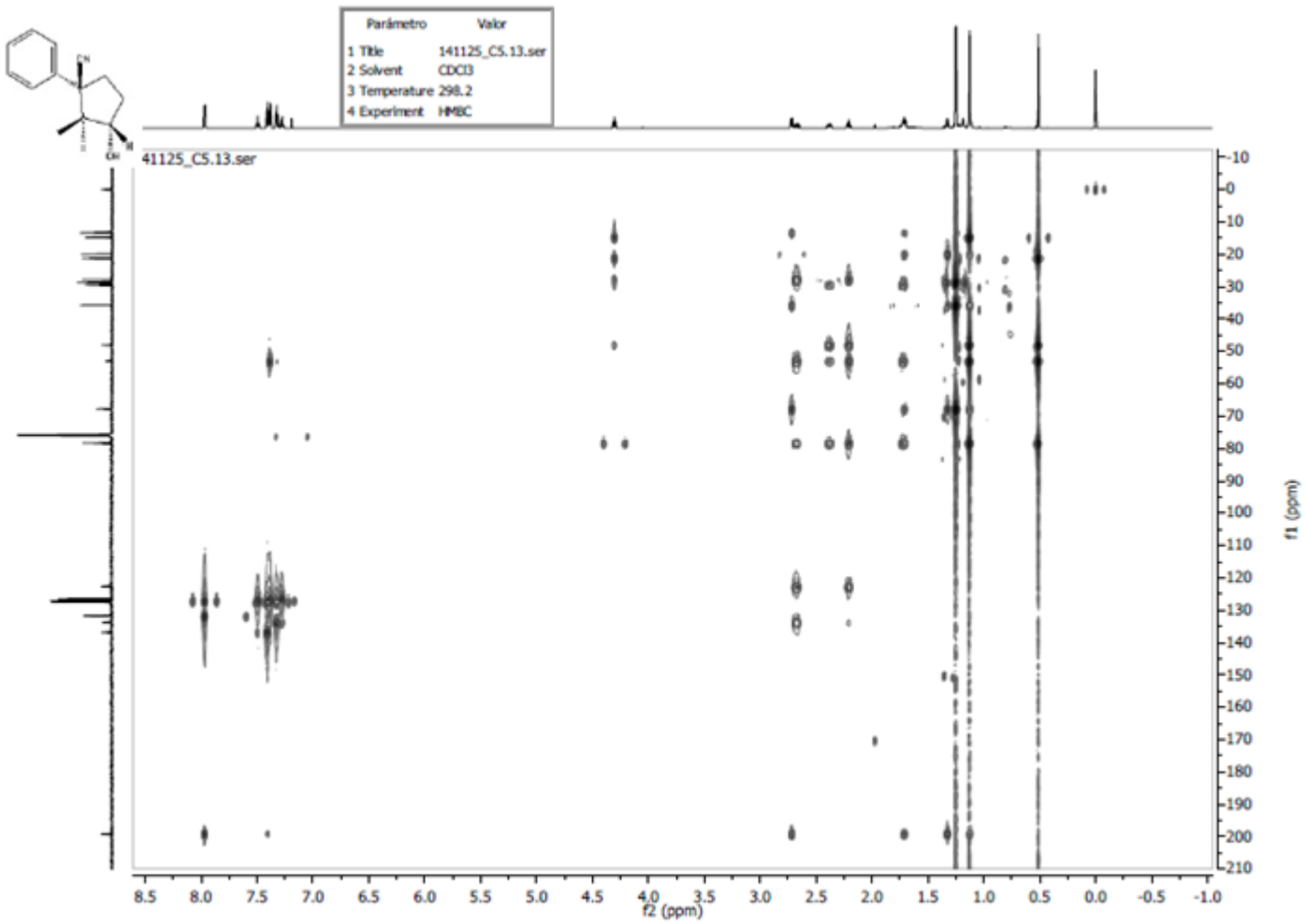

Figure S23. HMBC 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

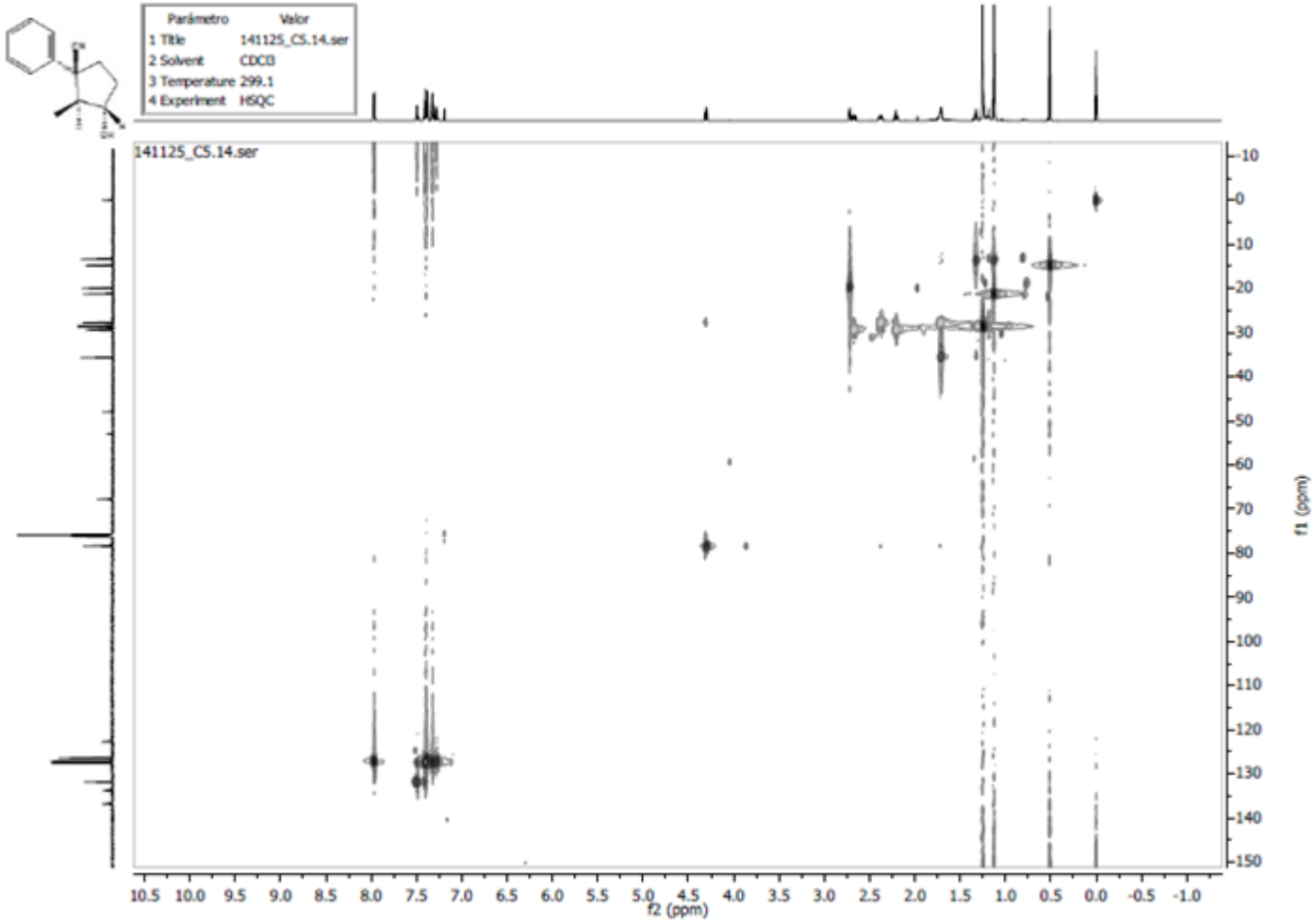

Figure S24. HSQC 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

