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Supporting Information

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Lewis Acid-Catalyzed Asymmetric Cycloadditions of Nitrones: α'-Hydroxy Enones as Efficient Reaction Partners

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INDEX **page**

A) General

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone. $Cu(OTf)_2$ was purchased from Aldrich Chemical Co. The salts were used without further purification. The 4Å powdered molecular sieves were received from Aldrich and were activated by heating to 150 ºC in high vacuum. Nitrones were synthesized using N-benzylhydroxylamine, N-phenylhydroxylamine, N-*o*-methoxybenzylhydroxylamine, N-methylhydroxylamine and N-benzydrylhydroxylamine according to general procedures in published literature[1].

Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0,25 mm silica gel 60-F plates. Visualization was accomplished with UV light and p-anisaldehyde solution followed by heating.

Melting points were measured with a Mettler FP 80 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer and are reported in ppm from internal $CHCl_3$. Analytical high performance liquid chromatography (HPLC) was performed on a Waters chromatograph equipped with a diode array UV detector, using the chiral column specified at the end of this report. Elemental analyses were performed with a Perkin-Elmer 240 C analyzer. Optical rotations were recorded on a JASCO-DIP-370 polarimeter.

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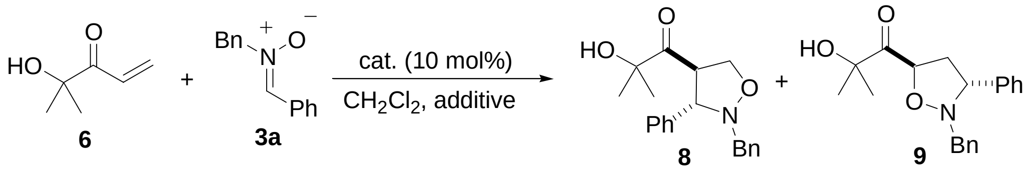
[1] a) Brüning, I.; Grashey, R.; Hauck, H.; Huisgen, R.; Seidl, H. *Org. Synth. Coll Vol V*, **1973**, 1124-1127. b) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363. c) Beckett, A. H.; Coutts, R. T.; Ogunbona, F. A. *Tetrahedron* **1973**, *29*, 4189-4193. d) Chan, K. S.; Yeung, M. L.; Chan, W.-K.; Wang, R.-J.; Mak, T. C. W. *J. Org. Chem.* **1995**, *60*, 1741-1747.

B) Screening of chiral catalysts for the enantioselective 1,3-DC of hydroxyenone 6

Table S-2. Effect of the metal and ligand architecture on the catalytic enantioselective 1,3-dipolar cycloaddition of α'-hydroxy enone **6** with nitrone **3a**.[a]



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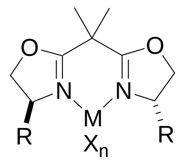
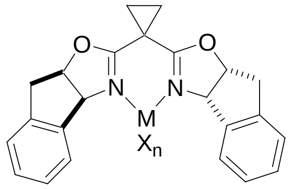


7, **17-20**



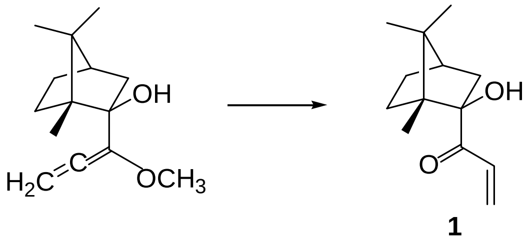
21

Cat.	R	MX$_n$	Additive	T, °C	t, h	Yield, %[b]	Ratio **8**:**9**[c]	*ee*, %[d]
7	^{t}Bu	Cu(OTf)$_2$	--	25	1	90	≥99:1	30
7	^{t}Bu		--	-20	48	98	85:15	56
7	^{t}Bu		MS 4A	-20	36	85	93:7	94
17	^{t}Bu	Zn(OTf)$_2$	--	25	1	--	--	0
18	^{t}Bu	Mg(OTf)$_2$	--	25	1	85	≥99:1	6
19	Ph	Cu(OTf)$_2$	MS 4A	-20	24	76	n.d.	20
20	Bn	Cu(OTf)$_2$	MS 4A	-20	24	17	n.d.	60
21		Cu(OTf)$_2$	MS 4A	-20	12	78	n.d.	70

[a] Reactions conducted at 0.5 mmol scale in CH_2Cl_2 (3.5 mL). Molar ratio of **6**:**3a** 2:1. [b] Referred to both regioisomers. [c] Determined by ^{13}C NMR. [d] Referred to isomer **8**. Determined by HPLC. n.d. = not determined.

C) Preparation of camphor-based α'-hydroxy ketones 1 and 2

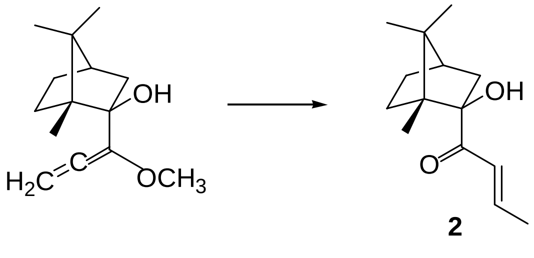
(1*R*)-2-*endo*-propenoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol[2] (1)



1

Methoxyallene (2.94 g, 42 mmol) was added to a solution of nBuLi (2.5 M in hexanes, 16 mL, 40 mmol) in THF (20 mL) cooled to -30 ºC under a nitrogen atmosphere. After stirring for 30 minutes at the same temperature, TMDA (6.1 mL, 40 mmol) and a solution of (1*R*)-(+)-camphor (3.04 g, 20 mmol) in THF (2.6 mL) were added dropwise. The resulting mixture was allowed to stir for 2 hours at -30 ºC and then was quenched with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), the combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by distillation (about 10% of the starting camphor was separated) and collected as a colorless liquid. Yield of (1*R*)-2-*endo*-1-methoxy-1,2-propanodienyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol: 3.33 g (75%); b.p. 70-72 ºC/0.1 torr; $[\alpha]_D^{25}$ + 38.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3585, 2950, 2924, 2868, 1951, 1066, 876; ^1H NMR ($CDCl_3$) δ 5.55 (d, 1H, HC=C, J= 7.7 Hz), 5.47 (d, 1H, HC=C, J= 7.7 Hz), 3.44 (s, 3H, OCH_3), 2.80 (s, 1H, OH), 2.06-1.95 (m, 1H, HCH), 1.80-1.73 (d, 1H, HCH, J= 13 Hz), 1.69-1.57 (m, 1H, HCH), 1.48-1.29 (m, 2H, HCH), 1.12 (s, 3H, CH_3), 1.08-0.88 (m, 2H, HCH), 1.00 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 197.5, 138.9, 92.1, 82.0, 56.4, 52.9, 49.8, 44.8, 42.5, 31.5, 26.6, 21.1, 20.9, 11.3. The distillate product was dissolved in CH_2Cl_2 (30 mL) and washed twice with 1M HCl (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the vinyl ketone **1** as a white solid. Purification was effected by flash silica gel column chromatography using a 1:30 ethyl acetate/hexane mixture as the eluant. Yield of (1*R*)-2-*endo*-propenoyl-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol (**1**): 3.12 g (75% from (1R)-(+)-camphor); m.p. 72-73 ºC; $[\alpha]_D^{25}$ - 34.5 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3488 (OH), 1685 (C=O); ^1H NMR ($CDCl_3$) δ 6.88 (dd, 1H, HC=C, J= 10.6 Hz, J'= 17.2 Hz), 6.34 (dd, 1H, HCH=C, J= 2.2 Hz, J'= 16.9 Hz), 5.67 (dd, 1H, HCH=C, J= 2.2 Hz, J'= 10.3 Hz), 2.88 (s, 1H, OH), 2.34-2.25 (m, 1H, HCH), 1.88-1.64 (m, 2H, HCH), 1.44-0.80 (m, 4H, HCH), 1.10 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.82 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.6, 131.8, 128.7, 86.9, 52.6, 50.6, 45.2, 41.3, 30.2, 26.5, 20.9, 20.4, 10.6; Anal. Calcd for $C_{13}H_{20}O_2$ (208.33) C, 74.94; H, 9.70. Found: C, 74.85; H, 10.01.

(1*R*)-2-*endo*-(2'-butenoyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol[2] (2)



2

To a solution of (1*R*)-2-*endo*-1-methoxy-1,2-propanodienyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (0.222 g, 1mmol) in THF (4 mL) at –78 ºC, nBuLi (2.5 M in hexanes, 1.2 mL, 3 mmol) was added and the reaction was stirred at –25 ºC for 4 h. Then, MeI (0.21 mL, 3.5 mmol) was added and the

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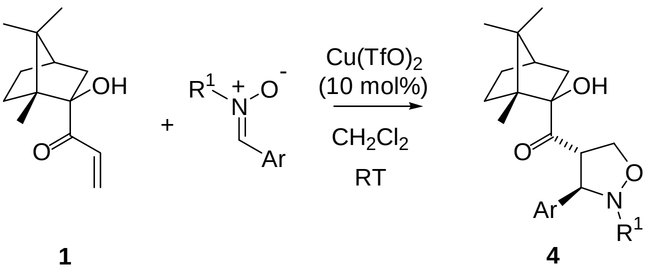
[2] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288-10289.

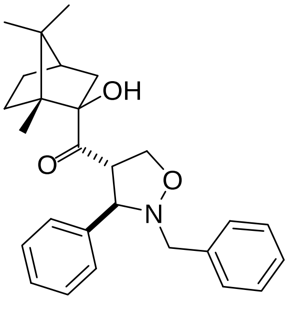
mixture was stirred for 2 h at the same temperature. The reaction was quenched with 1N HCl (5 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:60) to afford the corresponding enone. 0.150 g (67%); m.p. 82 ºC; $[\alpha]_D^{25}$ -54.0 (*c* 1.0, Cl_2CH_2); IR (neat, cm^{-1}) 3427 (OH), 1680 (CO); ^{1}H NMR ($CDCl_3$) δ 7.01-6.90 (dq, 1H, HC=C, J=7.0Hz, J'=14.7Hz), 6.61 (dq, 1H, HC=C, J=2.0Hz, J'=15.0Hz), 3.13 (s, 1H, OH), 2.24 (d, 1H, HCH, J=12.8Hz), 1.87 (d, 3H, CH_3, 7.0Hz), 1.80-1.61 (m, 2H, HCH), 1.40-1.14 (m, 3H, HCH), 1.08 (s, 3H, CH_3), 1.06-0.72 (m, 1H, HCH), 0.85 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.5, 143.5, 127.0, 86.6, 52.6, 50.5, 45.2, 41.1, 30.2, 26.6, 20.9, 20.4, 18.5, 10.6; Anal. calcd for $C_{14}H_{22}O_2$ (222.36) C, 75.62; H, 9.99. Found: C, 75.33; H, 10.07.

D) General procedure for the 1,3-dipolar cycloaddition of nitrones to 1



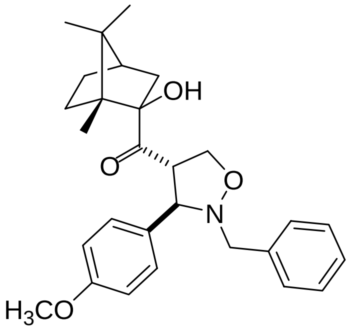
To a solution of (1*R*)-2-*endo*-propenoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **1** (0.104 g, 0.5 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere, $Cu(TfO)_2$ (0.0181 g , 0.050 mmol) was added at room temperature. Then the corresponding nitrone (0.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete. Then water (5 mL) was added and the reaction was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude. Purification was effected by flash silica gel column chromatography using ethyl acetate/hexane mixtures as the eluant.

(3*R*, 4*S*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-3-phenylisoxazolidine (4a)



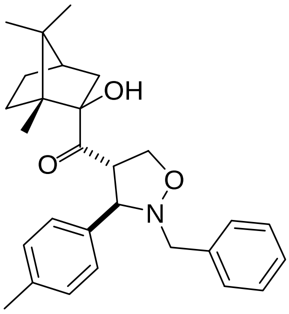
The title compound was prepared according to general procedure from **1** and (*Z*)-N-benzylidenebenzylamine N-oxide (0.106 g, 0.5 mmol) in 4 h. 0.185 g (88%); white solid; m.p. 151-153 ºC; $[\alpha]_D^{25}$ - 41.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3540, 1706, 1455, 698; ^{1}H NMR ($CDCl_3$) δ 7.55-7.15 (m, 10 H, arom.), 4.34 (dd, 1H, *H*CHON , J= 8.1 Hz, J'= 9.2 Hz), 4.26 (d, 1H, CHNO, J= 8.2 Hz), 4.04 (m, 1H, CHC=O), 3.99 (d, 1H, *H*CHPh, J=14.1 Hz), 3.85 (dd, 1H, *H*CHON, J= 5.7 Hz, J'= 7.6 Hz), 3.83 (d, 1H, *H*CHPh, J=14.1 Hz), 2.20 (m, 1H, CH), 2.05 (s, 1H, OH), 1.72 (m, 1H, CH), 1.58 (m, 2H, CH_2), 1.20 (m, 2H, CH_2), 1.04 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.3, 138.4, 137.6, 128.5, 128.3, 128.0, 127.9, 127.7, 126.9, 87.7, 74.0, 70.3, 61.4, 59.7, 52.1, 50.9, 44.8, 41.8, 29.6, 26.0, 20.7, 20.4, 10.4. Anal. Calcd for $C_{27}H_{33}NO_3$ (419.60) C, 77.28; H, 7.94; N, 3.33. Found: C, 77.40; H, 7.92; N, 3.43.

(3*R*, 4*S*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylcarbonyl]-3-*p*-methoxyphenylisoxazolidine (4b)



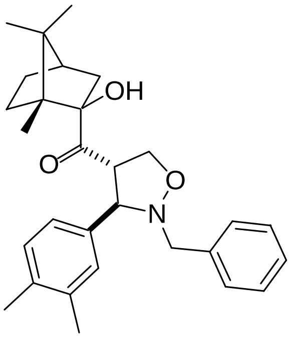
The title compound was prepared according to general procedure from **1** and (*Z*)-N-*p*-methoxybenzylidenebenzylamine N-oxide (0.121 g, 0.5 mmol) in 24 h. 0.153 g (68%); white solid; m.p. 175-177 ºC; $[\alpha]_D^{25}$ - 55.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3498, 1701, 1613, 1513, 1455, 1249, 1037; ^1H NMR ($CDCl_3$) δ 7.45-7.20 (m, 7H, arom.), 6.88 (d, 2H, ortho$C_6H_4OCH_3$, J= 8.9 Hz), 4.32 (dd, 1H, *H*CHON, J= 7.8 Hz, J’= 9.1 Hz), 4.19 (d, 1H, CHNO, J= 8.3 Hz), 4.04 (m, 1H, CHC=O), 4.10-3.80 (m, 3H, $PhCH_2$, *H*CHON), 3.83 (s, 3H, OCH_3), 2.18 (m, 1H, CH), 2.13 (s, 1H, OH), 1.85-1.50 (m, 3H, CH, CH_2), 1.20 (m, 2H, CH), 1.05 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.65 (m, 1H, CH), 0.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.5, 159.2, 137.8, 130.0, 129.0, 128.6, 128.1, 127.0, 120.6, 114.0, 87.9, 73.8, 70.3, 61.2, 59.7, 55.2, 52.4, 50.9, 44.9, 41.8, 29,7, 26.1, 20.7, 20.4, 10.6. Anal. Calcd for $C_{28}H_{35}NO_4$ (449.63) C, 75.35; H, 7.86; N, 3.11. Found: C, 75.02; H, 7.68; N, 2.90.

(3*R*, 4*S*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylcarbonyl]-3-*p*-methylphenylisoxazolidine (4c)



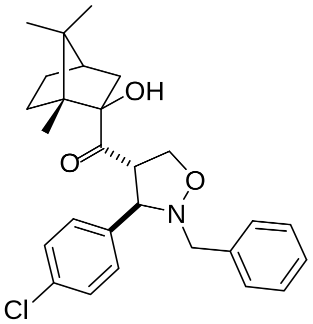
The title compound was prepared according to general procedure from **1** and (*Z*)-N-*p*-methylbenzylidenebenzylamine N-oxide (0.113 g, 0.5 mmol) in 8.5 h. 0.156 g (72%). Using 5 mol% of $Cu(OTf)_2$ instead, the reaction took 30 h and afforded the title compound in 70% yield. Data of compound: white solid; m.p. 137-138 ºC; $[\alpha]_D^{25}$ -54.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3513, 1702, 1454, 1118, 1041, 697; ^1H NMR ($CDCl_3$) δ 7.45-7.10 (m, 9H, arom.), 4.32 (dd, 1H, *H*CHON, J= 7.8 Hz, J’= 9.1 Hz), 4.21 (d, 1H, CHNO, J= 8.2 Hz), 4.01 (m, 1H, *H*CHON), 3.97 (d, 1H, *H*CHPh, J= 14.1 Hz), 3.84 (dd, 1H, *H*CHON, J= 5.6 Hz, J’= 7.8 Hz), 3.80 (d, 1H, *H*CHPh, J= 14.1 Hz), 2.36 (s, 3H, CH_3), 2.16 (m, 1H, CH), 2.12 (s, 1H, OH), 1.75 (m, 1H, CH), 1.60 (m, 2H, CH), 1.20 (m, 2H, CH_2), 1.04 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.60 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.4, 137.8, 137.7, 135.2, 129.3, 128.6, 128.1, 127.7, 127.0, 87.9, 74.1, 70.3, 61.2, 59.8, 52.4, 50.9, 44.9, 41.8, 29.8, 26.1, 21.2, 20.8, 20.4, 10.6. Anal. Calcd for $C_{28}H_{35}NO_3$ (433.63) C, 77.55; H, 8.15; N, 3.22. Found: C, 77.90; H, 7.95; N, 3.10.

(3*R*, 4*S*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylcarbonyl]-3-(3,4-dimethylphenyl)isoxazolidine (4d)



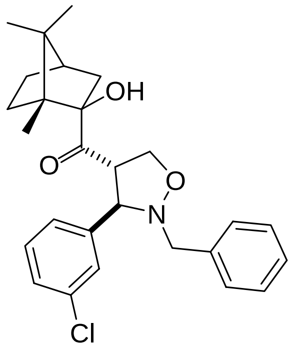
The title compound was prepared according to general procedure from **1** and (*Z*)-N-3,4-dimethylbenzylidenebenzyl-amine N-oxide (0.120 g, 0.5 mmol) in 8 h. 0.186 g (83%); white solid; m.p. 131-132 ºC; $[\alpha]_D^{25}$ - 47.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3513, 1704, 1496, 1454, 1370, 1119, 1042, 967, 696; ^1H NMR ($CDCl_3$) δ 7.45-7.10 (m, 8H, arom.), 4.34 (dd, 1H, *H*CHON, J= 8.0 Hz, J’= 8.1 Hz), 4.21 (d, 1H, CHNO, J= 8.2 Hz), 4.05 (m, 1H, CHC=O), 4.01 (d, 1H, *H*CHPh, J= 14.2 Hz), 3.85 (m, 1H, *H*CHON), 3.82 (d, 1H, *H*CHPh, J= 14.2 Hz), 2.28 (s, 6H, $(CH_3)_2C_6H_3$), 2.25 (m, 2H, CH, OH), 1.85-1.50 (m, 3H, CH_2, CH), 1.18 (m, 2H, CH), 1.07 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.75 (m, 1H, CH), 0.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.6, 137.8, 136.7, 136.1, 135.5, 129.8, 128.9, 128.6, 128.0, 126.9, 125.1, 87.8, 74.0, 70.3, 61.1, 59.8, 52.4, 50.9, 44.9, 41.8, 29.7, 26.1, 20.7, 20.4, 19.7, 19.5, 10.5. Anal. Calcd for $C_{29}H_{37}NO_3$ (447.66) C, 77.80; H, 8.35; N, 3.13. Found: C, 78.01; H, 8.37; N, 2.90.

(3*R*, 4*S*)-2-Benzyl-3-*p*-chlorophenyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl-carbonyl]isoxazolidine (4e)



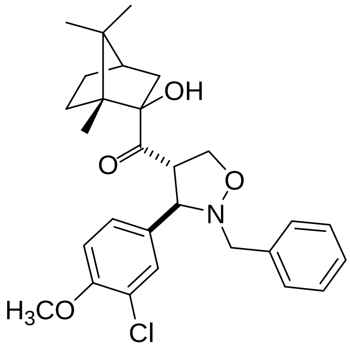
The title compound was prepared according to general procedure from **1** and (*Z*)-N-*p*-chlorobenzylidenebenzylamine N-oxide (0.123 g, 0.5 mmol) in 2 h. 0.205 g (90%). Using 5 mol% of $Cu(OTf)_2$ instead, the reaction took 9 h and afforded the title compound in 89% yield. Data of compound: white solid; m.p. 126-128 ºC; $[\alpha]_D^{25}$ - 52.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3514, 1703, 1492, 1455, 1090, 1015, 697; ^{1}H NMR ($CDCl_3$) δ 7.50-7.10 (m, 9H, arom.), 4.28 (m, 2H, *H*CHON , CHNO), 4.10-3.70 (m, 4H, CHC=O, CH_2Ph, *H*CHON), 2.23 (m, 1H, CH), 2.15 (s, 1H, OH), 1.85-1.45 (m, 3H, CH_2, CH), 1.02 (s, 3H, CH_3), 1.30-0.40 (m, 3H, CH), 0.74 (s, 3H, CH_3), 0.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 210.8, 137.3, 133.5, 129.0, 128.7, 128.6, 128.0, 127.0, 87.7, 72.9, 70.3, 61.5, 59.8, 52.2, 50.9, 44.8, 42.0, 29.7, 26.0, 20.7, 20.4, 10.7. Anal. Calcd for $C_{27}H_{32}ClNO_3$ (454.09) C, 71.41; H, 7.12; N, 3.08. Found: C, 71.29; H, 7.22; N, 3.24.

(3*R*, 4*S*)-2-Benzyl-3-m-chlorophenyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl-carbonyl]isoxazolidine (4f)



The title compound was prepared according to general procedure from **1** and (*Z*)-N-*m*-chlorobenzylidenebenzylamine N-oxide (0.123 g, 0.5 mmol) in 0.5 h. 0.206 g (91%); white solid; m.p. 123-124 ºC; $[\alpha]_D^{25}$ - 36.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3514, 1703, 1593, 1477, 1454, 1370, 1117, 1080, 1042, 966, 729, 695; ^{1}H NMR ($CDCl_3$) δ 7.55-7.15 (m, 9H, arom.), 4.36 (dd, 1H, *H*CHON, J= 7.9 Hz, J'= 9.1 Hz), 4.31 (d, 1H, CHNO, J= 7.9 Hz), 4.03 (m, 1H, CHC=O), 4.00 (d, 1H, *H*CHPh, J= 13.9 Hz), 3.90 (d, 1H, *H*CHPh, J=13.9 Hz), 3.85 (dd, 1H, *H*CHON, J= 5.8 Hz, J'= 7.9 Hz), 2.30 (m, 1H, CH), 2.20 (s, 1H, OH), 1.40-0.90 (m, 3H, CH_2, CH), 1.12 (m, 2H, CH_2), 1.08 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.75 (m, 1H, CH), 0.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 210.7, 141.1, 137.2, 134.4, 129.8, 128.6, 128.1, 127.6, 127.1, 125.8, 87.9, 72.9, 70.3, 61.7, 59.9, 52.3, 51.0, 44.9, 42.2, 29.7, 26.0, 20.8, 20.4, 10.6. Anal. Calcd for $C_{27}H_{32}ClNO_3$ (454.09) C, 71.41; H, 7.12; N, 3.08. Found: C, 71.48; H, 7.37; N, 3.18.

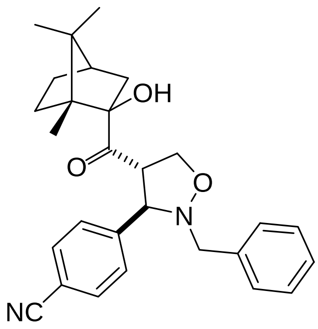
(3*R*, 4*S*)-2-Benzyl-3-(3-chloro-4-methoxyphenyl)-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]isoxazolidine (4g)



The title compound was prepared from **1** and (*Z*)-N-3-chloro-4-methoxybenzylidenebenzylamine N-oxide (0.138 g, 0.5 mmol) in 2 h according to general procedure. 0.219 g (90%); white solid; m.p. 164-166 ºC; $[\alpha]_D^{25}$ - 46.0 (*c* 1.0, CH_2Cl_2);

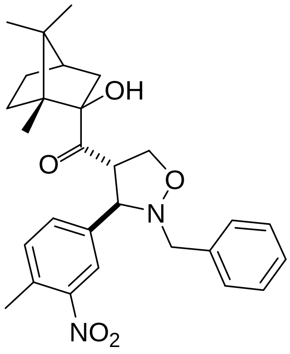
IR (neat, cm^{-1}) 3509, 1705, 1605, 1503, 1455, 1261, 1064, 1023, 801, 700; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, orthoC_6H_3Cl, J= 2.2 Hz), 7.40-7.20 (m, 6H, arom.), 6.89 (d, 1H, ortho$C_6H_3OCH_3$, J= 8.8 Hz), 4.32 (dd, 1H, *H*CHON, J= 7.9 Hz, J'= 9.1 Hz), 4.21 (d, 1H, CHNO, J= 8.1 Hz), 4.00 (m, 1H, CHC=O), 3.97 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.83 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.80 (dd, 1H, *H*CHON, J= 5.9 Hz, J'= 7.9 Hz), 3.90 (s, 3H, OCH_3), 2.27 (m, 1H, CH), 2.18 (s, 1H, OH), 1.90-1.50 (m, 3H, CH_2, CH), 1.18 (m, 2H, CH), 1.06 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.62 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.0, 154.4, 137.4, 131.6, 129.3, 128.6, 128.1, 127.2, 127.1, 122.5, 111.9, 87.3, 72.7, 70.2, 61.4, 59.8, 56.1, 52.3, 50.9, 44.9, 42.1, 29.7, 26.0, 20.7, 20.4, 10.7. Anal. Calcd for $C_{28}H_{34}ClNO_4$ (484.12) C, 69.46; H, 7.09; N, 2.89. Found: C, 69.60; H, 6.91; N, 2.71.

(3*R*, 4*S*)-2-Benzyl-3-*p*-cyanophenyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl-carbonyl]isoxazolidine (4h)



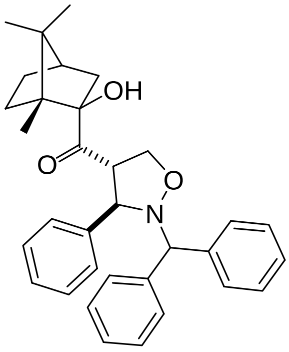
The title compound was prepared according to general procedure from **1** and (*Z*)-N-*p*-cyanobenzylidenebenzylamine N-oxide (0.118 g, 0.5 mmol) in 28 h. Data of major isomer: 0.170 g (76%); white solid; m.p. 145-146 ºC; $[\alpha]_D^{25}$ - 48.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3478, 2229, 1702, 1454; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H orthoC_6H_3CN, J= 8.4 Hz), 7.54 (d, 1H orthoC_6H_3CN, J= 8.6 Hz), 7.35-7.23 (m, 5H, arom.), 4.45-4.20 (m, 2H, CHNO, *H*CHON), 4.00-3.80 (m, 4H, CHC=O, CH_2Ph, *H*CHON), 2.30 (m, 1H, CH), 2.10 (s, 1H, OH), 1.90-1.50 (m, 3H, CH, CH_2), 1.30-0.80 (m, 2H, CH_2), 1.06(s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.57 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 210.1, 145.1, 136.8, 132.4, 128.7, 128.3, 128.2, 127.3, 118.5, 111.6, 88.0, 75.5, 70.4, 62.2, 60.2, 52.3, 51.1, 44.9, 42.5, 29.9, 26.0, 20.8, 20.5, 10.8. Anal. Calcd for $C_{28}H_{32}N_2O_3$ (444.60) C, 75.64; H, 7.27; N, 6.30. Found: C, 75.37; H, 7.08; N, 6.09.

(3*R*, 4*S*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-3-(4-methyl-3-nitrophenyl)isoxazolidine (4i)



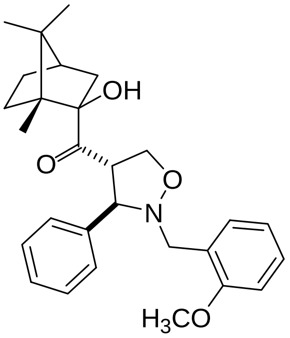
The title compound was prepared according to general procedure from **1** and (*Z*)-N-4-methyl-3-nitrobenzylidenebenzylamine N-oxide (0.135 g, 0.5 mmol) in 2 h. 0.214 g (89%); white solid; m.p. 131-133 ºC; $[\alpha]_D^{25}$ - 28.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3519, 1705, 1528, 1496, 1454, 1348, 117, 698; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 1H, ortho$C_6H_3NO_2$, J= 1.5 Hz), 7.57 (d, 1H, ortho$C_6H_3CH_3$, J= 1.5 Hz), 7.40-7.15 (m, 6H, arom.), 4.38 (m, 2H, CHNO, *H*CHON), 4.15-3.80 (m, 4H, CH_2Ph, *H*CHON, CHC=O), 2.58 (s, 3H, $\mathit{CH_3}C_6H_3$), 2.45 (s, 1H, OH), 2.30 (m, 1H, CH), 1.85-1.50 (m, 3H, CH, CH_2), 1.20 (m, 2H, CH), 1.07 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.75 (m, 1H, CH), 0.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 210.4, 148.9, 139.0, 136.8, 133.0, 132.8, 132.0, 128.6, 128.0, 127.1, 123.6, 87.7, 71.8, 70.3, 61.7, 59.9, 52.1, 51.0, 44.8, 42.2, 29.8, 25.9, 20.6, 20.4, 20.1, 10.8. Anal. Calcd for $C_{28}H_{34}N_2O_5$ (478.62) C, 70.26; H, 7.17; N, 5.85. Found: C, 70.01; H, 7.28; N, 6.01.

(3*R*, 4*S*)-2-Diphenylmethyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl-carbonyl]-3-phenylisoxazolidine (4j)



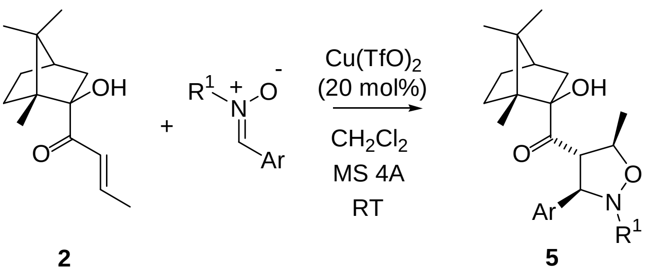
The title compound was prepared according to general procedure from **1** and (*Z*)-N-benzylidenediphenylmethyl-amine N-oxide (0.144 g, 0.5 mmol) in 8 h. Data of major isomer: 0.174 g (70%); colorless oil; $[\alpha]_D^{25}$ -21.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3479, 1701, 1494, 1454, 746, 701; ^1H NMR ($CDCl_3$) δ 7.65-7.05 (m, 15H, arom.), 5.30 (s, 1H, Ph_2CH), 4.45 (m, 2H, *H*CHON, PhCHNO), 4.12 (m, 1H, CHC=O), 3.96 (m, 1H, *H*CHON), 2.30 (m, 1H, CH), 2.21 (s, 1H, OH), 1.90-1.55 (m, 3H, CH_2, CH), 1.40-0.90 (m, 2H, CH_2), 1.08 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.1, 141.7, 141.3, 141.1, 128.3, 128.2, 128.1, 128.0, 127.2, 127.1, 87.9, 72.2, 70.9, 63.0, 52.2, 50.9, 44.8, 41.7, 29.9, 26.0, 20.7, 20.4, 10.5.

(3*R*, 4*S*)-4-[(1*R*)-2-*exo*-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-2-*o*-methoxybenzyl-3-phenylisoxazolidine (4k)



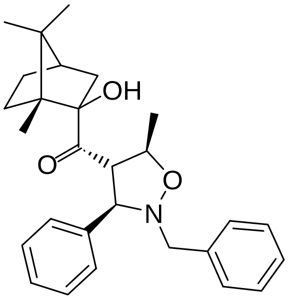
The title compound was prepared according to general procedure from **1** and (*Z*)-N-benzylidene-2-methoxybenzyl-amine N-oxide (0.121 g, 0.5 mmol) in 10 h. 0.189 g (84%); white solid; m.p. 140-141 ºC; $[\alpha]_D^{25}$ - 21.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3498, 1705, 1603, 1493, 1456, 1244, 752, 701; ^1H NMR ($CDCl_3$) δ 7.49 (m, 3H, arom.), 7.27 (m, 4H arom.), 6.94 (m, 1H, arom.), 6.81 (d, 1H, ortho$C_6H_4OCH_3$, J= 8.1 Hz), 4.35 (m, 2H, CHNO, *H*CHON), 4.15-3.80 (m, 4H, CH_2Ph, *H*CHON, CHC=O), 3.75 (s, 3H, OCH_3), 2.20 (m, 2H, CH, OH), 1.85-1.50 (m, 3H, CH_2, CH), 1.35-0.85 (m, 2H, CH), 1.05 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.57 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.3, 157.0, 138.4, 129.9, 128.4, 128.0, 127.8, 126.1, 120.2, 110.0, 87.3, 74.3, 70.2, 61.5, 55.1, 54.0, 52.4, 50.9, 44.9, 41.8, 29.7, 26.1, 20.7, 20.4, 10.4. Anal. Calcd for $C_{28}H_{35}NO_4$ (449.63) C, 74.79; H, 7.86; N, 3.11. Found: C, 74.68; H, 7.81; N, 2.87.

E) General procedure for the 1,3-dipolar cycloaddition of nitrones to 2



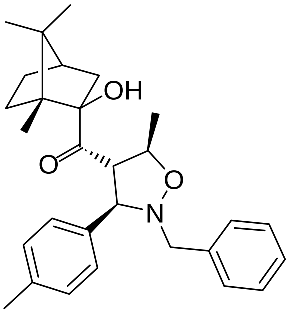
To a solution of (1*R*)-2-*endo*-2'-butenoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **2** (0.111 g, 0.5 mmol) in dry CH_2Cl_2 (1.5 mL) with powdered molecular sieves (4Å) (250 mg) under a nitrogen atmosphere, $Cu(TfO)_2$ (0.0362 g , 0.10 mmol) was added at room temperature. Then the corresponding nitrone (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete. Then water (5 mL) was added and the reaction was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude. Purification was effected by flash silica gel column chromatography using ethyl acetate/hexane mixtures as the eluant.

(3*R*, 4*S*, 5*R*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-5-methyl-3-phenylisoxazolidine (5a)



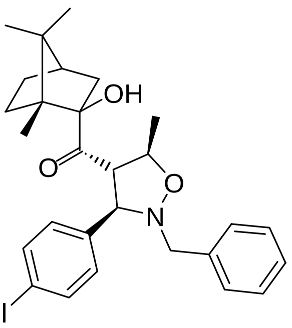
The title compound was prepared according to general procedure from **2** and (*Z*)-N-benzylidenebenzylamine N-oxide (0.212 g, 1.0 mmol) in 22 h. 0.182 g (84 %); white solid; m.p. 182-183 ºC; $[\alpha]_D^{25}$ –3.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3501, 1690, 1453, 700; ^{1}H NMR ($CDCl_3$) δ 7.40-7.18 (m, 10 H, arom.), 4.23 (d, 1H, C*H*Ph, J= 7.8 Hz), 4.14 (m, 1H, C*H*CH_3), 4.00 (d, 1H, *H*CHPh, J= 14.3 Hz), 3.85 (d, 1H, *H*CHPh, J= 14.4 Hz), 3.69 (dd, 1H, CHC=O, J= 4.9 Hz, J'= 7.8 Hz), 2.24 (m, 1H, CH), 1.93 (s, 1H, OH), 1.70 (m, 1H, CH_2), 1.56 (m, 2H, CH_2), 1.53 (d, 3H, CHC*H*$_3$, J= 6.1 Hz) 1.14 (m, 2H, CH_2), 1.00 (s, 3H, CH_3), 0.71 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.44 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.3, 139.2, 138.1, 128.6, 128.2, 128.0, 127.9, 126.7, 88.3, 78.7, 75.7, 68.4, 59.3, 52.3, 51.0, 44.9, 42.1, 29.9, 26.0, 21.1, 20.8, 20.4, 10.3. Anal. Calcd for $C_{28}H_{34}NO_3$ (432.62) C, 77.73; H, 7.94; N, 3.24. Found: C, 77.78; H, 7.90; N, 3.30.

(3*R*, 4*S*, 5*R*)-2-Benzyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-5-methyl-3-*p*-metilphenylisoxazolidine (5c)



The title compound was prepared according to general procedure from **2** and (*Z*)-N-*p*-methylbenzylidenebenzylamine N-oxide (0.226 g, 1.0 mmol) in 50 h. 0.157 g (70 %); white solid; m.p. 176-177 ºC; $[\alpha]_D^{25}$ -5.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3502, 2955, 2929, 1691, 1447, 1082, 698; ^{1}H NMR ($CDCl_3$) δ 7.40-7.22 (m, 7 H, arom.), 7.14 (d, 2H arom., J= 7.9 Hz), 4.23 (d, 1H, C*H*Ph, J= 7.9 Hz), 4.18 (m, 1H, C*H*CH_3), 4.03 (d, 1H, *H*CHPh, J= 14.6 Hz), 3.86 (d, 1H, *H*CHPh, J= 14.5 Hz), 3.73 (dd, 1H, CHC=O, J= 4.8 Hz, J'= 7.8 Hz), 2.35 (s, 3H, C*H*$_3$Ph), 2.27 (m, 1H, CH), 2.03 (s, 1H, OH), 1.75 (m, 2H, CH_2), 1.67 (m, 1H, CH), 1.53 (d, 3H, CHC*H*$_3$, J= 6.1 Hz) 1.19 (m, 2H, CH_2), 1.06 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.70 (m, 1H, CH), 0.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.5, 138.1, 137.5, 135.9, 129.2, 128.1, 128.0, 127.8, 126.7, 126.7, 88.2, 78.6, 75.5, 68.2, 59.1, 52.3, 50.9, 44.9, 42.0, 29.9, 26.0, 21.2, 21.1, 20.7, 20.4, 10.4. Anal. Calcd for $C_{29}H_{37}NO_3$ (447.66) C, 77.80; H, 8.35; N, 3.13. Found: C, 77.77; H, 8.38; N, 3.10.

