10.1071/CH14129_AC

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Investigation of *cis*- and *trans*-4-fluoroprolines as enantioselective catalysts in a variety of organic transformations

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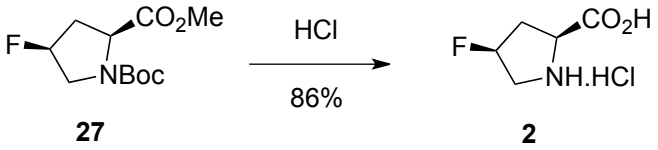
SUPPLEMENTARY MATERIAL

Contents:

Synthetic procedures

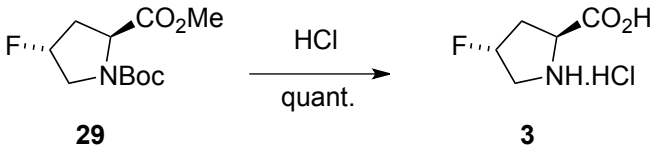
Cis-4-fluoroproline hydrochloride (2)



27 **2**

A solution of ester **27** (0.101 g, 0.410 mmol) in 2M aq. HCl (2.0 mL) was refluxed overnight. The solution was cooled, diluted with ethanol, decolourised with activated charcoal, and filtered through Celite®. The filtrate was concentrated *in vacuo* to give the title compound as a white solid (59.9 mg, 86%); m.p. 154–156 ºC; ^{1}H NMR (300 MHz, D_2O) δ 5.51 (ddd, *J* = 2.8, 5.6, 51.8 Hz, 1H, FCH), 4.67–4.62 (m, 1H, C(O)CH), 3.90–3.79 (ddd, *J* = 2.1, 13.9, 19.0 Hz, 1H, NCHH), 3.67–3.49 (ddd, *J* = 3.4, 13.9, 37.1 Hz, 1H, NCHH), 2.76–2.55 (m, 2H, CF–CH_2–CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ –175.0 (m, 1F); ^{1}H NMR data in accordance with literature values.[1]

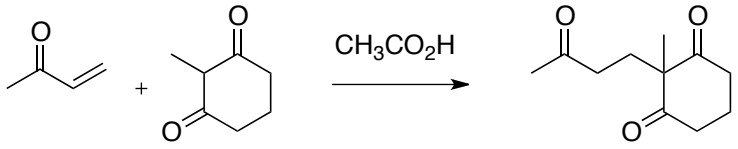
Trans-4-fluoroproline hydrochloride (3)



29 **3**

A solution of ester **29** (0.198 g, 0.802 mmol) in 2M HCl (3.5 mL) was refluxed overnight, then cooled, diluted with ethanol, decolourised with activated charcoal, and filtered through Celite®. The filtrate was then concentrated *in vacuo* to give the title compound as a white solid (0.152 g, >99%); m.p. 104–106 ^{o}C; ^{1}H NMR (300 MHz, MeOD) δ 5.42 (d, *J* = 51.6 Hz, 1H, FCH), 4.63 (m, 1H, C(O)CH), 3.84–3.49 (m, 2H, NCH_2), 2.79–2.60 (m, 2H, CF–CH_2–CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ –175.8 (m, 1F); ^{1}H NMR data in accordance with literature values.[1]

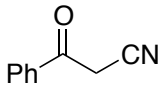
2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (14)



12 **13** **14**

Acetic acid (0.10 mL), hydroquinone (45.5 mg) and freshly distilled methyl vinyl ketone (1.3 mL, 16 mmol) were added to a well-stirred suspension of 2-methyl-1,3-cyclohexanedione (1.01 g, 7.99 mmol) and distilled water (12 mL). The mixture was stirred at 75 ºC for 1 h, then cooled to room temperature. NaCl (4.00 g) was added, followed by ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude ketone **14** as a yellow oil (0.950 g, 61%). In some cases the crude product was further purified by flash chromatography (95:1 hexane / ethyl acetate). Data for **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77–2.57 (m, 4H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 2.10 (t, J = 7.2Hz, 2H), 1.89–1.87 (m, 2H), 1.23 (s, 3H); ^{1}H NMR data in accordance with literature values.[6]

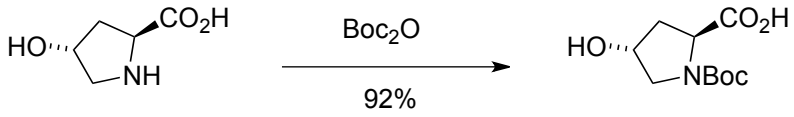
Benzoylacetonitrile (24)



24

A mixture of ethyl benzoate (10 mL, 70 mmol), freshly prepared sodium methoxide (12.7 g, 234 mmol) and acetonitrile (90 mL) was refluxed for 3 h. After cooling to room temperature, the formed white precipitate was filtered, redissolved in 3 M HCl (200 mL) and the mixture was extracted with DCM (2 × 300 mL). The combined organic layer was then washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (3:1 *n*-hexane/ethyl acetate) provided nitrile **28** as a white solid (5.78 g, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.90 (m, 2H, ArH), 7.65 (m, 1H, ArH), 7.53–7.49 (m, 2H, ArH), 4.11 (s, 2H, CH_2); ^{1}H NMR data in accordance with literature values.[7]

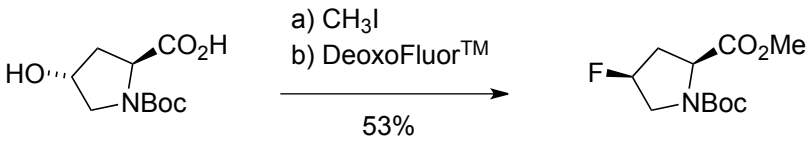
***N*-Boc-*trans*-4-hydroxyproline (26)**



26

Trans-4-hydroxyproline (5.02 g, 38.3 mmol) was dissolved in 2:1 THF/H_2O (50 mL), after which 2M NaOH solution (21 mL) and Boc_2O (10.0 g, 46.0 mmol) were added. The resulting solution was stirred overnight, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, and sat. aq. $KHSO_4$ was added to adjust to pH = 2. The solution was extracted with ethyl acetate (3 × 70 mL), and the combined organic extracts were washed with water (50 mL) and brine (50 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* to give the title compound as a pale yellow syrup (8.11 g, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49–4.32 (m, 2H, C<u>H</u>OH and C(O)CH), 3.63–3.45 (m, 2H, NCH_2), 2.39–2.06 (m, 2H, COH–C<u>H$_2$</u>–CH), 1.43 (s, 9H, $C(CH_3)_3$), rotamers; ^{1}H NMR data in accordance with literature values.[2]

***N*-Boc-*cis*-4-fluoroproline methyl ester (27)**

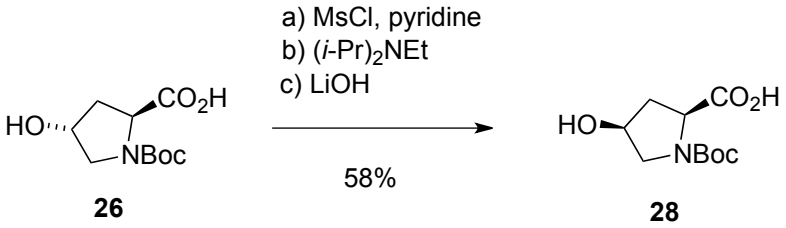


26 **27**

Iodomethane (2.5 mL, 40 mmol) was added to a mixture of acid **26** (7.56 g, 32.7 mmol), DMF (120 mL) and K_2CO_3 (22.4 g) at 0 ºC, and the mixture was stirred overnight. The solution was then quenched with water (120 mL), extracted with ethyl acetate (5 × 50 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to give *N*-Boc-*trans*-4-hydroxyproline methyl ester as a yellow syrup (5.73 g, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48–4.36 (m, 2H, C<u>H</u>OH and C(O)CH), 3.73 (s, 3H, OCH_3), 3.66–3.42 (m, 2H, NCH_2), 2.34–2.02 (m, 2H, COH–C<u>H$_2$</u>–CH), 1.43 (s, 9H, $C(CH_3)_3$), rotamers; ^{1}H NMR data in accordance with literature values.[3]

A solution of *N*-Boc-*trans*-4-hydroxyproline methyl ester (3.18 g, 13.0 mmol) in dry DCM (200 mL) was cooled to –78 ºC. DeoxoFluor™ (3.7 mL, 20.1 mmol) was added, and the mixture was stirred overnight while gradually warming to room temperature. The solution was then quenched with sat. $NaHCO_3$, and the organic portion was then washed with water (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (3:1 *n*-hexane/ethyl acetate) provided the title compound as a yellow syrup (2.36 g, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (d, *J* = 53.2 Hz, 1H, FCH), 4.47 (dd, *J* = 9.5, 35.2 Hz, 1H, OC–CH), 3.89–3.48 (m, 5H, OCH_3 and NCH_2), 2.53–2.20 (m, 2H, CF–C$\underline{H_2}$–CH), 1.44 (s, 9H, $C(CH_3)_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ –173.1 (m, 1F), rotamers; ^{1}H NMR data in accordance with literature values.[4]

_N_-Boc-_cis_-4-hydroxyproline (28)



26 **28**

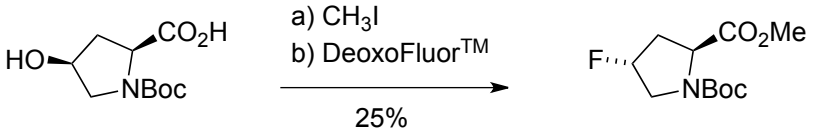
Pyridine (0.23 mL, 2.8 mmol) was added to a solution of acid **26** (0.328 g, 1.42 mmol) in anhydrous DCM (10 mL) at 0 ºC. Mesyl choride (0.22 mL, 2.8 mmol) was added, and the mixture was stirred overnight at 0 ºC. The reaction was then quenched with water (10 mL) and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* without heating to give an intermediate mesylate compound as an orange-brown syrup (0.342 g, 78%). This compound was used directly in the subsequent step without purification or characterisation.

Diisopropylethylamine (7.9 mL, 45 mmol) was added to a solution of the intermediate mesylate compound (14.0 g, 45.1 mmol) in dioxane (200 mL). The mixture was heated at 95 ºC for 2 h, then cooled and concentrated *in vacuo*. The residue was dissolved in DCM (150 mL) and washed

with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield an intermediate lactone compound as a dark brown syrup (7.50 g, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (br, 1H, OCH), 4.41–4.22 (m, 1H, NCH), 3.89–3.34 (m, 2H, NCH_2), 2.66–1.89 (m, 2H, CH–C<u>H</u>$_2$–CH), 1.41–1.13 (s, 9H, $C(CH_3)_3$), rotamers; ^{1}H NMR data in accordance with literature values.[5]

LiOH (5.35 g, 223 mmol) was added to a solution of the intermediate lactone compound (15.9 g, 74.4 mmol) in MeOH:THF:water (2:2:3, 400 mL), and the mixture was stirred overnight. The solvent was removed *in vacuo*, and ethyl acetate (200 mL) was added. The pH was adjusted to 2 by addition of sat. aq. $KHSO_4$. The solution was then saturated by addition of NaCl, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a dark brown syrup (16.3 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50–4.33 (m, 2H, C<u>H</u>OH and C(O)CH), 3.88–3.50 (m, 2H, NCH_2), 2.74–2.21 (m, 2H, COH–C<u>H</u>$_2$–CH), 1.45 (s, 9H, $C(CH_3)_3$), rotamers; ^{1}H NMR data in accordance with literature values.[2]

_N_-Boc-*trans*-4-fluoroproline methyl ester (29)

