Electronic Supplementary Information for:

Enolate addition to bicyclobutanes enables expedient access to 2-oxo-bicyclohexane scaffolds

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I: General

Materials. All solvents and common organic reagents were purchased from commercial suppliers and used without further purification. Organic building blocks and starting materials were purchased from Oakwood Chemicals and MilliporeSigma and used as received. Anhydrous solvents (SureSeal) were purchased from MilliporeSigma and used as received.

Techniques. All air-free manipulations were performed under a dry nitrogen atmosphere using an MBraun glovebox.

Analysis and Spectroscopy. All NMR spectra were acquired on either a Bruker AVANCE 300 MHz spectrometer or a Bruker AVANCE Neo 500 MHz spectrometer. All ^{1}H and ^{13}C NMR chemical shifts are calibrated to residual protio-solvents. All NMR spectroscopic data is processed using MestReNova v14.2.2. High-resolution electrospray ionization mass spectrometric analysis was performed using a Thermo Scientific Ultimate 3000 ESI-Orbitrap Exactive Plus.

X-Ray Crystallography. A suitable crystal of each sample (**3c**, **4b**, and **4d**) was selected for analysis and mounted in a polyimide loop. All measurements were made on a Rigaku Oxford Diffraction Supernova Eos CCD with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2, the structure was solved with the ShelXT structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization.

The structure of compounds **3c** and **4b** were refined without restraint.

The structure of compound **4d** was refined to model conformational disorder. The morpholinyl group was modeled over two positions with similarity restraints placed on bond distances and atomic thermal parameters.

CIFs of **3c**, **4b**, and **4d** are available from the Cambridge Crystallographic Data Centre (CCDC):

CCDC 2290170-2290171, 2298459.

Author Contributions.

K. J. W.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft.

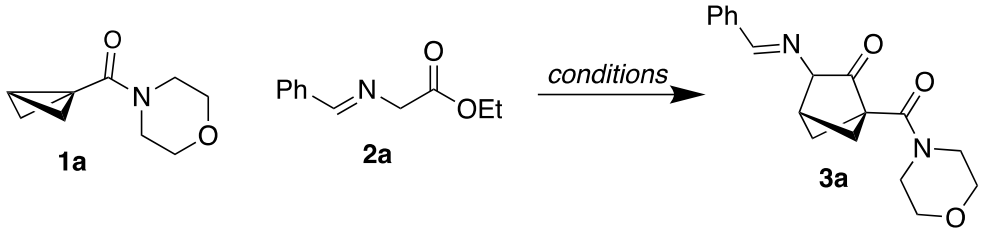
K. D. D.: investigation, methodology.

N. D. S.: formal analysis (XRD).

D. C. L.: conceptualization, funding acquisition, project administration, supervision, writing – review & editing.

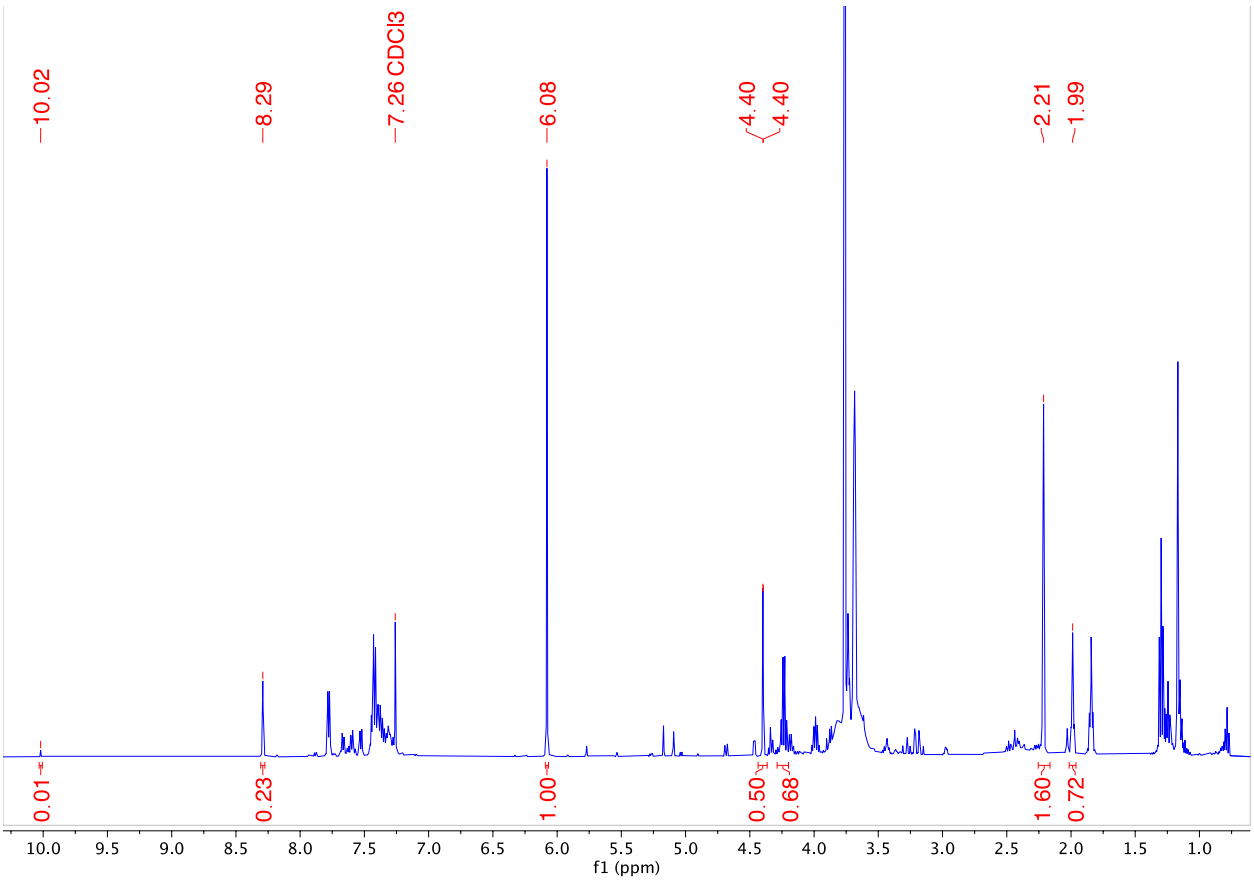
II: Optimization and Control Reactions

Table 1 (main text) reaction conditions



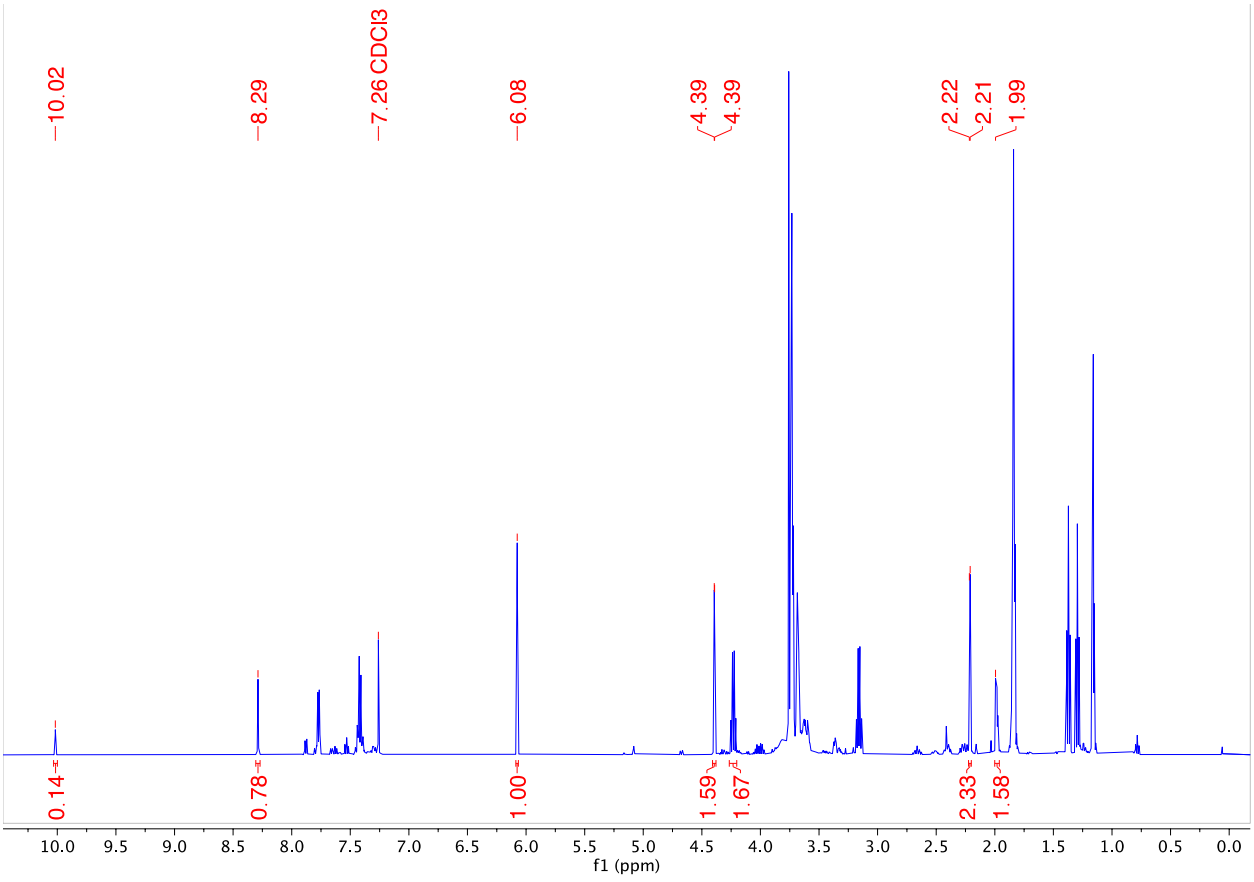
a) Table 1, entry 1

In one vial, the bicyclobutane (8.4 mg, 1 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and to another vial, the imine (9.6 mg, 1 eq.), silver acetate (0.8 mg, 0.1 eq.) and triethylamine (2.1 μL, 0.3 eq.) were added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.05 mmol) was added to each vial then the imine solution was added to the bicyclobutane, and the reaction was left to stir for 24 hours at room temperature. The solvent was evaporated, and the amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). No product, 25% imine (4.40 ppm peak), 1% benzaldehyde (from imine hydrolysis, 10.02 ppm peak), and 72% bicyclobutane (1.99 ppm peak).



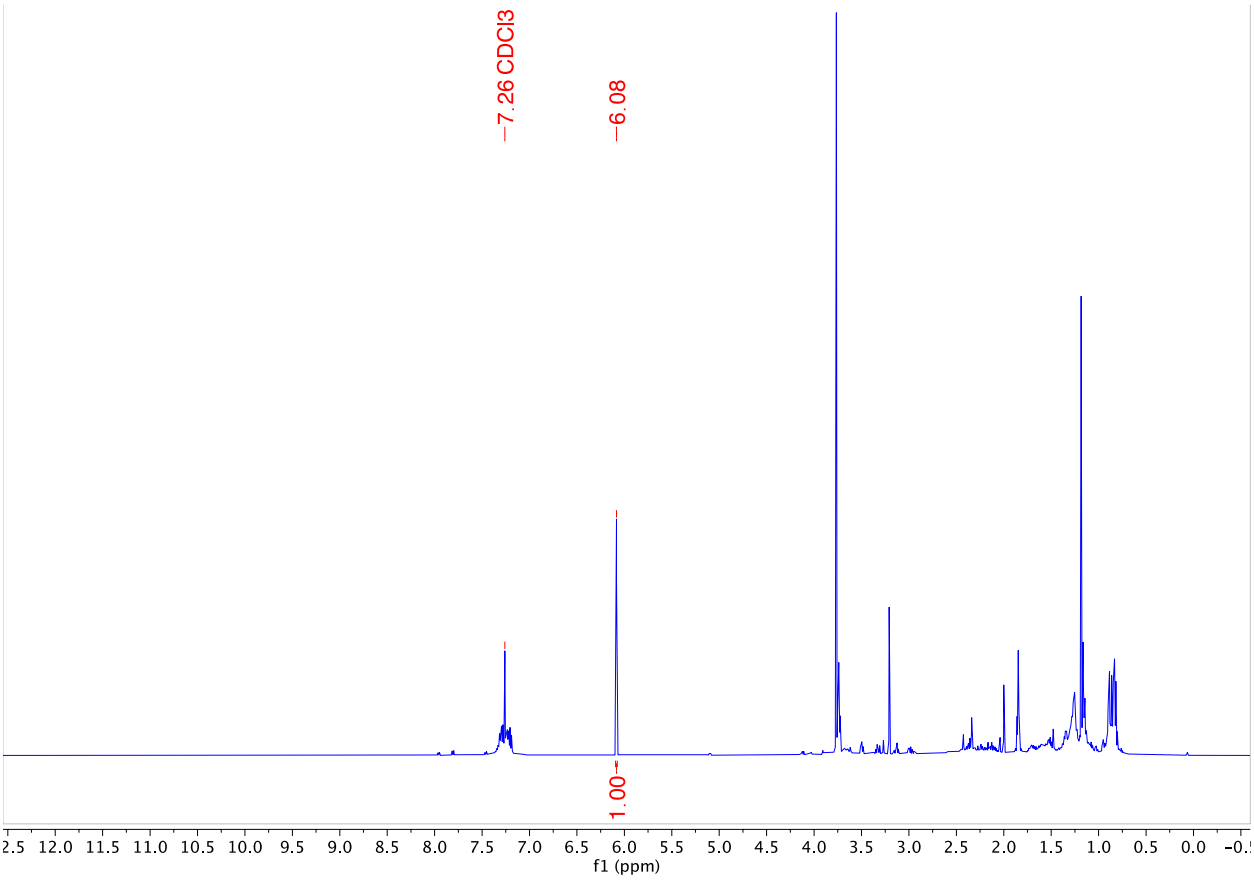
b) Table 1, entry 2

In one vial, the bicyclobutane (8.4 mg, 1 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and to another vial, the imine (9.6 mg, 1 eq.), $Ga(Otf)_3$ (2.6 mg, 0.1 eq.) and triethylamine (2.1 μL, 0.3 eq.) were added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.05 mmol) was added to each vial then the imine solution was added to the bicyclobutane, and the reaction was left to stir for 24 hours at room temperature. The solvent was evaporated, and the amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). No product, 78% imine (4.39 ppm peak), 14% benzaldehyde (from imine hydrolysis, 10.02 ppm peak), and 100% bicyclobutane (1.99 ppm peak).



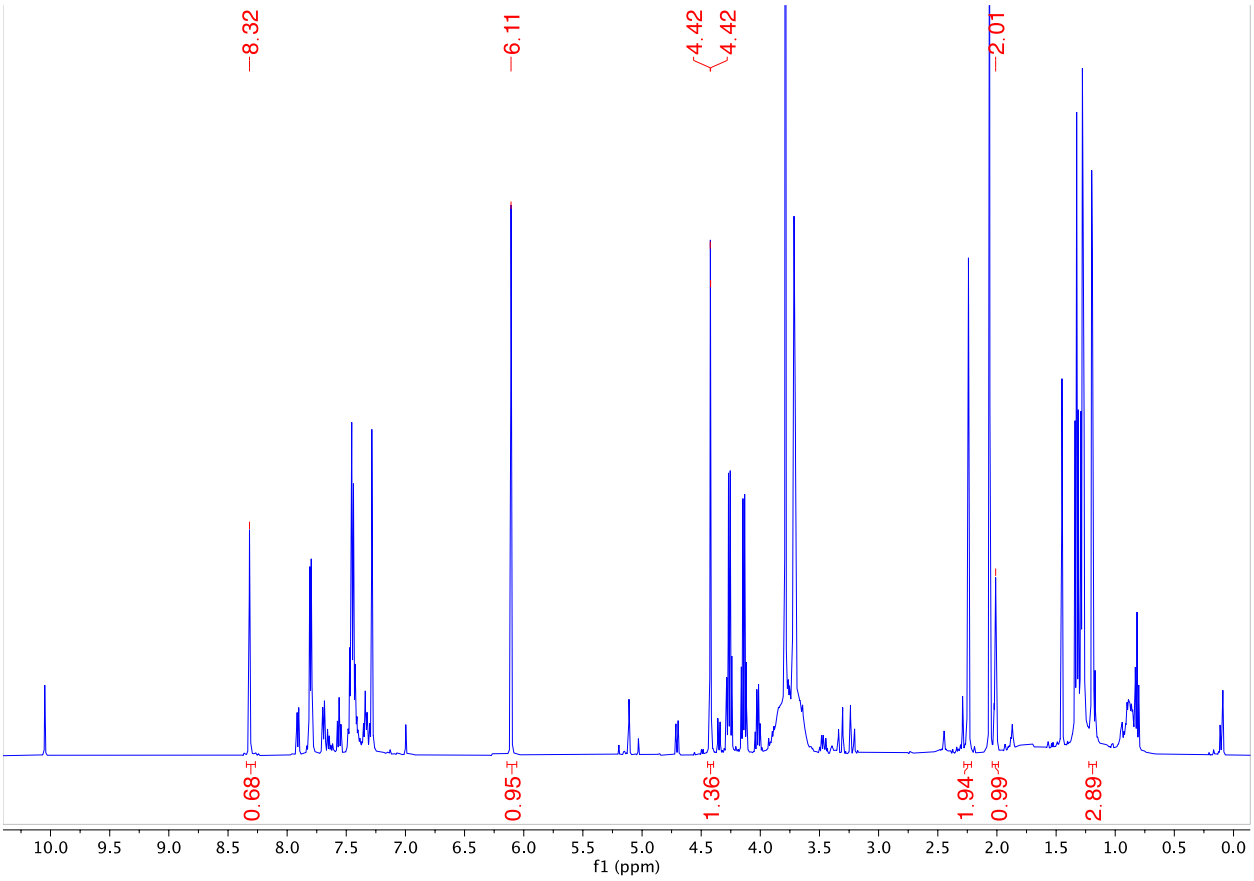
c) Table 1, entry 3

In one vial, the bicyclobutane (8.4 mg, 1 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added followed by 50% of the THF solvent (1 mL total, 0.05 M). To another vial, the imine (9.6 mg, 1 eq.), was added under a nitrogen atmosphere and dissolved in 25% of the THF solvent. In another vial n-BuLi (2.5 M in hexanes, 0.022 mL, 1.1 eq.) was added and dissolved in 25% of the THF solvent and placed in the freezer for 10 minutes. Diisopropylamine (8 μL, 1.1 eq.) was then added to the n-BuLi vial and stirred for 10 minutes before the imine dissolved in 25% of the THF vial was added. This mixture was stirred for 10 minutes before being cooled in the freezer for 10 minutes along with the bicyclobutane vial. The imine vial was then added dropwise to the bicyclobutane, and the mixture was left to stir at room temperature overnight. The reaction was quenched with NH_4Cl and extracted with TBME. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. the amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). No product, imine, or BCB were observed.



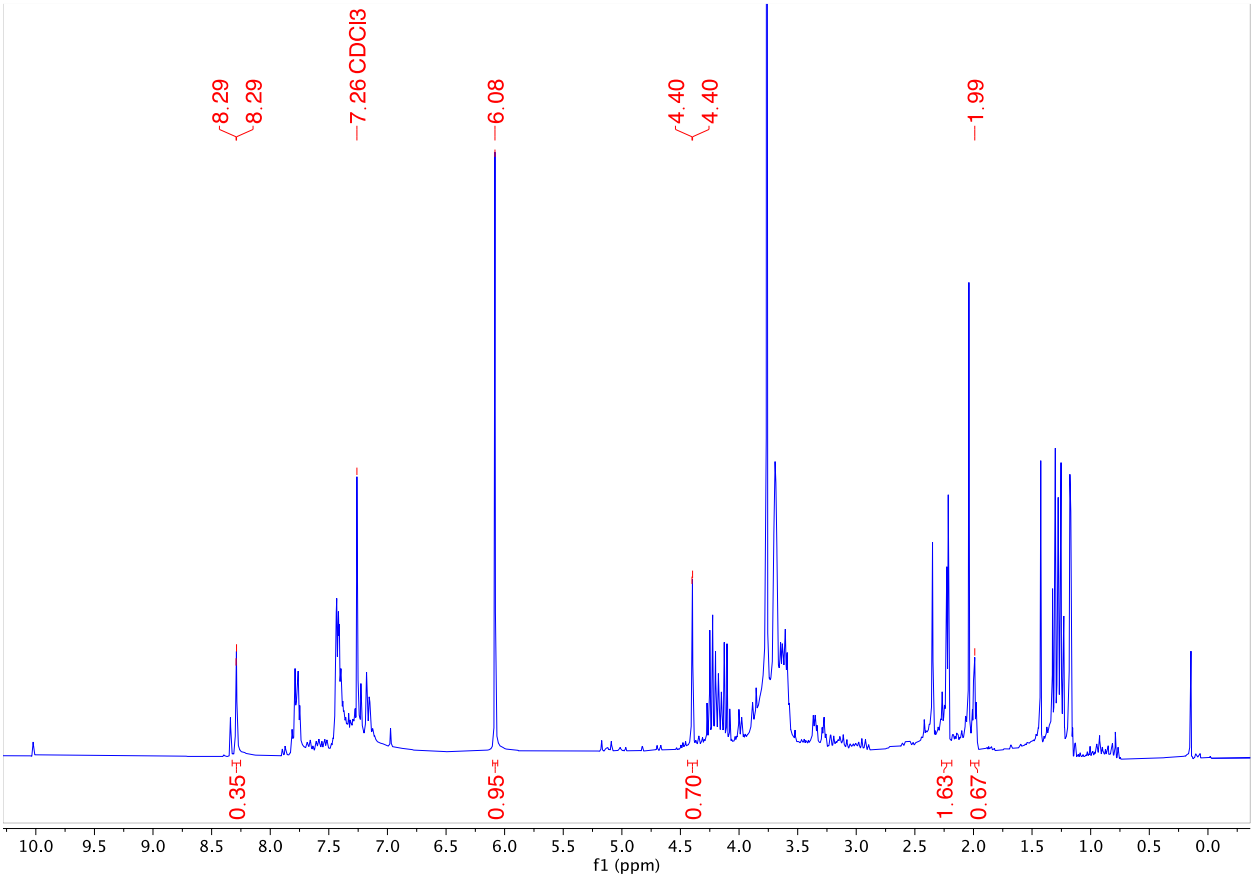
d) Table 1, entry 4

In one vial, the bicyclobutane (8.4 mg, 1 eq.), imine (14.3 mg, 1.5 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and flushed with nitrogen followed by the addition of 50% of the anhydrous THF solvent (1 mL total, 0.05 M). To another vial, NaH in 60% mineral oil (2.2 mg, 2 eq.) was added and flushed with nitrogen and then dissolved in 50% of the anhydrous THF solvent. The NaH solution was then added dropwise to the BCB, and imine solution and the mixture was left to stir at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. the amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). No product, 68% imine (4.42 ppm peak) and 99% BCB (2.01 ppm peak) was observed.



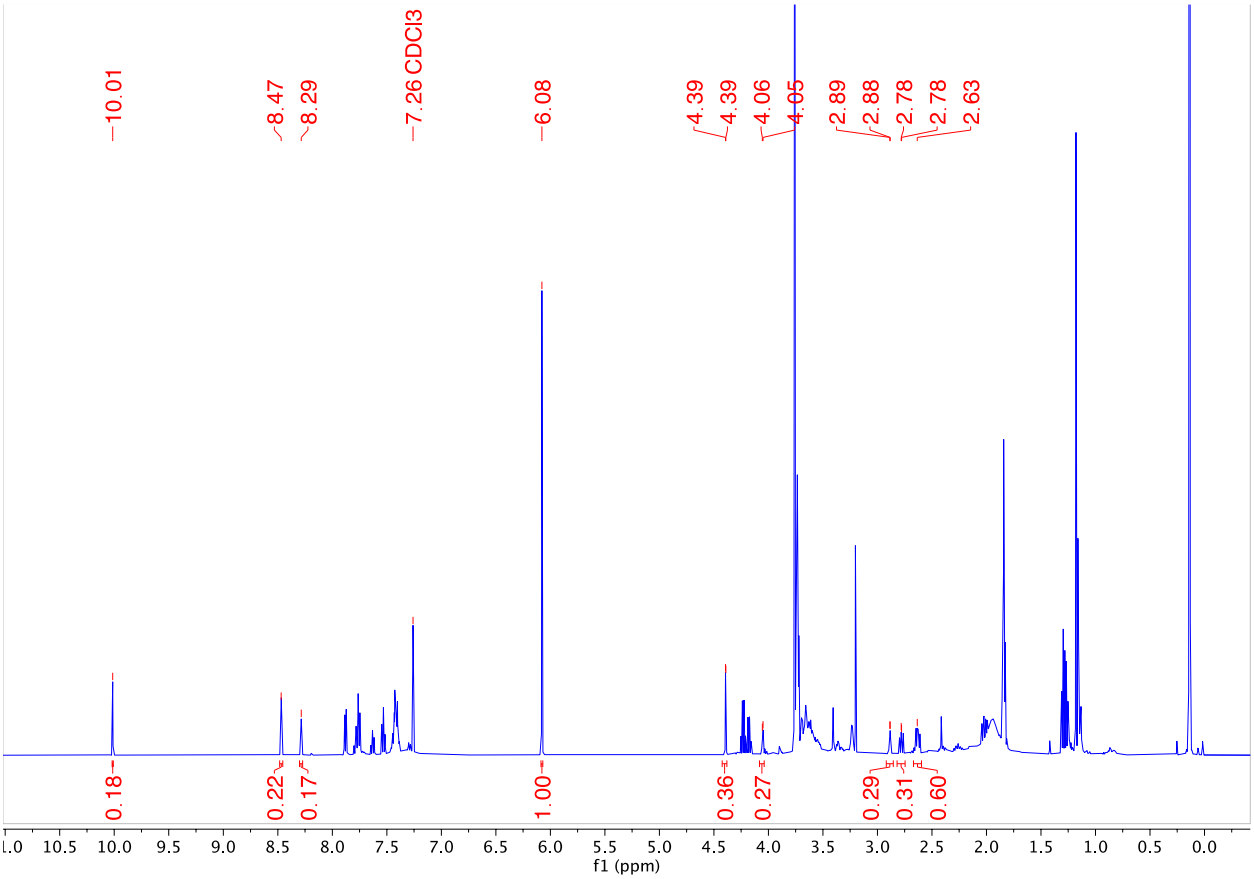
e) Table 1, entry 5

In one vial, the bicyclobutane (8.4 mg, 1 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and to another vial, the imine (11.5 mg, 1.2 eq.), was added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.05 mmol) was added to the bicyclobutane and 25% of the THF was added to the imine and 25% to a separate vial that contained KHMDS (0.5 M in toluene, 0.15 mL, 1.5 eq.). The imine was added dropwise to the KHMDS and left to stir for 10 minutes at room temperature. The imine/KHMDS mixture was added dropwise to the bicyclobutane vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with water and the organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). No product, 35% imine (4.40 ppm peak), and 67% bicyclobutane (1.99 ppm peak) was observed.



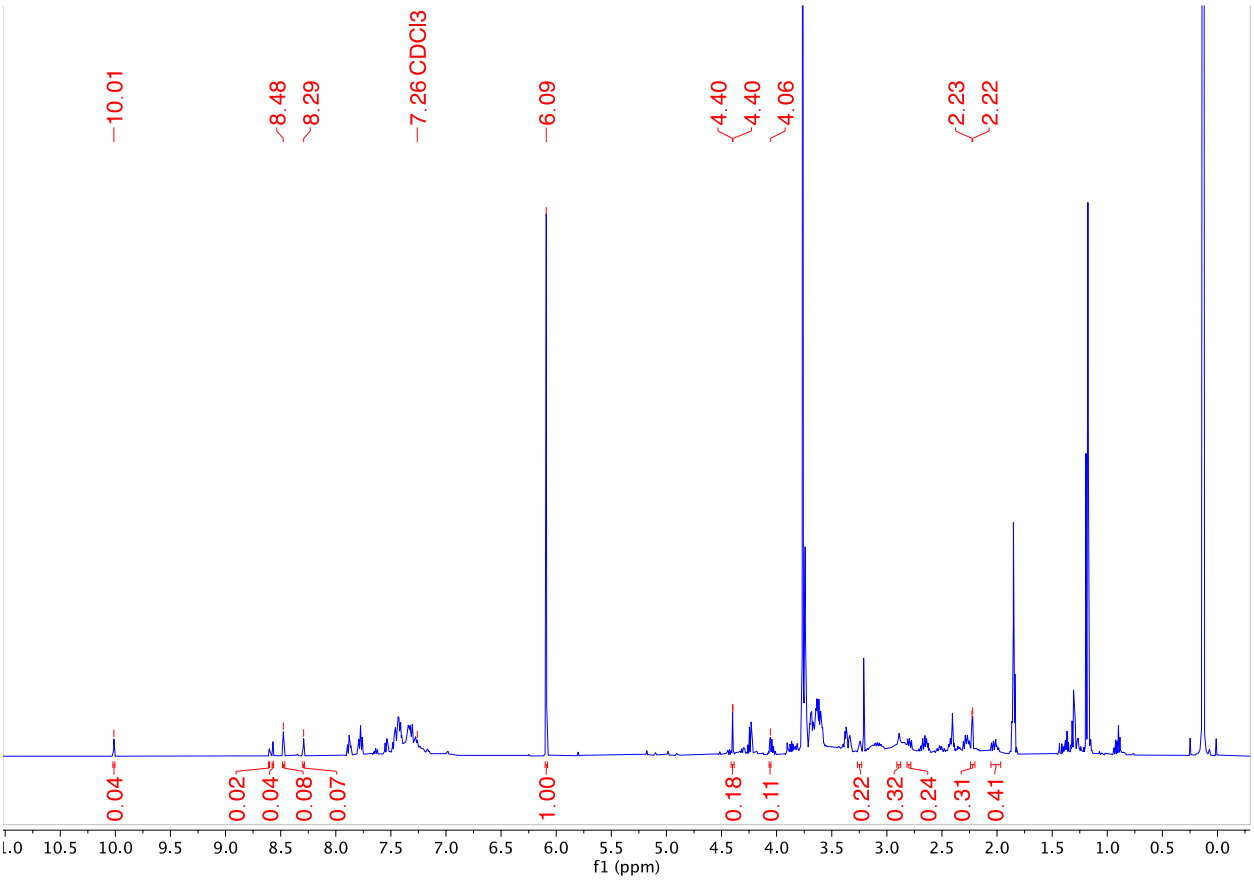
f) Table 1, entry 6

In one vial, the bicyclobutane (8.4 mg, 1 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and to another vial, the imine (9.6 mg, 1 eq.), was added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.05 mmol) was added to the bicyclobutane and 25% of the THF was added to the imine and 25% to a separate vial that contained LiHMDS (1.0M in THF, 0.05 mL, 1 eq.). The imine was added dropwise to the LiHMDS and left to stir for 10 minutes at room temperature. The imine/LiHMDS mixture was added dropwise to the bicyclobutane vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with NH_4Cl, and the organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 20% product (4.06 ppm peak), 17% imine (4.39 ppm peak), 18% benzaldehyde (from imine hydrolysis, 10.02 ppm peak), and no bicyclobutane.



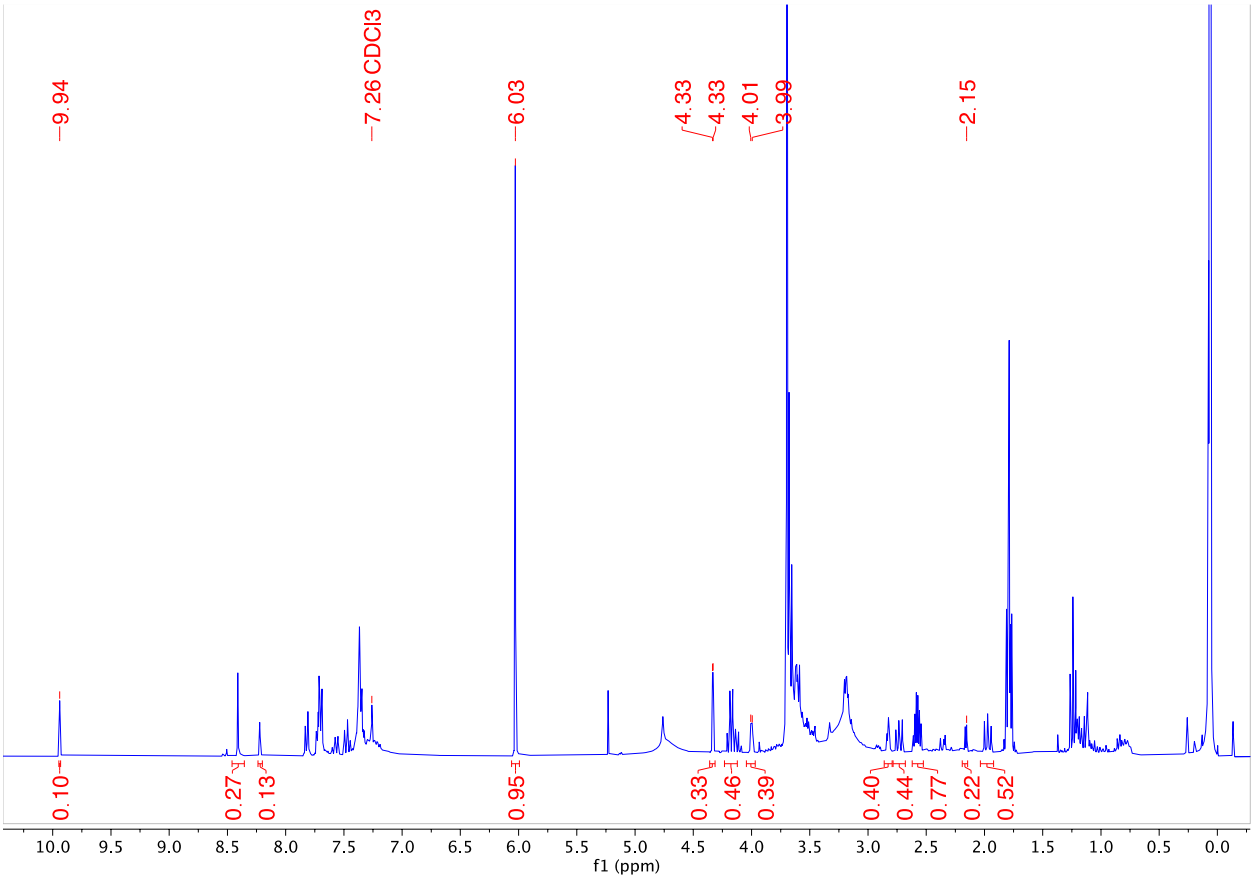
g) Table 1, entry 7

In one vial, the bicyclobutane (50.2 mg, 1 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.33 eq.) were added and to another vial, the imine (57.4 mg, 1 eq.), was added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.05 mmol) was added to the bicyclobutane and 25% of the THF was added to the imine and 25% to a separate vial that contained LiHMDS (1.0M in THF, 0.30 mL, 1 eq.). The imine was added dropwise to the LiHMDS and left to stir for 10 minutes at room temperature. The imine/LiHMDS mixture was added dropwise to the bicyclobutane vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with NH_4Cl, and the organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 11% product (4.06 ppm peak), 9% imine (4.39 ppm peak), 4% benzaldehyde (from imine hydrolysis, 10.02 ppm peak), and 15% bicyclobutane (2.22 ppm peak).



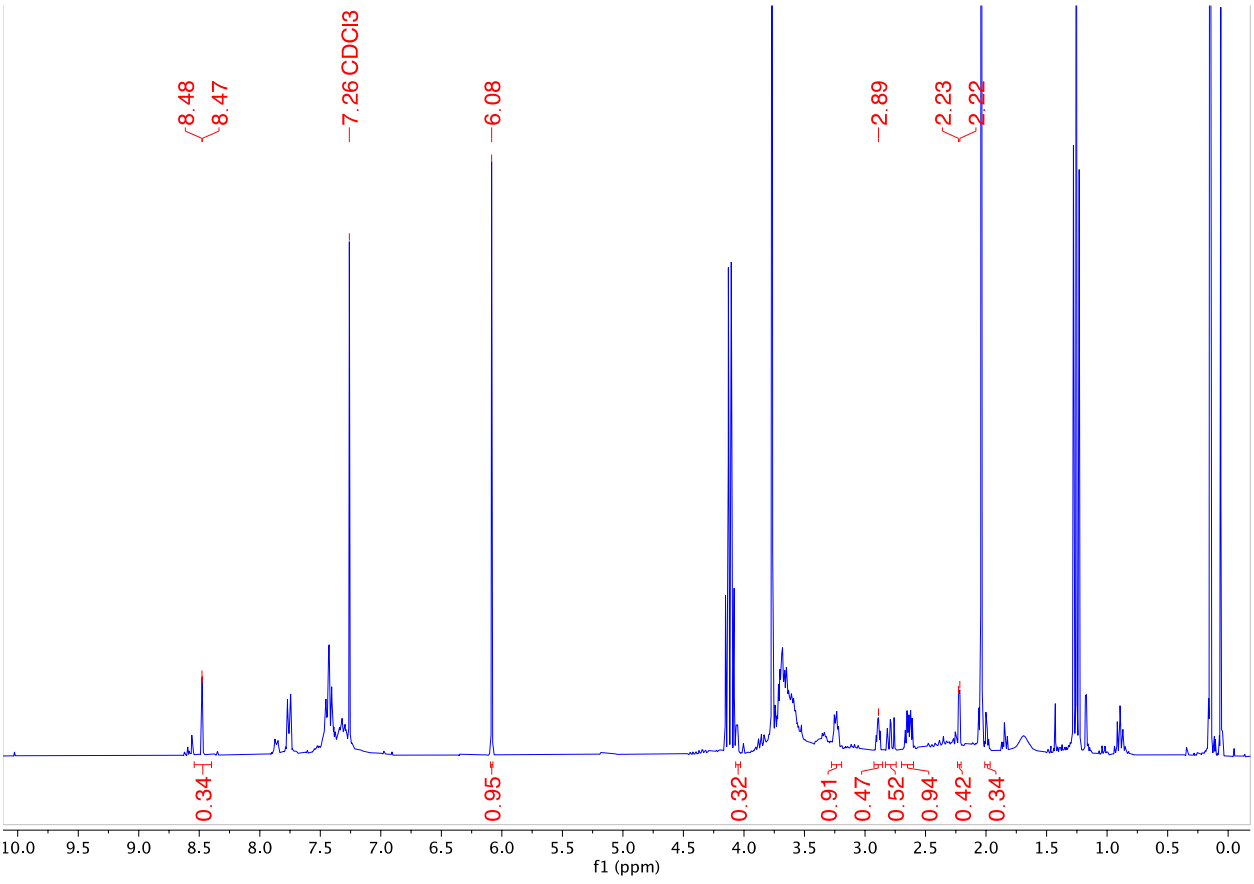
h) Table 1, entry 8

In one vial, the bicyclobutane (50.2 mg, 1 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.33 eq.) were added and to another vial, the imine (68.8 mg, 1.2 eq.), was added under a nitrogen atmosphere. 50% of the THF solvent (6 mL total, 0.05 mmol) was added to the bicyclobutane and 25% of the THF was added to the imine and 25% to a separate vial that contained LiHMDS (1.0M in THF, 0.45 mL, 1.5 eq.). The imine was added dropwise to the LiHMDS and left to stir for 10 minutes at room temperature. The imine/LiHMDS mixture was added dropwise to the bicyclobutane vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with $NaHCO_3$, and the organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 39% product (4.01 ppm peak), 17% imine (4.33 ppm peak), 10% benzaldehyde (from imine hydrolysis, 9.94 ppm peak), and 11% bicyclobutane (2.15 ppm peak).



i) Table 1, entry 9

In one vial, the bicyclobutane (50.2 mg, 1 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.33 eq.) were added and to another vial, the imine (68.8 mg, 1.2 eq.), was added under a nitrogen atmosphere. 50% of the THF solvent (1 mL total, 0.3 mmol) was added to the bicyclobutane and 50% of the THF was added to the imine. LiHMDS (1.0M in THF, 0.45 mL, 1.5 eq.) was added to the imine vial and left to stir for 10 minutes at room temperature. The two vials were then cooled in the freezer for 10 minutes followed by a dropwise addition of the BCB to the enolate vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate 3 times. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 47% product (2.89 ppm peak) and 21% bicyclobutane (2.22 ppm peak).

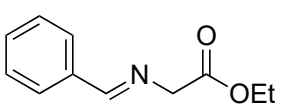


III: Substrate Synthesis

Imine Synthesis

General Procedure: The aldehyde (1 eq.) and amine (1.2 eq.) were added to a vial and dissolved in Toluene (0.6 M). Then DIPEA (1.3 eq) and excess anhydrous Na_2SO_4 was added to the vial, and it was left to stir at room temperature for 24 hours. The solution was then filtered, and the solvent was evaporated to give the desired imine without further purification.

Imine **2b** was purchased from Oakwood chemicals.



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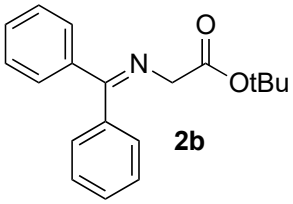
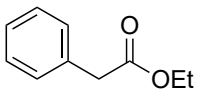


2b

Ethyl Ester Acetate Synthesis

General Procedure: The acetic acid derivative (1 eq.) was dissolved in ethanol in a vial and sulfuric acid was added (0.5 eq). The vial was heated to 70°C overnight then the vial was cooled, and the solvent was evaporated. The residue was quenched with $NaHCO_3$ until the solution was basic, determined by pH indicator paper. The solution was then extracted by TBME, dried with Mg_2SO_4, filtered and the solvent was evaporated to give the desired ethyl ester acetate without further purification.



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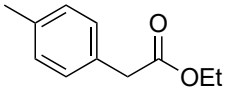

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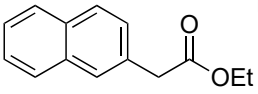

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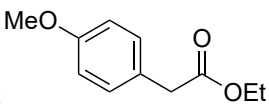

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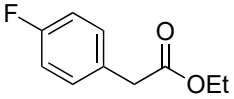

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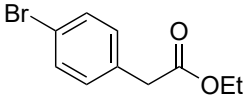

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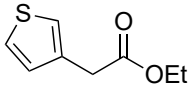

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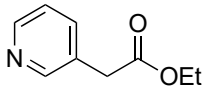

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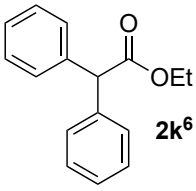

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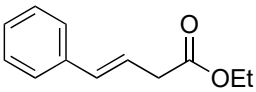
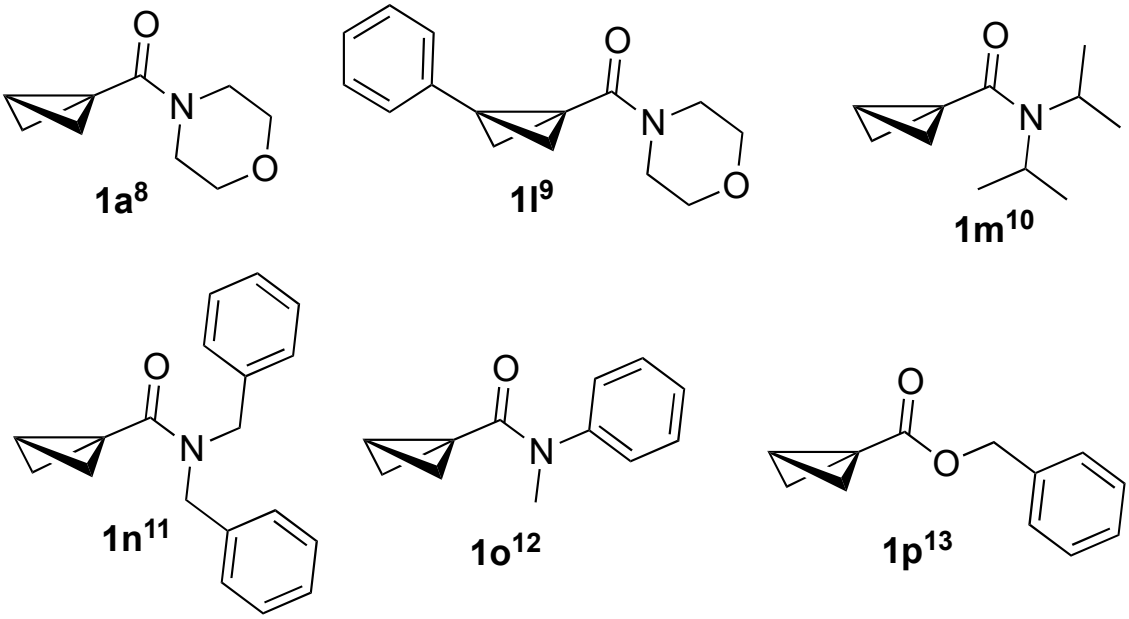


2p[7]

Bicyclobutane Synthesis



General Procedure 1a (Amidation/Esterification from acyl chloride)[9]

The alcohol or amide (1.2 eq.) and DIPEA (1 eq.) was added to the reaction vessel, dissolved in DCM, and then cooled to 0 °C. 3-oxocyclobutane-1-carbonyl chloride (1 eq.) dissolved in DCM was added dropwise to the solution. The reaction mixture was then warmed to room temperature and left to stir overnight. The reaction mixture was quenched with water and extracted with DCM. The organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography.