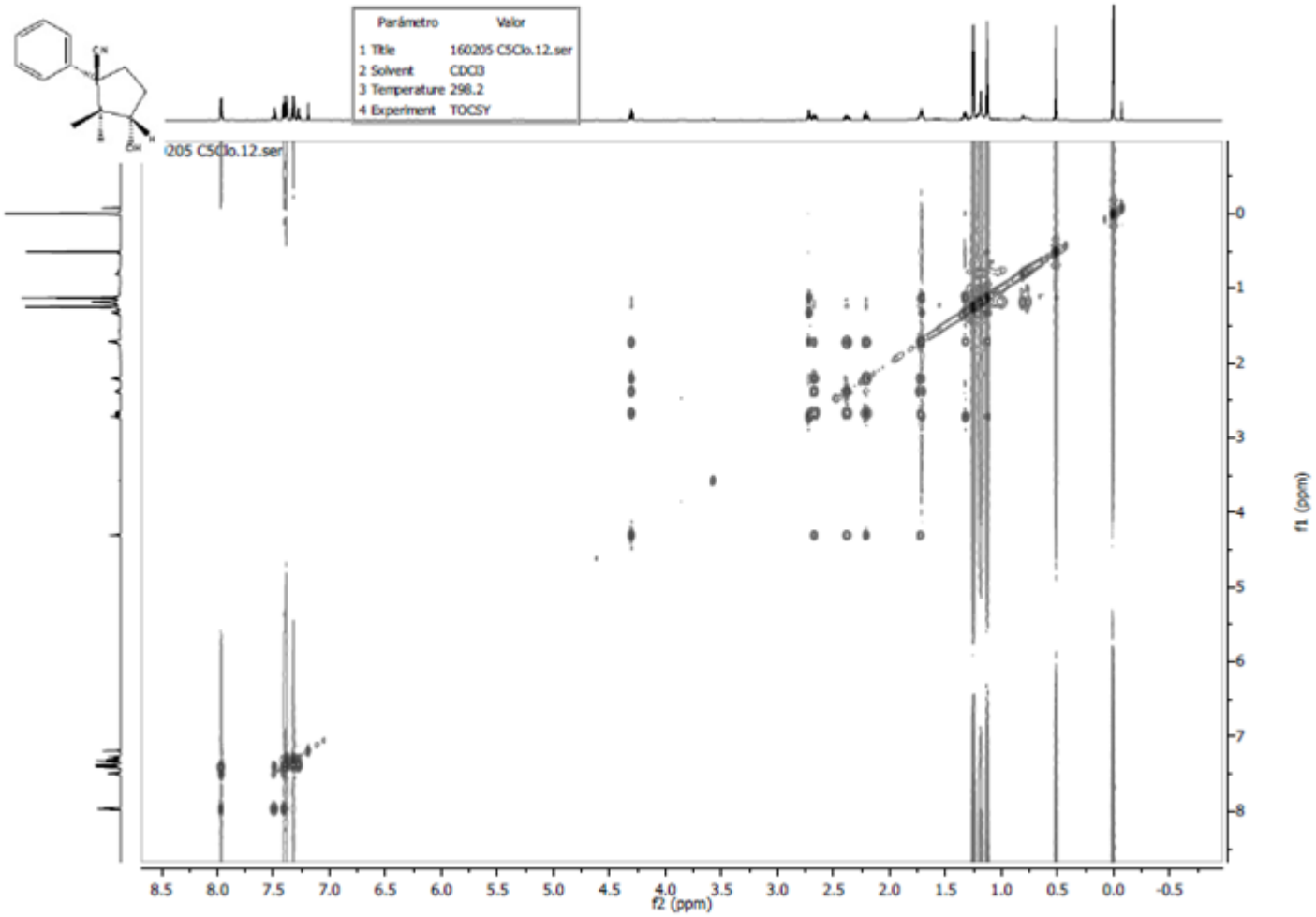

Figure S25. TOCSY 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

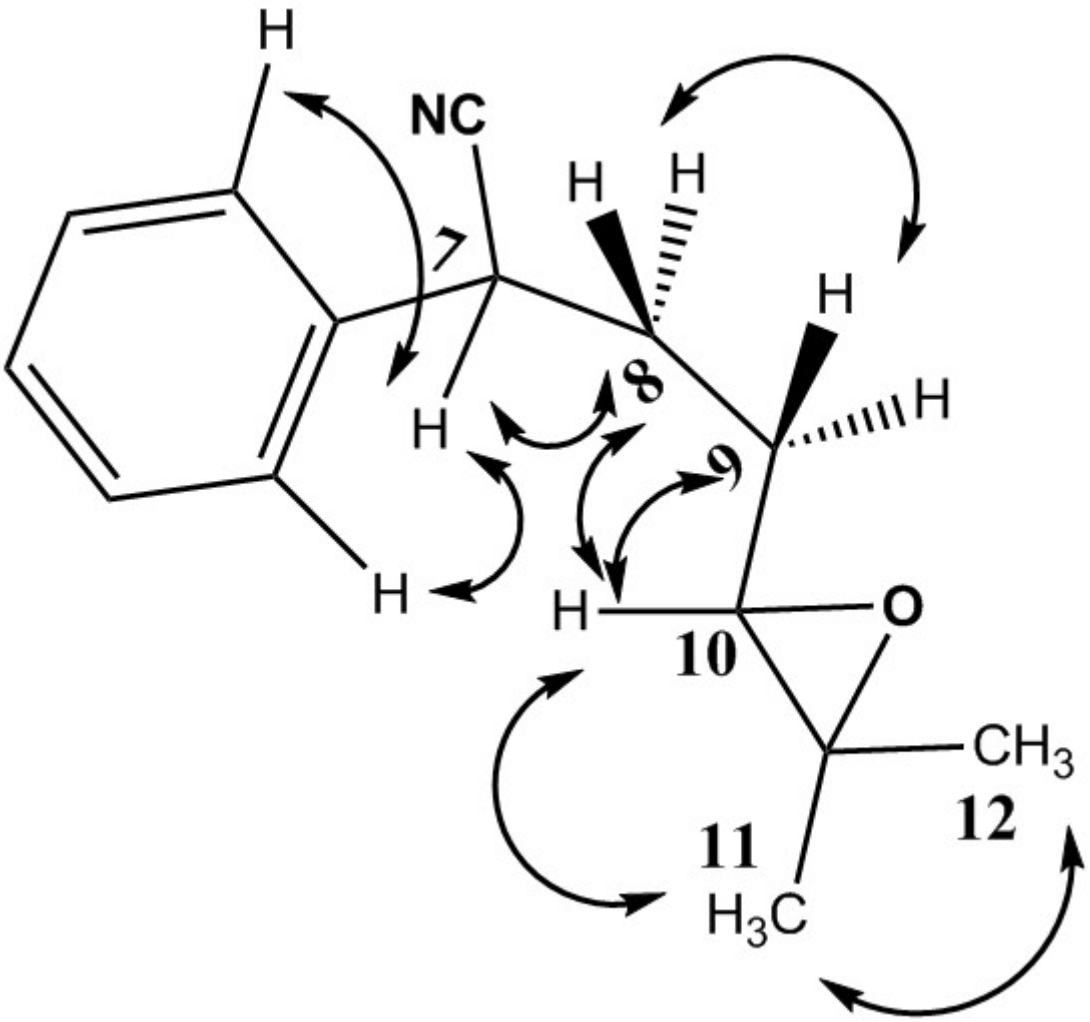

Figure S26. Key NOE correlation 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile

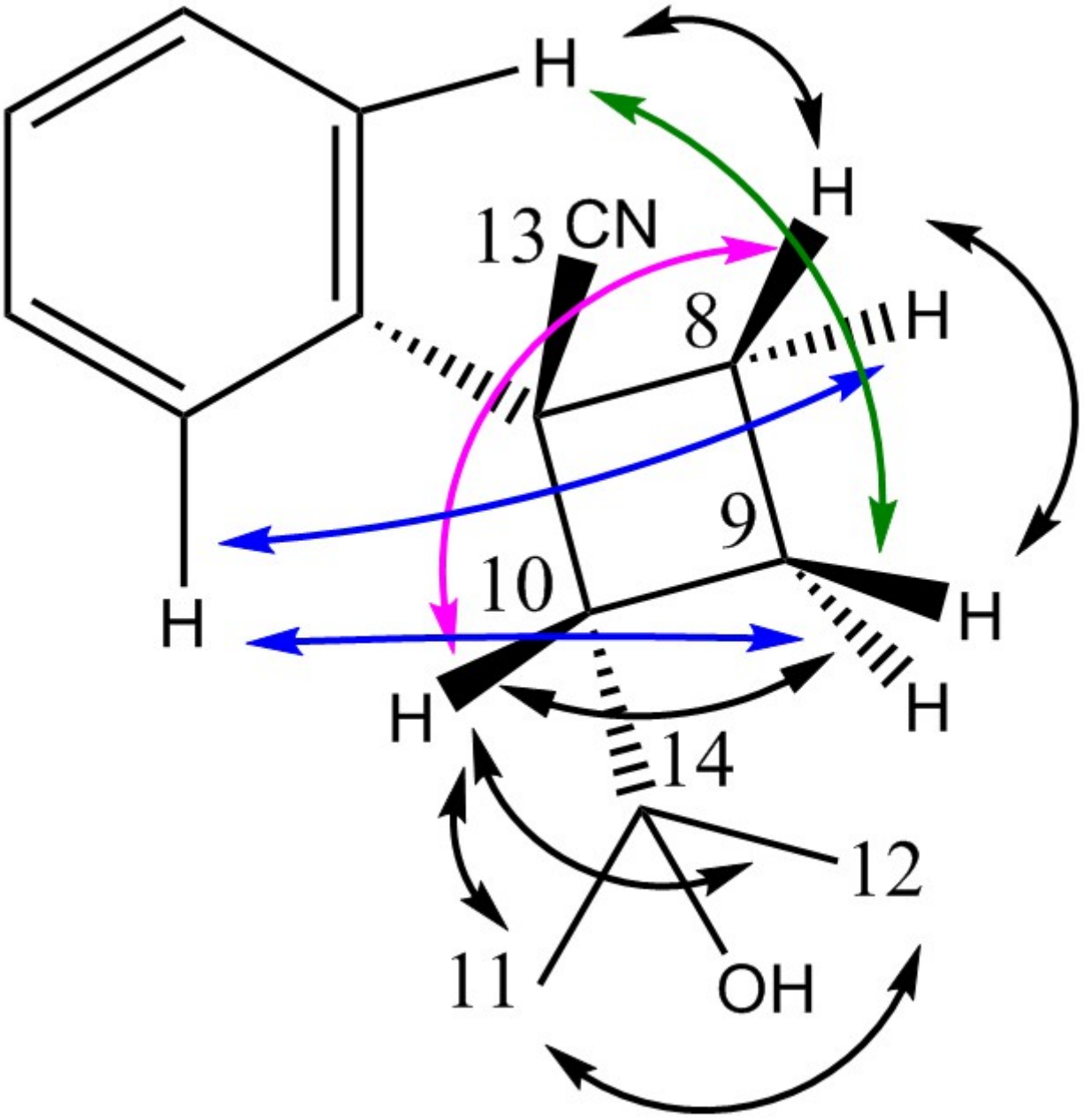

Figure S27. Key NOE correlation 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile

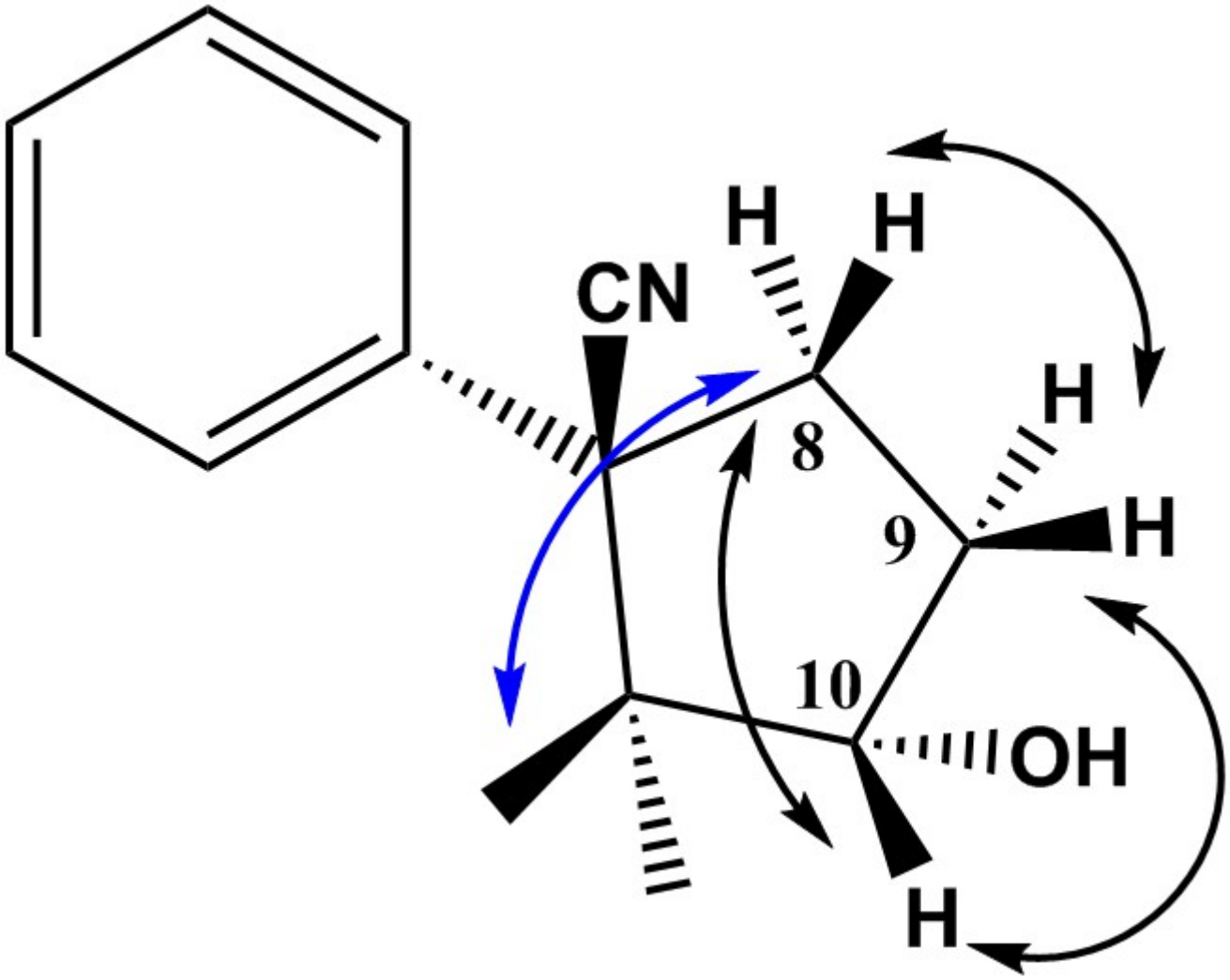

Figure S28. Key NOE correlation 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile

1.5 Anisotropic titration

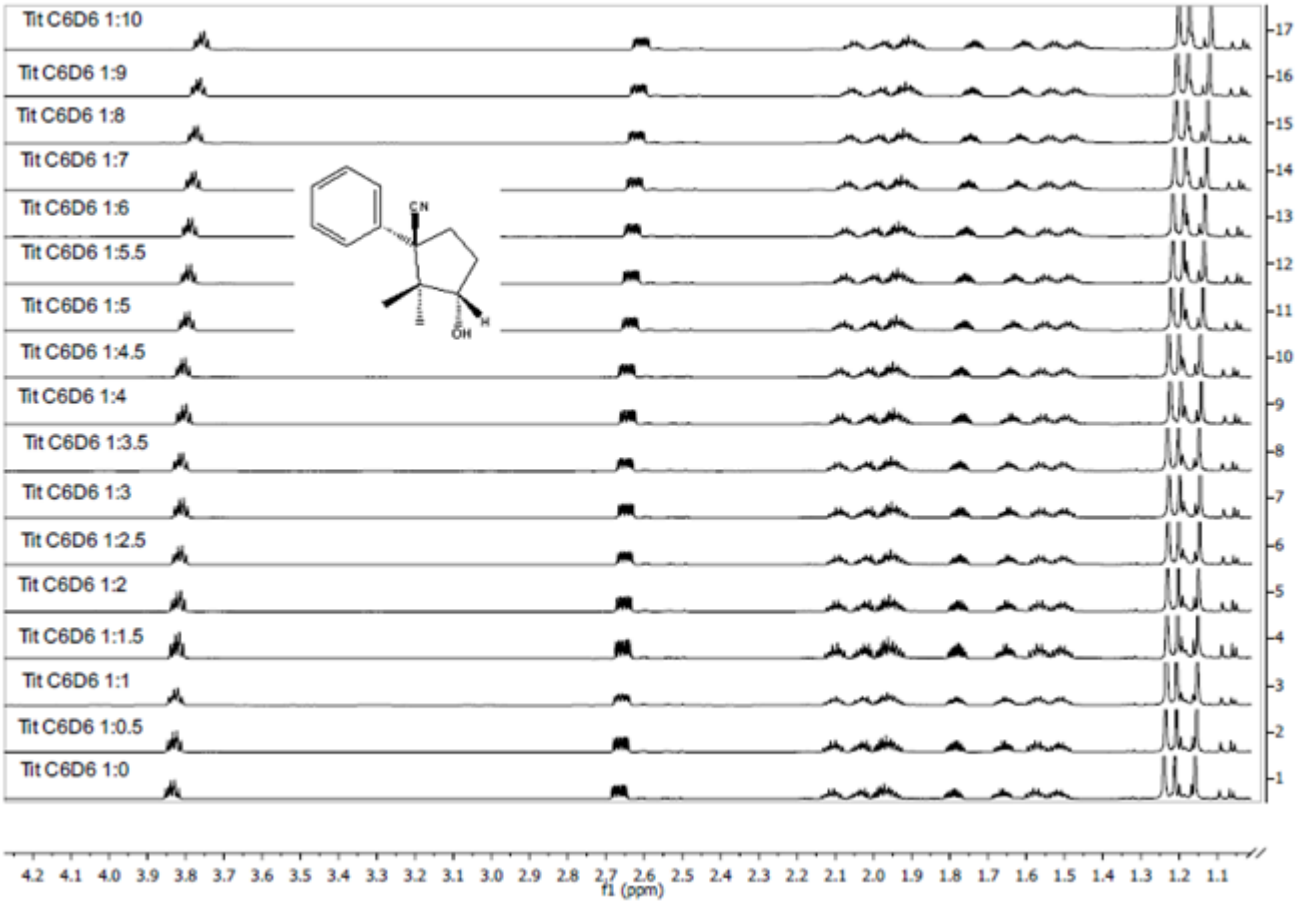

Figure S29. 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile ($CDCl_3$, benzene-d^6 additions)

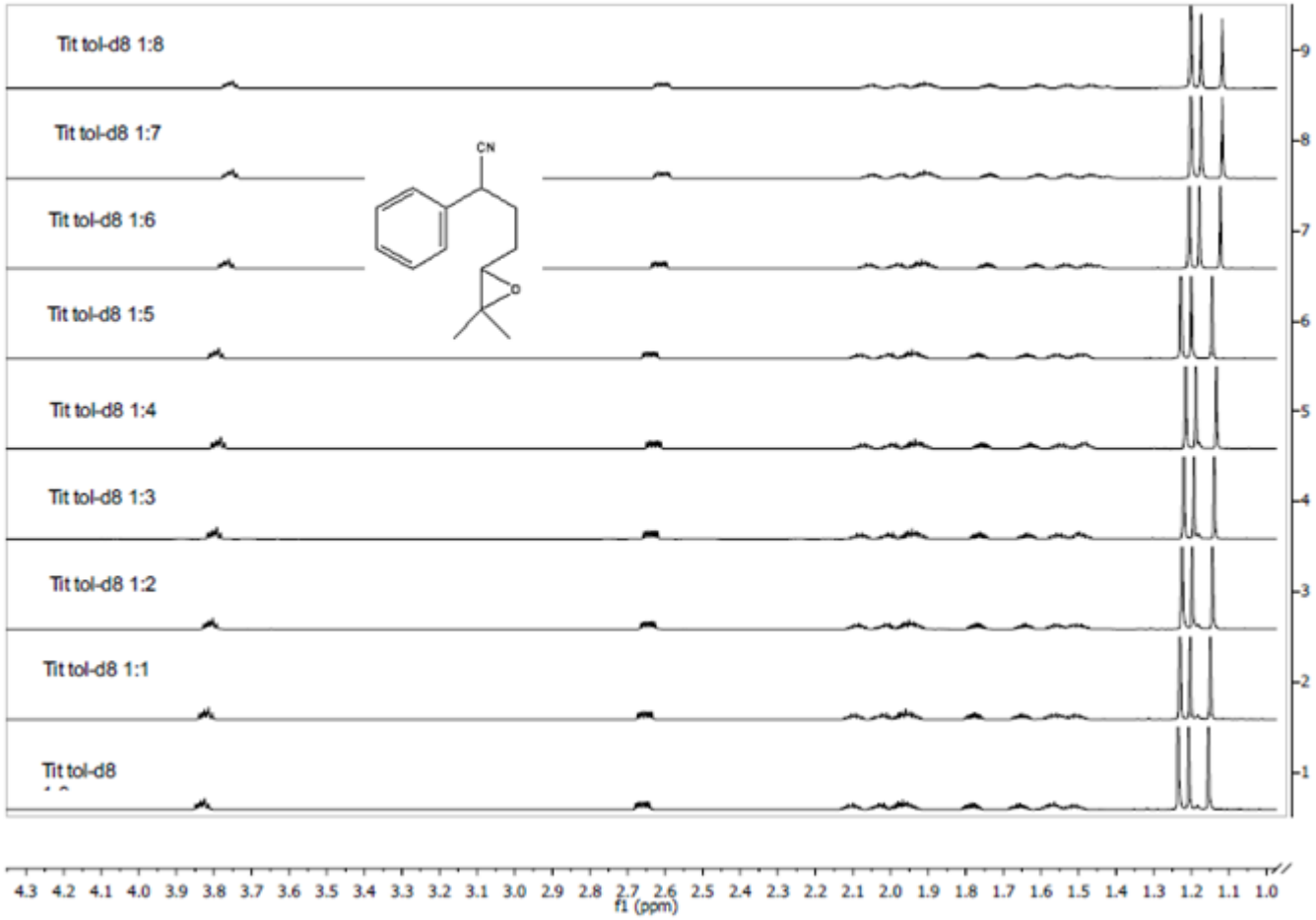

Figure S30. 4-(3,3-dimethyloxiran-2-yl)-2-phenylbutanenitrile ($CDCl_3$, toluene-d^8 additions)