(3*R*, 4*S*, 5*R*)-2-Benzyl-3-*p*-chlorophenyl-4-[(1*R*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-carbonyl]-5-methylisoxazolidine (5e)



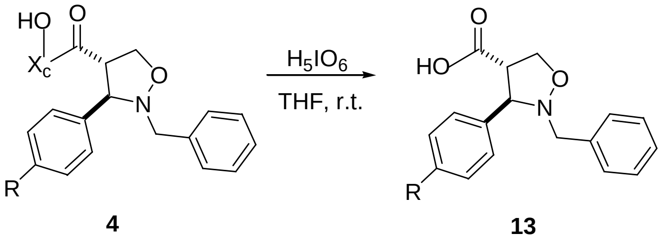
The title compound was prepared according to general procedure from **2** and (*Z*)-N-*p*-chlorobenzylidenebenzylamine N-oxide (0.246 g, 1.0 mmol) in 48 h. 0.166 g (71%); white solid; m.p. 167-168 ºC; $[\alpha]_D^{25}$ -6.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3497, 2954, 2929, 1688, 1487, 1090, 693; ^{1}H NMR ($CDCl_3$) δ 7.38-7.23 (m, 9 H, arom.), 4.28 (d, 1H, C*H*Ph, J= 7.7

Hz), 4.19 (m, 1H, C*H*CH$_3$), 4.02 (d, 1H, *H*CHPh, J= 14.4 Hz), 3.85 (d, 1H, *H*CHPh, J= 14.3 Hz), 3.68 (dd, 1H, CHC=O, J= 5.0 Hz, J'= 7.6 Hz), 2.31 (m, 1H, CH), 1.97 (s, 1H, OH), 1.77 (m, 2H, CH$_2$), 1.69 (m, 1H, CH), 1.57 (d, 3H, CHC*H*$_3$, J= 6.1 Hz), 1.20 (m, 2H, CH$_2$), 1.06 (s, 3H, CH$_3$), 0.78 (s, 3H, CH$_3$), 0.71 (m, 1H, CH), 0.52 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 210.9, 138.0, 137.7, 133.5, 129.1, 128.8, 128.2, 128.0, 126.8, 88.3, 78.8, 74.6, 68.4, 59.3, 52.2, 51.0, 44.8, 42.3, 29.9, 26.0, 21.0, 20.8, 20.5, 10.6. Anal. Calcd for $C_{28}H_{34}ClNO_3$ (468.07) C, 71.84; H, 7.34; N, 2.99. Found: C, 71.79; H, 7.38; N, 2.91.

F) Oxidative elaboration of adducts 4

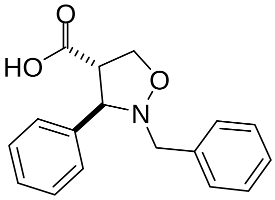
For all the following oxidation processes, during product purification by means of column chromatography, optically pure (1R)-(+)-camphor was recovered from the first fractions of the column in yields within the range 80-95%, and could be reused.

F-1) General procedure for the direct oxidation of 4



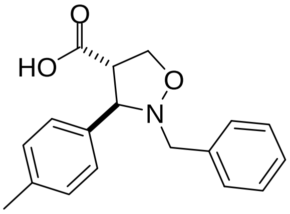
To a solution of the corresponding α-hydroxy ketone (1 mmol) in dry THF (2 mL) at room temperature, under a nitrogen atmosphere, periodic acid (2.28 g**,** 10 mmol) was added in portions during 1 hour. The reaction mixture was stirred until TLC analysis indicated that the reaction was complete. The solvent was decanted and the remaining white solid was washed twice with CH$_2$Cl$_2$. The crude product obtained after removing the solvent was directly purified by column chromatography to afford the corresponding carboxylic acid **13**.

(3*R*, 4*S*)-2-Benzyl-3-phenylisoxazolidin-4-carboxylic acid (13a)



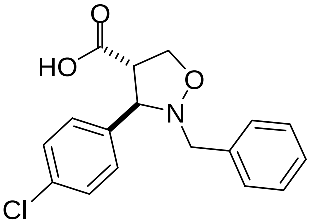
The acid was obtained from the cycloadduct **4a** (0.42 g, 1 mmol) as indicated in the general procedure in 10 h. (0.24 g) (86%); white solid; m.p. 132-133 ºC; $[\alpha]_D^{25}$ + 20.0 (*c* 1.0, CH$_2$Cl$_2$); IR (neat, cm^{-1}) 3646-3134, 3031, 2880, 2571, 1710, 1495, 1455, 702; ^{1}H NMR (CDCl$_3$) δ 8.47 (s$_b$, 1H, OH), 7.70-7.10 (m, 10 H, arom), 4.32 (d, 2H, CH$_2$, J= 6.7 Hz), 4.13 (d, 1H, PhCHNO, J= 7.5 Hz), 4.00 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.81 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.52 (m, 1H, C*H*COOH); ^{13}C NMR (CDCl$_3$) δ 178.2, 138.0, 137.1, 128.7, 128.6, 128.2, 128.1, 127.8, 127.2, 73.2, 68.4, 59.6, 56.8; Anal. Calcd for $C_{17}H_{17}NO_3$ (283.34) C, 72.06; H, 6.06; N, 4.94. Found: C, 72.16; H, 5.96; N, 4.89.

(3*R*, 4*S*)-2-Benzyl-3-*p*-methylphenylisoxazolidin-4-carboxylic acid (13c)



The acid was obtained from the cycloadduct **4c** (0.43 g, 1 mmol) according to general procedure in 12 h. (0.25 g) (85%); Yellow oil; $[\alpha]_D^{25}$ + 8.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2612, 2880, 1710, 1454, 1216, 699; ^1H NMR ($CDCl_3$) δ 11.09 (s_b, 1H, COOH), 7.60-7.20 (m, 9H, arom.), 4.37 (d, 2H, CH_2O, J= 6.6 Hz), 4.16 (d, 1H, CHNO, J= 7.7 Hz), 4.07 (d, 1H, *H*CHPh, J= 14.1 Hz), 3.85 (d, 1H, *H*CHPh, J=14.1 Hz), 3.58 (m, 1H, C*H*COOH), 2.46 (s, 3H, $CH_3C_6H_4$); ^{13}C NMR ($CDCl_3$) δ 178.0, 137.9, 137.0, 134.7, 129.4, 128.7, 128.0, 127.7, 127.2, 73.0, 68.3, 59.4, 56.6, 21.2.

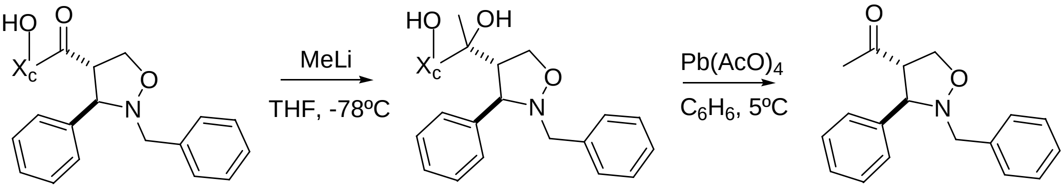
(3*R*, 4*S*)-2-Benzyl-3-*p*-chlorophenylisoxazolidin-4-carboxylic acid (13e)



The title compound was obtained from **4e** (0.45 g, 1 mmol) according to general procedure in 12 h. (0.31 g) (96%); white solid; mp 136-137 ºC; $[\alpha]_D^{25}$ – 3.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3027, 2878, 1709, 1492, 1180, 1090, 1043, 1014, 822, 733, 698; ^1H NMR ($CDCl_3$) δ 10.71 (s_b, 1H, COOH), 7.60-7.20 (m, 9H, arom.), 4.35 (m, 2H, CH_2O), 4.16 (d, 1H, CHNO, J= 7.5 Hz), 4.02 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.87 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.50 (m, 1H, C*H*COOH); ^{13}C NMR ($CDCl_3$) δ 177.6, 136.6, 136.5, 133.9, 129.1, 128.9, 128.7, 128.1, 127.3, 72.3, 68.2, 59.5, 56.7. ; Anal. Calcd for $C_{17}H_{16}NO_3Cl$ (317.78) C, 64.25; H, 5.08; N, 4.40. Found: C, 64.29; H, 4.92; N, 4.52.

F-2) Sequential alkyllithium addition and diol oxidation:

(3*R*, 4*S*)-4-Acetyl-2-benzyl-3-phenylisoxazolidine (14)

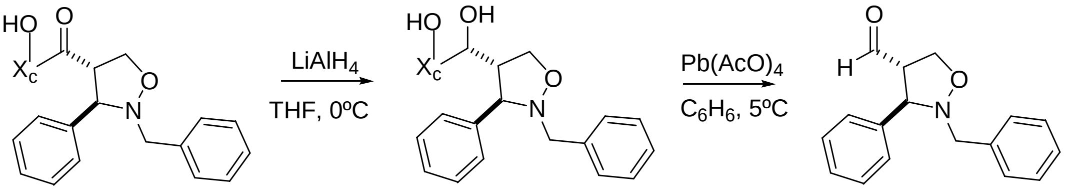


4a **14**

MeLi (1.4 M in Et_2O, 2.14 mL, 3 mmol) was added to a solution of the corresponding α'-hydroxy ketone **4a** (0.42, 1 mmol) in THF (3 mL) at -78°C and the solution was stirred at the same temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL) and the resulting mixture was allowed to warm to room temperature, after which the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue thus obtained was subjected to oxidative scission by treatment with $Pb(AcO)_4$ (0.87 g, 2 mmol) in benzene (4 mL) at 5° C. After 1 h of stirring, aqueous saturated solution of $NaHCO_3$ was slowly added (4 mL). The resulting mixture was filtered through a Celite pad followed by elution with CH_2Cl_2 (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and dried over $MgSO_4$. Removal of solvent resulted in an oil residue which was purified by column chromatography affording the title compound. (0.24 g) (84%) as a white solid. m.p. 77-78 ºC; IR (neat, cm^{-1}) 1736, 1716, 1455, 1365, 1216, 700; ^1H NMR ($CDCl_3$) δ 7.50-7.25 (m, 10 H, arom.), 4.20 (m, 2H, CH_2O), 3.97 (d, 1H, PhCHNO, J= 7.3 Hz), 3.91 (d, 1H, *H*CHPh, J = 14.0 Hz), 3.73 (d, 1H, *H*CHPh, J = 14.0 Hz), 3.57 (m, 1H, CHC=O), 2.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 205.4, 138.4, 137.2, 128.8, 128.6, 128.2, 128.1, 127.9, 127.2, 72.6, 67.7, 64.9, 59.6, 30.0; Anal. Calcd for $C_{18}H_{19}NO_2$ (281.37) C, 76.83; H, 6.82; N, 4.98. Found: C, 77.01; H, 6.80; N, 4.82.

F-3) Sequential reduction and diol oxidation:

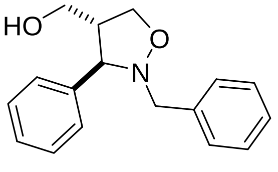
(3*R*, 4*S*)-2-Benzyl-3-phenylisoxazolidin-4-carbaldehyde (15)



4a **15**

The title compound was obtained from cycloadduct **4a** (0.21 g, 0.5 mmol) by reduction with $LiAlH_4$ (1.0 M in Et_2O) (1.5 mmol, 1.5 mL) in dry THF (2.5 mL) at 0ºC for 30 min. The reaction mixture was quenched with 1N HCl (1 mL) and extracted with Et_2O (3 x 3 mL). The crude product obtained after removing the solvent was sufficiently pure to use in the next step. $Pb(AcO)_4$ (0.44 g, 1 mmol) was added in portions to a solution of the crude oil in benzene (2 mL) at 5ºC. After 20 min. of stirring, aqueous saturated solution of $NaHCO_3$ was slowly added (2 mL). The resulting mixture was filtered through a Celite pad eluting with CH_2Cl_2 (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and dried over $MgSO_4$. The solvent was evaporated and the resulting crude product was purified by column chromatography providing the corresponding aldehyde as a colorless oil. (0.12 g) (87%); $[\alpha]_D^{25}$ + 64.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3030, 2875, 1721, 1495, 1454, 1041, 1028, 756, 696; ^1H NMR ($CDCl_3$) δ 9.81 (d, 1H, CHO, J= 2.1 Hz), 7.70-7.20 (m, 10H, arom.), 4.28 (m, 2H, CH_2O), 4.09 (d, 1H, PhCHNO, J= 7.4 Hz), 4.03 (d, 1H, *H*CHPh, J= 14.3 Hz), 3.80 (d, 1H, *H*CHPh, J= 14.2 Hz), 3.45 (m, 1H, C*H*CHO); ^{13}C NMR ($CDCl_3$) δ 198.6, 137.9, 137.1, 128.8, 128.6, 128.2, 128.1, 127.7, 127.2, 70.6, 65.8, 64.3, 59.6.

(3*R*, 4*R*)-2-Benzyl-4-hydroxymethyl-3-phenylisoxazolidine

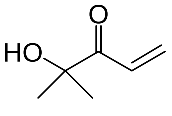


The title compound was obtained from aldehyde **15** (0.107 g, 0.4 mmol) by reduction with $NaBH_4$ (0.030 g, 0.8 mmol) in dry MeOH (2.0 mL) at 0ºC for 20 min. The reaction mixture was quenched with 1N HCl (1 mL) and extracted with Et_2O (3 x 3 mL). The resulting crude product was purified by column chromatography affording the alcohol (0.102 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ + 88.0 (*c*

1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3404, 3029, 2940, 2872, 1494, 1454, 1030, 756, 698; ^1H NMR ($CDCl_3$) δ 7.60-7.10 (m, 10 H, arom.), 4.20 (t, 1H, *H*CHON, J= 8.1 Hz), 3.98 (d, 1H, *H*CHPh, J= 14.6 Hz), 3.93 (m, 1H, *H*CHON), 3.73 (m, 3H, *H*CHPh, C*H*$_2$OH), 3.50 (d, 1H, PhCHNO, J= 7.3 Hz), 2.78 (m, 1H, C*H*CH_2OH), 1.85 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 139.2, 137.5, 128.7, 128.6, 128.1, 127.9, 127.8, 127.0, 73.4, 69.1, 63.1, 59.9, 54.8.

G) Preparation of α'-hydroxy enones 6 and 10

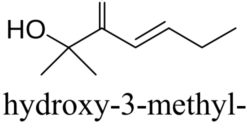
2-Hydroxy-2-methylpent-4-en-3-one (6)[3]



To a solution of methoxyallene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at -40°C, nBuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at -40°C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 3-methoxy-2-methyl-3,4-pentadien-2-ol as a yellow liquid (5.65 g) (82%) that was employed in the next step without further purification.

3-Methoxy-2-methyl-3,4-pentadien-2-ol, (5.65 g, 44 mmol) was added dropwise to 5% aq H_2SO_4 (110 mL) at 0°C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 x 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone **6** as a colorless liquid (4.42 g) (88%); b.p. 45°C (13 mmHg); IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O); ^1H NMR ($CDCl_3$) δ 6.73 (dd, 1H, CH, J= 9.5 Hz, J'= 16.8 Hz), 6.50 (dd, 1H, HCH, J= 2.2 Hz, J'= 16.8 Hz), 5.82 (dd, 1H, HCH, J= 2.2 Hz, J'= 10.3 Hz), 1.38 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 202.3, 131.1, 128.8, 75.4, 26.1.

2-Hydroxy-2-methylhept-4-en-3-one (10)[5]



To a cooled (-78°C) solution of diisopropylamine (14 mL, 100 mmol) in dry THF (100 mL), nBuLi (2.5 M in hexanes, 40 ml, 100 mmol) was added dropwise under nitrogen. After 30 min. of stirring, 3-hydroxy-3-methyl-2-butanone (4.4 mL, 40 mmol) was added. The mixture was stirred at -78°C for 30 min and then freshly distilled propanal (8.8 mL, 120 mmol) was added dropwise. After 3 h at the same temperature the reaction was quenched with a saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The organic layer was dried over $MgSO_4$ and the solvent removed in vacuum to afford the crude aldol 2,5-dihydroxy-2-methylheptan-3-one, that was purified by flash silicagel column chromatography (ethyl acetate/hexane 1:10). (4.48 g) (70 %).

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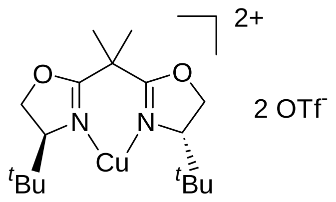
[3] a) Zimmer, R. *Synthesis* **1993**, 165-178. b) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179-1184.

[5] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942-13943.

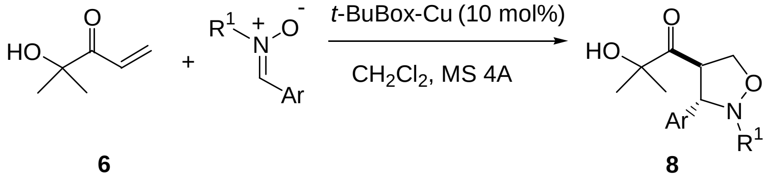
To a stirred suspension of 2,5-dihydroxy-2-methylheptan-3-one (3.20 g, 20 mmol) and cerium(III) chloride heptahydrate (11.2 g, 30 mmol) in acetonitrile (200 mL) was added sodium iodide (4.4 g, 30 mmol) and the resulting mixture was stirred for 3 h at reflux. After that time the reaction mixture was diluted with ether and treated with 0.5 M HCl (150 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution (150 mL) and a saturated NaCl solution (150 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by column chromatography (ethyl acetate/hexane 1:20) to give 2.27 g (80%) of the enone **10** as a colorless liquid; b.p. 90°C (5 mbar); IR (neat, cm^{-1}); 3458 (OH), 1687 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 1H, CHC=O), 6.39 (ddd, 1H, HC=C, J= 1.5 Hz, J'= 2.2 Hz, J''= 15.4 Hz), 3.99 (s, 1H, OH), 2.27 (m, 2H, CH_2), 1.37 (s, 1H, 6H, $2CH_3$), 1.08 (t, 3H, CH_3, J= 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 202.2, 152.2, 121.1, 75.1, 26.5, 26.3, 25.8, 12.2.

H) Preparation of Cu(II)/bisoxazoline catalyst (7)[4]



Copper (II) triflate (16.2 mg, 0.050 mmol) and the bisoxazoline ligand (18.1 mg, 0.06 mmol) were combined under a nitrogen atmosphere and anhydrous CH_2Cl_2 (1mL) was added. The solution was stirred for 3 h at ambient temperature and was employed as a catalyst solution (0.05 M) for the enantioselective 1,3-Dipolar cycloadditions.

I) General Procedure for Cu(II):t-BOX-catalyzed 1,3-DC of nitrones to 6



A flame dried flask was charged with 2-hydroxy-2-methylpent-4-en-3-one **6** (0.114 g, 1.0 mmol) and dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The solution was cooled to -20ºC and powdered molecular sieves (4Å) freshly dried (250 mg), the corresponding nitrone (0.5 mmol) in CH_2Cl_2 (1 mL) and finally the catalyst solution (*tert*-BuBox/Cu($OTf)_2$) previously prepared (1 mL, 0.05 M) were added consecutively.

The resulting mixture was stirred at -20ºC until completion of reaction. The reaction mixture was then diluted with 5 mL of 1:1 ethyl acetate/hexane and directly applied to a short silica gel column (1.5 cm x 1.5 cm). It was eluted with approximately 50 mL of 1:1 ethyl acetate/hexane and concentration afforded the crude product. Subsequent

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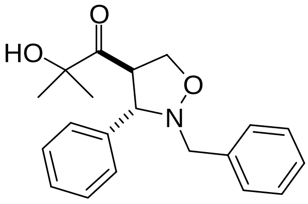
[4] Evans D.A.; Barnes D.M.; Johnson J.S.; Lectka T.; Von Matt P.; Miller S.J.; Murry J.A.; Norcross R.D.; Shaughnessy E.A.; Campos K.R. *J. Am. Chem. Soc.* **1999**, *121*, 7582-7594.

purification by column chromatography (silica gel, 1:15 ethyl acetate/hexane) afforded the corresponding cycloadduct.

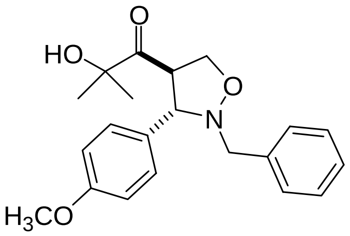
(3*S*, 4*R*)-2-Benzyl-4-(2-hydroxy-2-methylpropanoyl)-3-phenylisoxazolidine (8a)



The title compound was prepared according to general procedure from **6** and (*Z*)-N-benzylidenebenzylamine N-oxide (0.106 g, 0.5 mmol) in 36 h. Combined yield of both regoisomers 0.138 g (85%). Data of major regioisomer (94%ee); colorless oil; IR (neat, cm^{-1}) 3475, 1711, 1495, 1455, 699; ^{1}H NMR (CDCl$_3$) δ 7.46-7.25 (m, 10 H, arom.), 4.31 (m, 1H, *H*CHON), 4.21 (d, 1H, CHNO, J= 8.2 Hz), 3.98 (m, 3H, CHC=O, *H*CHON, CH$_2$Ph), 3.90 (d, 1H, *H*CHPh, J= 13.9 Hz), 1.58 (s, 1H, OH), 1.26 (s, 3H, CH$_3$), 1.03 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 212.6, 137.9, 137.3, 128.7, 128.6, 128.2, 128.1, 127.4, 127.1, 76.4, 74.1, 69.5, 59.7, 58.4, 25.6, 25.5.

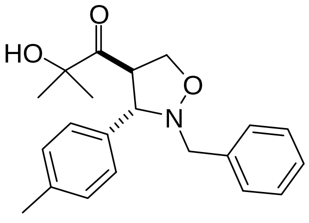
Data for the regioisomer 2-benzyl-5-(2-hydroxy-2-methylpropanoyl)-3-phenylisoxazolidine **9a**: m. p. 119-120 ºC; IR (neat, cm^{-1}) 2991, 1373, 1173, 1076, 958; ^{1}H NMR (CDCl$_3$) δ 7.31 (m, 10 H, arom.), 4.98 (dd, 1H, CHON, J= 6.0 Hz, J'= 9.2 Hz), 3.88 (m, 3H, CH$_2$Ph, CHPh), 2.83 (m, 1H, *H*CHCHPh), 2.59 (m, 1H, *H*CHCHPh), 1.56 (s, 1H, OH), 1.37 (s, 6H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 211.2, 138.4, 136.9, 128.9, 128.7, 128.2, 128.0, 127.6, 127.3, 78.4, 77.0, 69.2, 60.2, 41.6, 26.7, 26.5; Anal. Calcd for $C_{20}H_{23}NO_3$ (325.43) C, 73.81; H, 7.14; N, 4.30. Found: C, 74.01; H, 7.21; N, 4.23.

(3*S*, 4*R*)-2-Benzyl-4-(2-hydroxy-2-methylpropanoyl)-3-*p*-methoxyphenylisoxazolidine (8b)



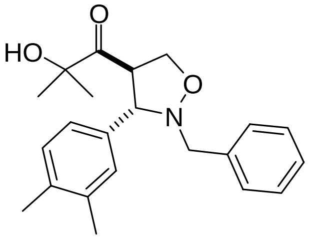
The title compound was prepared according to general procedure from **6** and (*Z*)-N-*p*-methoxybenzylidenebenzylamine N-oxide (0.121 g, 0.5 mmol) in 23 h. Combined yield of both regoisomers 0.176 g (99%). Data of major regioisomer (92%ee): white solid; m.p. 84-85 ºC; IR (neat, cm^{-1}) 3485, 1711, 1612, 1512, 1247, 1031, 699; ^{1}H NMR (CDCl$_3$) δ 7.37-7.25 (m, 7H, arom.), 6.90 (d, 2H, orthoC$_6$H$_4$OCH$_3$, J= 8.9 Hz), 4.23 (m, 3H, CHNO, CH$_2$ON), 3.97 (m, 2H, CHC=O, *H*CHPh), 3.82 (s, 3H, OCH$_3$), 3.80 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.32 (s, 1H, OH), 1.26 (s, 3H, CH$_3$), 1.03 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 212.9, 159.4, 137.5, 129.3, 128.7, 128.6, 128.1, 127.1, 114.2, 76.5, 74.2, 69.6, 59.6, 58.1, 55.2, 25.5, 25.4; Anal. Calcd for $C_{21}H_{25}NO_4$ (355.46); C, 70.95; H, 7.10; N, 3.94. Found: C, 70.55; H, 6.95; N, 4.00.

(3*S*, 4*R*)-2-Benzyl-4-(2-hydroxy-2-methylpropanoyl)-3-*p*-methylphenylisoxazolidine (8c)



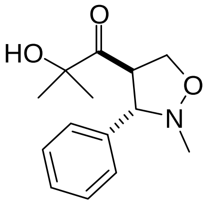
The title compound was prepared according to general procedure from **6** and (*Z*)-N-*p*-methylbenzylidenebenzyl-amine N-oxide (0.113 g, 0.5 mmol) in 12 h. Combined yield of both regoisomers 0.137 g (81%). Data of major regioisomer (92%ee): white solid, m.p. 77-78 ºC; IR (neat, cm^{-1}) 3460, 1711, 1514, 1496, 733, 697; ^{1}H NMR (CDCl$_3$) δ 7.45-7.10 (m, 9H, arom.), 4.29-3.78 (m, 6H), 3.43 (s, 1H, OH), 2.35 (s, 3H, CH$_3$Ph), 1.23 (s, 3H, CH$_3$), 1.05 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 212.8, 137.9, 137.4, 134.6, 129.4, 128.6, 128.0, 127.3, 127.0, 76.4, 74.1, 69.6, 59.6, 58.2, 25.6, 25.5, 21.1. Anal. Calcd for $C_{21}H_{25}NO_3$ (339.46) C, 74.30; H, 7.44; N, 4.12. Found: C, 74.21; H, 7.31; N, 4.20.

(3*S*, 4*R*)-2-Benzyl-4-(2-hydroxy-2-methylpropanoyl)-3-(3,4-dimethylphenyl)isoxazolidine (8d)



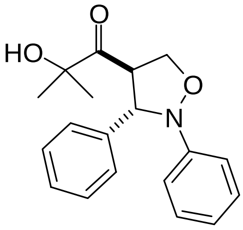
The title compound was prepared according to general procedure from **6** and (*Z*)-N-2,3-dimethylbenzylidenebenzylamine N-oxide (0.120 g, 0.5 mmol) in 15 h. Combined yield of both regoisomers 0.166 g (94%). Data of major regioisomer (90%ee): white solid; m.p. 62-63 ºC; IR (neat, cm^{-1}) 3469, 2979, 2870, 1712, 1496, 1454, 1141, 970, 698; ^{1}H NMR (CDCl$_3$) δ 7.40-7.11 (m, 8H, arom.), 4.30 (m, 1H, *H*CHON), 4.16-3.93 (m, 4H, *H*CHON, CHC=O, *H*CHPh, CHNO), 3.83 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.37 (s, 1H, OH) 2.29 (s, 6H, 2 CH$_3$), 1.27 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 212.9, 137.5, 137.0, 136.6, 134.9, 130.0, 128.6, 128.5, 128.1, 127.1, 124.9, 76.5, 74.4, 69.6, 59.7, 58.2, 25.6, 25.5, 19.8, 19.5; Anal. Calcd for $C_{22}H_{27}NO_3$ (353.50) C, 74.75; H, 7.71; N, 3.96. Found: C, 74.65; H, 7.85; N, 4.15.

(3*S*, 4*R*)-4-(2-Hydroxy-2-methylpropanoyl)-2-methyl-3-phenylisoxazolidine (8l)



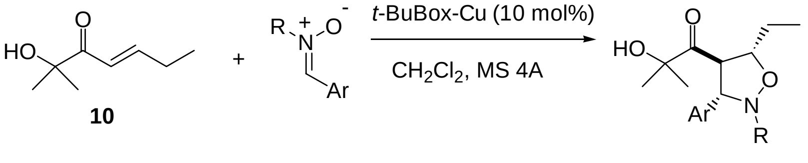
The title compound was prepared according to general procedure from **6** and (*Z*)- N-benzylidenemethylamine N-oxide (0.068 g, 0.5 mmol) in 3 d. Combined yield of both regoisomers 0.068 g (55%). Data of major regioisomer (96%ee): yellow oil; IR (neat, cm^{-1}) 3360, 2970, 1739, 1455, 1366, 964, 752, 700; ^{1}H NMR (CDCl$_3$) δ; 7.30 (m, 5H, arom.), 4.28 (m, 1H, *H*CHON), 4.10-3.80 (m, 3H, *H*CHON, CHC=O, CHPh), 2.63 (s, 3H, CH$_3$N), 1.21 (s, 3H, CH$_3$), 0.97 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 212.7, 137.3, 128.8, 128.3, 127.4, 76.5, 76.4, 69.4, 58.6, 42.9, 25.6, 25.5.

(3*S*, 4*R*)-2,3-Diphenyl-4-(2-hydroxy-2-methylpropanoyl)isoxazolidine (8m)



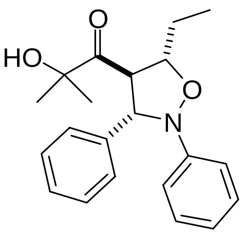
The title compound was prepared according to general procedure from **6** and (*Z*)-N-benzylidenephenylamine N-oxide (0.099 g, 0.5 mmol) in 3 h at -40ºC. Combined yield of exo/endo isomers 0.153 g (98%). Data for *endo* isomer (≥99%ee): white solid; m.p. 107-108 ºC; IR (neat, cm^{-1}) 3431, 1716, 1598, 1486, 748, 697; ^{1}H NMR (CDCl$_3$) δ 7.55-7.20 (m, 8H, arom.), 6.98 (m, 2H, arom.), 5.01 (d, 1H, CHPh, J= 6.6 Hz), 4.50 (t, 1H, *H*CHON, J= 7.3 Hz), 4.12 (m, 1H, CHC=O), 4.01 (t, 1H, *H*CHON, J= 7.3 Hz), 3.10 (s, 1H, OH), 1.31 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 210.8, 150.6, 140.7, 128.9, 128.7, 127.9, 126.4, 122.2, 115.1, 76.7, 73.4, 70.6, 61.1, 25.9, 25.8; Anal. Calcd for $C_{19}H_{21}NO_3$ (311.40) C, 73.28; H, 6.81; N, 4.50. Found: C, 73.47, H, 6.91, N, 4.21.

J) General Procedure for Cu(II):t-BOX-catalyzed 1,3-DC of nitrones to 10



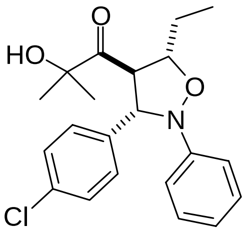
A flame dried flask was charged with 2-hydroxy-2-methyl-hept-4-en-3-one **10** (0.071 g, 0.5 mmol) and dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The solution was cooled to 0ºC and powdered molecular sieves (4Å) freshly dried (250 mg), the corresponding nitrone (0.5 mmol) in CH_2Cl_2 (1 mL) and finally the catalyst solution (*tert*-BuBox/Cu(OTf)$_2$) previously prepared (1 mL, 0.05 M) were added consecutively. The resulting mixture was stirred at 0ºC until completion of reaction. The reaction mixture was then diluted with 5 mL of 1:1 ethyl acetate/hexane and directly applied to a short silica gel column (1.5 cm x 1.5 cm). It was eluted with approximately 50 mL of 1:1 ethyl acetate/hexane and concentration afforded the crude product. Subsequent purification by column chromatography (silica gel, 1:15 ethyl acetate/hexane) afforded the corresponding cycloadduct.

(3*S*, 4*R*, 5*S*) -2,3-Diphenyl-5-ethyl-4-(2-hydroxy-2-methylpropanoyl)isoxazolidine (11)



The title compound was prepared according to general procedure from **10** and (*Z*)-N-benzylidenephenylamine N-oxide (0.099 g, 0.5 mmol) in 16 h at 0ºC. 0.127 g (75%); (≥99%ee, *endo* isomer); white solid; m.p. 88-89 ºC; $[\alpha]_D^{25}$ – 81.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3496, 2972, 1707, 1597, 1487, 1454, 1357, 755, 696; ^{1}H NMR ($CDCl_3$) δ 7.48-7.19 (m, 8H, arom.), 6.93 (m, 2H, arom.), 4.80 (d, 1H, CHPh, J= 7.5 Hz), 4.29 (dt, 1H, C*H*CH$_2$CH$_3$, J= 4.0 Hz, J'= 8.2 Hz), 3.86 (dd, 1H, CHC=O, J= 7.9 Hz, J'= 8.3 Hz), 3.16 (s, 1H, OH), 1.82 (m, 2H, CH$_2$), 1.21 (s, 3H, CH$_3$), 1.14 (t, 3H, C*H*$_2$CH$_3$, J= 7.4 Hz), 0.96 (s, 3H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 211.8, 151.7, 141.1, 129.2, 128.9, 128.3, 126.9, 122.0, 114.8, 84.9, 76.9, 65.3, 26.1, 25.8, 25.6, 11.0; Anal. Calcd for $C_{21}H_{25}NO_3$ (339.46) C, 74.30; H, 7.44; N, 4.12. Found: C, 74.36, H, 7.39, N, 4.08.

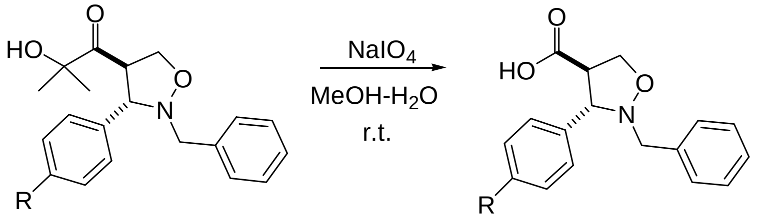
(3*S*, 4*R*, 5*S*)-5-Ethyl-2,3-diphenyl-4-(2-hydroxy-2-methylpropanoyl)isoxazolidine (12)



The title compound was prepared according to general procedure from **10** and (*Z*)-N-*p*-chlorobenzylidenephenylamine N-oxide (0.115 g, 0.5 mmol) in 16 h at 0ºC. 0.147 g (79%); (≥99%ee, *endo* isomer); clear yellow oil; $[\alpha]_D^{25}$ - 68.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3490, 2972, 1705, 1597, 1487, 1346, 1089, 754, 693; ^{1}H NMR ($CDCl_3$) δ 7.42-7.18 (m, 7H, arom.), 6.93 (m, 2H, arom.), 4.80 (d, 1H, CHPh, J= 7.2 Hz), 4.26 (dt, 1H, C*H*CH$_2$CH$_3$, J= 4.3 Hz, J'= 7.9 Hz), 3.81 (dd, 1H, CHC=O, J= 7.2 Hz, J'= 7.9 Hz), 3.10 (s, 1H, OH), 1.79 (m, 2H, CH$_2$), 1.20 (s, 3H, CH$_3$), 1.12 (t, 3H, C*H*$_2$CH$_3$, J= 7.3 Hz), 1.02 (s, 3H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 211.4, 151.0, 139.6, 133.7, 129.1, 128.8, 128.1, 122.0, 114.6, 84.6, 76.8, 75.6, 64.9, 26.0, 25.7, 25.6, 10.7.

K) Oxidative elaboration of adducts 8

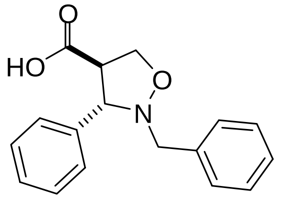
K-1) General procedure for the direct oxidation of 8



8 **ent-10**

To a solution of the corresponding α-hydroxy ketone (1 mmol) in methanol (6.6 mL) a suspension of sodium periodate $NaIO_4$ (2.14 g, 10 mmol) in water (3.3 mL) was added. The reaction mixture was stirred at room temperature until completion of reaction (monitored by TLC). Then the solvent was removed under reduced pressure. Water (15 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid.

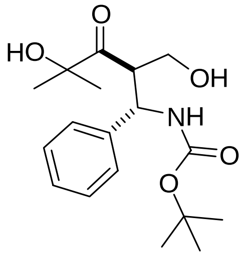
(3*S*, 4*R*)-2-Benzyl-3-phenylisoxazolidin-4-carboxylic acid (ent-13a)



The acid was obtained from the cycloadduct **8a** (0.325 g, 1 mmol) as indicated in the general procedure, in 18 h. (0.238 g) (84%); white solid; m.p. 132-133 ºC; $[\alpha]_D^{25}$ −18.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3646-3134, 3031, 2880, 2571, 1710, 1495, 1455, 702; ^1H NMR ($CDCl_3$) δ 8.47 (s_b, 1H, OH), 7.70-7.10 (m, 10 H, arom), 4.32 (d, 2H, CH_2, J= 6.7 Hz), 4.13 (d, 1H, CHPh, J= 7.5 Hz), 4.00 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.81 (d, 1H, *H*CHPh, J= 14.0 Hz), 3.52 (m, 1H, CHC=O); ^{13}C NMR ($CDCl_3$) δ 178.2, 138.0, 137.1, 128.7, 128.6, 128.2, 128.1, 127.8, 127.2, 73.2, 68.4, 59.6, 56.8; Anal. Calcd for $C_{17}H_{17}NO_3$ (283.34) C, 72.06; H, 6.06; N, 4.94. Found: C, 72.14; H, 6.09; N, 4.88.

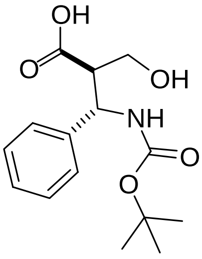
K-2) Sequential hydrogenolytic opening of the isoxazolidine ring and oxidation:

(4*R*, 5*S*)-5-*tert*Butoxycarbonylamino-2-hydroxy-4-hydroxymethyl-2-methyl-5-phenyl-pentan-3-one



A mixture of cycloadduct **8a** (0.325 g,1.0 mmol), MeOH (6 mL), C/Pd (10%) (0.106 g), and di-*tert*-butyl dicarbonate (0.252 mL, 1.02 mmol) was kept overnight under 1 atm hydrogen pressure. The reaction mixture was then directly applied to a Celite pad, eluting with CH_2Cl_2. The crude product was purified by column chromatography affording the title compound as a white solid (0.325 g) (96%); m.p. 163-164 ºC; IR (neat, cm^{-1}); 3368, 2978, 1690, 1514, 1367, 1167, 701; ^1H NMR ($CDCl_3$) δ 7.31 (m, 5H, arom.), 5.67 (d, 1H, NH, J= 8.8 Hz), 5.35 (t, 1H, C*H*NH, J= 8.2 Hz), 4.16 (m, 2H, OH), 4.02-3.78 (m, 3H C*H*C*H*$_2$OH), 1.43 (s, 9H, Boc), 1.15 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 215.7, 155.9, 140.0, 128.5, 127.6, 126.9, 80.3, 77.6, 61.6, 54.0, 53.2, 28.3, 26.3, 25.7; Anal. Calcd for $C_{18}H_{27}NO_5$ (337.45) C, 64.06; H, 8.08; N, 4.15. Found: C, 64.14; H, 8.03; N, 4.33.

(2*R*,3*S*)-3-(Boc-Amino)-2-hydroxymethylhydrocinnamic acid (16)



To a solution of the previous product (0.169 g, 0.5 mmol) in methanol (6.6 mL) a suspension of sodium periodate $NaIO_4$ (0.22 g, 1 mmol) in water (3.3 mL) was added. Sodium periodate (1.28 g, 6 mmol) was added in portions during 8 hour. The reaction mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete (30 h). Then the solvent was removed under reduced pressure. Water (15 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. The crude was purified by washing with dry hexane. (0.130g) (88%); white solid; m.p. 120-121 ºC; $[\alpha]_D^{25}$ – 50.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}); 3350, 2979, 2870, 1689, 1508, 1393, 1369, 1251, 1163, 1143; ^{1}H NMR (DMSO-d$_6$, 90 ºC) δ 7.55-7.17 (m, 5H, arom.), 6.98 (d, 1H, NH, J= 8.5 Hz), 4.79 (t, 1H, C*H*NH, J= 9.1 Hz), 3.71 (d, 2H, C*H*$_2$OH, J= 6.1 Hz), 2.90 (dt, 1H, C*H*COOH, J= 6.1 Hz, J'= 9.1 Hz), 1.99 (s, 1H, OH), 1.36 (s, 9H, Boc); ^{13}C NMR (DMSO-d$_6$, 90 ºC) δ 173.6, 154.9, 141.8, 128.1, 127.4, 127.1, 78.2, 61.0, 60.0, 54.1, 53.9, 28.4, 14.4

L) Determination of isomeric ratios (also, see pages 58-60)

The isomeric ratio of compounds **4a-4k** and **5a,c,e** was determined by ^{13}C NMR of the crude products. In Table 1, ≥98:2 indicates that no peaks assignable to other isomer are detected.