General Procedure 1b (Amidation/Esterification from carboxylic acid)[14]

3-Oxocyclobutane-1-carboxylic acid (1 eq.) was dissolved in THF (0.40 M) in a round bottom flask and the solution was cooled down to 0°C. Carbonyl diimidazole (1.05 eq.) was added to the flask. The solution was warmed to room temperature and left to stir for 2-3 hours before the solution was cooled back down to 0°C and the amine (1.05 eq.) was added dropwise. The solution was then warmed to room temperature and left to stir overnight. The reaction was then quenched with NH_4Cl and then extracted with DCM. The combined organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. The compound was purified by column chromatography.

General Procedure 2 (Cyclobutanone reduction)[15]

The cyclobutanone ester or amide (1 eq.) was dissolved in methanol and cooled down to 0 °C. Sodium borohydride was added portion-wise to the reaction mixture. The solution was allowed to warm to room temperature and left to stir for 2-3 hours at room temperature. The solution was quenched with NH_4Cl and extracted with DCM. The organic layer was dried with Mg_2SO_4, filtered and the solvent was evaporated to give the product which was used without further purification.

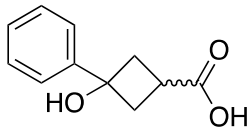
General Procedure 3 (Tosylation)[15]

The cyclobutane alcohol (1 eq.) was dissolved in DCM and cooled down to 0°C. 4-toluenesulfonyl chloride (1.3 eq.) was added to the reaction mixture followed by triethylamine (1.3 eq). The solution was then heated to 40°C for 24 hours. The reaction was quenched with NH_4Cl and then extracted with DCM. The organic solvent was dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography.

General Procedure 4 (Bicyclobutane synthesis)[15]

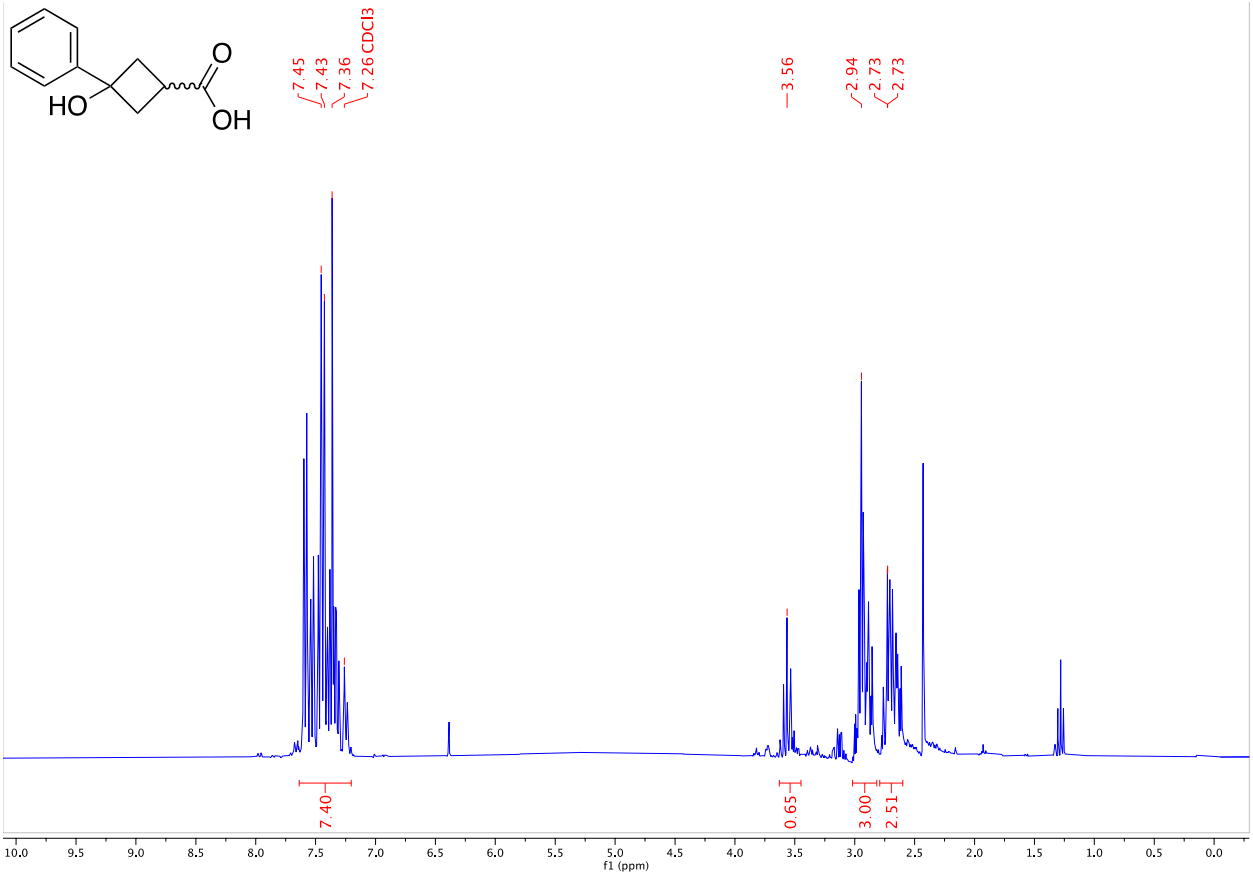
The cyclobutane tosylate (1 eq.) was dissolved in THF (0.15 M) under a nitrogen atmosphere. The reaction was cooled down to 0°C then potassium *tert*-butoxide (1.1 eq.) was added to the reaction mixture. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with NH_4Cl and extracted with TBME. The organic layer was washed with $NaHCO_3$, brine before being dried with Mg_2SO_4, filtered and the solvent was evaporated to give the product without further purification.

3-Phenyl-3-hydroxycyclobutane-1-carboxylic acid[16-18]

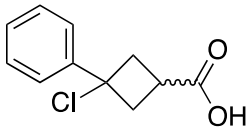


Solid 3-oxocyclobutane carboxylic acid was added to a 3-necked round bottom flask containing a stir bar and fitted with a gas inlet adapter, a septum, and an addition funnel. The apparatus was purged with nitrogen gas. Anhydrous THF was transferred to the flask via cannula, and the 3-oxocyclobutane carboxylic acid was dissolved with stirring. A solution of the Grignard reagent (2.05 eq) was added to an addition funnel via cannula transfer, followed by slow dropwise addition to the reaction mixture over 6 hours. After the addition was complete, the reaction mixture was quenched with 6 M HCl. The aqueous layer was extracted with diethyl ether and the organic layer was dried with $MgSO_4$. The solvent was removed under vacuum and the product was re-dissolved in saturated $NaHCO_3$. An equal amount of diethyl ether was added to extract the aqueous layer. The aqueous layer was acidified using concentrated HCl and a precipitate was formed which was filtered with vacuum filtration. The product was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.64 – 7.20 (m, 7H), 3.56 (s, 1H), 2.94 (s, 3H), 2.73 (d, J = 0.6 Hz, 3H).

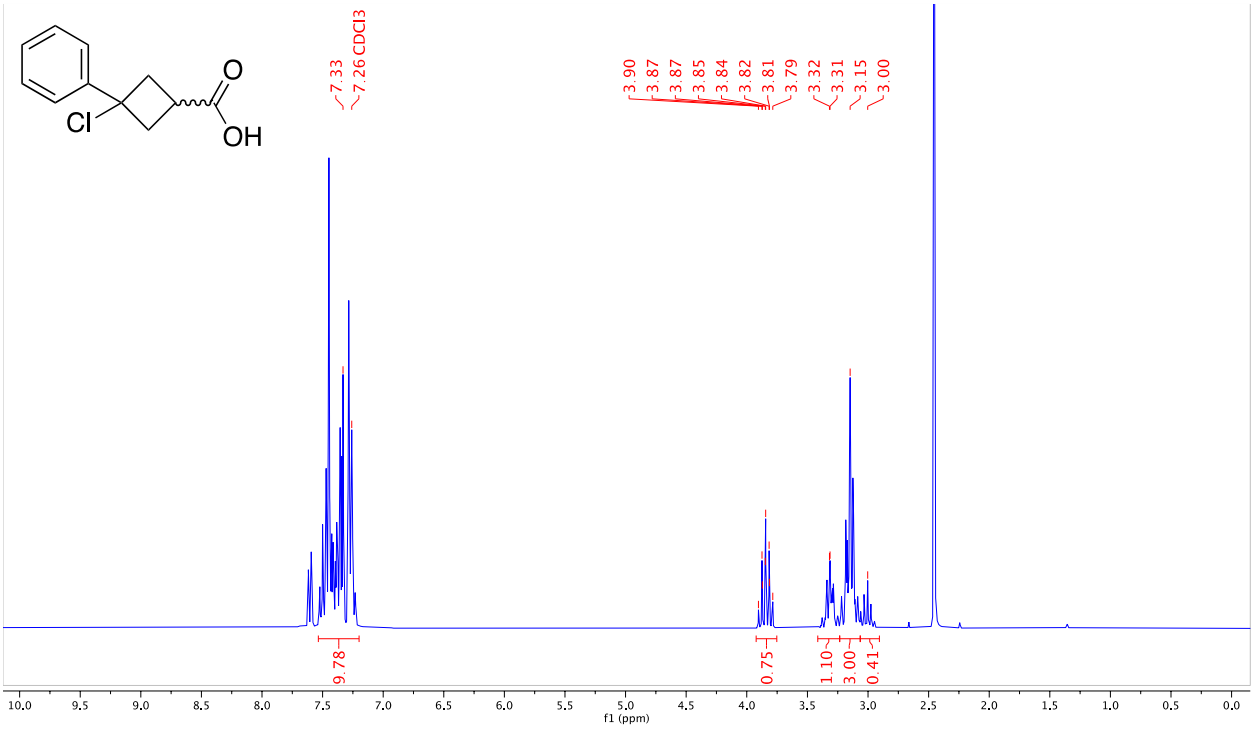


3-Phenyl-3-chlorocyclobutane-1-carboxylic acid[16]

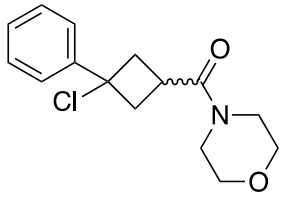


The 3-hydroxy-3-arylcyclobutane carboxylic acid was dissolved in toluene and then an equal volume of concentrated hydrochloric acid was added. The reaction mixture was stirred at room temperature for 6 hours. The two layers were separated, and the aqueous layer was extracted with toluene. The organic layers were combined and washed with water and brine. The solution was then dried with MgSO4 and the solvent was removed under vacuum. The product was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.33 (s, 5H), 3.92 – 3.75 (m, 0.7H), 3.32 (m, 1H), 3.15 (m, 3H), 3.00 (m, 0.4H).

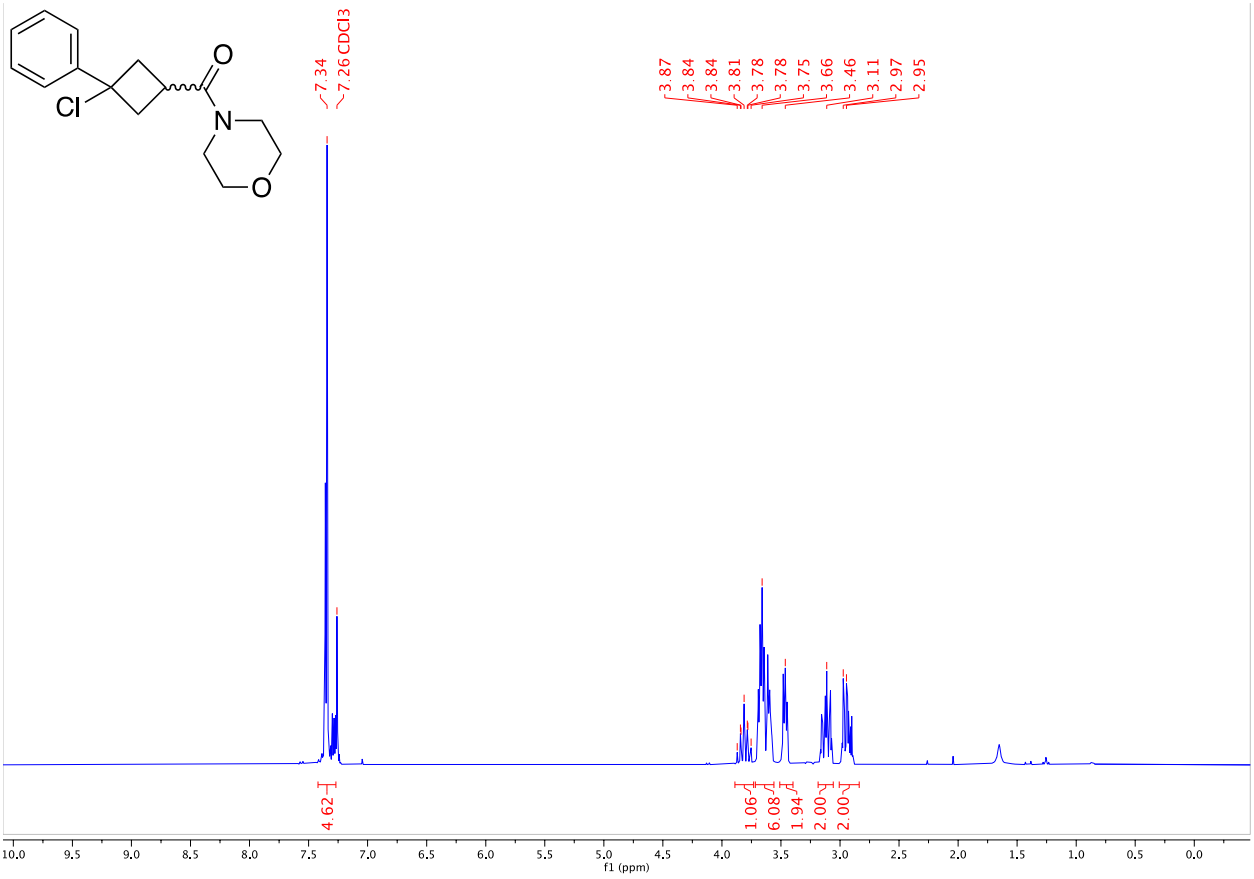


(3-Chloro-3-phenylcyclobutyl)(morpholino)methanone

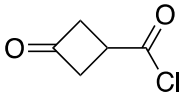


This product was prepared using general procedure 1b. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 43% EtOAc). 876 mg of an orange oil was obtained (66% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.34 (m, 5H), 3.89 – 3.73 (m, 1H), 3.66 (m, 6H), 3.46 (m, 2H), 3.11 (m, 2H), 2.96 (m, 2H).

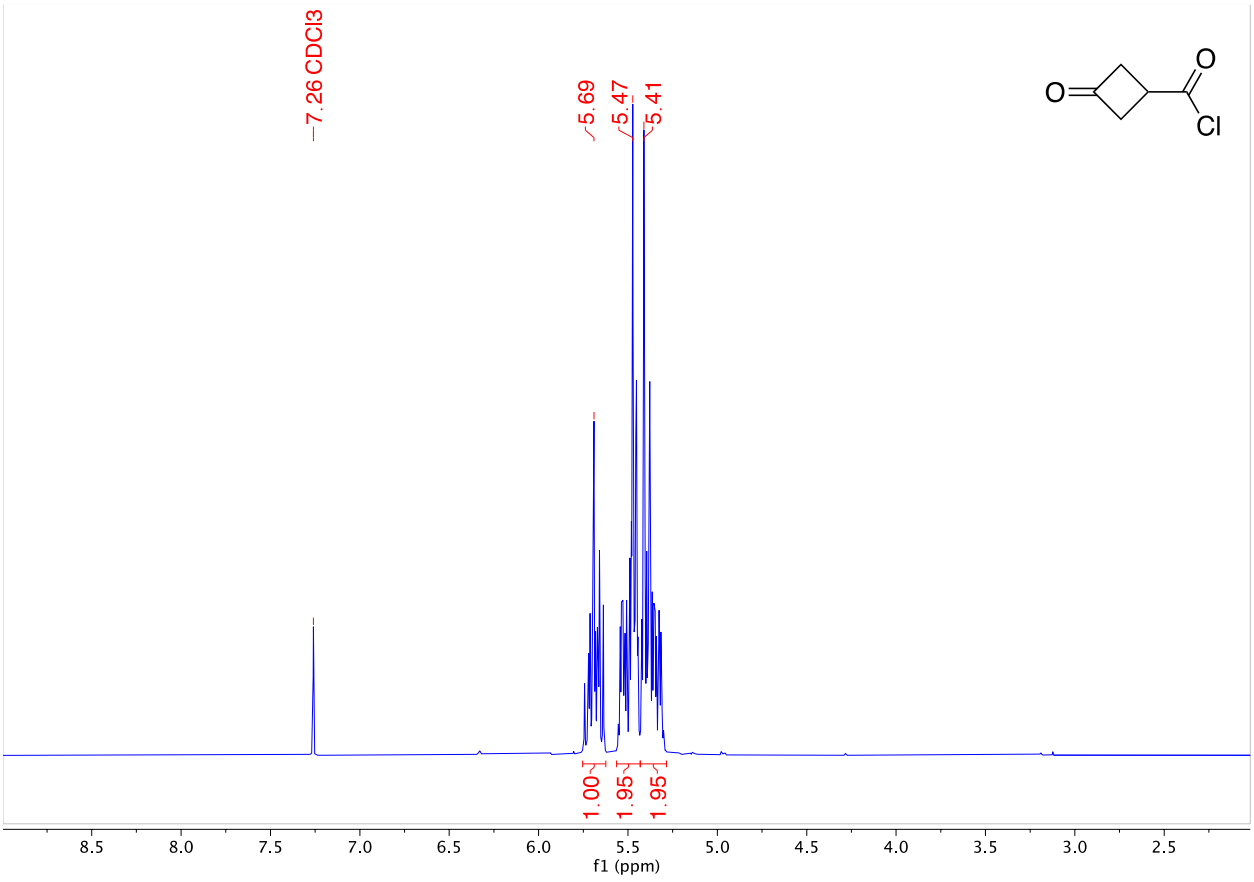


3-Oxocyclobutane-1-carbonyl chloride[9]

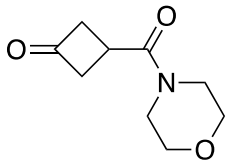


3-oxocyclobutane-1-carboxylic acid (5.0 g. 43.8 mmol) was added to a round bottom flask and dissolved in DCM. A drop of DMF was added and the solution was cooled down to 0°C. Oxalyl chloride (5.6 mL, 1.5 eq) was added dropwise to the reaction flask. The solution was allowed to warm to room temperature and was left to stir for 24 hours. The solvent was then evaporated to give the product with quantitative yield as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 5.62-5.75 (m, 1H), 5.43-5.57 (m, 2H), 5.28-5.43 (m, 2H).

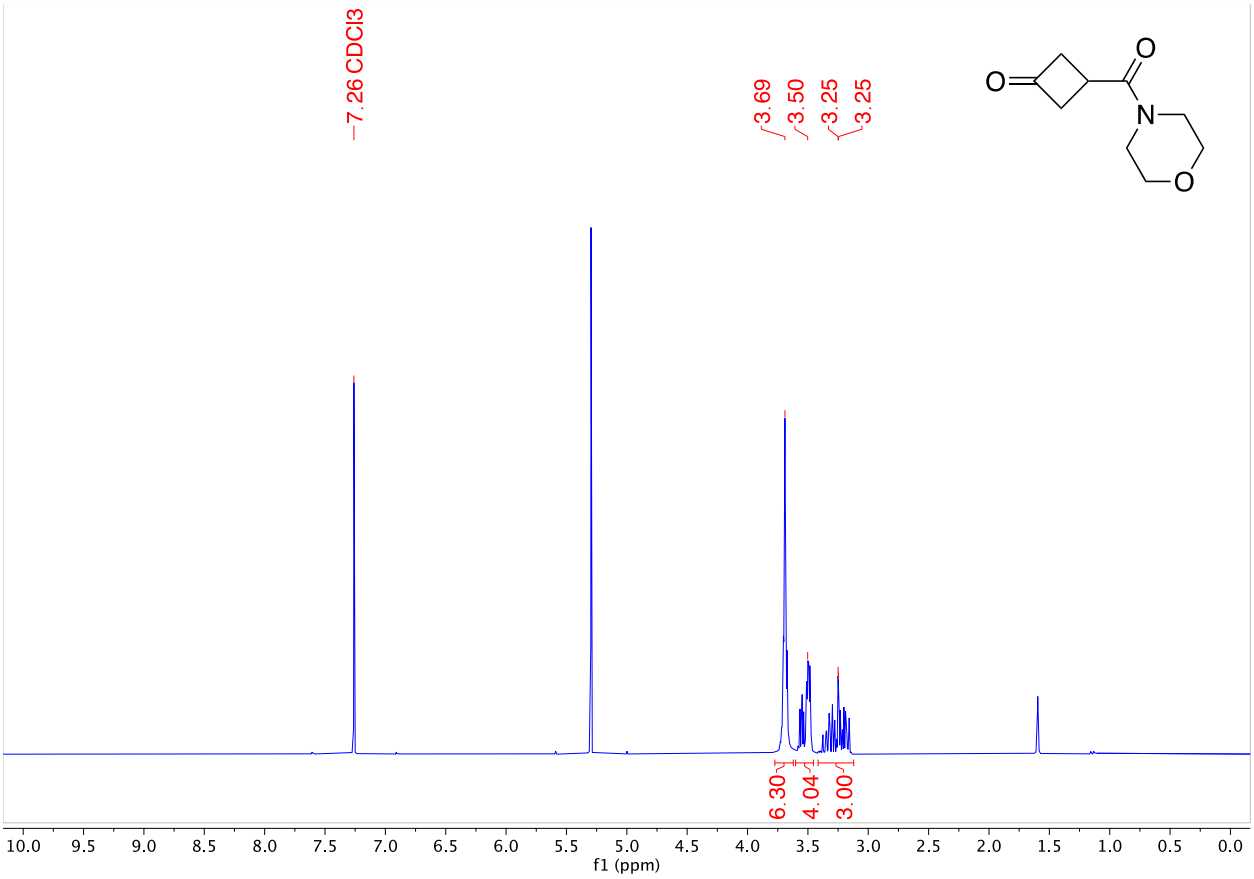


3-(Morpholine-4-carbonyl)cyclobutan-1-one

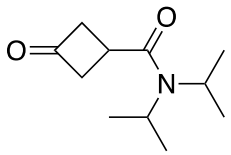


This product was prepared using general procedure 1b. The compound was purified by column chromatography (Biotage® Sfär 50g Column, 0-100% MeOH/DCM, eluted at 15% MeOH). 3.03 grams of an orange oil was obtained (94% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 3.74-3.62 (m, 6H), 3.58-3.46 (m, 4H), 3.39-3.13 (m, 3H).

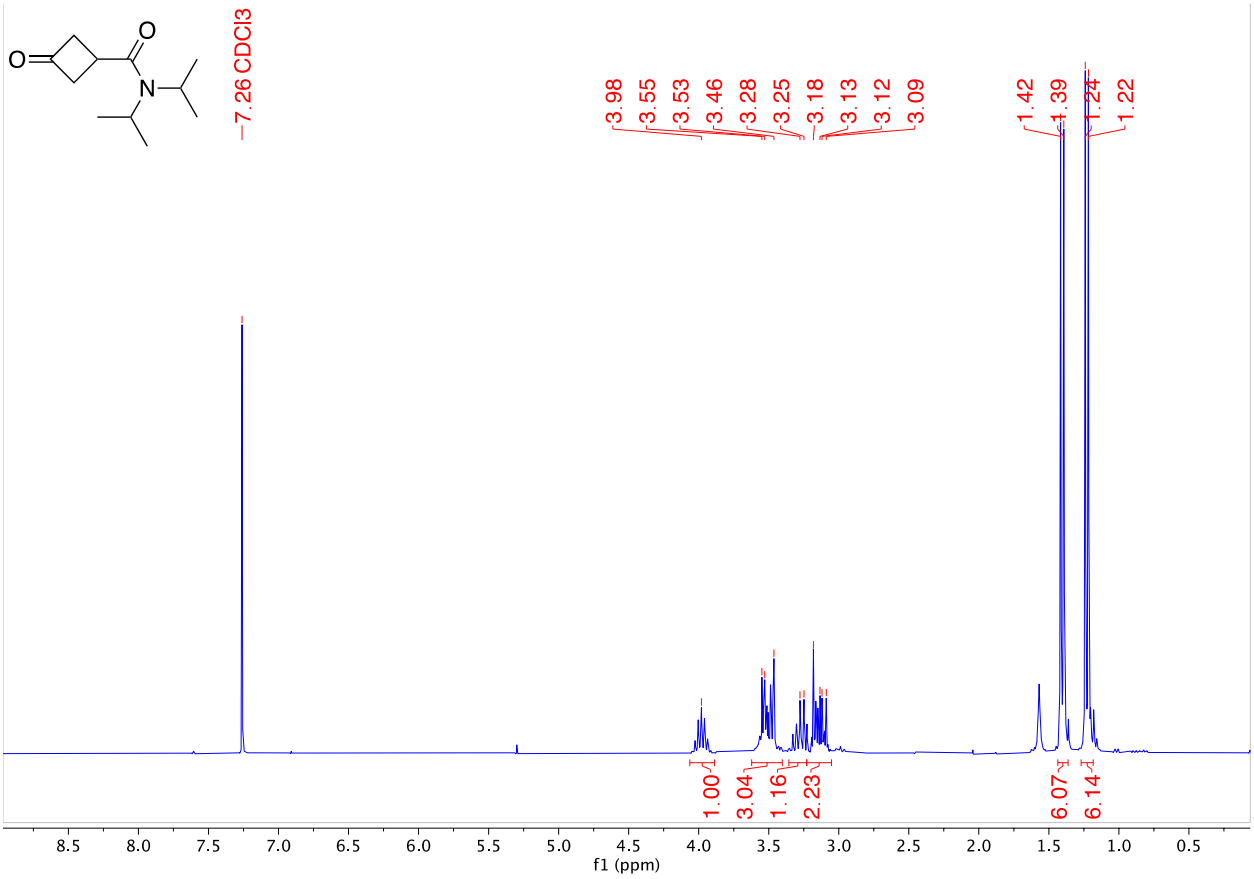


***N,N*-Diisopropyl-3-oxocyclobutane-1-carboxamide**

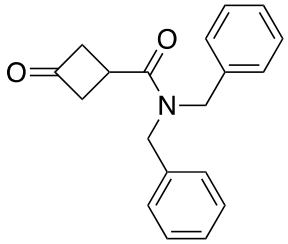


This product was prepared using general procedure 1a. Isolated 689 mg of an orange oil (93% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 3.98 (septet, 1H), 3.62-3.41 (m, 3H), 3.35-3.21 (m, 1H), 3.20-3.07 (m, 2H), 1.40 (d, 6H), 1.23 (d, 6H).

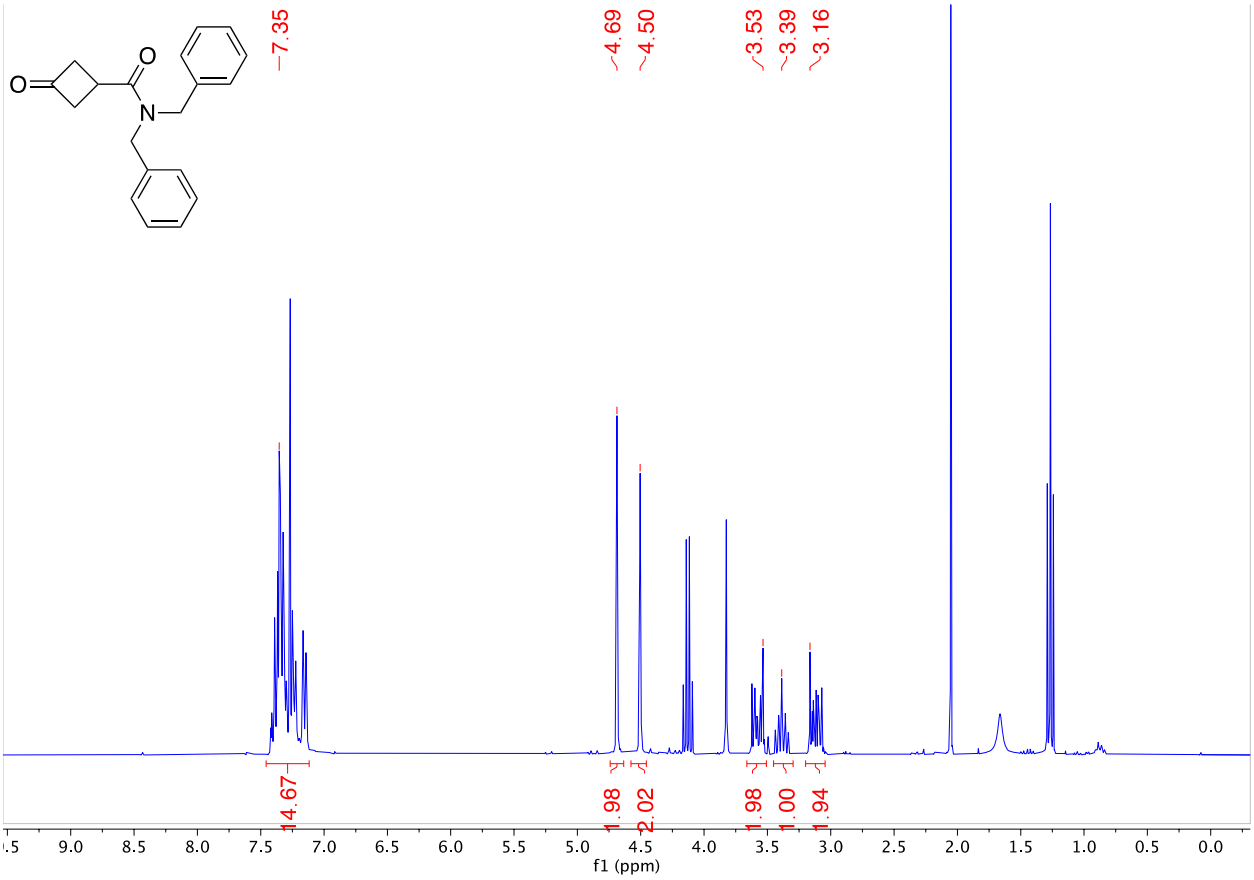


***N,N*-Dibenzyl-3-oxocyclobutane-1-carboxamide**

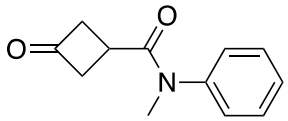


This product was prepared using general procedure 1b. The compound was purified by column chromatography (Biotage® Sfär 50g Column, 0-100% EtOAc/hexanes, eluted at 24% EtOAc). 3.3 g of a yellow oil was obtained (100% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.35 (m, 10H), 4.69 (s, 2H), 4.50 (s, 2H), 3.53 (m, 2H), 3.39 (m, 1H), 3.16 (m, 2H).

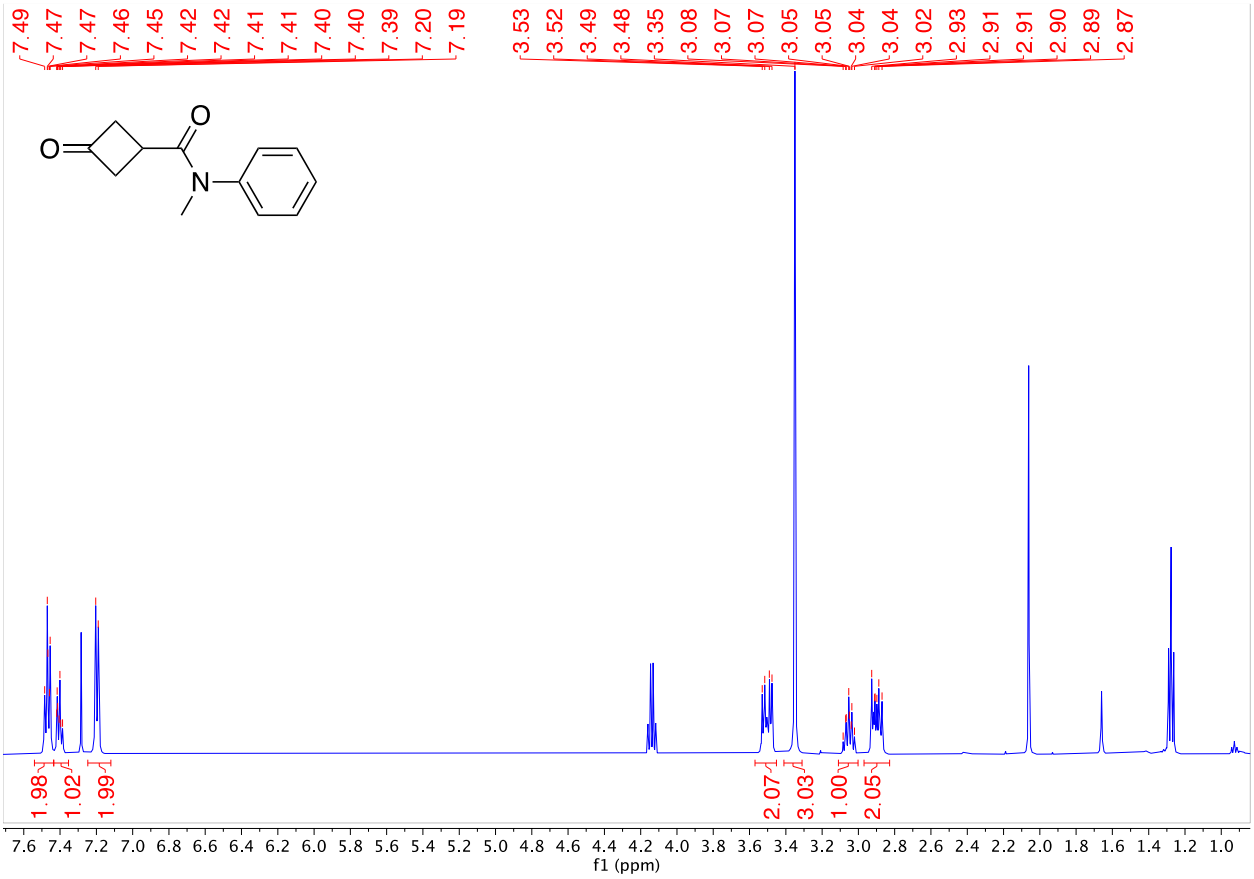


***N*-Methyl-3-oxo-*N*-phenylcyclobutane-1-carboxamide**

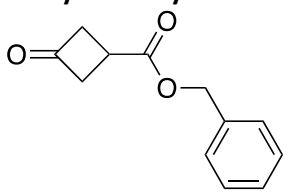


This product was prepared using general procedure 1b. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 35% EtOAc). 890 mg of a yellow oil was obtained (28% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.47 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.44 – 7.35 (m, 1H), 7.20 (d, *J* = 7.0 Hz, 2H), 3.50 (m, 2H), 3.35 (s, 3H), 3.05 (dq, *J* = 9.0, 7.2 Hz, 1H), 2.97 – 2.83 (m, 2H).

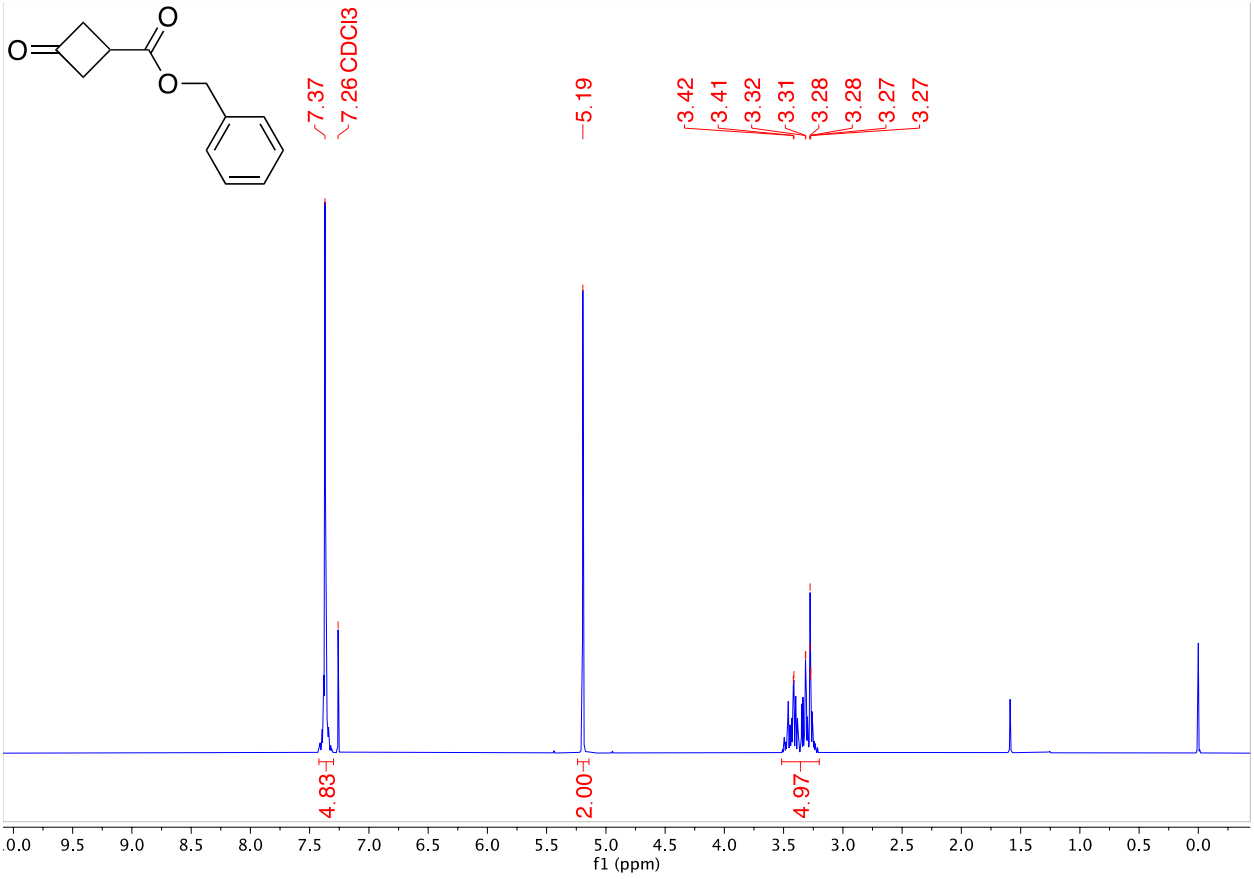


Benzyl 3-oxocyclobutane-1-carboxylate[19]

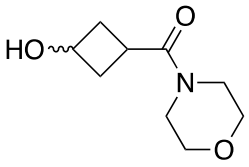


3-Oxocyclobutane carboxylic acid (2.0 g, 17.5 mmol) was dissolved in acetonitrile in a round bottom flask and potassium carbonate (3.63 g, 1.5 eq.) was added. Then benzyl bromide (2.29 mL, 1.1 eq.) was added to the flask and the reaction was left to stir overnight at 50 °C. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to obtain the crude product. The compound was purified by column chromatography (Biotage® Sfär 50g Column, 0-100% EtOAc/hexanes, eluted at 35% EtOAc). 1.84 grams of a white solid was obtained (51% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.37 (m, 5H), 5.19 (s, 2H), 3.52 – 3.20 (m, 5H).

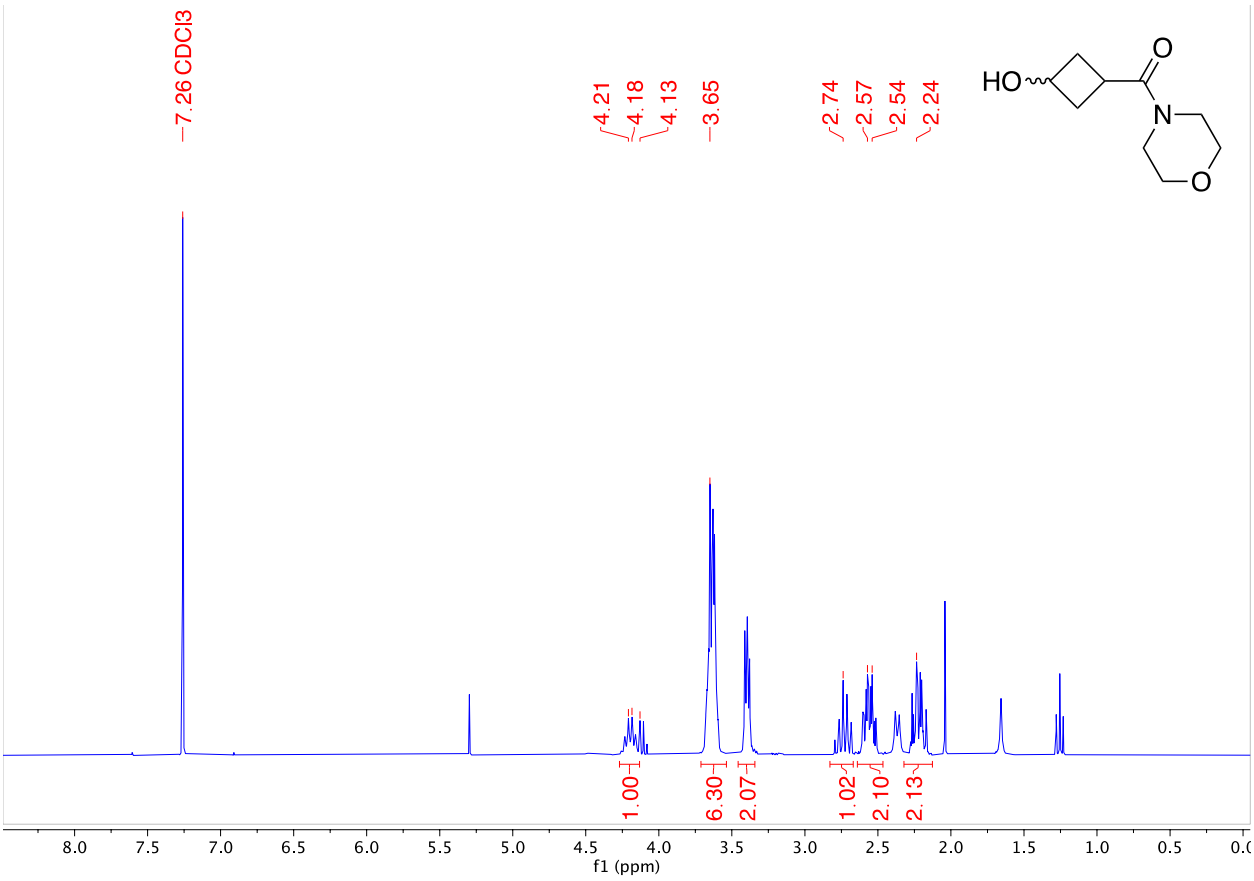


(3-Hydroxycyclobutyl)(morpholino)methanone

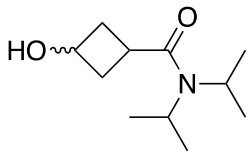


This product was prepared using general procedure 2. Isolated 4.21 grams of a white powder (94% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 4.18 (septet, 1H), 3.69-3.58 (m, 6H), 3.43-3.36 (m, 2H), 2.80-2.67 (m, 1H), 2.62-2.49 (m, 2H), 2.28-2.15 (m, 2H).

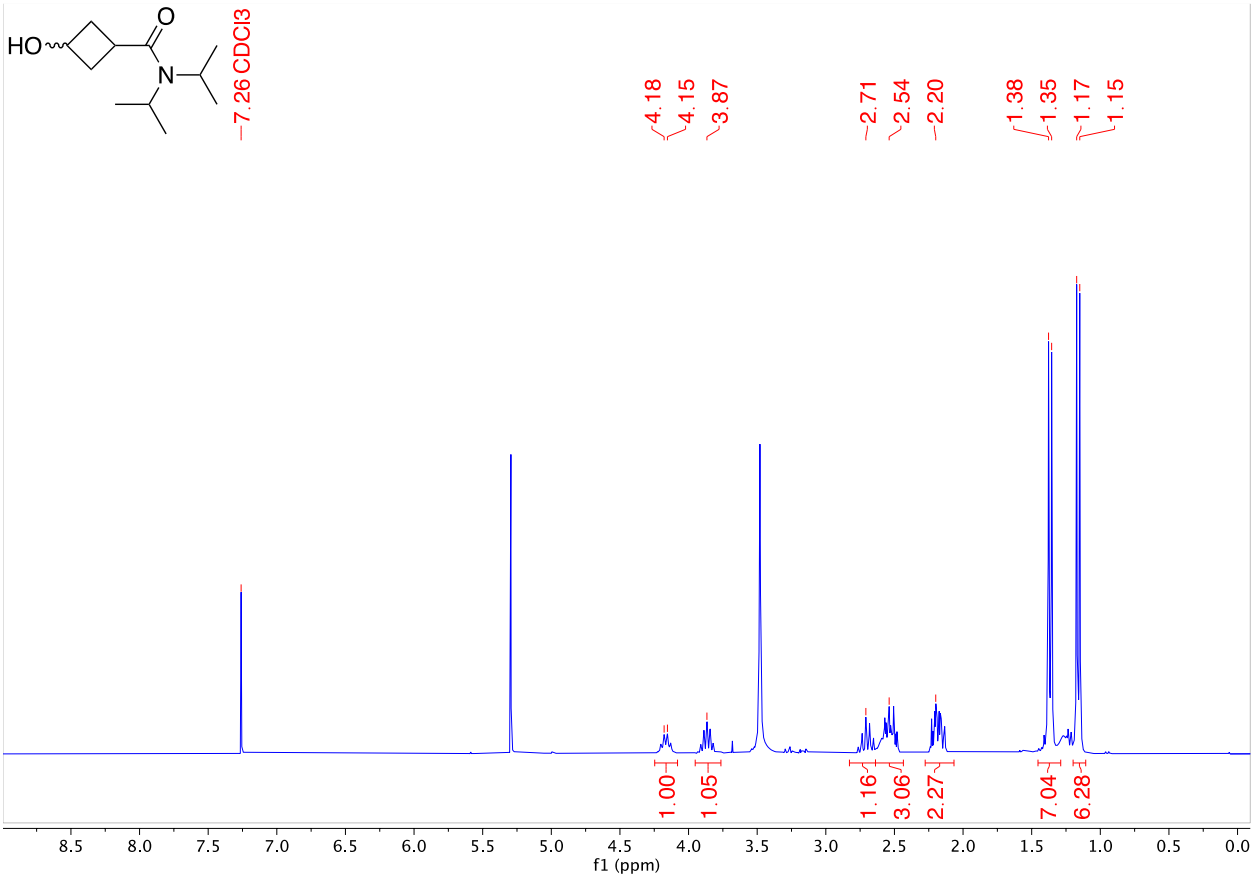


3-Hydroxy-*N,N*-diisopropylcyclobutane-1-carboxamide

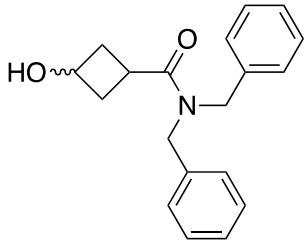


This product was prepared using general procedure 2. Isolated 600 mg of a brown solid (86% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 4.17 (sextet, J = 7.3 Hz, 1H), 3.87 (s, 1H), 2.71 (m, 1H), 2.54 (s, 3H), 2.20 (s, 2H), 1.37 (d, J = 6.8 Hz, 7H), 1.16 (d, J = 6.7 Hz, 6H).