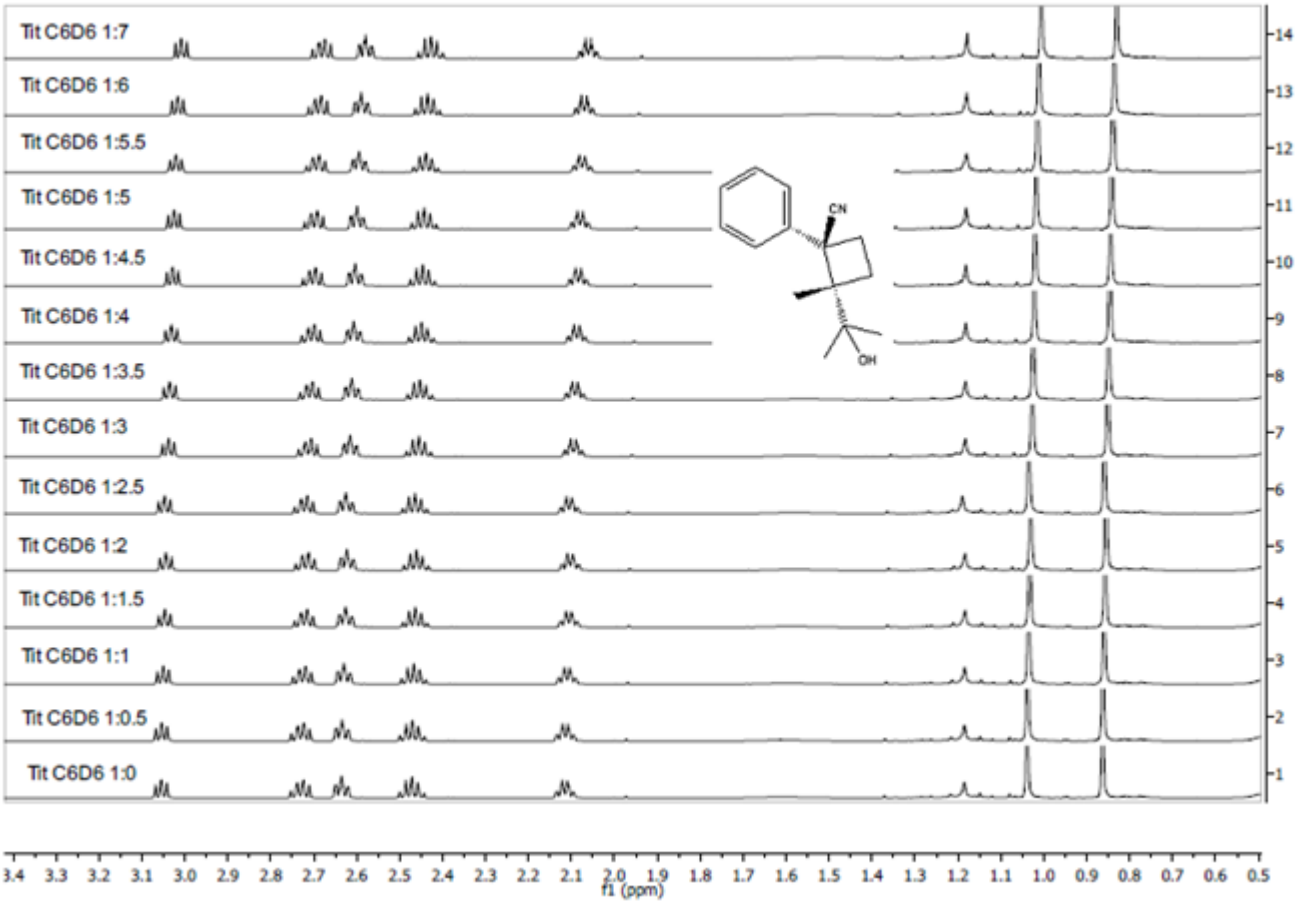

Figure S31. 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile ($CDCl_3$, benzene-d^6 additions)