The ratio of regioisomers and of endo/exo products in adducts **8** was determined by ^{13}C and ^{1}H NMR of the crude products. In Table 2, ≥98:2 indicates that no peaks assignable to other isomer are detected.

The ratio of regioisomers and of endo/exo products in adducts **11** and **12** was determined by ^{13}C NMR of the crude products

The enantiomeric purity of compounds **8** was determined by HPLC analysis using a Chiralcel OD-H column and a mixture of hexane/isopropanol 95/5 (for **8a**, **8d** and **8l**) or hexane/isopropanol 98/2 (for **8b**, **8c** and **8m**) as the eluants (flow 0.5 mL/min).

The enantiomeric purity of compounds **11** and **12** was determined by HPLC analysis using Chiralcel OD-H and OB-H columns respectively and a mixture of hexane/isopropanol 99/1 as eluant (flow 0.5 mL/min).

The enantiomeric purity of carboxylic acids **13a** and **ent-13a** was determined by HPLC analysis of the derived methyl esters using a Chiralcel OB-H column and a mixture of hexane/isopropanol 98/2 as the eluant (flow 0.5 mL/min). The enantiomeric purity of ketone **11** was determined by HPLC analysis using a Chiralcel OD-H column and a mixture of hexane/isopropanol 95/5 as the eluant (flow 0.5 mL/min). The enantiomeric purity of aldehyde **12** was determined by HPLC analysis of the corresponding alcohol using a Chiralcel OD-H column and a mixture of hexane/isopropanol 95/5 as the eluant (flow 0.5 mL/min).

The enantiomeric purity of carboxylic acids **16** and **ent-16** (see below) was determined by HPLC analysis of the methyl esters using a Chiralpak AS column and a mixture of hexane/isopropanol 96/4 as the eluant (flow 1.0 mL/min).

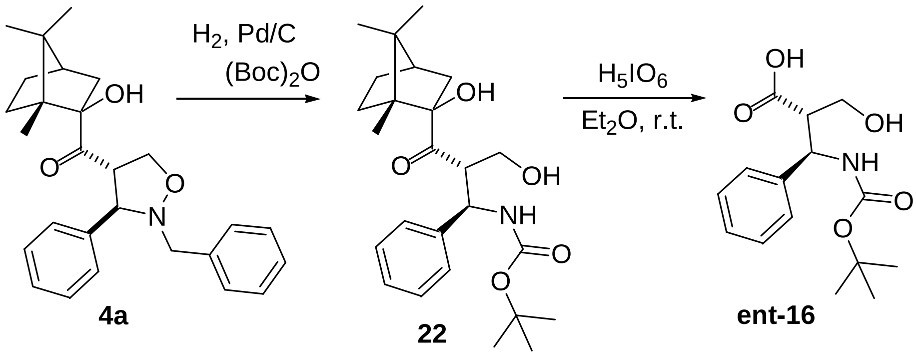
M) Assignment of structure and configuration for adducts

The structure (regioisomer identity) and configuration of adducts **4a** and **5a** were determined by X-Ray analysis (see ORTEP diagrams on pages 61-63). The structure of the remaining adducts **4**/**5** was assigned by analogy.

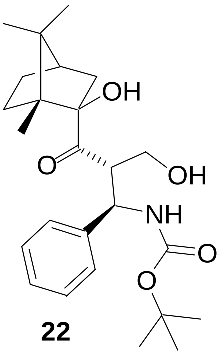
The structure (regioisomer identity) and relative configuration of adducts **8** and **9** were determined by X-Ray analysis of products **8m** and **9a** (see ORTEP diagrams on pages 64-65). The structure of the remaining adducts **8**/**9** was assigned by analogy.

The absolute configuration of **8a** was established by chemical correlation with **4a** as follows: the optical activity values of ent-**13a** and **16**, both derived from **8a**, were compared with those of **13a** and ent-**16**, the latter compounds being synthesized from **4a** (see the scheme below for the preparation of ent-**16** from **4a**). The assignment of the absolute configuration for the remaining compounds **8** was made by analogy.

Sequential hydrogenolytic opening of the isoxazolidine ring and oxidation:



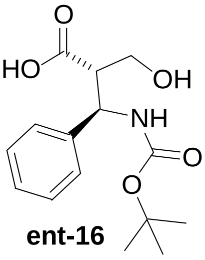
(1*R*)-2-*endo*-[(2*S*,3R)-3-(Boc-Amino)-2-hydroxymethylhydrocinnamoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (22)



22

A mixture of cycloadduct **4a** (0.209 g, 0.5 mmol), MeOH (3 mL), C/Pd (10%) (0.053 g), and di-*tert*-butyl dicarbonate (0.126 mL, 0.51 mmol) was kept overnight under 1 atm hydrogen pressure. The reaction mixture was then directly filtered through a Celite pad, eluting with CH_2Cl_2. The crude product was purified by column chromatography affording the title compound as a white solid (0.273 g) (96%); m.p. 74-75 ºC; $[\alpha]_D^{25}$ -7.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3375, 2952, 1692, 1519, 1391, 1367, 1167; ^1H NMR (DMSO-d_6, 90ºC) δ 7.35-7.15 (m, 5H. arom.), 7.09 (d, 1H, NH, J= 9.5 Hz), 5.32 (m, 2H, OH), 4.88 (dd, 1H, C*H*NH, J= 8.8 Hz, J'= 9.5 Hz), 3.95-3.82 (m, 2H, C*H*$_2$OH), 3.67-3.54 (m, 1H, CHC=O), 2.00 (m, 1H, CH), 1.72-1.57 (m, 3H, CH_2, CH), 1.35 (s, 9H, Boc), 1.05 (s, 3H, CH_3), 1.00-0.82 (m, 2H, CH_2) 0.67 (s, 3H, CH_3), 0.52 (s, 3H, CH_3), 0.28-0.41 (m, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 214.1, 156.0, 140.3, 128.5, 127.5, 127.4, 88.3, 80.2, 62.6, 55.2, 54.4, 52.5, 51.1, 44.9, 43.9, 28.9, 28.3, 26.4, 21.1, 20.5, 11.1; Anal. Calcd for $C_{25}H_{37}NO_5$ (431.62) C, 69.56; H, 8.66; N, 3.24. Found: C, 69.82; H, 8.54; N, 2.98.

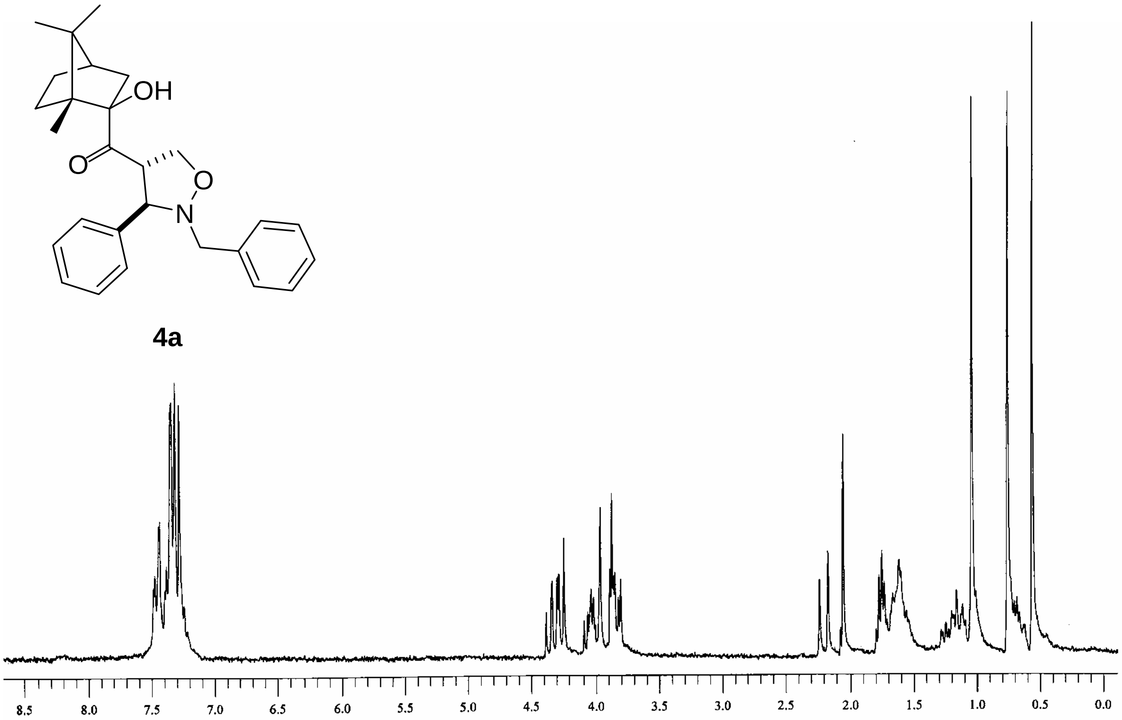
(2*S*,3*R*)-3-(Boc-Amino)-2-hydroxymethylhydrocinnamic acid (ent-16)

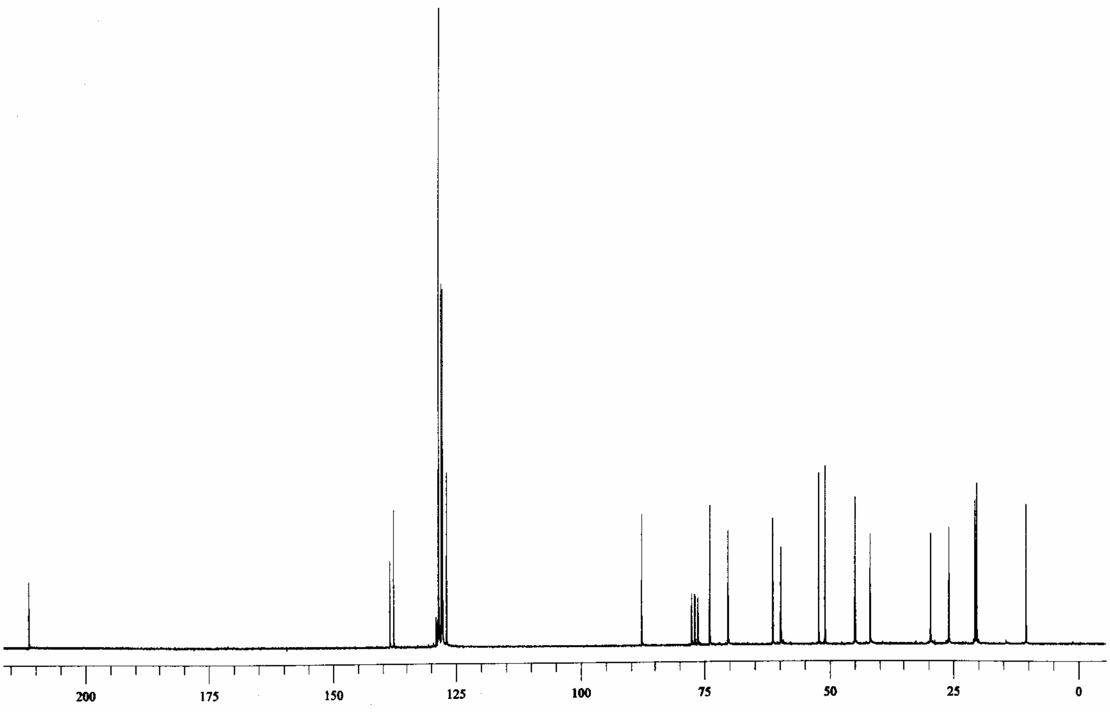


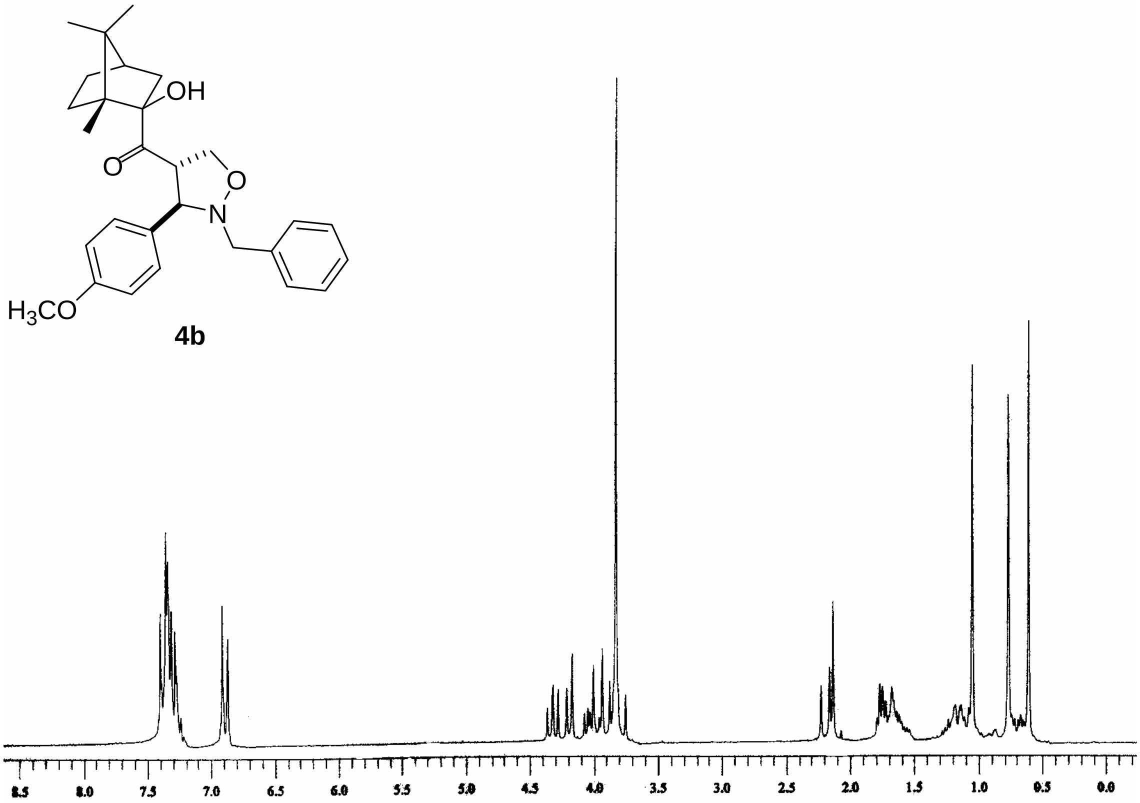
ent-16

To a solution of **22** (0,432 g, 1 mmol) in dry Et_2O (10 mL) at room temperature, under a nitrogen atmosphere, periodic acid (0.46 g**,** 2 mmol) was added in portions during 1 hour. The reaction mixture was stirred until TLC analysis indicated that the reaction was complete (10 h). The mixture was filtered through a silica gel pad and washed with Et_2O. The solvent was removed and the crude was purified by column chromatography affording the title compound (0.236 g) (80%); white solid; m.p. 120-121 ºC; $[\alpha]_D^{25}$ + 51.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}); 3350, 2979, 2870, 1689, 1508, 1393, 1369, 1251, 1163, 1143; ^1H NMR (DMSO-d_6, 90ºC) δ 7.55-7.17 (m, 5H, arom.), 6.98 (d, 1H, NH, J= 8.5 Hz), 4.79 (t, 1H, C*H*NH, J= 9.1 Hz), 3.71 (d, 2H, C*H*$_2$OH, J= 6.1 Hz), 2.90 (dt, 1H, C*H*COOH, J= 6.1 Hz, J'= 9.1 Hz), 1.99 (s, 1H, OH), 1.36 (s, 9H, Boc); ^{13}C NMR (DMSO-d_6, 90ºC) δ 173.6, 154.9, 141.8, 128.1, 127.4, 127.1, 78.2, 61.0, 60.0, 54.1, 53.9, 28.4, 14.4; Anal. Calcd for $C_{15}H_{21}NO_5$ (295.36) C, 70.00; H, 7.18; N, 4.74. Found: C, 70.16; H, 7.03; N, 4.69.

N) ^{1}H and ^{13}C NMR data of selected compounds



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4b

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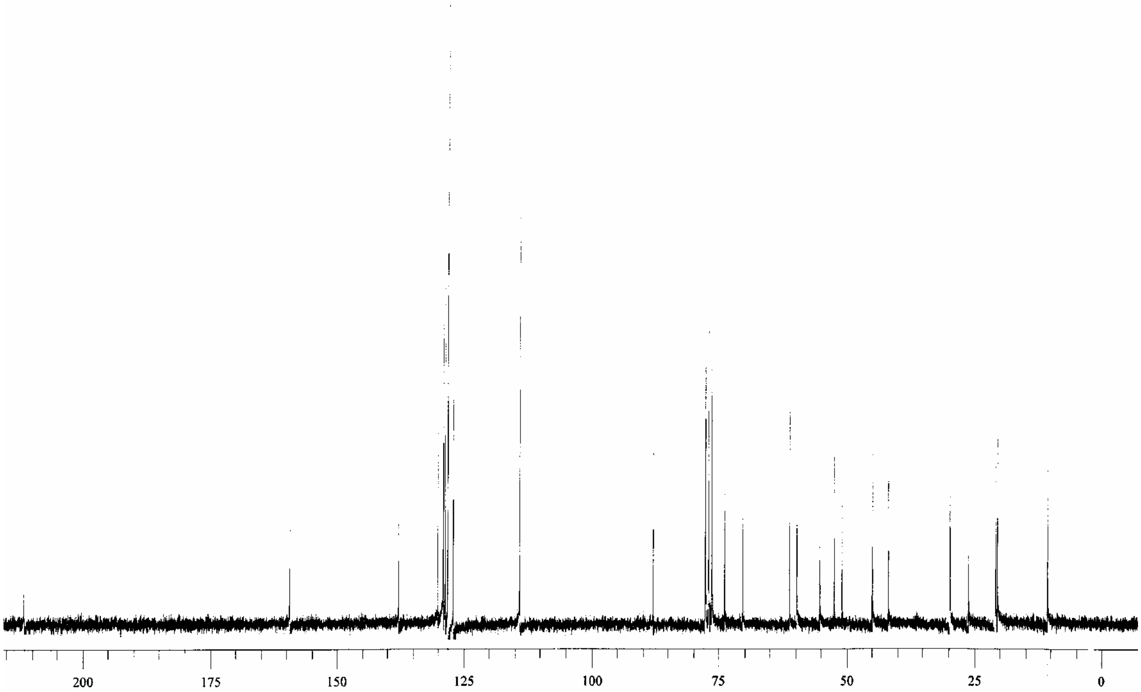
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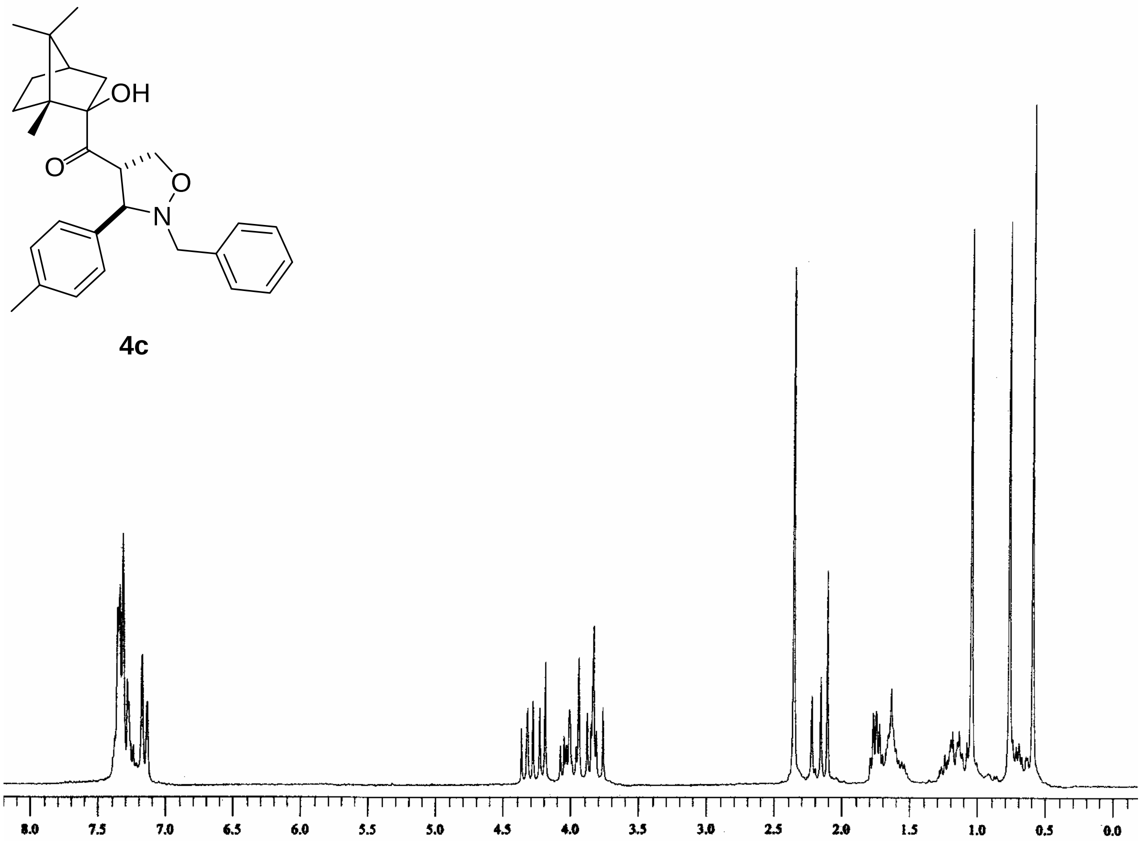
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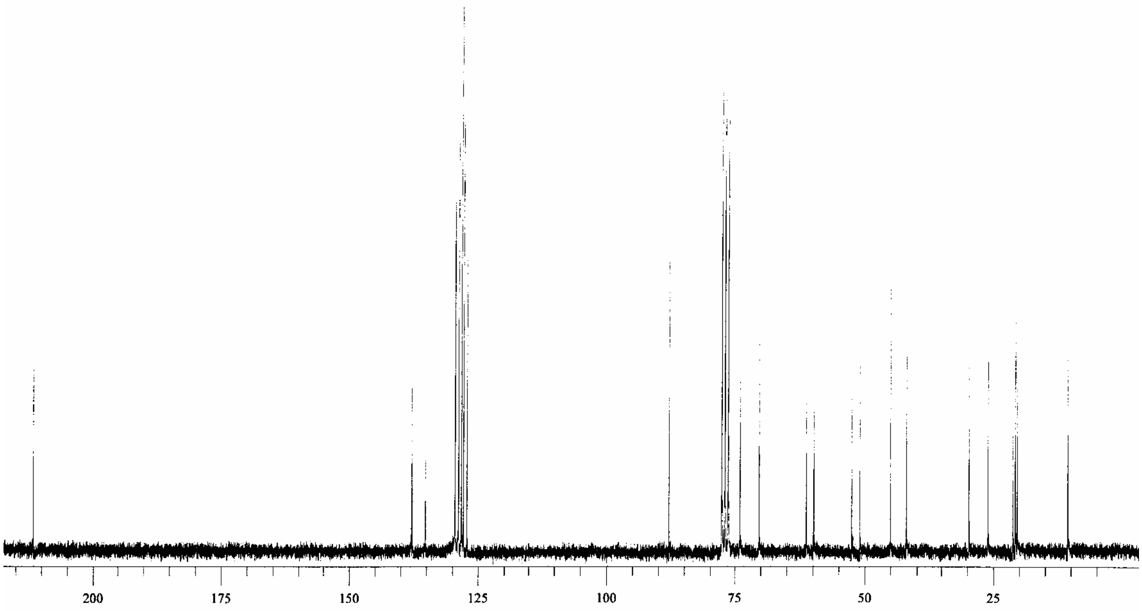
4c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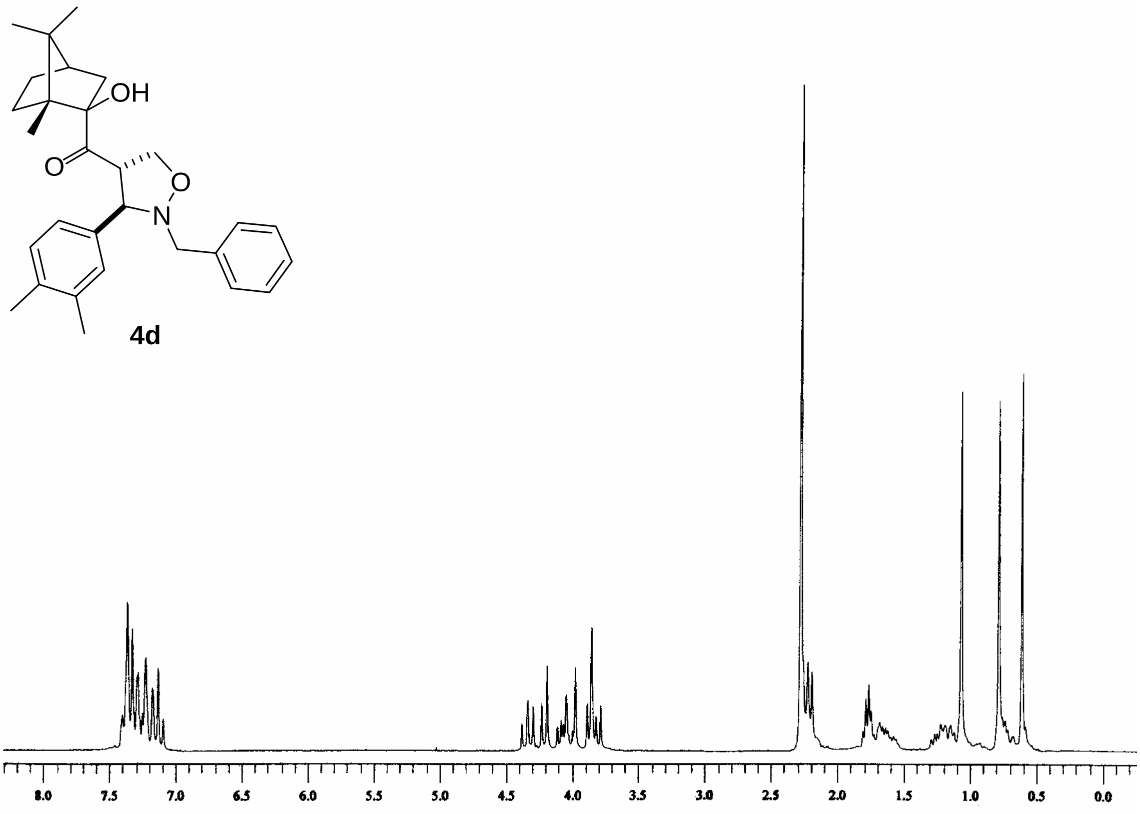

4d

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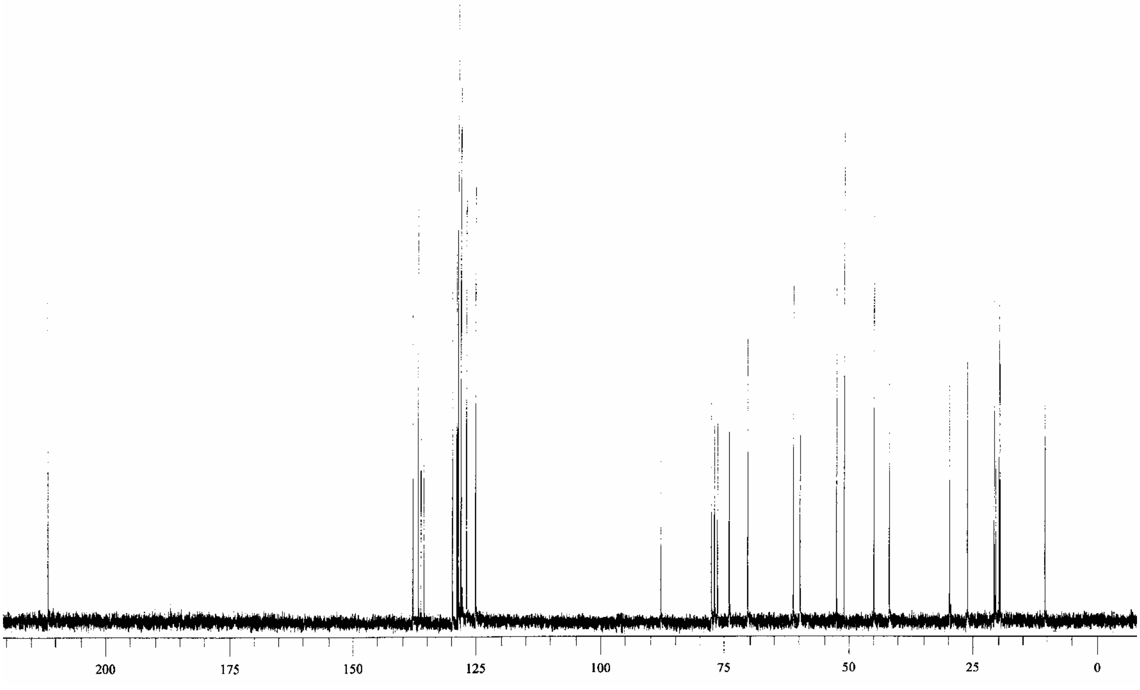

200
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150
125
100
75
50
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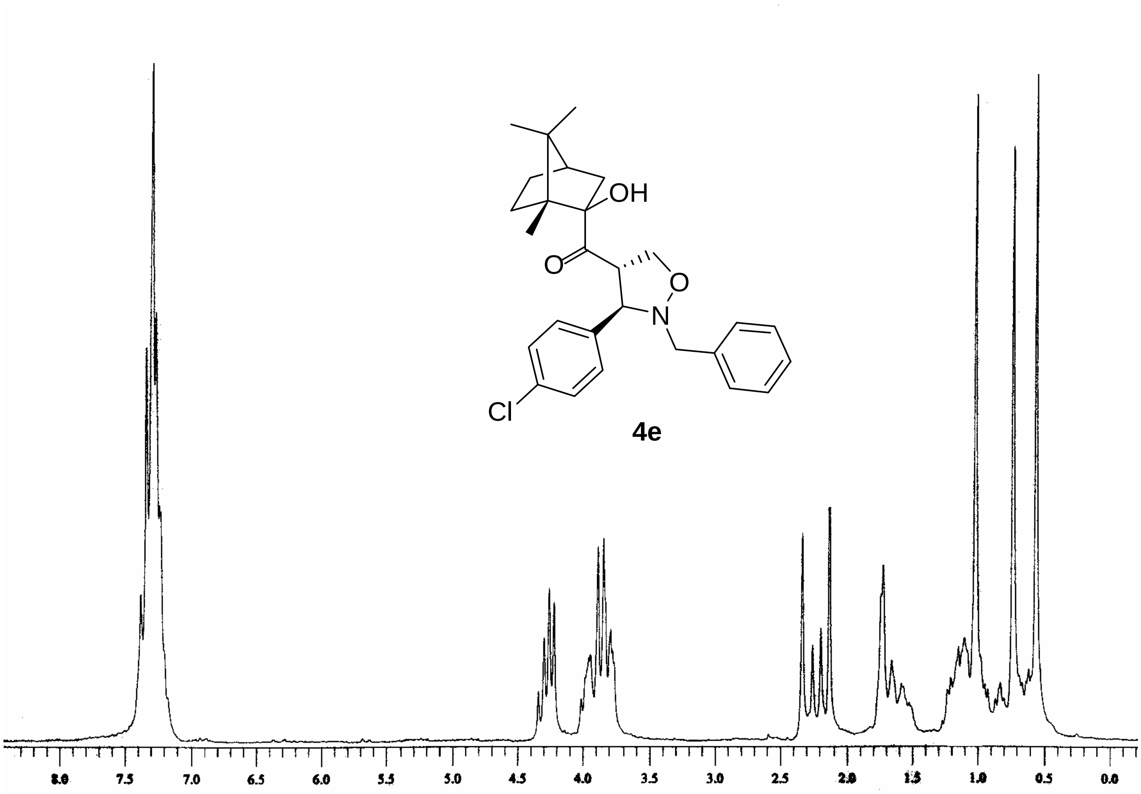
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O
N
Cl
4e
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6.5
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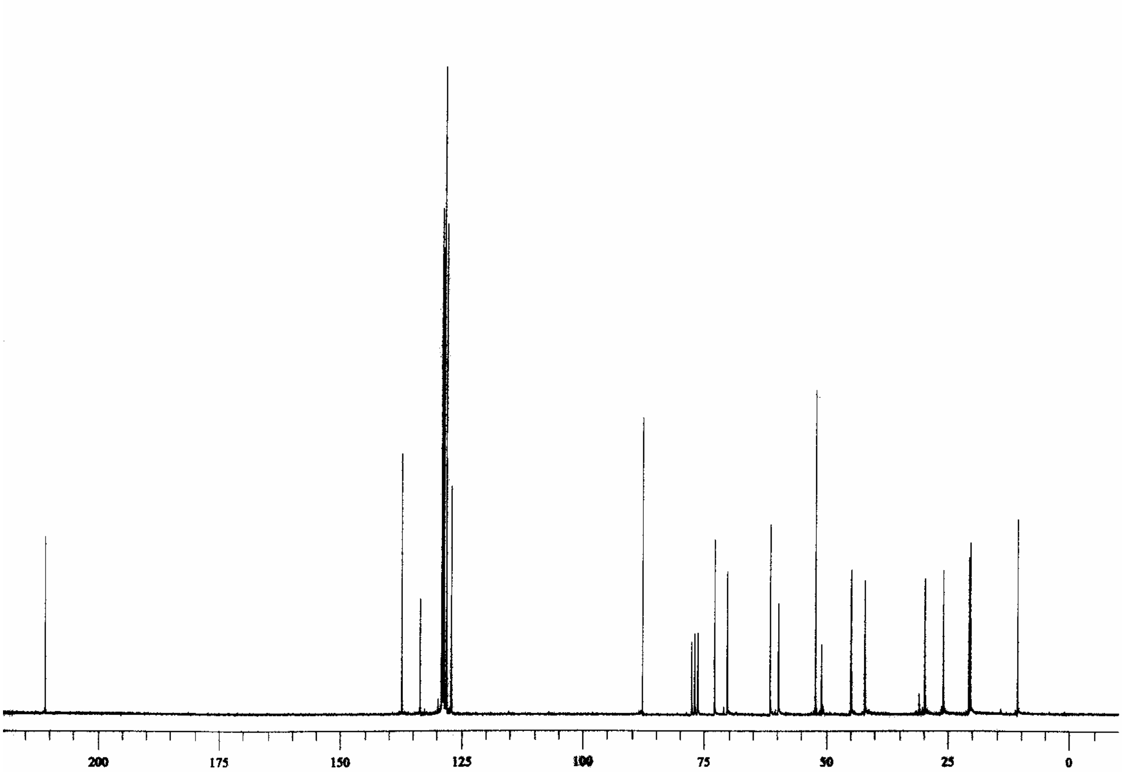
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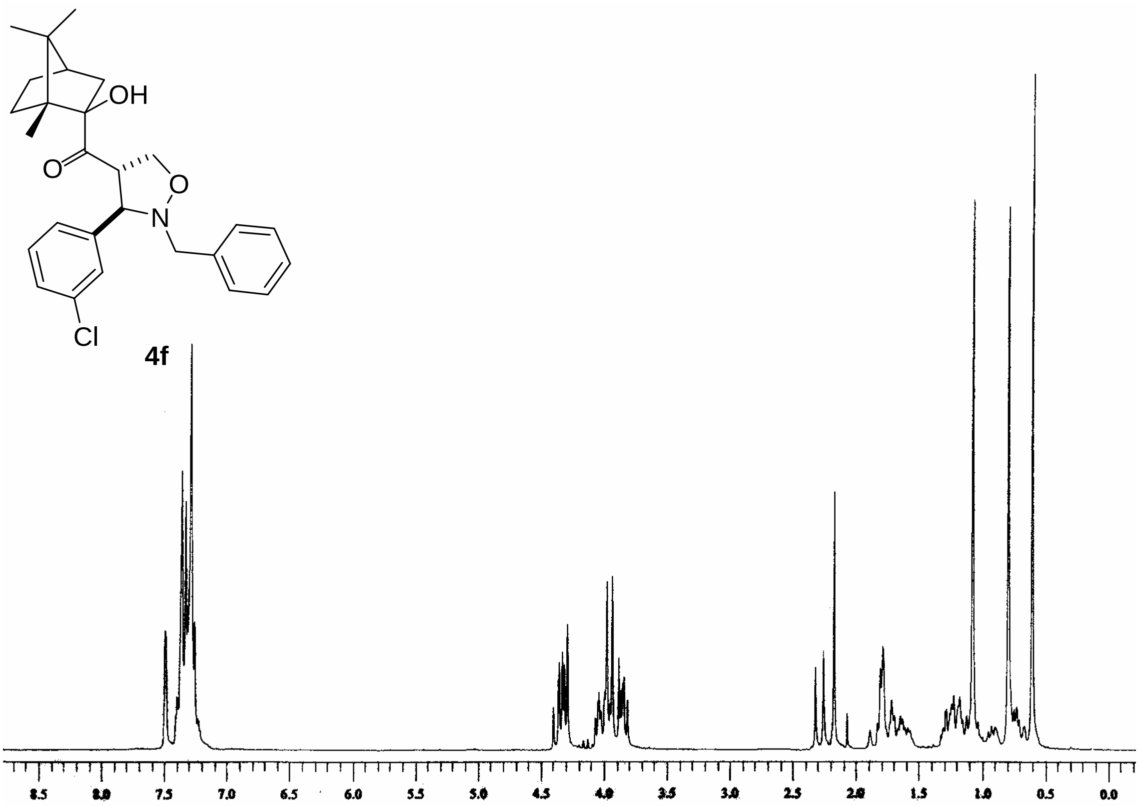
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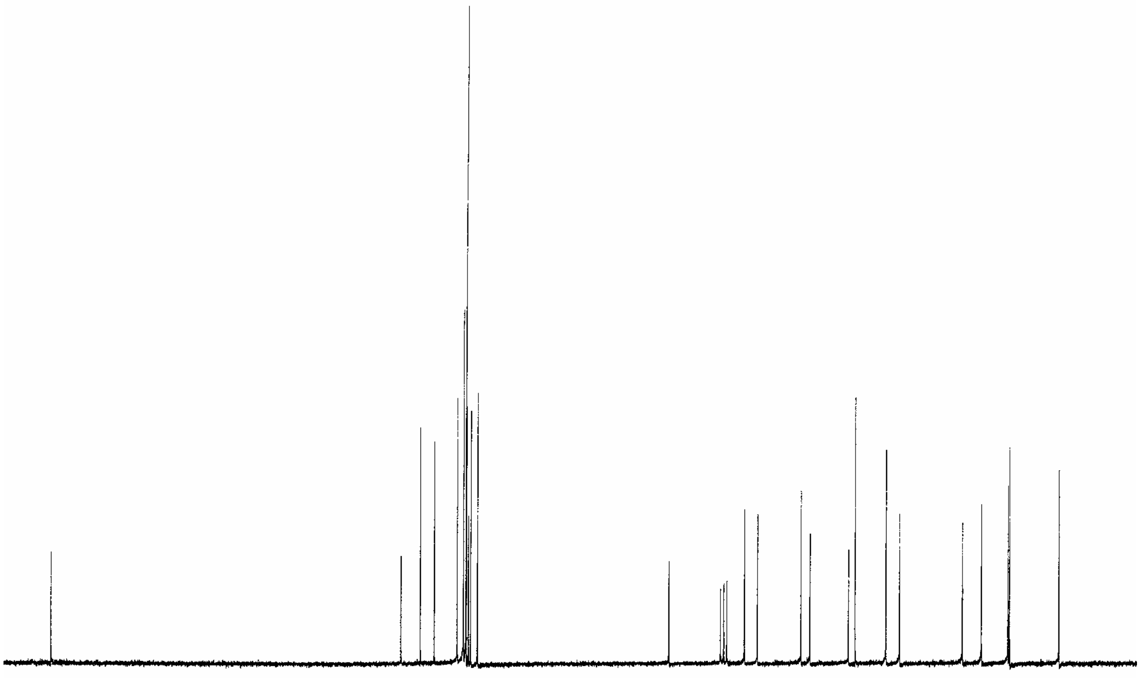
4f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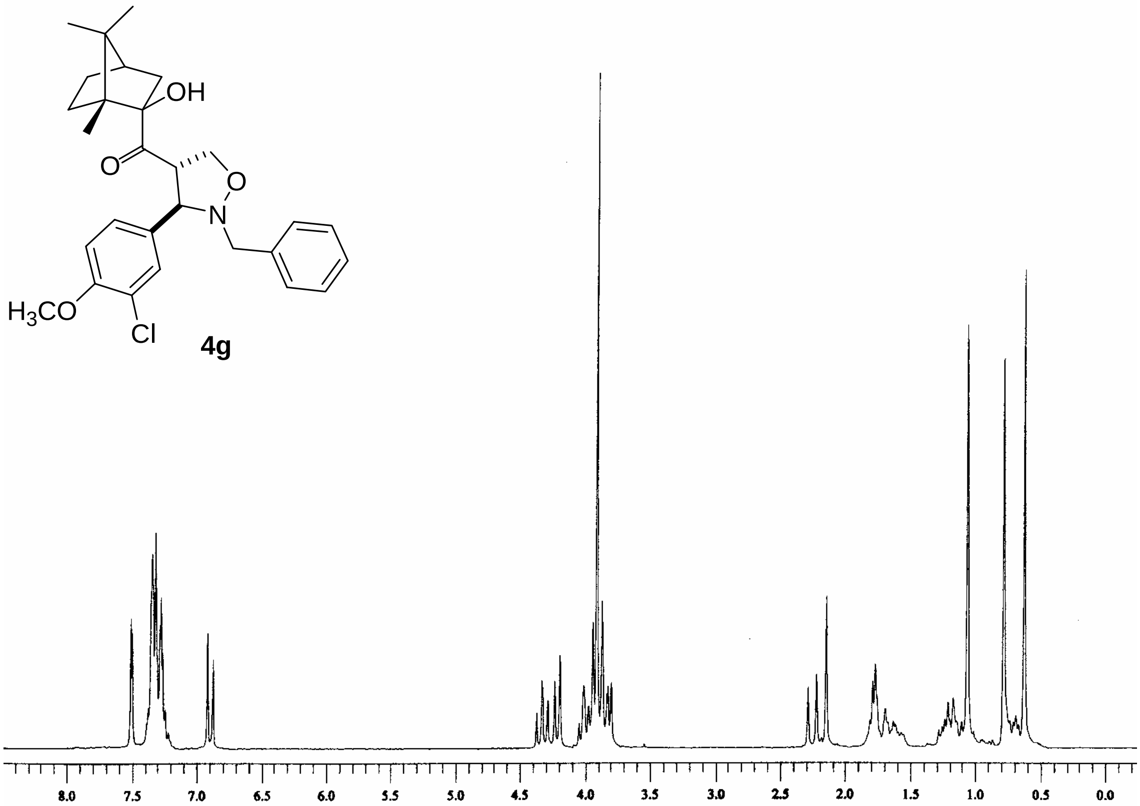
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O
N
H3CO
Cl