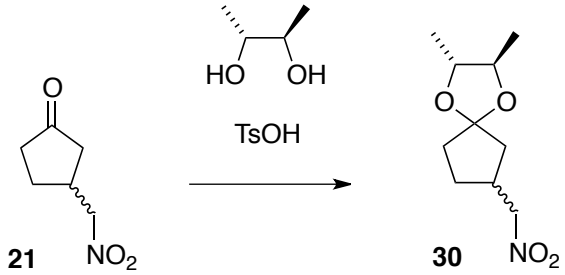


28 **29**

Iodomethane (40 μL, 0.64 mmol) was added to a mixture of acid **28** (96.2 mg, 0.416 mmol), DMF (10 mL) and K_2CO_3 (1.00 g) at 0 ºC. The mixture was stirred overnight at 0 ºC. The mixture was then quenched with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-Boc-*cis*-4-hydroxyproline methyl ester as a yellow syrup (75.7 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49–4.31 (m, 2H, C<u>H</u>OH and C(O)CH), 3.73 (s, 3H, OCH_3), 3.68–3.42 (m, 2H, NCH_2), 2.34–2.02 (m, 2H, COH–C<u>H</u>$_2$–CH), 1.43 (s, 9H, $C(CH_3)_3$), rotamers; ^{1}H NMR data in accordance with literature values.[3]

A solution of *N*-Boc-*cis*-4-hydroxyproline methyl ester (0.737 g, 3.00 mmol) in dry DCM (60 mL) was cooled to –78 ºC. DeoxoFluor™ (0.83 mL, 4.5 mmol) was added, and the mixture was stirred overnight while gradually warming to room temperature. The solution was then quenched with sat. $NaHCO_3$, and the layers were separated. The organic phase was washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (4:1 *n*-hexane/ethyl acetate) provided the title compound as a pale yellow syrup (0.252 g, 34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (d, *J* = 53.2 Hz, 1H, FCH), 4.46 (dd, *J* = 9.4, 34.8 Hz, 1H, C(O)CH), 3.88–3.47 (m, 5H, OCH_3 and NCH_2), 2.52–2.19 (m, 2H, CF–C<u>H</u>$_2$–CH), 1.43 (s, 9H, $C(CH_3)_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ –173.0 (m, 1F), rotamers; ^{1}H NMR data in accordance with literature values.[4]

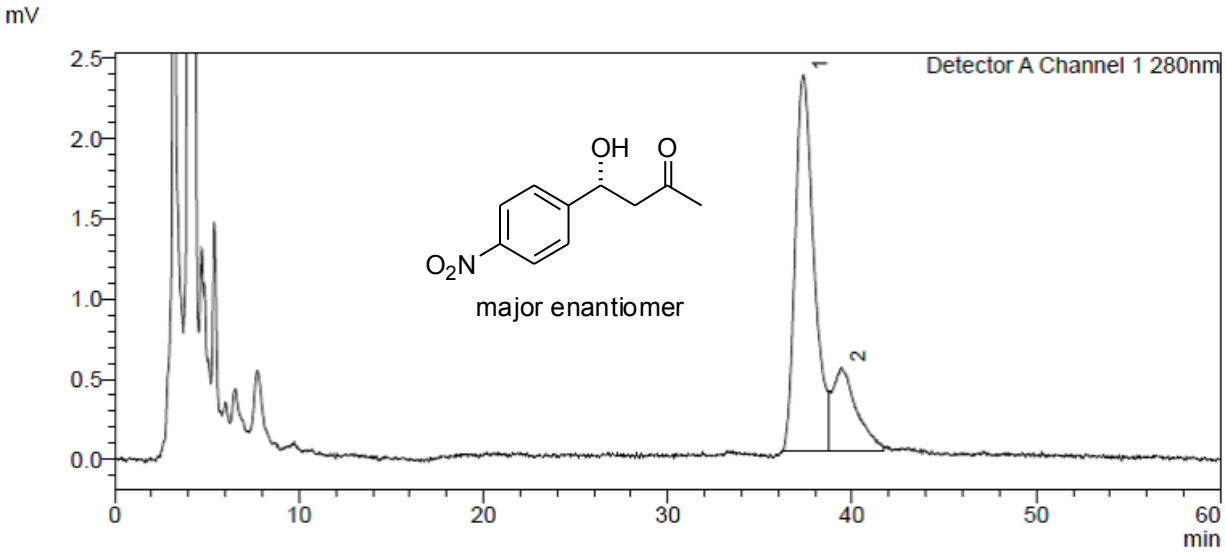
Determining the optical purity of ketone 21: formation of diastereoisomeric acetals (30)



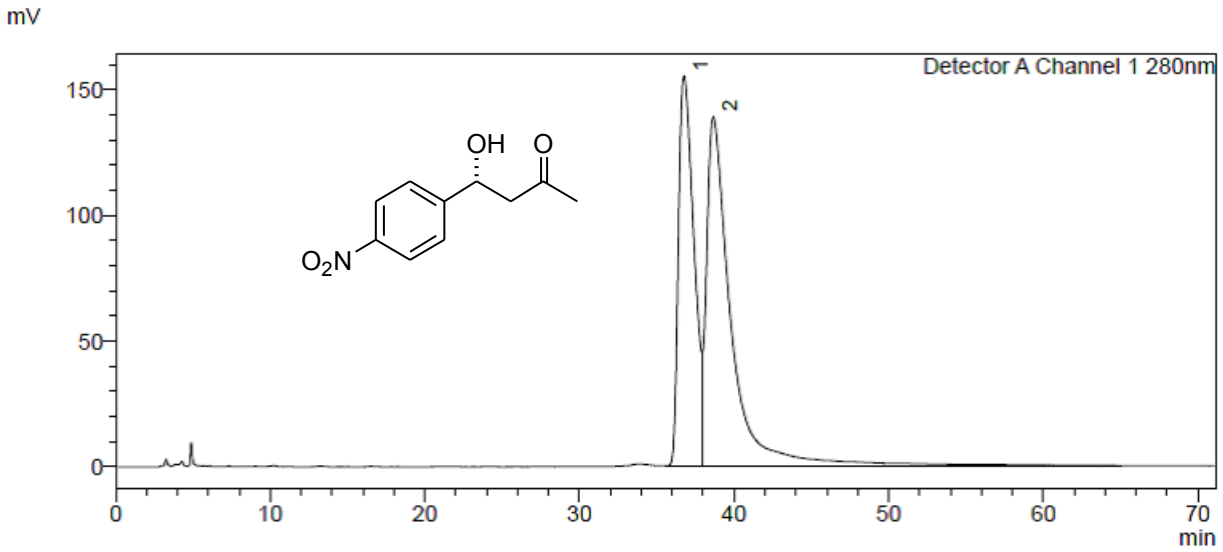
A mixture of ketone **21** (7.8 mg, 0.055 mmol), (2*R*,3*R*)-2,3-butanediol (10 µl, 0.11 mmol) and *p*-toluenesulfonic acid (5 mol%) in dry benzene (3.0 mL) was refluxed for 1 h, then cooled to room temperature, extracted with ethyl acetate (20 mL) and washed with sat. aq. $NaHCO_3$ (3 × 15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude acetal as a yellow oil (11.6 mg). The diastereoisomeric ratio was determined by ^{13}C{^{1}H} NMR analysis (100 MHz, $CDCl_3$), observing signals at δ 43.0 / 42.6, 38.4 / 38.1, 37.0 / 36.7 and 28.8 / 28.4.

HPLC Traces

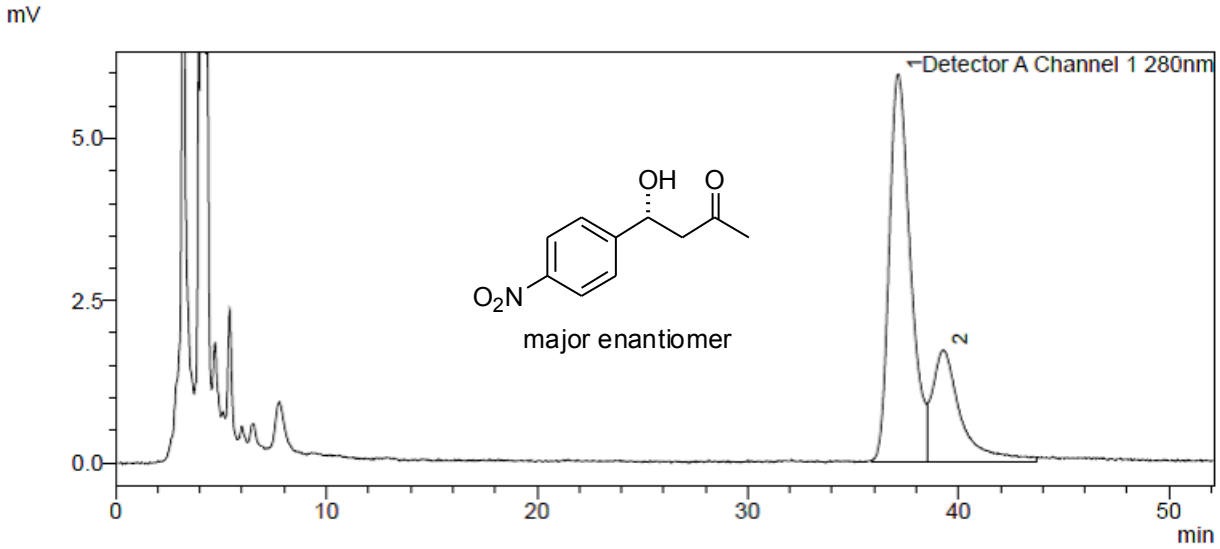
β-Hydroxyketone **11** (obtained using L-proline **1** as catalyst)



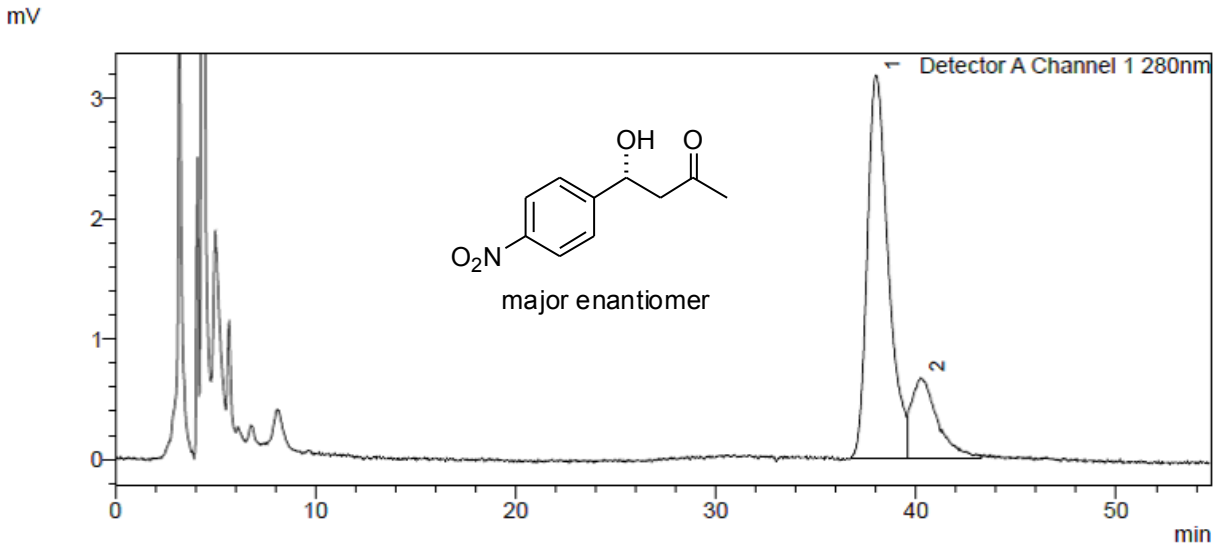
β-Hydroxyketone **11** (obtained using DL-proline as catalyst)