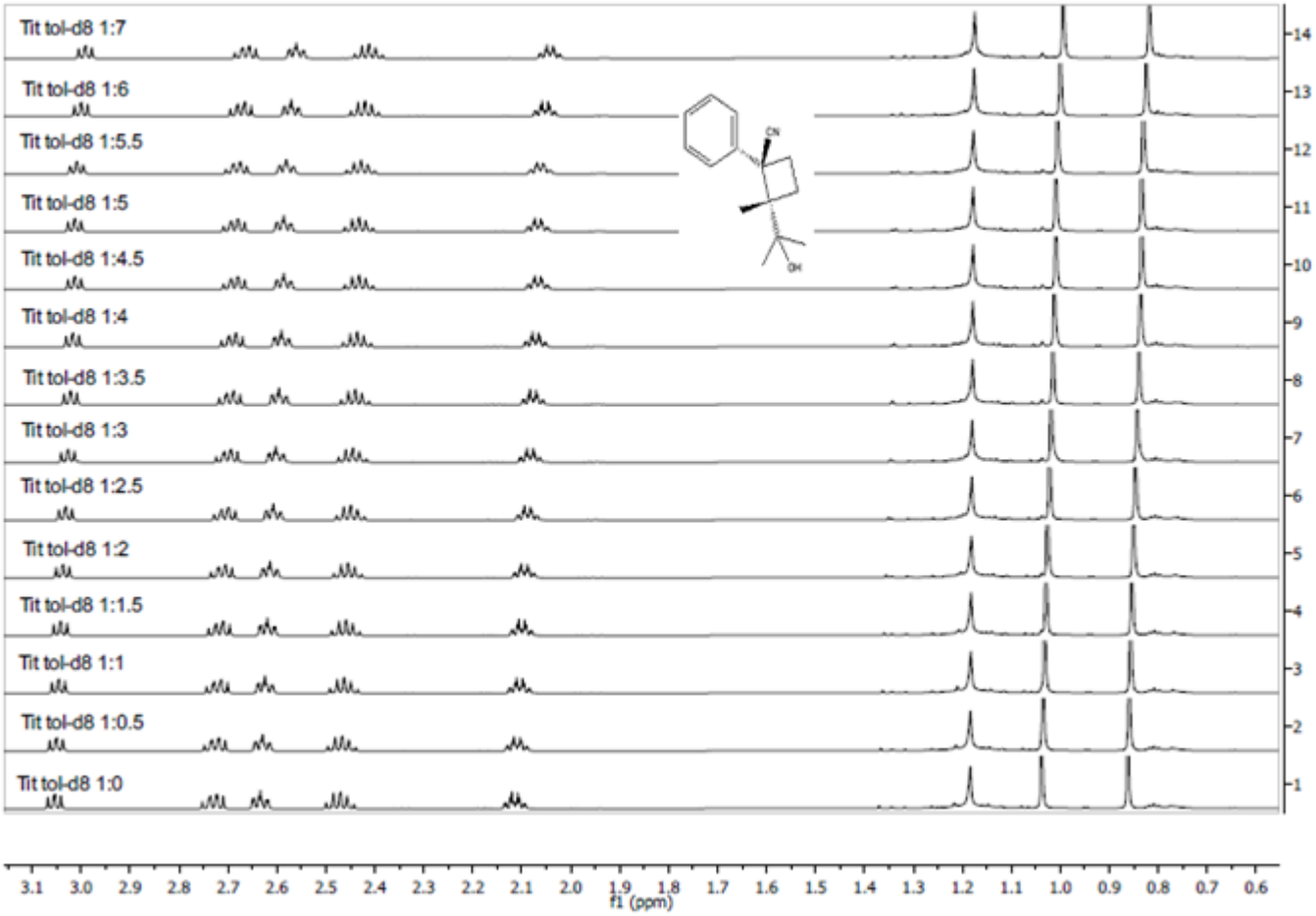

Figure S32. 2-(2-hydroxypropan-2-yl) 1-phenylcyclobutane-1- carbonitrile ($CDCl_3$, toluene-d^8 additions)

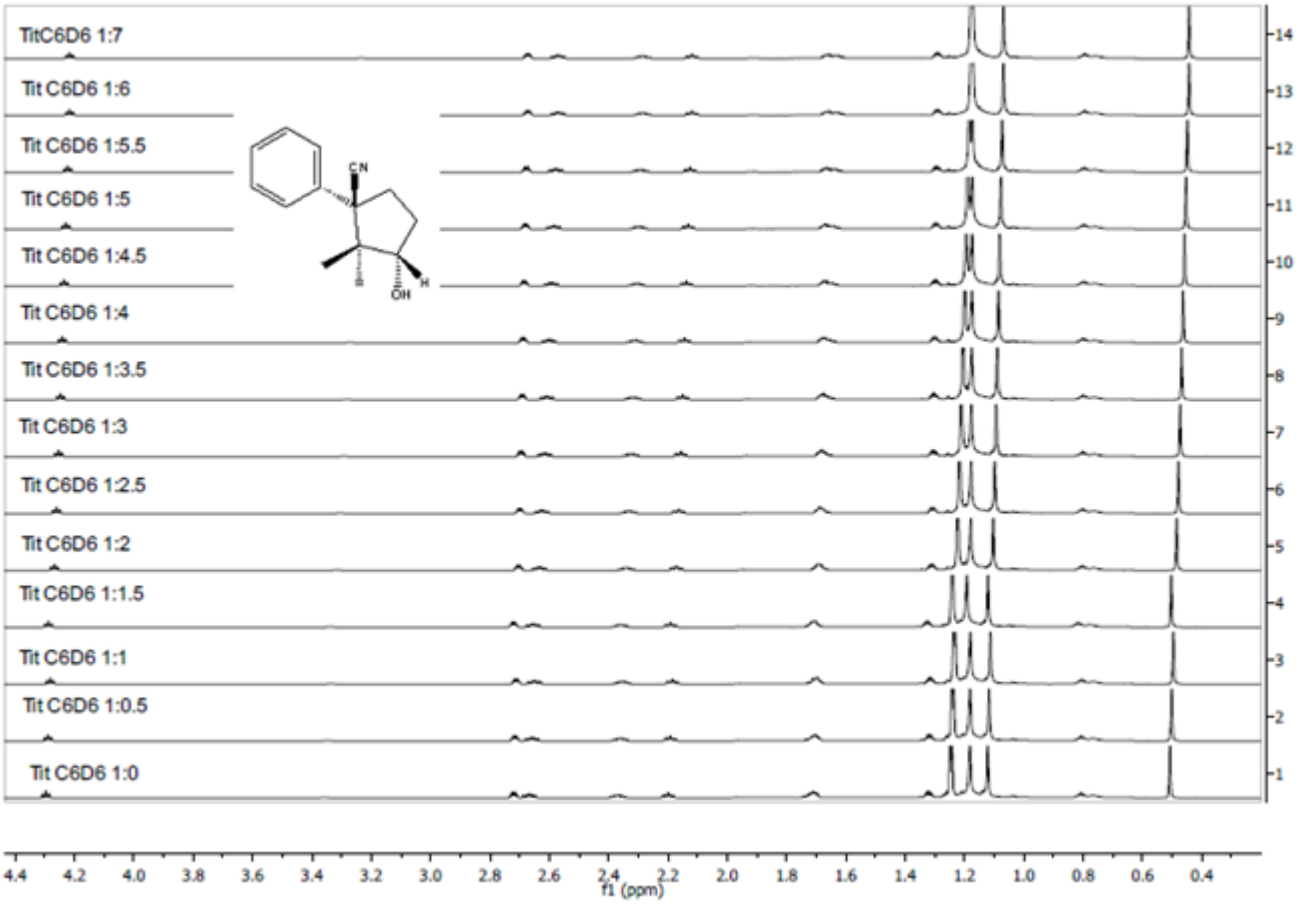

Figure S33. 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile ($CDCl_3$, benzene-d^6 additions)