4g

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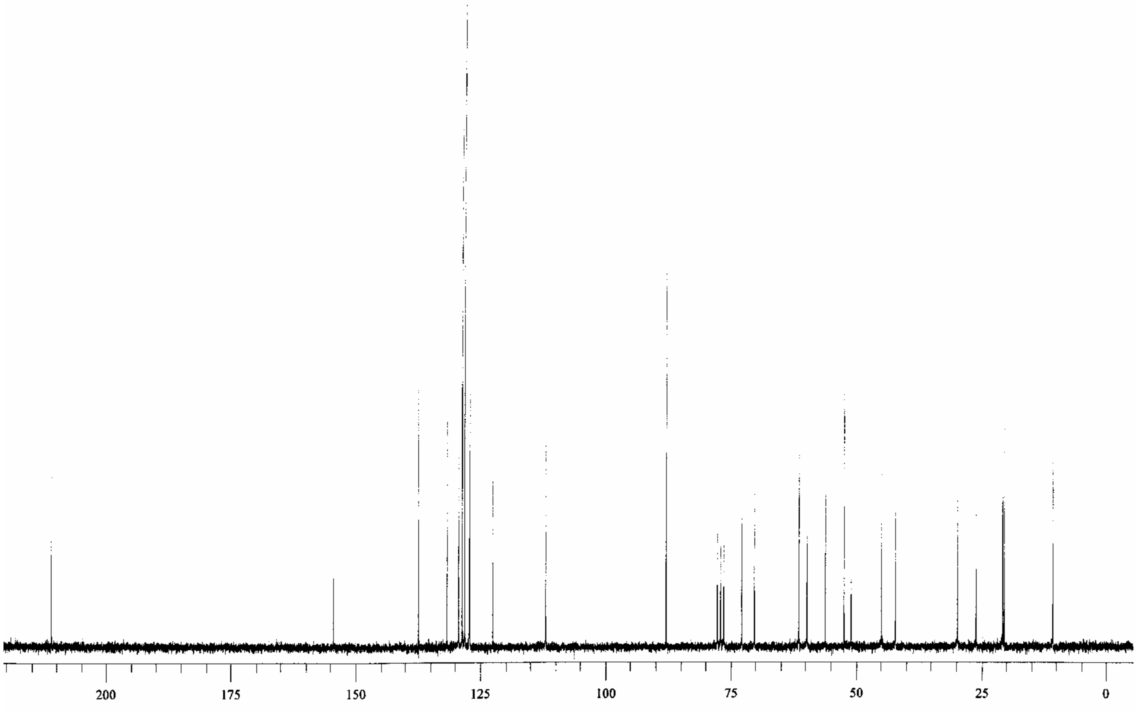
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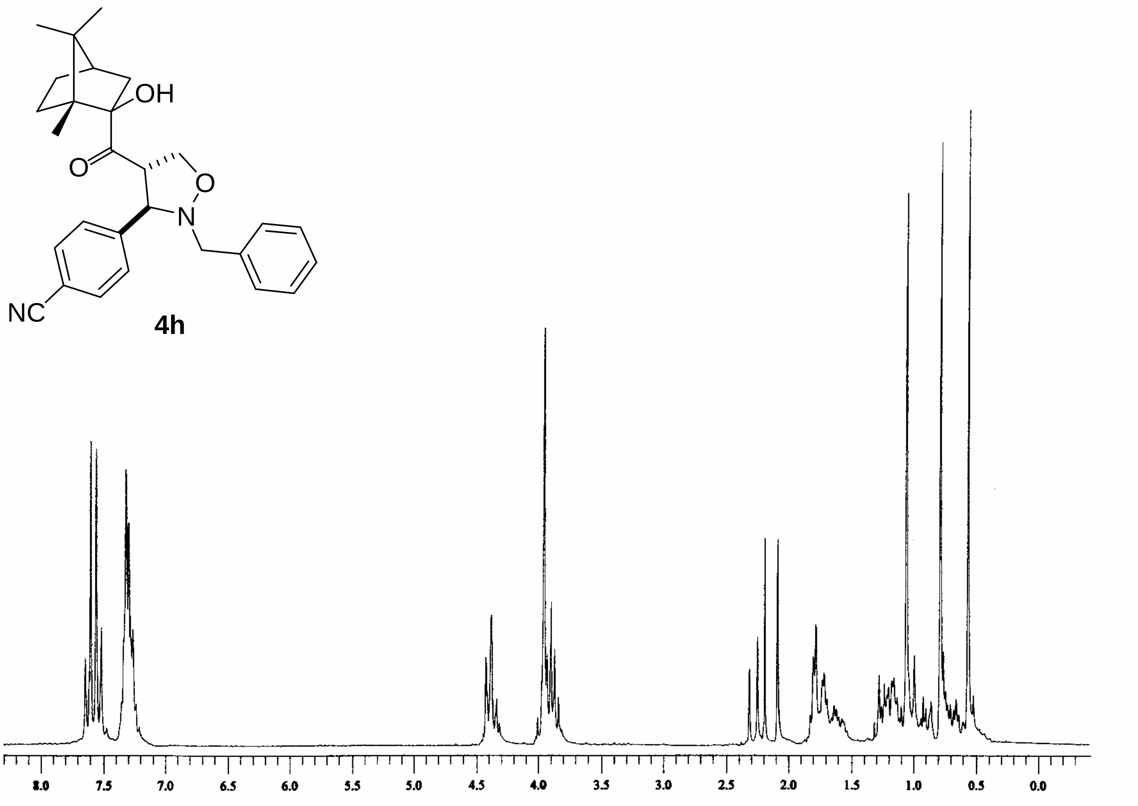
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O
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NC
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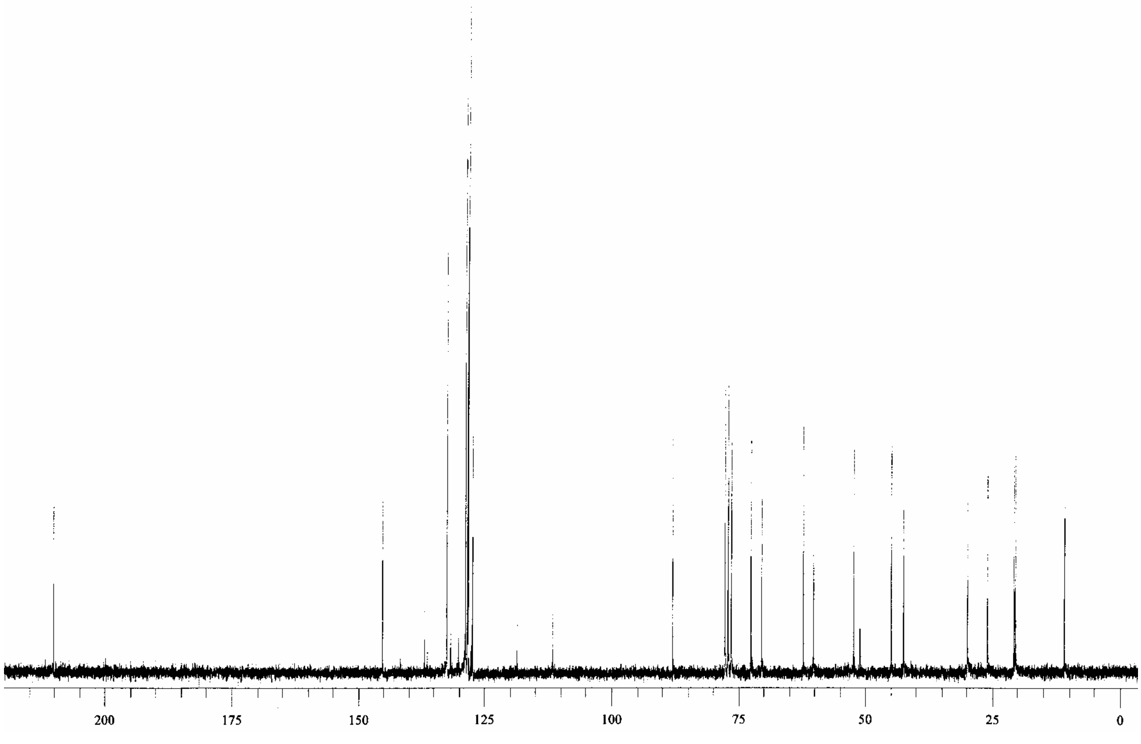
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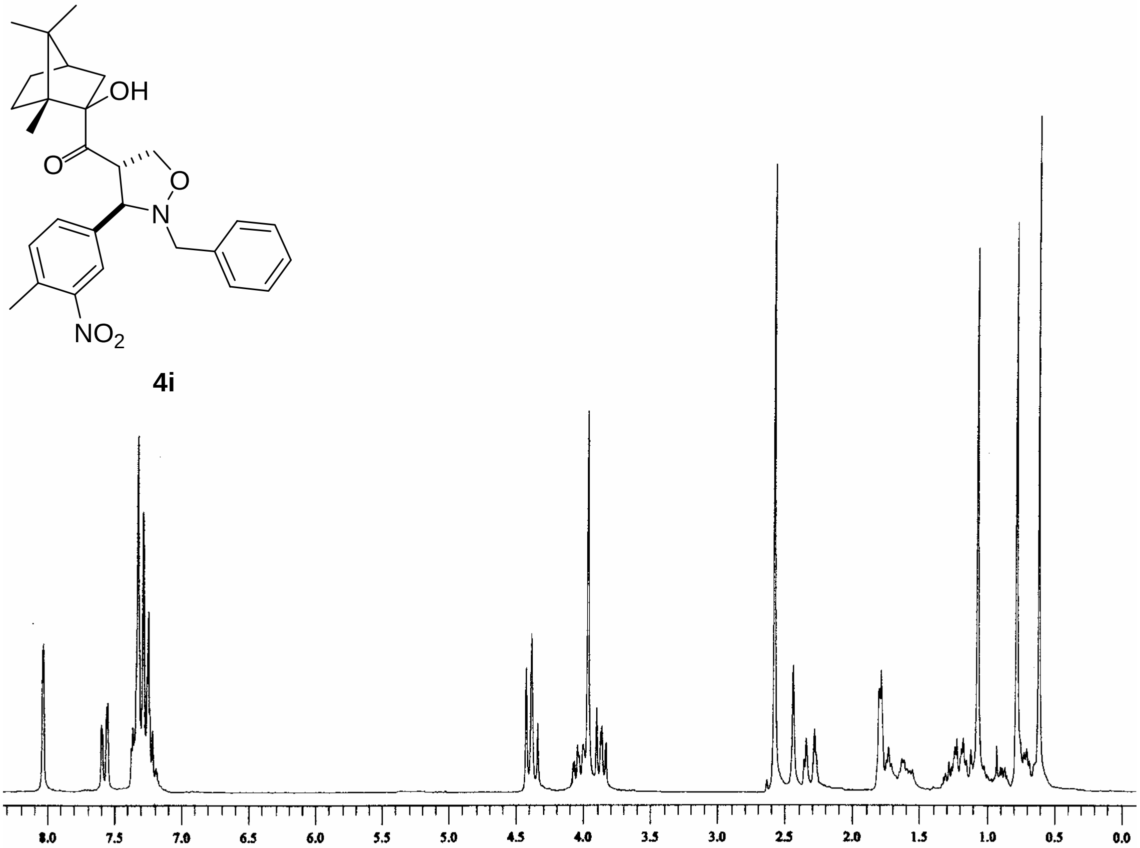
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N
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6.0
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1.5
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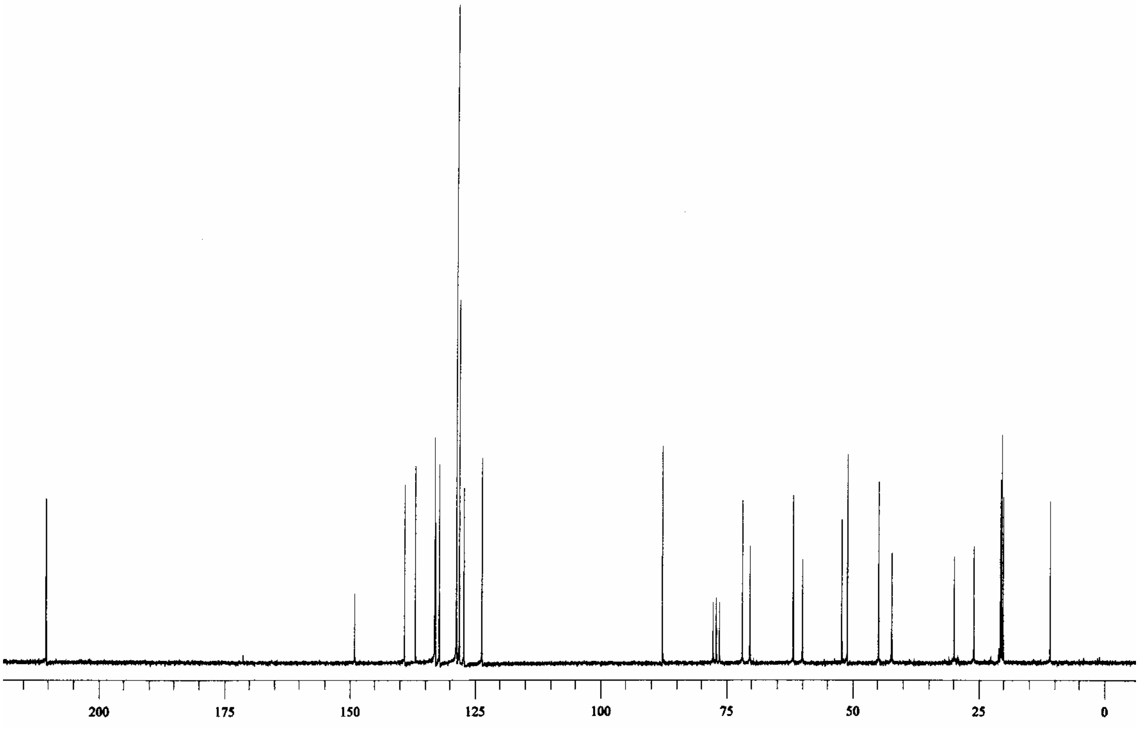
0.0

4i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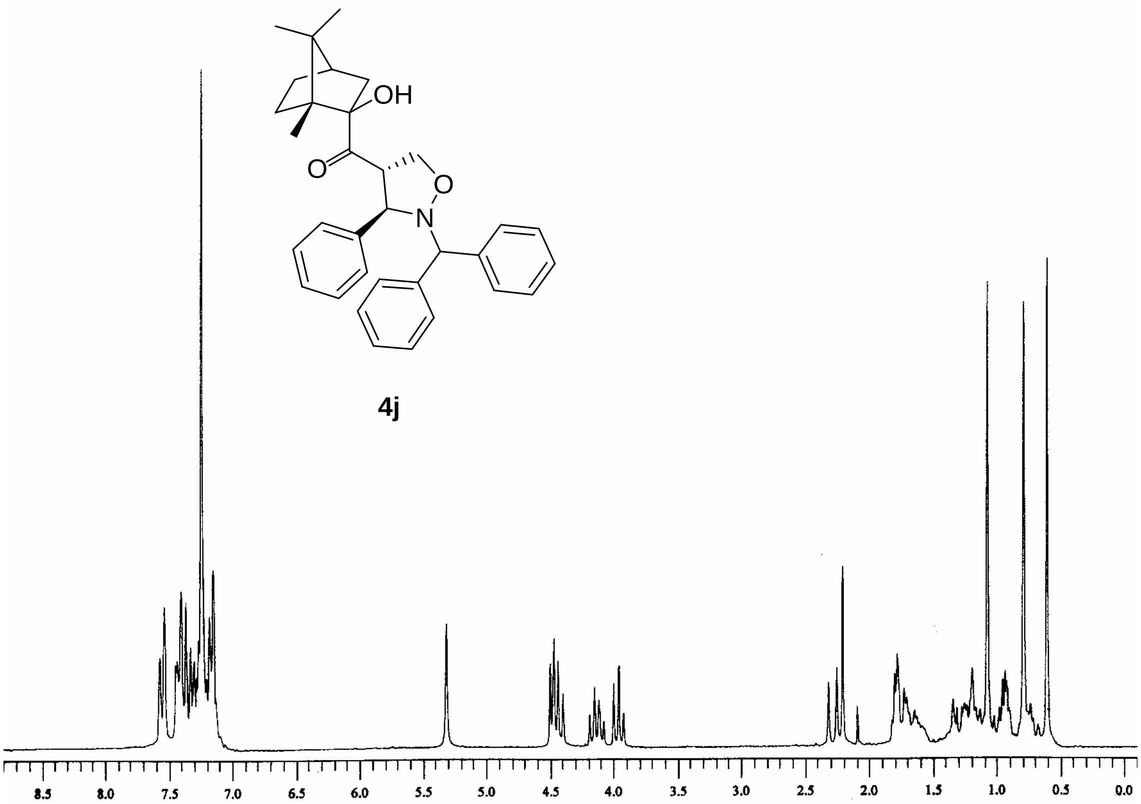

OH
O
O
N
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6.0
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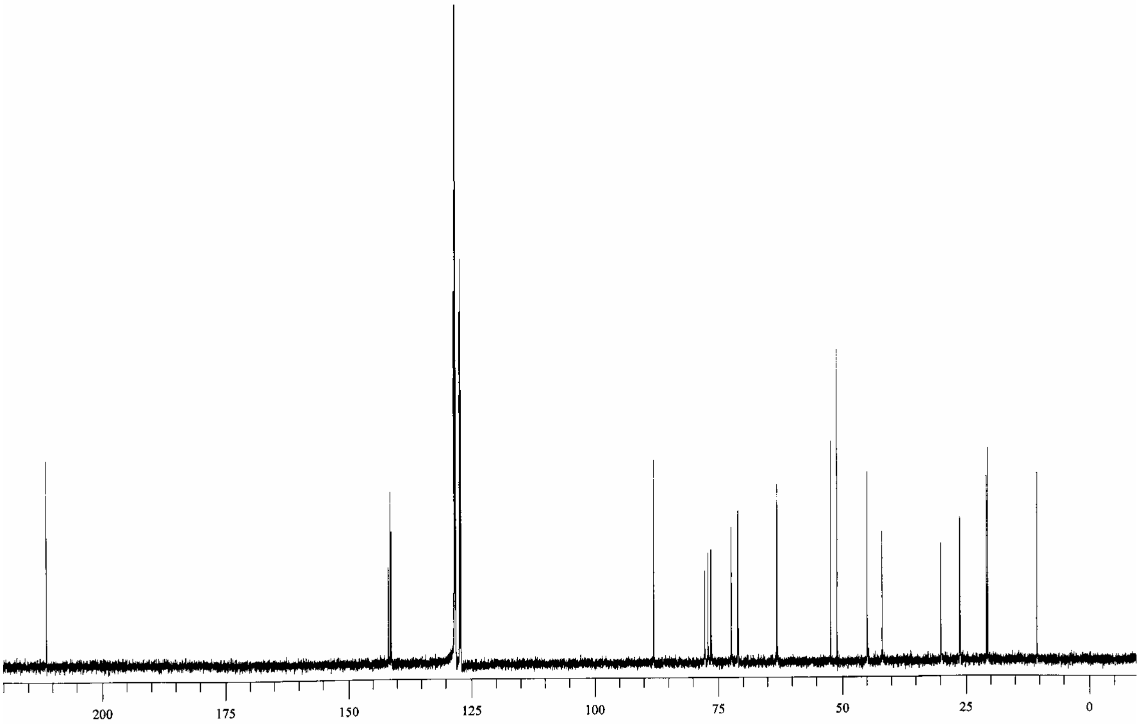
0.0

4j



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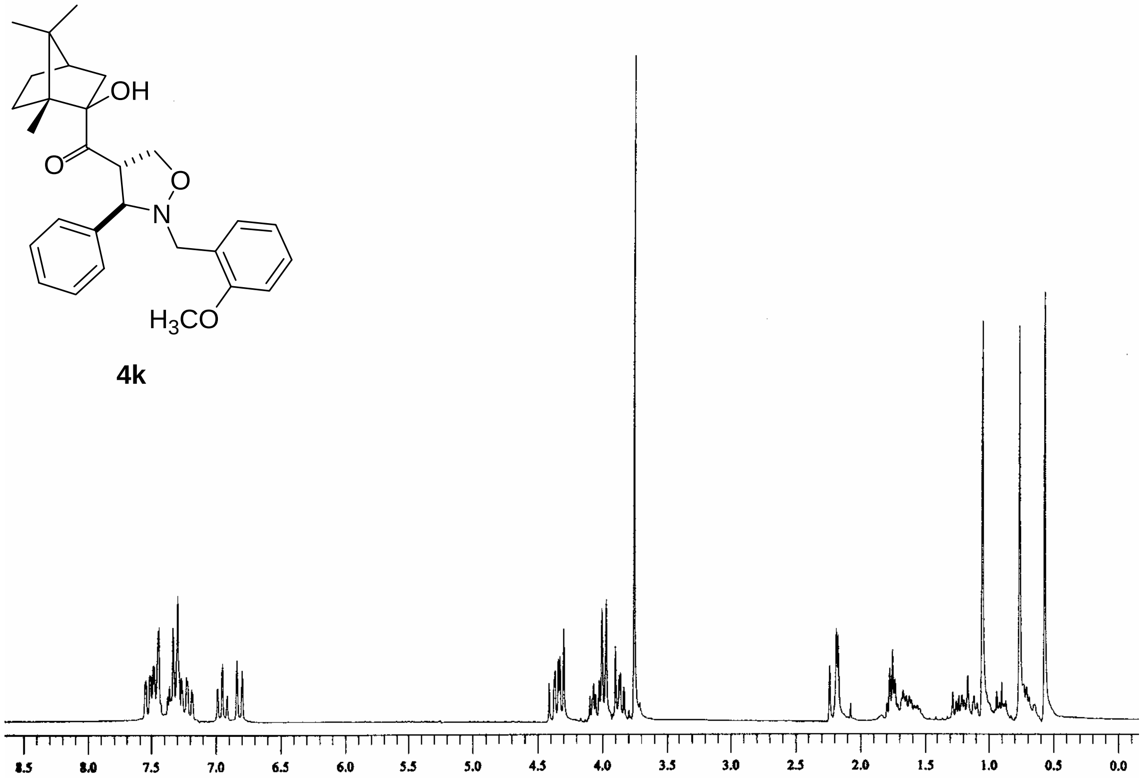
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N
H3CO
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6.5
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5.5
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4.0
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3.0
2.5
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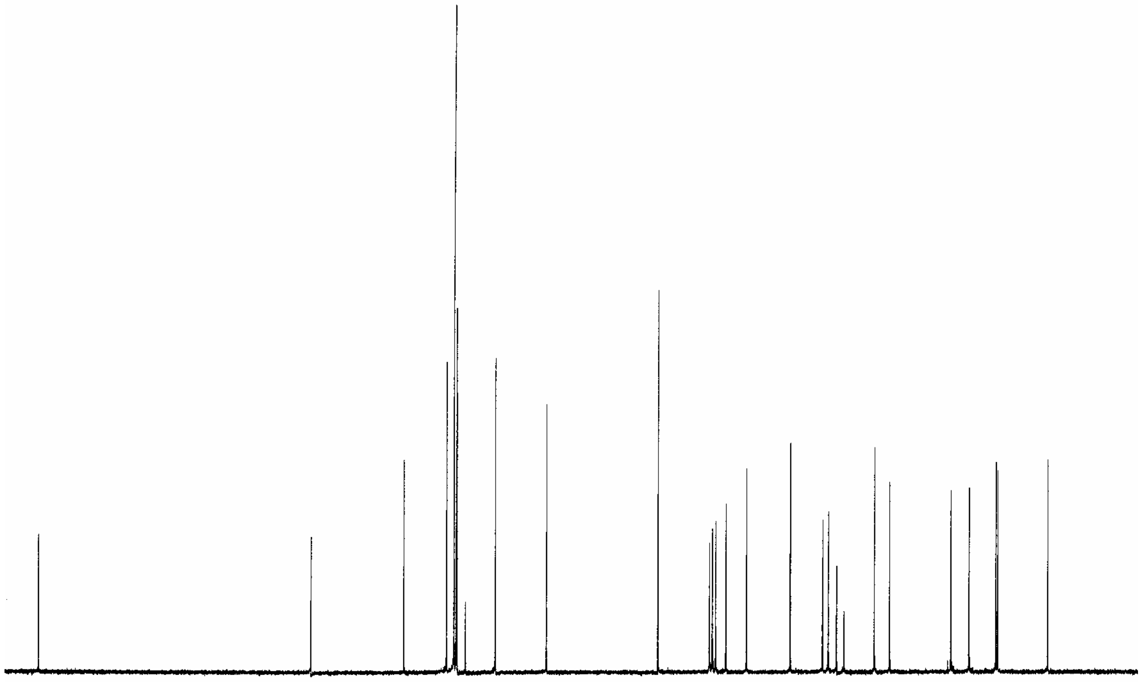
1.5
1.0
0.5
0.0

4k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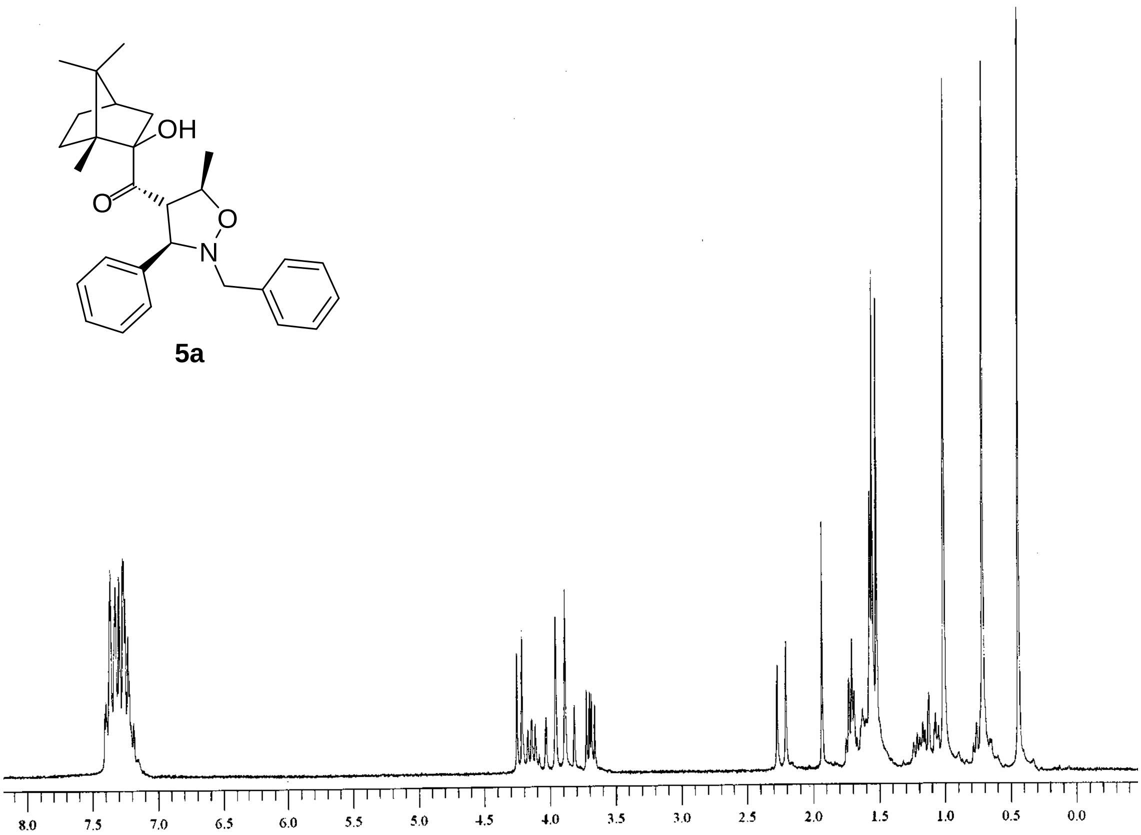
5a

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O
N
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6.5
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3.0
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2.0
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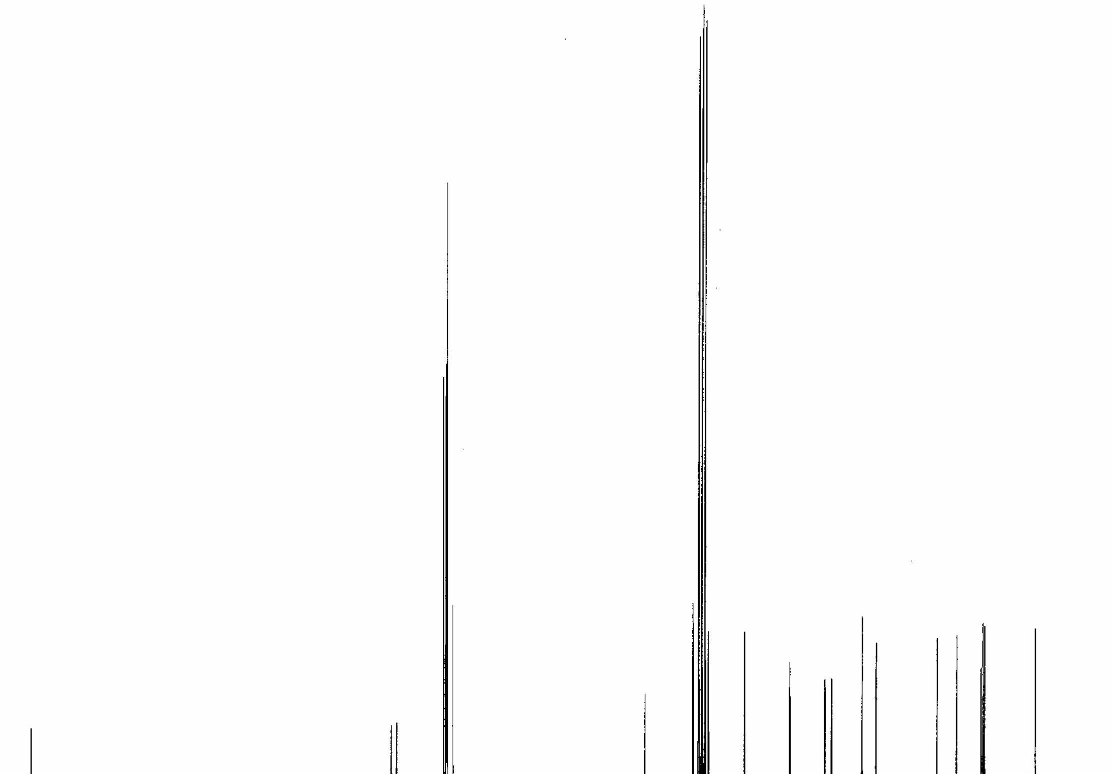
0.0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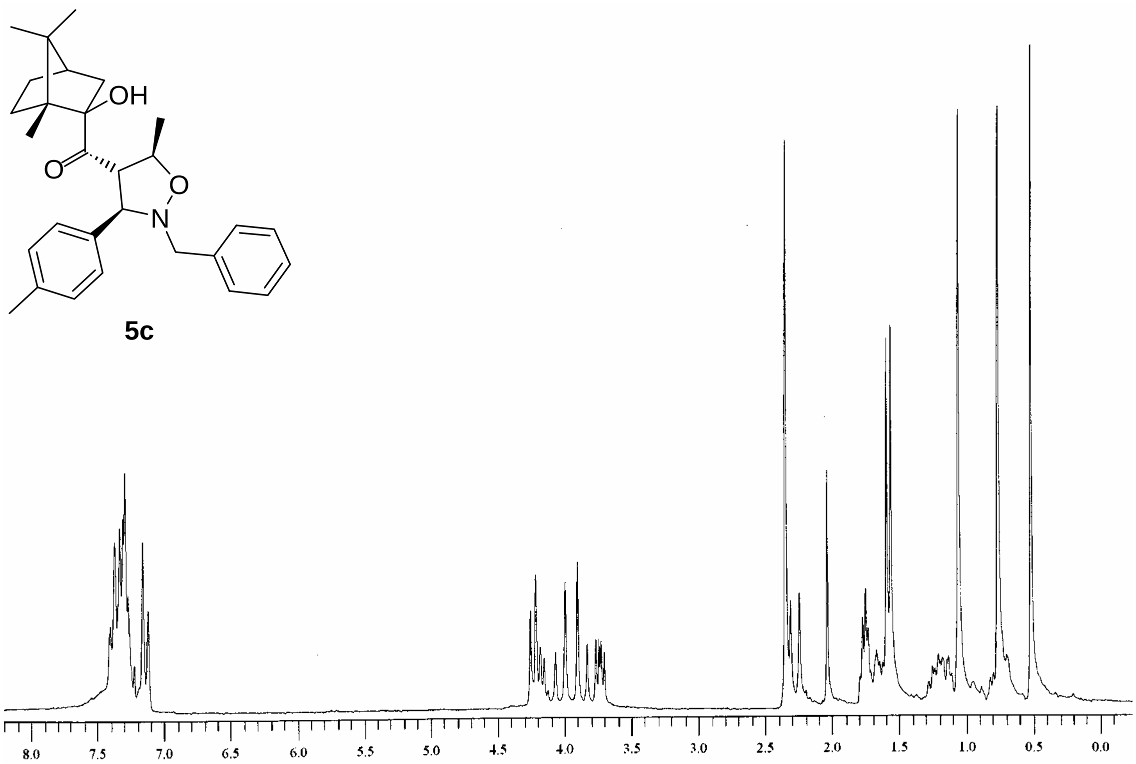
5c