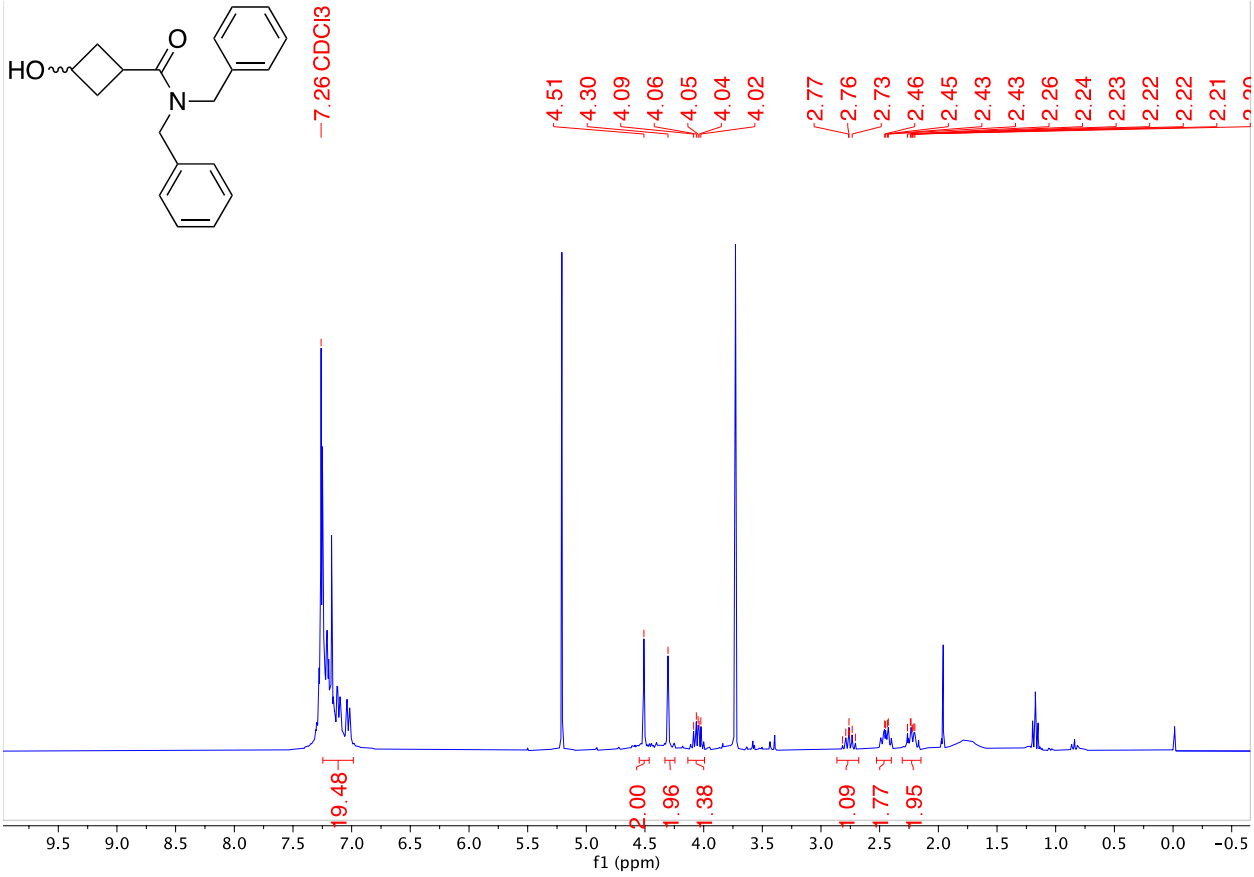


***N,N*-Dibenzyl-3-hydroxycyclobutane-1-carboxamide**

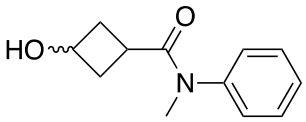


This product was prepared using general procedure 2. Isolated 3.23 grams of a clear colourless oil (100% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.25 – 6.99 (m, 10H), 4.51 (s, 2H), 4.30 (s, 2H), 4.13 – 3.99 (m, 1H), 2.86 – 2.68 (m, 1H), 2.44 (m, 2H), 2.31 – 2.15 (m, 2H).

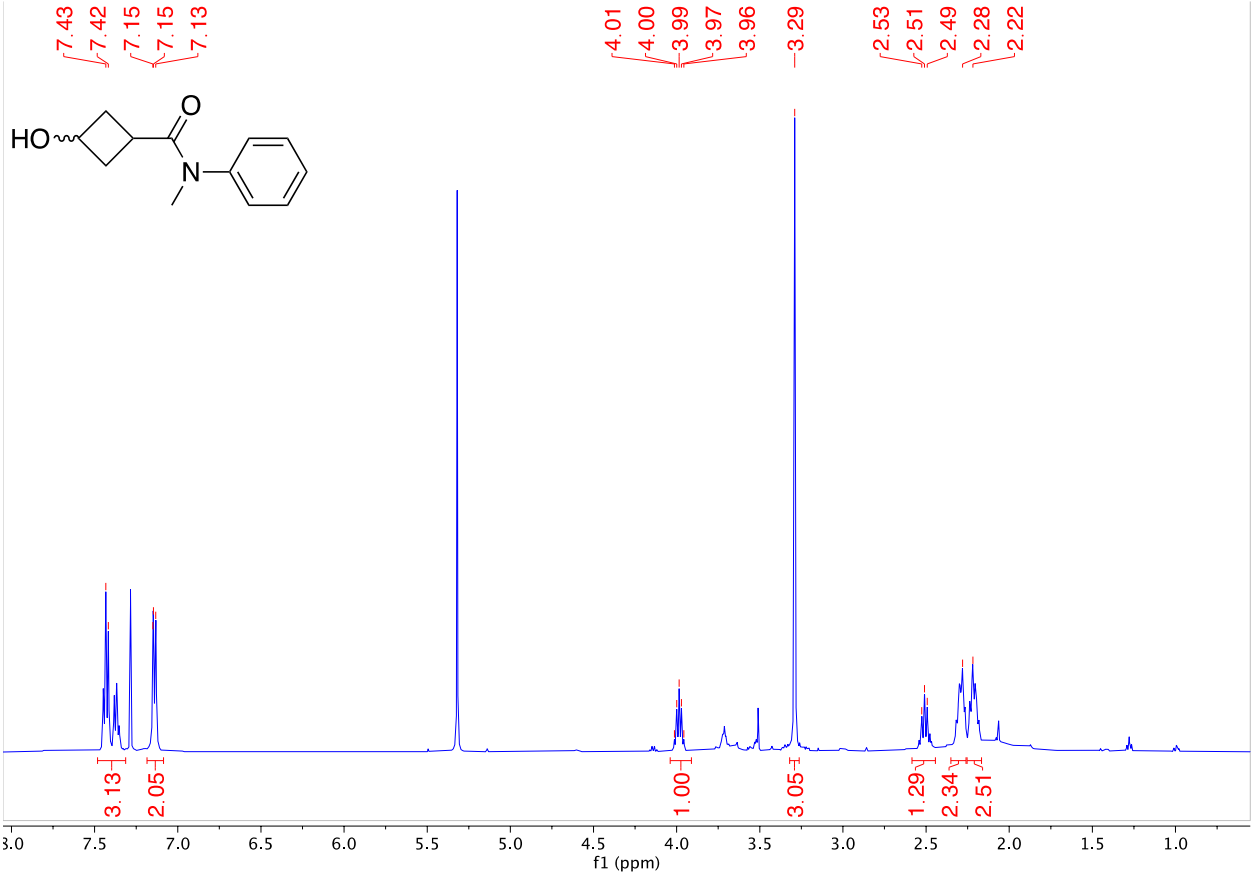


3-Hydroxy-*N*-methyl-*N*-phenylcyclobutane-1-carboxamide

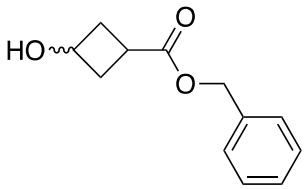


This product was prepared using general procedure 2. Isolated 740.7 mg of a white powder (82% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.43 (m, 3H), 7.19 – 7.09 (m, 2H), 3.99 (p, J = 7.1 Hz, 1H), 3.29 (s, 3H), 2.58 – 2.44 (m, 1H), 2.28 (m, 2H), 2.22 (m, 2H).

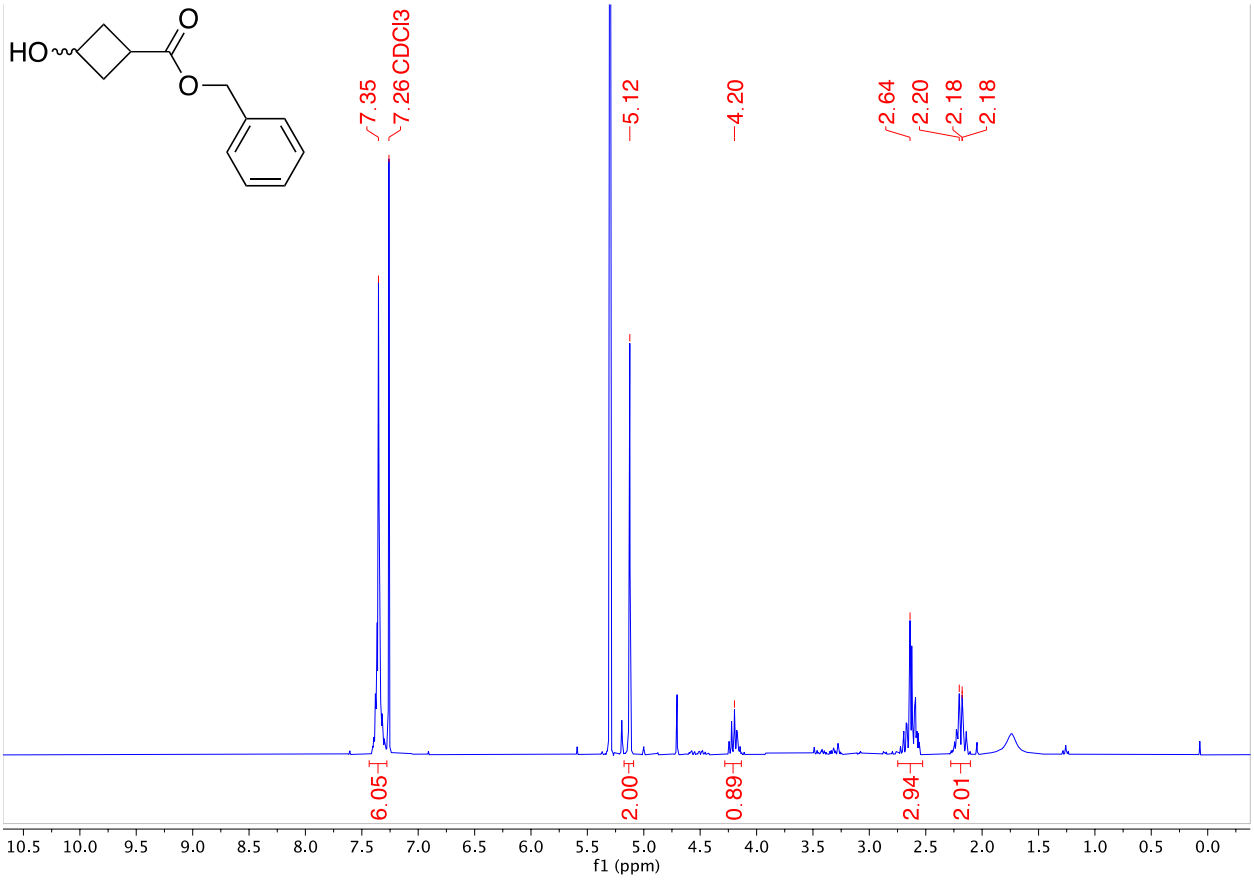


Benzyl 3-hydroxycyclobutane-1-carboxylate

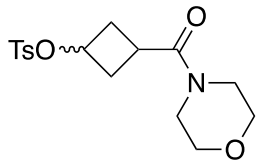


This product was prepared using general procedure 2. Isolated 1.32 grams of a white powder (100% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.35 (m, 6H), 5.12 (s, 2H), 4.20 (m, 1H), 2.64 (m, 3H), 2.28 – 2.10 (m, 2H).

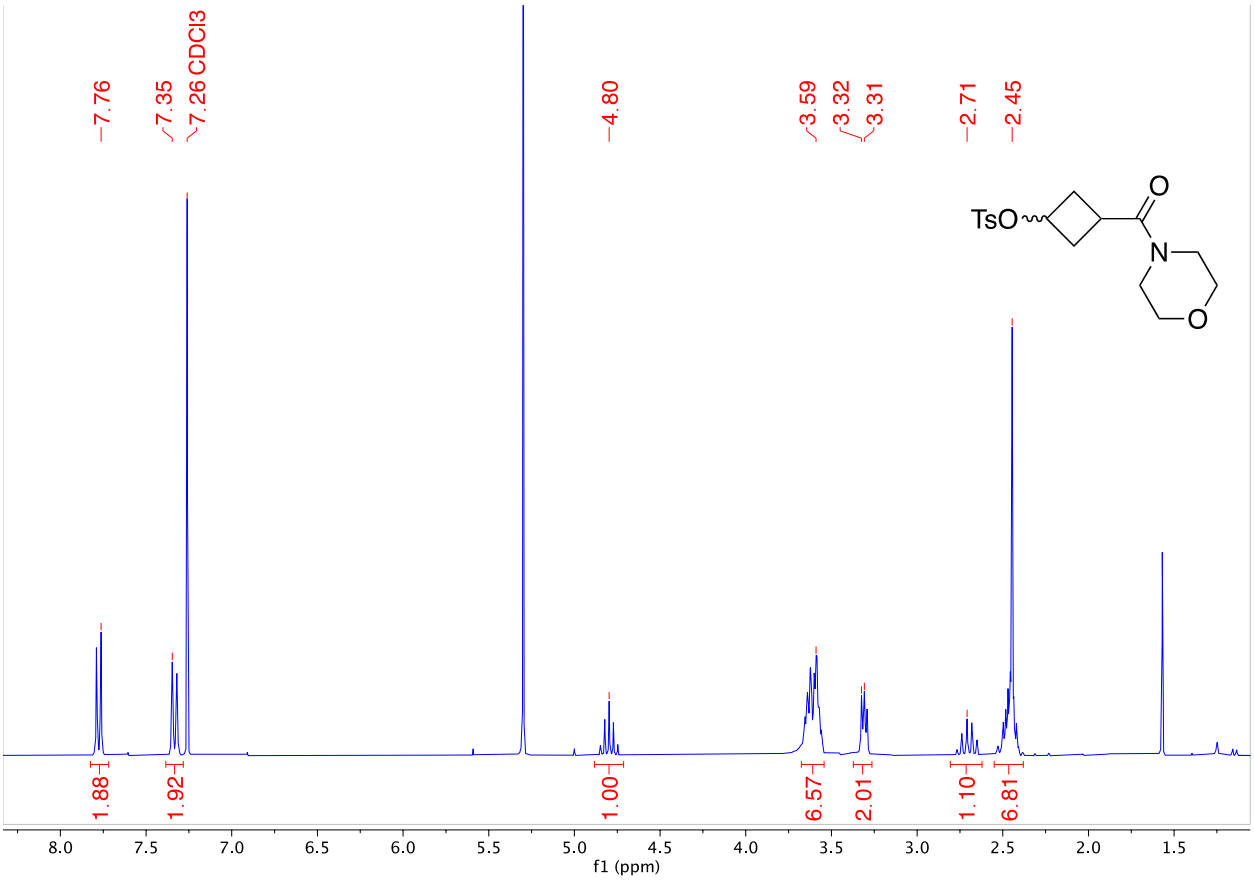


3-(Morpholine-4-carbonyl)cyclobutyl 4-methylbenzenesulfonate

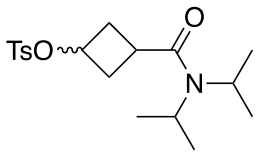


This product was prepared using general procedure 3. The compound was purified by column chromatography (Biotage® Sfär 50g Column, 0-100% MeOH/DCM, eluted at 10% MeOH). 6.86 grams of a yellow oil was obtained (89% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.76 (d, 2H), 7.35 (d, 2H), 4.80 (quintet, 1H), 3.67-3.53 (m, 6H), 3.34-3.27 (m, 2H), 2.78-2.64 (m, 1H), 2.54-2.39 (m, 7H).

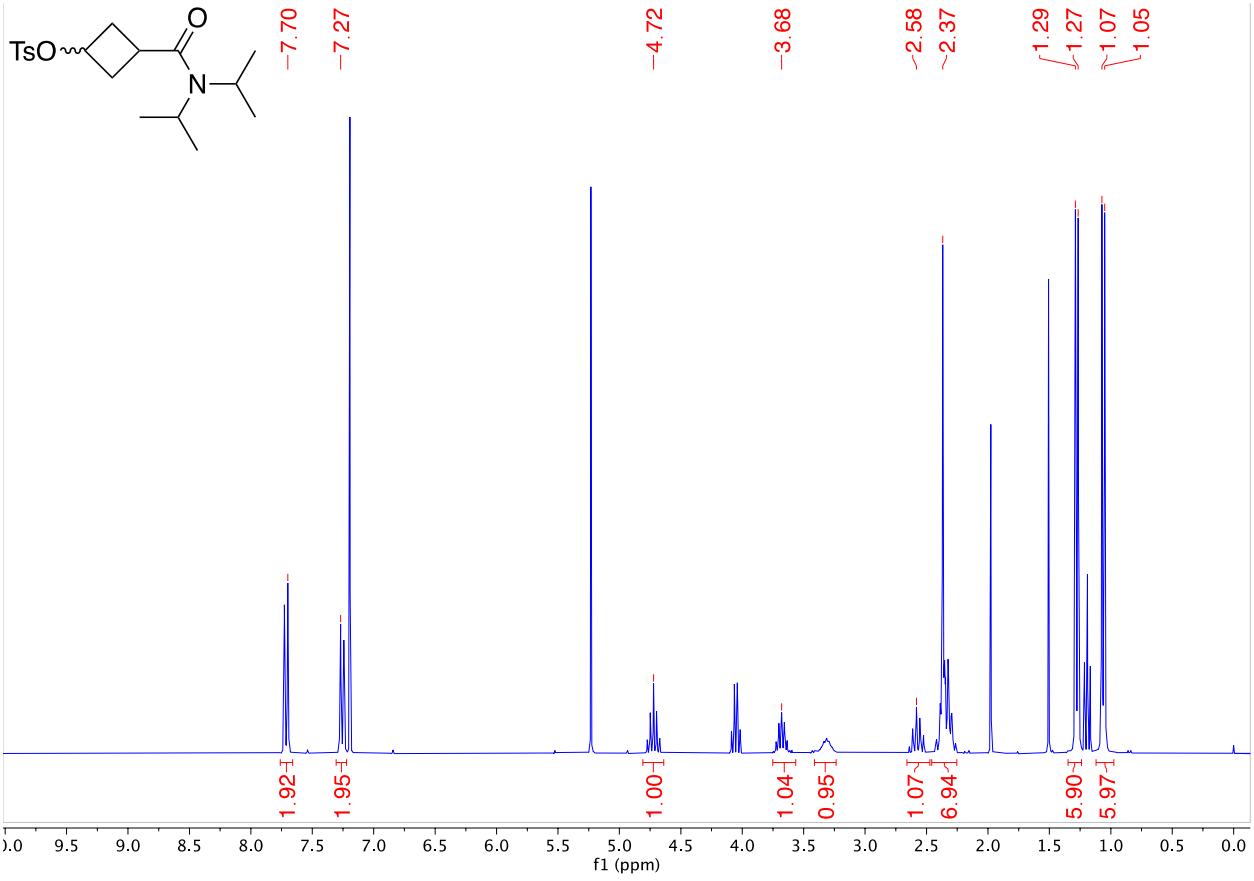


3-(Diisopropylcarbamoyl)cyclobutyl 4-methylbenzenesulfonate

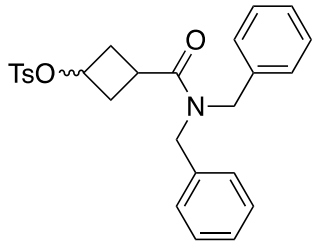


This product was prepared using general procedure 3. The compound was purified by column chromatography (Biotage® Sfär 50g Column, 0-100% MeOH/DCM, eluted at 13% MeOH). 2.11 grams of a white solid was obtained (60% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.71 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.72 (m, 1H), 3.68 (hept, J = 6.6 Hz, 1H), 3.41 – 3.24 (m, 1H), 2.58 (m, 1H), 2.37 (s, 7H), 1.28 (d, J = 6.8 Hz, 6H), 1.06 (d, J = 6.7 Hz, 6H).

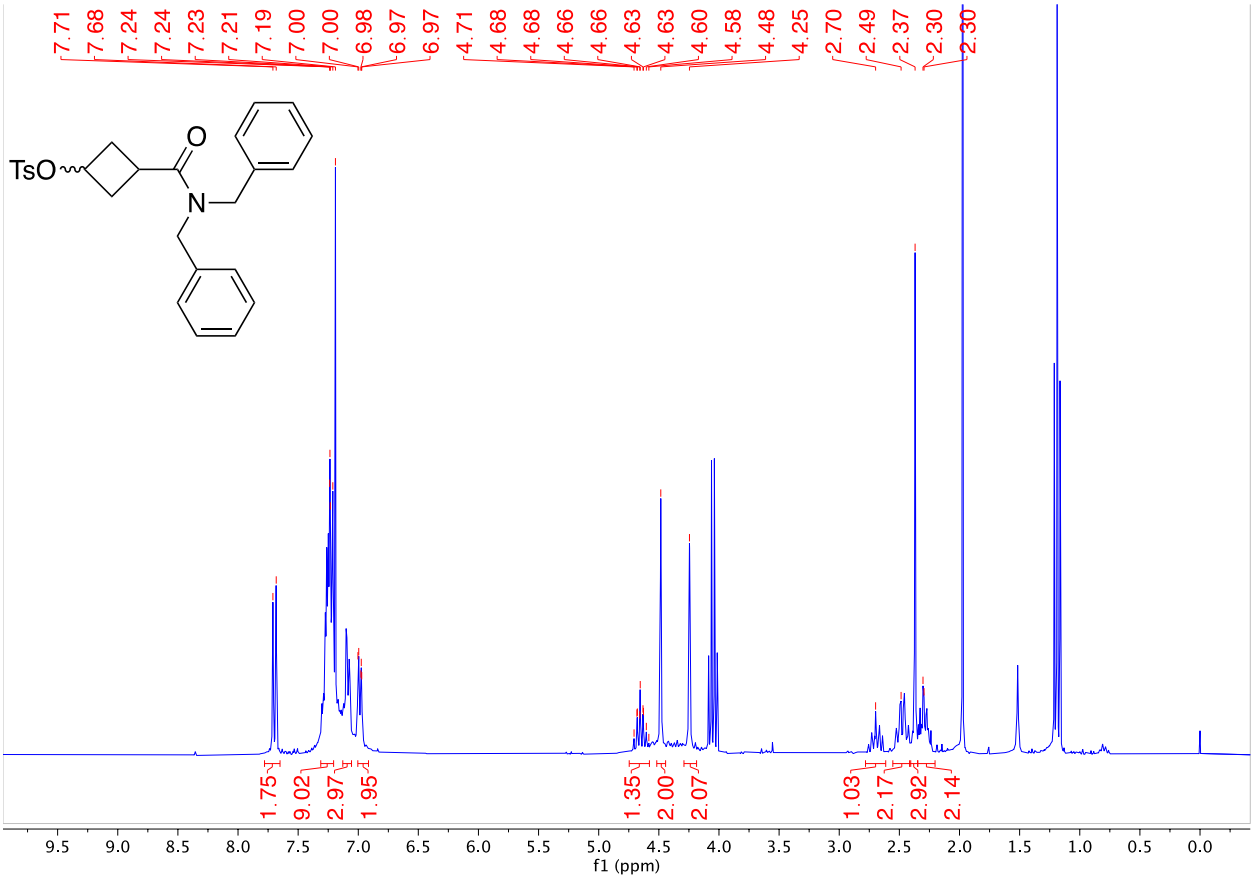


3-(Dibenzylcarbamoyl)cyclobutyl 4-methylbenzenesulfonate

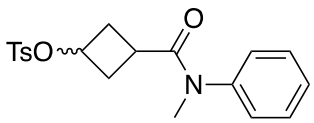


This product was prepared using general procedure 3. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 30% EtOAc). 2.32 grams of an orange oil was obtained (47% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.70 (d, J = 8.3 Hz, 2H), 7.31 – 7.20 (m, 7H), 7.09 (m, 3H), 7.00 – 6.91 (m, 2H), 4.75 – 4.58 (m, 1H), 4.48 (s, 2H), 4.25 (s, 2H), 2.70 (m, 1H), 2.49 (m, 2H), 2.37 (s, 3H), 2.30 (m, 2H).

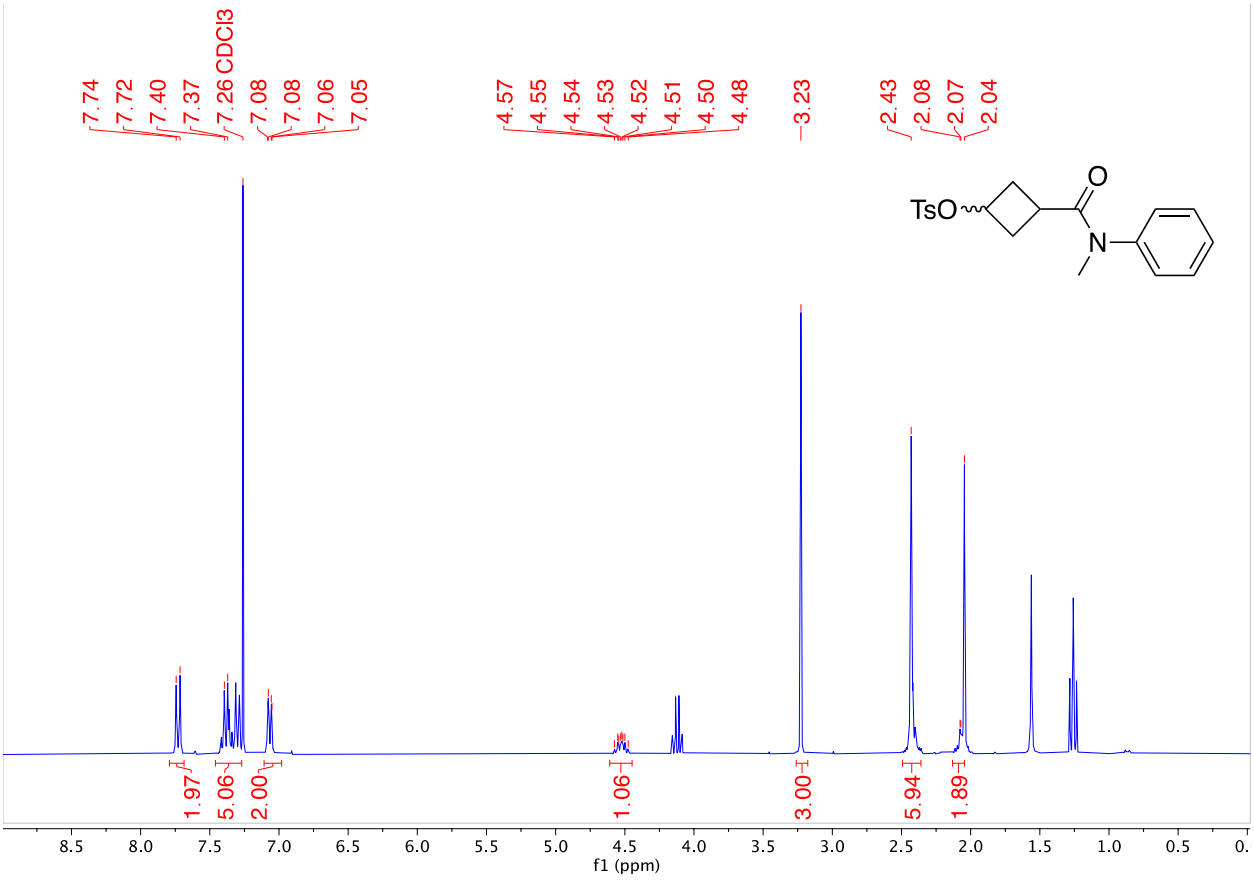


3-(Methyl(phenyl)carbamoyl)cyclobutyl 4-methylbenzenesulfonate

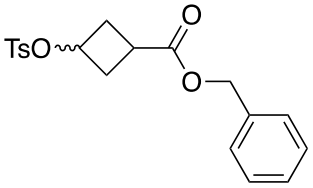


This product was prepared using general procedure 3. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 40% EtOAc). 1.21 grams of a yellow oil was obtained (93% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.73 (d, J = 8.3 Hz, 2H), 7.38 (m, 5H), 7.07 (m, 2H), 4.61 – 4.45 (m, 1H), 3.23 (s, 3H), 2.43 (m, 6H), 2.07 (m, 2H).

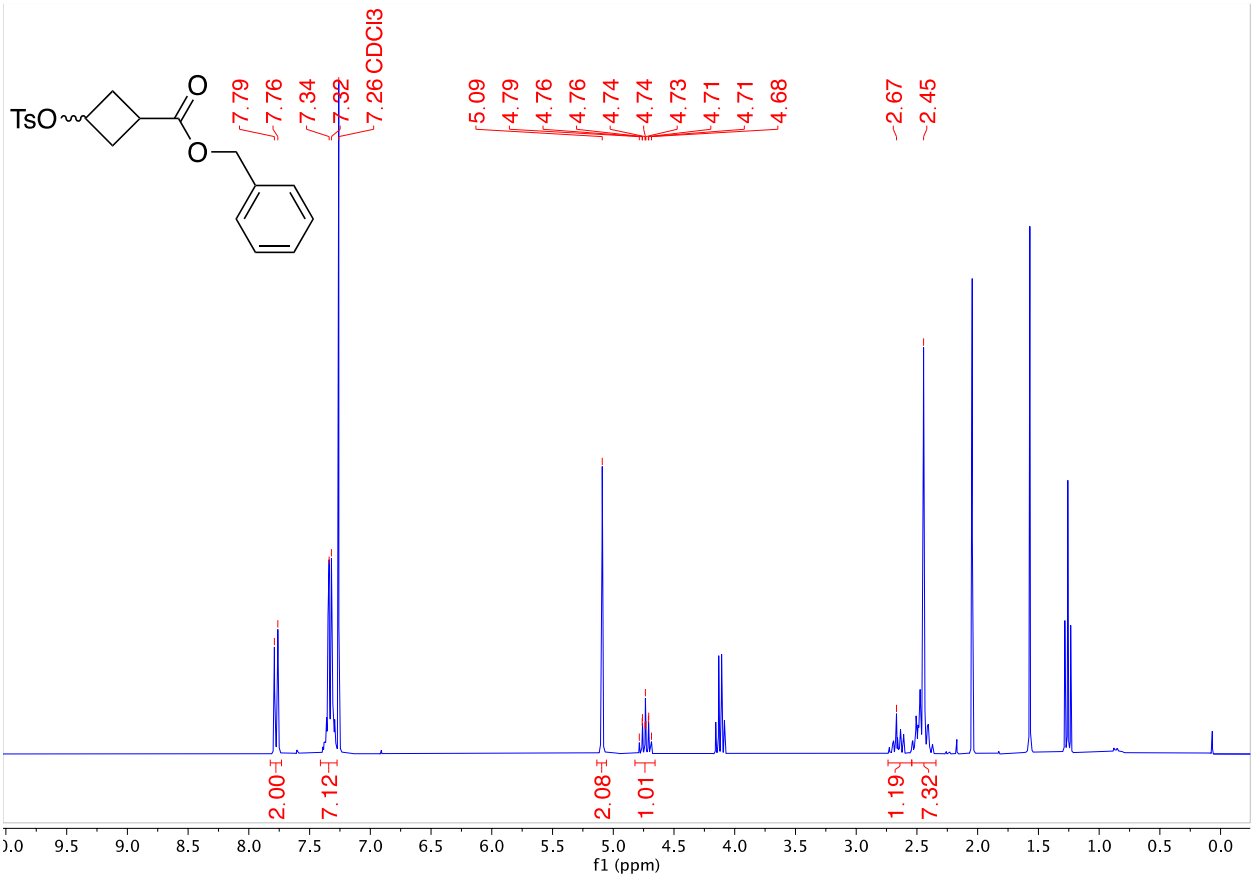


Benzyl 3-(tosyloxy)cyclobutane-1-carboxylate

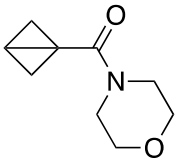


This product was prepared using general procedure 3. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 35% EtOAc). 1.02 grams of a white solid was obtained (44% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (m, J = 5.7 Hz, 7H), 5.09 (s, 2H), 4.74 (m, 1H), 2.67 (m, 1H), 2.45 (m, 7H).

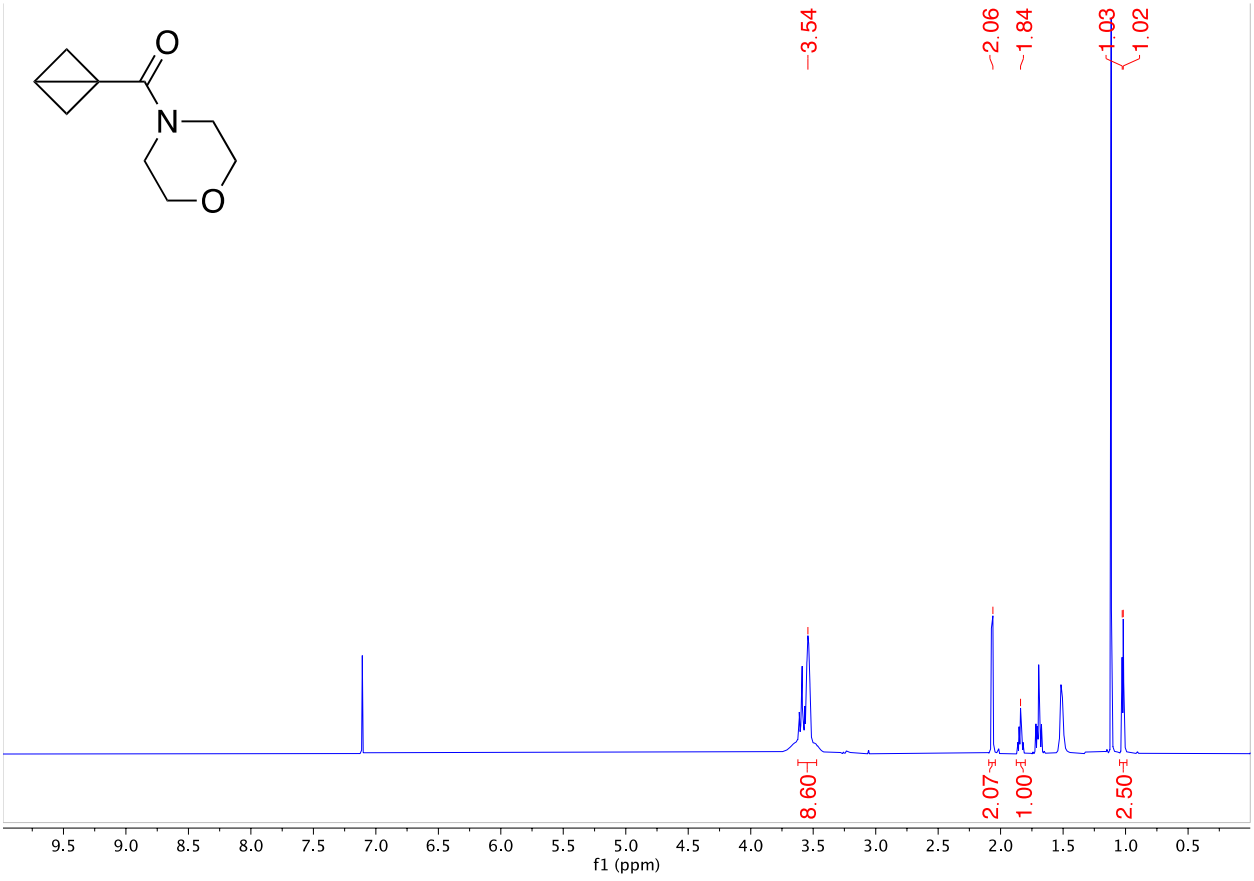


Bicyclo[1.1.0]butan-1-yl(morpholino)methanone (1a)[8]

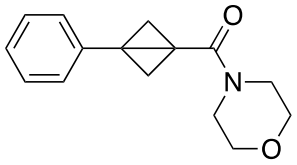


This product was prepared using general procedure 4. 338 mg of an orange oil was obtained (89% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 3.54 (m, 8H), 2.07 (d, J = 3.4 Hz, 2H), 1.84 (m, 1H), 1.02 (d, J = 2.5 Hz, 2H).

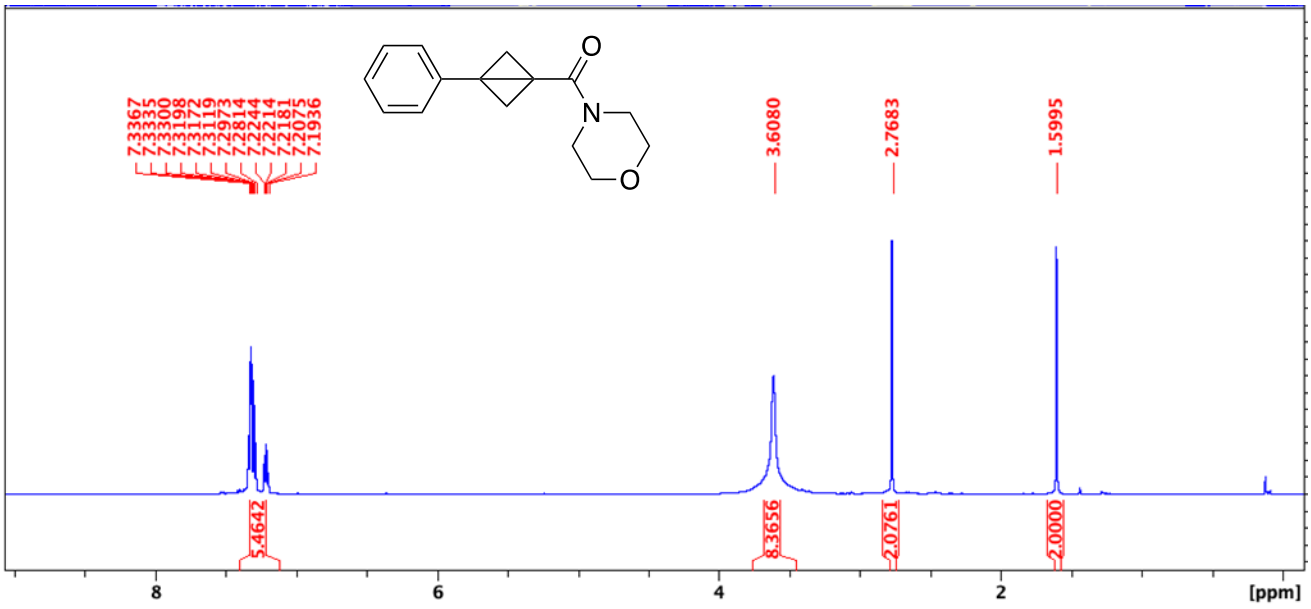


Morpholino(3-phenylbicyclo[1.1.0]butan-1-yl)methanone (1l)[9]

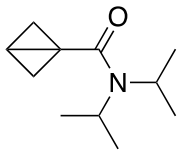


(3-chloro-3-phenylcyclobutyl)(morpholino)methanone (0.4776g, 1.70 mmol) was added to a 20 mL vial and dissolved in 5 mL THF under a N_2 atmosphere at 0 °C. NaHDMS (2.04 mL, 2.04 mmol) was added to the vial and the reaction mixture was stirred at 0 °C for 4 hours. The reaction mixture was diluted with DCM and washed with water. The organic layer was dried with $MgSO_4$ and the solvent was removed by evaporation. The product was isolated as an orange solid and used without further purification (0.394 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$, 292 K, ppm): δ 7.37-7.18 (m, 5H), 3.61 (s, 8H), 2.77 (s, 2H), 1.60 (s, 2H).

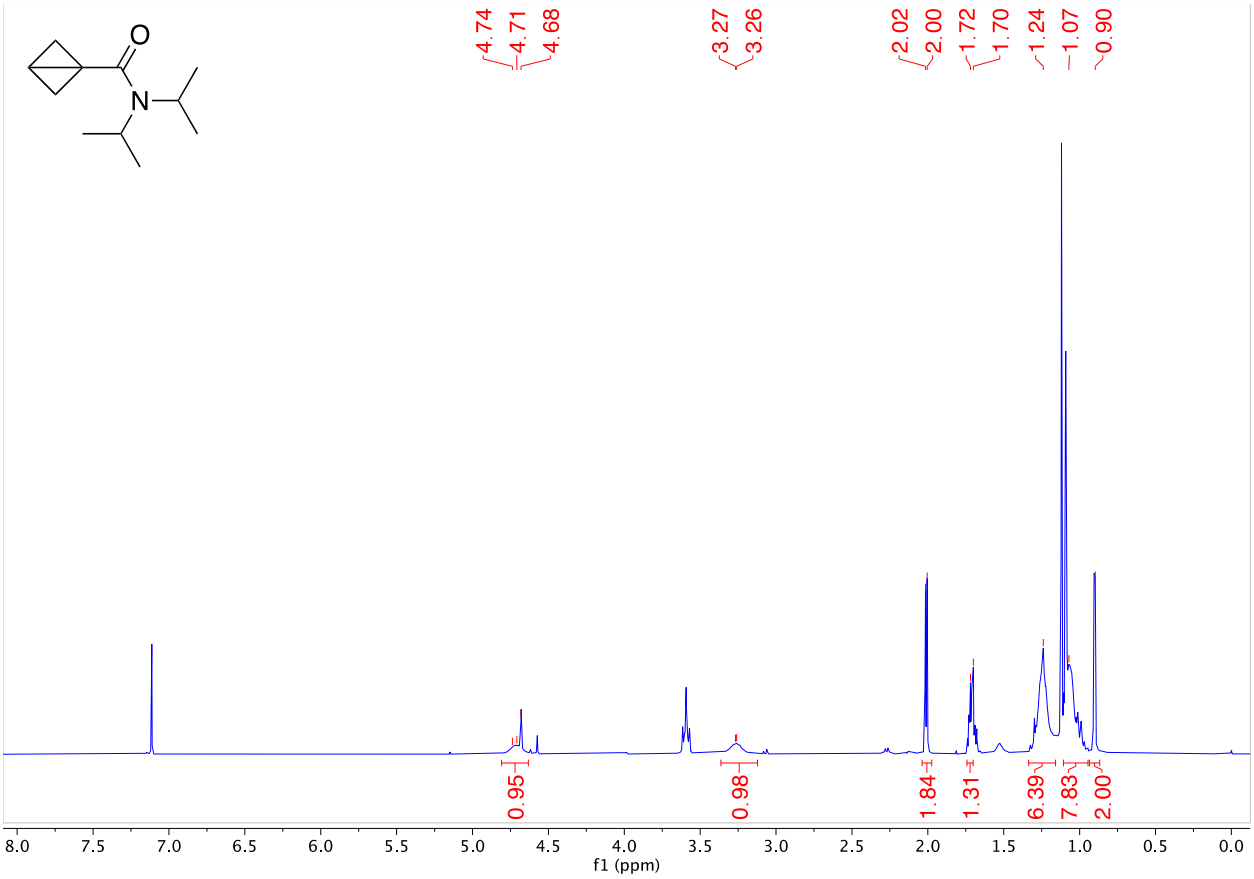


***N*,*N*-Diisopropylbicyclo[1.1.0]butane-1-carboxamide (1m)[10]**

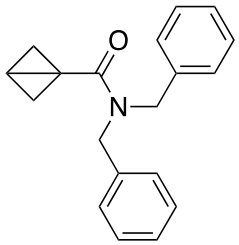


This product was prepared using general procedure 4. 896 mg of an orange solid was obtained (83% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 4.71 (broad s, 1H), 3.36 (broad s, 1H), 2.01 (d, J = 3.3 Hz, 2H), 1.72 (m, 1H), 1.24 (m, 6H), 1.07 (m, 6H), 0.90 (d, J = 2.2 Hz, 2H).