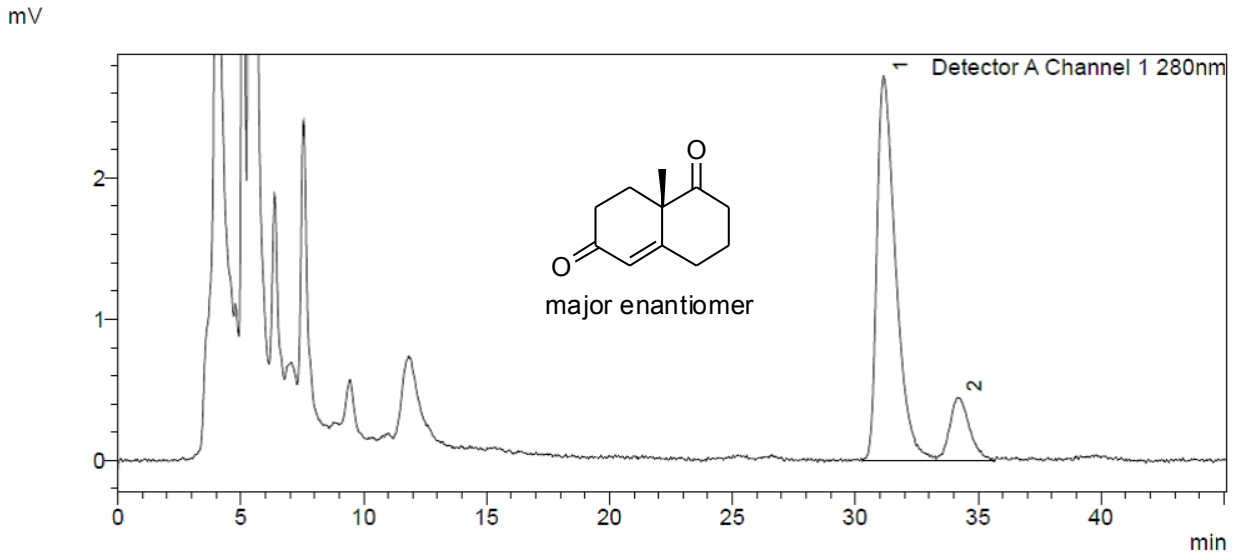
β-Hydroxyketone **11** (obtained using *cis*-4-fluoroproline **2** as catalyst)



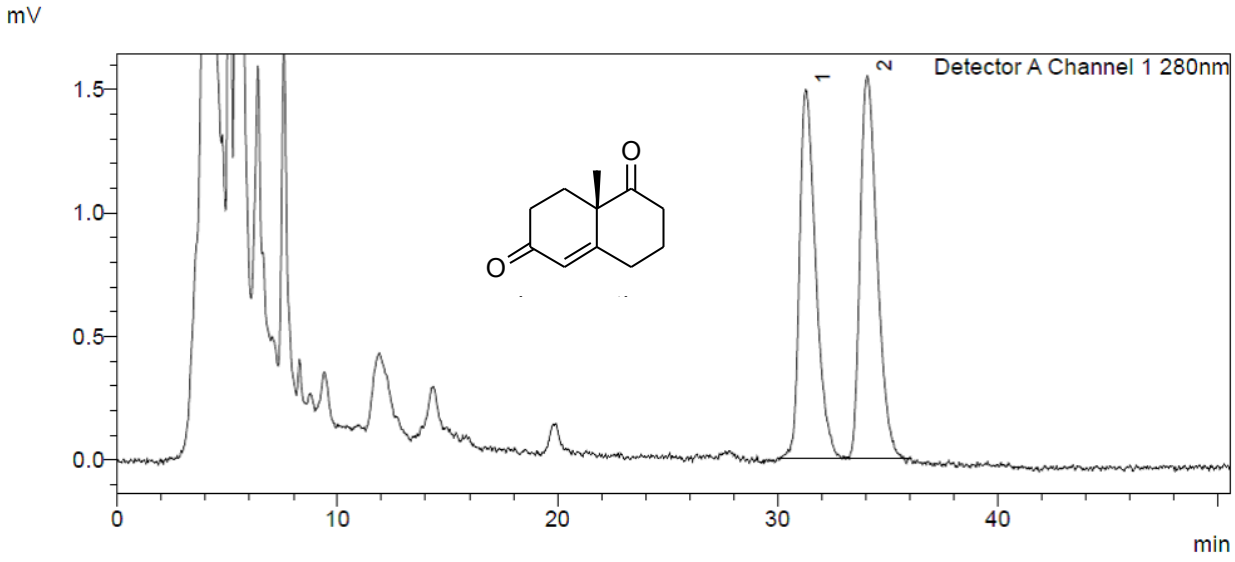
β-Hydroxyketone **11** (obtained using *trans*-4-fluoroproline **3** as catalyst)



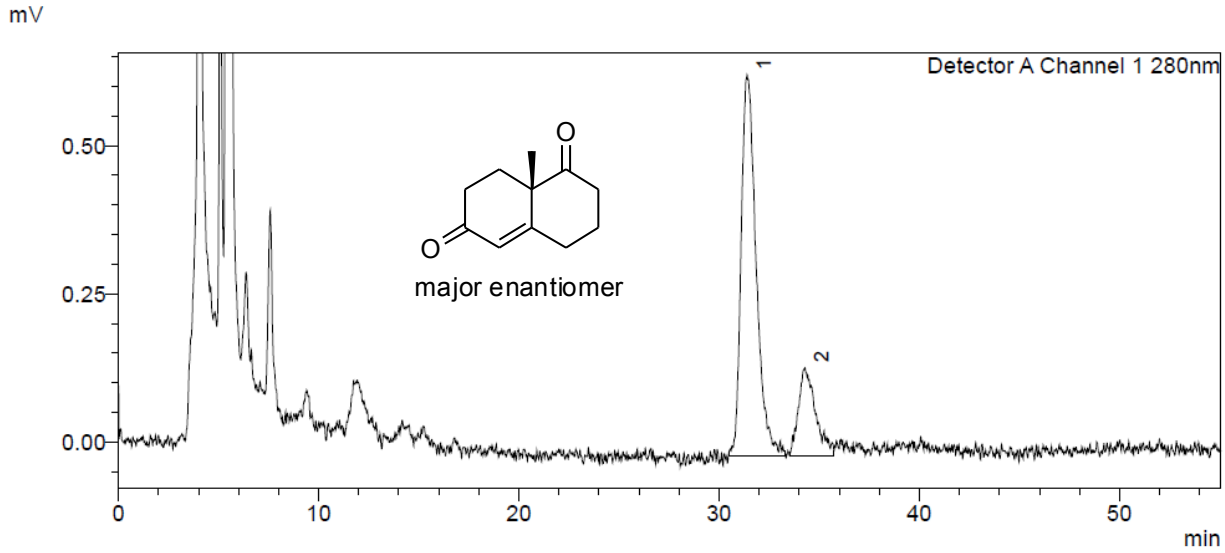
Robinson product **15** (obtained using L-proline **1** as catalyst)



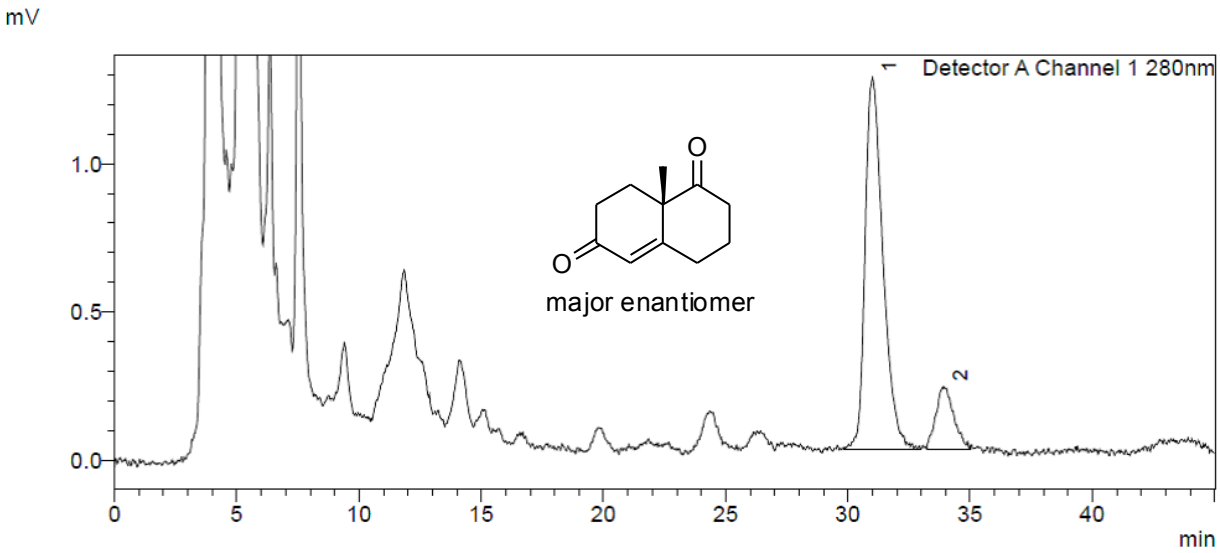
Robinson product **15** (obtained using DL-proline as catalyst)



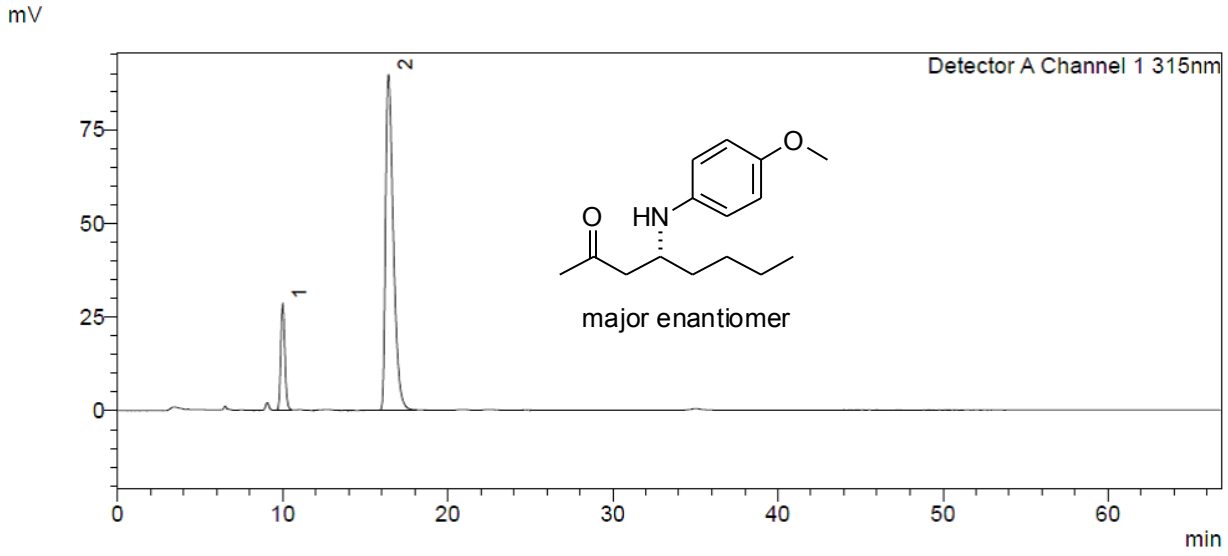
Robinson product **15** (obtained using *cis*-4-fluoroproline **2** as catalyst)