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O
O
N
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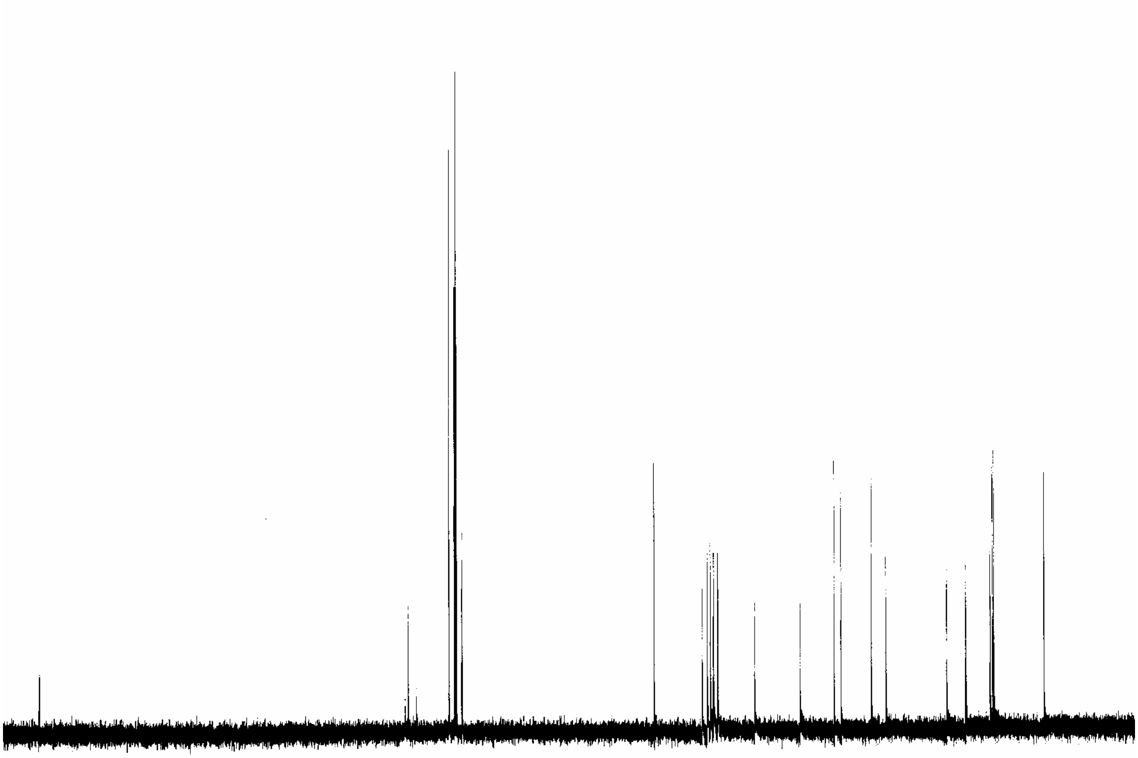
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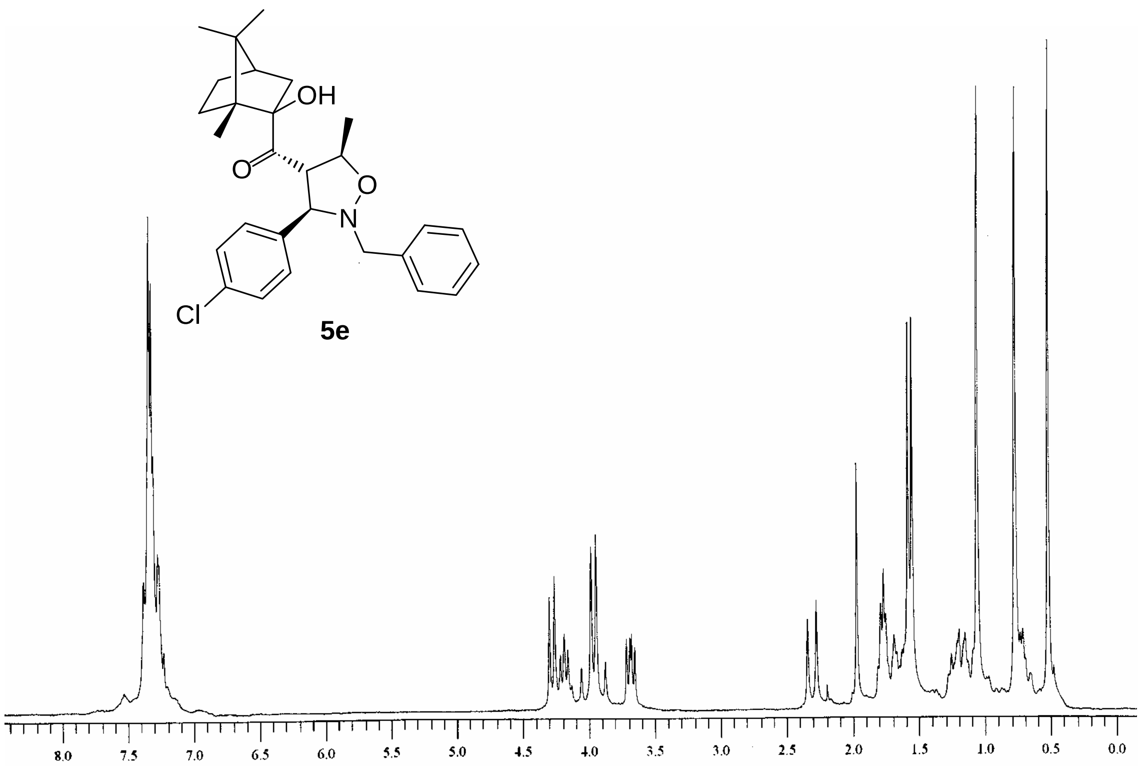
5e

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O
O
N
Cl
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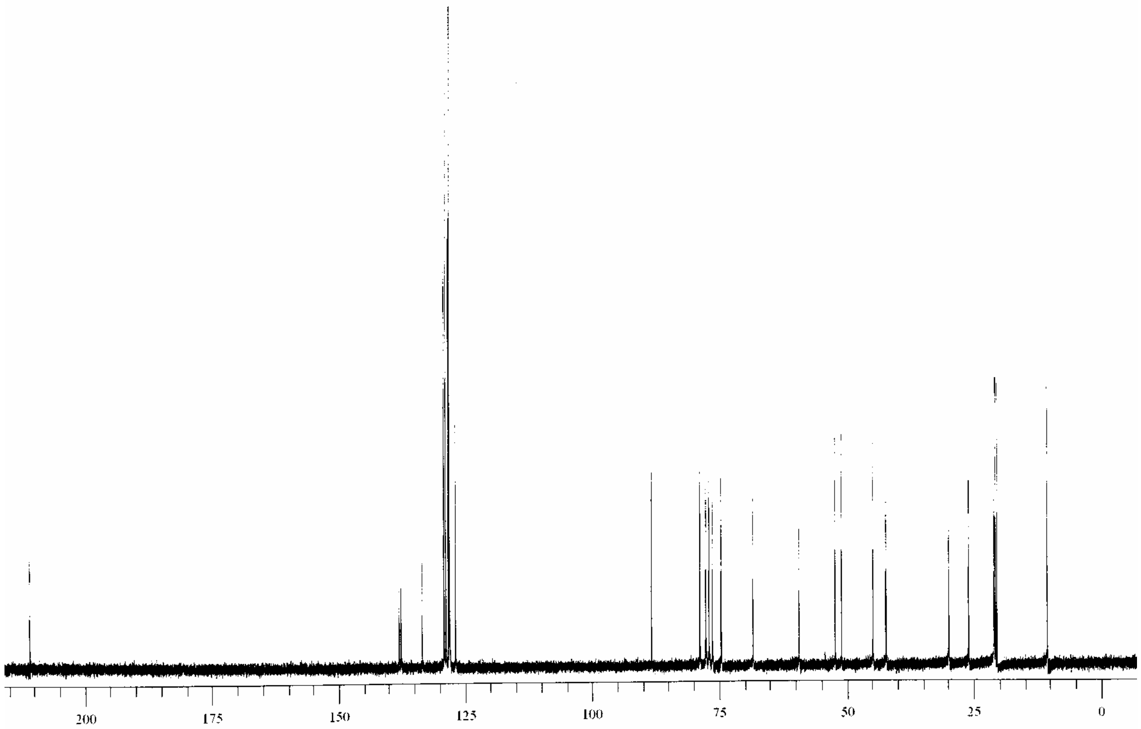
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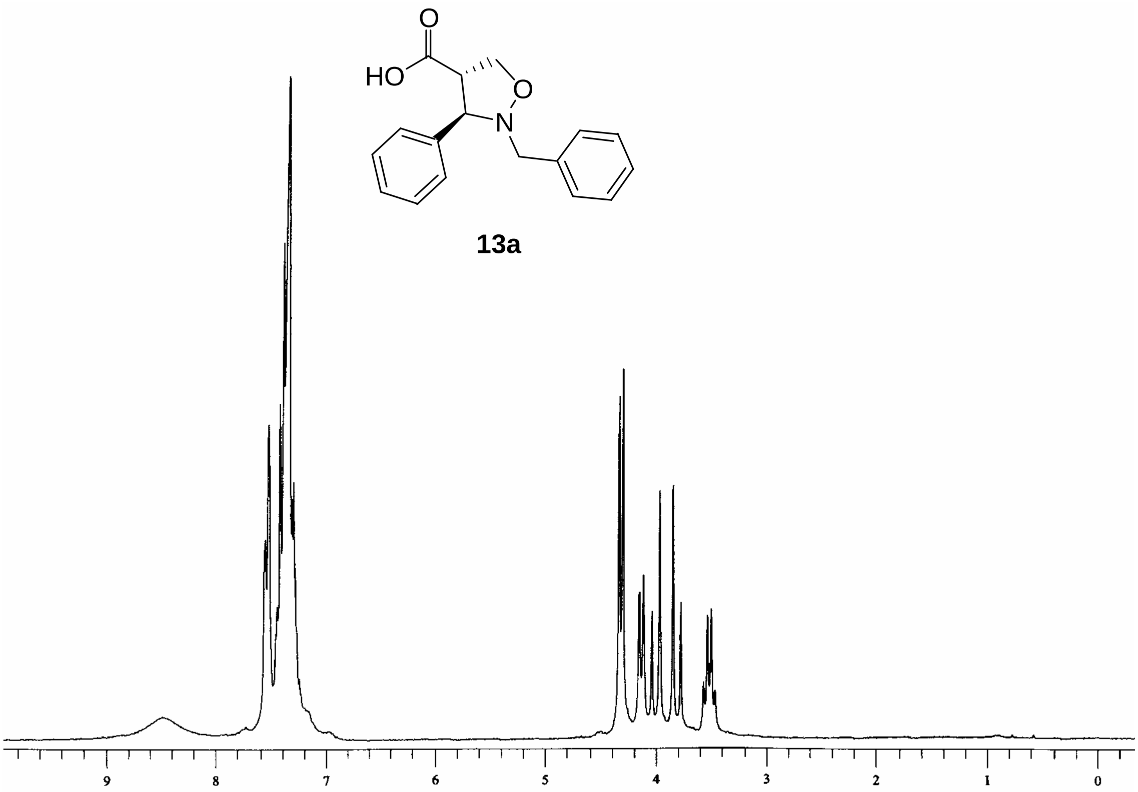
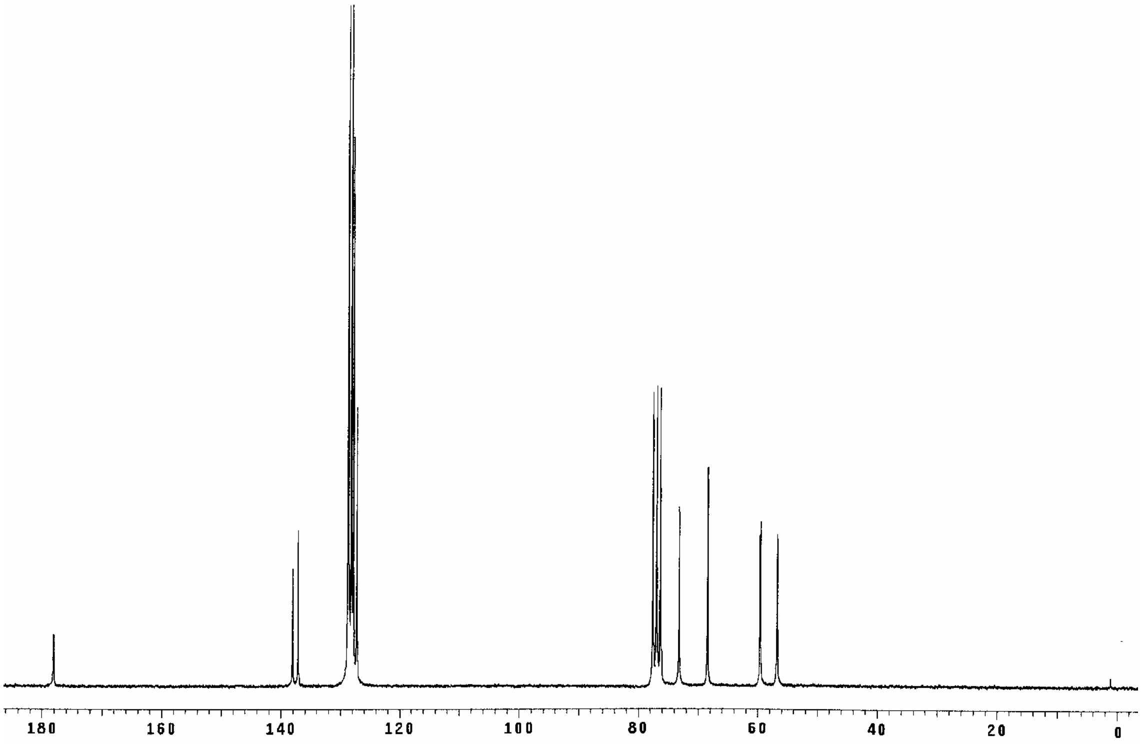
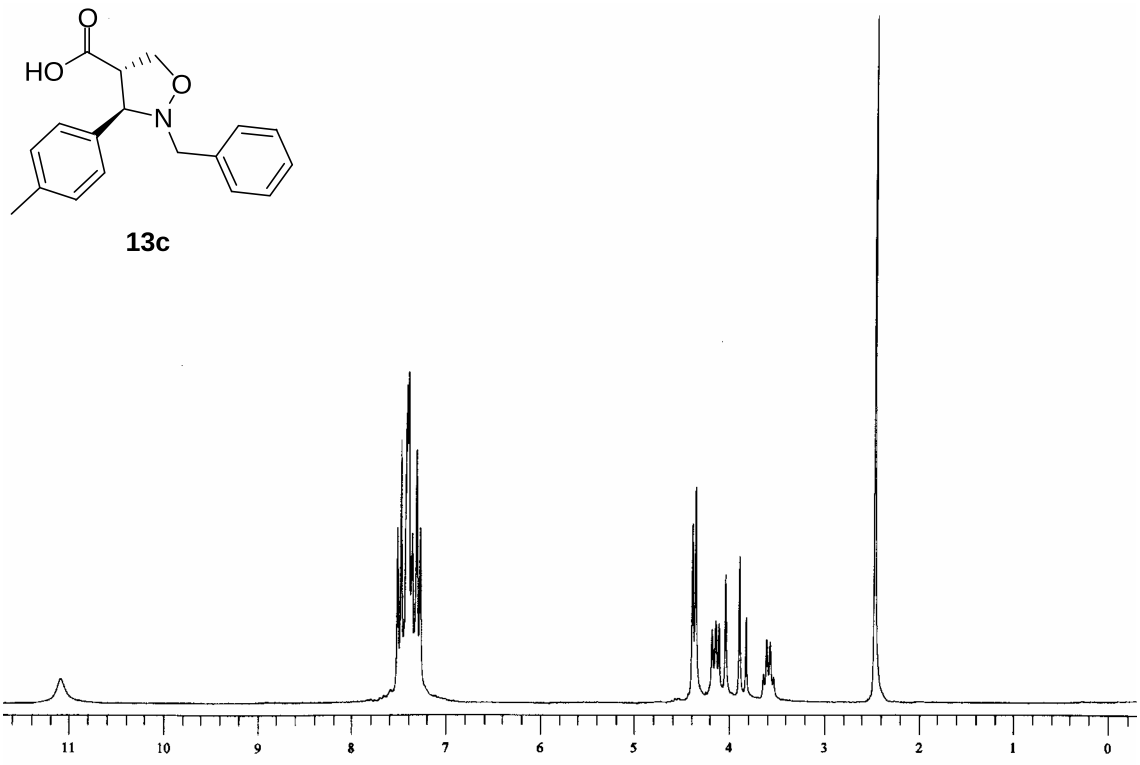


13a





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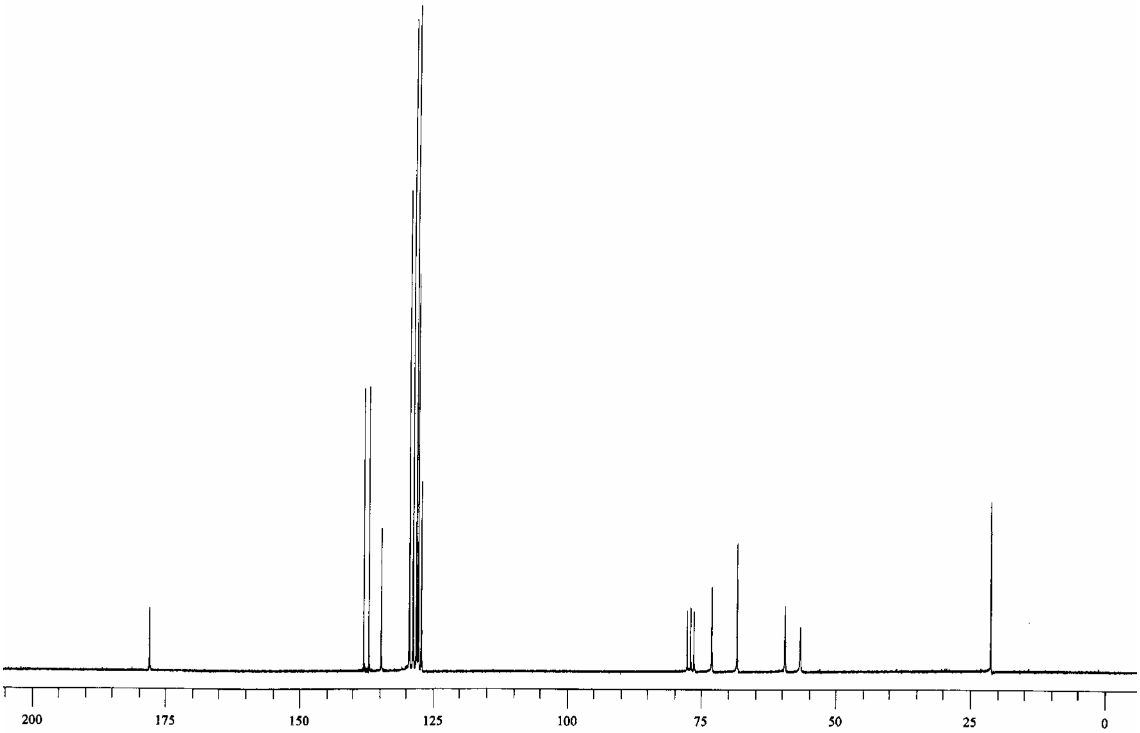

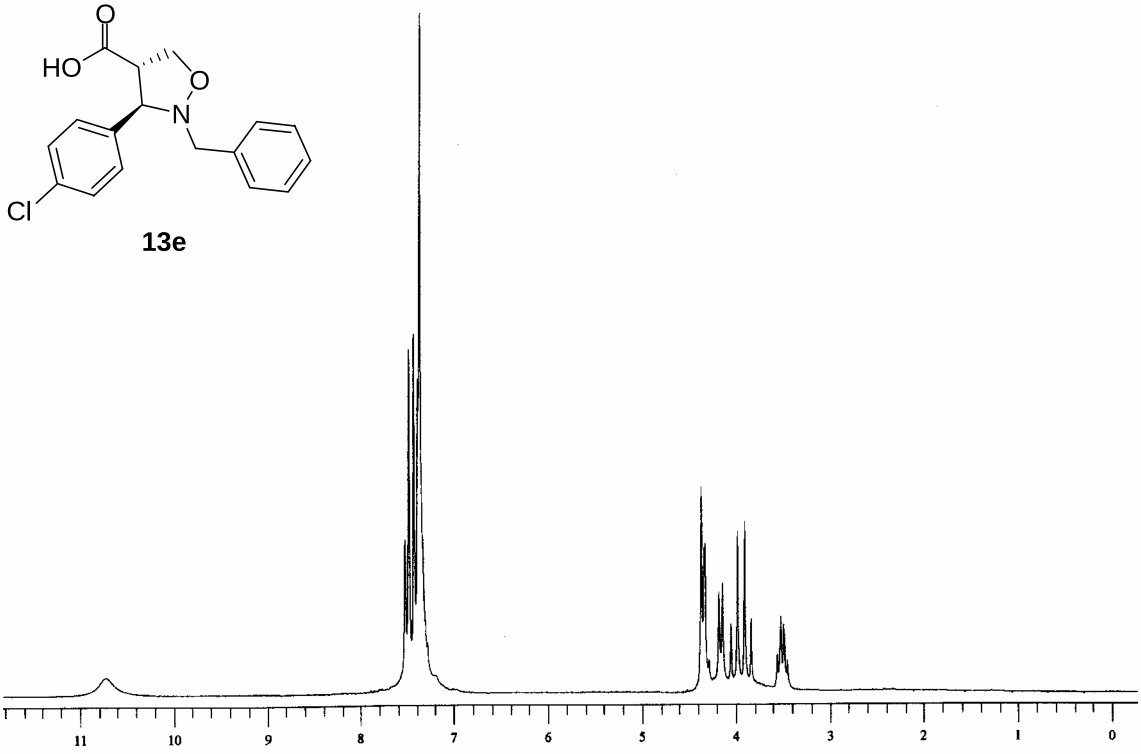

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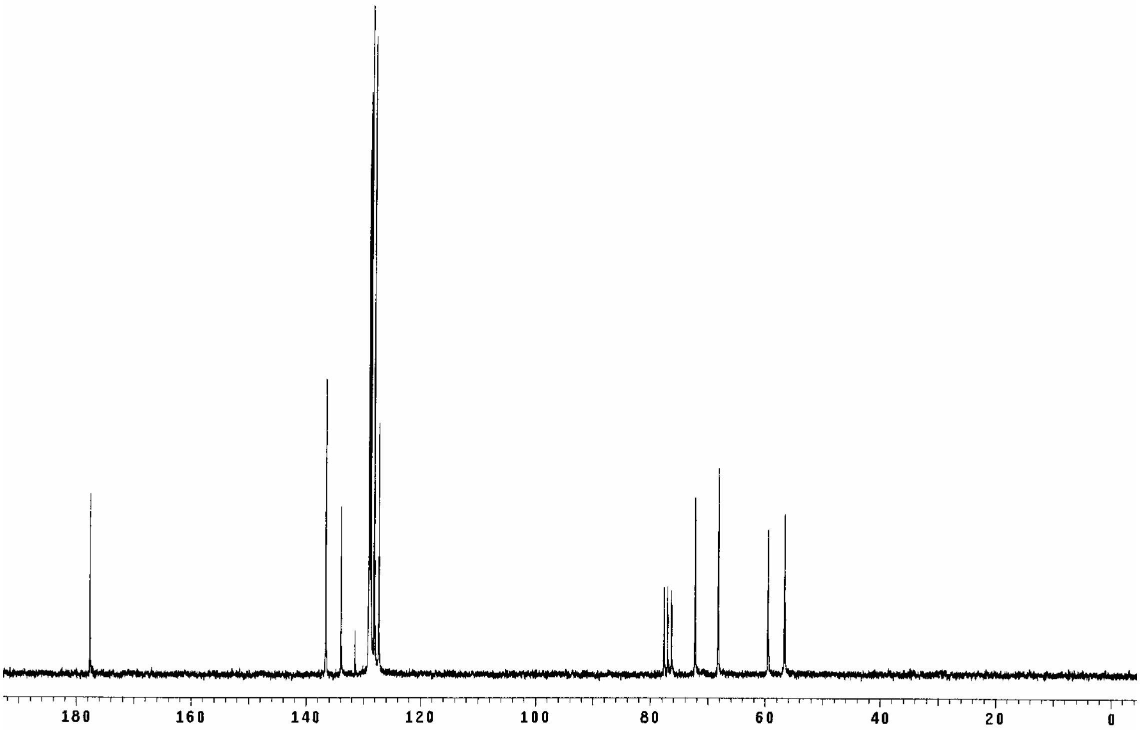
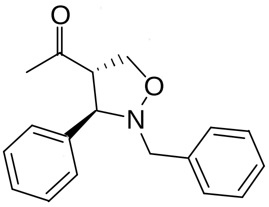
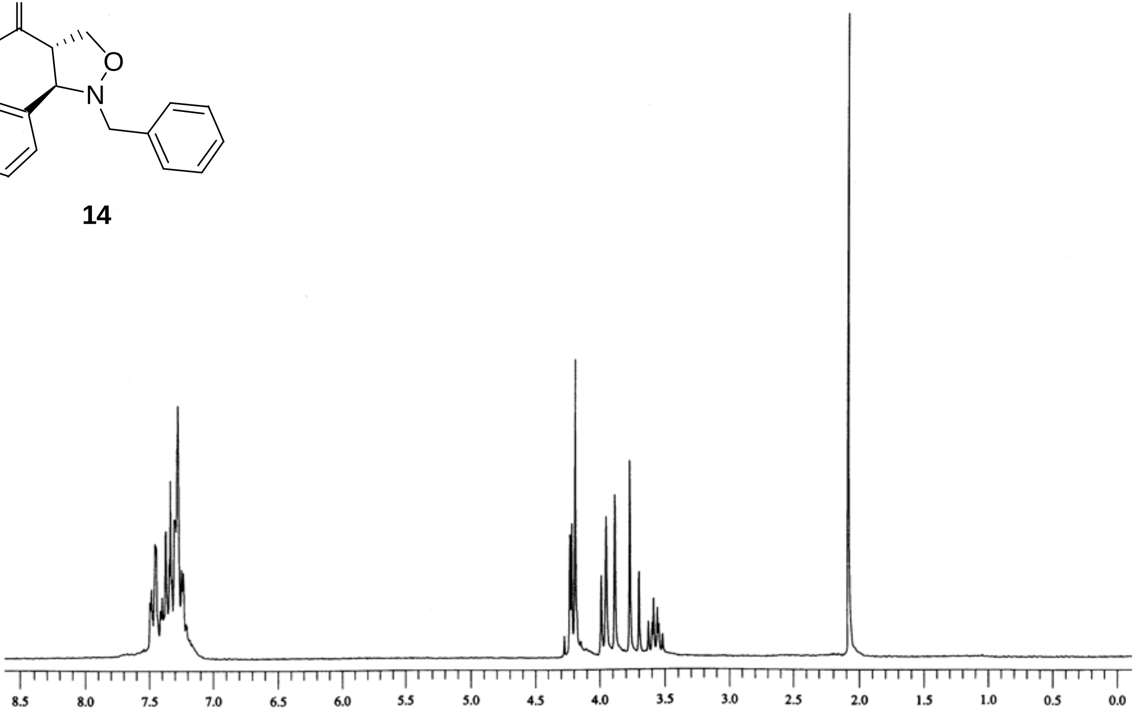



O
O
N

14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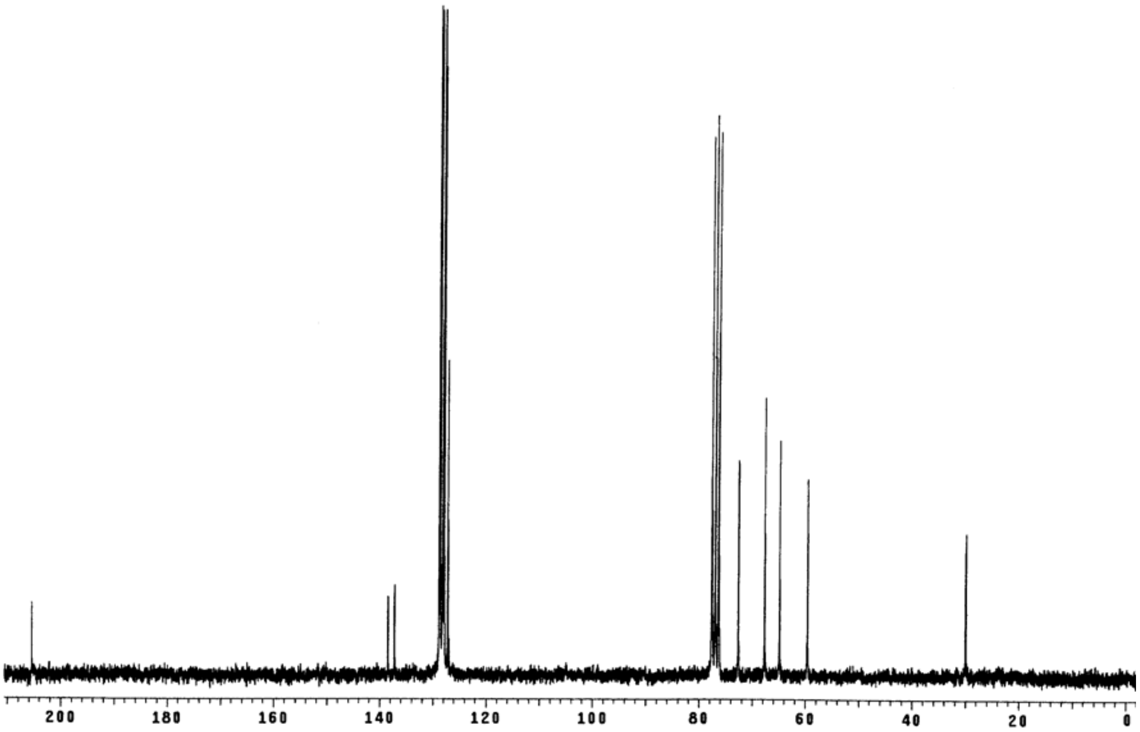
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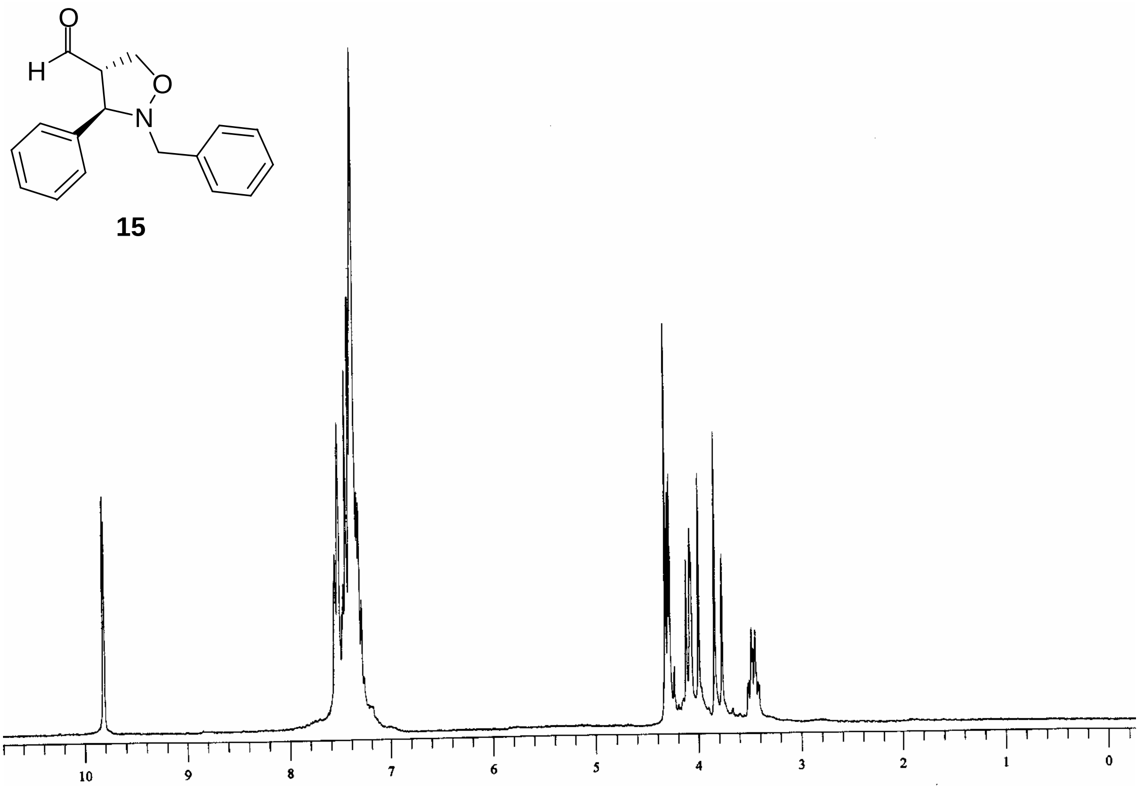
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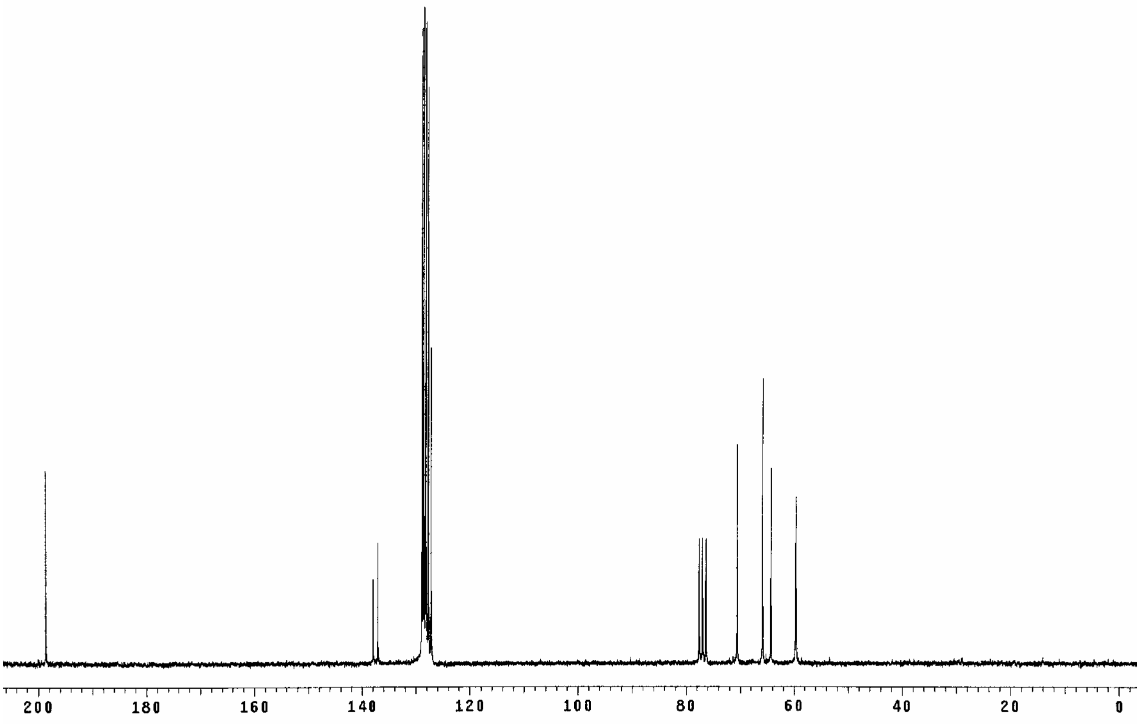

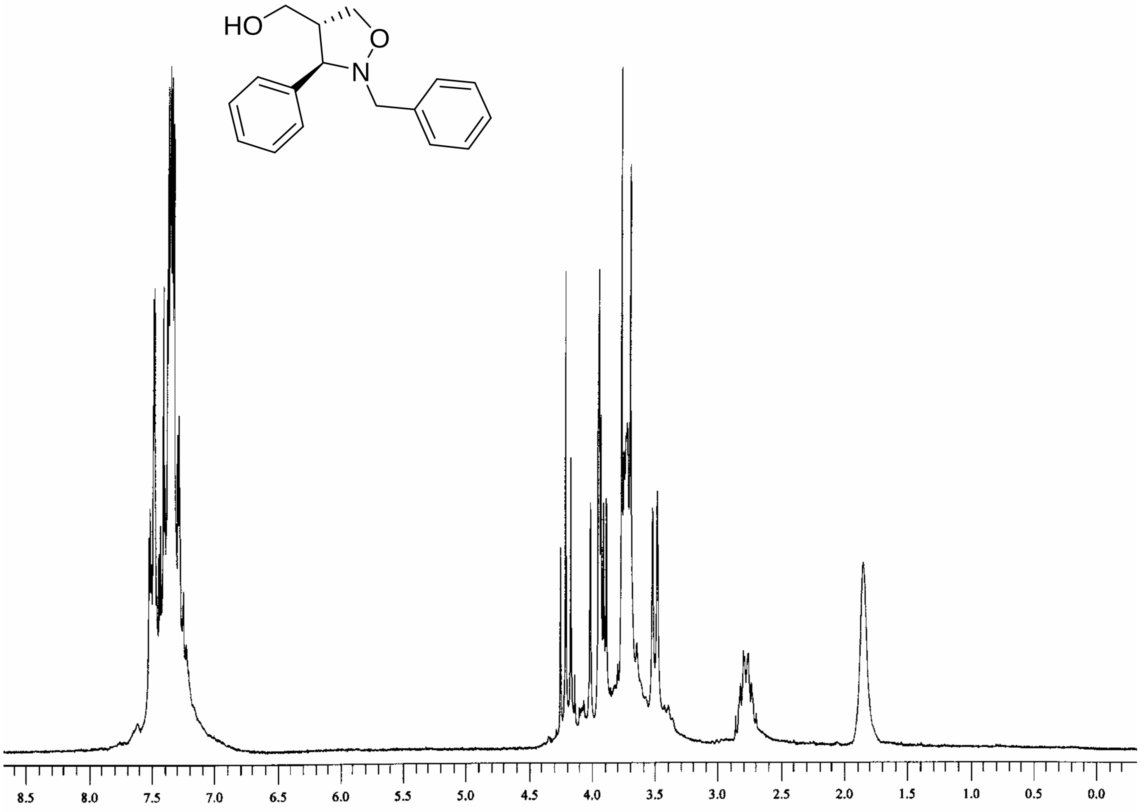
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N
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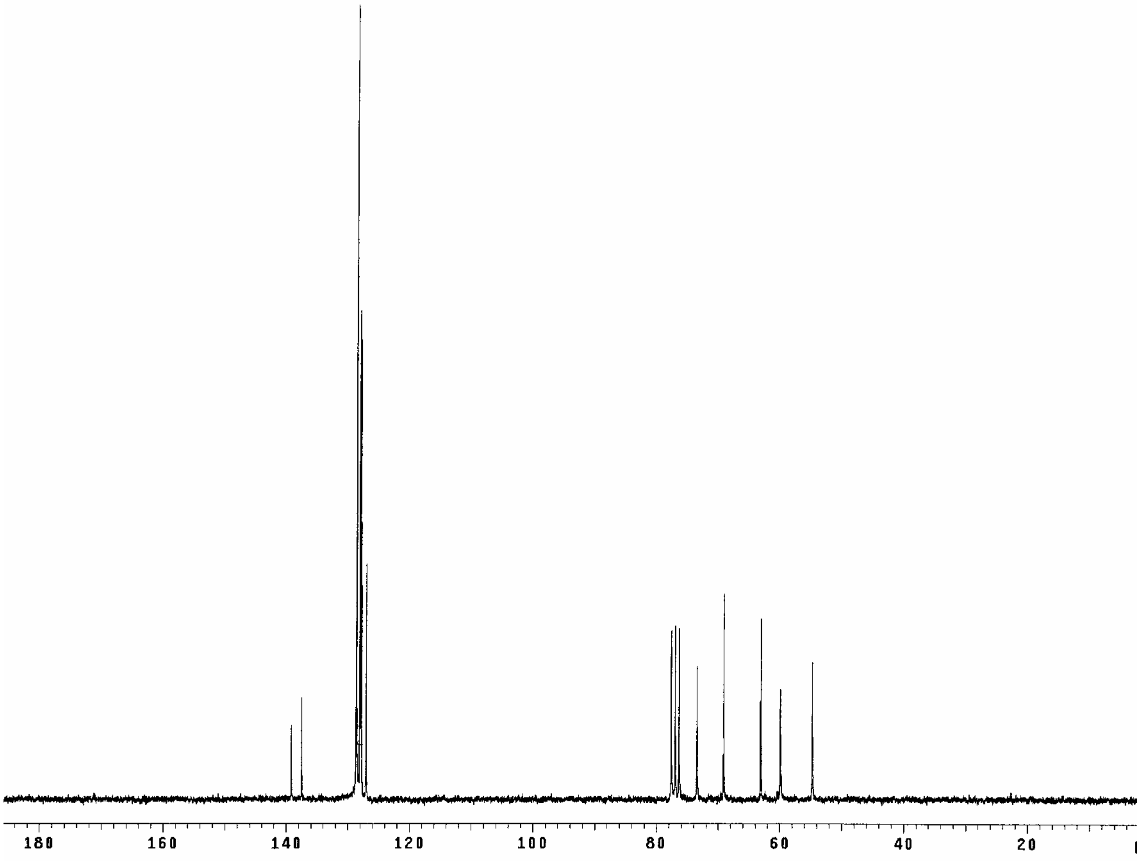
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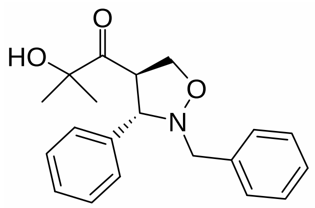
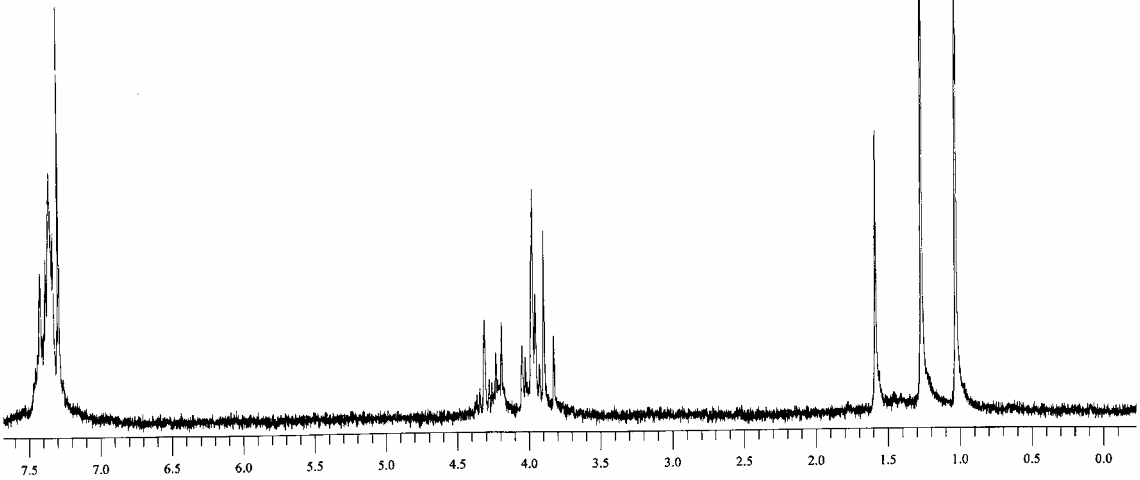