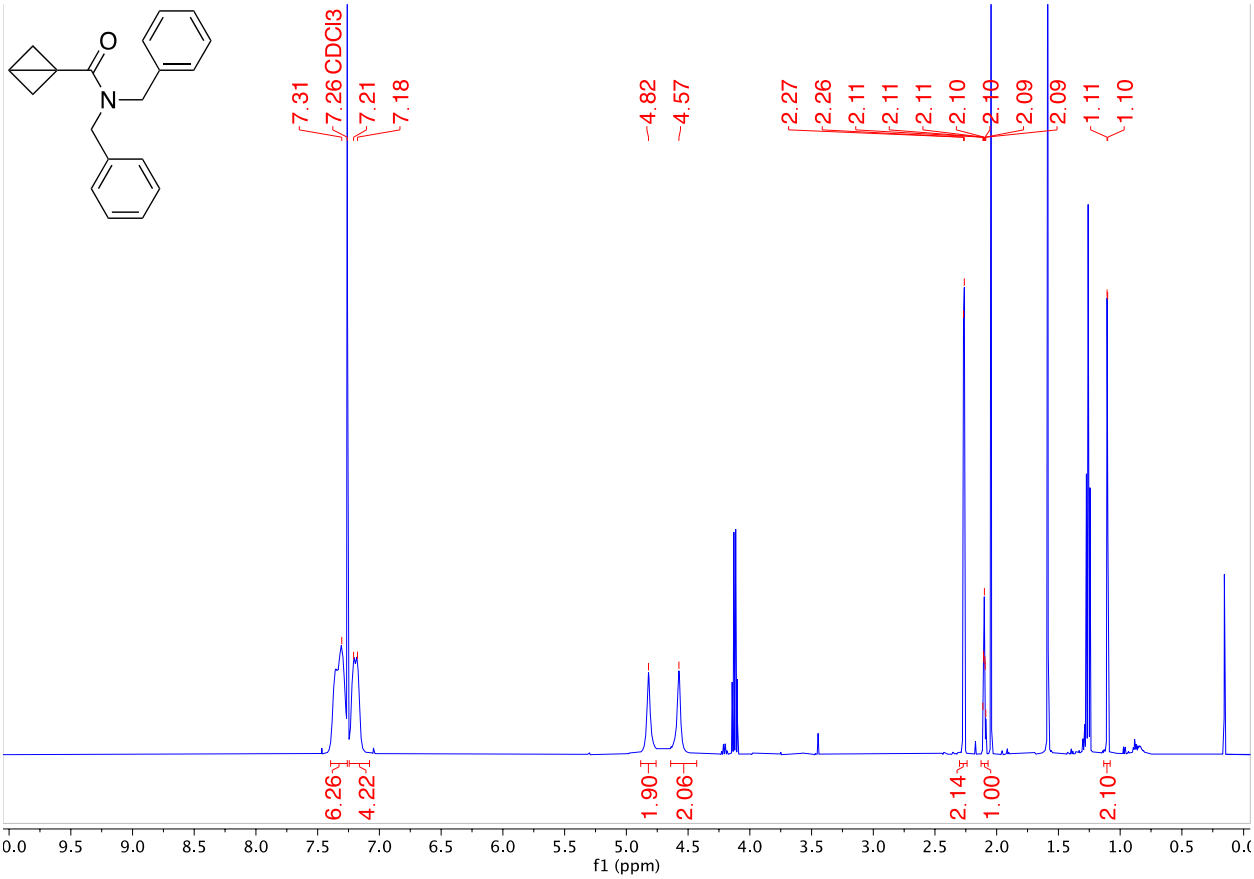


***N,N*-Dibenzylbicyclo[1.1.0]butane-1-carboxamide (1n)[11]**

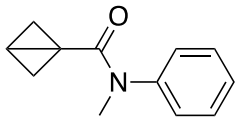


Synthesis adapted from Agasti *et al.*[19] 3-(Dibenzylcarbamoyl)cyclobutyl 4-methylbenzenesulfonate (1 eq.) was dissolved in THF (0.15 M) under a nitrogen atmosphere. The reaction was cooled down to 0°C then NaHMDS (1.0M in THF, 1.1 eq.) was added to the reaction mixture. The reaction was stirred at 0°C for 2 hours. The reaction was quenched with NH_4Cl and extracted with ethyl acetate. The organic layers were washed with $NaHCO_3$ and brine. The organic layer was then dried with Mg_2SO_4, filtered and the solvent was evaporated. The crude compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 28% EtOAc). 109.5 mg of a clear colourless oil was obtained (68% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.31 (m, 6H), 7.21 (m, 4H), 4.82 (s, 2H), 4.57 (s, 2H), 2.27 (d, J = 3.4 Hz, 2H), 2.13 – 2.07 (m, 1H), 1.11 (d, J = 2.4 Hz, 2H).

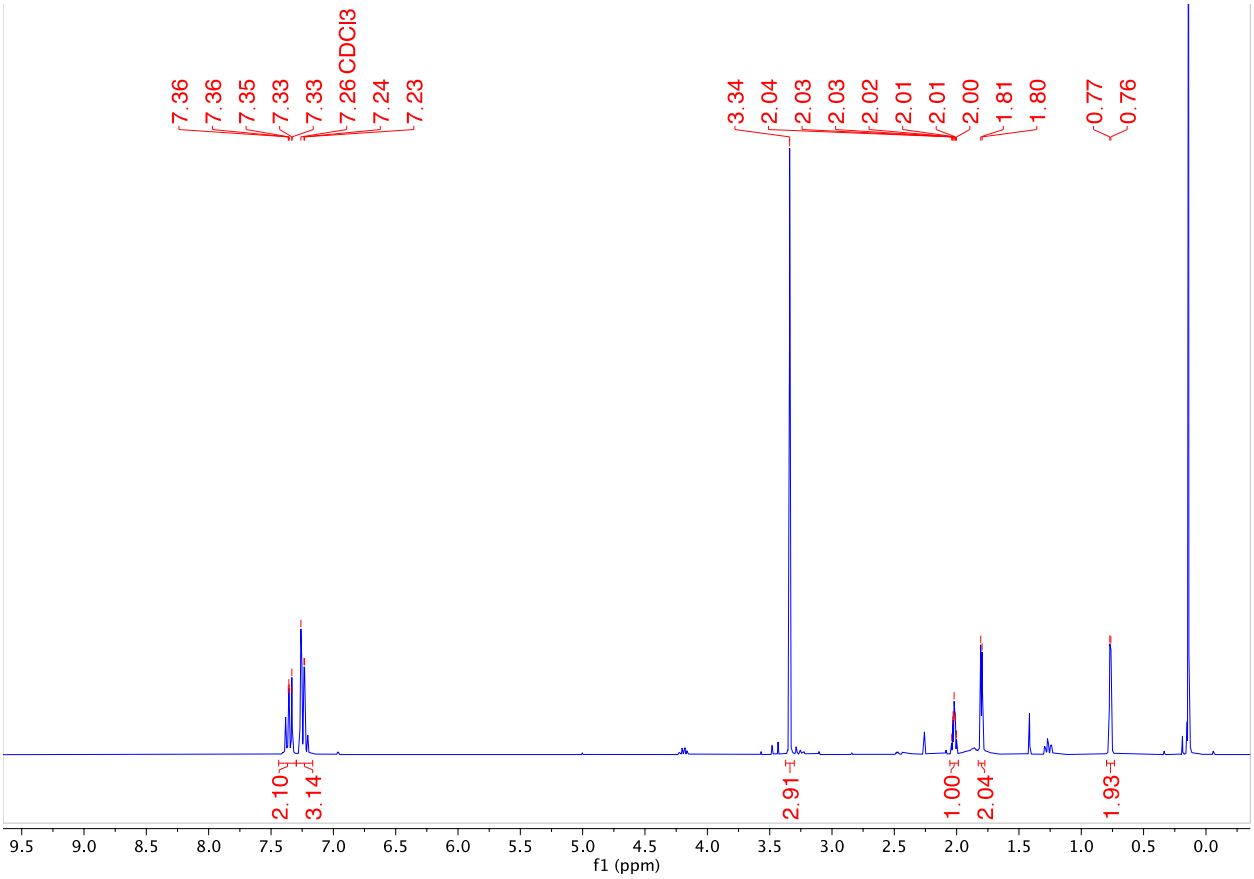


_N_-Methyl-_N_-phenylbicyclo[1.1.0]butane-1-carboxamide (1o)[12]

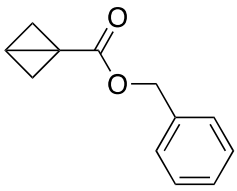


Synthesis adapted from Agasti *et al.*[20] 3-(Methyl(phenyl)carbamoyl)cyclobutyl 4-methylbenzenesulfonate (1 eq.) was dissolved in THF (0.15 M) under a nitrogen atmosphere. The reaction was cooled down to 0°C then NaHMDS (1.0M in THF, 1.1 eq.) was added to the reaction mixture. The reaction was stirred at 0°C for 1.5 hours. The reaction was quenched with NH_4Cl and extracted with ethyl acetate. The organic layers were washed with $NaHCO_3$ and brine. The organic layer was then dried with Mg_2SO_4, filtered and the solvent was evaporated to give the product without further purification. 126 mg of a yellow solid was obtained (80% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.44 – 7.30 (m, 2H), 7.23 (m, 3H), 3.34 (s, 3H), 2.02 (ddd, J = 5.8, 3.3, 2.5 Hz, 1H), 1.80 (d, J = 3.3 Hz, 2H), 0.77 (d, J = 2.6 Hz, 2H).

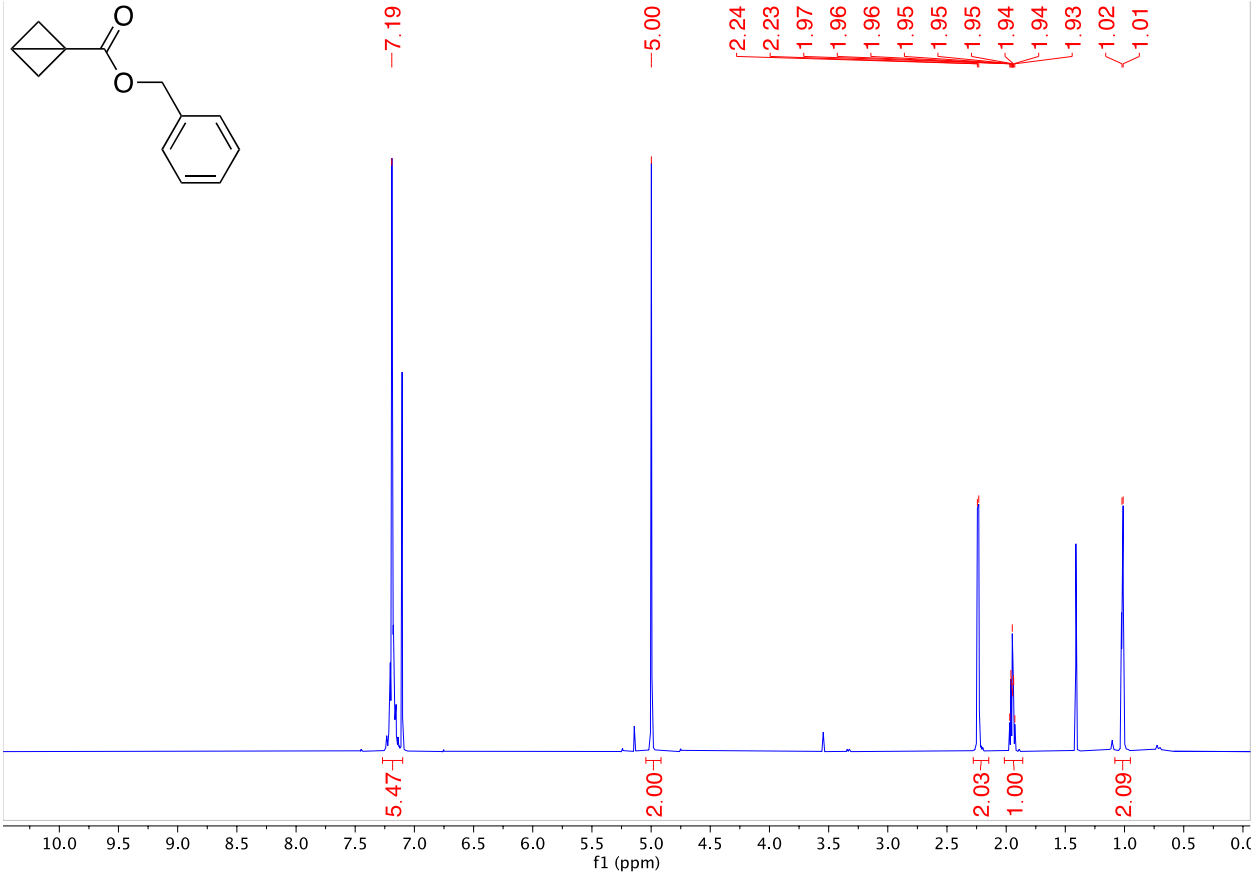


Benzyl bicyclo[1.1.0]butane-1-carboxylate (1p)[13]



Benzyl 3-(tosyloxy)cyclobutane-1-carboxylate (1 eq.) was dissolved in THF (0.19 M) under a nitrogen atmosphere. The reaction was cooled down to 0°C then LiHMDS (1.0M in THF, 1.1 eq.) was added to the reaction mixture. The reaction was stirred at rt overnight. The reaction was quenched with NH_4Cl and extracted with ethyl acetate. The organic layer was then dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography (Biotage® Sfär 25g Column, 0-100% EtOAc/hexanes, eluted at 12% EtOAc). 718 mg of a clear colourless oil was obtained (40% Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 292 K, ppm): δ 7.19 (m, 5H), 5.00 (s, 2H), 2.24 (m, 2H), 1.95 (m, 1H), 1.02 (m, 2H).

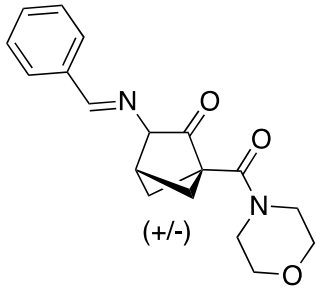


IV: Imine Bicyclohexane Transformations

General Procedure for Bicyclohexane Synthesis

In two separate vials, the bicyclobutane **1** (1 eq.) and acetate **2** (1.2 eq) were added and put under a nitrogen atmosphere. The acetate was dissolved in 50% of the THF and LiHMDS (1.0M in THF, 1.5 eq.) was added to the vial and then left to stir for 15 minutes at room temperature to form the enolate. Then 50% of the THF solvent was added to the bicyclobutane vial and then it was cooled in the glovebox freezer for 15 minutes along with the enolate vial. The bicyclobutane was then added dropwise to the enolate vial. The reaction was left to stir at room temperature overnight. The reaction was quenched with $NaHCO_3$ and extracted three times with ethyl acetate. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product **3**.

3-((Benzylidene)amino)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3a)

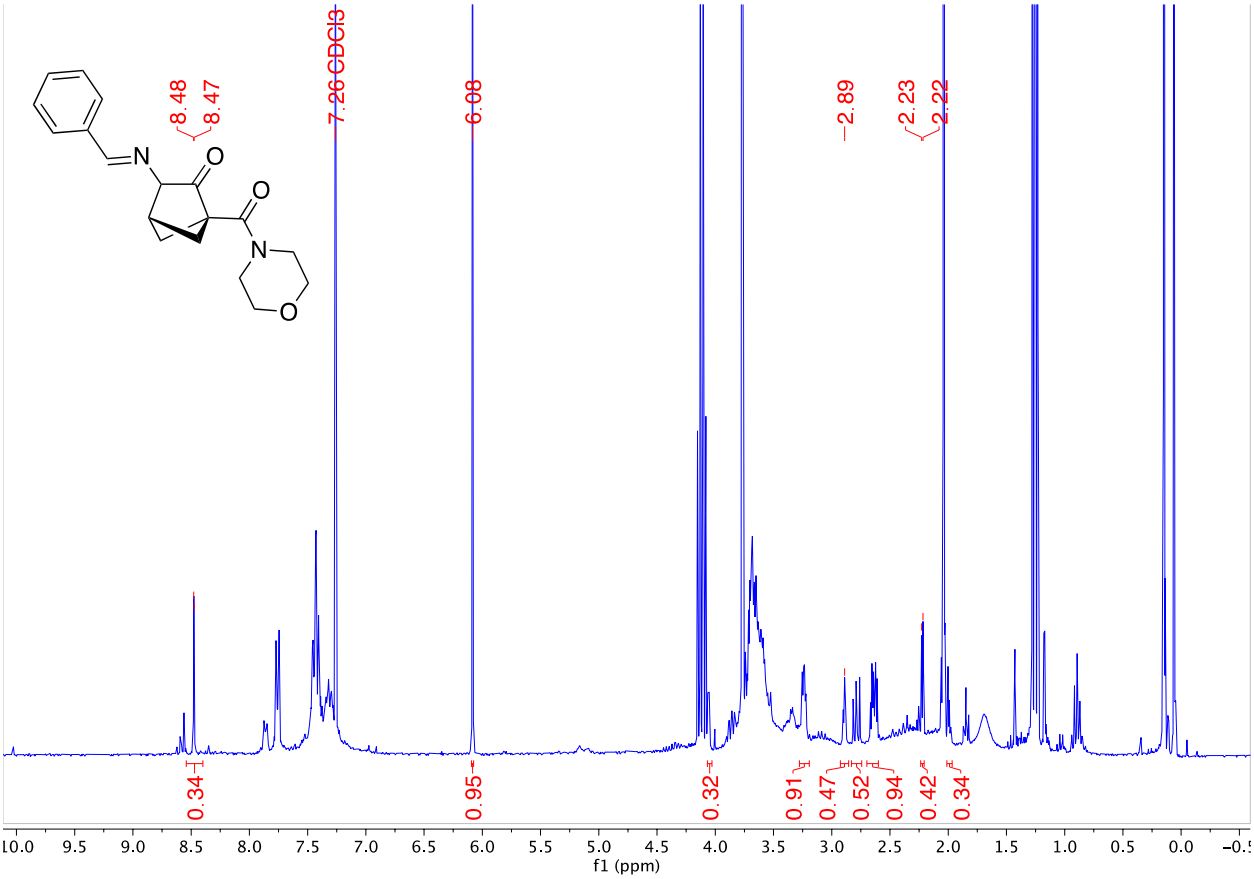


The product was prepared following the general procedure for bicyclohexane synthesis and carried into the next transformation without purification. Amount of reagents used: bicyclo[1.1.0]butan-1-yl(morpholino)methanone **1a** (83.6 mg, 1 eq.), ethyl (E)-2-(benzylideneamino)acetate **2a** (105.2 mg, 1.1 eq.), LiHMDS (1.0 M in THF, 0.75 mL, 1.5 eq.) and THF (10 mL, 0.06 M). This was used directly in the next step without purification. Crude NMR yield of 47%.

One sample was isolated and purified by column chromatography for characterization (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 100% EtOAc). Isolated 8 mg of a yellow oil (13% yield).

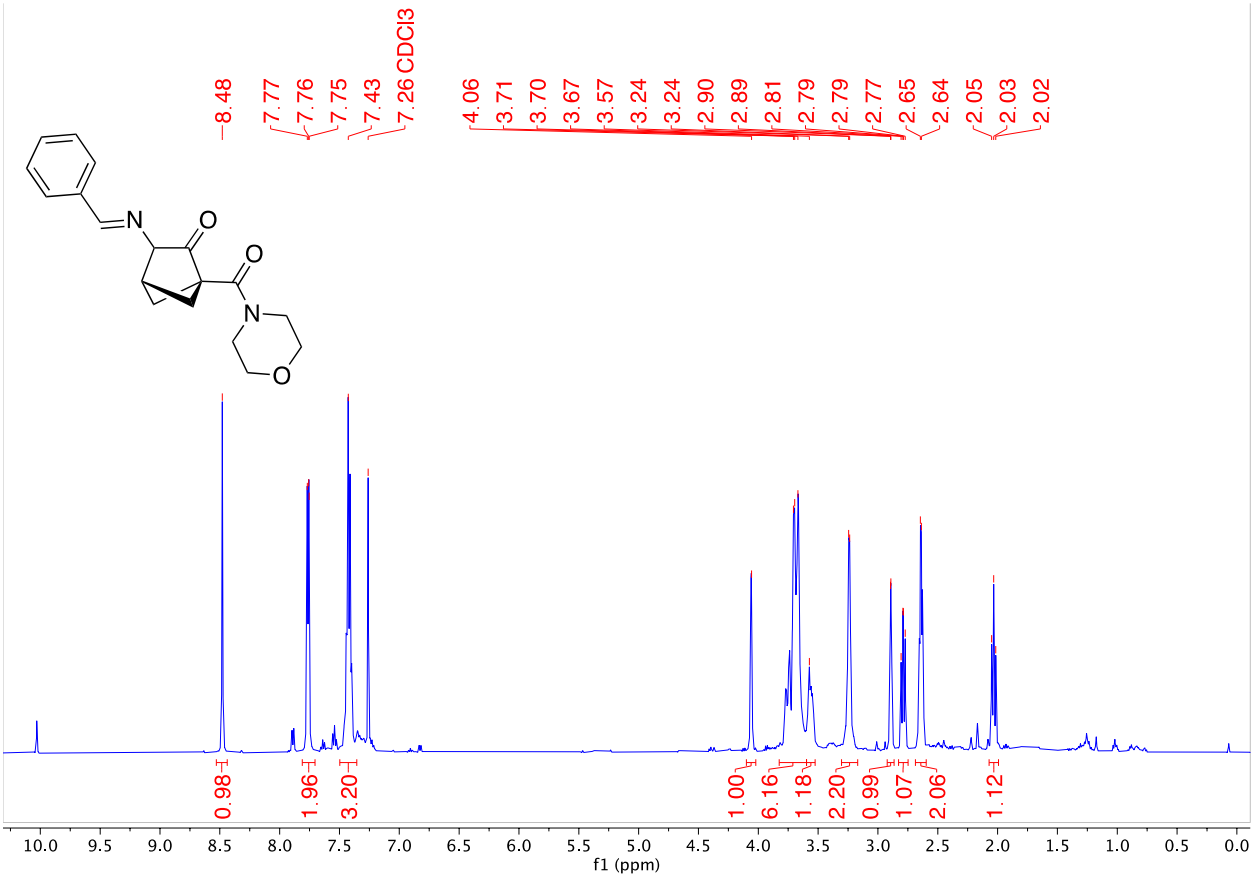
HRMS(ESI): calc'd for [$C_{18}H_{20}N_2O_3 + H^+$], 313.15467; found: 313.15446

Crude ^{1}H NMR spectrum, including 1,3,5-trimethoxybenzene as internal standard (500 MHz, $CDCl_3$, 292K):

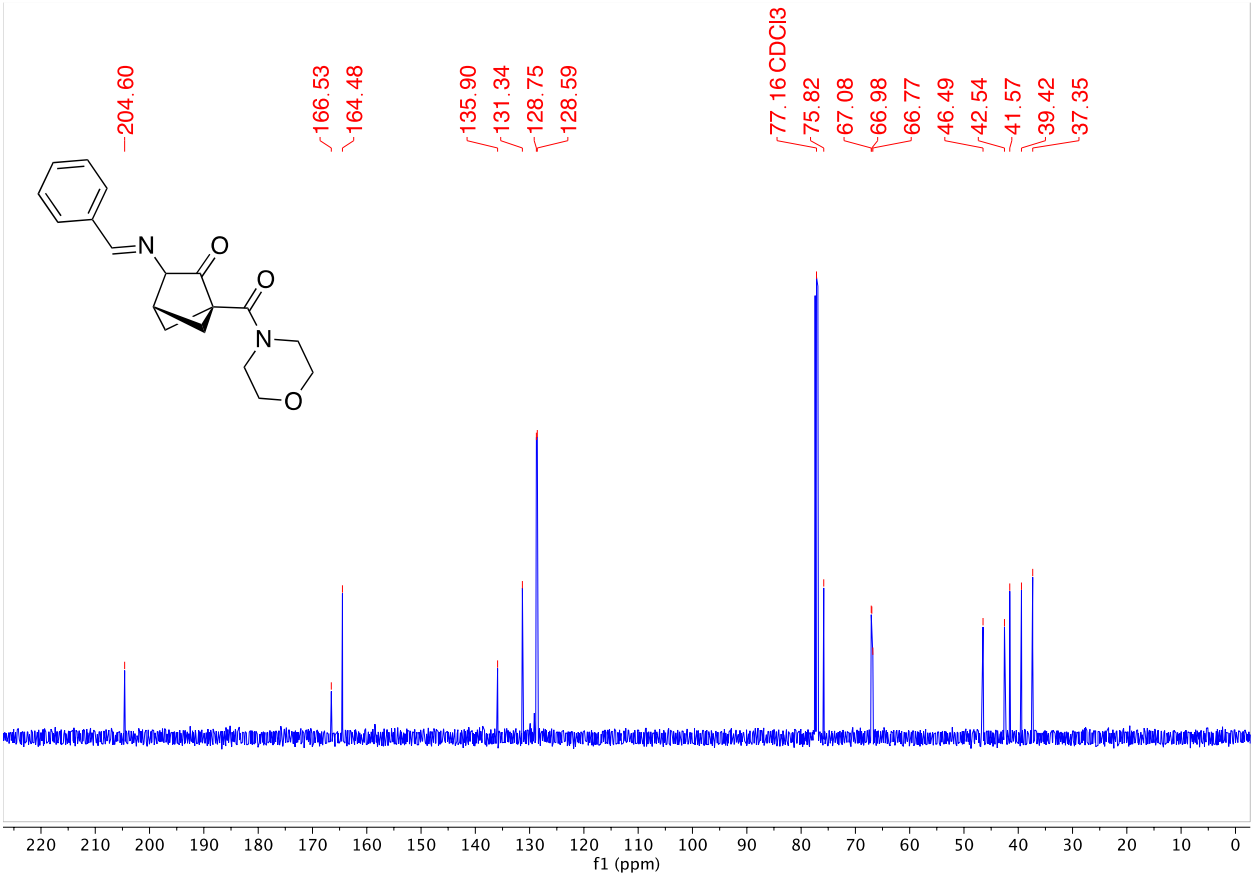


Isolated sample of 3a after chromatography:

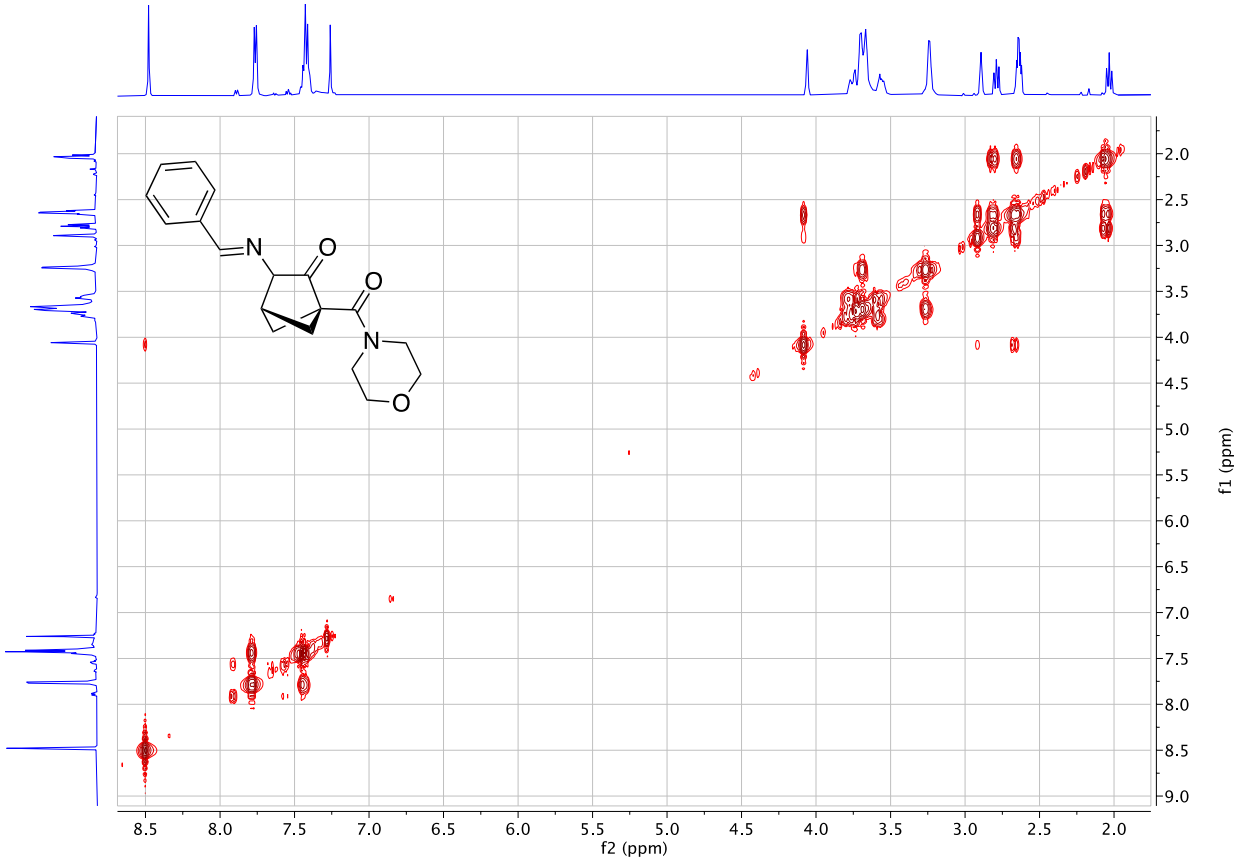
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 8.48 (s, 1H), 7.81 – 7.70 (m, 2H), 7.43 (m, 3H), 4.06 (s, 1H), 3.83 – 3.60 (m, 6H), 3.57 (m, 1H), 3.24 (d, J = 4.4 Hz, 2H), 2.89 (m, 1H), 2.79 (dd, J = 9.4, 7.5 Hz, 1H), 2.64 (m, 2H), 2.03 (t, J = 8.7 Hz, 1H).



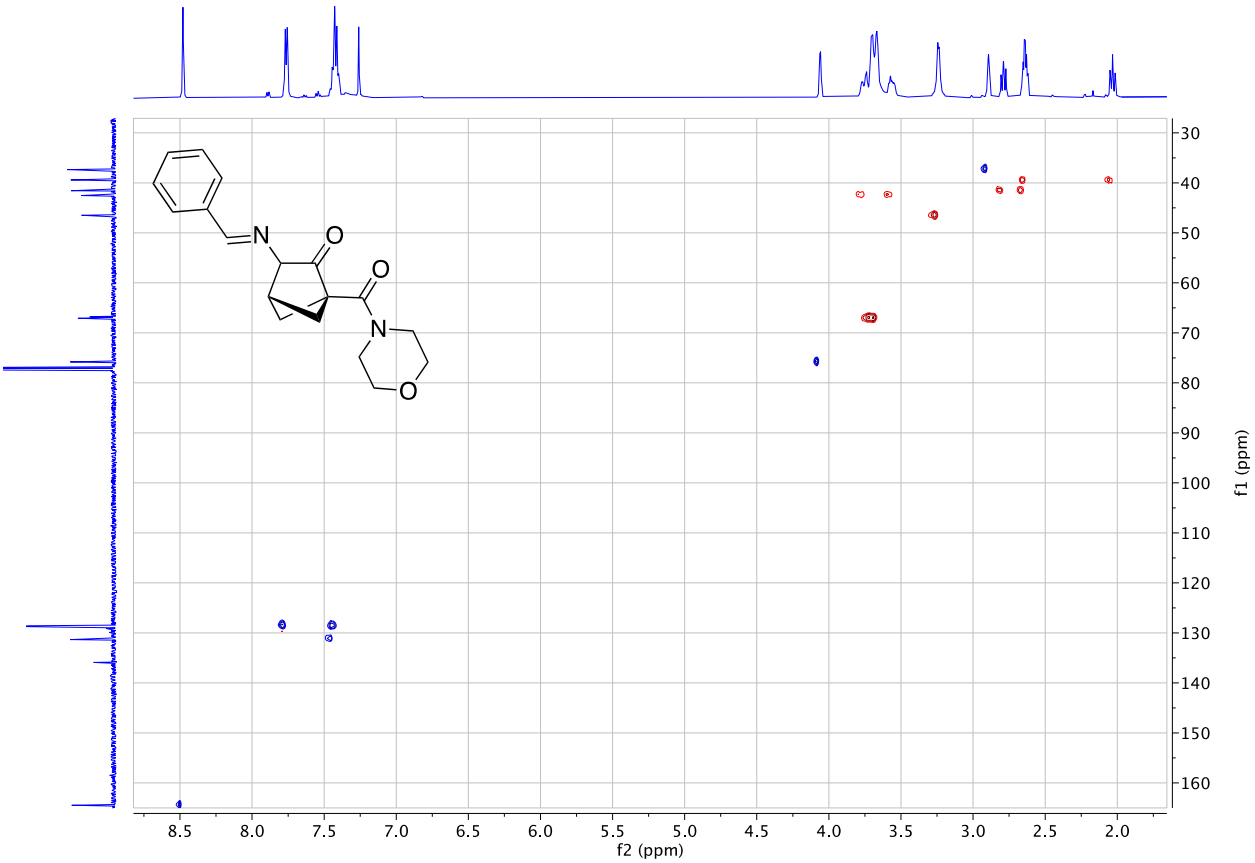
^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 204.60, 166.53, 164.48, 135.90, 131.34, 128.75, 128.59, 75.82, 67.08, 66.98, 66.77, 46.49, 42.54, 41.57, 39.42, 37.35.



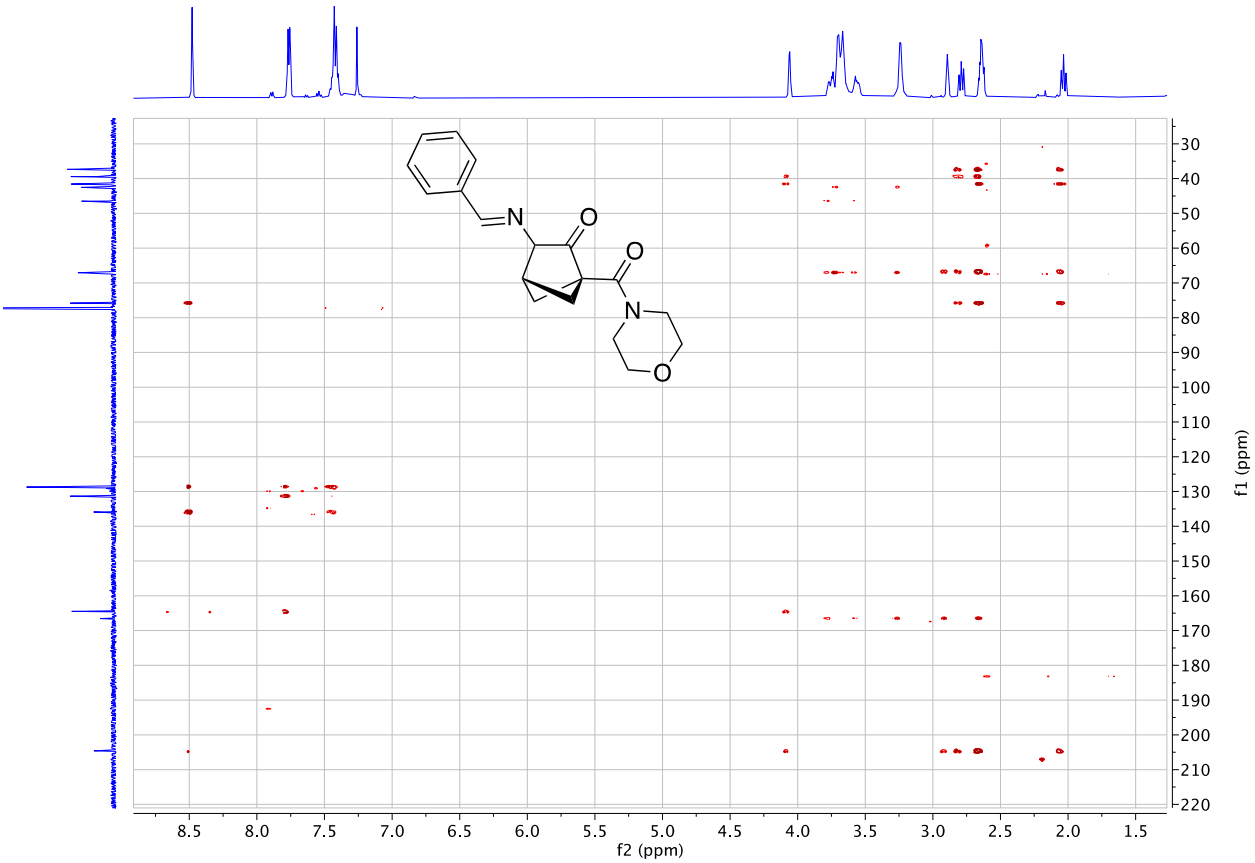
^{1}H-^{1}H COSY (3a):



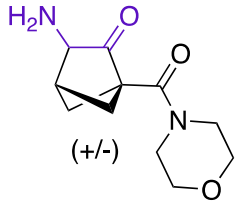
^{1}H-^{13}C HSQC (3a):



^{1}H-^{13}C HMBC (3a):



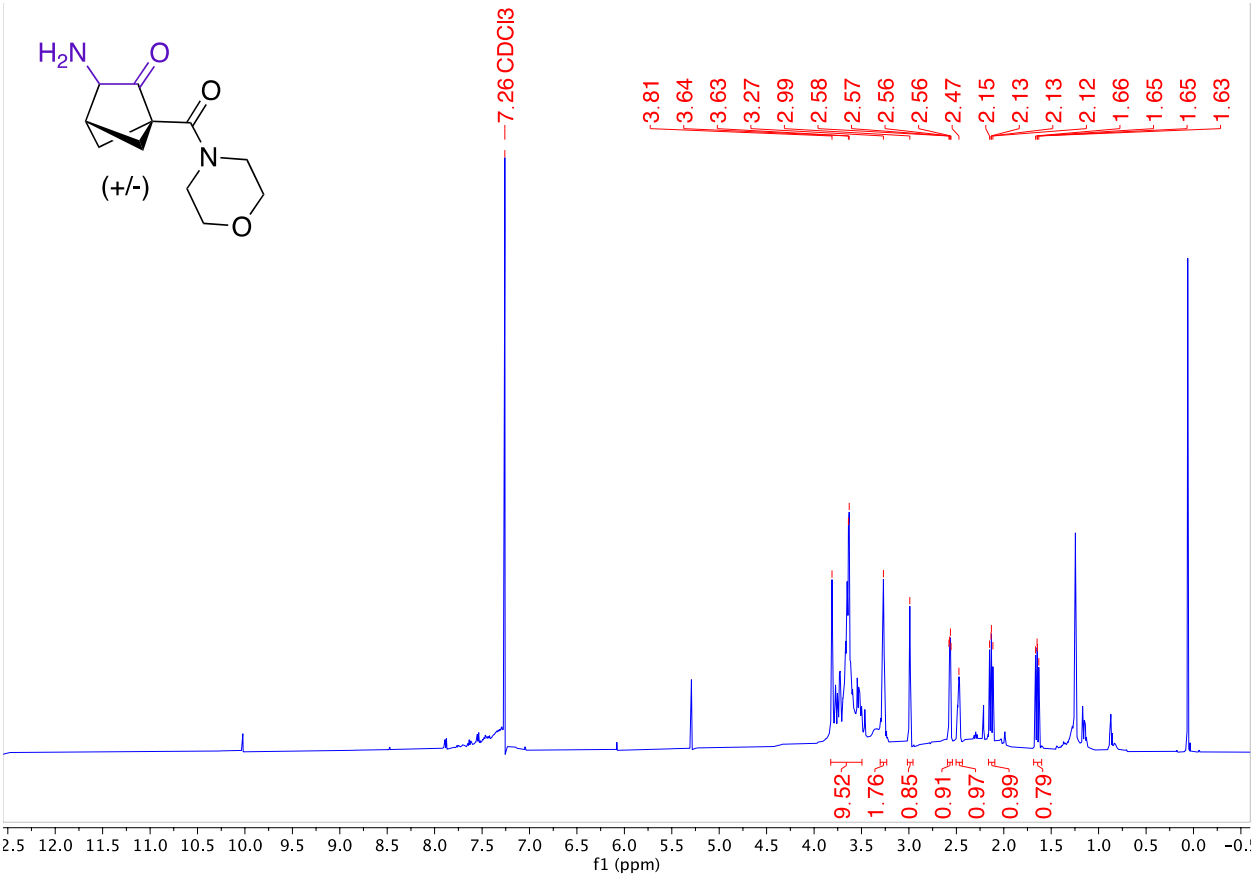
3-Amino-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (4a)



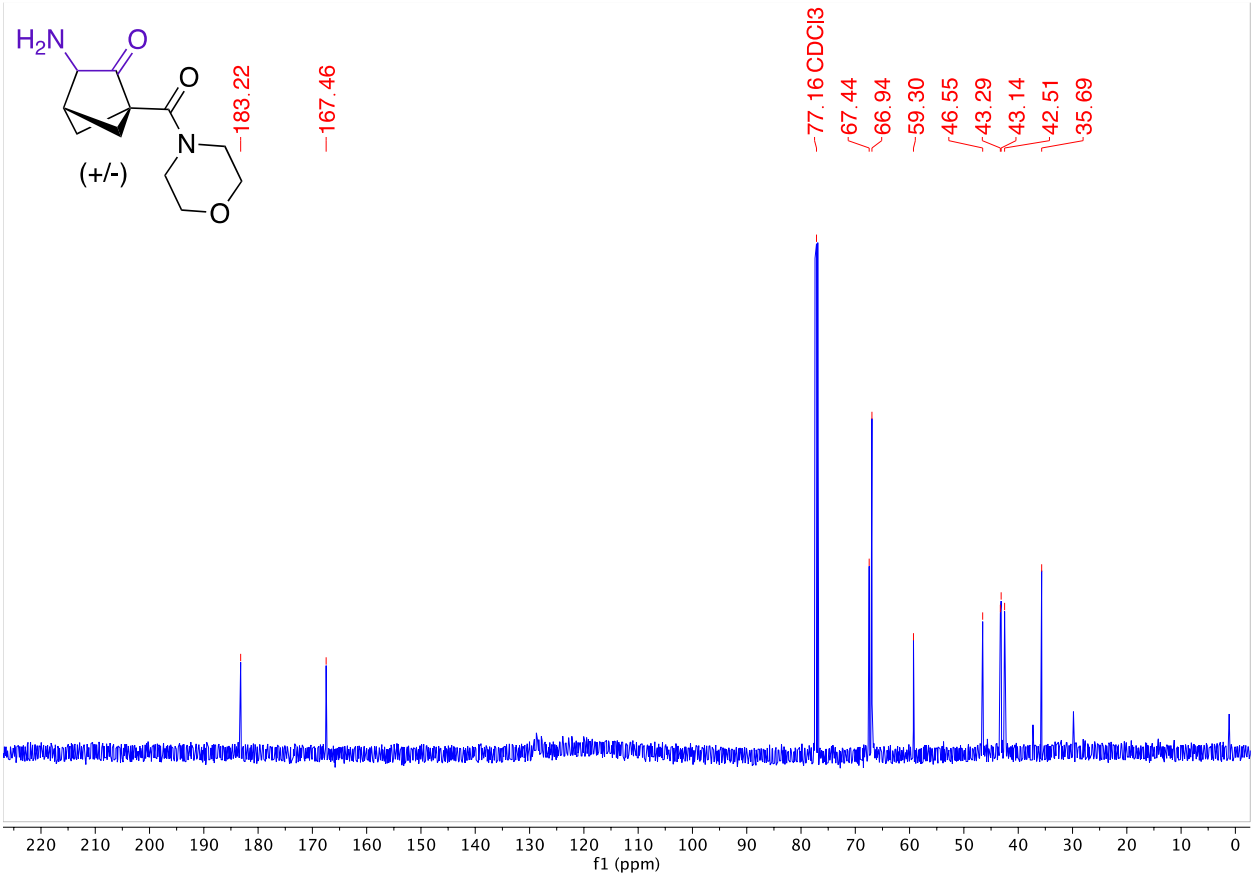
Crude **3a** was dissolved in DCM (3 mL) and silica gel was added to the vial (0.875 g). The mixture was stirred overnight at room temperature. The mixture was then filtered, and the silica was washed with DCM (3 times) to remove benzaldehyde from the hydrolysis and any organic impurities. The silica was then washed with 50% MeOH/DCM and the organic layer was collected, dried with Mg_2SO_4, filtered and evaporated to give the primary amine product **4a**. Isolated 23.3 mg of an orange solid (35% yield over two steps).