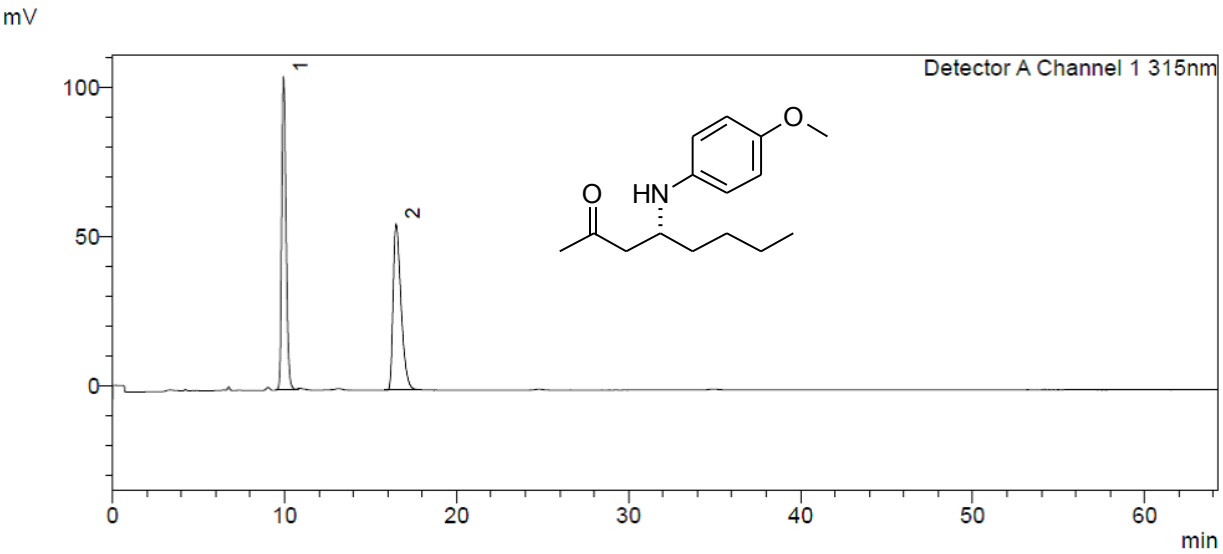
Robinson product **15** (obtained using *trans*-4-fluoroproline **3** as catalyst)



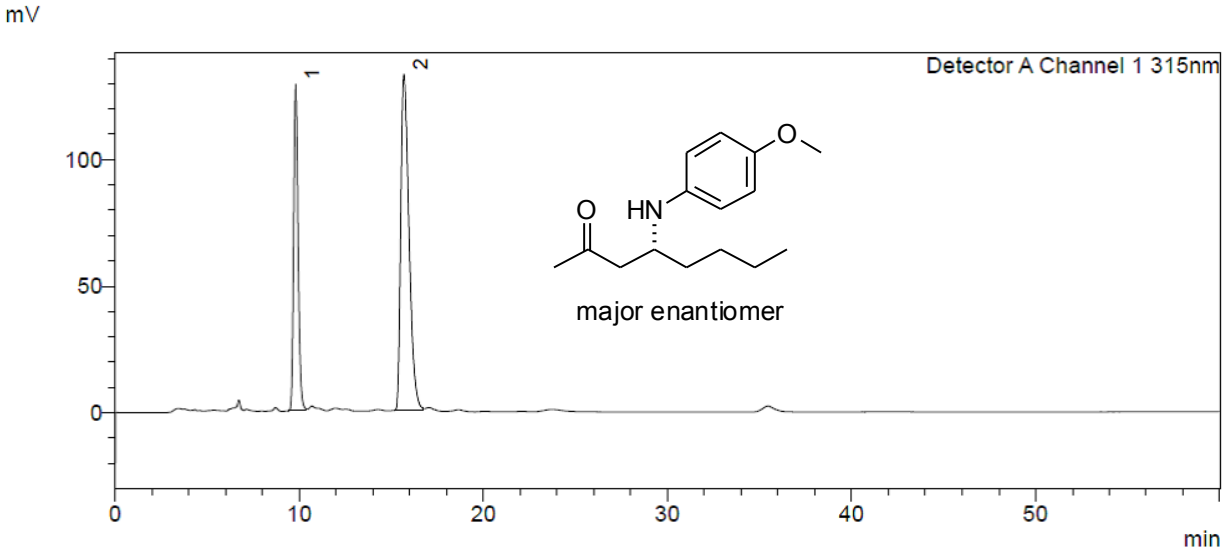
Mannich product **18** (obtained using L-proline **1** as catalyst)



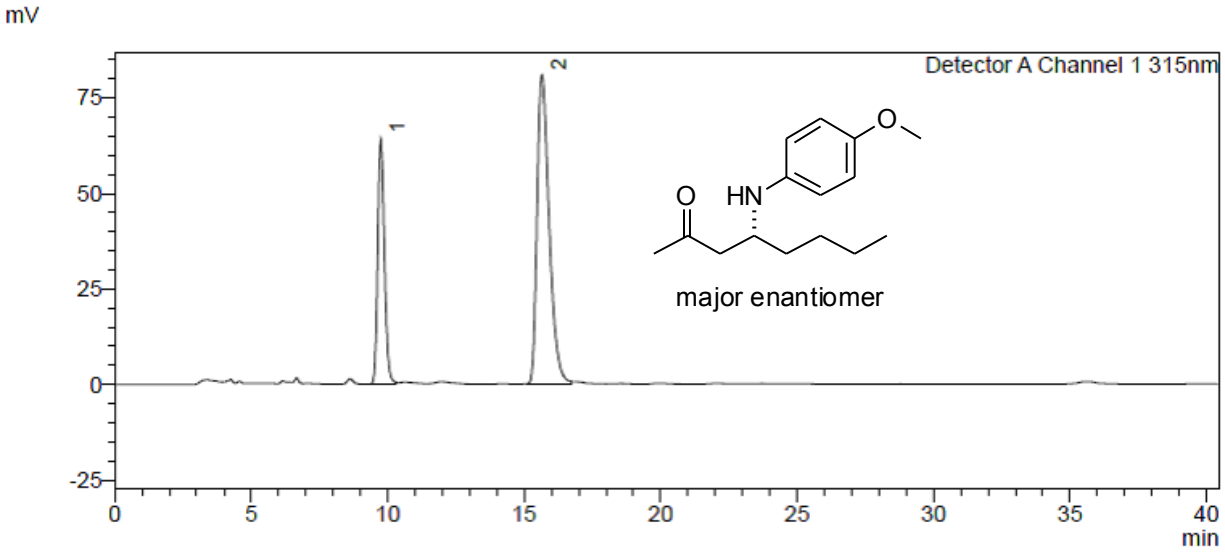
Mannich product **18** (obtained using DL-proline as catalyst)



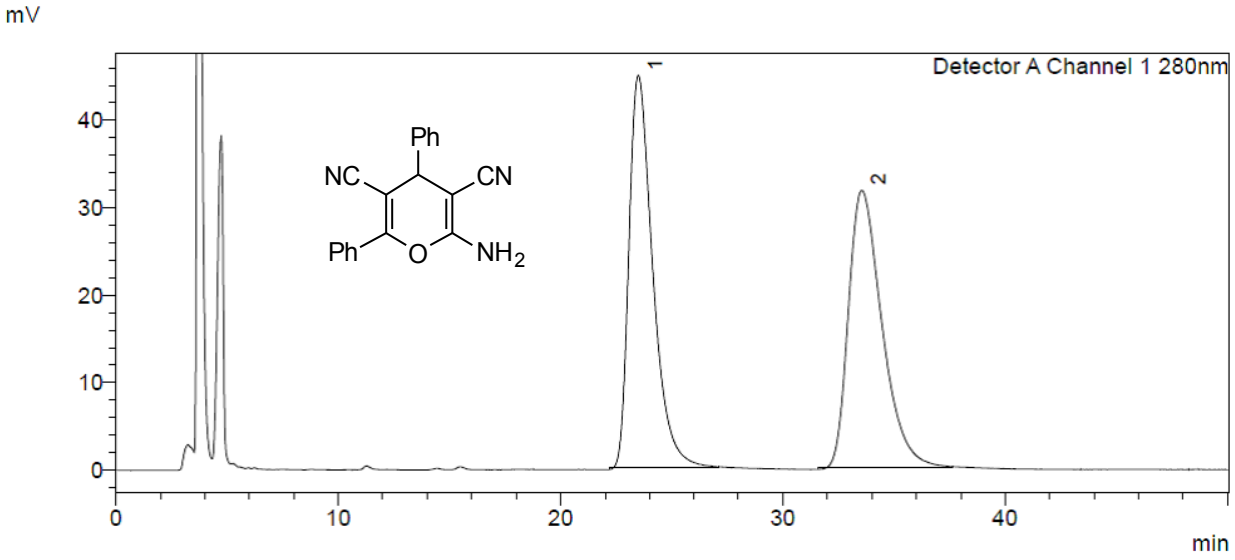
Mannich product **18** (obtained using *cis*-4-fluoroproline **2** as catalyst)



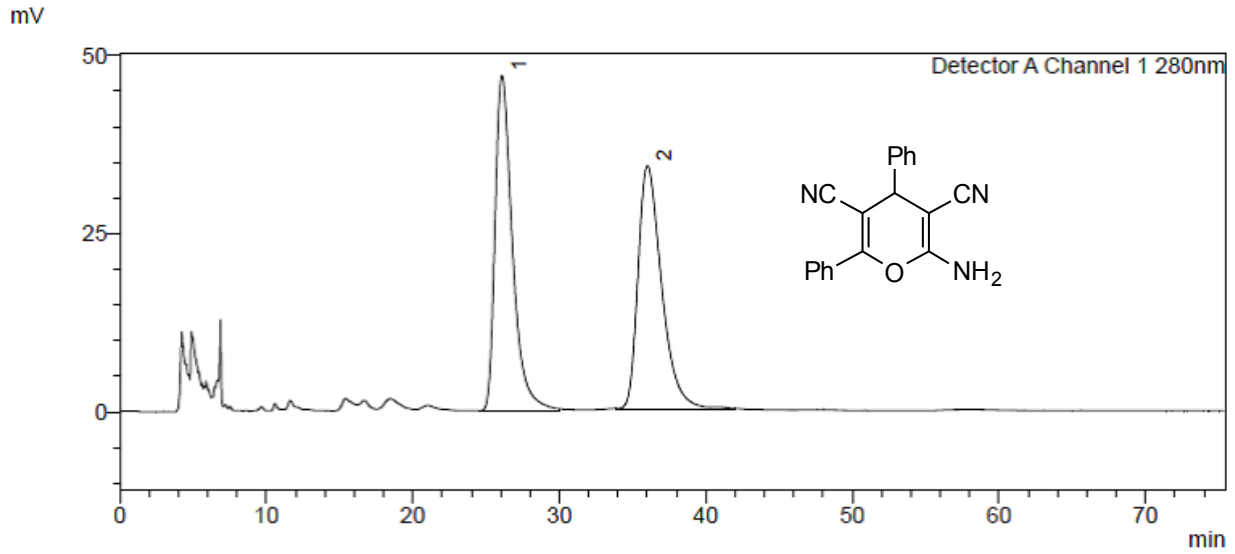
Mannich product **18** (obtained using *trans*-4-fluoroproline **3** as catalyst)