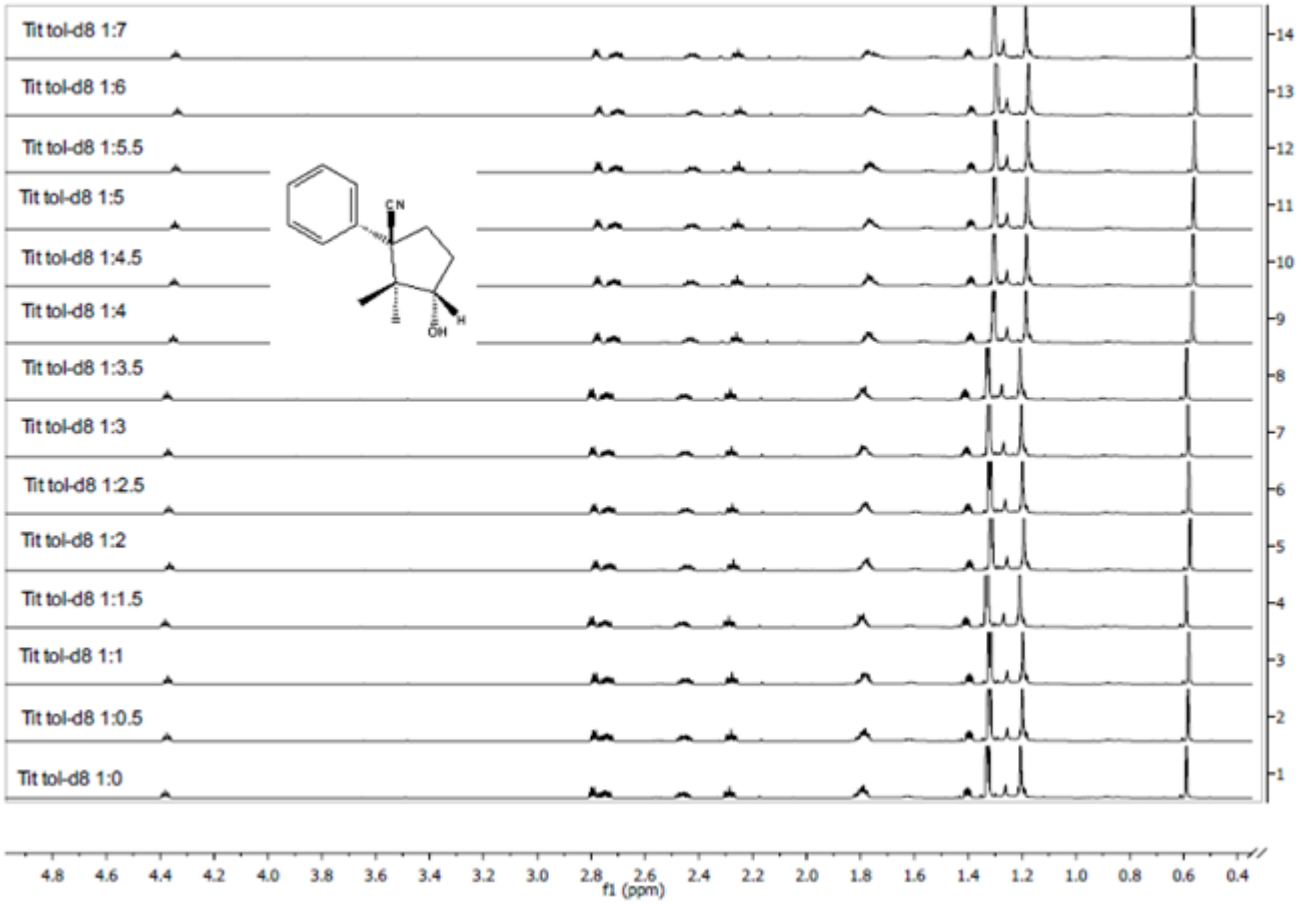

Figure S34. 3-hydroxy-2,2-dimethyl-1-phenylcyclopentane-1-carbonitrile ($CDCl_3$, toluene-d^8 additions)

1.6 Calorimetric determinations

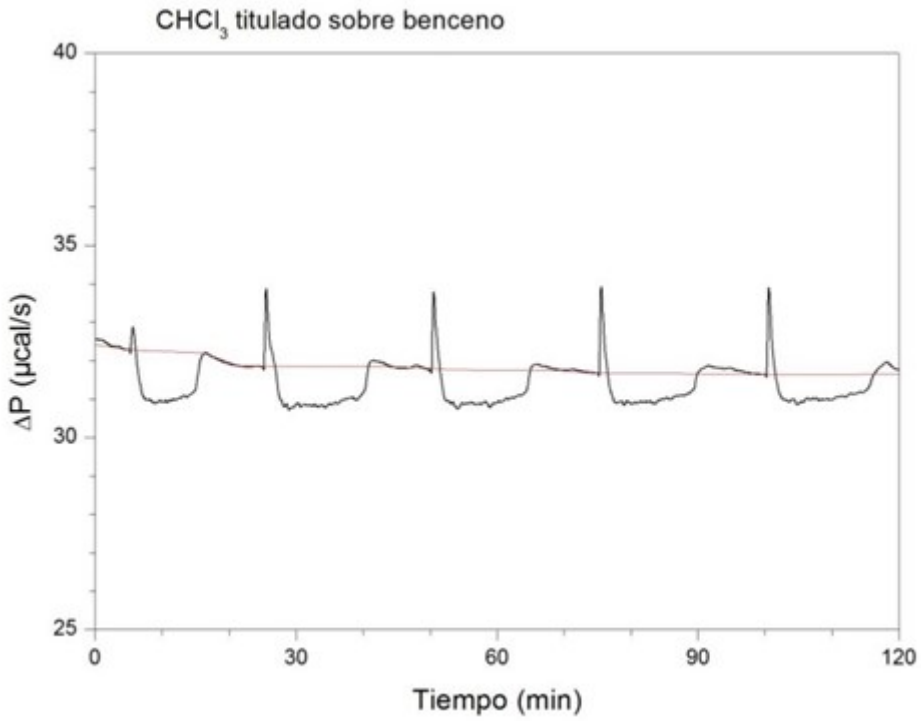

Figure S35. CHCl3 determination in benzene.

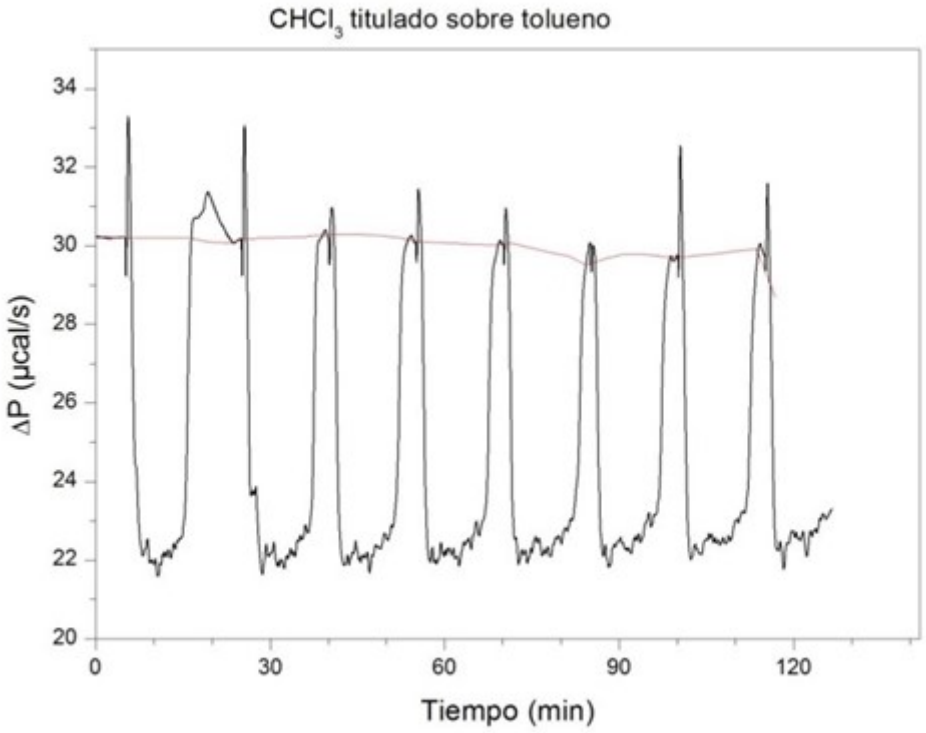

Figure S36. CHCl3 determination in toluene.