HRMS(ESI): calc'd for [$C_{11}H_{17}N_2O_3$ + H^+], 225.12337; found: 225.12335

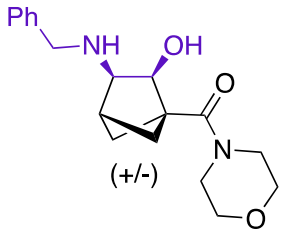
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 3.64 (m, 9H), 3.27 (m, 2H), 3.00 (d, J = 2.9 Hz, 1H), 2.57 (dd, J = 7.6, 3.5 Hz, 1H), 2.48 (m, 1H), 2.14 (dd, J = 9.6, 7.6 Hz, 1H), 1.65 (dd, J = 9.6, 7.5 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 183.22, 167.46, 67.44, 66.94, 59.30, 46.55, 43.29, 43.14, 42.51, 35.69.



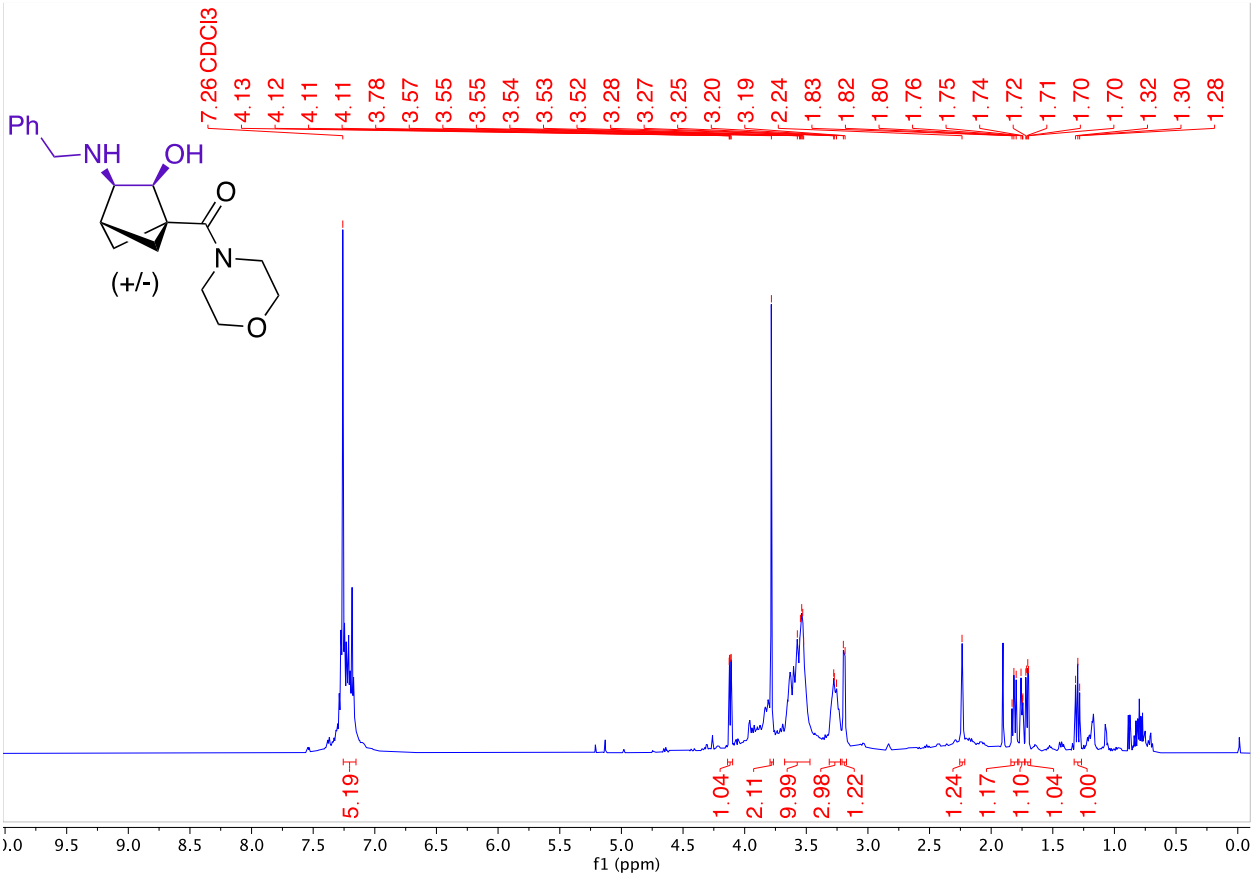
3-(benzylamino)-2-hydroxybicyclo[2.1.1]hexan-1-yl)(morpholino)methanone (4b)



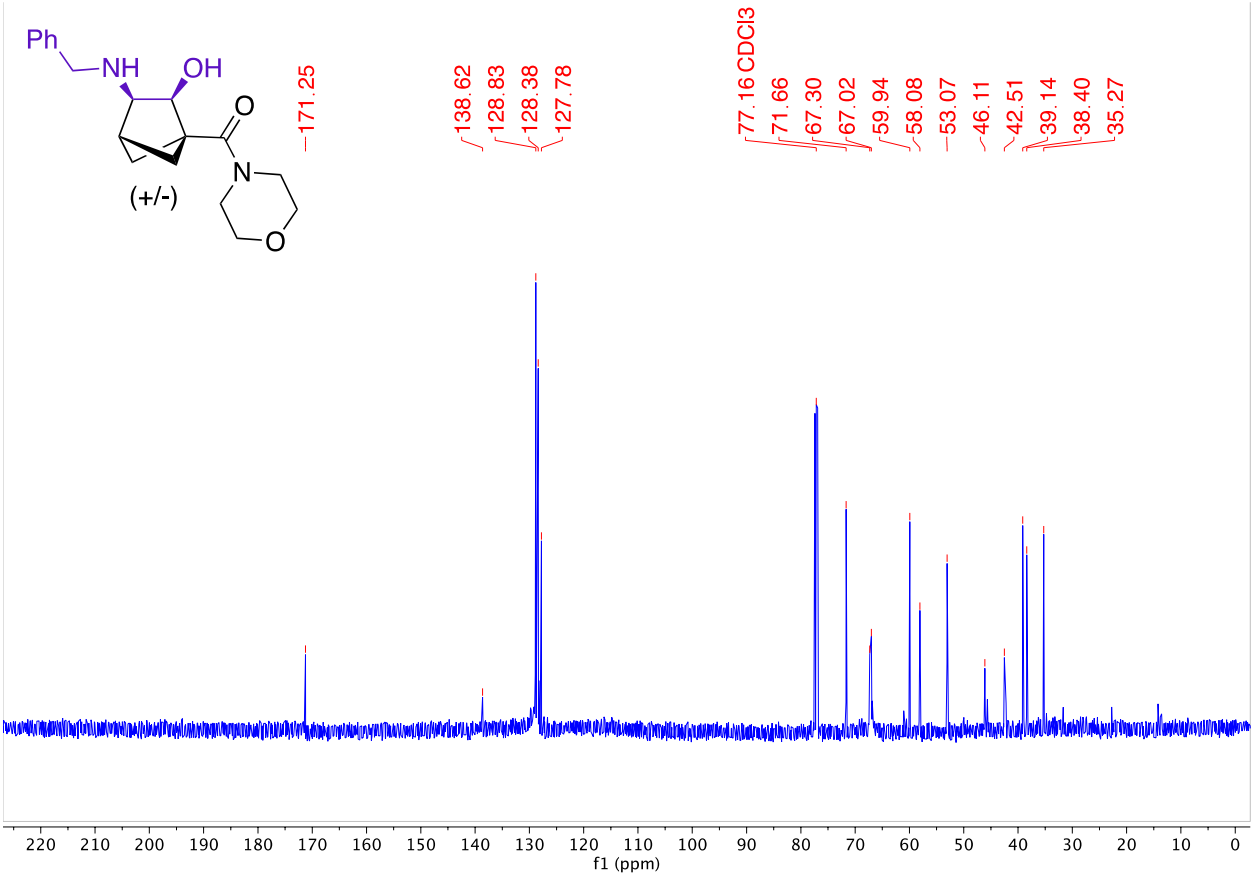
Crude **3a** was dissolved in methanol (5 mL, 0.1 M) then $NaBH_4$ (94.6 mg, 5 eq.) was added and then the reaction was stirred at room temperature overnight. The reaction was quenched with $NaHCO_3$ and extracted with DCM. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 20% EtOAc). 60 mg of a red oil was obtained as a single diastereomer (35% Yield over two steps). Syn stereochemistry was assigned through NOESY and 2D NMR experiments.

HRMS(ESI): calc'd for [$C_{18}H_{24}N_2O_3$ + H^+],317.18597; found: 317.18601

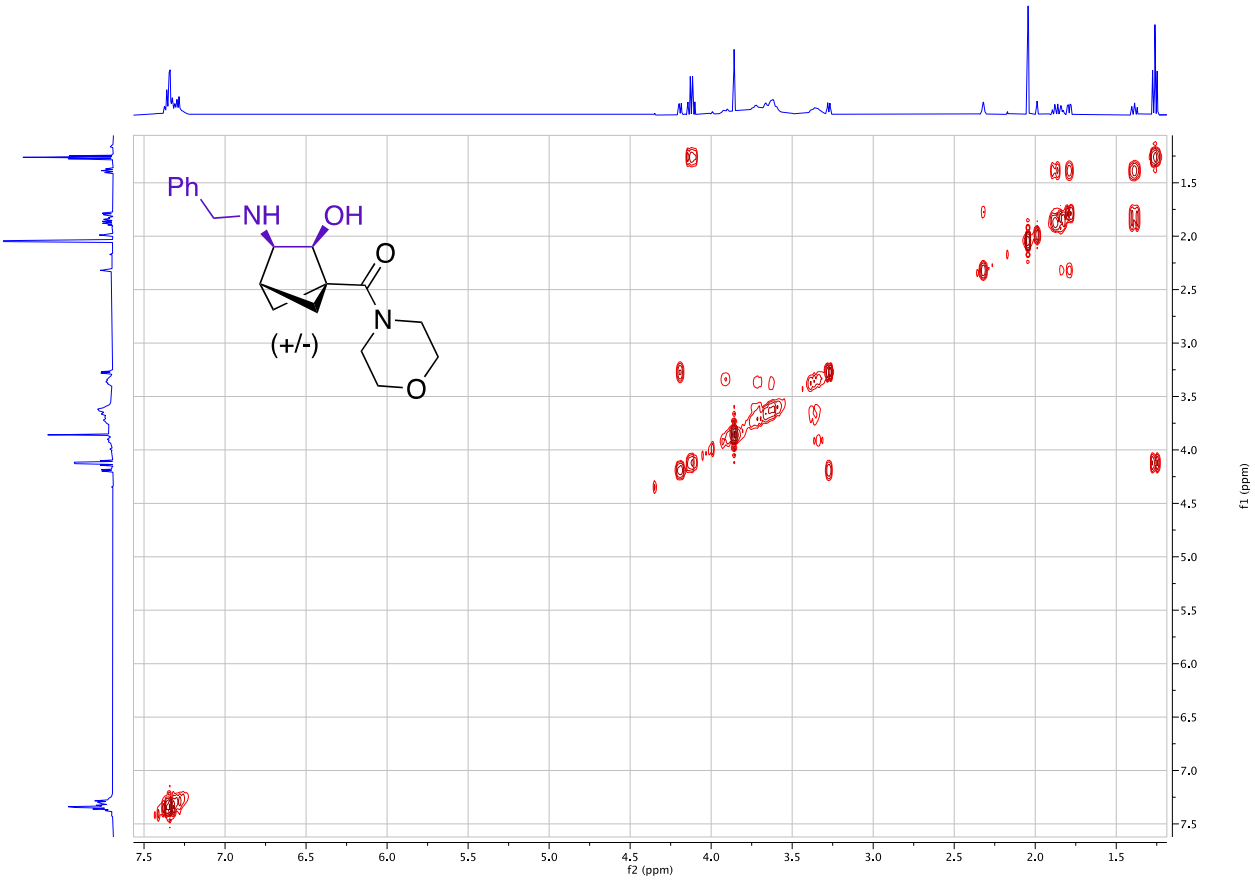
^{1}H NMR (500 MHz, $CDCl_3$, 292 K, ppm): 7.26 – 7.15 (m, 5H), 4.12 (dd, J = 6.5, 1.5 Hz, 1H), 3.78 (s, 2H), 3.68 – 3.47 (m, 6H), 3.31 – 3.22 (m, 2H), 3.19 (d, J = 6.5 Hz, 1H), 2.24 (s, 1H), 1.84 – 1.79 (m, 1H), 1.75 (m, 1H), 1.71 (dd, J = 7.9, 3.4 Hz, 1H), 1.33 – 1.27 (m, 1H).



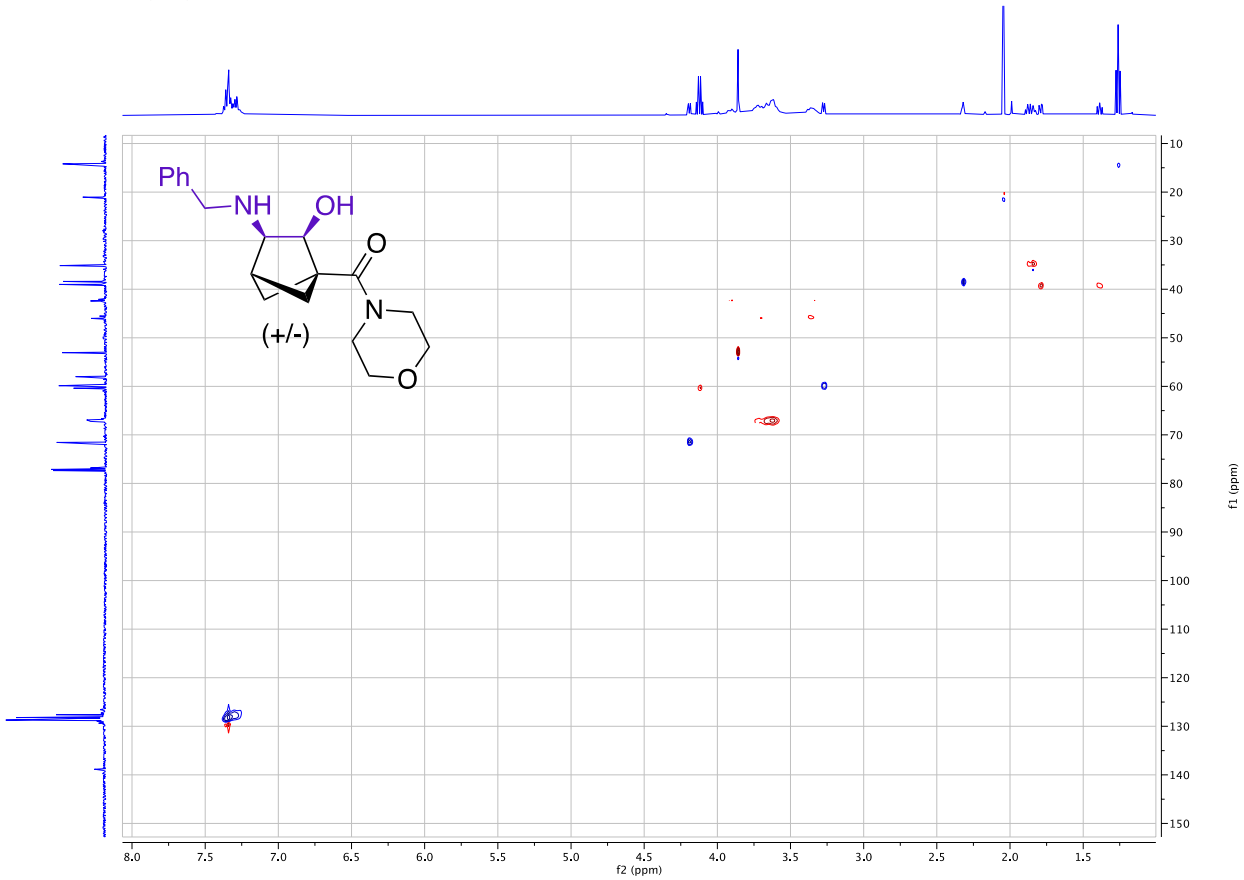
^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 171.25, 138.62, 128.83, 128.38, 127.78, 71.66, 67.30, 67.02, 59.94, 58.08, 53.07, 46.11, 42.51, 39.14, 38.40, 35.27.



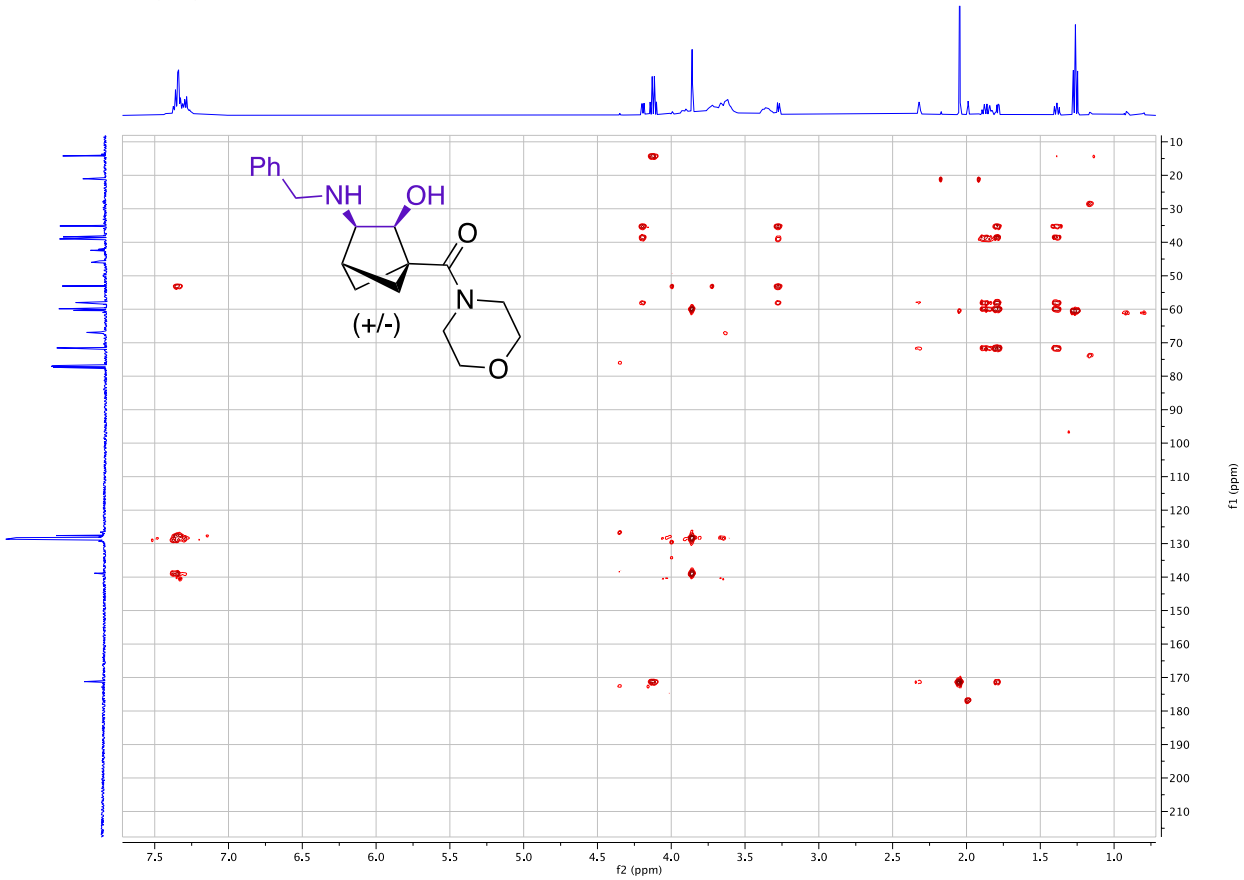
^{1}H-^{1}H COSY (4b):



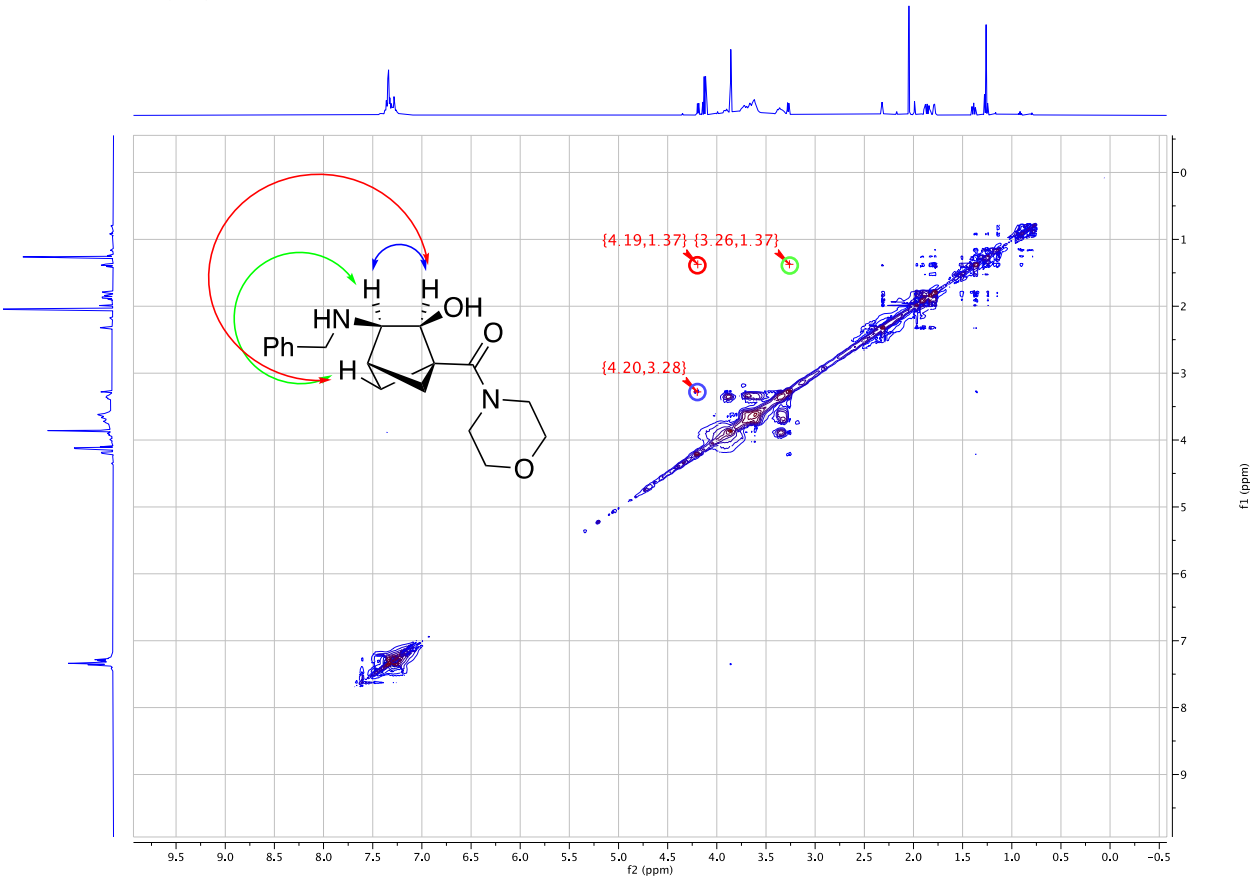
^{1}H-^{13}C HSQC (4b):

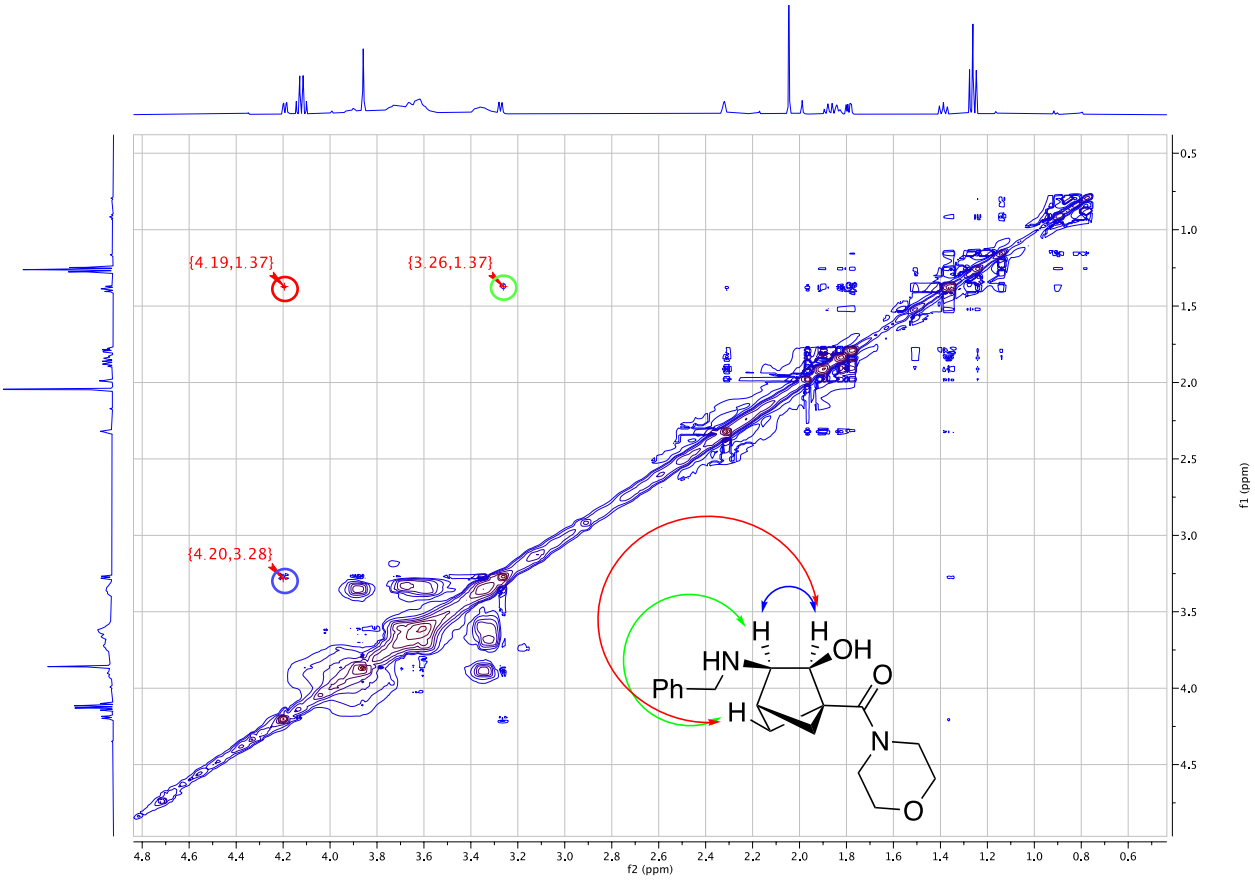


^{1}H-^{13}C HMBC (4b):

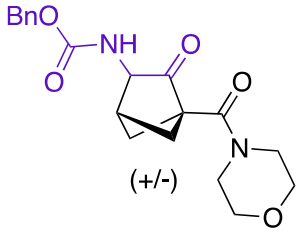


^{1}H-^{1}H NOESY (4b):




{4.19,1.37}
{3.26,1.37}
{4.20,3.28}
HN
Ph
H
H
OH
O
N
O
f2 (ppm)
f1 (ppm)

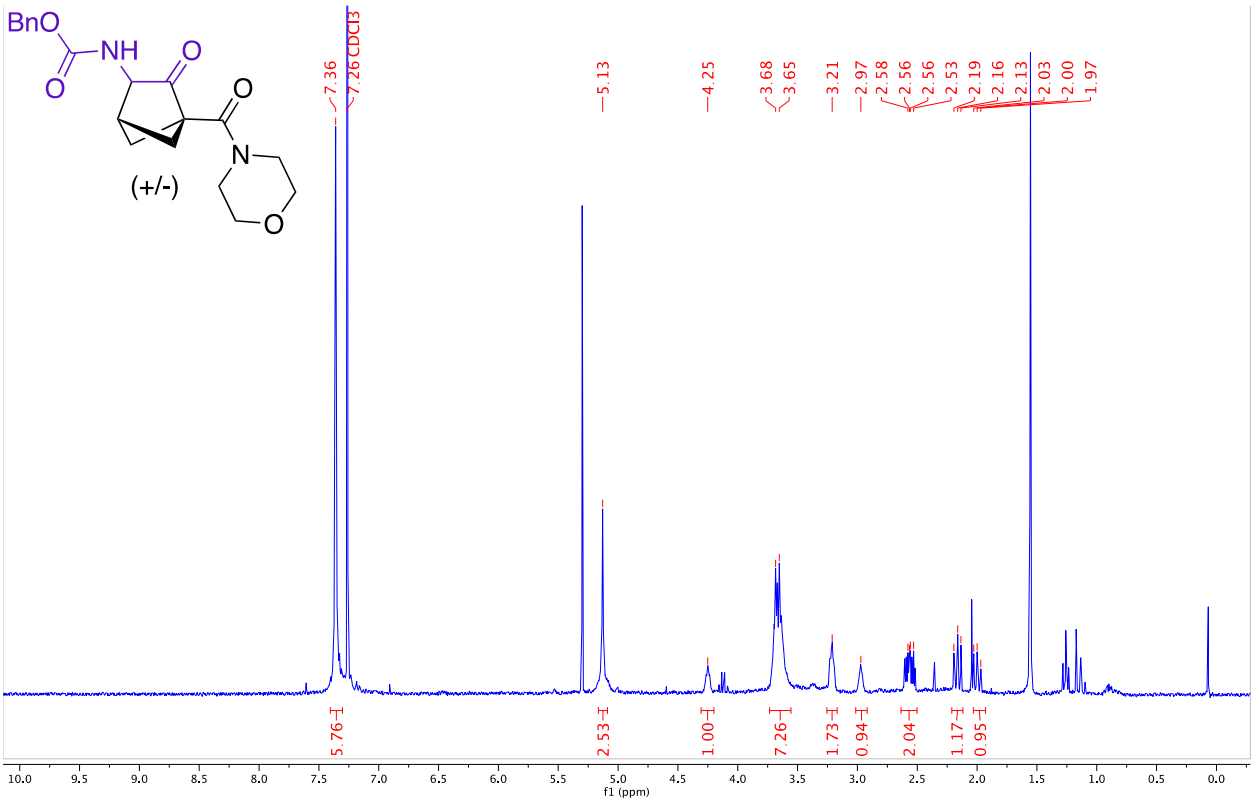
Benzyl (4-(morpholine-4-carbonyl)-3-oxobicyclo[2.1.1]hexan-2-yl)carbamate (4c)



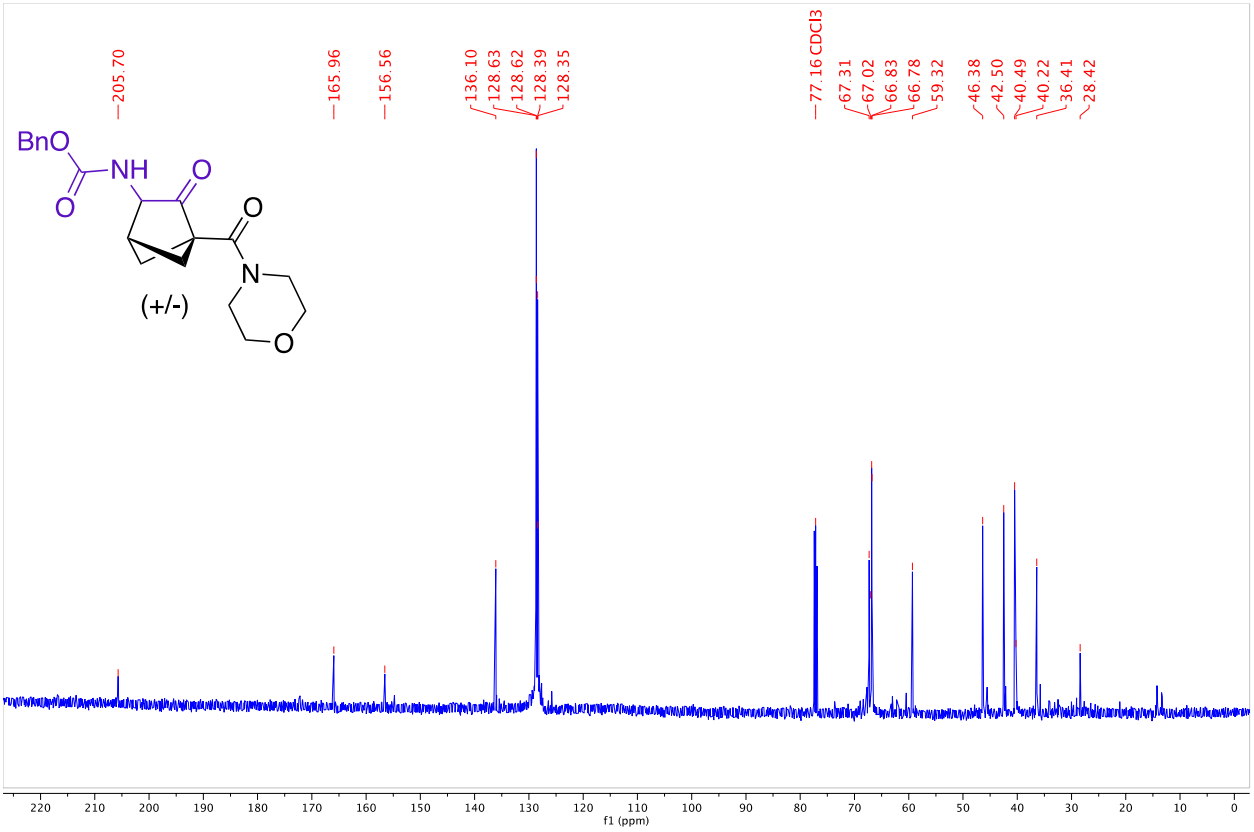
3a was dissolved in DCM (5 mL, 0.1 M) and benzyl chloroformate (0.284 mL, 4 eq.) was added and then the reaction was stirred at room temperature overnight. The reaction was quenched with $NaHCO_3$ and extracted with DCM. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% MeOH/EtOAc/hexanes, eluted at 8% MeOH). 74 mg of a yellow solid was obtained (47% Yield over two steps).

HRMS(ESI): calc'd for [$C_{19}H_{22}N_2O_5$ + Na^+], 381.14209; found: 381.14193

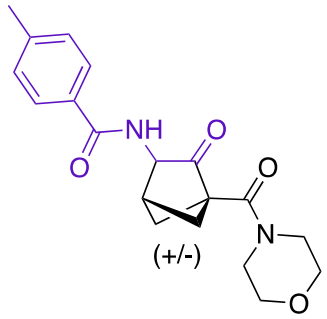
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.36 (m, 5H), 5.13 (s, 2H), 4.26 (m, 1H), 3.68 (m, 7H), 3.21 (m, 2H), 2.97 (m, 1H), 2.56 (m, 2H), 2.19 (t, J = 8.9 Hz, 1H), 1.97 (t, J = 8.7 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 205.70, 165.96, 156.56, 136.10, 128.63, 128.39, 128.35, 67.31, 67.02, 66.83, 66.78, 59.32, 46.38, 42.50, 40.49, 40.22, 36.41, 28.42.



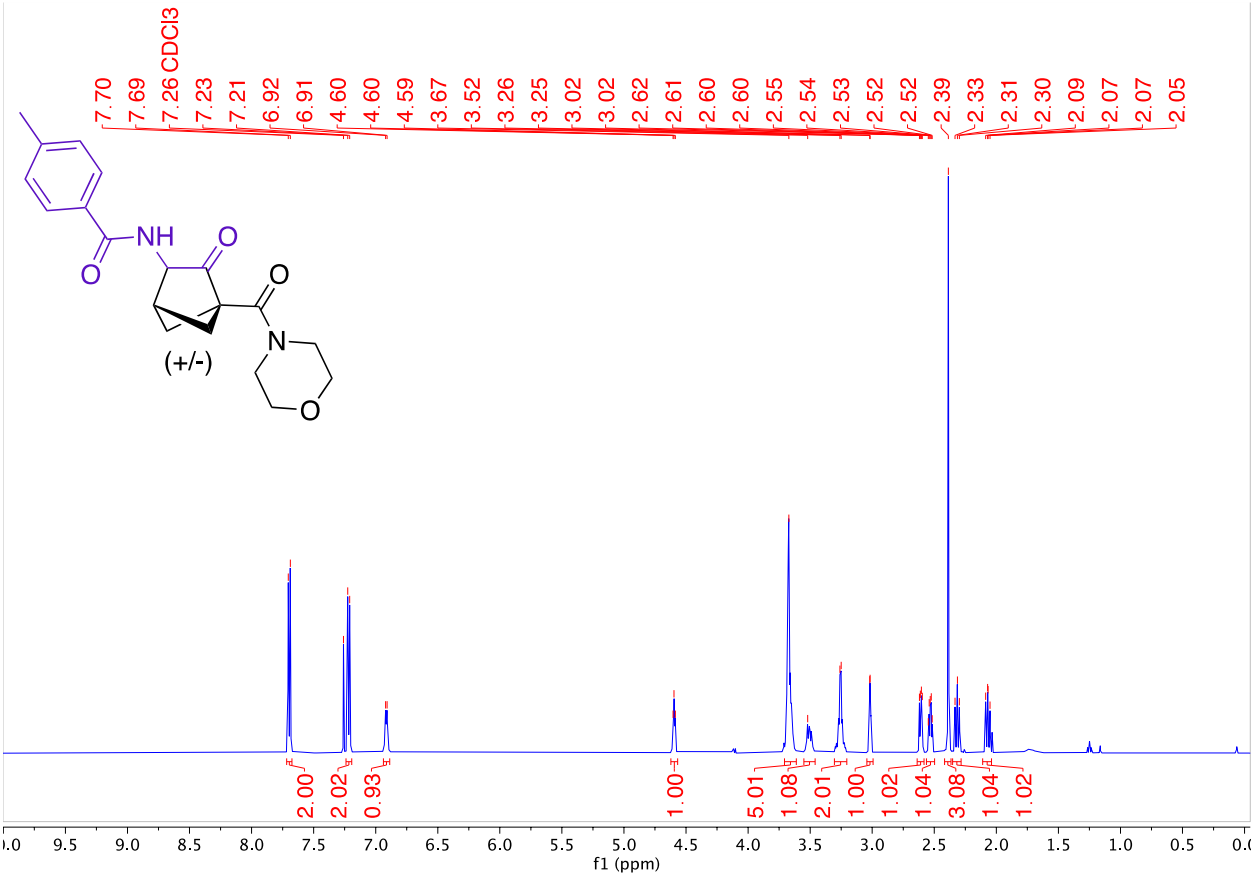
4-methyl-N-(4-(morpholine-4-carbonyl)-3-oxobicyclo[2.1.1]hexan-2-yl)benzamide (4d)



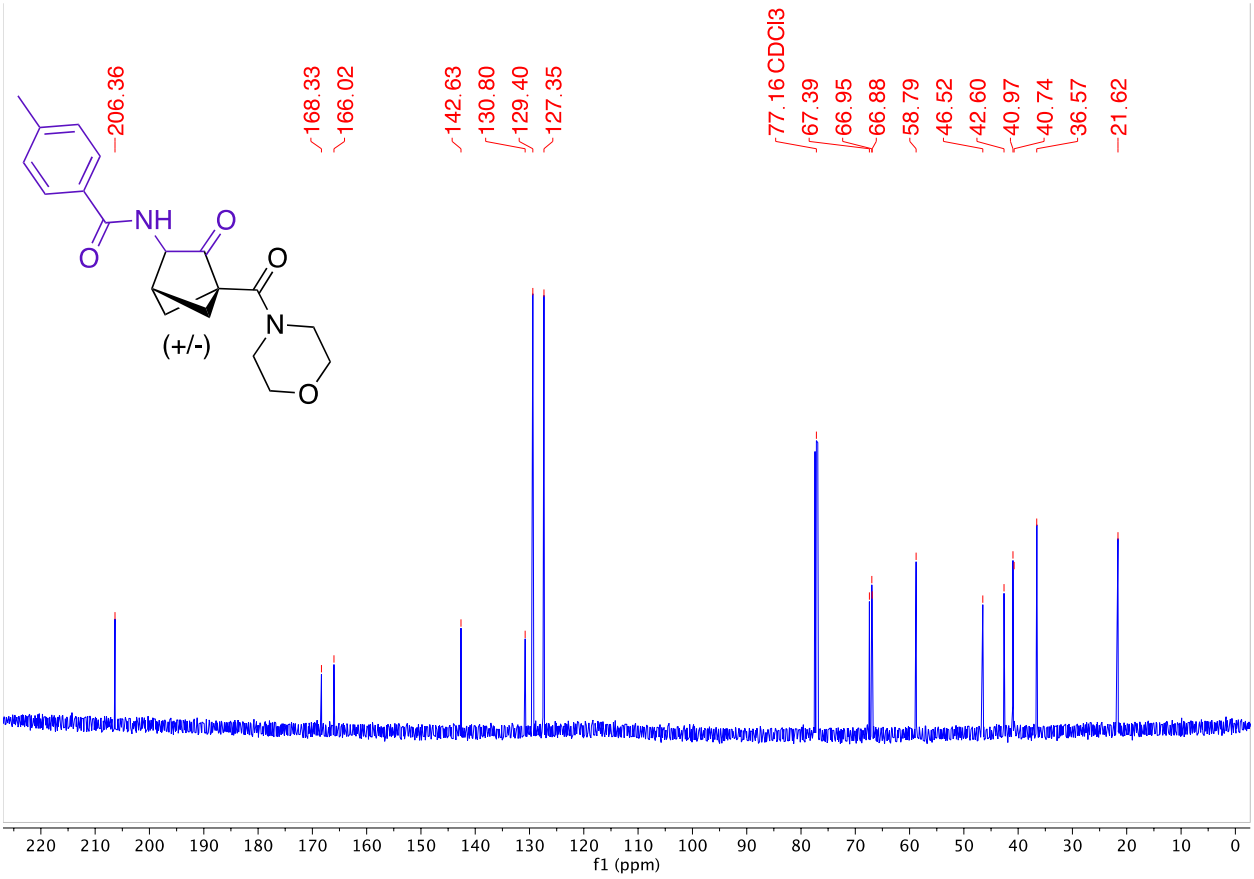
3a was dissolved in DCM (5 mL, 0.1 M) and p-toluoyl chloride (0.264 mL, 4 eq.) was added and then the reaction was stirred at room temperature overnight. The reaction was quenched with $NaHCO_3$ and extracted with DCM. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 100% EtOAc). 44 mg of a white solid was obtained (28% Yield over two steps).

HRMS(ESI): calc'd for [$C_{19}H_{22}N_2O_4$ + H^+], 343.16524; found: 343.16528

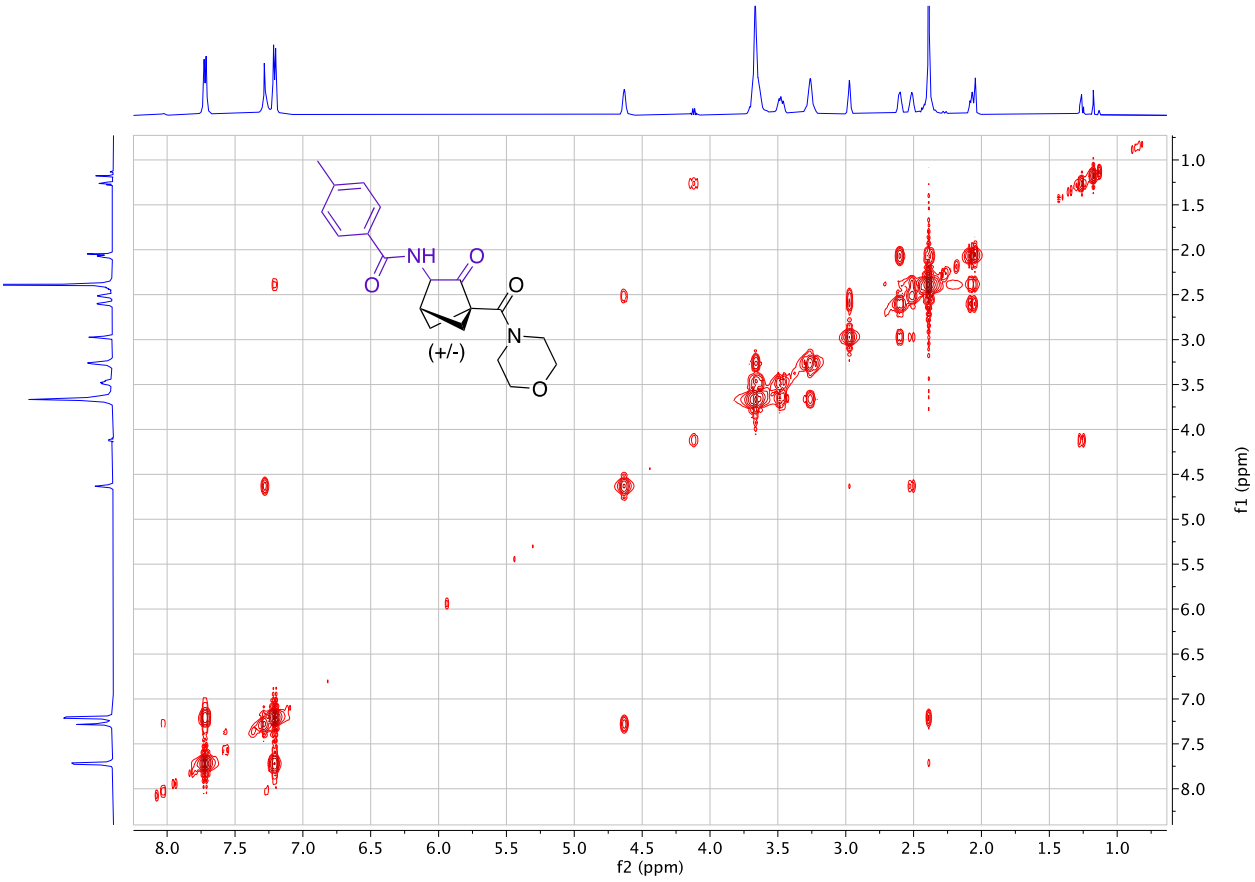
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.70 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 6.1 Hz, 1H), 4.60 (t, J = 4.7 Hz, 1H), 3.67 (m, 5H), 3.52 (m, 1H), 3.26 (m, 2H), 3.02 (m, 1H), 2.61 (dd, J = 7.9, 3.9 Hz, 1H), 2.53 (dt, J = 7.7, 3.7 Hz, 1H), 2.39 (s, 3H), 2.35 – 2.28 (m, 1H), 2.07 (dd, J = 9.5, 7.9 Hz, 1H).