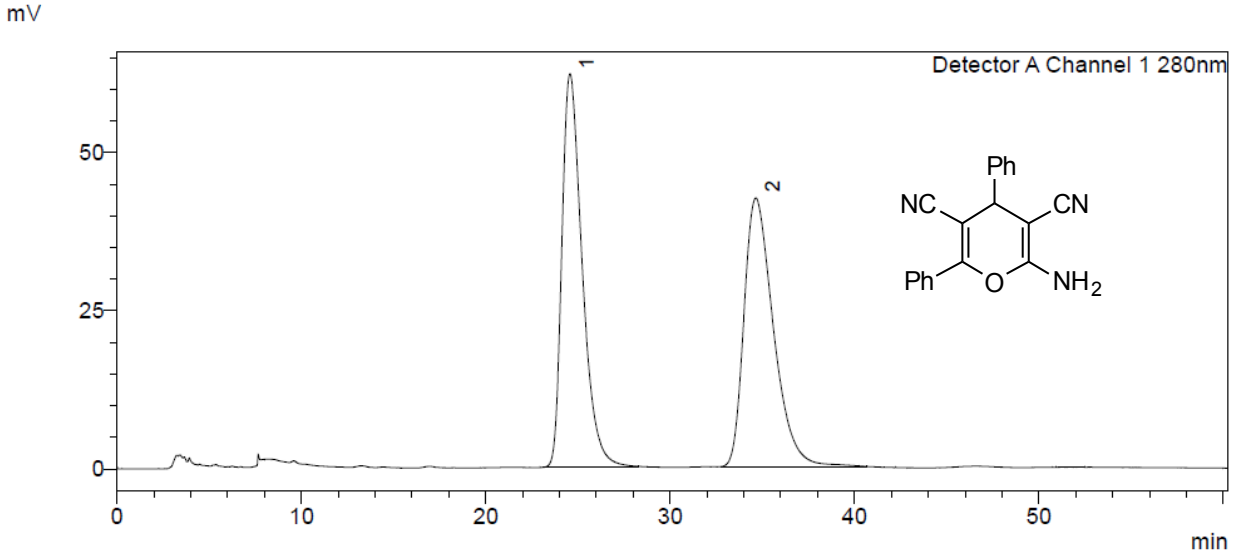
Pyran **25** (obtained using L-proline **1** as catalyst)



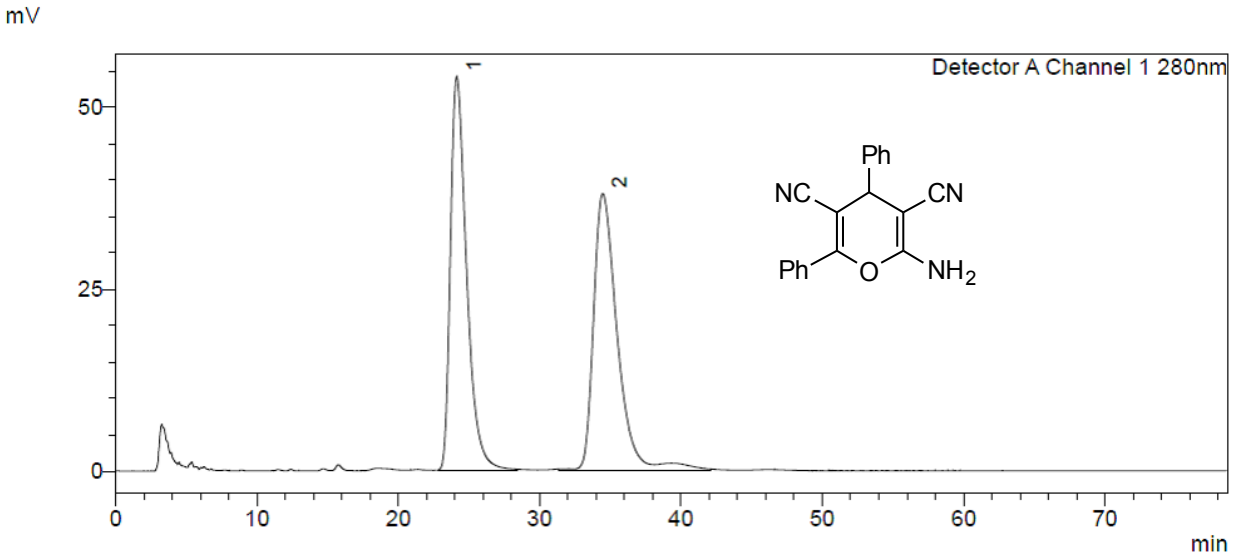
Pyran **25** (obtained using DL-proline as catalyst)



Pyran **25** (obtained using *cis*-4-fluoroproline **2** as catalyst)

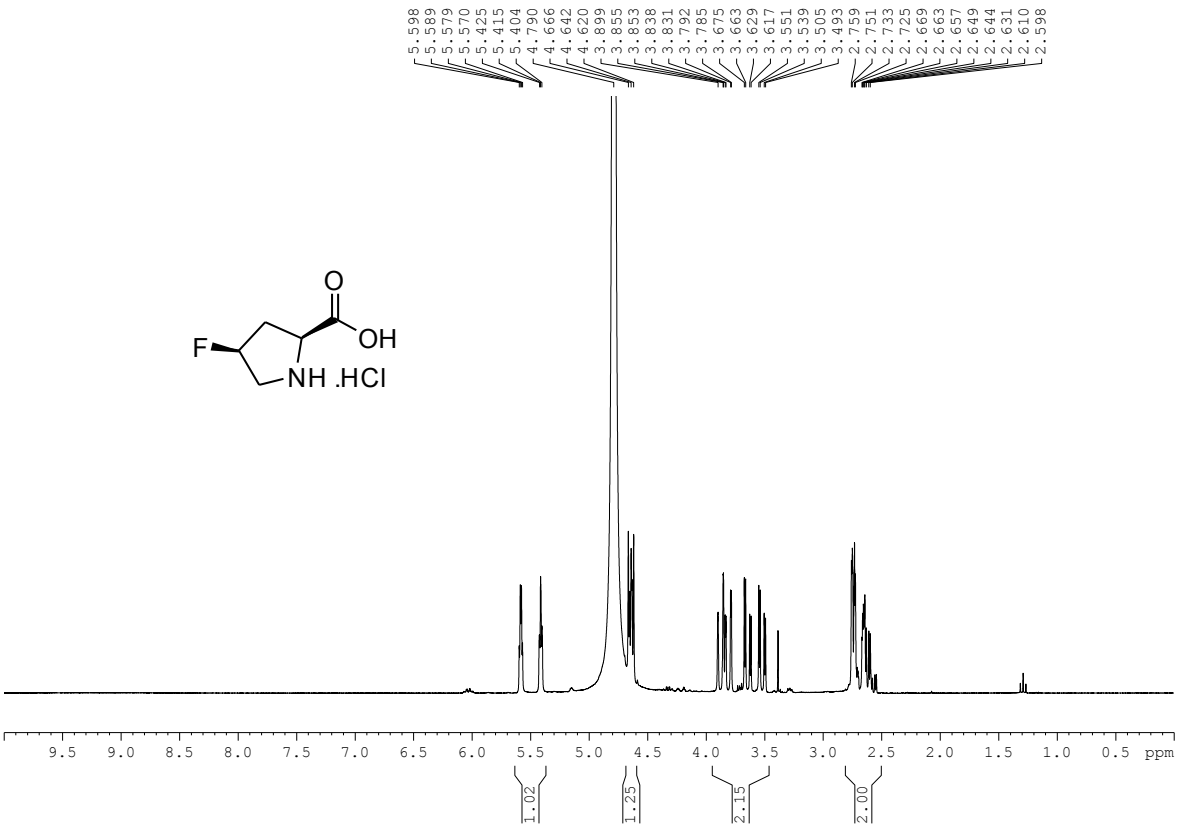


Pyran **25** (obtained using *trans*-4-fluoroproline **3** as catalyst)