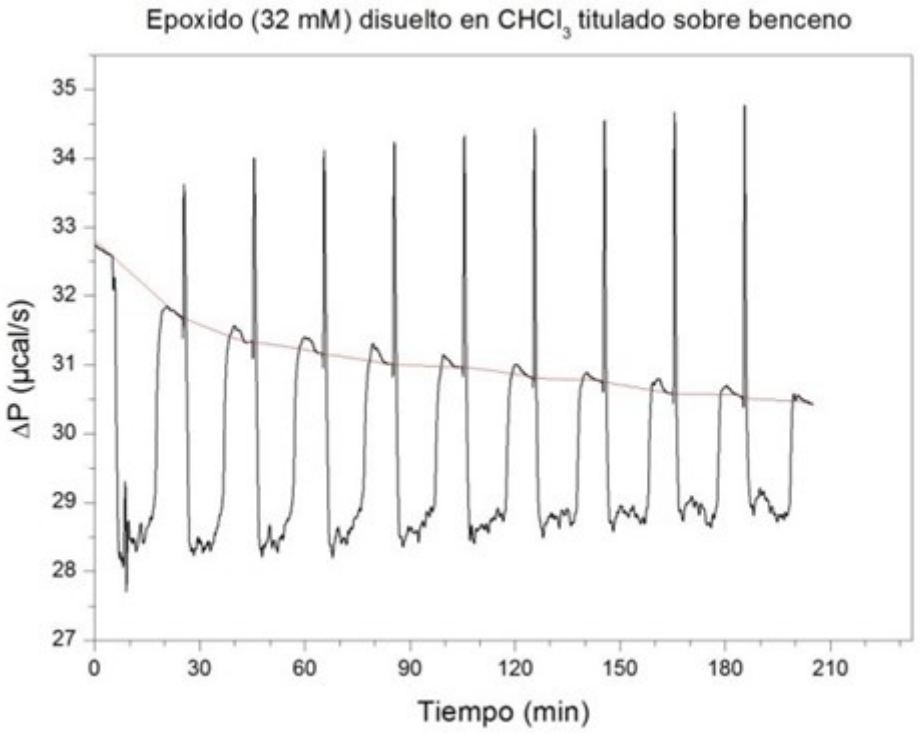

Figure S37. Compound 1 solvated in CHCl3, benzene additions

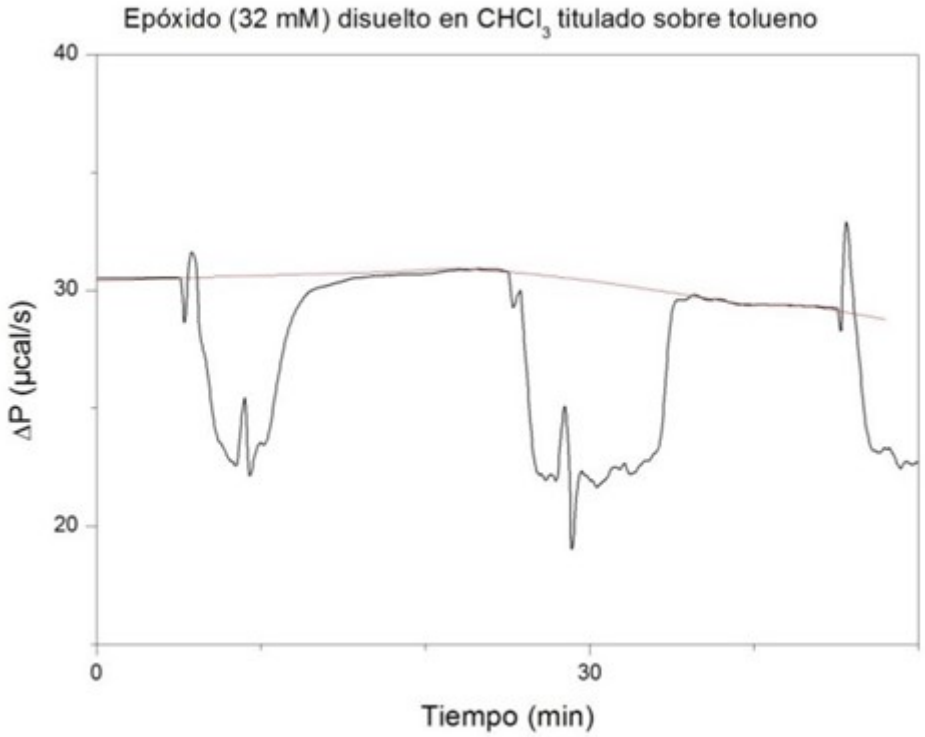

Figure S38. Compound 1 solvated in CHCl3, toluene additions.

1.7 IRC

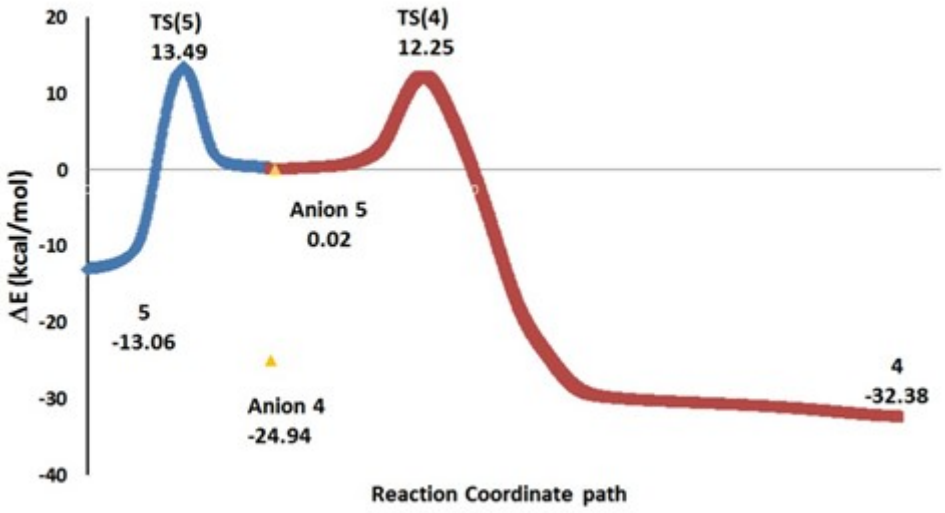

Figure S39. IRC in gas phase for both reaction paths.

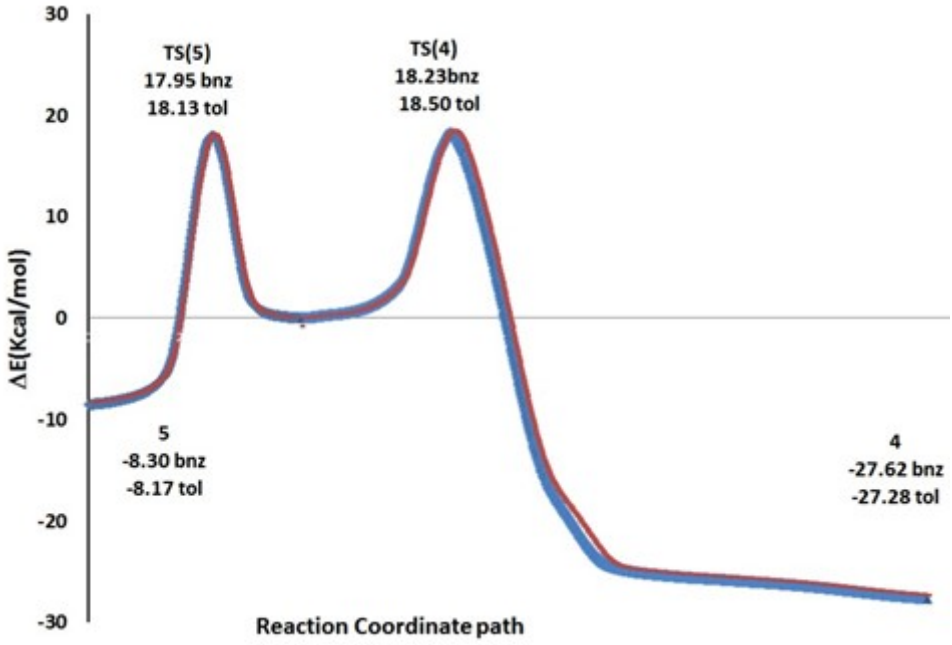

Figure S40. IRC in continuum solvent for both reaction paths.

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