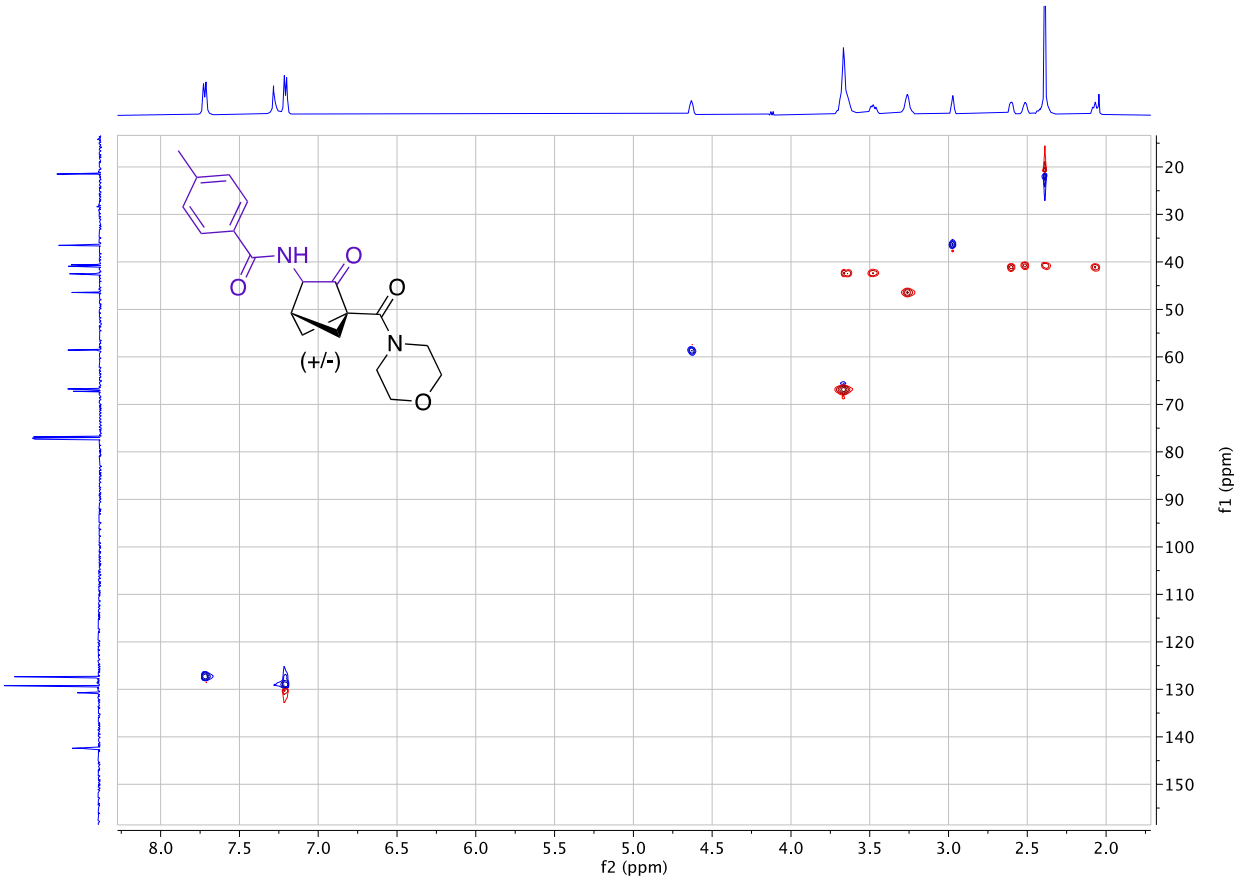
^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.36, 168.33, 166.02, 142.63, 130.80, 129.40, 127.35, 67.39, 66.95, 66.88, 58.79, 46.52, 42.60, 40.97, 40.74, 36.57, 21.62.



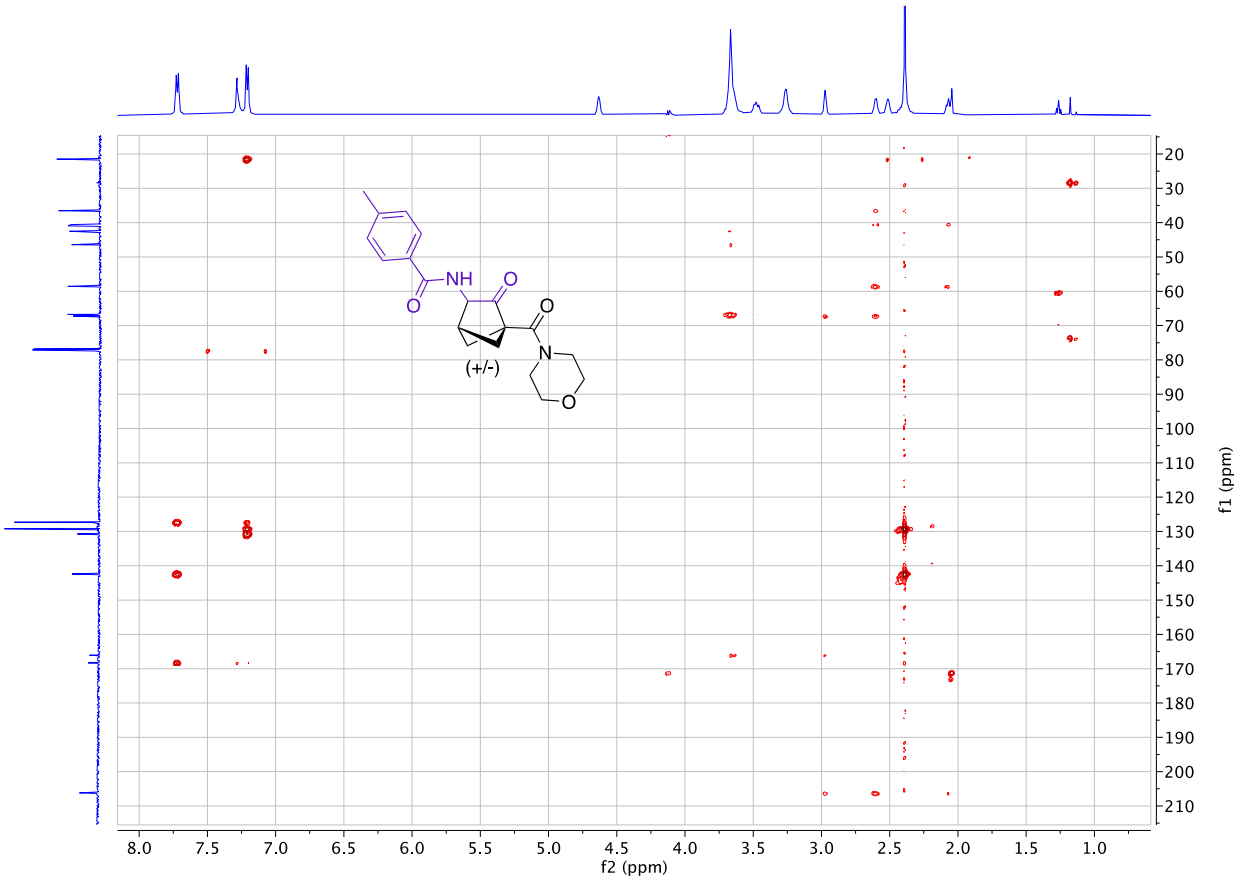
^{1}H-^{1}H COSY (4d):



^{1}H-^{13}C HSQC (4d):



^{1}H-^{13}C HMBC (4d):

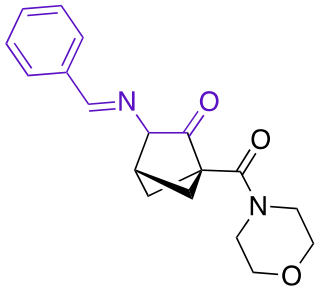


V: Bicyclohexane Synthesis Scope

General Procedure for Bicyclohexane Synthesis

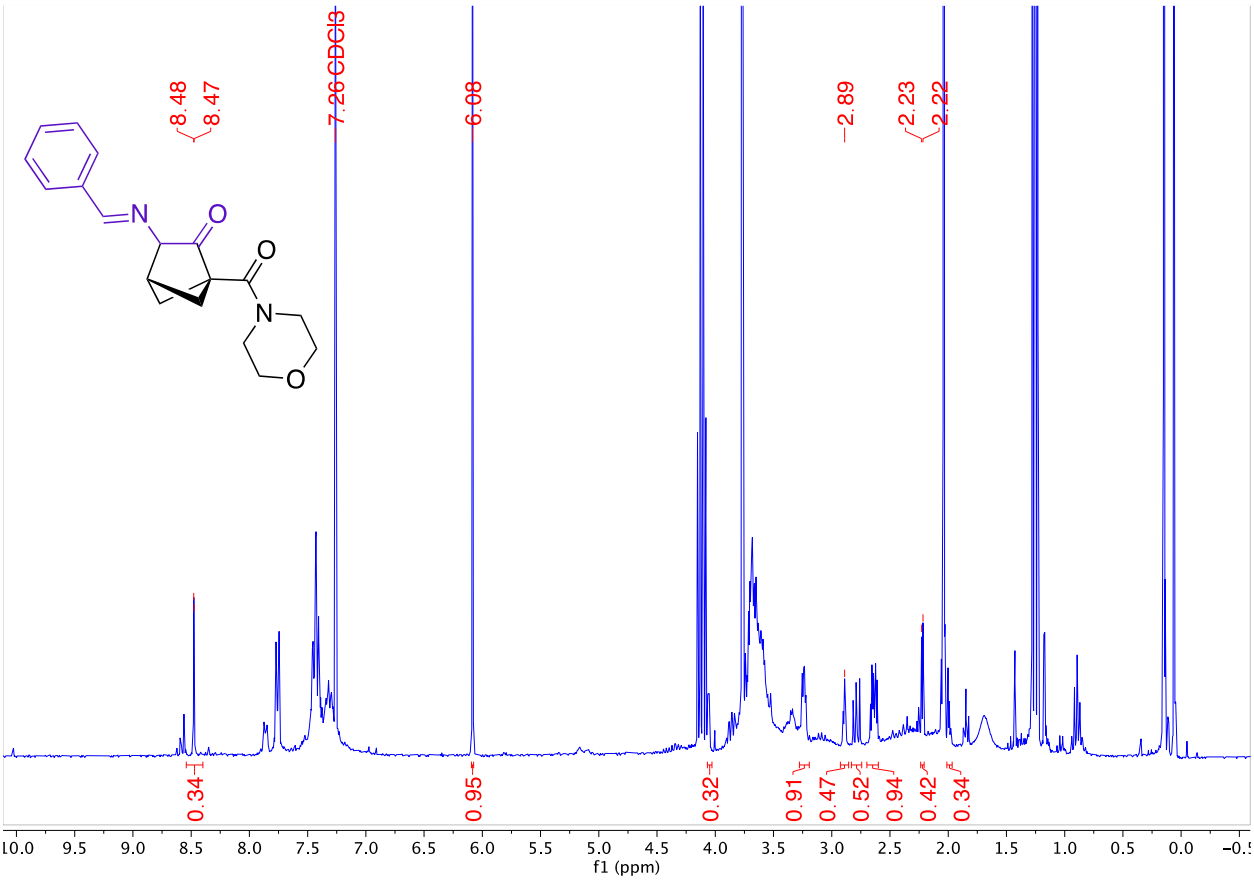
In two separate vials, the bicyclobutane **1** (1 eq.) and enolate precursor **2** (1.2 eq) were added and put under a nitrogen atmosphere. The acetate was dissolved in 50% of the THF (0.3 M) and LiHMDS (1.0M in THF, 1.5 eq.) was added dropwise to the vial containing the acetate and then left to stir for 15 minutes at room temperature to form the enolate. 50% of the THF solvent was added to the bicyclobutane vial and then it was cooled in the freezer for 15 minutes along with the enolate vial. The bicyclobutane was then added dropwise to the enolate. The reaction was left to stir at room temperature overnight. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate (3 times). The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated to give the crude product. Products were purified by column chromatography.

3-((Benzylidene)amino)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3a)

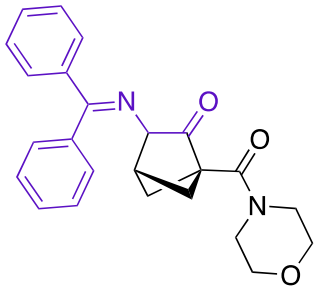


The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2a** on a 0.30 mmol bicyclobutane scale. 1,3,5-Trimethoxybenzene was used as an internal standard for calculating a solution yield of 47%.

^{1}H NMR (500 MHz, $CDCl_3$, 292 K, ppm):



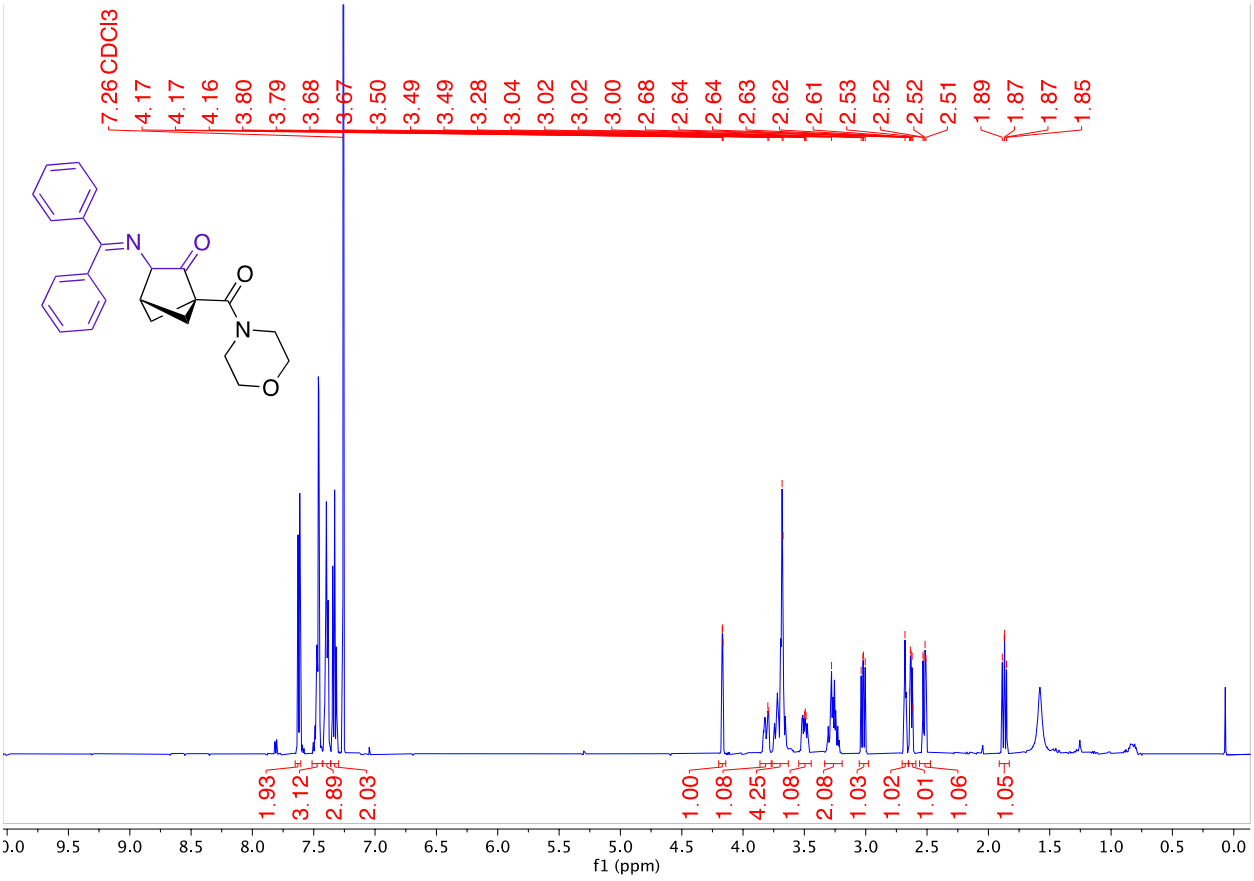
3-((Diphenylmethylene)amino)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3b)



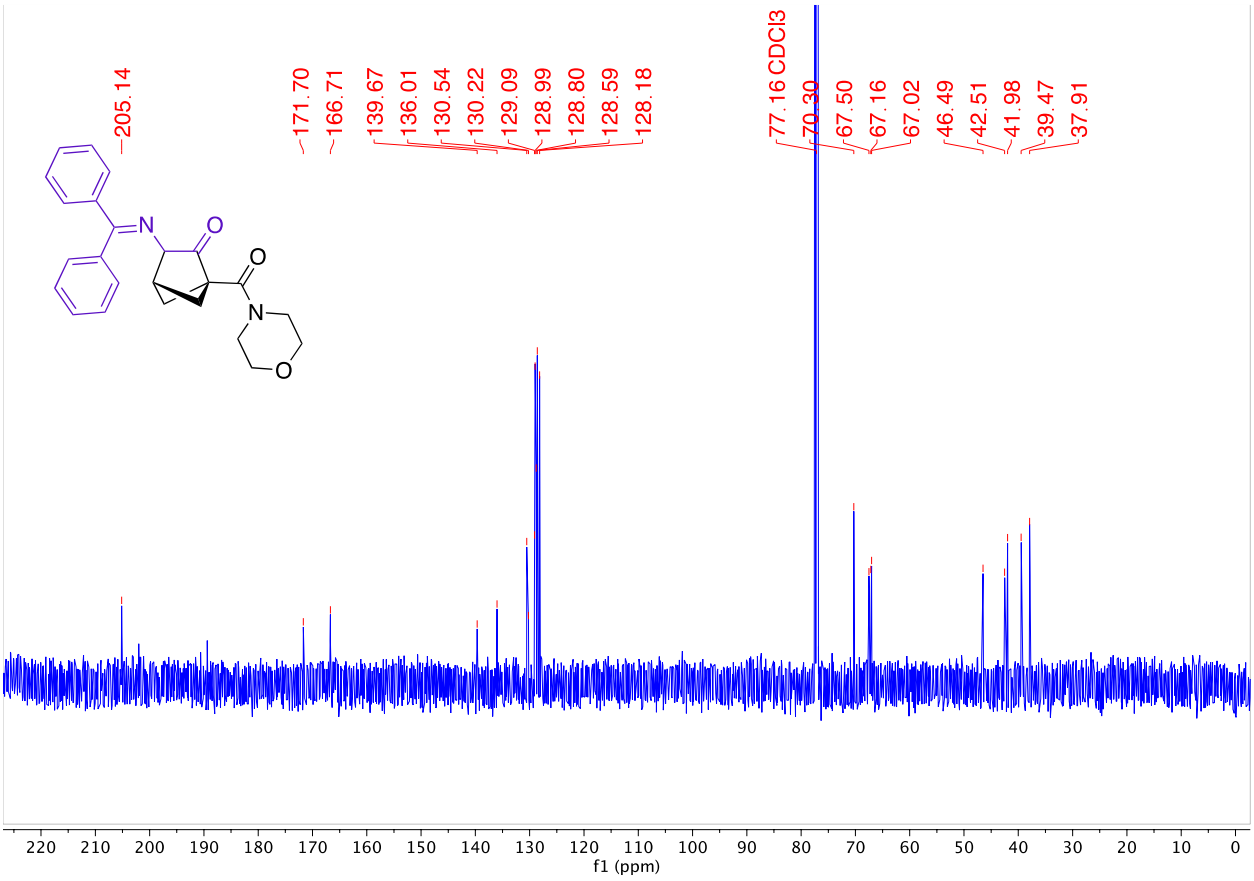
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2b** on a 0.30 mmol bicyclobutane scale with a reaction concentration of 0.1 M. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 75% EtOAc). 45 mg of a white solid was obtained (42% Yield).

HRMS(ESI): calc'd for [$C_{24}H_{24}N_2O_3$ + H^+], 389.18597; found: 389.18601

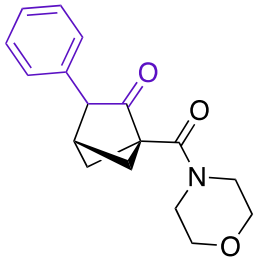
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.65 – 7.61 (m, 2H), 7.51 – 7.43 (m, 3H), 7.42 – 7.36 (m, 3H), 7.36 – 7.30 (m, 2H), z14 (m, 1H), 3.79 (m, 1H), 3.68 (m, 4H), 3.55 – 3.44 (m, 1H), 3.28 (m, 2H), 3.02 (dd, J = 9.4, 7.2 Hz, 1H), 2.68 (m, 1H), 2.63 (dt, J = 7.1, 3.5 Hz, 1H), 2.52 (dd, J = 8.1, 3.9 Hz, 1H), 1.87 (dd, J = 9.3, 8.1 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 205.14, 171.70, 166.71, 139.67, 136.01, 130.54, 130.22, 129.09, 128.99, 128.80, 128.59, 128.18, 70.30, 67.50, 67.16, 67.02, 46.49, 42.51, 41.98, 39.47, 37.91.



1-(Morpholine-4-carbonyl)-3-phenylbicyclo[2.1.1]hexan-2-one (3c):

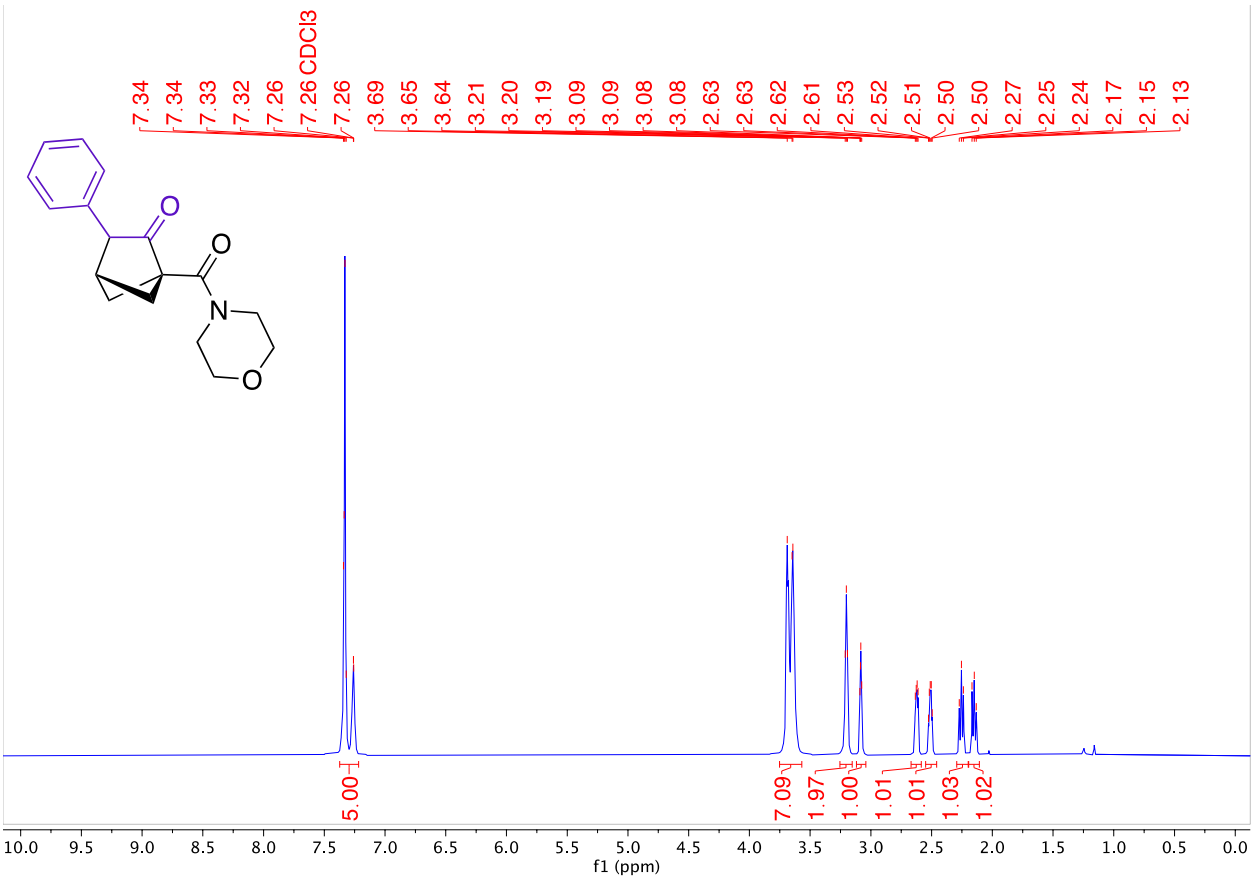


The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2c** on a 0.50 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 80% EtOAc). 120.6 mg of a white solid was obtained (85% Yield).

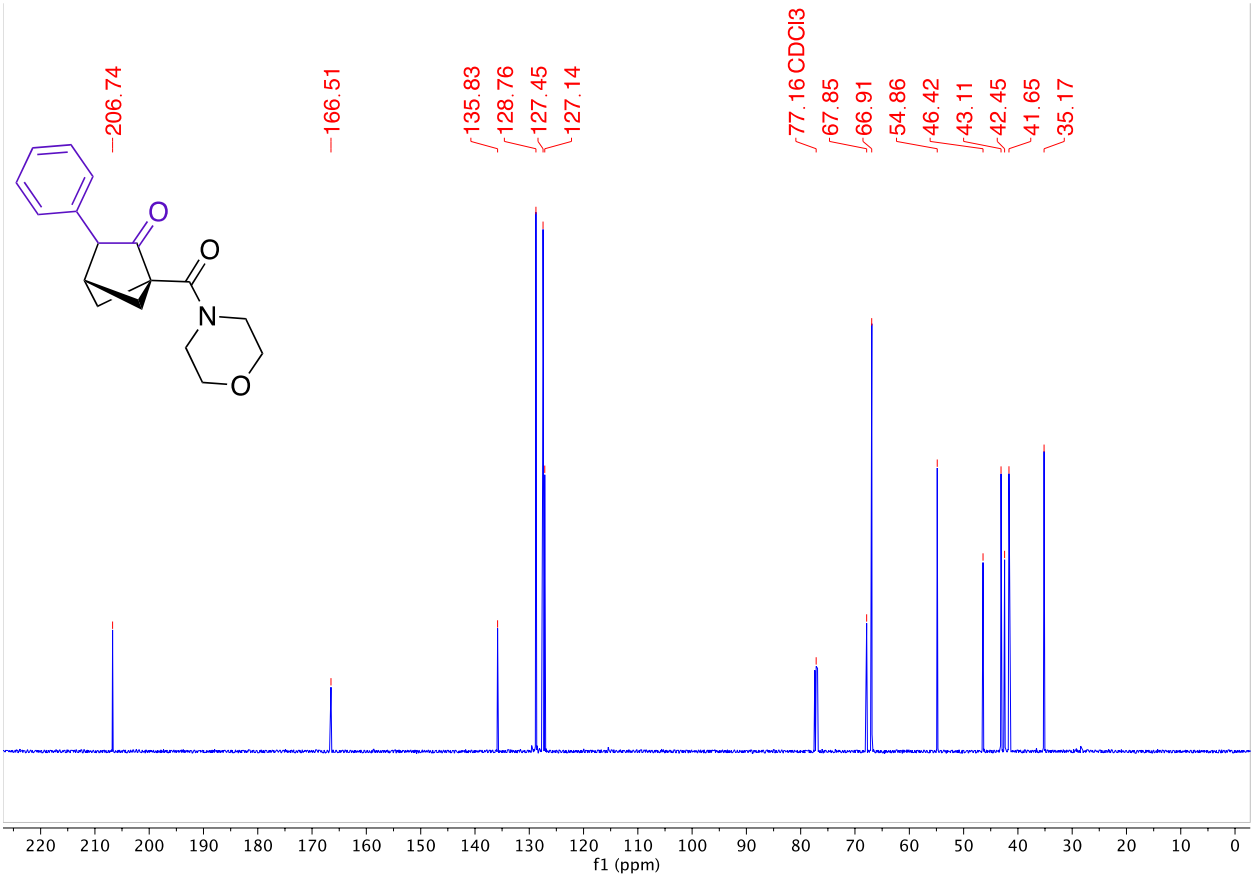
This product was also prepared following the general procedure for bicyclohexane synthesis using 3 mmol of **1a** with an increase of concentration to 0.60 M. The compound was purified by column chromatography (Biotage® Sfär 10g Column, 0-100% EtOAc/hexanes, eluted at 72% EtOAc). 513.5 mg of a white solid was obtained (60% Yield). On larger scale, an enolate addition product **3cc** is also observed as a mixture of diastereomers, but can be separated from the desired product by column chromatography.

HRMS(ESI): calc'd for [$C_{17}H_{19}NO_3 + H^+$], 286.14377; found: 286.14379

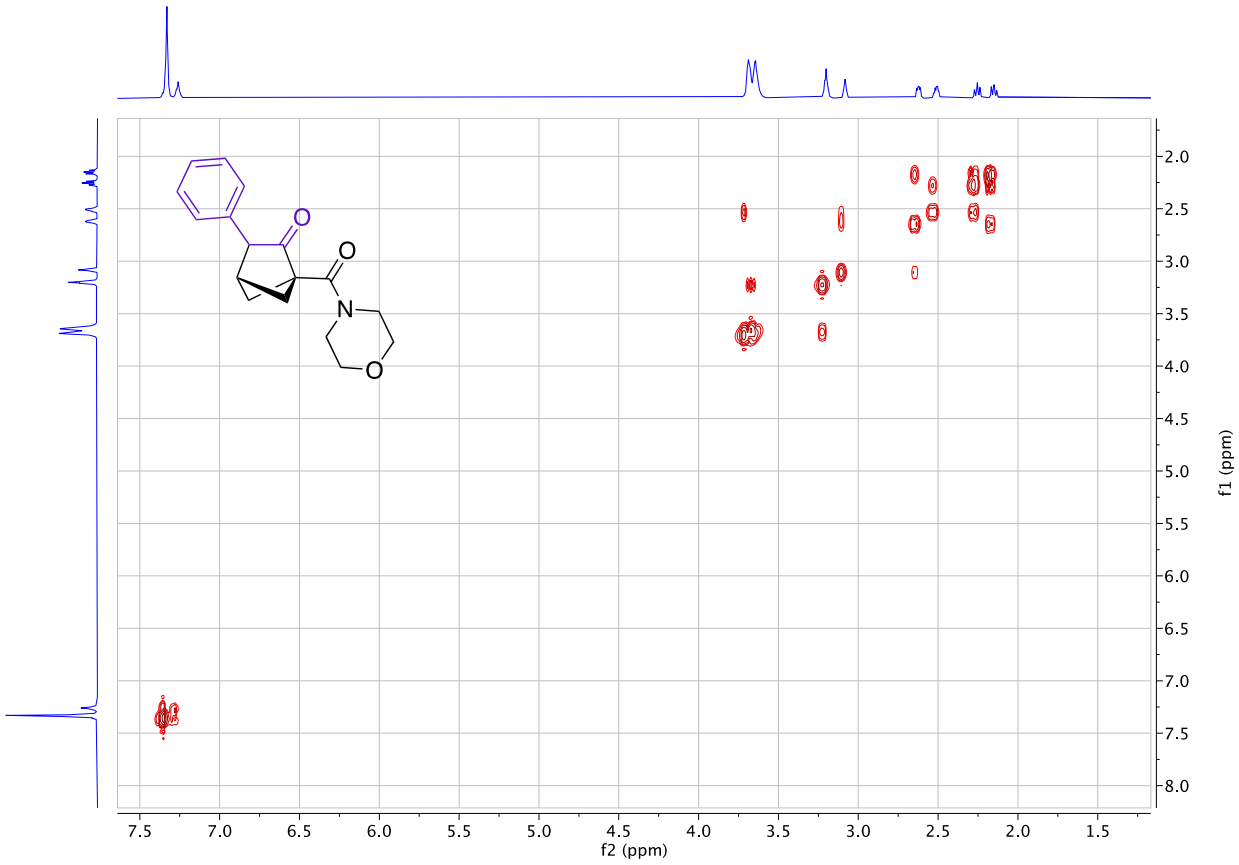
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.37 – 7.22 (m, 5H), 3.75 – 3.57 (m, 7H), 3.20 (t, *J* = 4.8 Hz, 2H), 3.08 (t, *J* = 3.7 Hz, 1H), 2.62 (dd, *J* = 7.6, 3.8 Hz, 1H), 2.51 (dt, *J* = 7.8, 3.7 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.19 – 2.11 (m, 1H).


7.34
7.34
7.33
7.32
7.26
7.26 CDCl3
7.26
3.69
3.65
3.64
3.21
3.20
3.19
3.09
3.09
3.08
3.08
2.63
2.63
2.62
2.61
2.53
2.52
2.51
2.50
2.50
2.27
2.25
2.24
2.17
2.15
2.13
O
O
N
O
5.00
7.09
1.97
1.00
1.01
1.01
1.03
1.02
10.0 9.5 9.0 8.5 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
f1 (ppm)

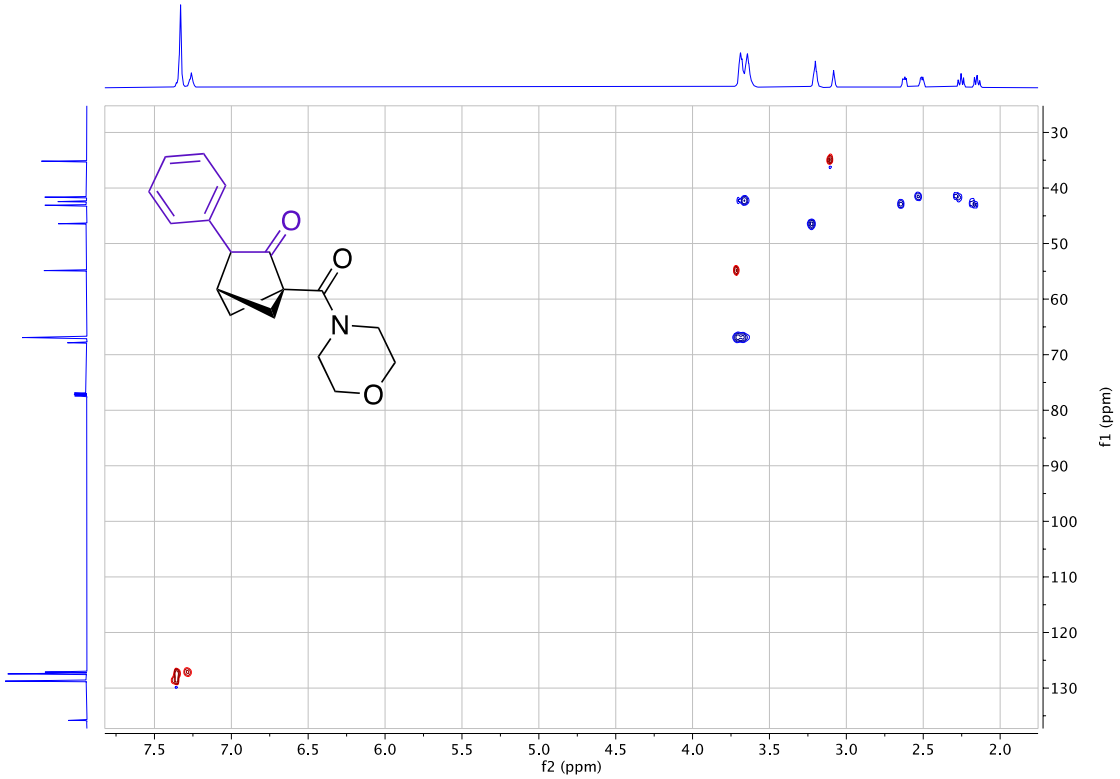
^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.74, 166.51, 135.83, 128.76, 127.45, 127.14, 67.85, 66.91, 54.86, 46.42, 43.11, 42.45, 41.65, 35.17.



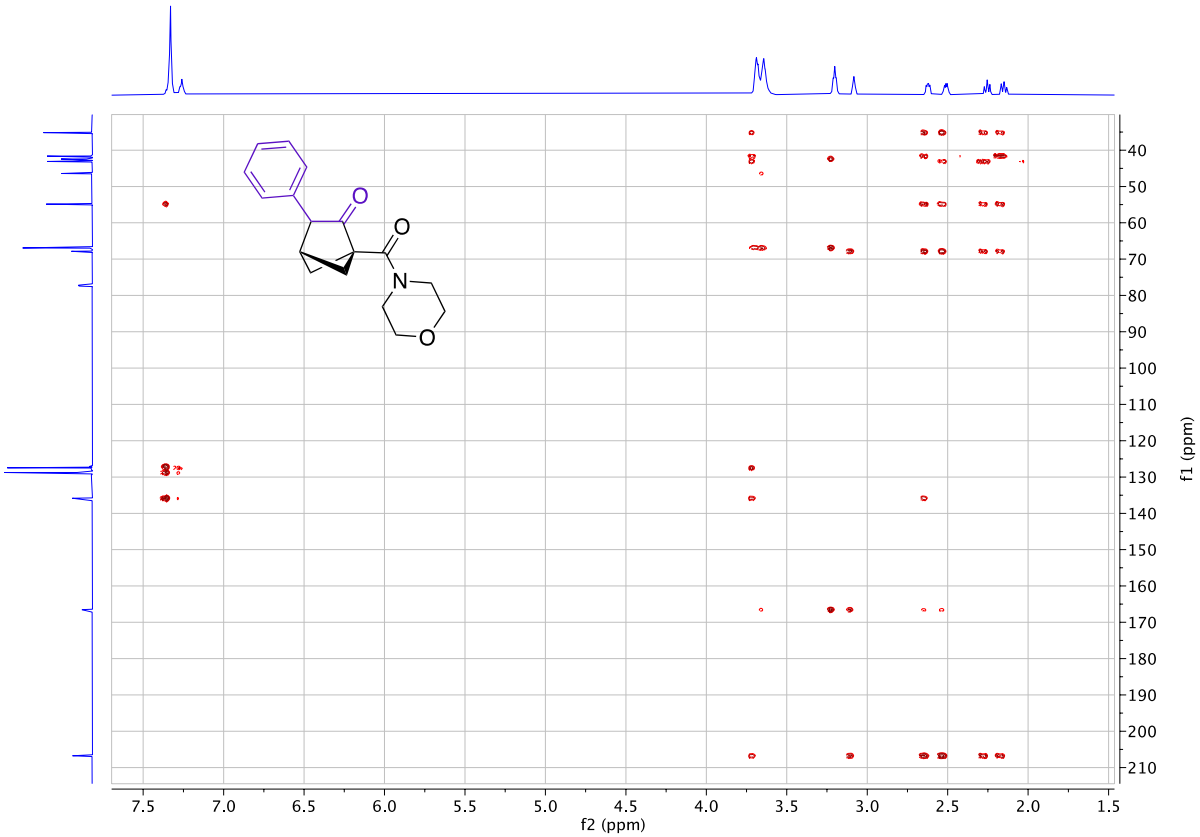
^{1}H-^{1}H COSY (3c):


O
O
N
O
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
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

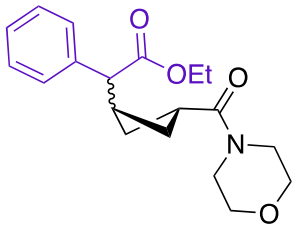
^{1}H-^{13}C HSQC (3c):



^{1}H-^{13}C HMBC (3c):

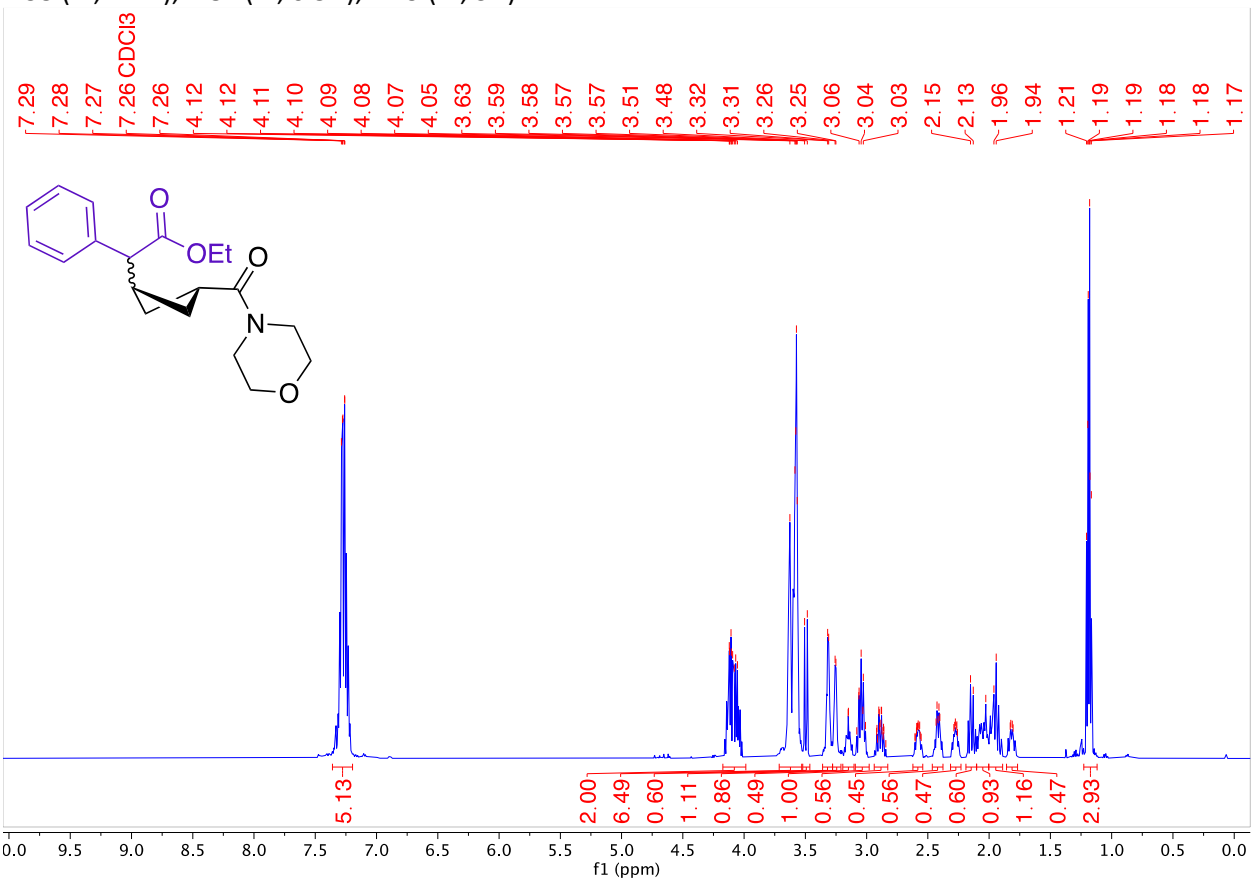


Ethyl 2-(3-(morpholine-4-carbonyl)cyclobutyl)-2-phenylacetate (3cc):



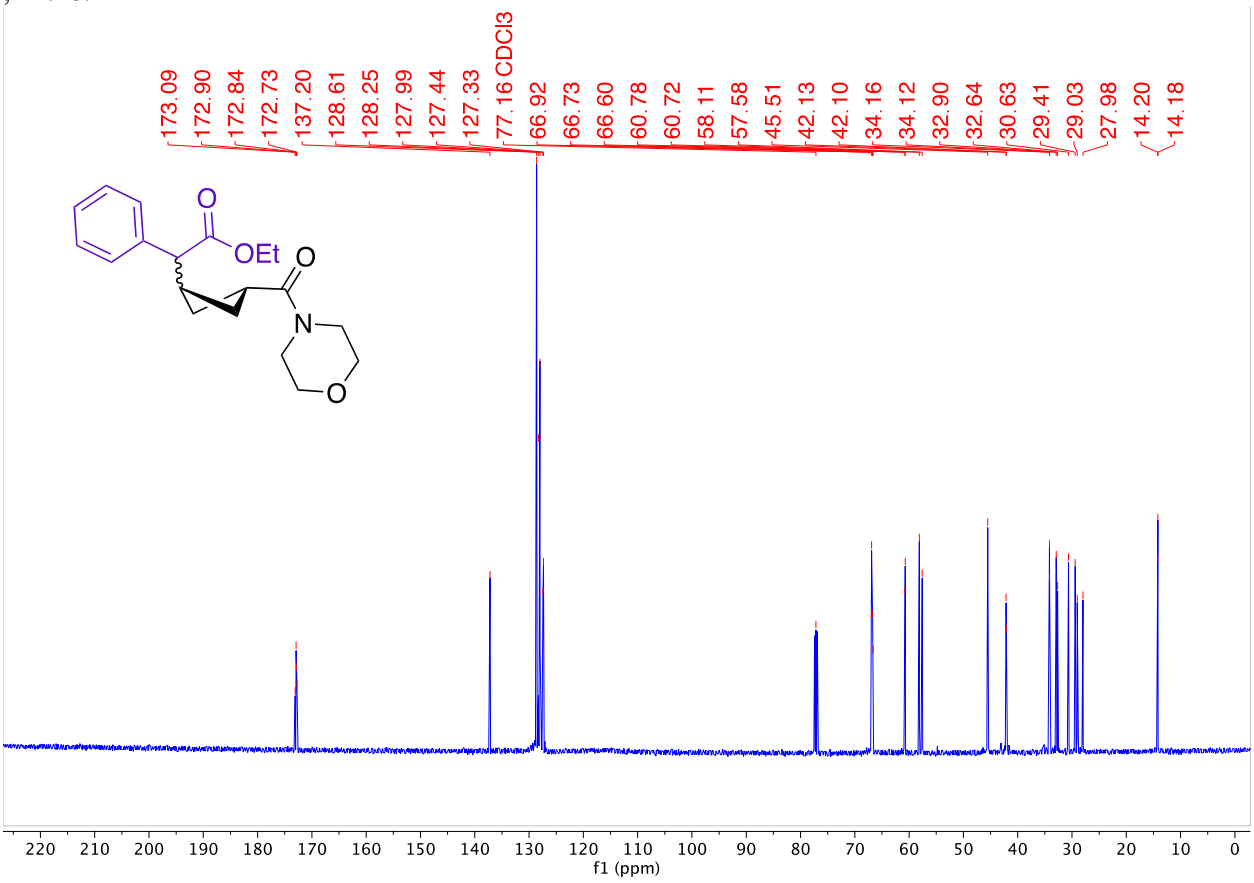
HRMS(ESI): calc'd for [$C_{19}H_{25}NO_4$ + H^+], 332.18564; found: 332.18565.