O
HO
O
N

8a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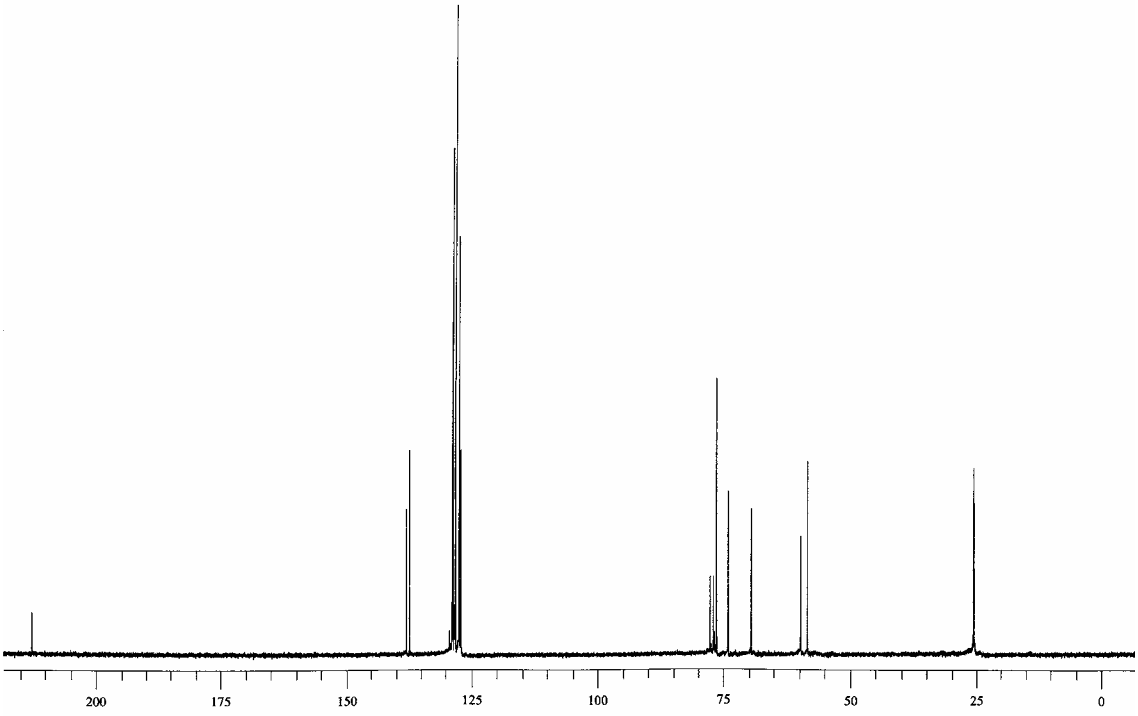
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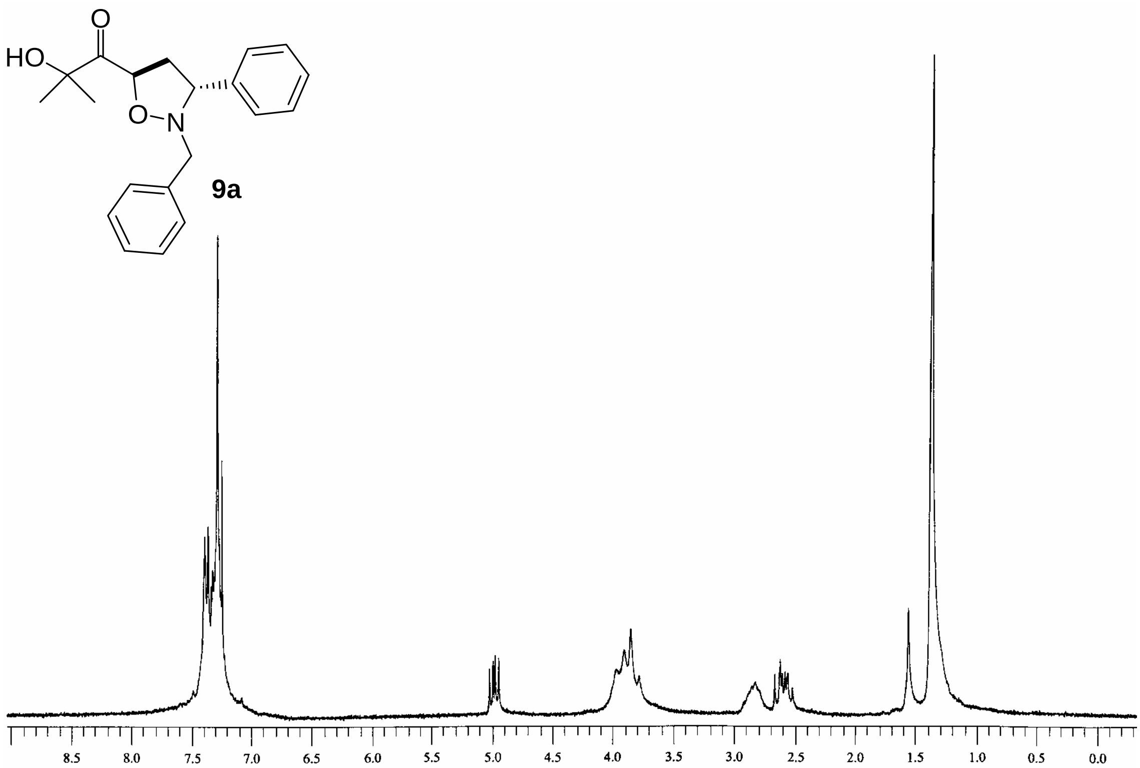
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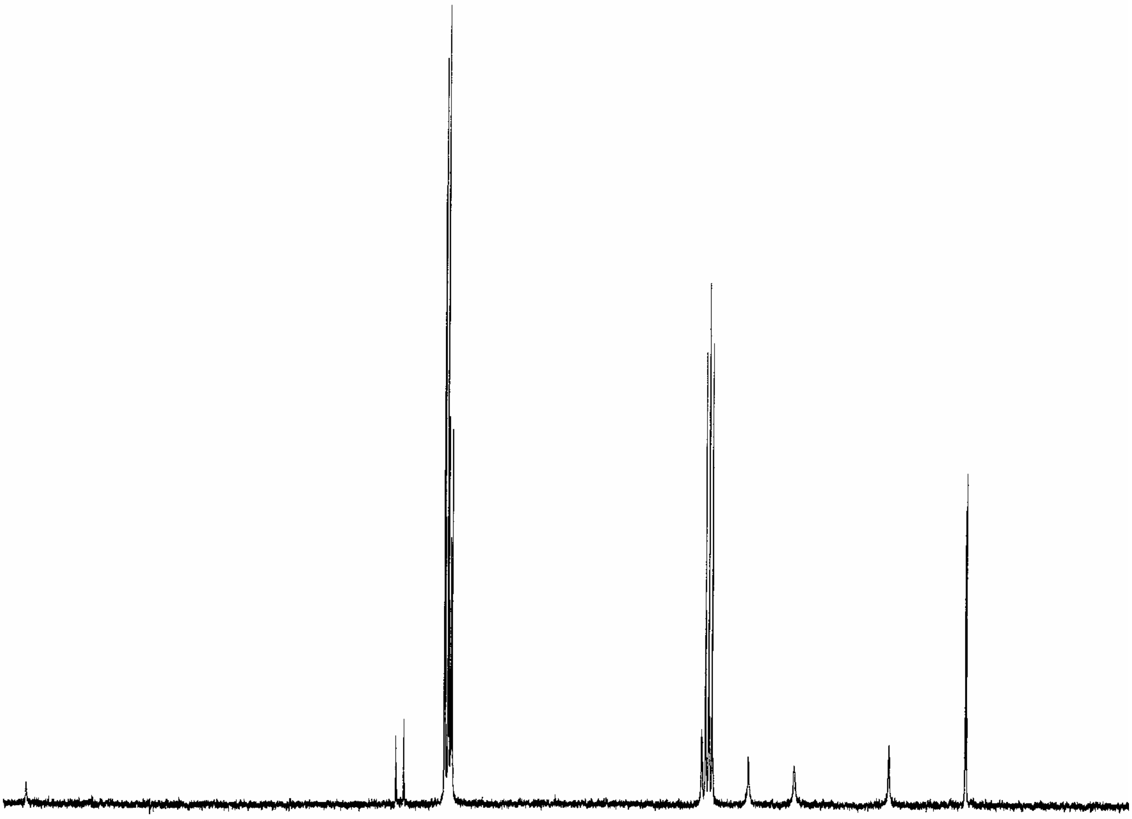
9a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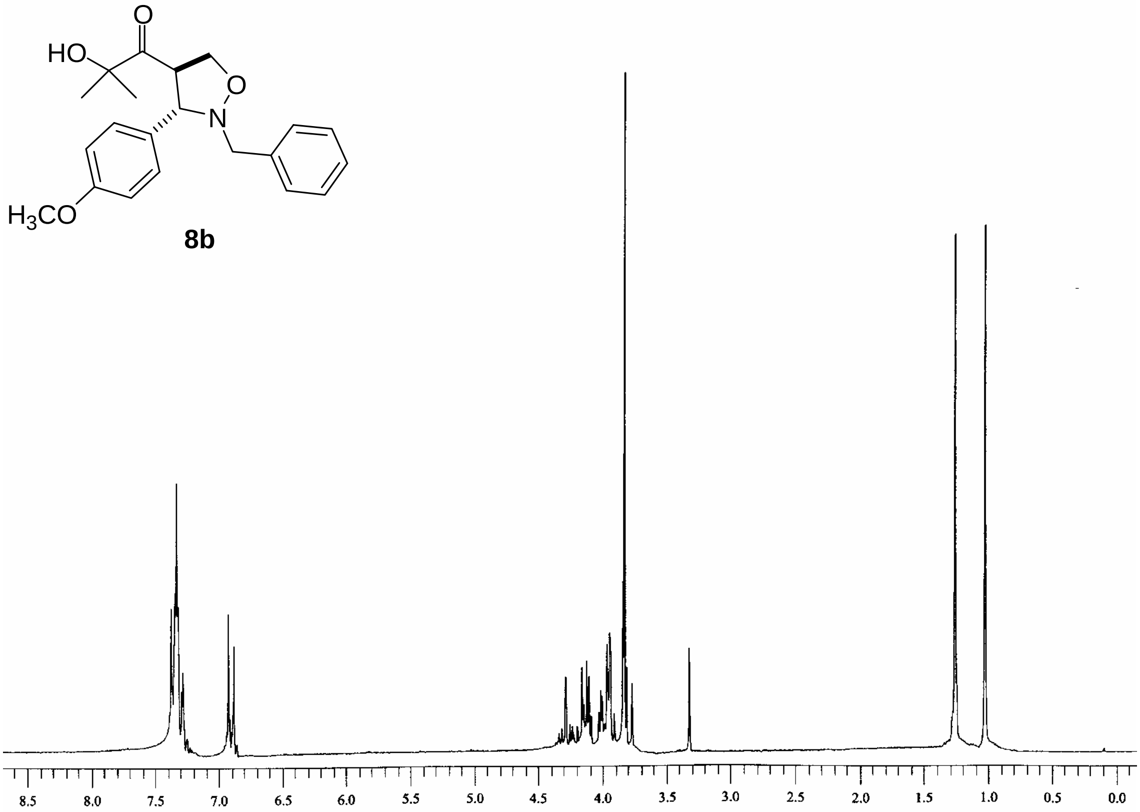
HO
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O
N
H3CO

8b

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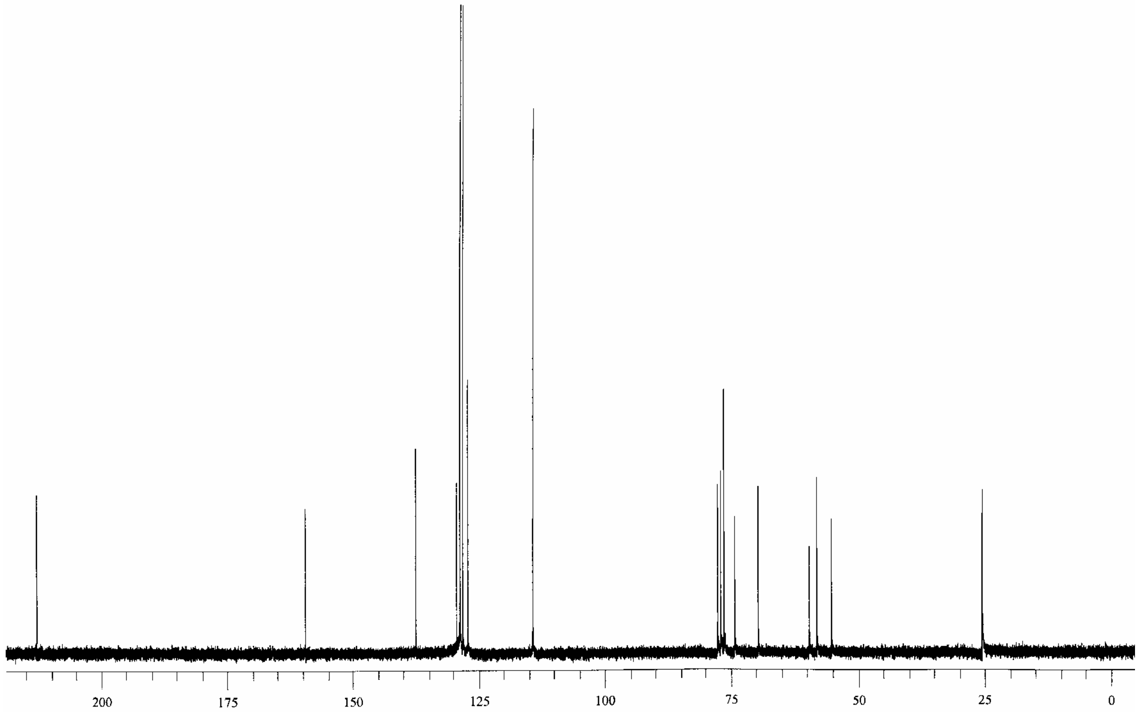
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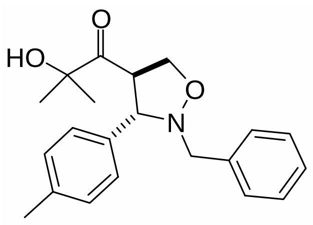
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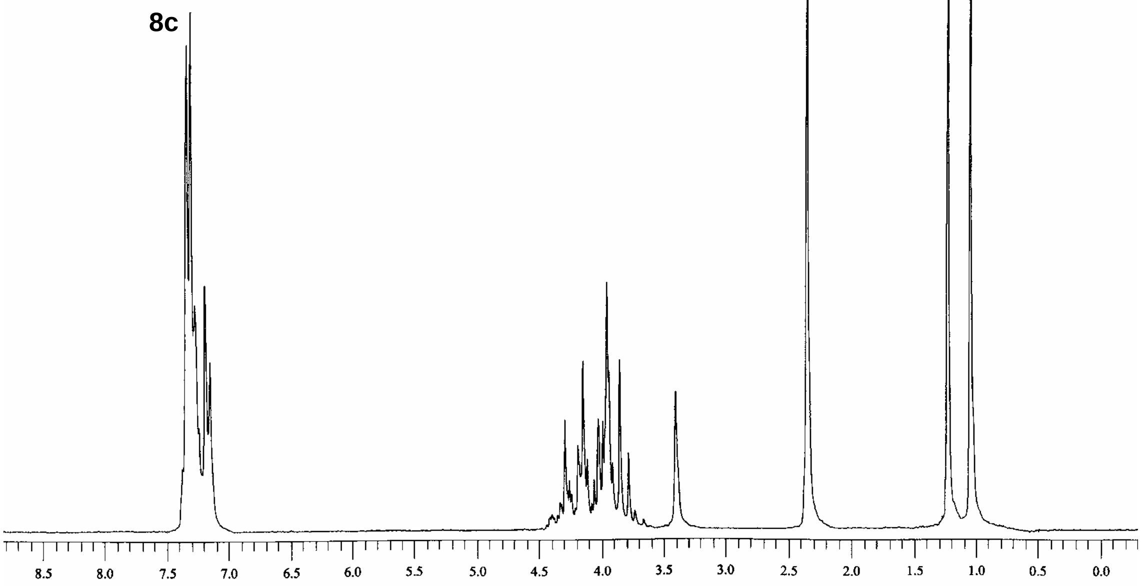
N

8c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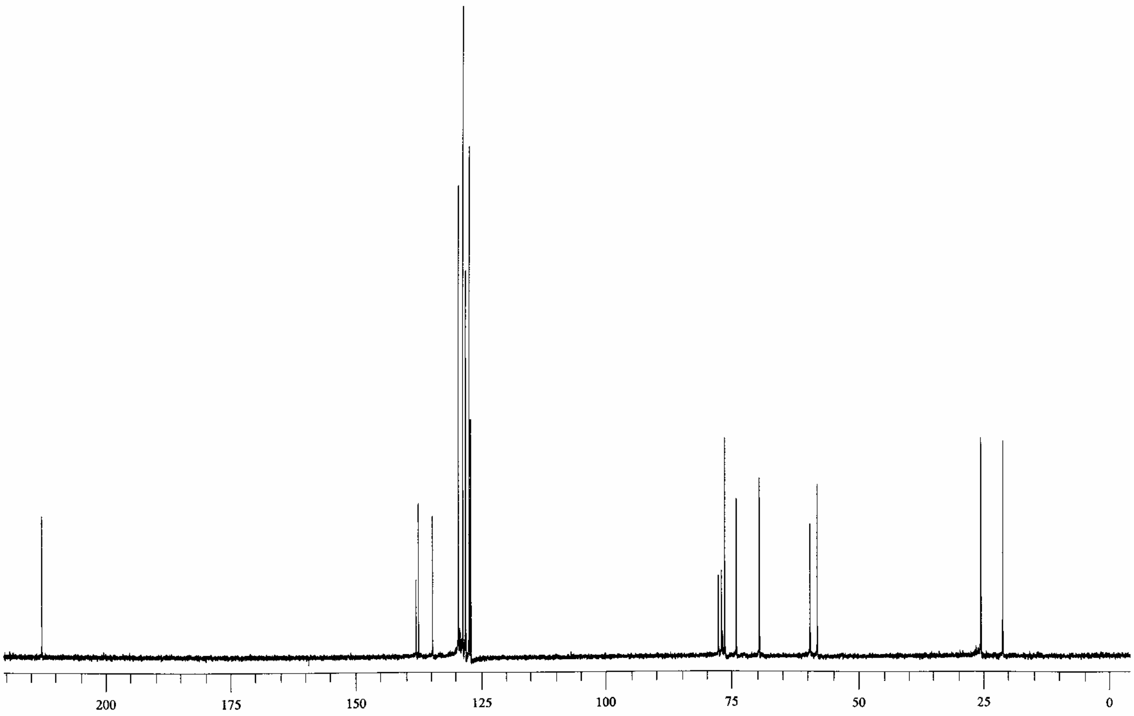
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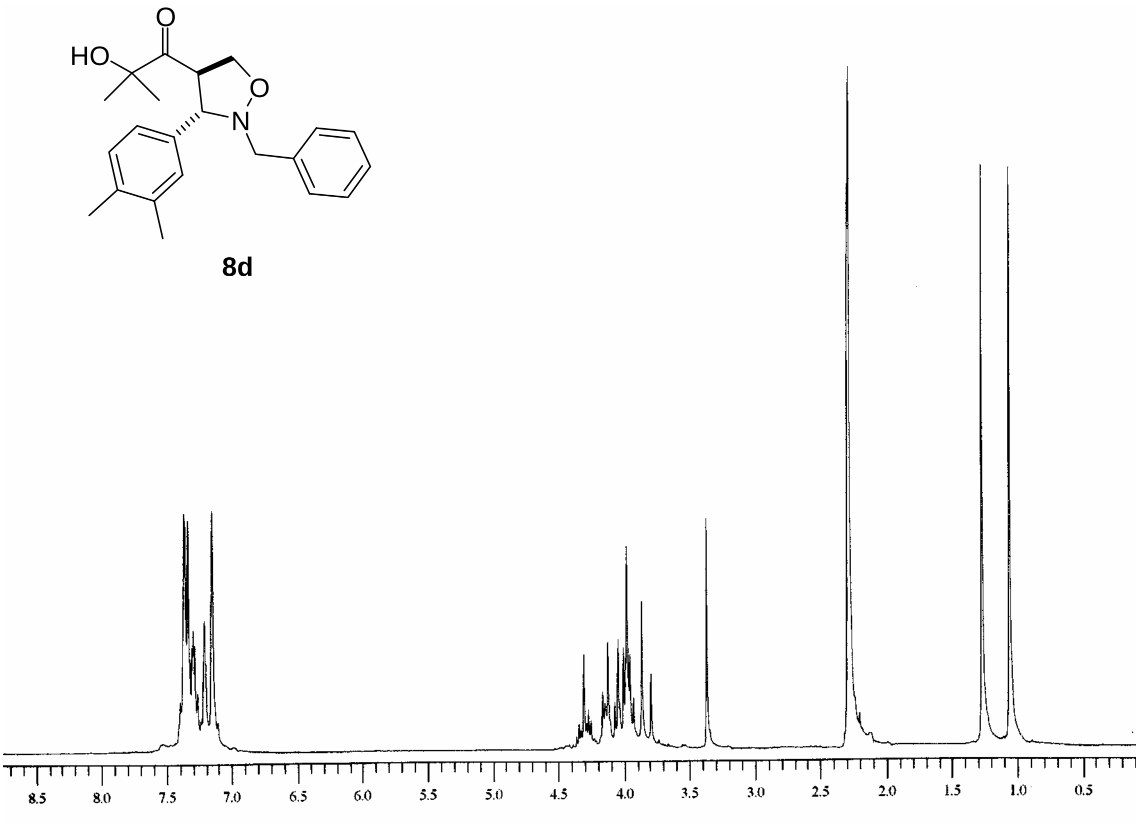
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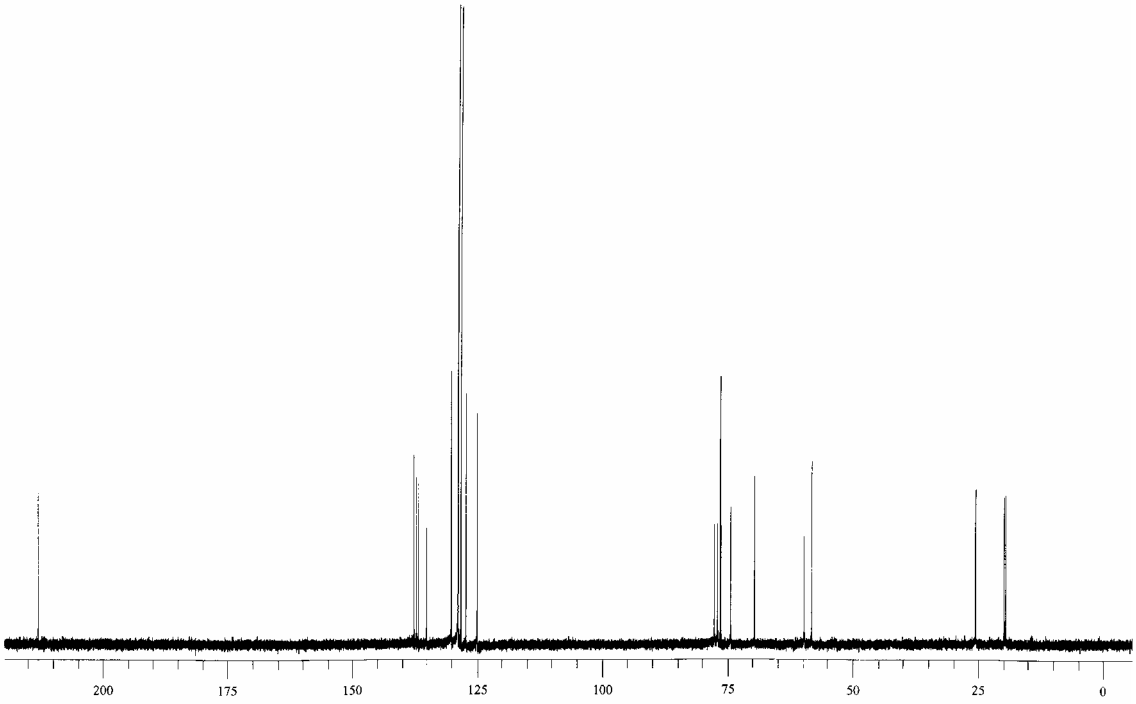
8d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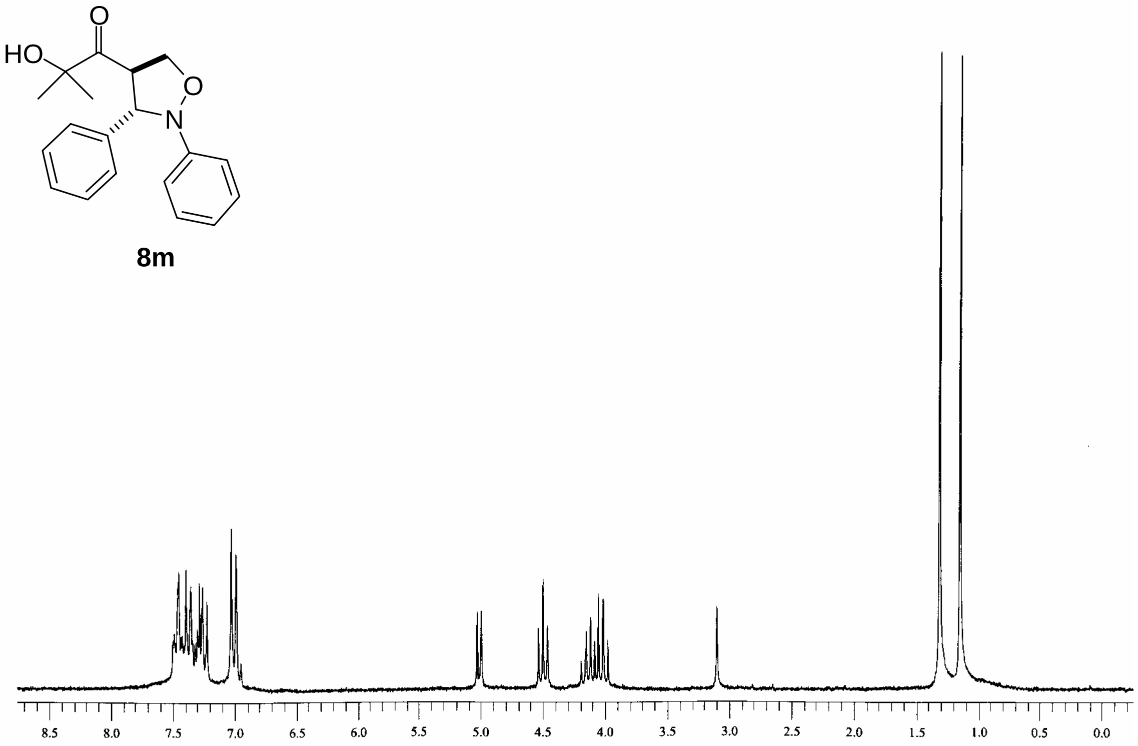

O
HO
O
N

8m

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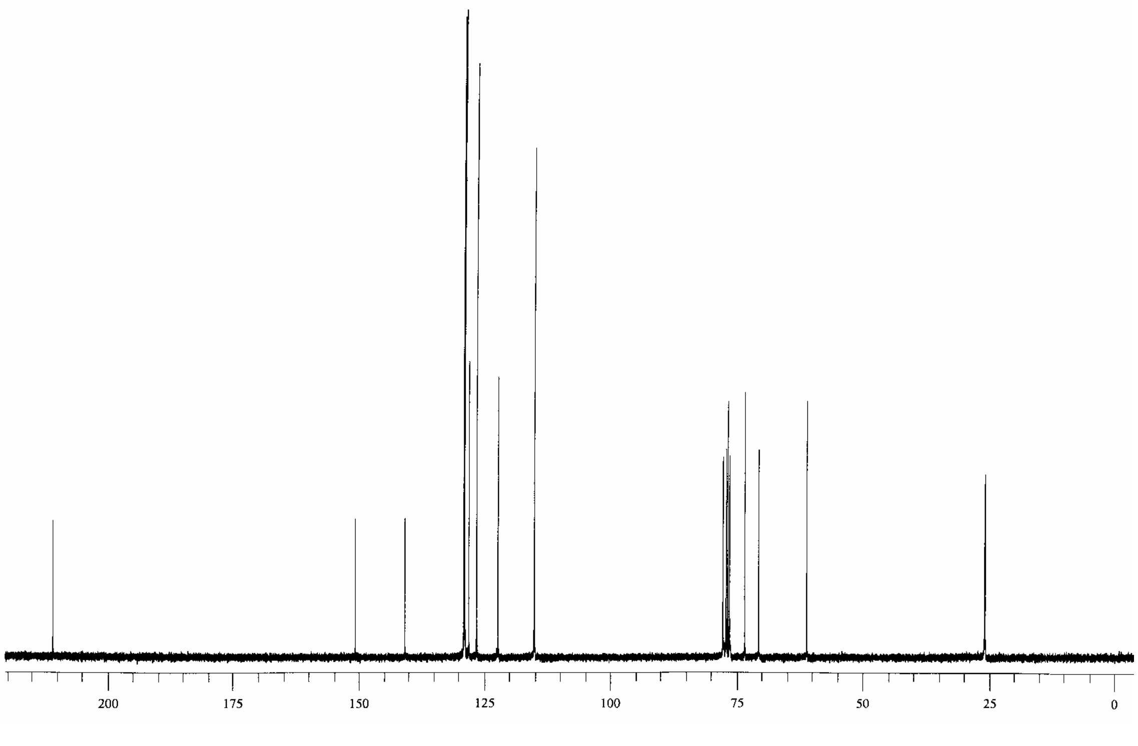

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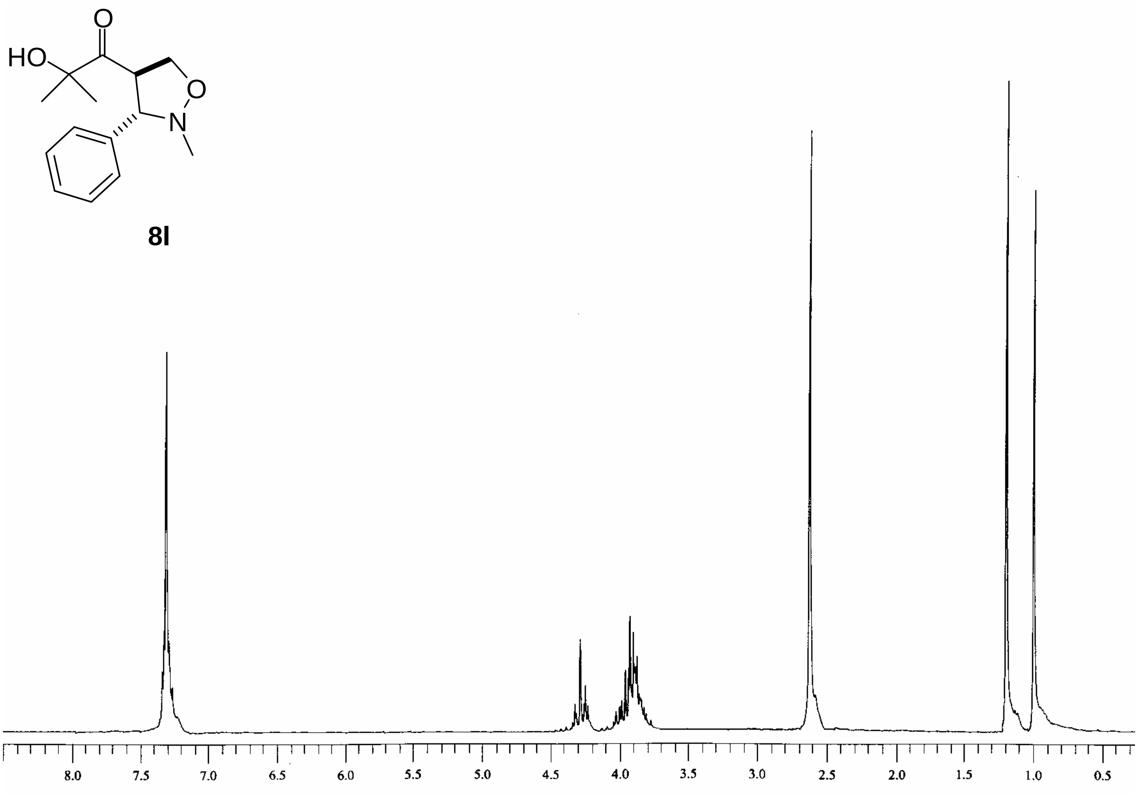
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O
N
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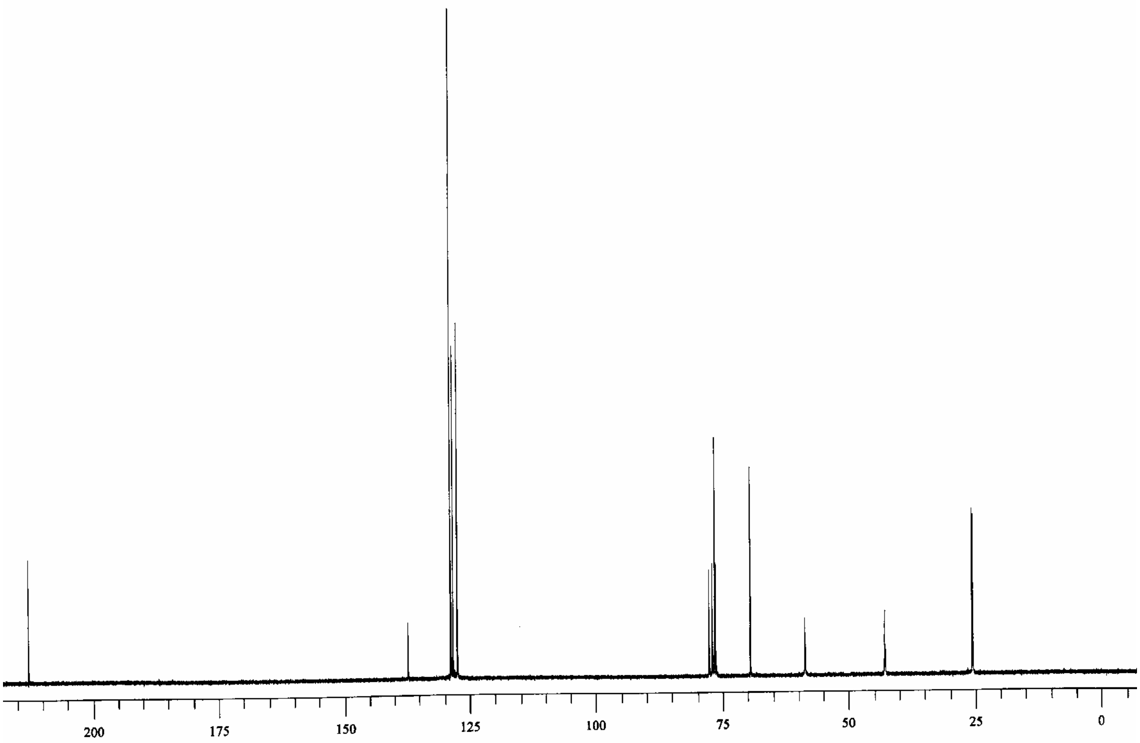
8l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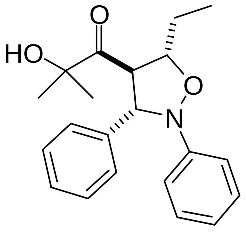
HO
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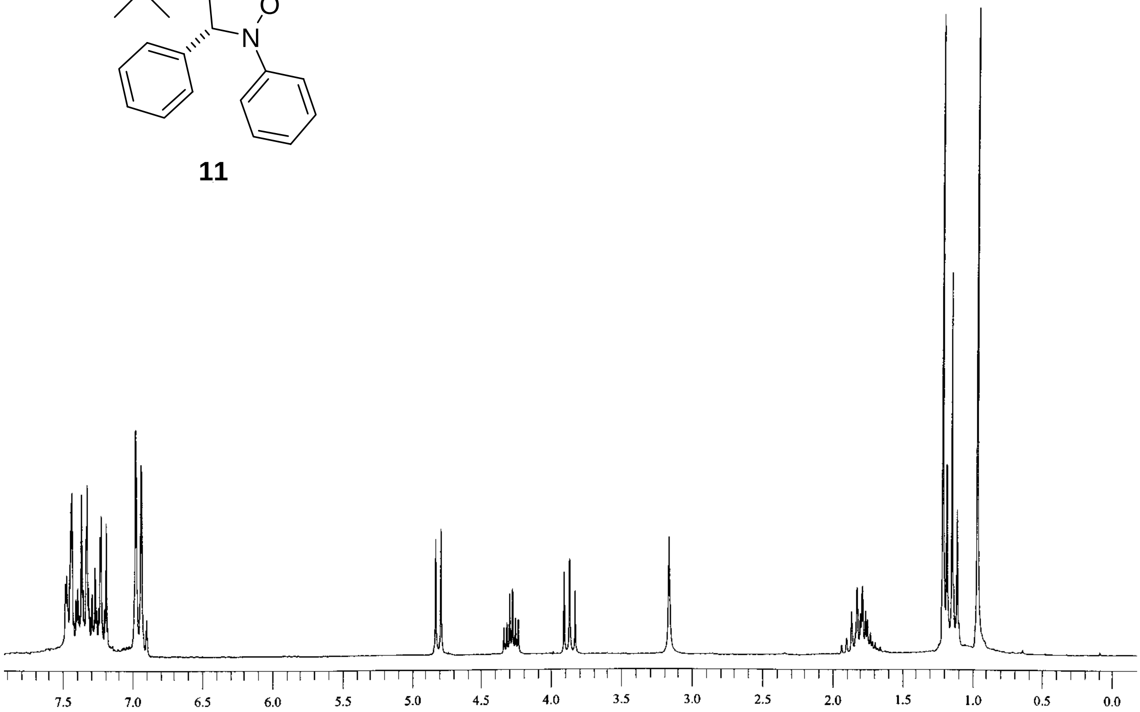
O
N