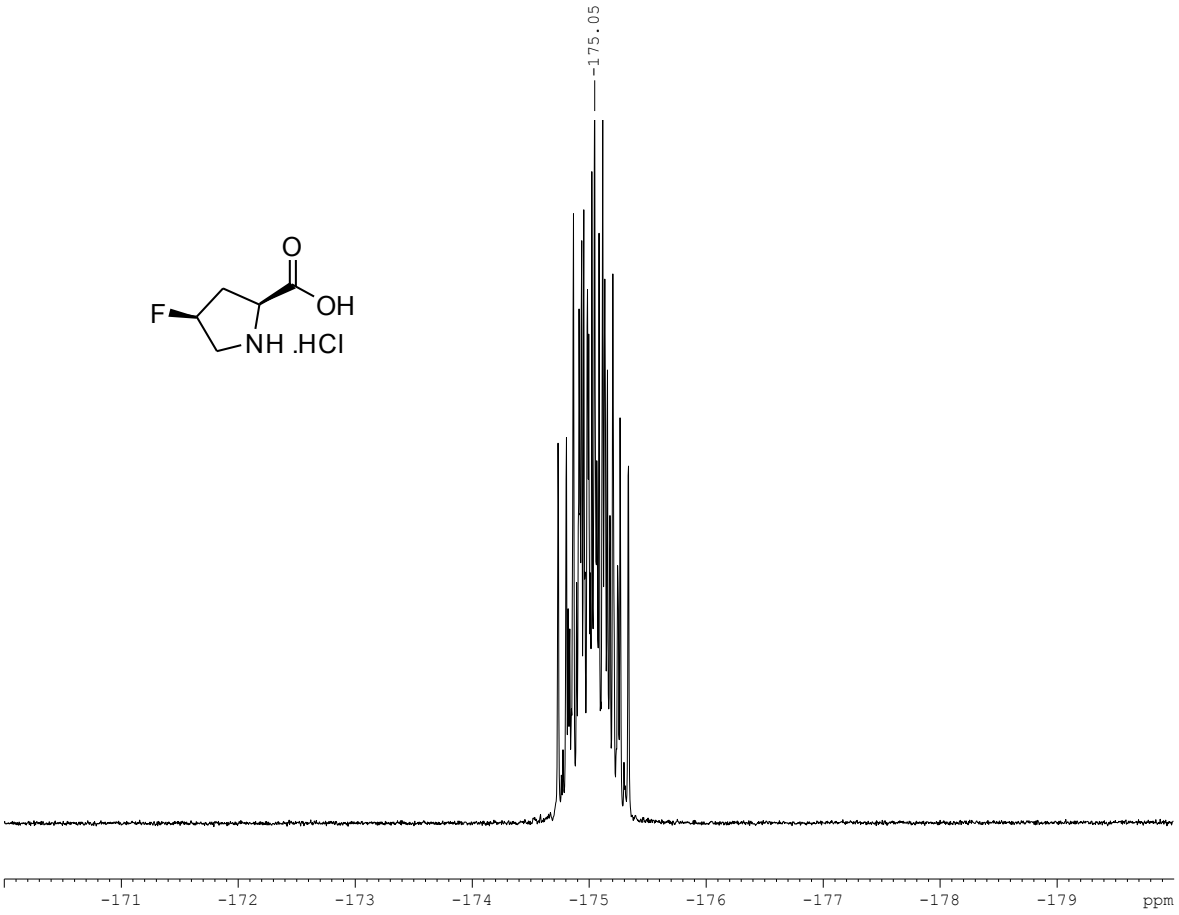


NMR Spectra

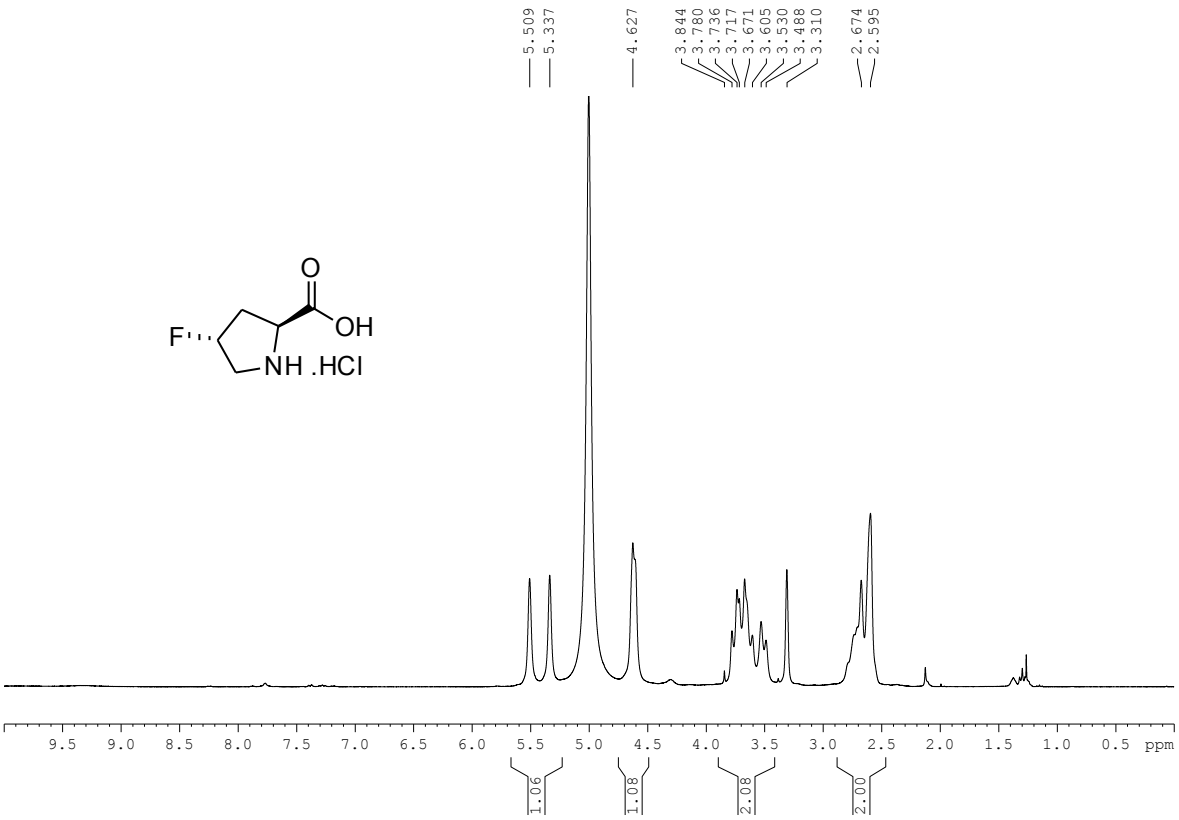
^{1}H NMR (300 MHz, D_2O) of acid **2**



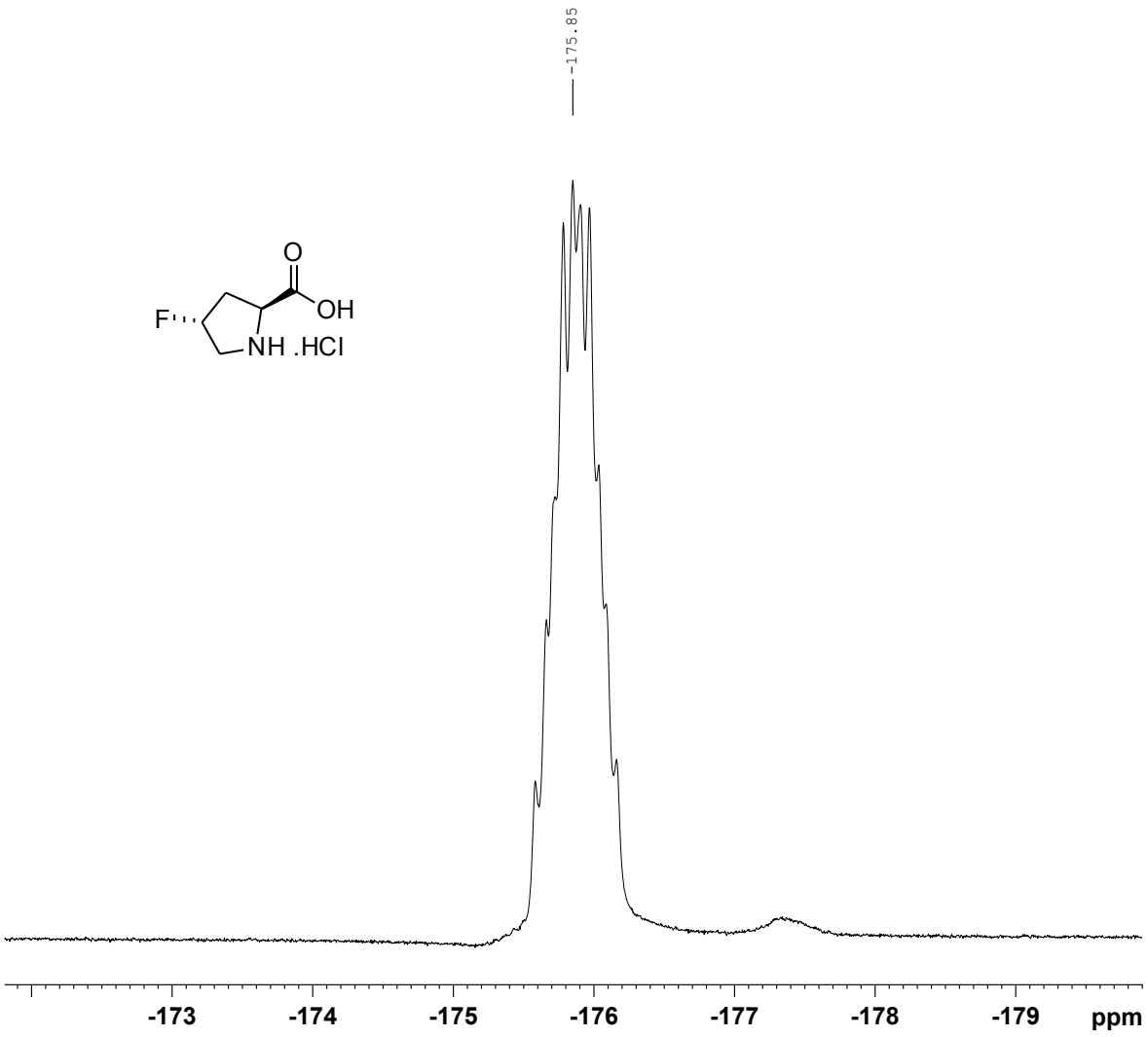
^{19}F NMR (282 MHz, D_2O) of acid **2**



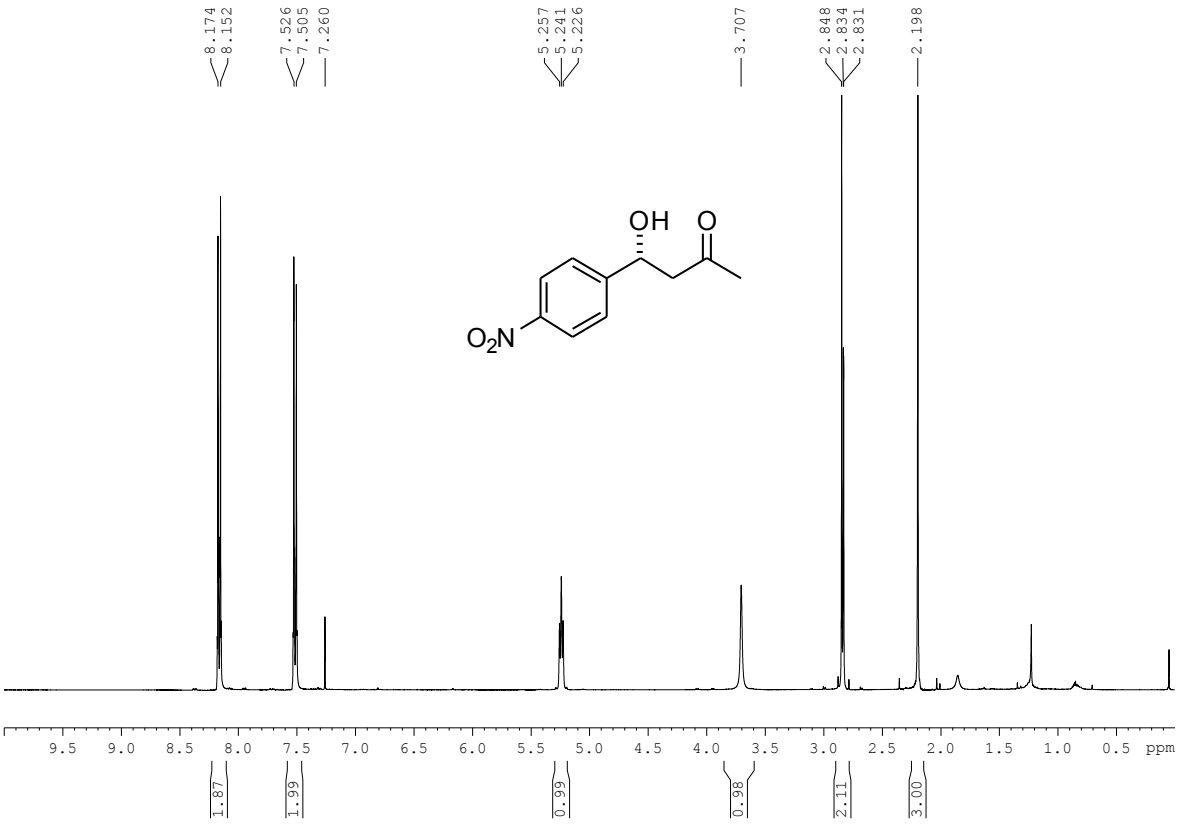
[1]H NMR (300 MHz, MeOD) of acid **3**



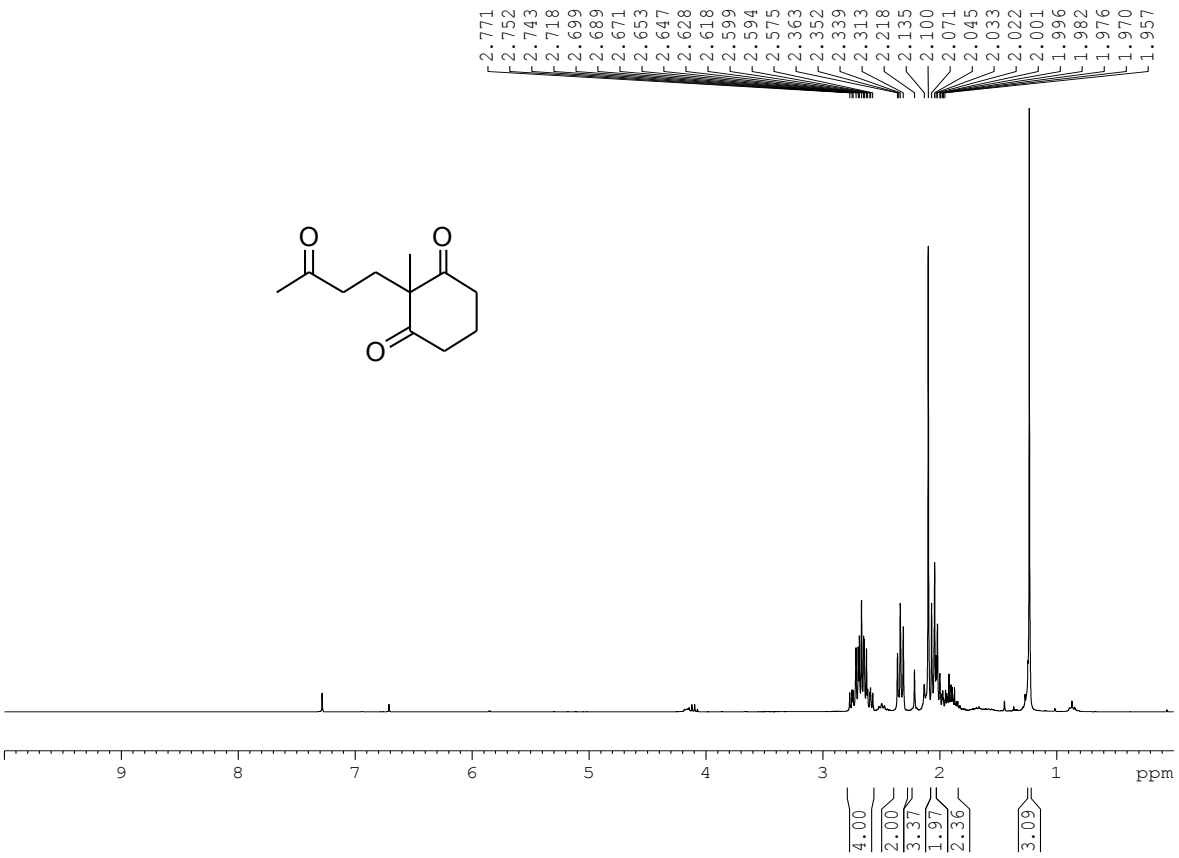
^{19}F NMR (282 MHz, MeOD) of acid **3**