^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.36 – 7.20 (m, 5H), 4.17 – 3.99 (m, 2H), 3.71 – 3.53 (m, 6H), 3.50 (d, J = 11.0 Hz, 0.6H), 3.31 (d, J = 4.6 Hz, 1.1H), 3.25 (d, J = 3.4 Hz, 0.8H), 3.15 (m, 0.5H), 3.09 – 2.98 (m, 1H), 2.94 – 2.83 (m, 0.6H), 2.57 (m, 0.5H), 2.46 – 2.38 (m, 1H), 2.27 (m, 0.5H), 2.14 (m, 0.6H), 2.03 (m, 1H), 1.95 (m, 1.2H), 1.82 (m, 0.5H), 1.19 (m, 3H).

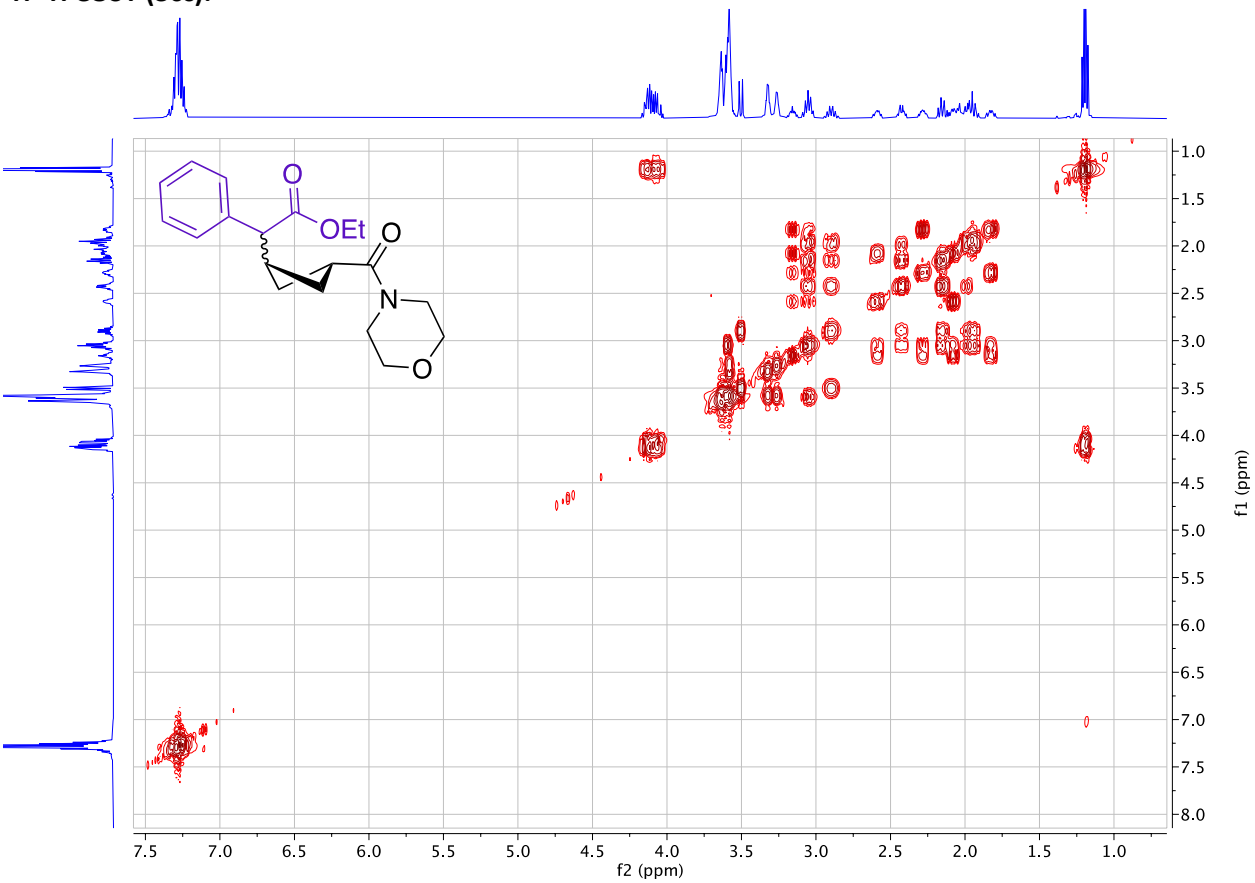


^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm):

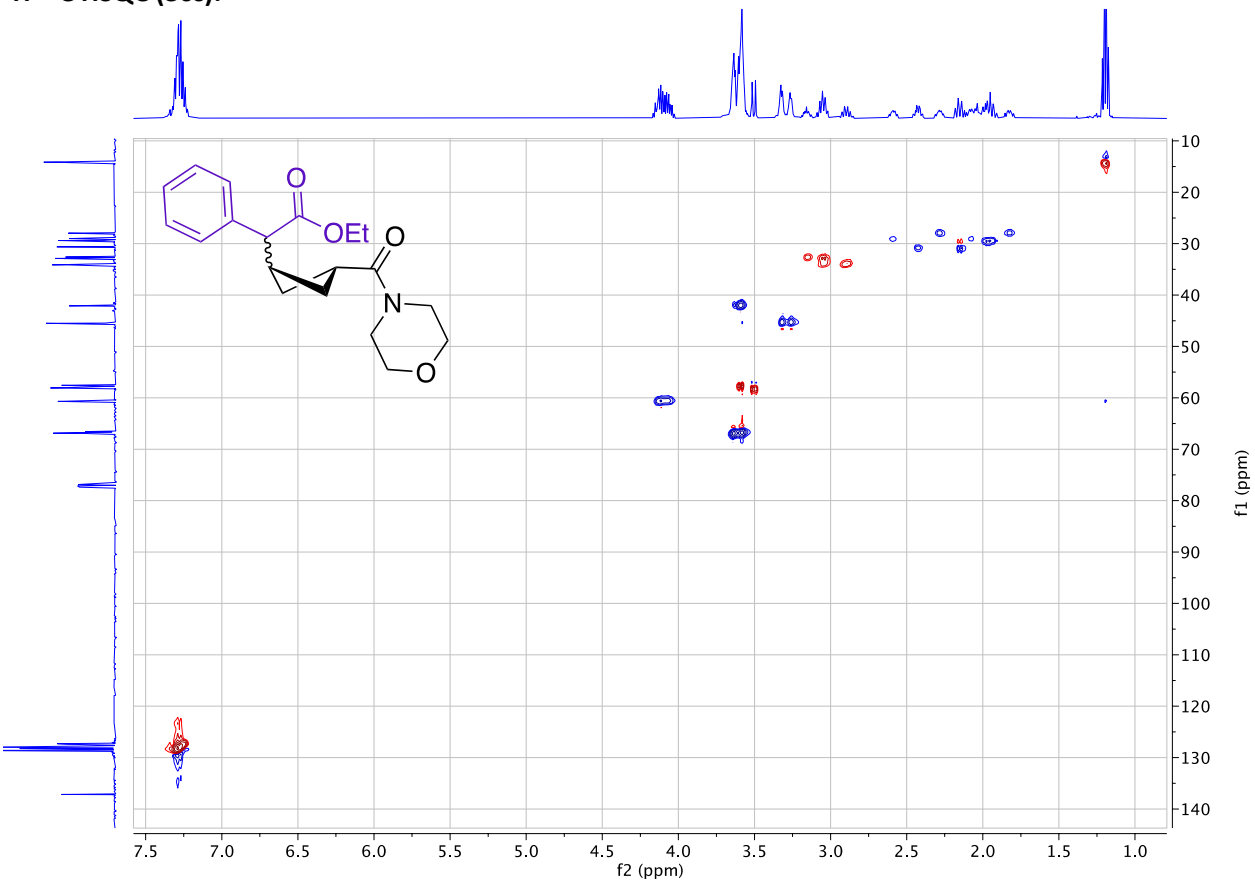
δ 173.09, 172.90, 172.84, 172.73, 137.20, 128.61, 128.25, 127.99, 127.44, 127.33, 66.92, 66.73, 66.60, 60.78, 60.72, 58.11, 57.58, 45.51, 42.13, 42.10, 34.16, 34.12, 32.90, 32.64, 30.63, 29.41, 29.03, 27.98, 14.20, 14.18.



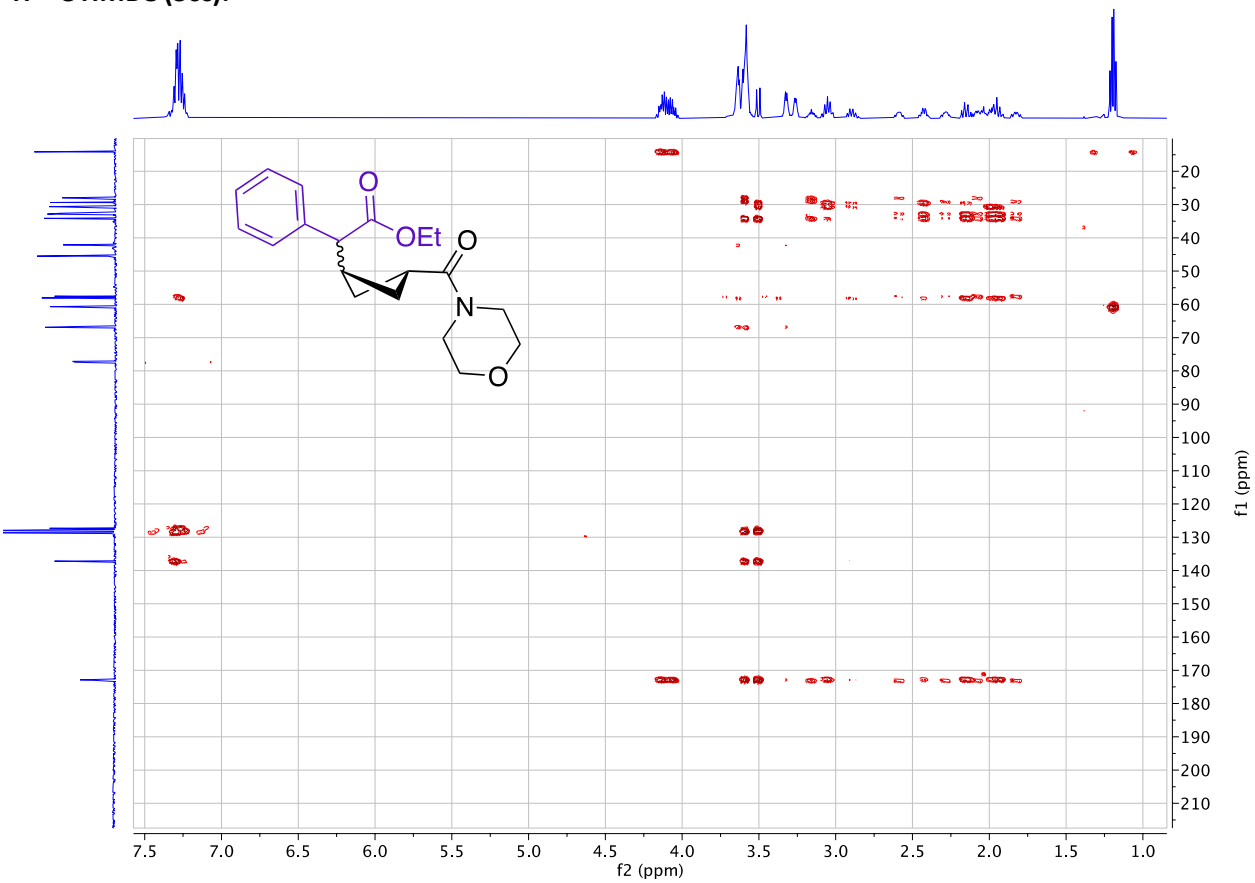
^{1}H-^{1}H COSY (3cc):



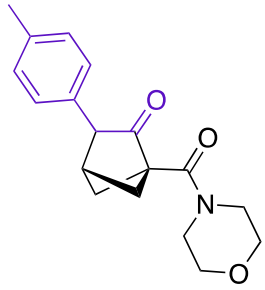
^{1}H-^{13}C HSQC (3cc):



^{1}H-^{13}C HMBC (3cc):



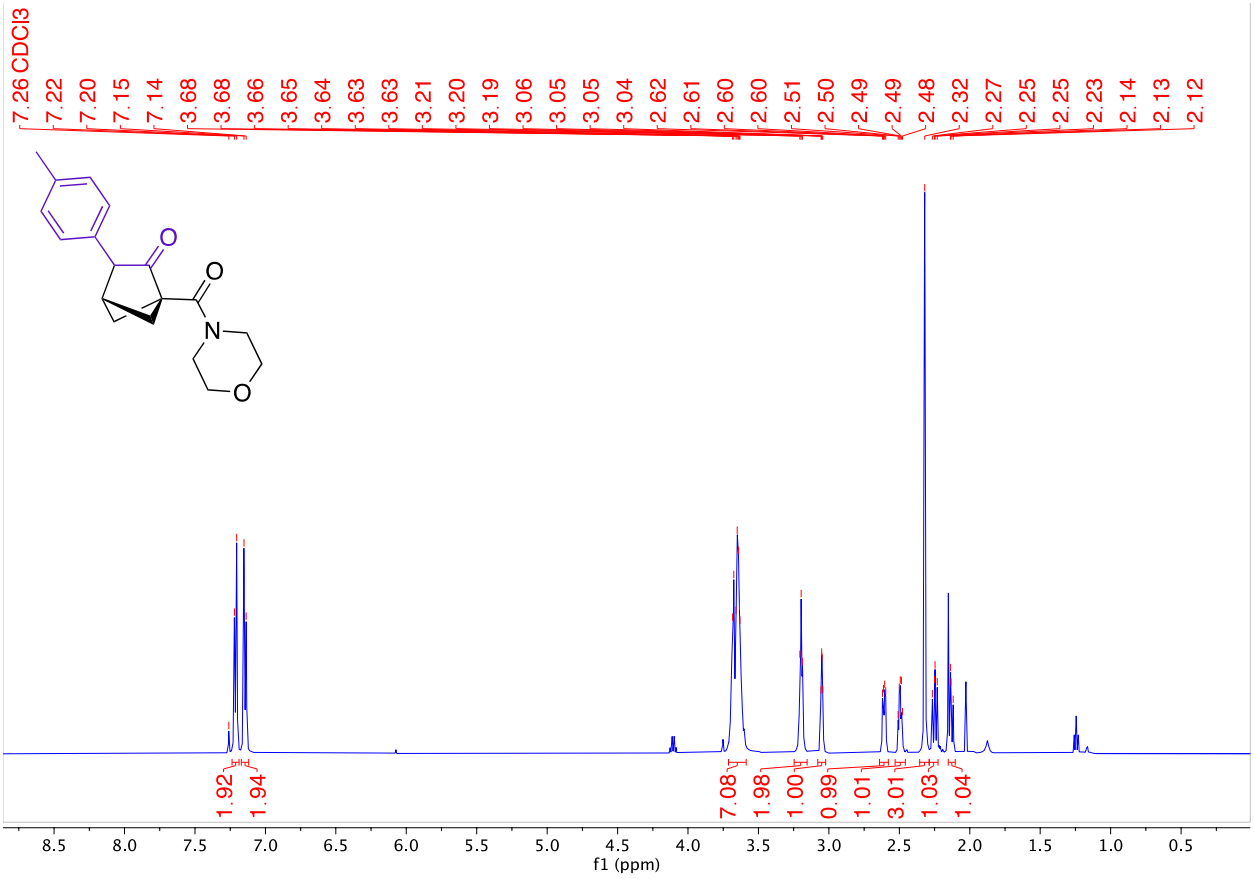
1-(Morpholine-4-carbonyl)-3-(*p*-tolyl)bicyclo[2.1.1]hexan-2-one (3d)



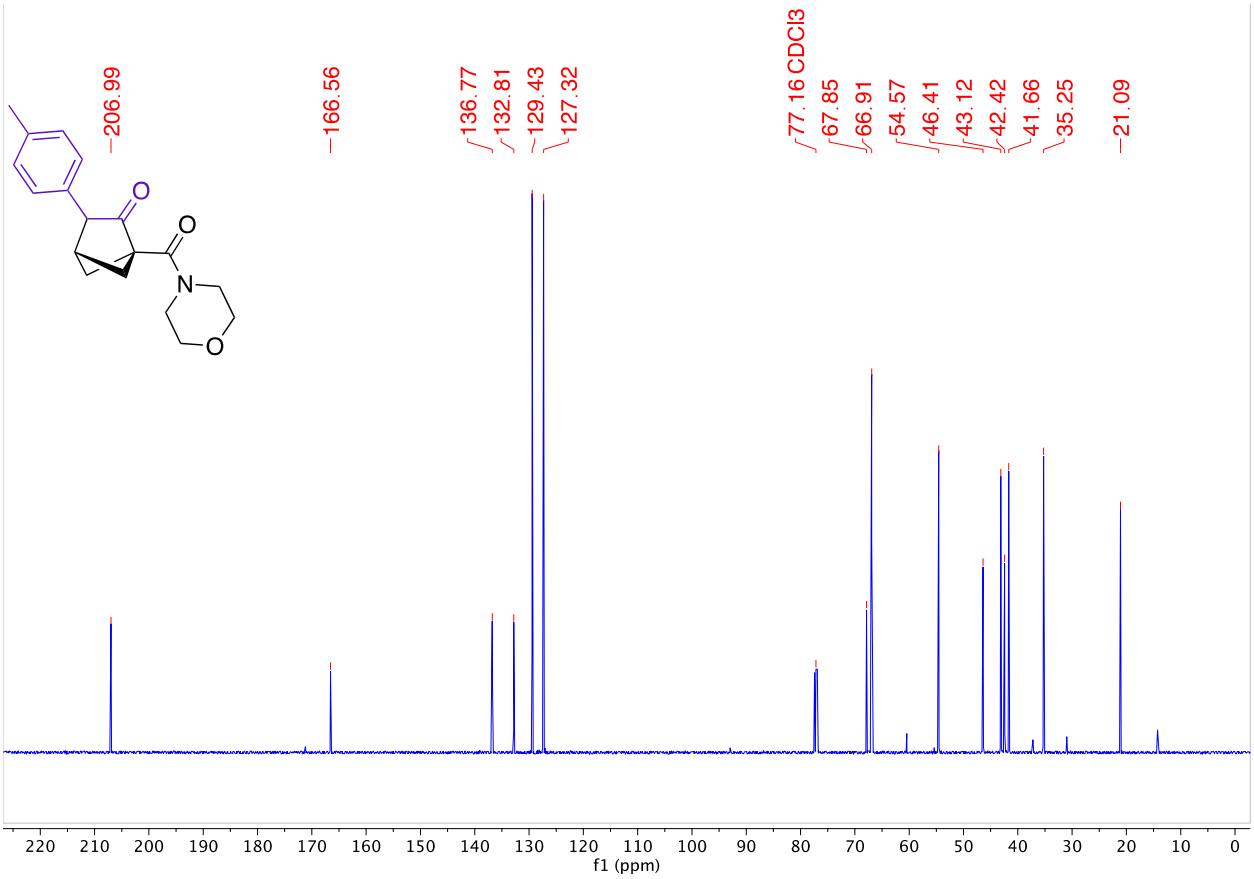
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2d** on a 0.30 mmol bicyclobutane scale. The crude compound was crystallized in a vial and was washed with hexanes. 58 mg of a white solid was obtained (65% Yield).

HRMS(ESI): calc'd for [$C_{18}H_{21}NO_3$ + H^+], 300.15942; found: 300.15946

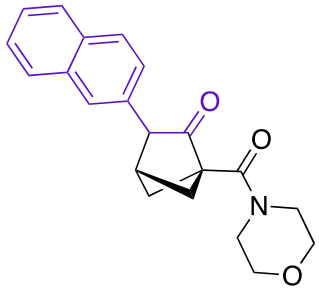
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.21 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2zH), 3.71 – 3.56 (m, 7H), 3.20 (t, *J* = 4.8 Hz, 2H), 3.05 (td, *J* = 3.7, 1.4 Hz, 1H), 2.61 (ddd, *J* = 7.6, 3.9, 1.0 Hz, 1H), 2.49 (dt, *J* = 7.7, 3.8 Hz, 1H), 2.32 (s, 3H), 2.25 (dd, *J* = 9.5, 7.7 Hz, 1H), 2.14 (dd, *J* = 9.5, 7.5 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.99, 166.56, 136.77, 132.81, 129.43, 127.32, 67.85, 66.91, 54.57, 46.41, 43.12, 42.42, 41.66, 35.25, 21.09.



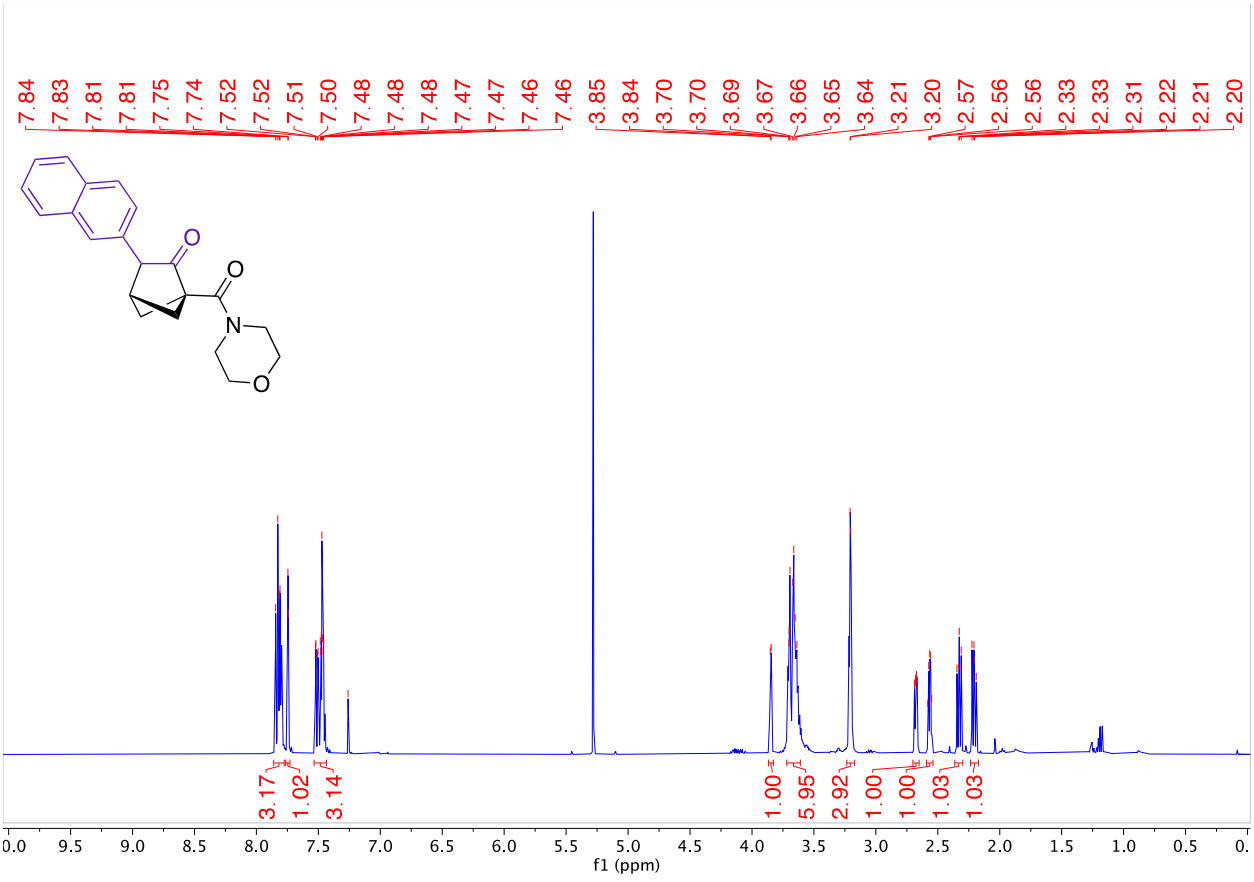
1-(Morpholine-4-carbonyl)-3-(naphthalen-2-yl)bicyclo[2.1.1]hexan-2-one (3e)



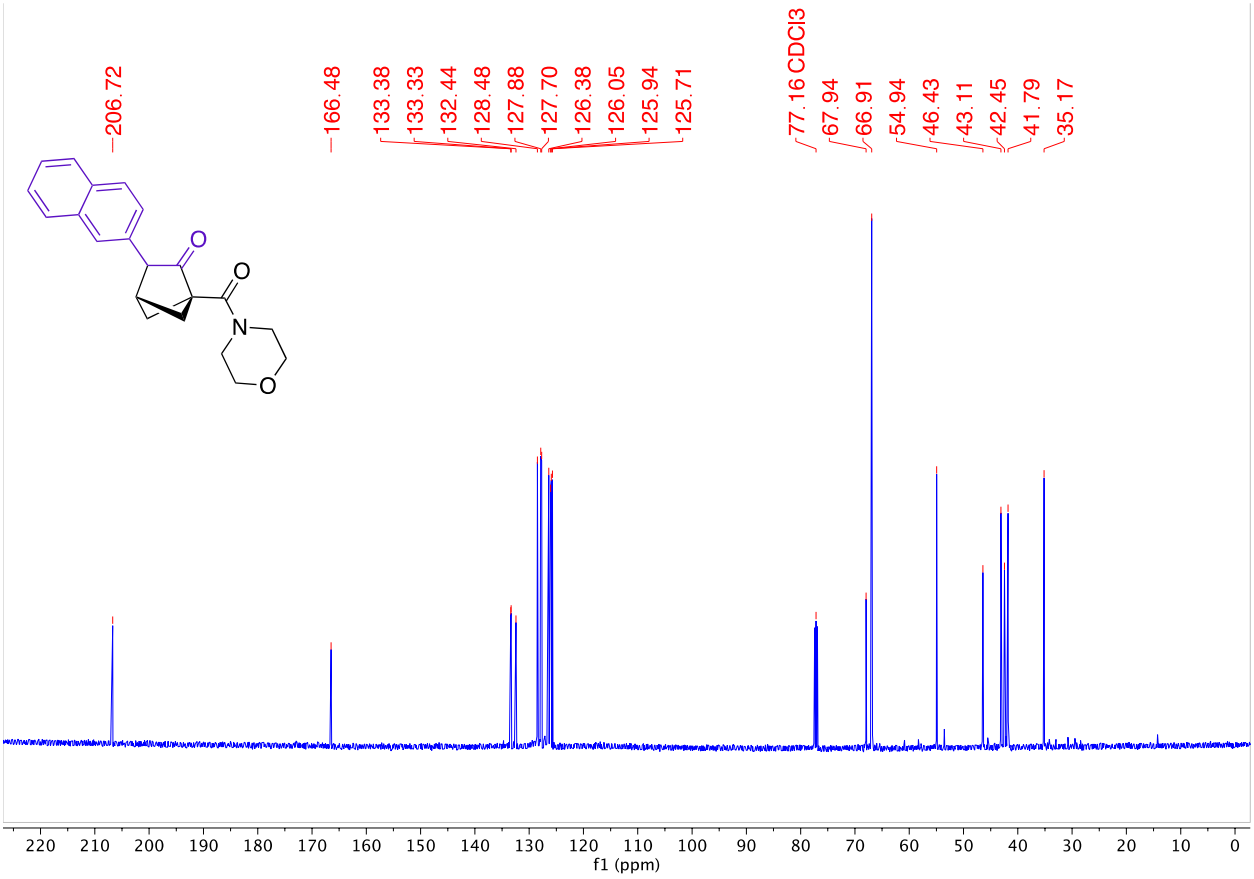
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2e** on a 0.50 mmol bicyclobutane scale using a reaction concentration of 0.05 M. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 80% EtOAc). 127 mg of a light brown solid was obtained (76% Yield).

HRMS(ESI): calc'd for [$C_{21}H_{21}NO_3$ + H^+], 336.15942; found: 336.15947

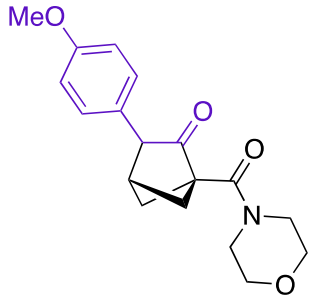
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.86 – 7.78 (m, 3H), 7.74 (sz, 1H), 7.53 – 7.43 (m, 3H), 3.85 (d, *J* = 3.9 Hz, 1H), 3.72 – 3.61 (m, 5H), 3.21 (m, 3H), 2.68 (ddd, *J* = 7.5, 3.9, 1.0 Hz, 1H), 2.56 (dt, *J* = 7.7, 3.8 Hz, 1H), 2.33 (dd, *J* = 9.5, 7.8 Hz, 1H), 2.21 (dd, *J* = 9.5, 7.6 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.72, 166.48, 133.38, 133.33, 132.44, 128.48, 127.88, 127.70, 126.38, 126.05, 125.94, 125.71, 67.94, 66.91, 54.94, 46.43, 43.11, 42.45, 41.79, 35.17.



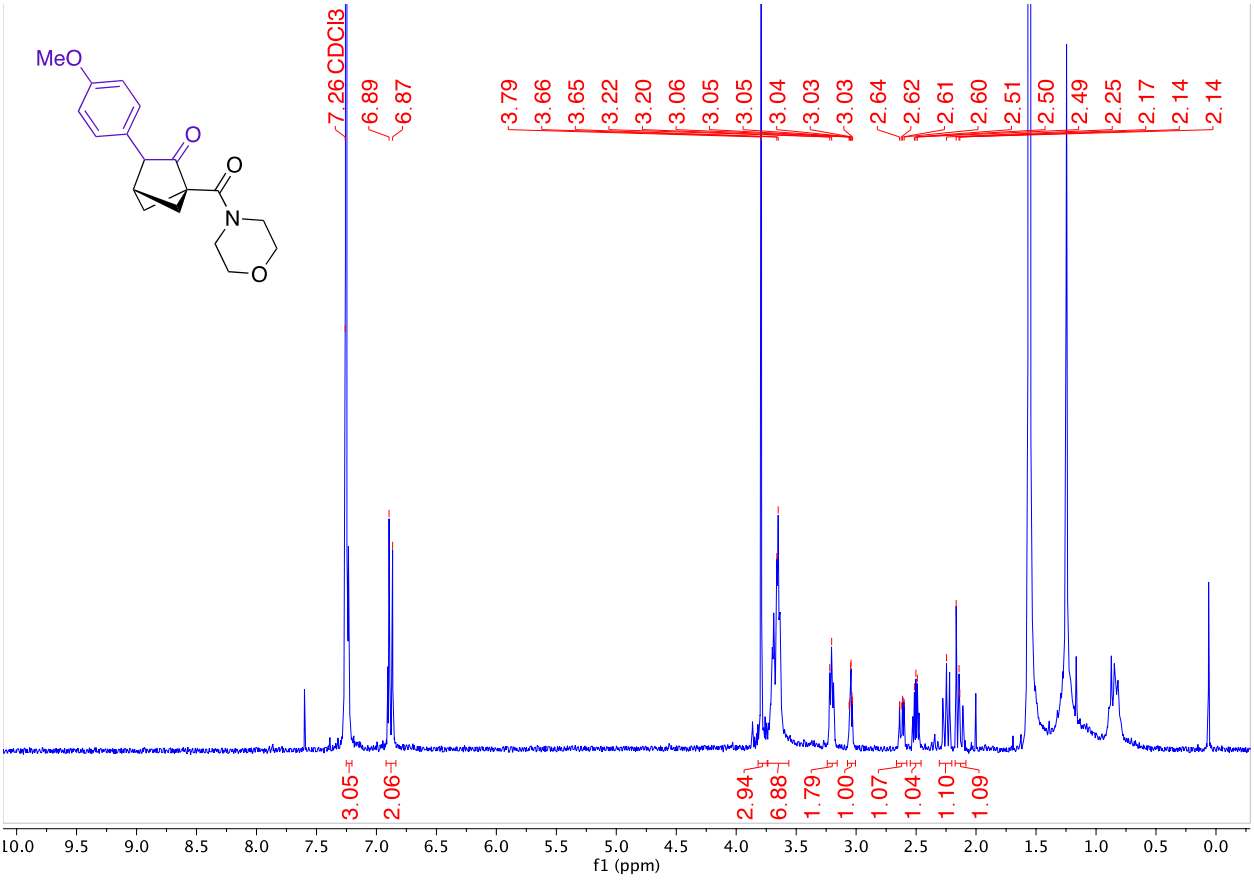
3-(4-Methoxyphenyl)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3f)



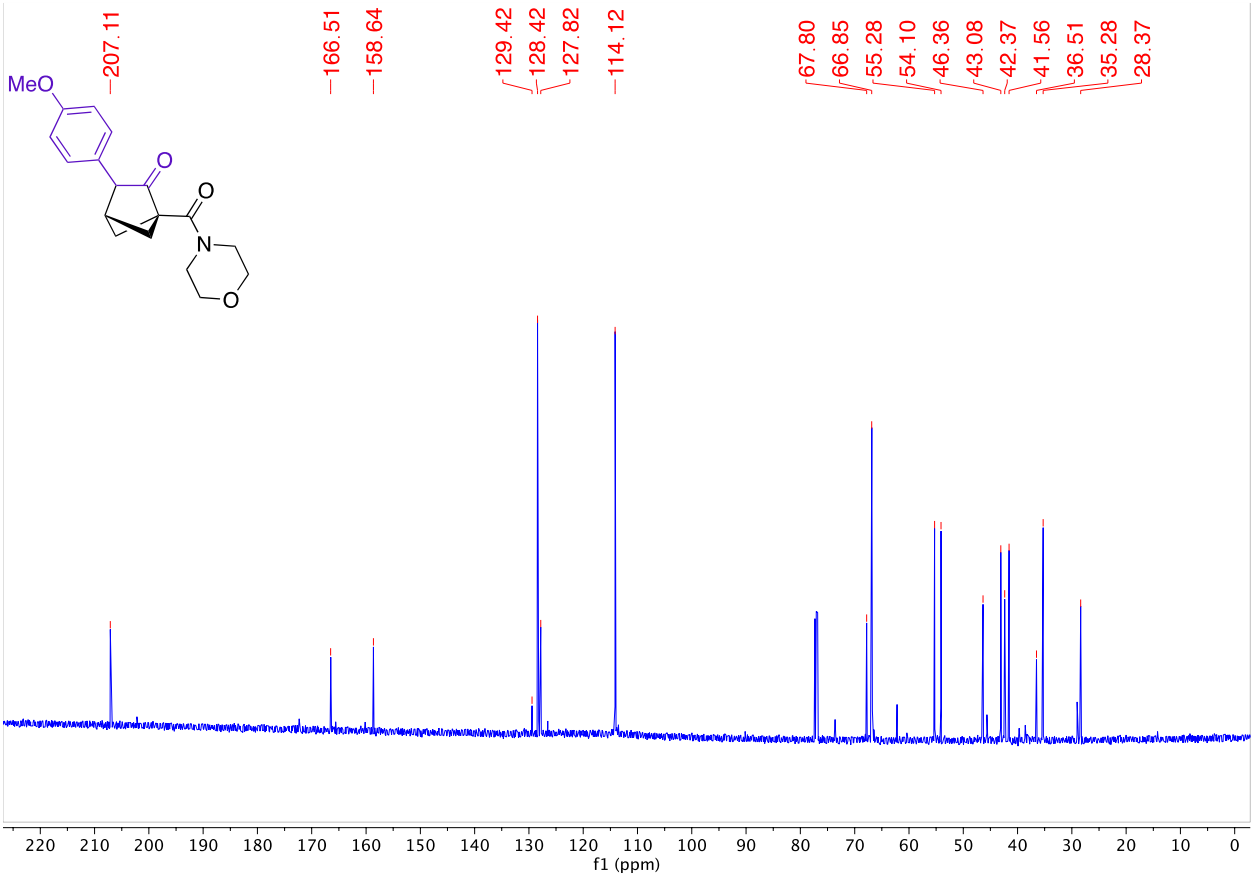
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2f** on a 0.50 mmol bicyclobutane scale using a reaction concentration of 0.1 M. The compound was purified by column chromatography (Biotage® Sfär 10g Column, 0-100% EtOAc/hexanes, eluted at 68% EtOAc). 37.2 mg of a clear colourless oil was obtained (24% Yield).

HRMS(ESI): calc'd for [$C_{18}H_{21}NO_4$ + Na^+], 338.13628; found: 338.13626.

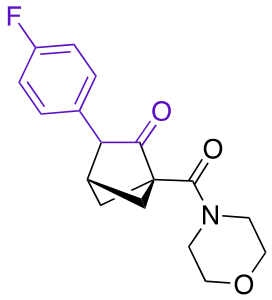
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.24 (m, 2H), 6.91 – 6.86 (m, 2H), 3.80 (s, 3H), 3.65 (m, 7H), 3.21 (t, J = 4.8 Hz, 2H), 3.05 (td, J = 3.7, 1.4 Hz, 1H), 2.62 (ddd, J = 7.6, 3.9, 0.9 Hz, 1H), 2.51 (dt, J = 7.7, 3.8 Hz, 1H), 2.25 (dd, J = 9.5, 7.7 Hz, 1H), 2.15 (dd, J = 9.5, 7.6 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.11, 166.51, 158.64, 129.42,128.42, 127.82, 114.12, 67.80, 66.85, 55.28, 54.10, 46.36, 43.08, 42.37, 41.56, 36.51, 35.28, 28.37.



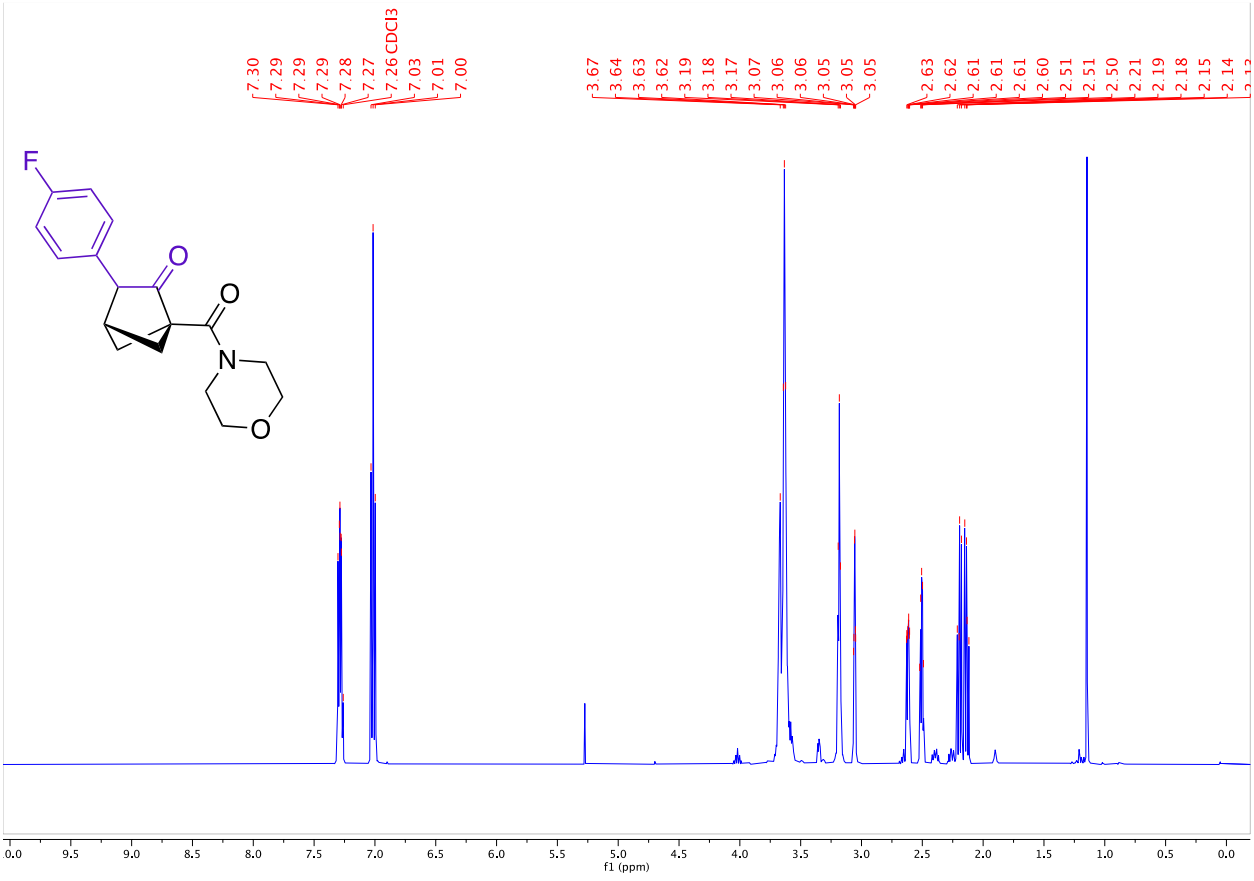
3-(4-Fluorophenyl)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3g)



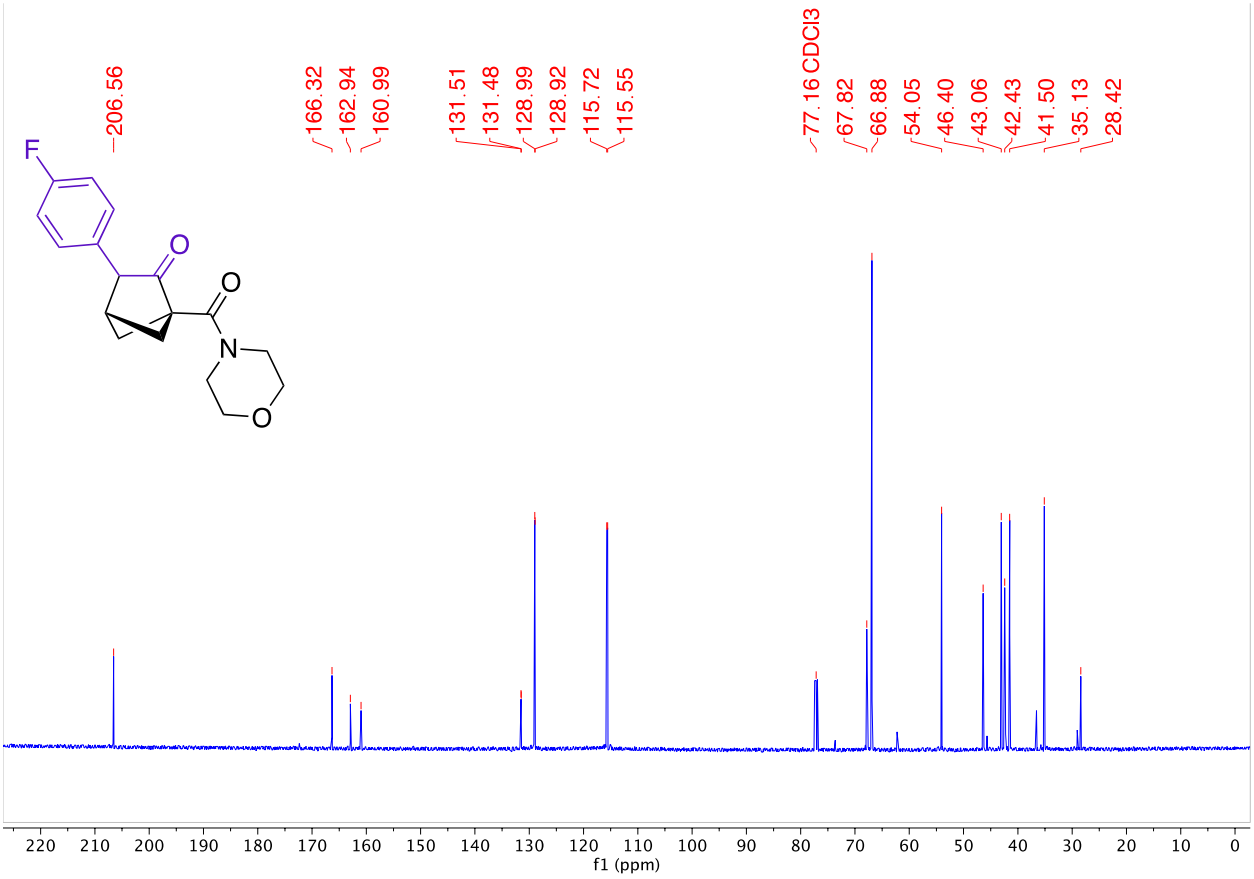
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2g** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 82% EtOAc). 74 mg of a white solid was obtained (68% Yield).