11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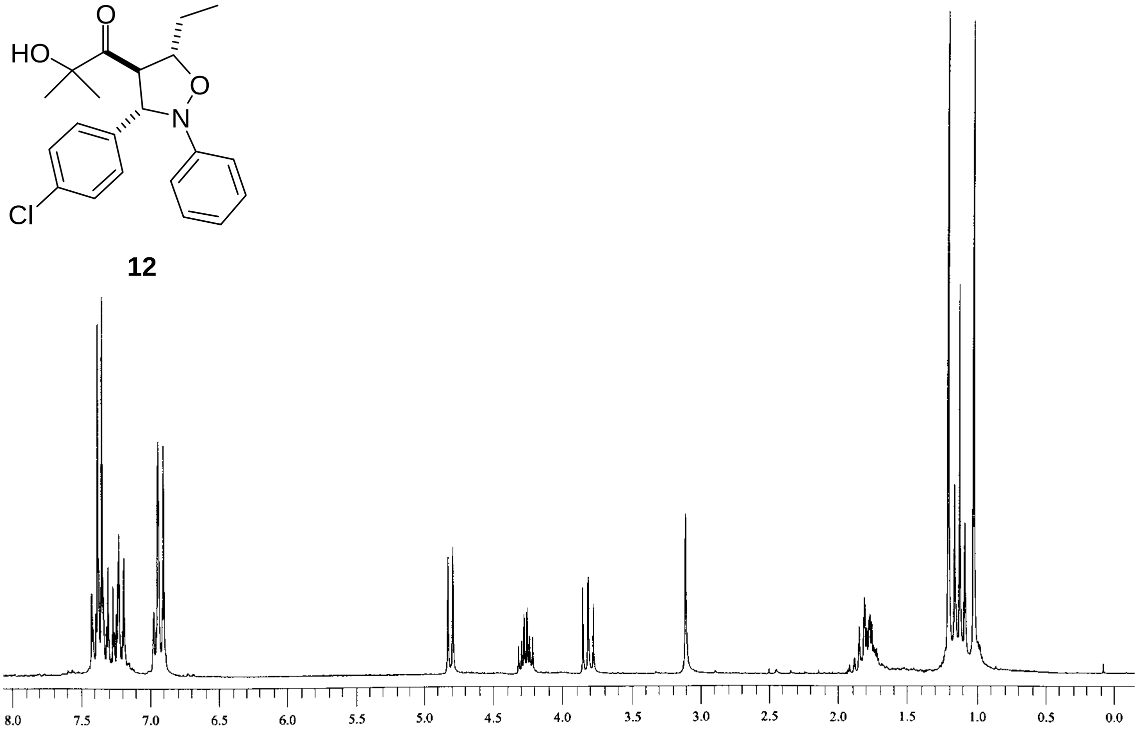
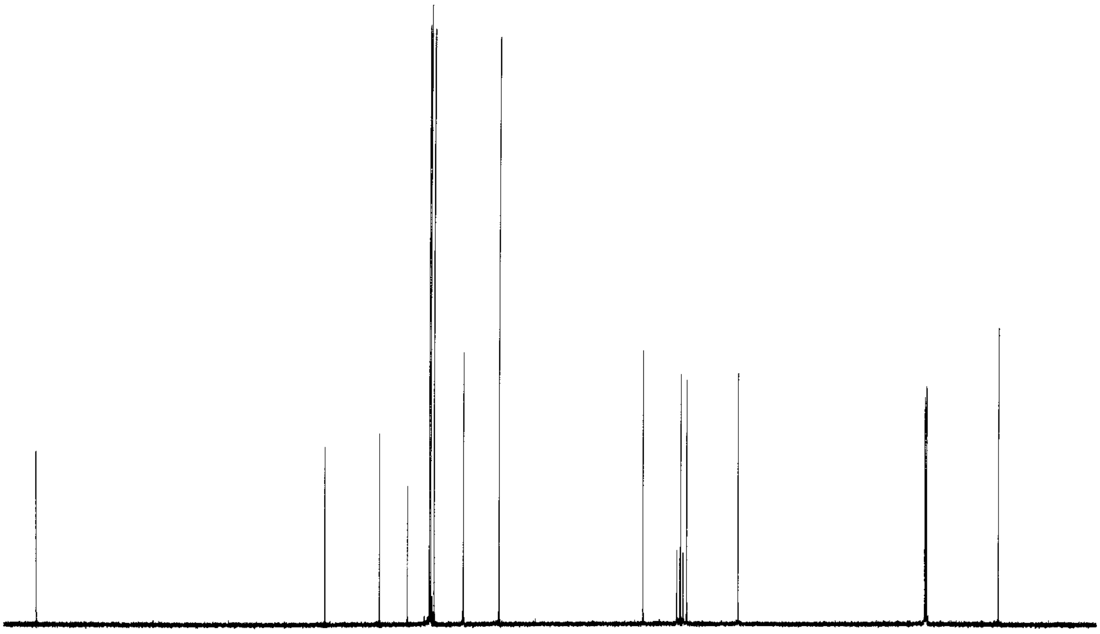
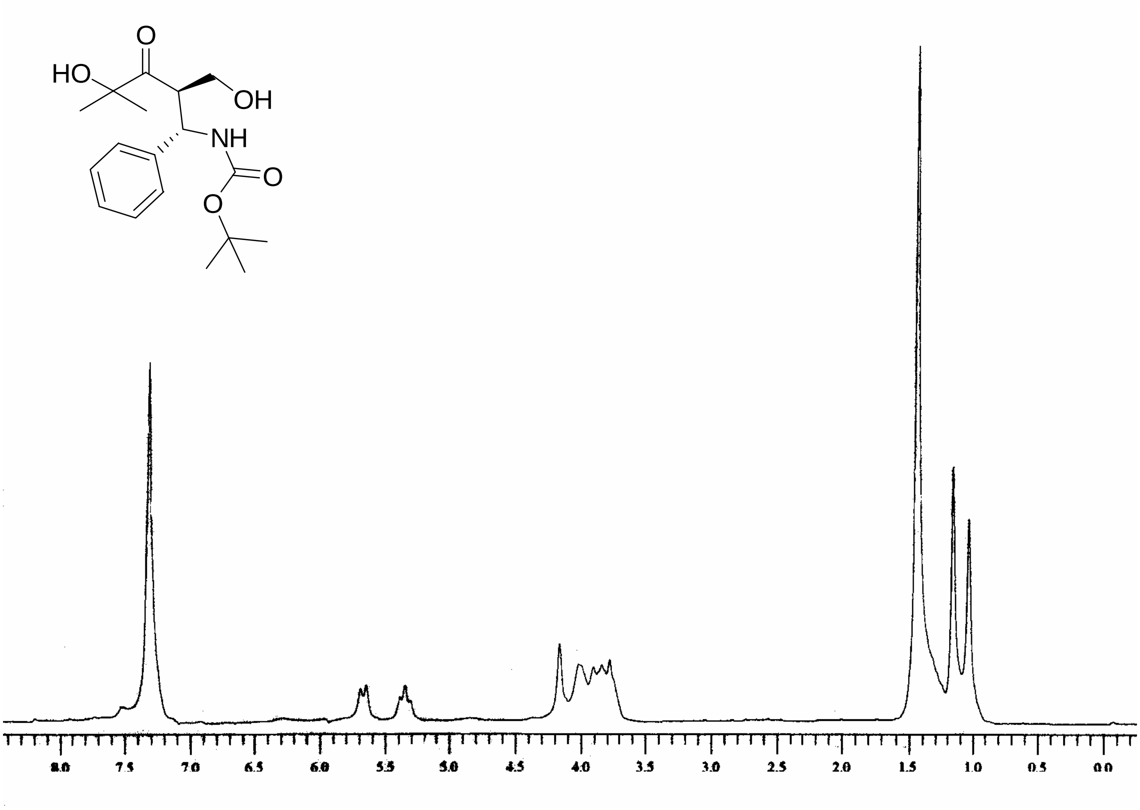


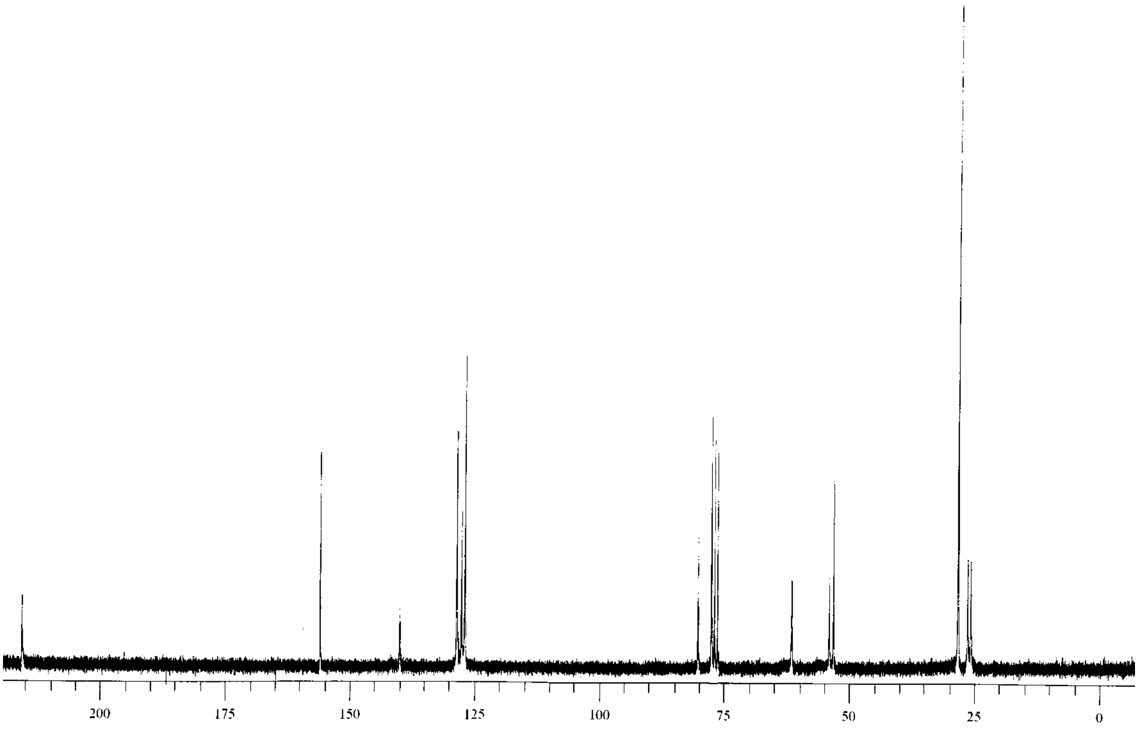
12

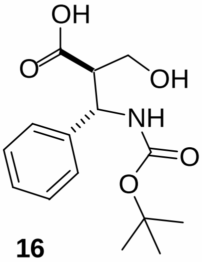
HO
O
O
N
Cl
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



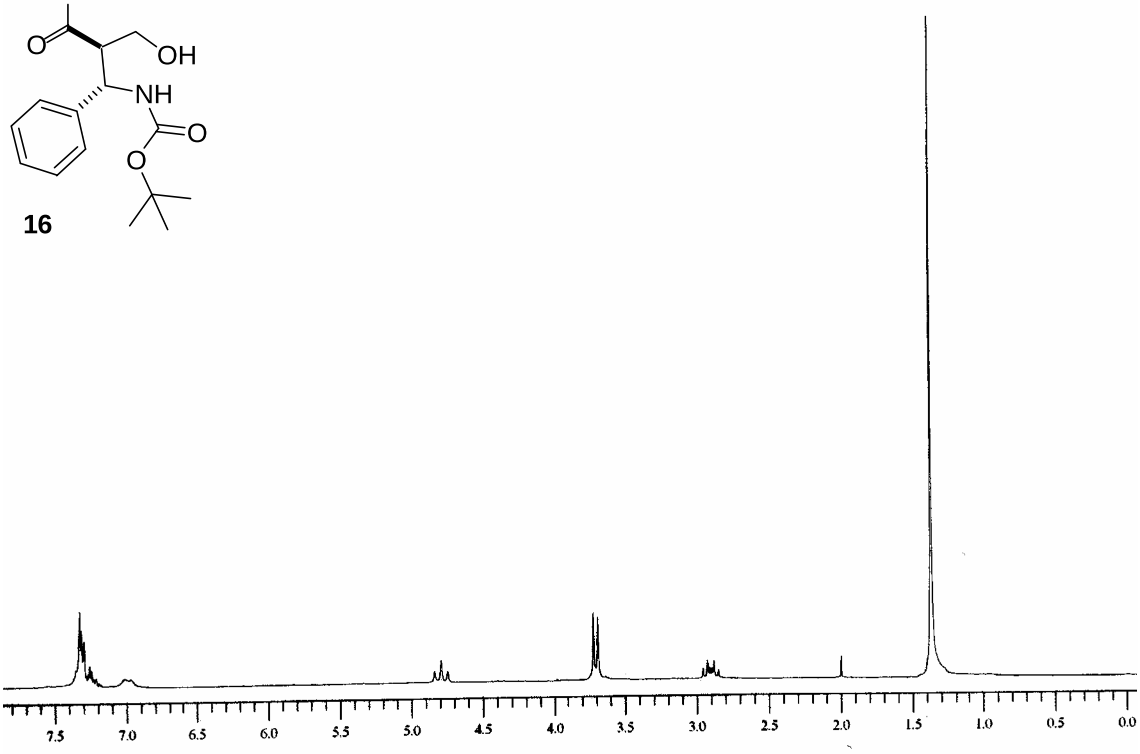
200
175
150
125
100
75
50
25
0

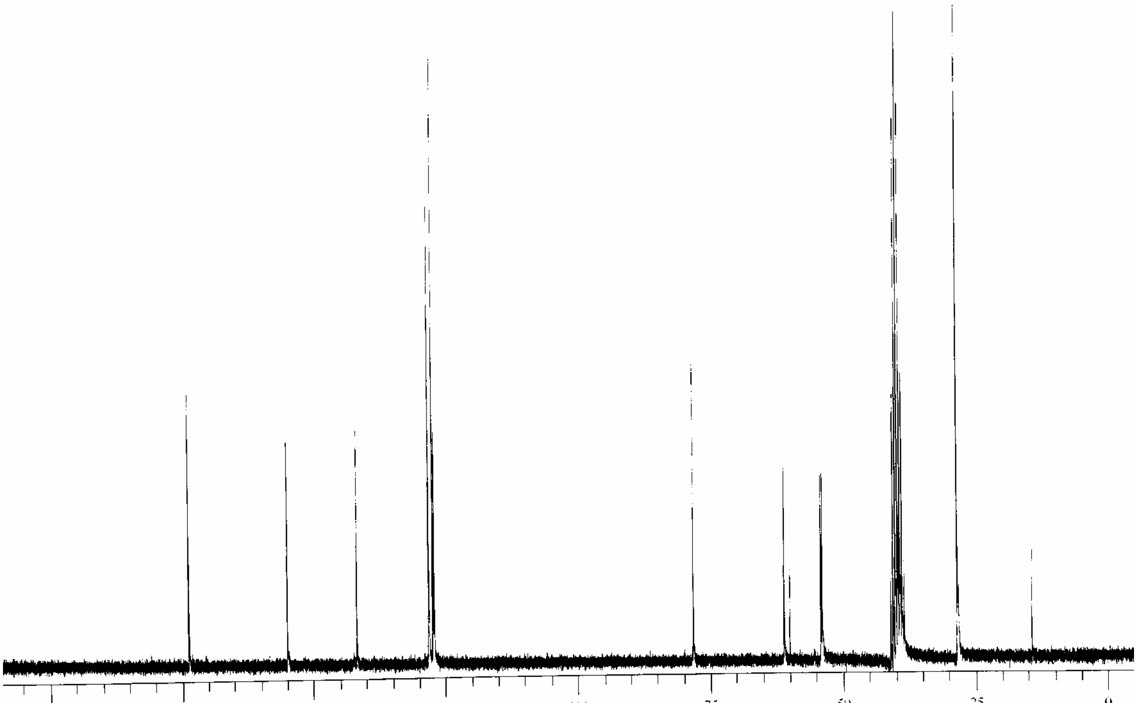

O
HO
OH
NH
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

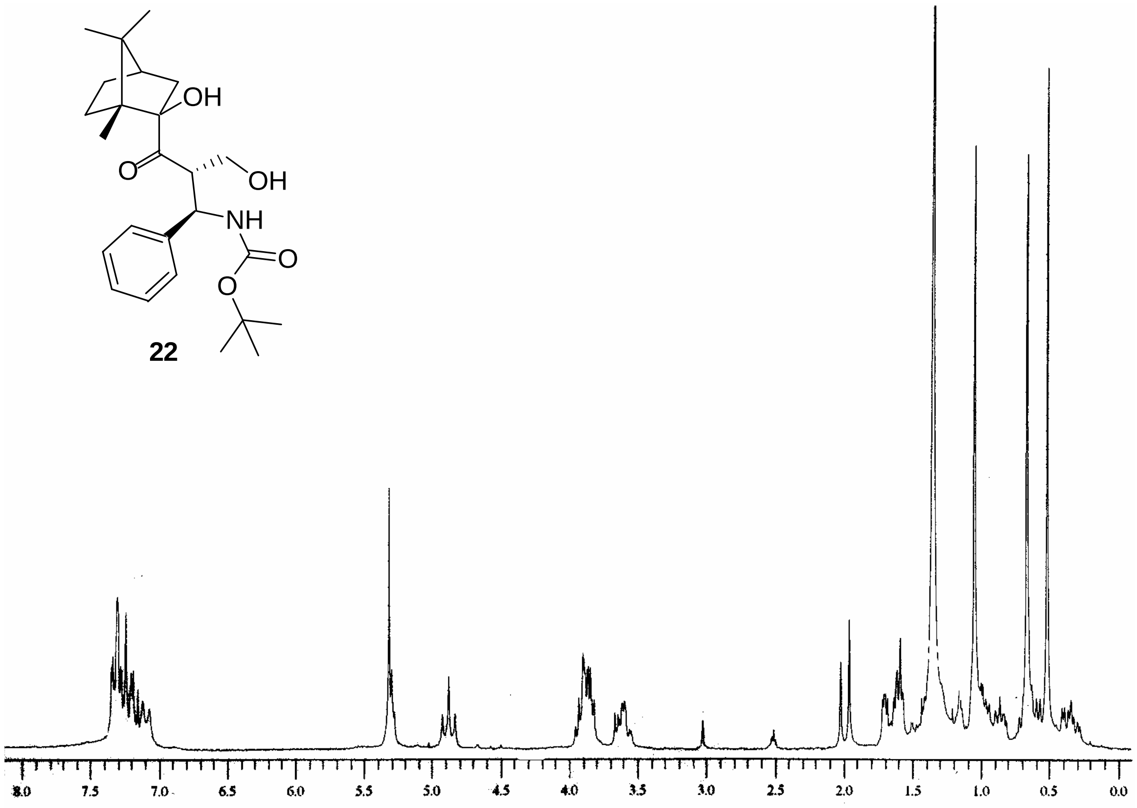

200
175
150
125
100
75
50
25
0


OH
O
OH
NH
O
O

16

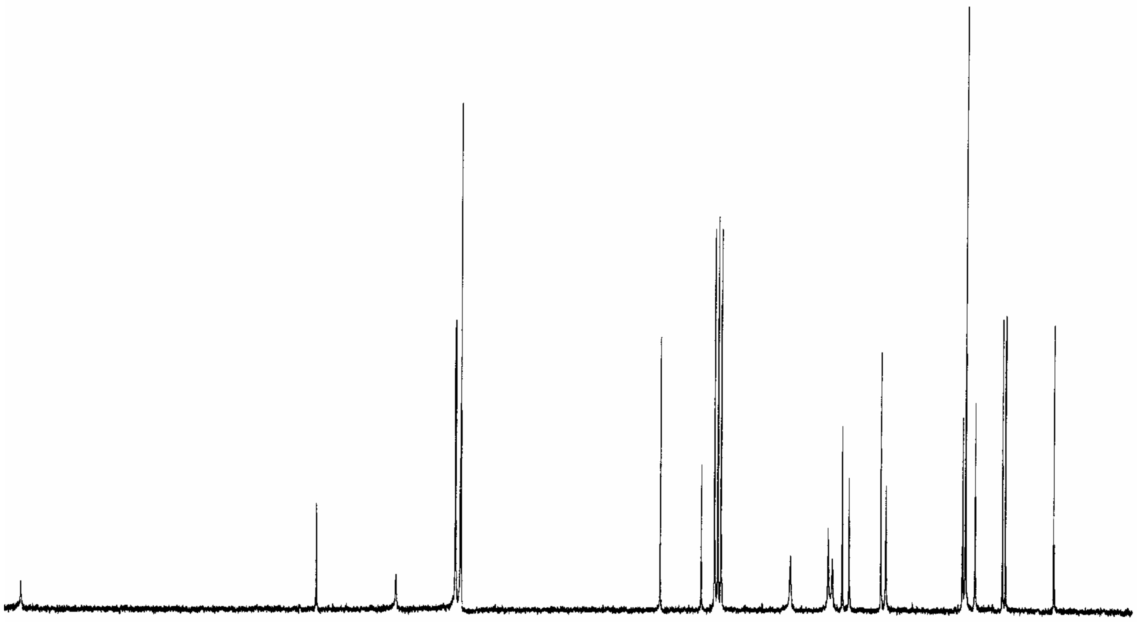

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


200
175
150
125
100
75
50
25
0



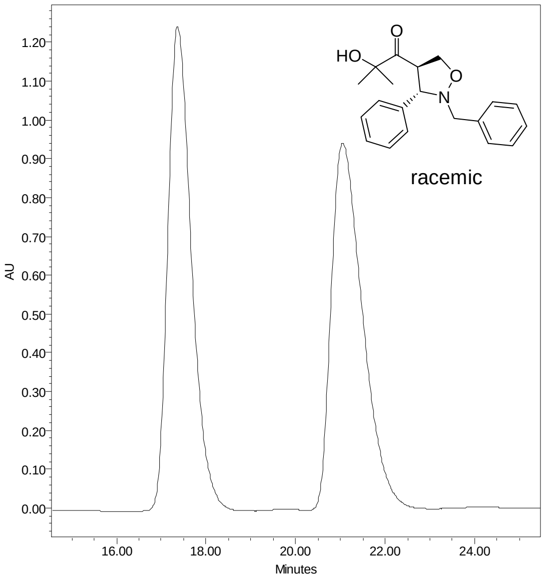
22

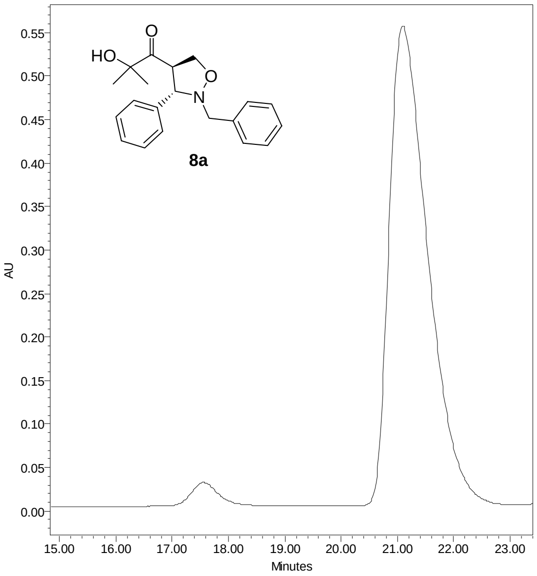
OH
O
OH
NH
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



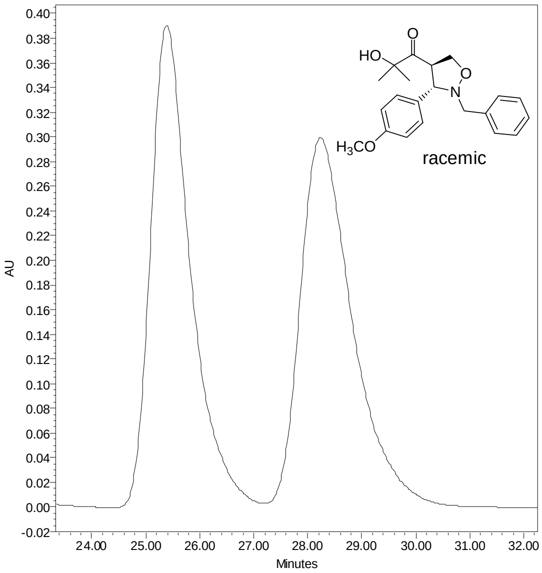
200
180
160
140
120
100
80
60
40
20
0

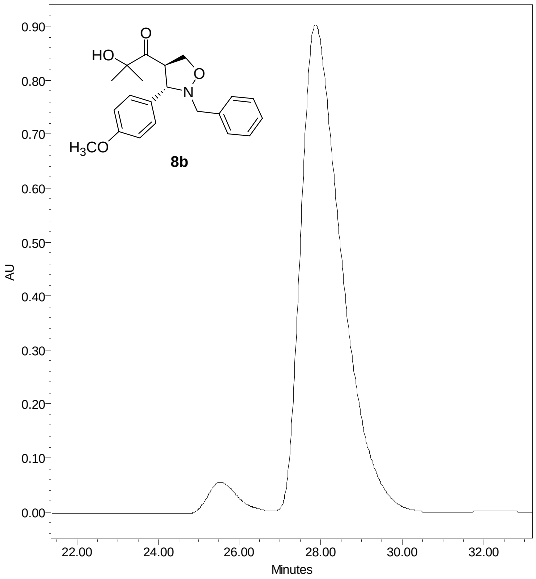
O) HPLC chromatograms of selected compounds



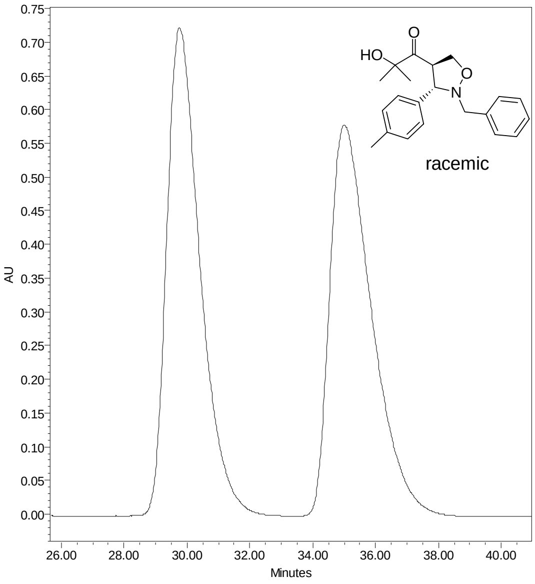


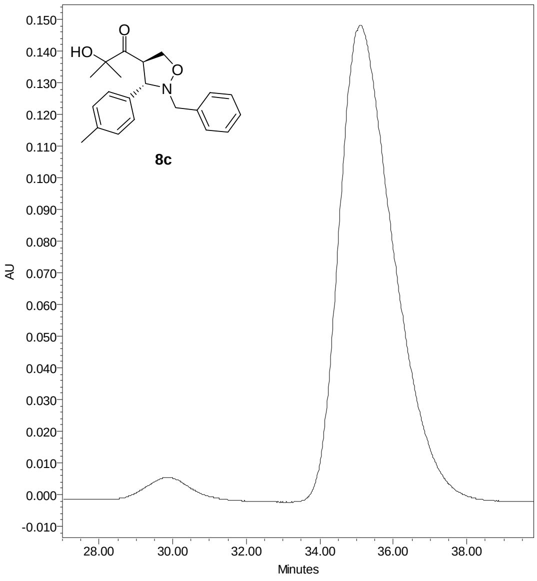
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		17.550	840544	3.12	26360	bb	Unknown
2		21.098	26141345	96.88	551130	bb	Unknown



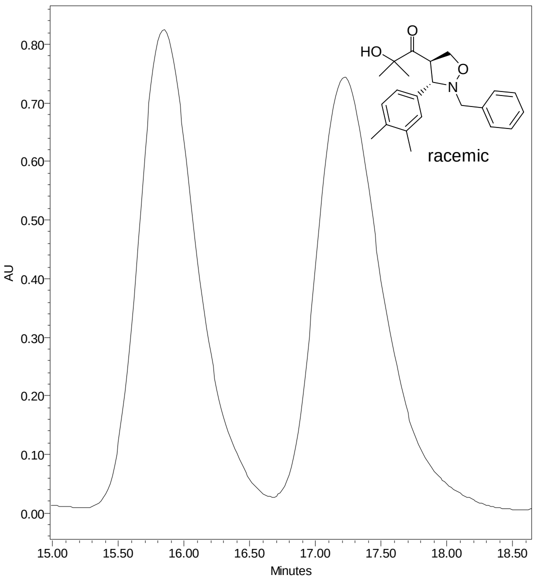


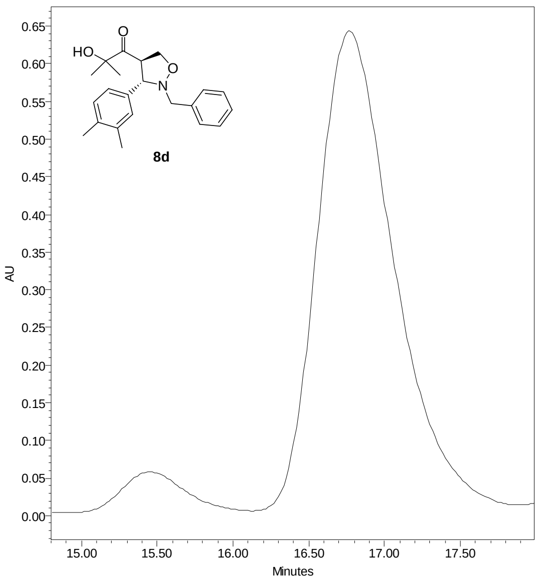
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		25.524	2734468	4.18	55657	bb	Unknown
2		27.870	62662561	95.82	901989	bb	Unknown



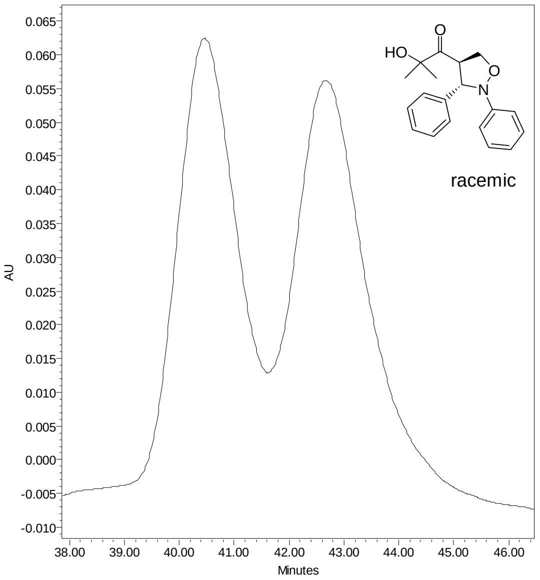


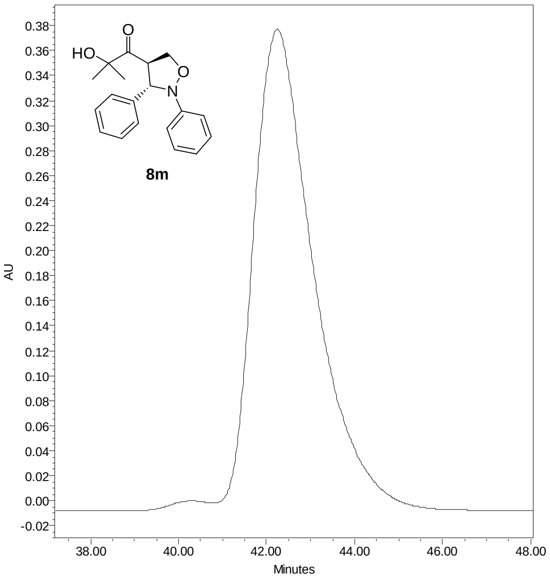
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		29.872	571613	3.56	6924	bb	Unknown
2		35.111	15485514	96.44	150464	bb	Unknown



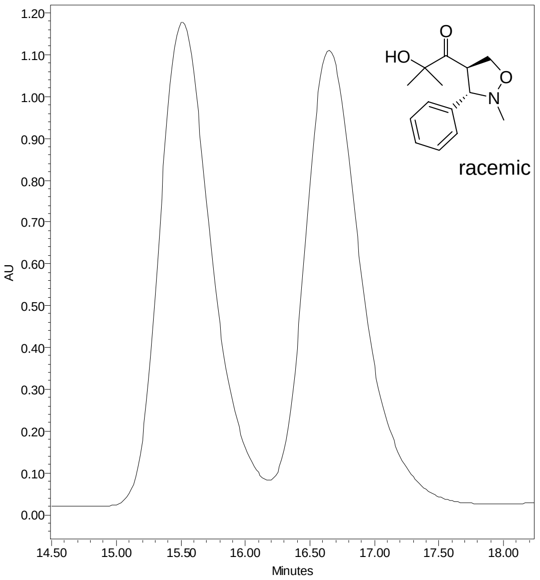


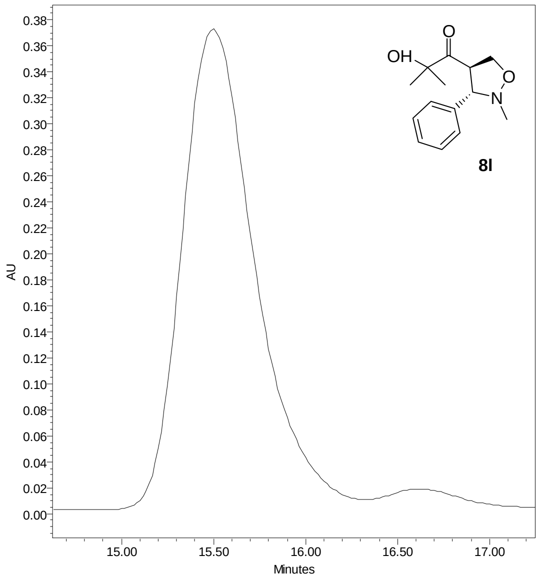
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		15.451	697404	4.90	28673	bb	Unknown
2		16.767	13549245	95.10	389773	bb	Unknown



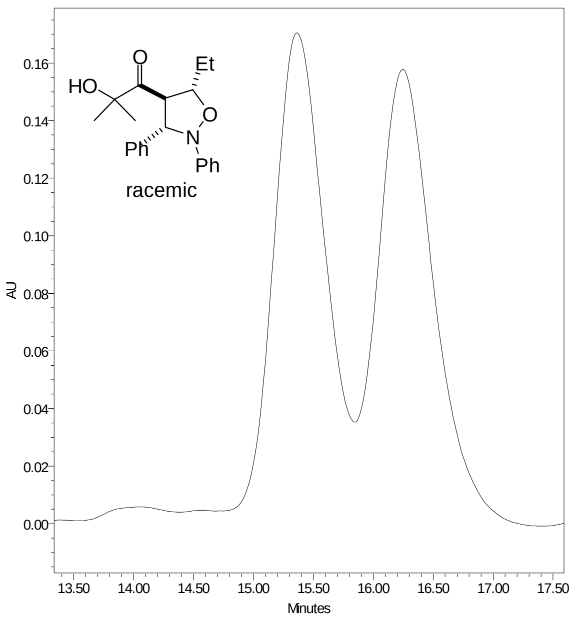


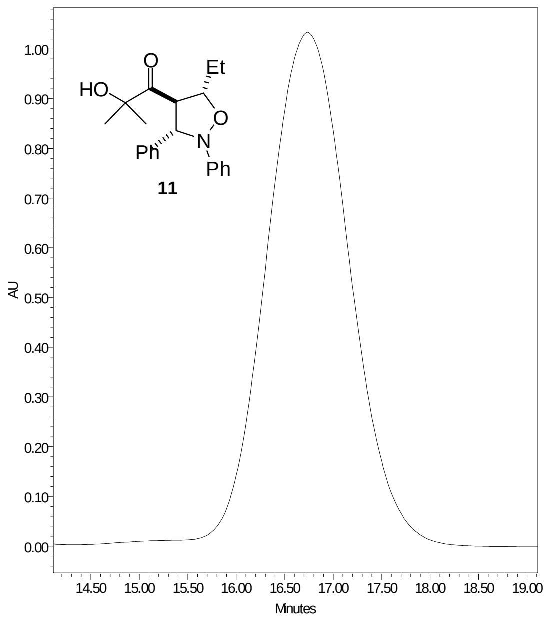
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		40.183	168620	0.47	3812	bb	Unknown
2		42.250	35506001	99.53	380297	bb	Unknown



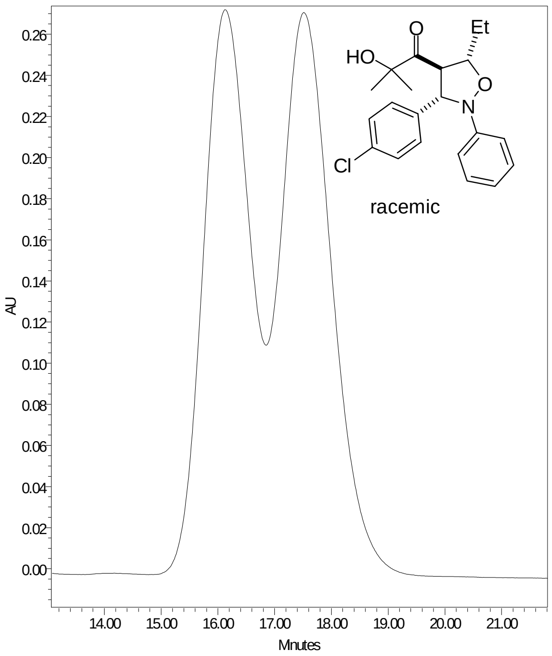


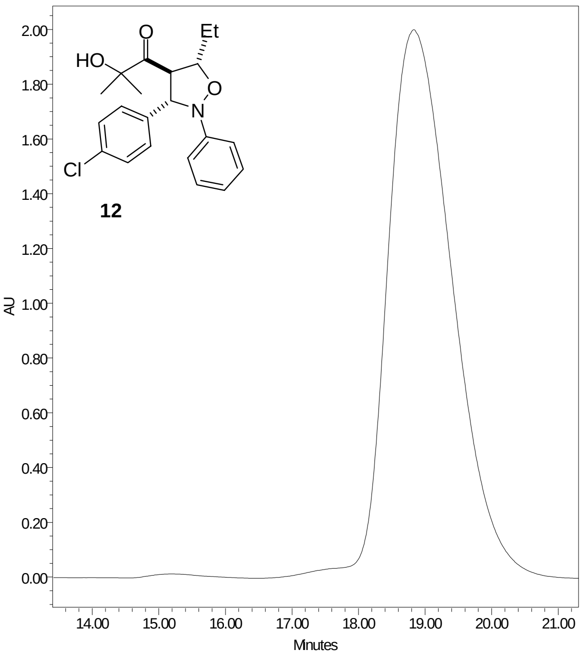
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		15.498	9892132	97.79	366257	bb	Unknown
2		16.617	223595	2.21	10215	bb	Unknown


HO
O
Et
O
N
Ph
Ph
racemic
AU
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
13.50
14.00
14.50
15.00
15.50
16.00
16.50
17.00
17.50
Minutes