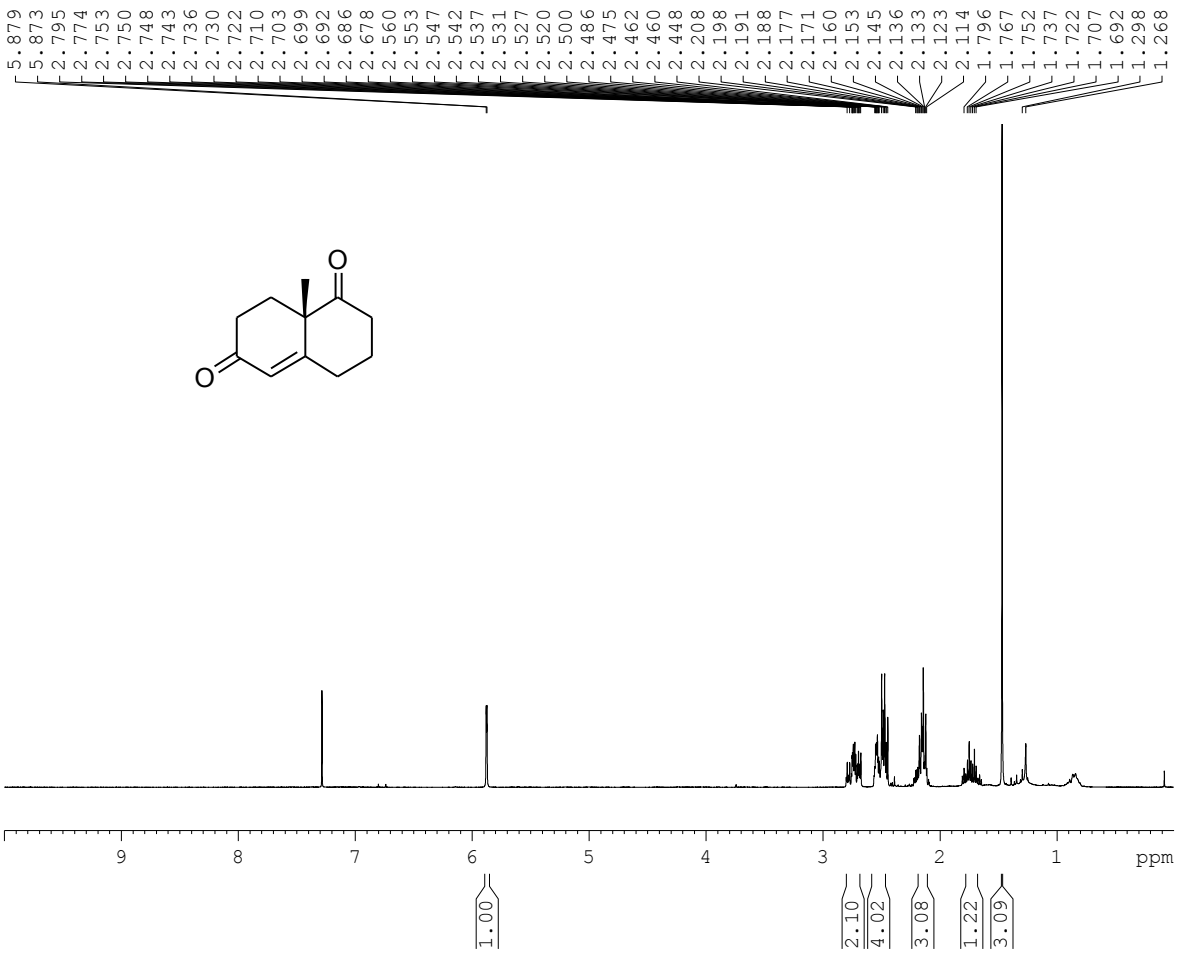
^{1}H NMR (400 MHz, $CDCl_3$) of β-hydroxyketone **11**



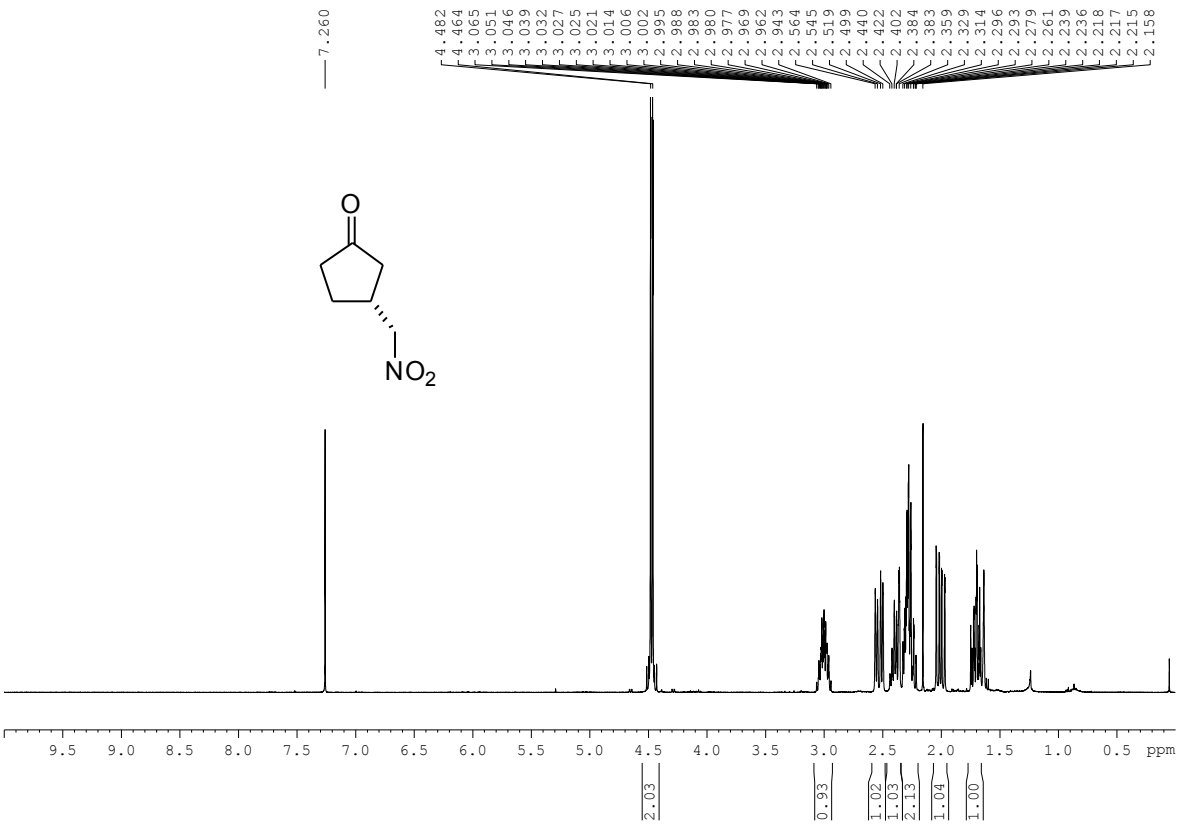
^{1}H NMR (300 MHz, $CDCl_3$) of Robinson triketone intermediate **14**



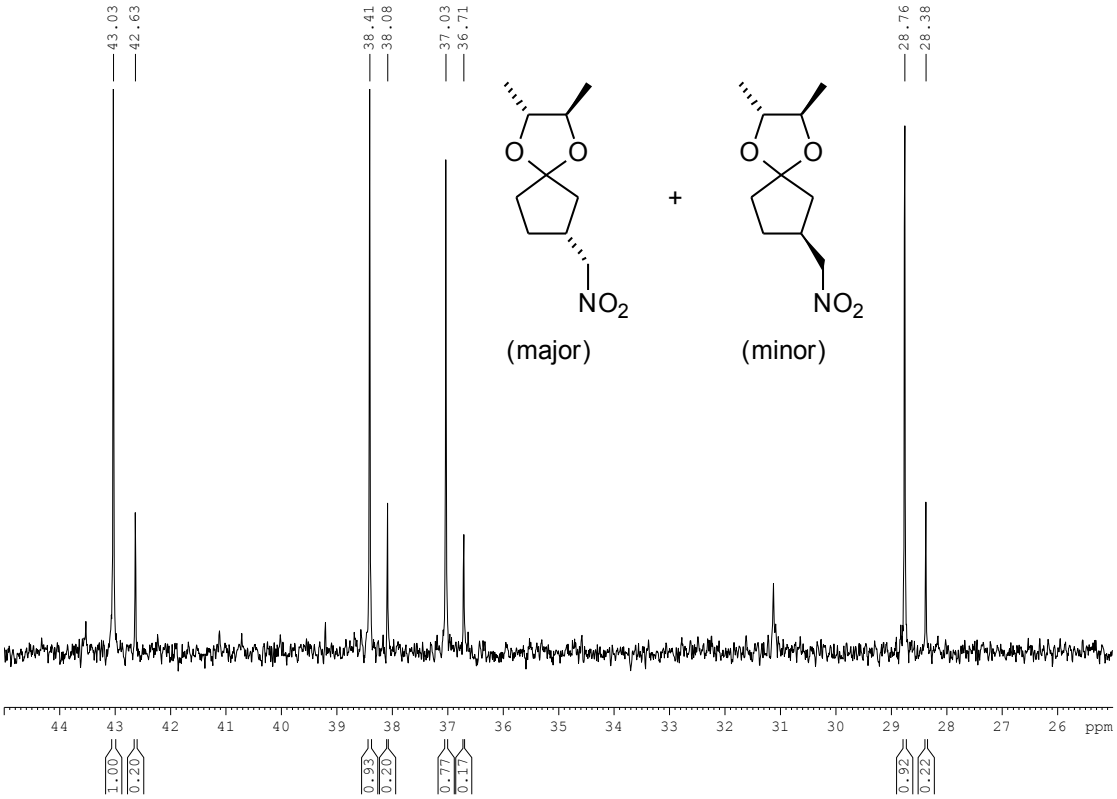
^{1}H NMR (400 MHz, $CDCl_3$) of Robinson product **14**