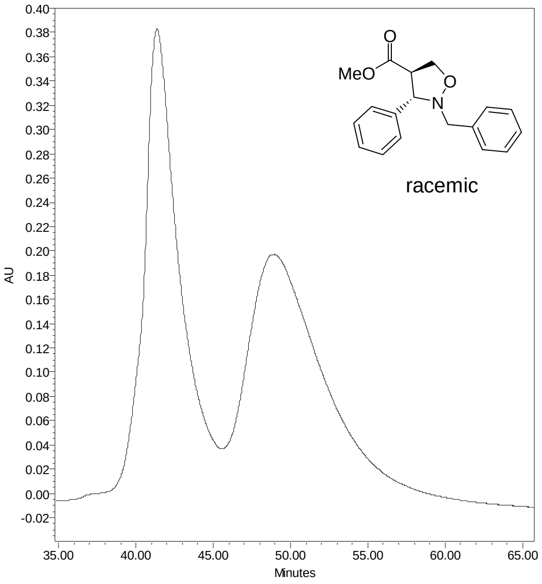

HO
O
Et
O
N
Ph
Ph
AU
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
14.50
15.00
15.50
16.00
16.50
17.00
17.50
18.00
18.50
19.00
Minutes

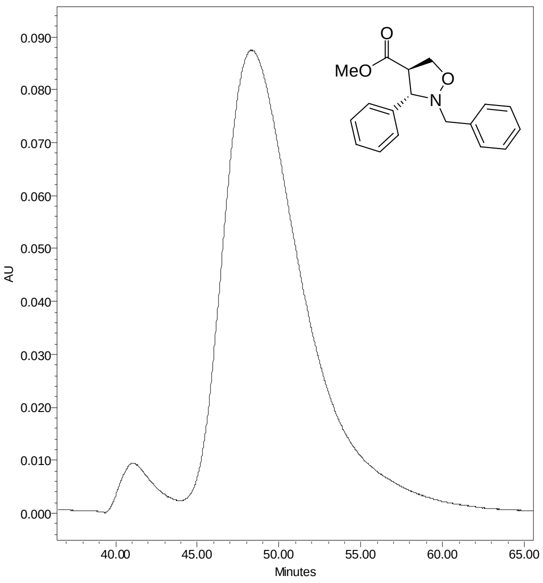
11


HO
O
Et
O
N
Cl
racemic
AU
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
14.00
15.00
16.00
17.00
18.00
19.00
20.00
21.00
Minutes

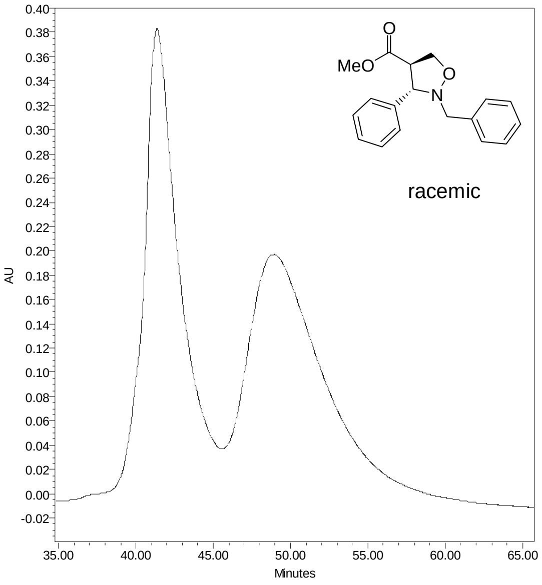

HO
O
Et
O
N
Cl
AU
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
14.00
15.00
16.00
17.00
18.00
19.00
20.00
21.00
Minutes

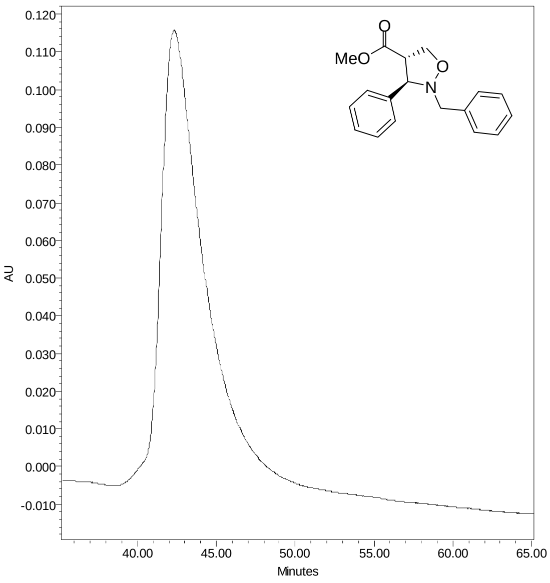
12

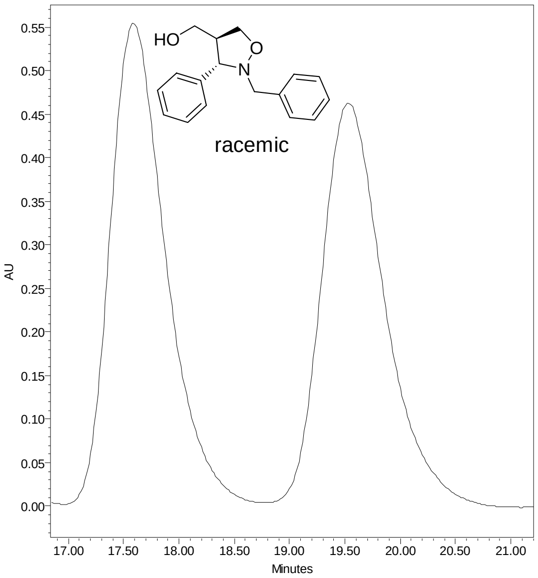


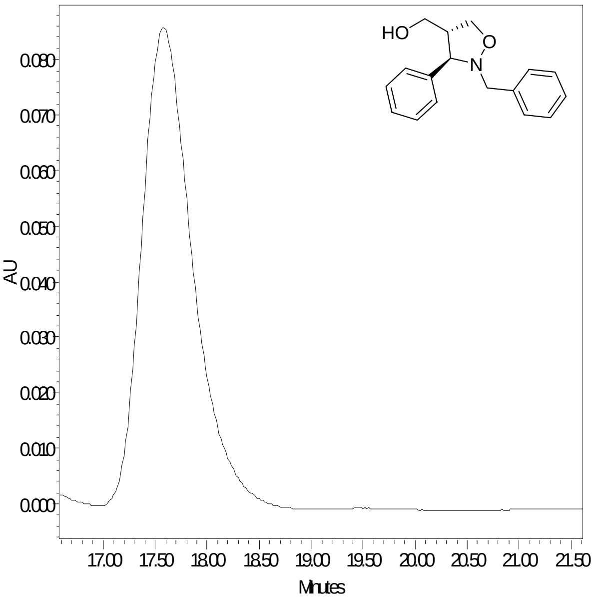


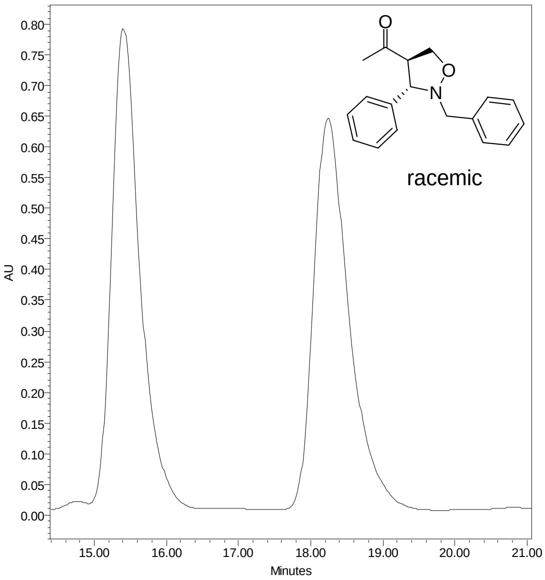
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		41.054	921716	3.15	7968	bb	Unknown
2		48.314	28301621	96.85	85489	bb	Unknown

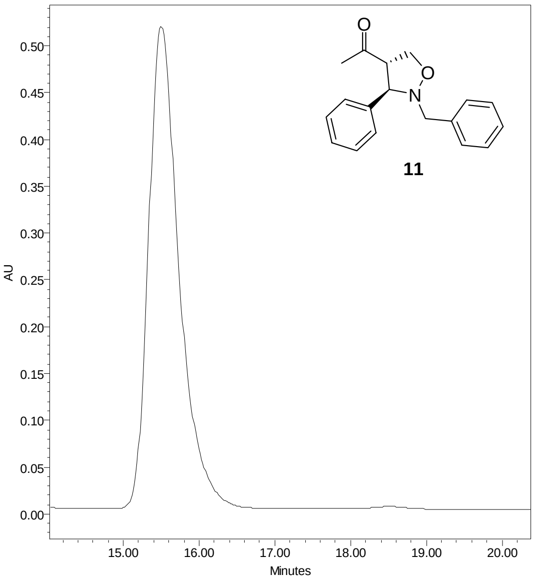




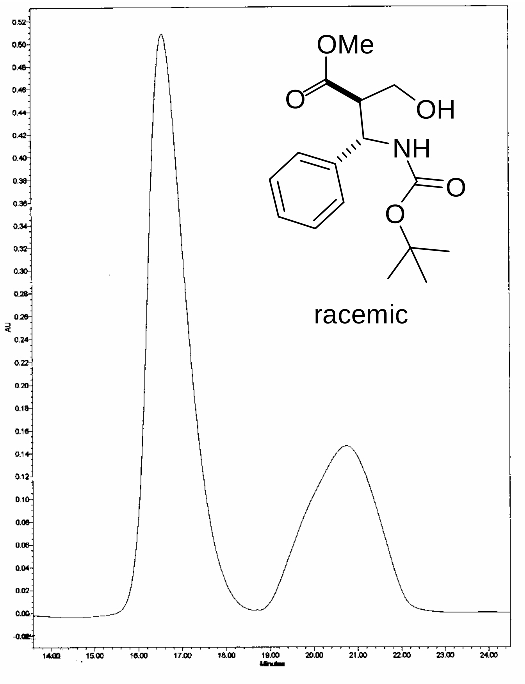

HO
O
N
racemic
AU
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
17.00
17.50
18.00
18.50
19.00
19.50
20.00
20.50
21.00
Minutes

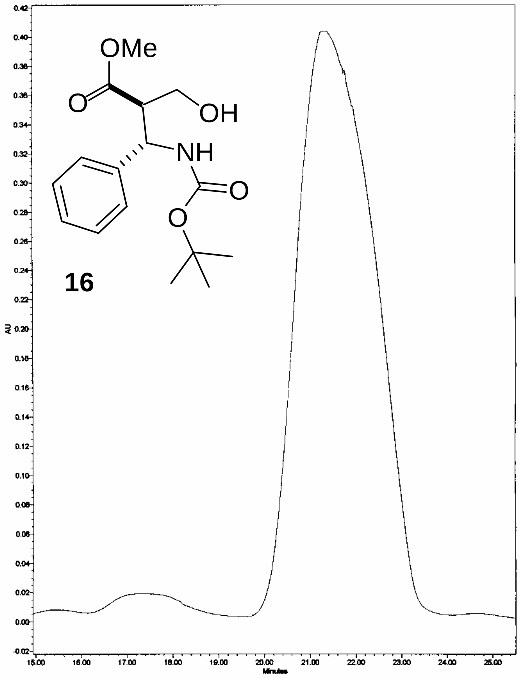

HO
O
N
AU
0.080
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
17.00
17.50
18.00
18.50
19.00
19.50
20.00
20.50
21.00
21.50
Minutes


O
O
N
racemic
AU
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
15.00
16.00
17.00
18.00
19.00
20.00
21.00
Minutes

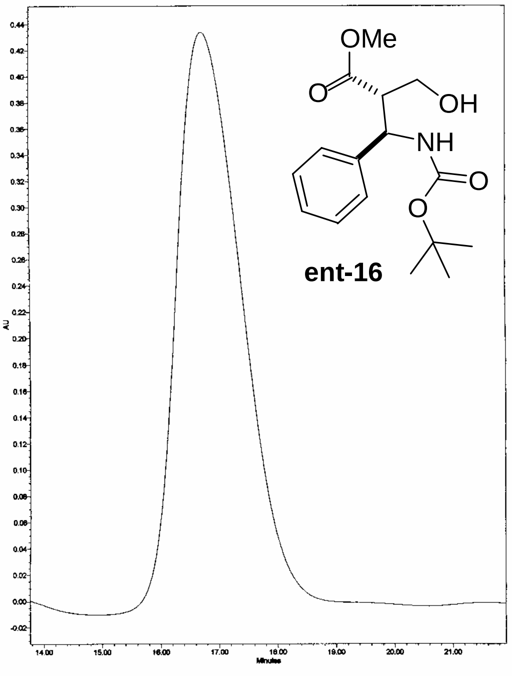

O
O
N
AU
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
15.00
16.00
17.00
18.00
19.00
20.00
Minutes

11

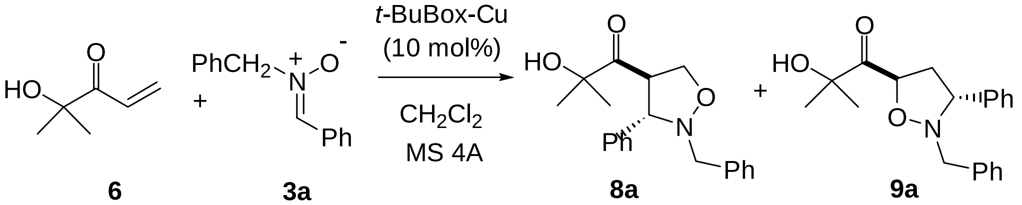


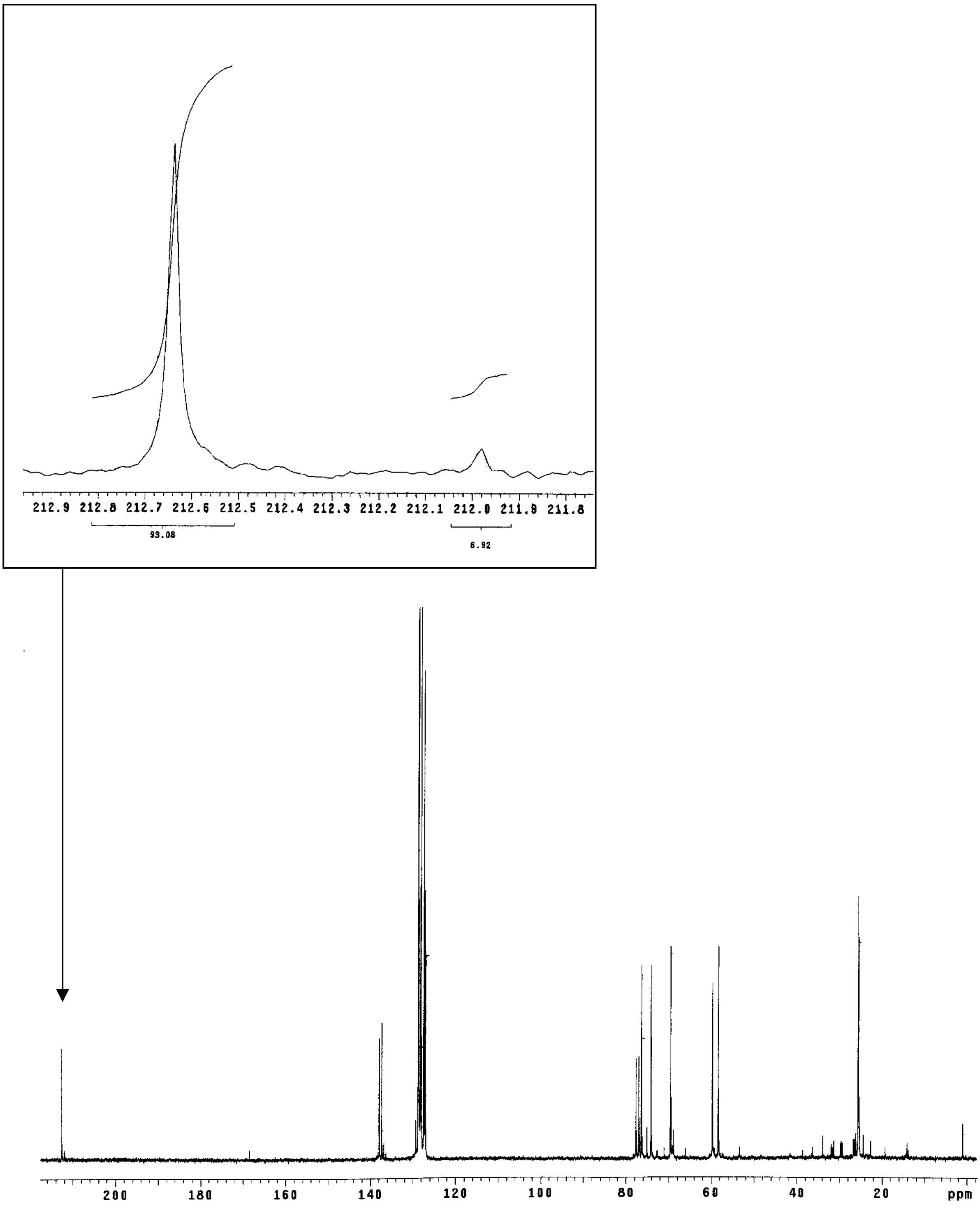

16

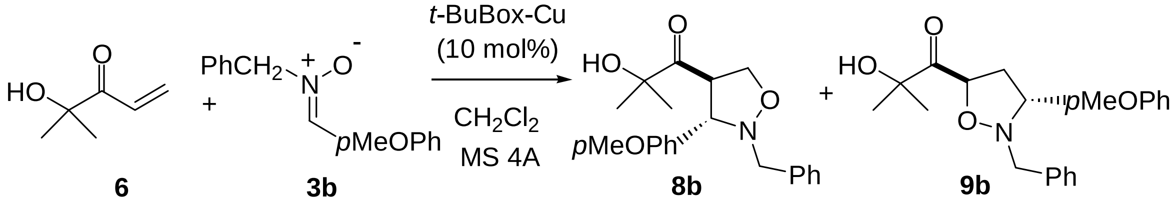
	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type	Peak Codes
1		17.167	720529	3.01	8816	bb	Unknown	I08
2		21.320	23210482	96.99	188006	bb	Unknown	

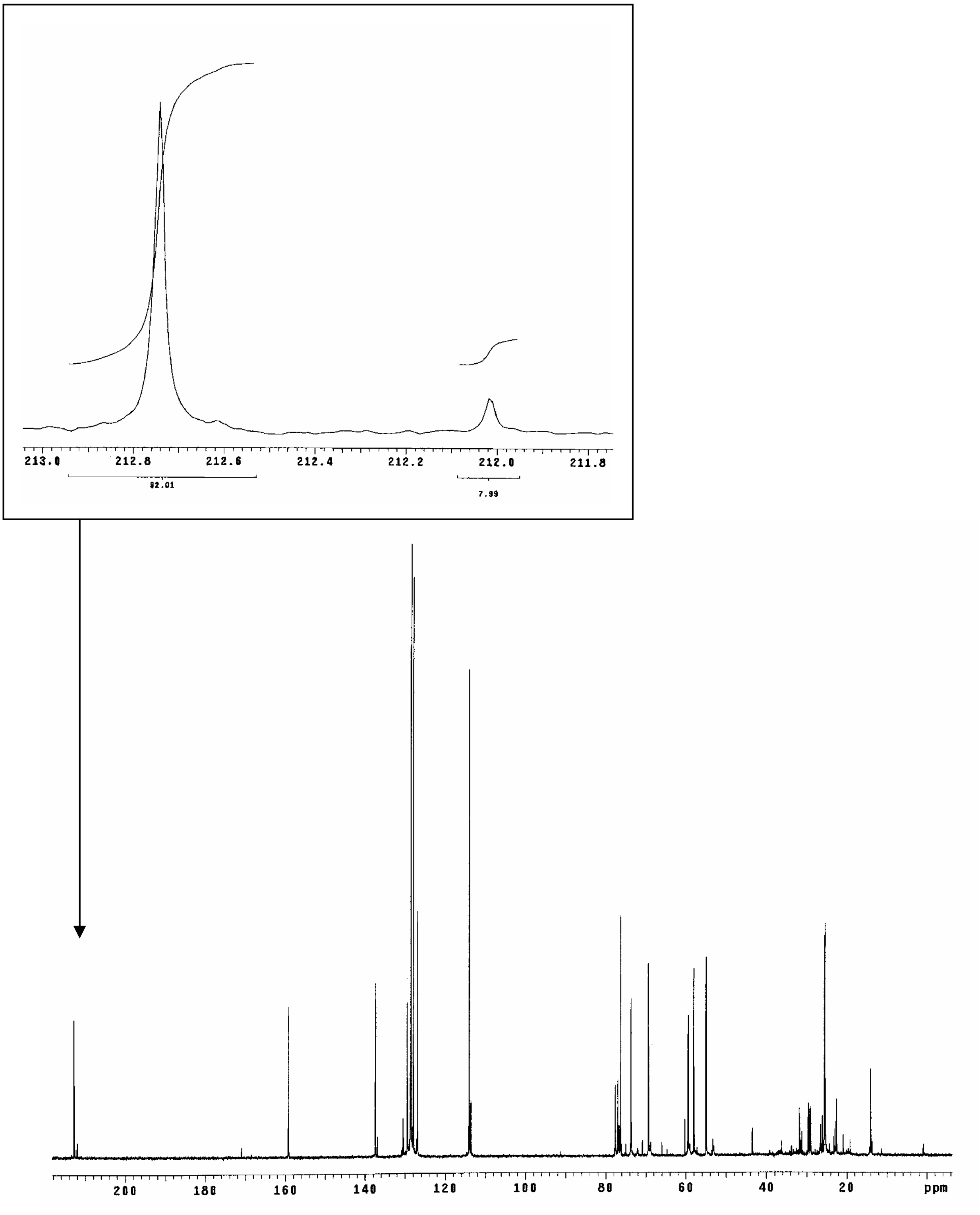

ent-16

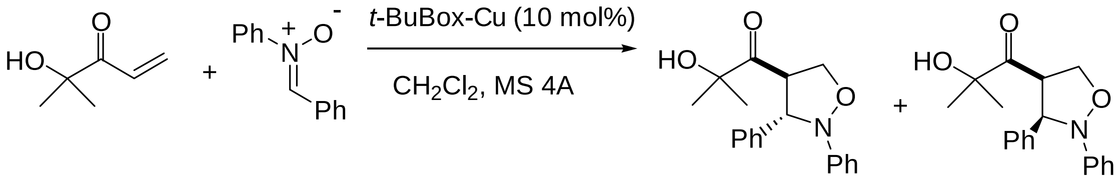
P) Determination of isomeric ratios by ^{1}H NMR



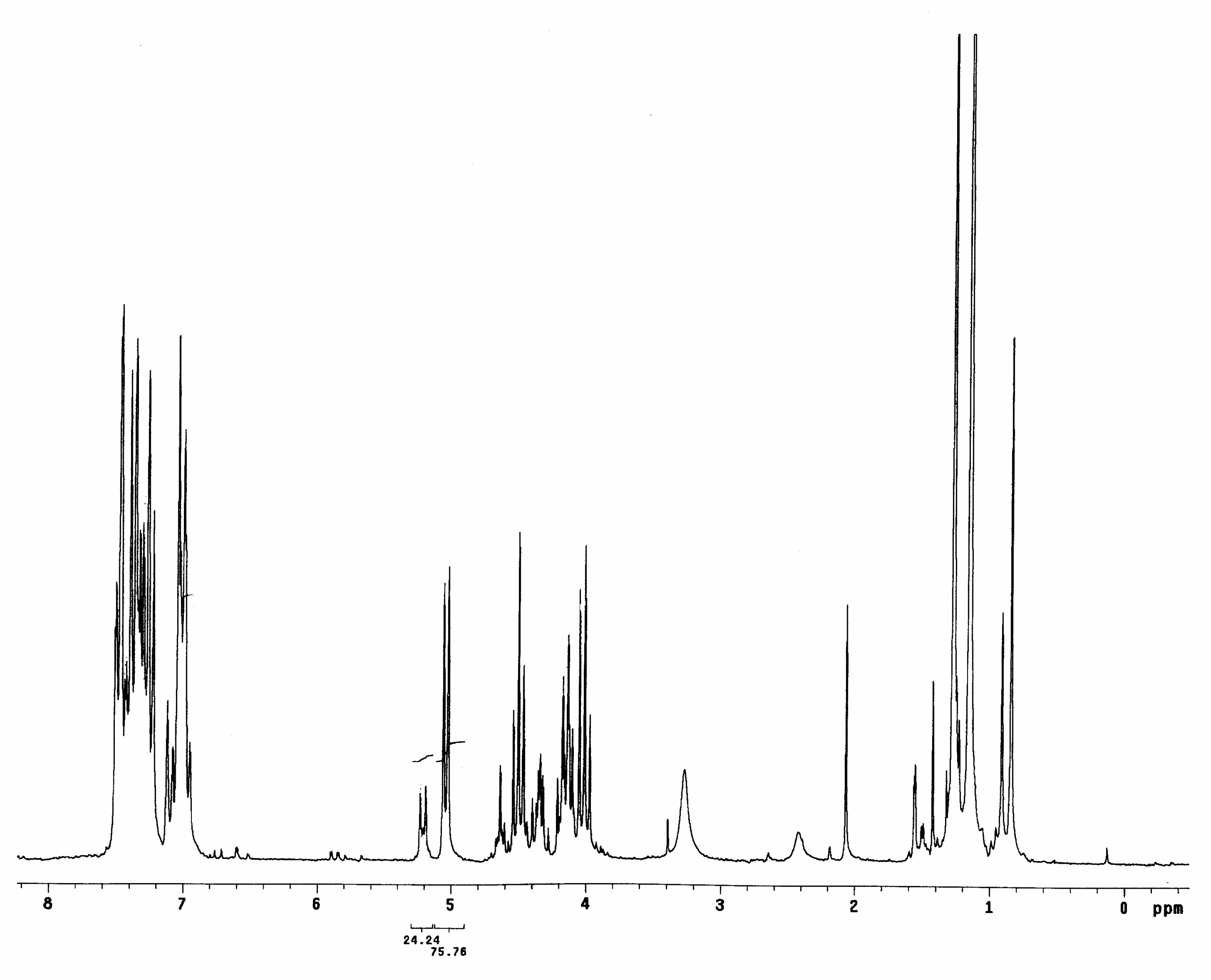



t-BuBox-Cu
(10 mol%)
CH_2Cl_2
MS 4A
HO
O
PhCH2
N
O
pMeOPh
Ph
6
3b
8b
9b


213.0
212.8
212.6
212.4
212.2
212.0
211.8
92.01
7.99
200
180
160
140
120
100
80
60
40
20
ppm

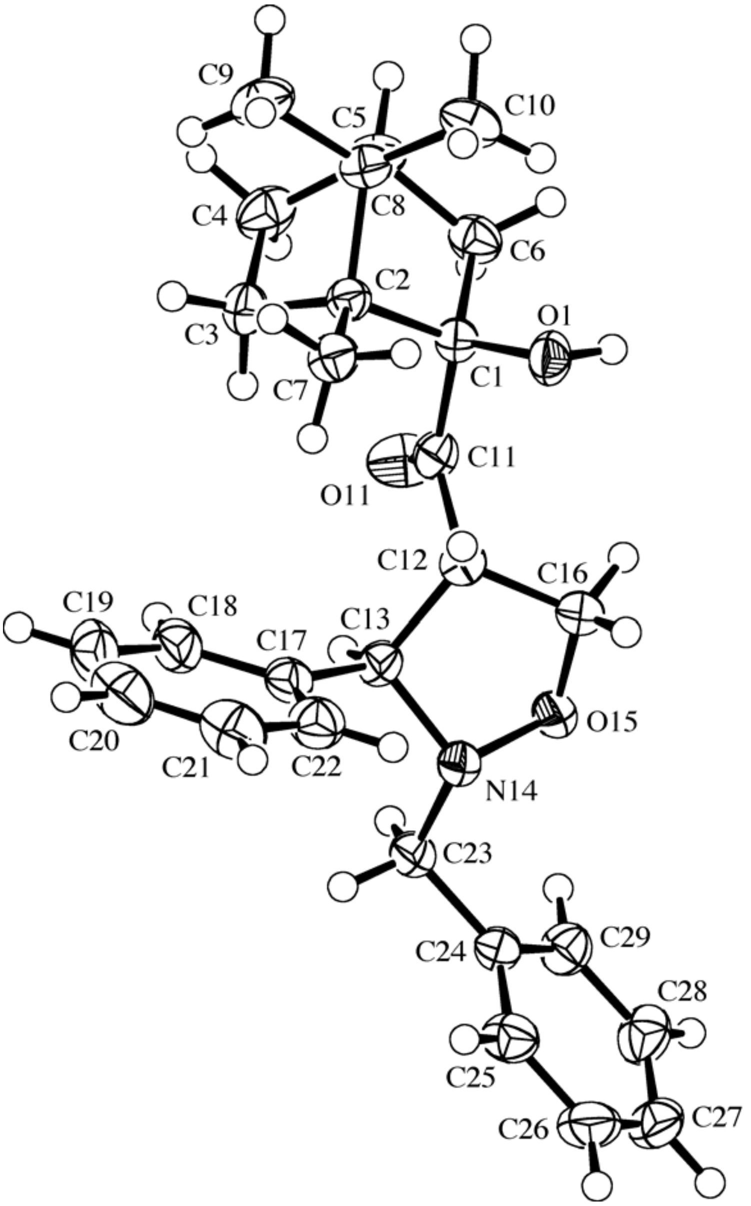


6 **3m** **8m endo** **8m exo**

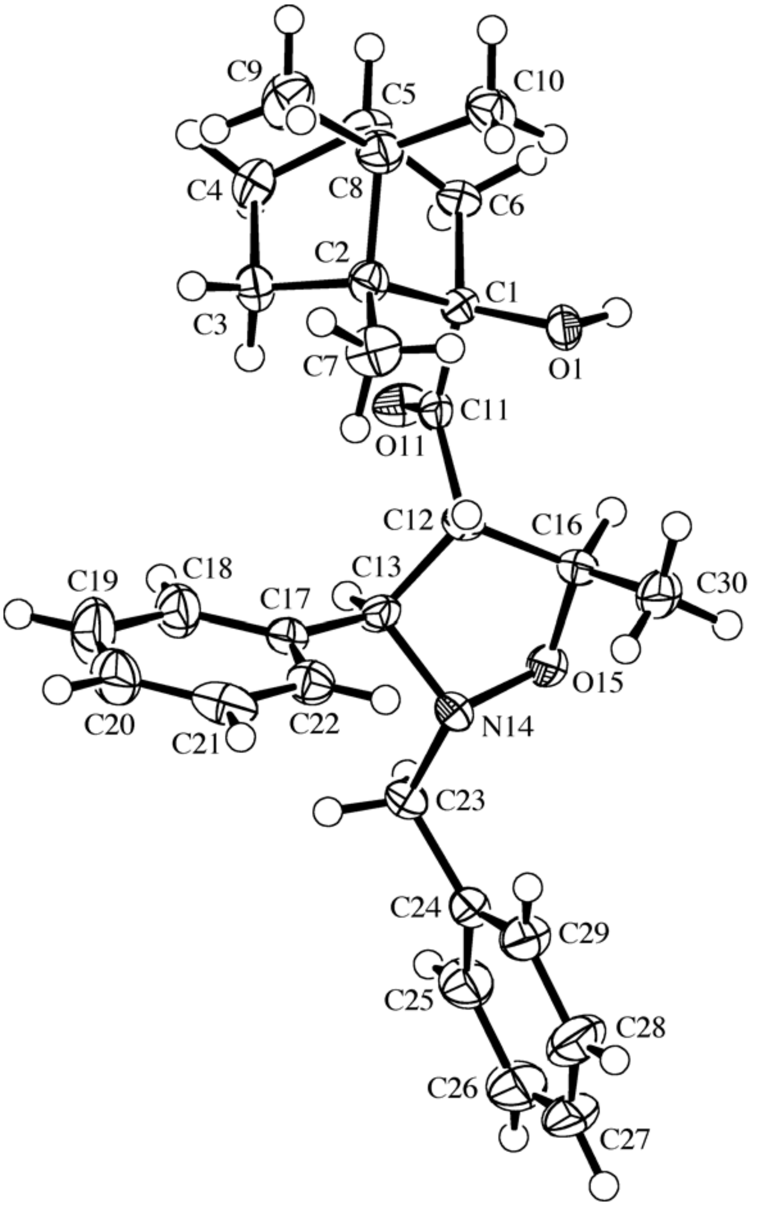


Q) ORTEP diagrams of compounds **4a**, **5a**, **8m**, and **9a**.

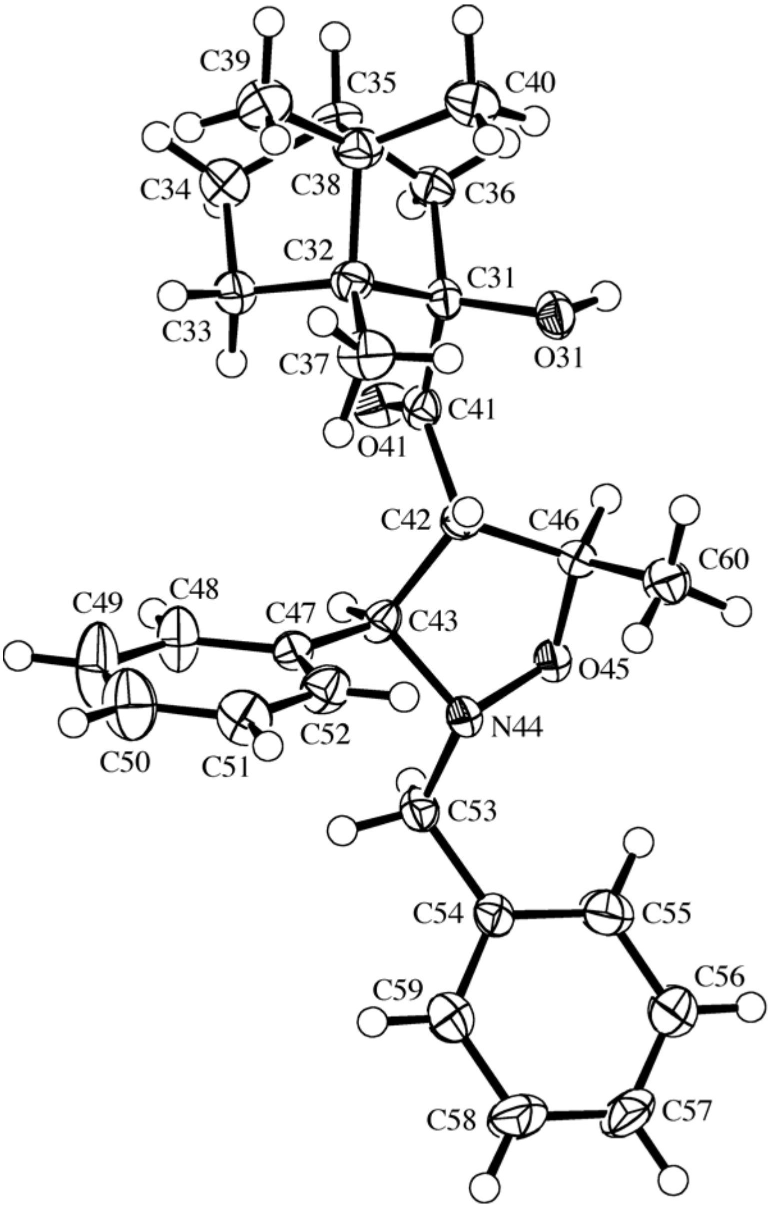
ORTEP diagram of compound **4a**



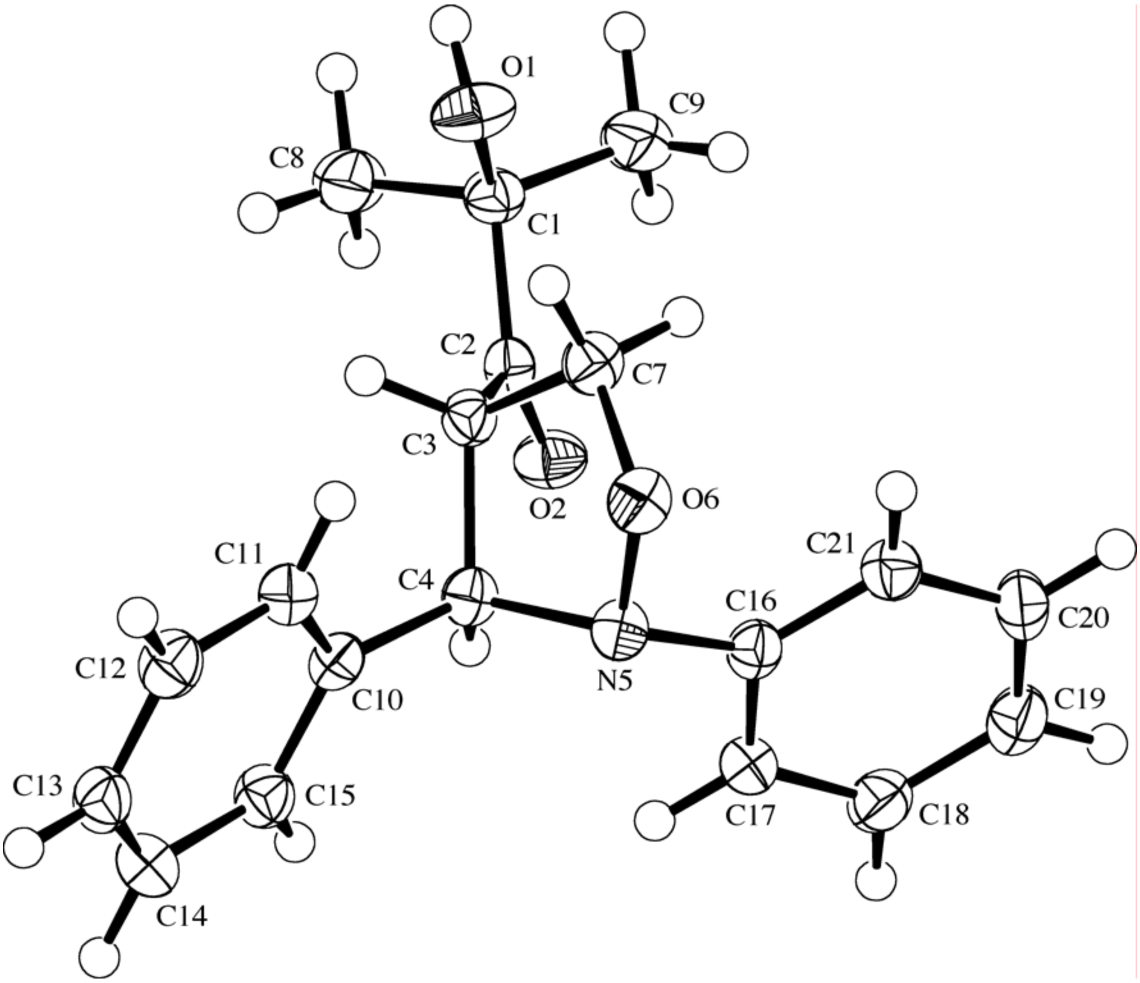
ORTEP diagram of compound **5a** (Molecule A)



ORTEP diagram of compound **5a** (Molecule B)



ORTEP diagram of compound **8m**



ORTEP diagram of compound **9a**