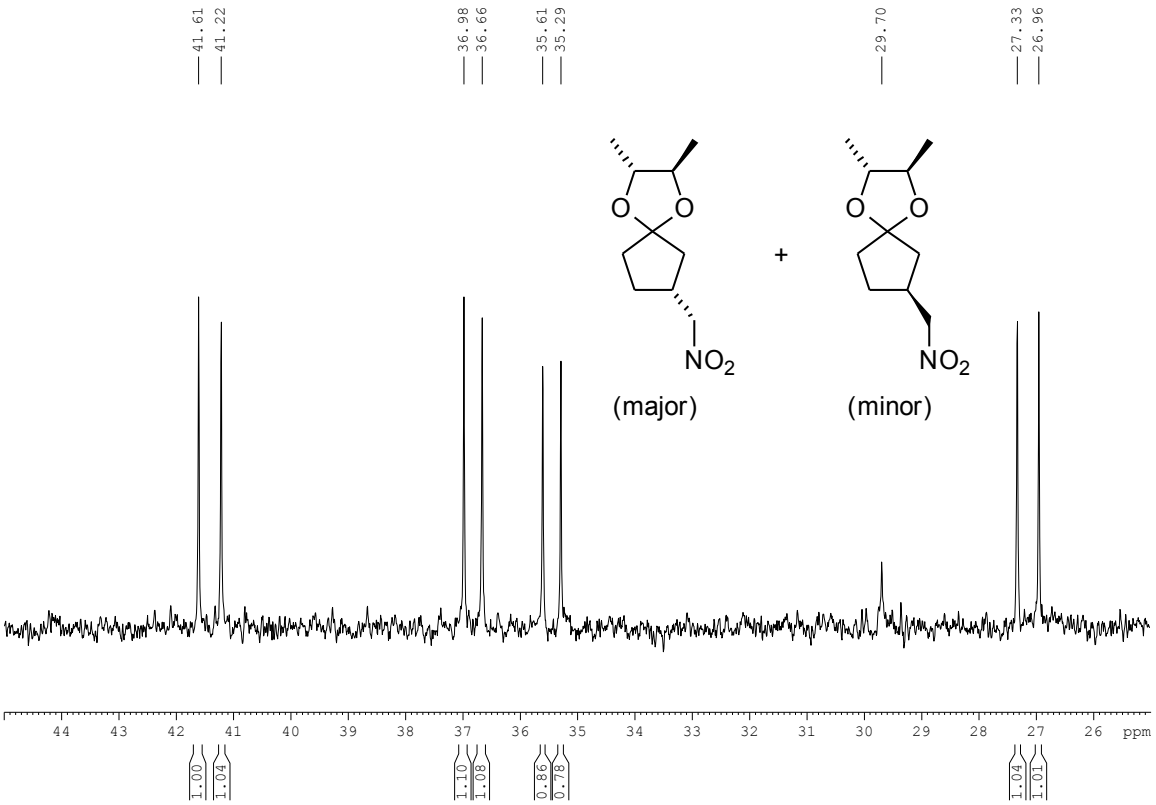
^{1}H NMR (400 MHz, $CDCl_3$) of Michael product **21**



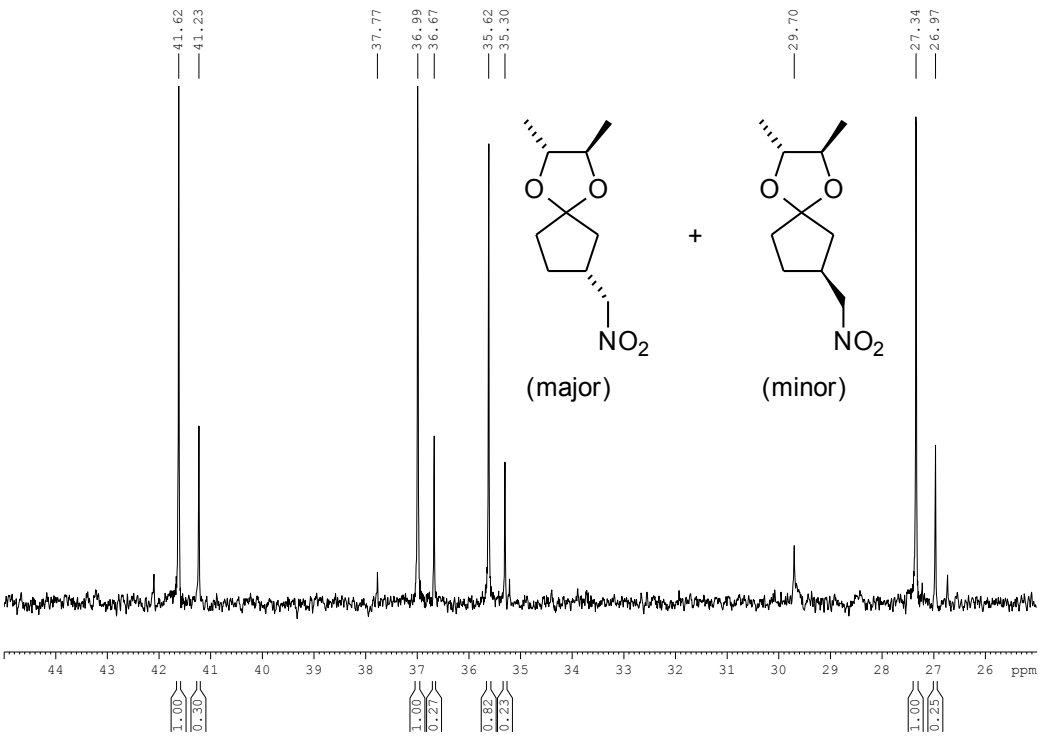
^{13}C $\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of acetals **30** (obtained using L-proline **1** as catalyst)



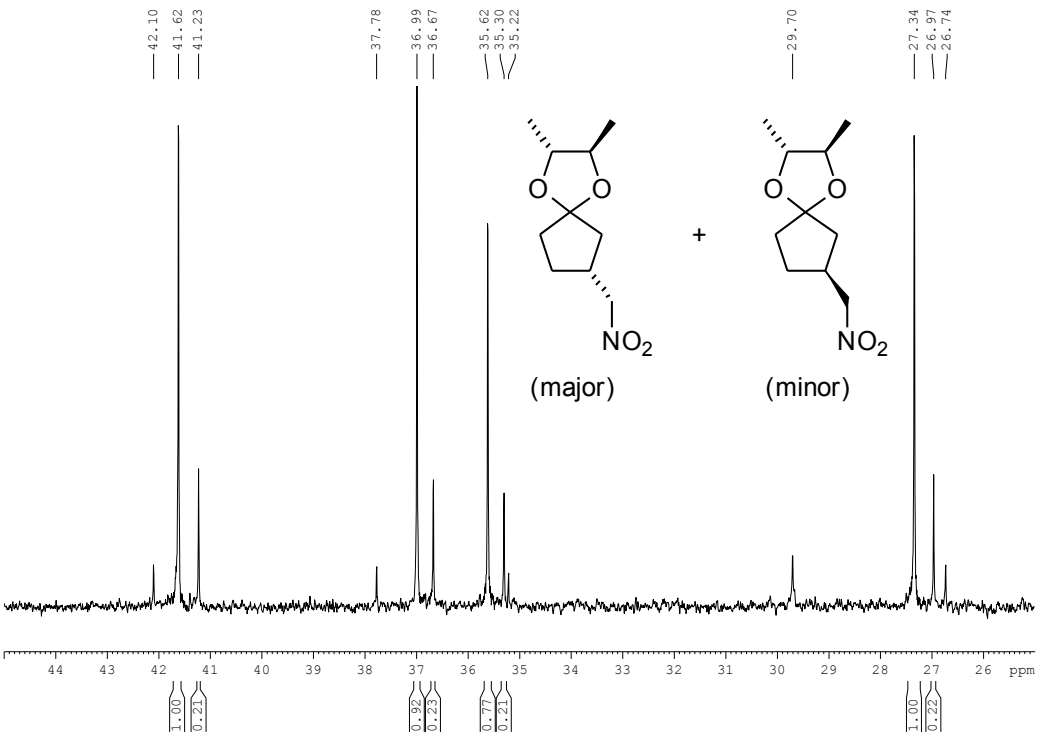
^{13}C $\{^{1}H\}$ NMR (76 MHz, $CDCl_3$) of acetals **30** (obtained using DL-proline as catalyst)



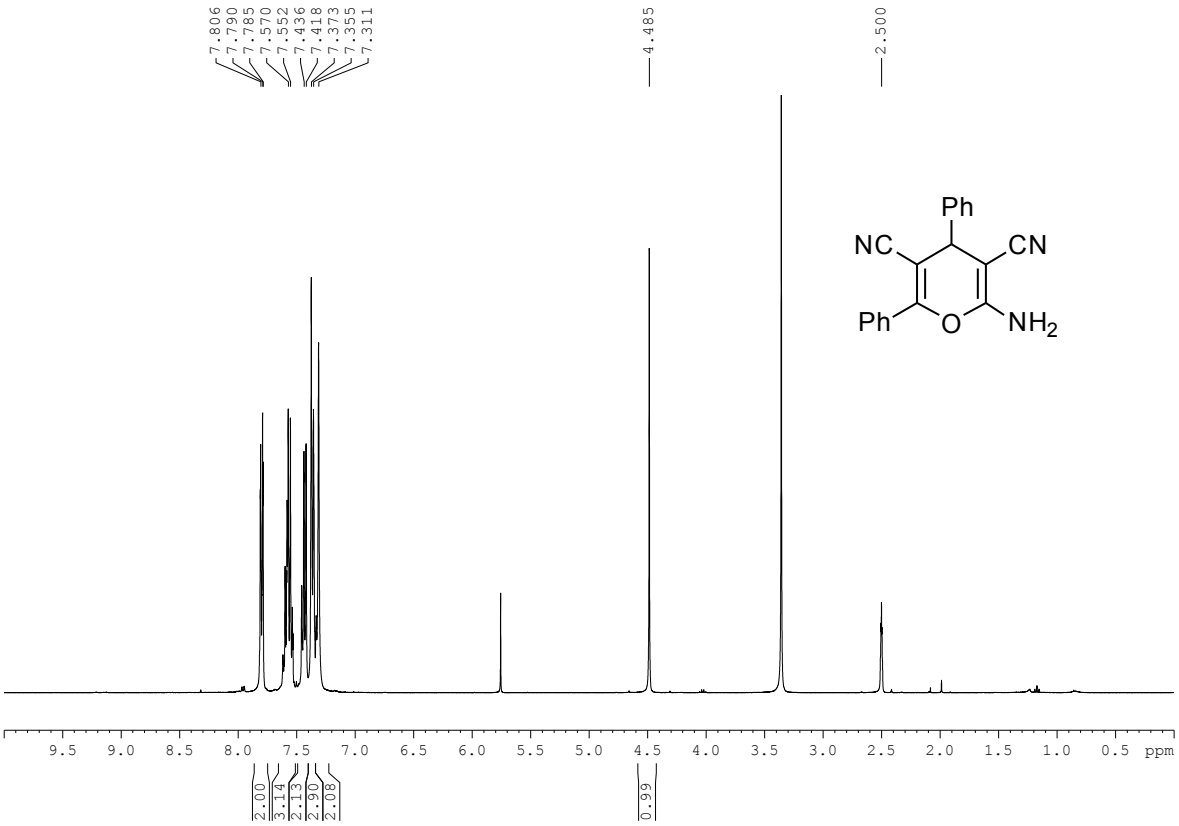
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of acetals **30** (obtained using *cis*-4-fluoroproline **2** as catalyst)



^{13}C $\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of acetals **30** (obtained using *trans*-4-fluoroproline **3** as catalyst)



[1]H NMR (400 MHz, DMSO) of pyran **25**



References

[1] M. Hudlický, *J. Fluorine Chem.* **1993**, *60*, 193.

[2] S. Yang, J. He, *Chem. Commun.* **2012**, *48*, 10349.

[3] F. Z. Liu, H. Fang, H. W. Zhu, Q. Wang, Y. Yang, W. F. Xu, *Bioorg. Med. Chem.* **2008**, *16*, 578.

[4] J. Chiba, G. Takayama, T. Takashi, M. Yokoyama, A. Nakayama, J. J. Baldwin, E. McDonald, K. J. Moriarty, C. R. Sarko, K. W. Saionz, R. Swanson, Z. Hussain, A. Wong, N. Machinaga, *Bioorg. Med. Chem.* **2006**, *14*, 2725.

[5] J. Seo, P. Martasek, L. J. Roman, R. B. Silverman, *Bioorg. Med. Chem.* **2007**, *15*, 1928.

[6] R. Pedrosa, J. M. Andrés, R. Manzano, C. Pérez-López, *Tetrahedron Lett.* **2013**, *54*, 3101.

[7] M. S. Gowda, S. S. Pande, R. A. Ramakrishna, K. R. Prabhu, *Org. Biomol. Chem.* **2011**, *9*, 5365.