HRMS(ESI): calc'd for [$C_{17}H_{18}FNO_3$ + H^+], 304.13435; found: 304.13435

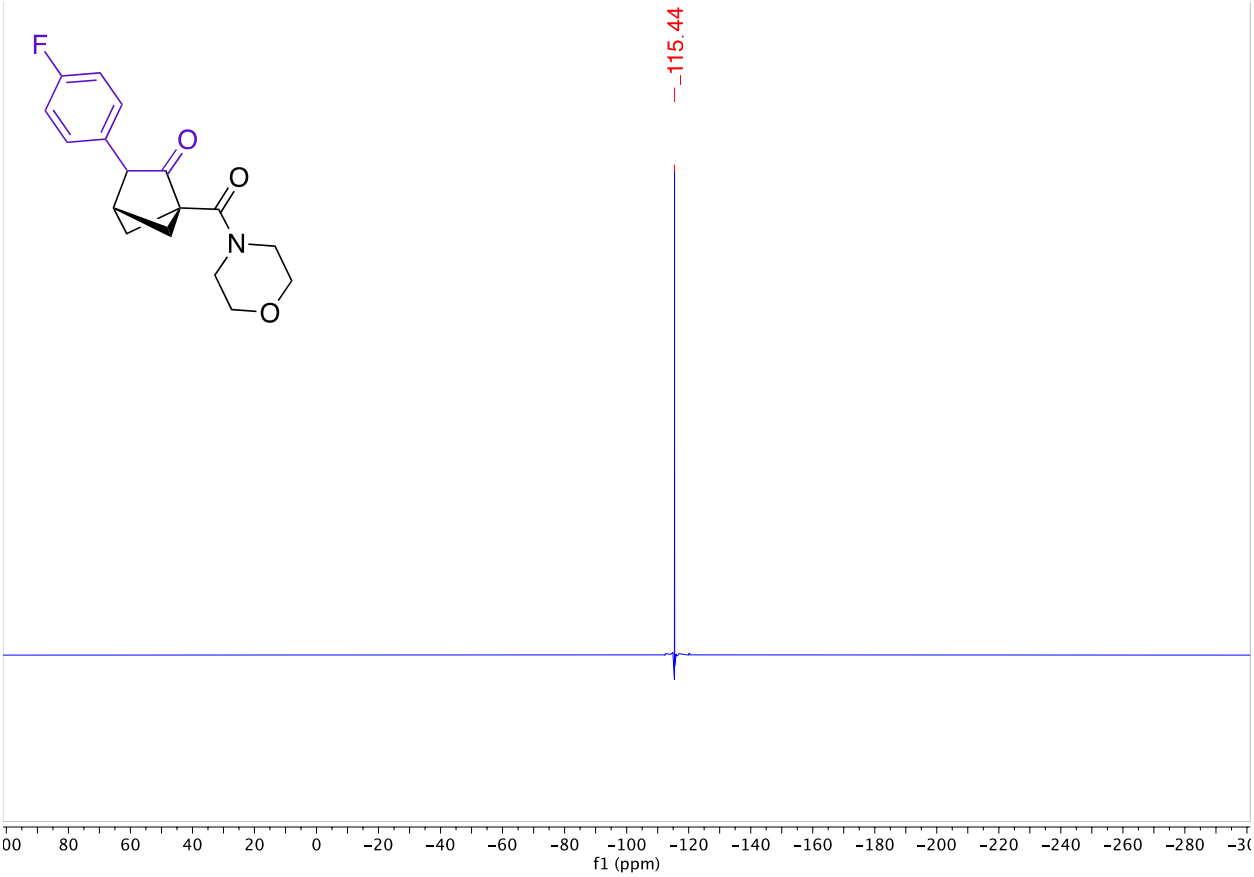
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.32 – 7.26 (m, 2H), 7.01 (m, 2H), 3.70 – 3.59 (m, 7H), 3.18 (t, J = 4.8 Hz, 2H), 3.06 (td, J = 3.7, 1.4 Hz, 1H), 2.62 (ddd, J = 7.5, 3.8, 1.0 Hz, 1H), 2.51 (dt, J = 7.6, 3.8 Hz, 1H), 2.20 (dd, J = 9.6, 7.6 Hz, 1H), 2.13 (dd, J = 9.5, 7.5 Hz, 1H).



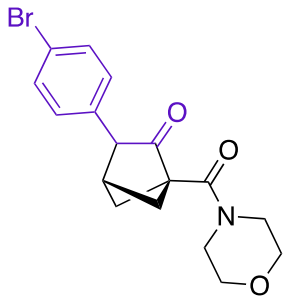
^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.56, 166.32, 162.94, 160.99, 131.51, 131.48, 128.99, 128.92, 115.72, 115.55, 67.82, 66.88, 54.05, 46.40, 43.06, 42.43, 41.50, 35.13, 28.42.



^{19}F NMR (500 MHz, $CDCl_3$, ppm): δ 115.44.



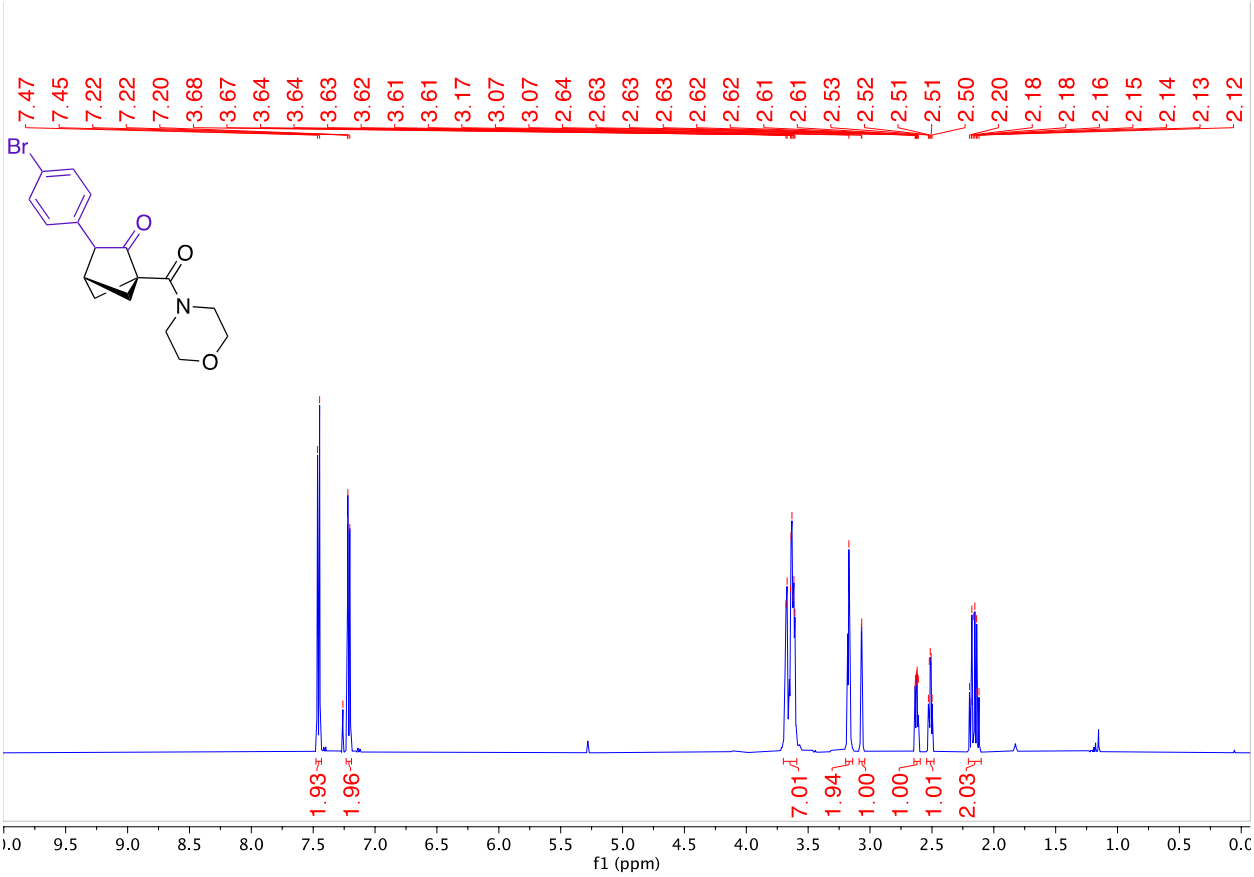
3-(4-Bromophenyl)-1-(morpholine-4-carbonyl)bicyclo[2.1.1]hexan-2-one (3h)



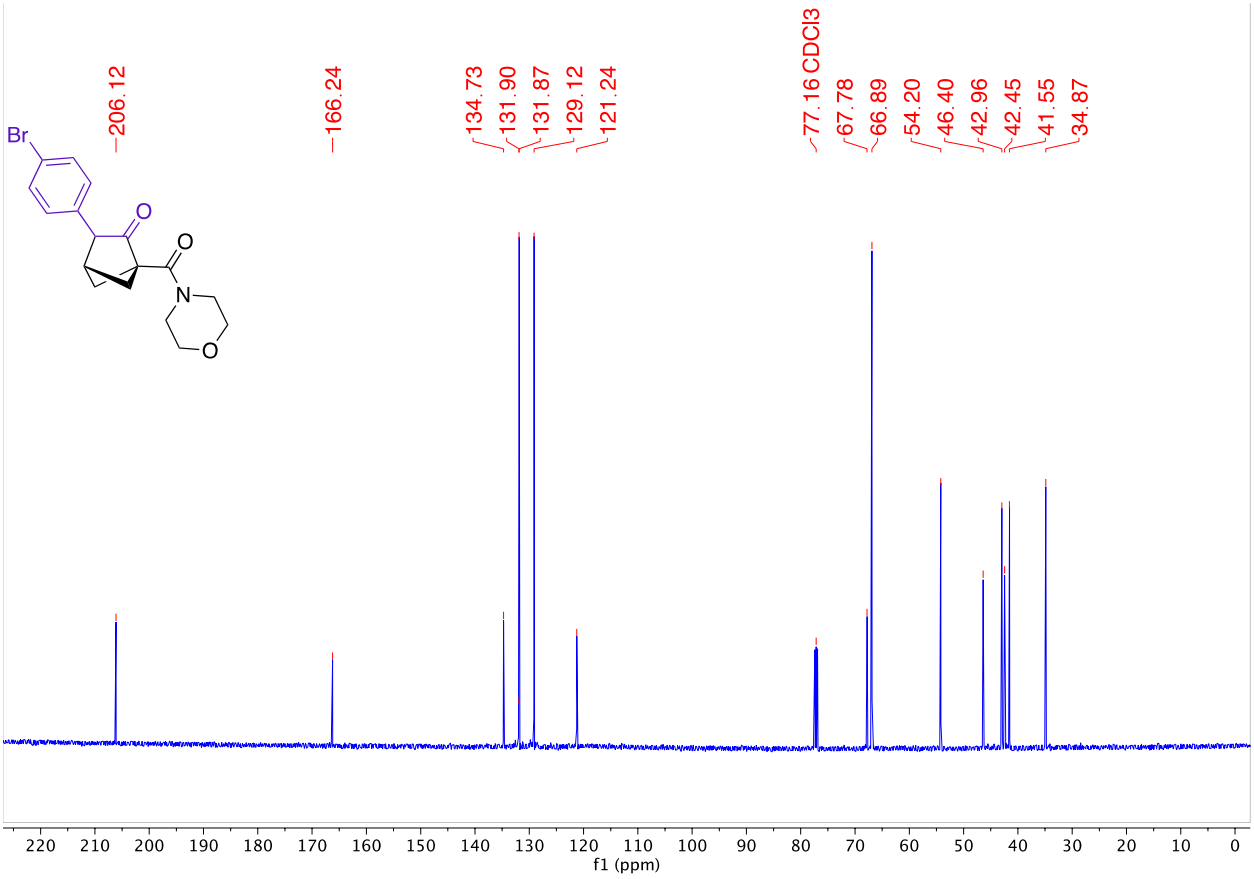
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2h** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 82% EtOAc). 62 mg of a white solid was obtained (57% Yield).

HRMS(ESI): calc'd for [$C_{17}H_{18}BrNO_3$ + H^+], 364.05429; found: 364.05441.

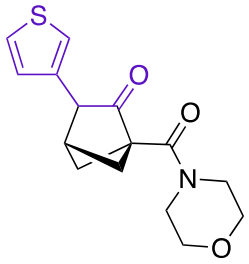
^{z1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.19 (m, 2H), 3.70 – 3.59 (m, 7H), 3.17 (m, 2H), 3.07 (m, 1H), 2.62 (ddd, *J* = 7.3, 3.9, 0.9 Hz, 1H), 2.51 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.21 – 2.10 (m, 2H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 206.12, 166.24, 134.73, 131.87, 129.12, 121.24, 67.78, 66.89, 54.20, 46.40, 42.96, 42.45, 41.55, 34.87.



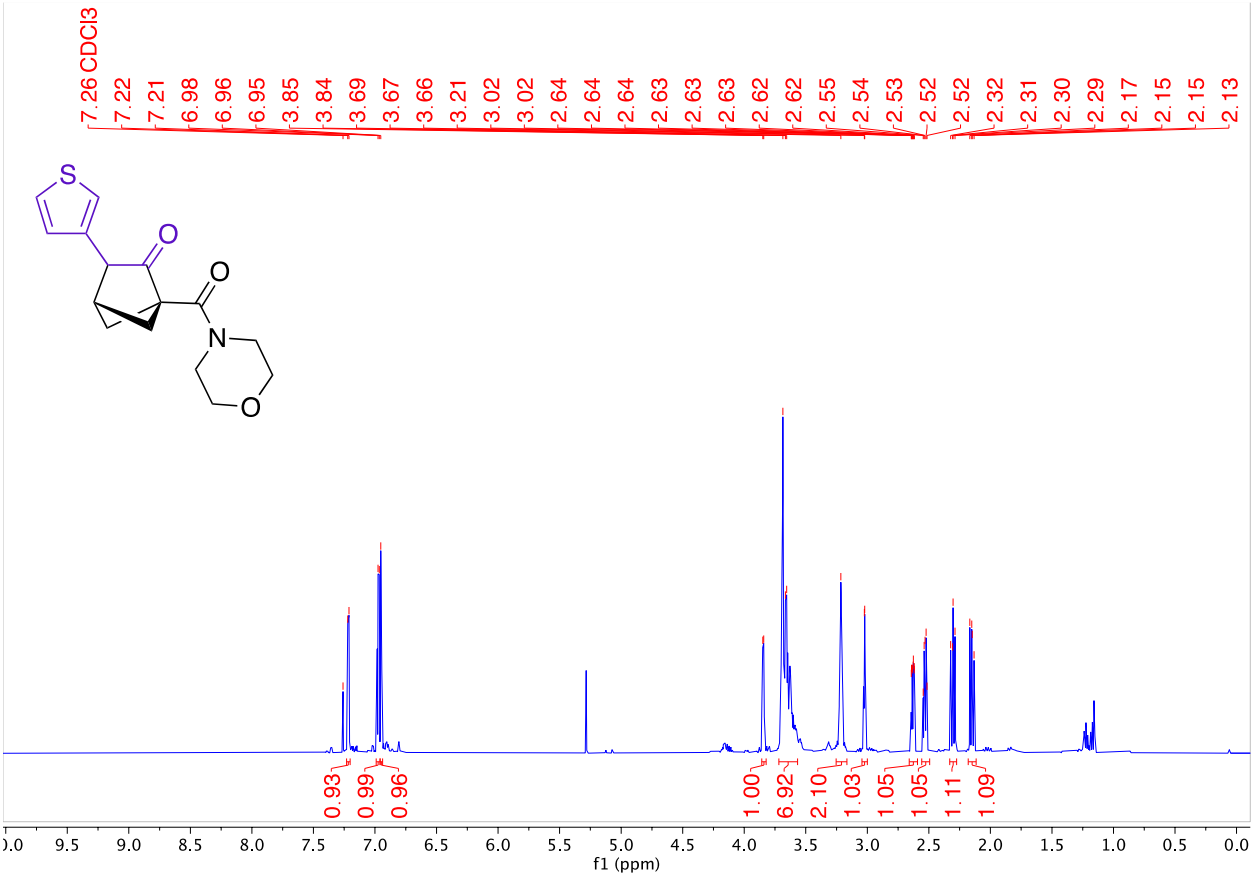
1-(Morpholine-4-carbonyl)-3-(thiophen-3-yl)bicyclo[2.1.1]hexan-2-one (3i)



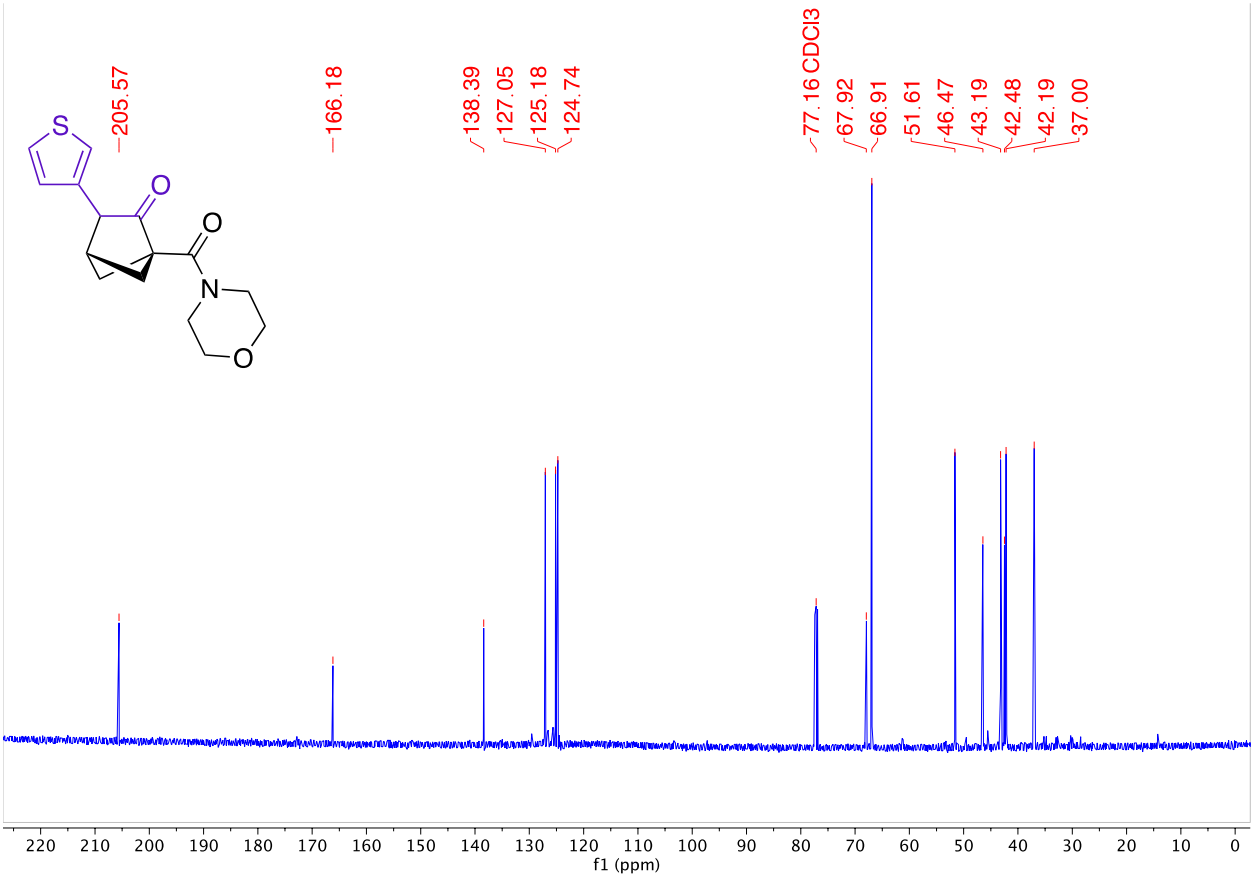
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2i** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 75% EtOAc). 23 mg of a white solid was obtained (27% Yield).

HRMS(ESI): calc'd for [$C_{15}H_{17}NO_3S + H^+$], 292.10019; found: 292.10017.

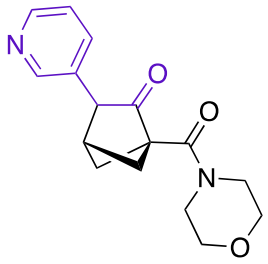
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.22 (m, 1H), 6.97 (m, 1H), 6.95 (m, 1H), 3.85 (d, J = 3.8 Hz, 1H), 3.67 (m, 7H), 3.21 (m, 2H), 3.02 (m, 1H), 2.63 (ddd, J = 7.7, 3.8, 0.9 Hz, 1H), 2.53 (dt, J = 7.7, 3.7 Hz, 1H), 2.30 (dd, J = 9.6, 7.9 Hz, 1H), 2.15 (dd, J = 9.6, 7.7 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 205.57, 166.18, 138.39, 127.05, 125.18, 124.74, 67.92, 66.91, 51.61, 46.47, 43.19, 42.48, 42.19, 37.00.



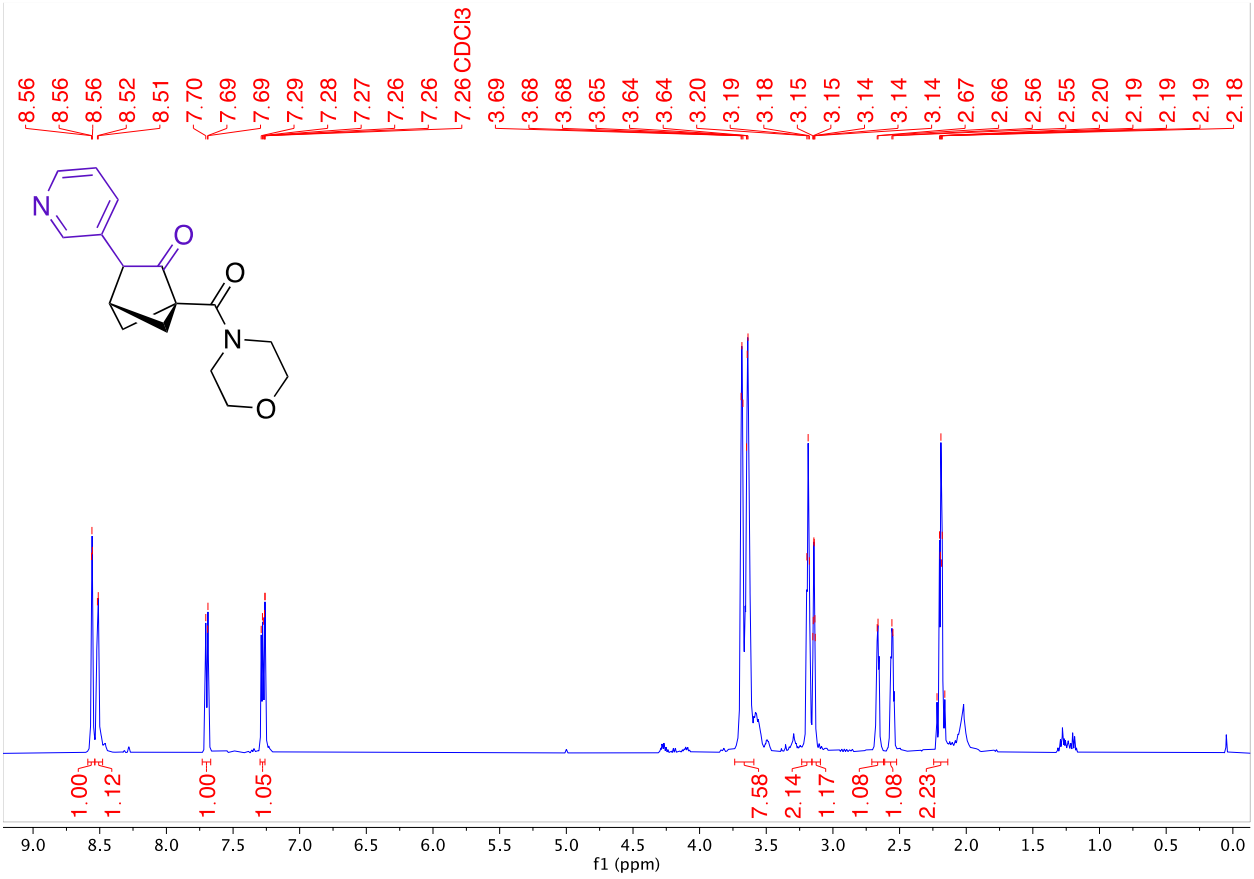
1-(Morpholine-4-carbonyl)-3-(pyridin-3-yl)bicyclo[2.1.1]hexan-2-one (3j)



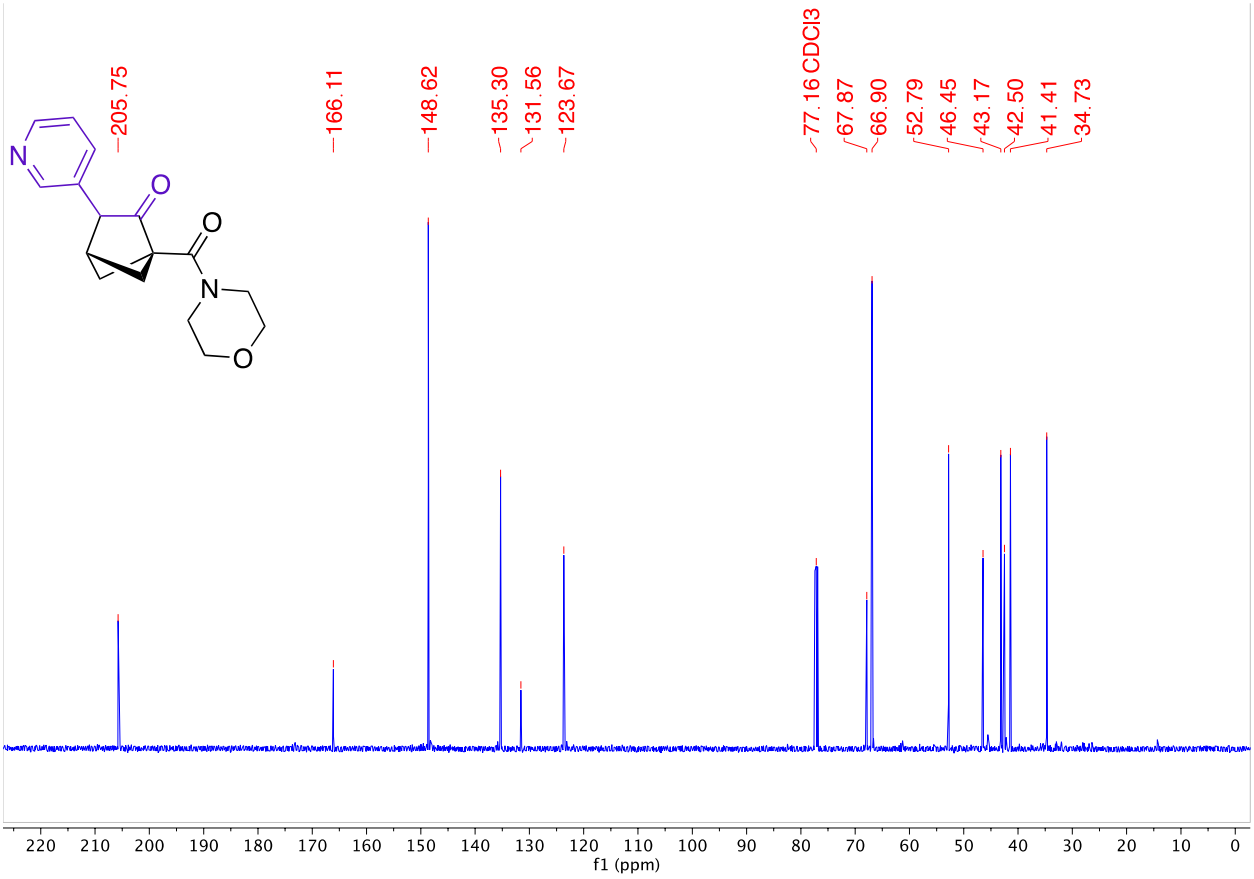
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2j** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% MeOH/EtOAc, eluted at 44% MeOH). 57 mg of a white solid was obtained (67% Yield).

HRMS(ESI): calc'd for [$C_{16}H_{18}N_2O_3$ + H^+], 287.13902; found: 287.13889.

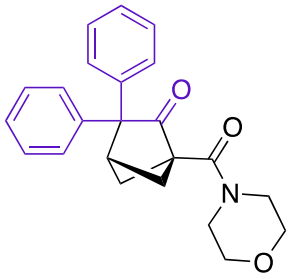
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 8.59 – 8.54 (m, 1H), 8.51 (m, 1H), 7.73 – 7.67 (m, 1H), 7.30 – 7.26 (m, 1H), 3.74 – 3.59 (m, 7H), 3.19 (t, *J* = 4.8 Hz, 2H), 3.14 (td, *J* = 3.7, 1.3 Hz, 1H), 2.66 (d, *J* = 3.1 Hz, 1H), 2.55 (d, *J* = 3.7 Hz, 1H), 2.24 – 2.14 (m, 2H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 205.75, 166.11, 148.62, 135.30, 131.56, 123.67, 67.87, 66.90, 52.79, 46.45, 43.17, 42.50, 41.41, 34.73.



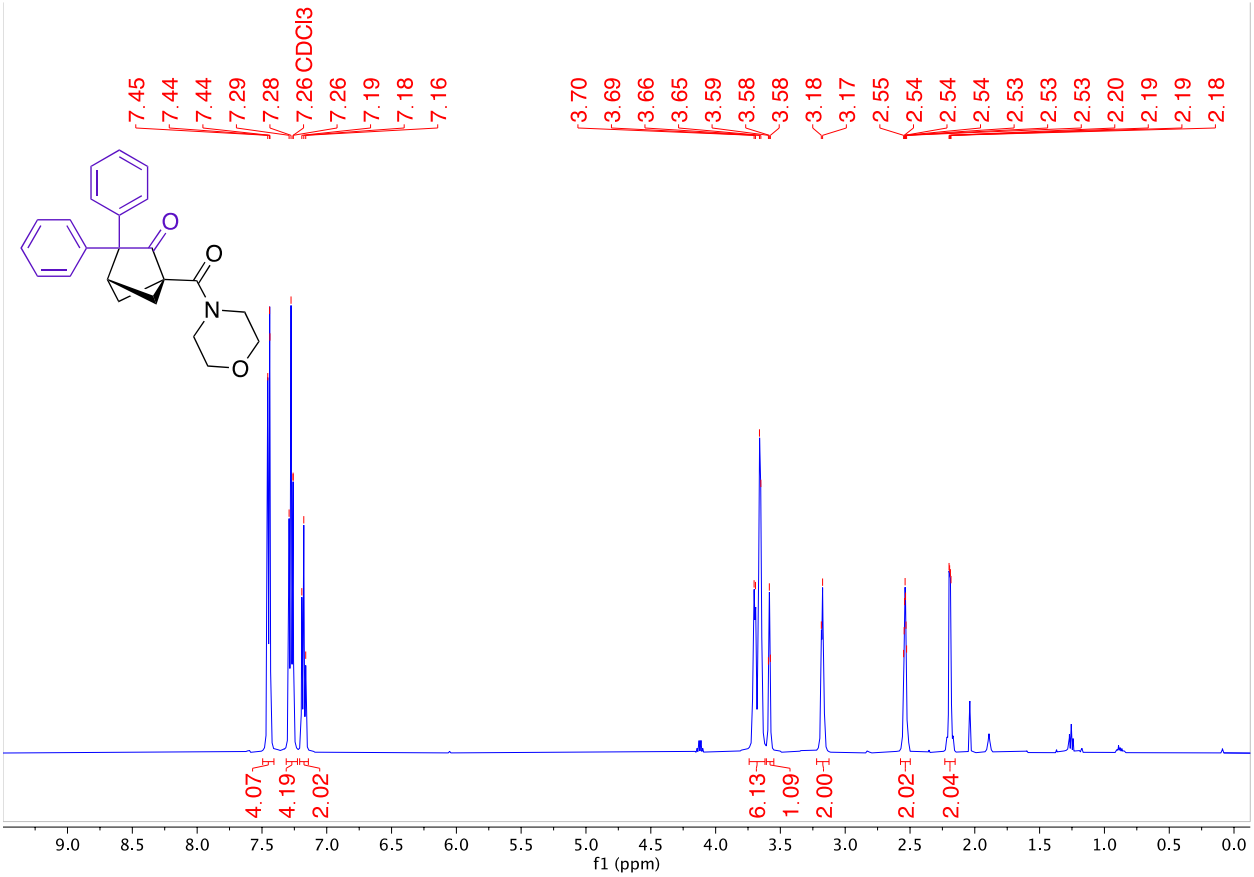
1-(Morpholine-4-carbonyl)-3,3-diphenylbicyclo[2.1.1]hexan-2-one (3k)



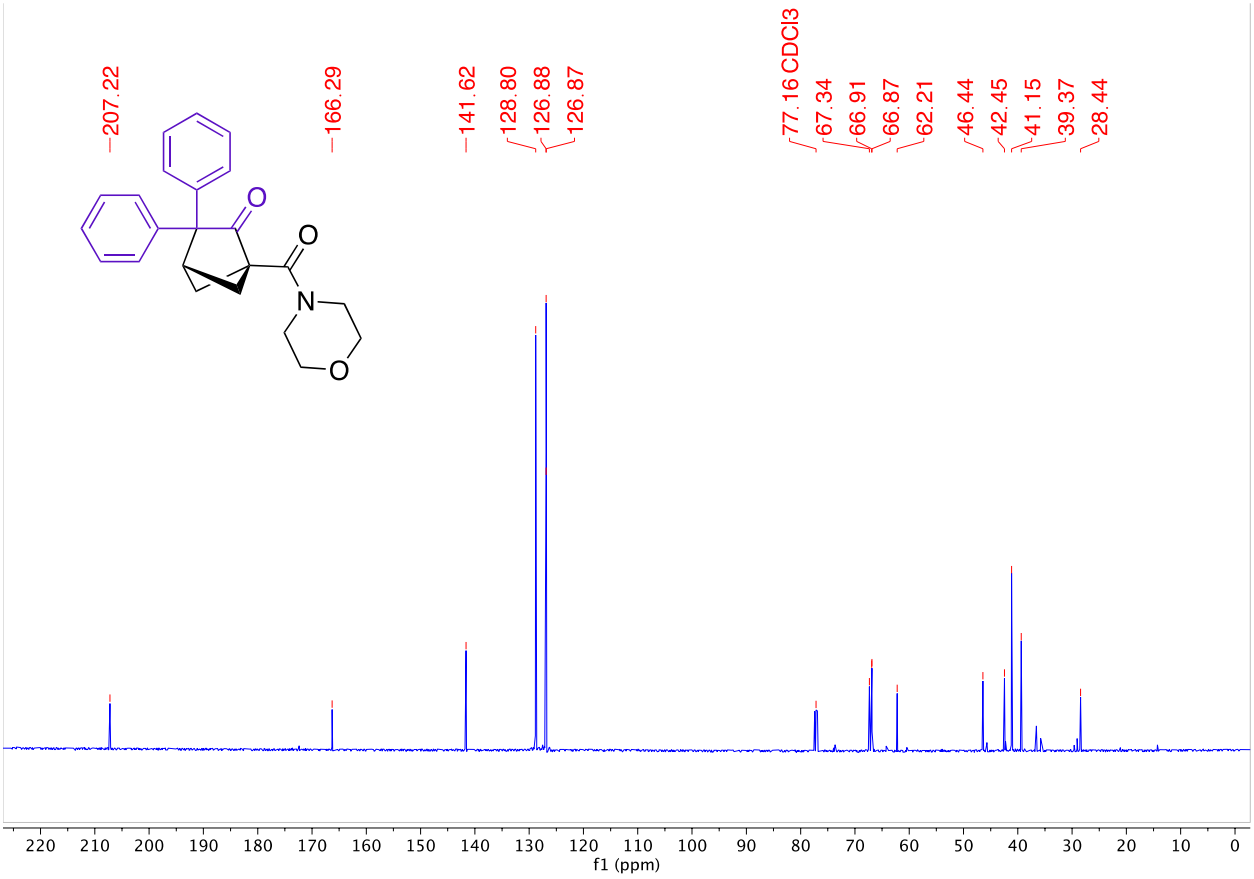
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2k** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 62% EtOAc). 80 mg of a white solid was obtained (74% Yield).

HRMS(ESI): calc'd for [$C_{23}H_{23}NO_3$ + H^+], 362.17507; found: 362.17477.

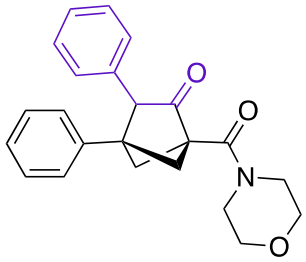
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.49 – 7.41 (m, 4H), 7.28 (t, *J* = 7.8 Hz, 4H), 7.18 (t, *J* = 7.4 Hz, 2H), 3.68 (dd, *J* = 20.8, 5.1 Hz, 6H), 3.58 (t, *J* = 3.8 Hz, 1H), 3.18 (d, *J* = 4.8 Hz, 2H), 2.54 (ddd, *J* = 5.6, 3.7, 2.2 Hz, 2H), 2.19 (dd, *J* = 5.2, 2.3 Hz, 2H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.22, 166.29, 141.62, 128.80, 126.88, 126.87, 67.34, 66.91, 66.87, 62.21, 46.44, 42.45, 41.15, 39.37, 28.44.



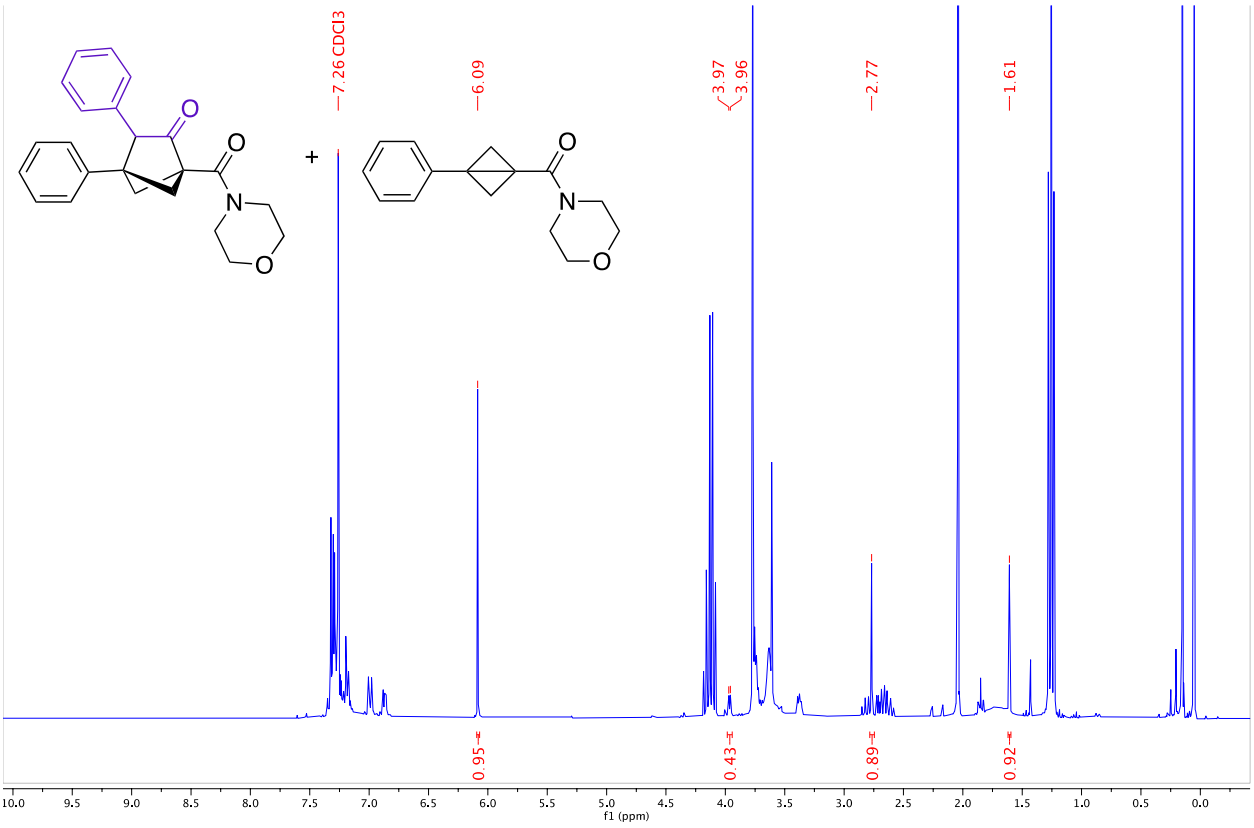
1-(Morpholine-4-carbonyl)-3,4-diphenylbicyclo[2.1.1]hexan-2-one (3l):



The product was prepared following the general procedure for bicyclohexane synthesis from **1l** and **2c** on a 0.30 mmol bicyclobutane scale. An NMR yield of 43% (3.97 ppm peak) is reported compared to internal standard (1,3,5-trimethoxybenzene). The compound was attempted to be purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes) but the product and bicyclobutane starting material co-eluted at 43% ethyl acetate. 64.3 mg of a yellow solid was obtained as a mixture of **3o** and unreacted bicyclobutane (1 : 0.87 mol ratio) (37% Yield of **3o**, 32% of bicyclobutane).

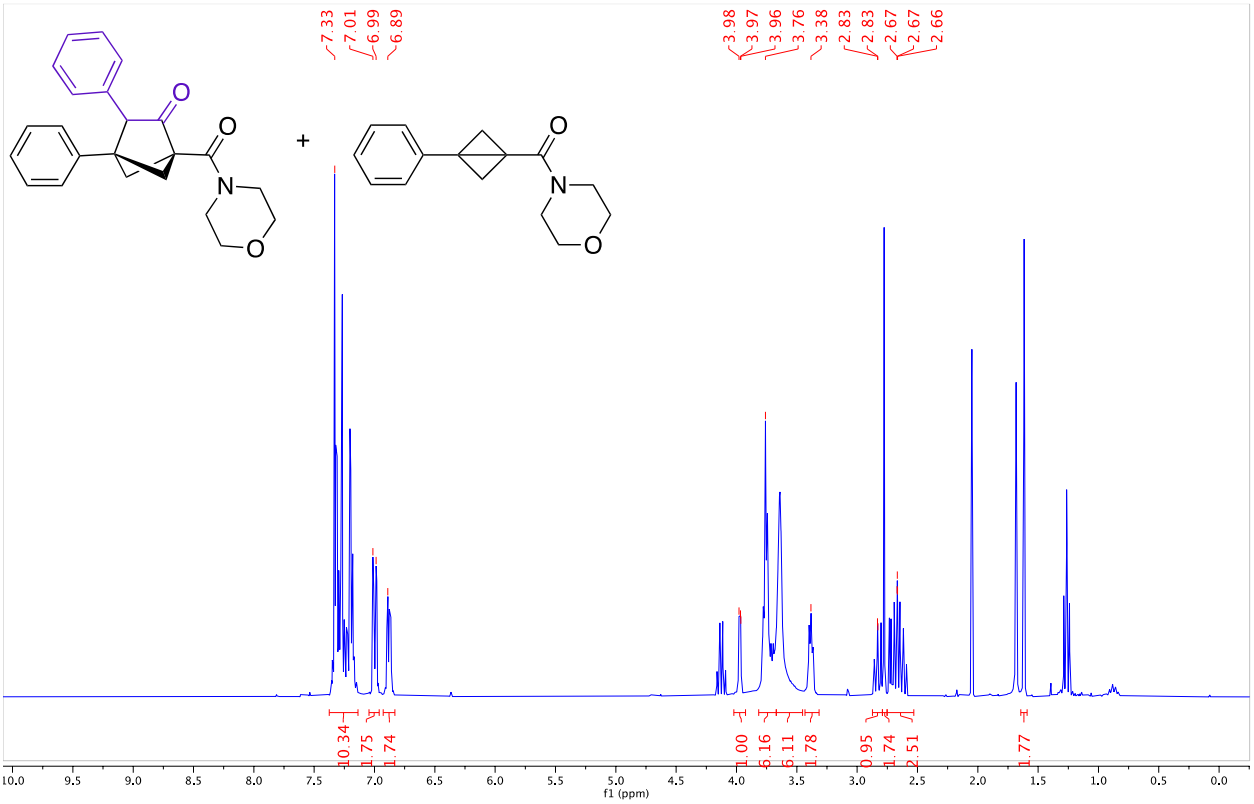
HRMS(ESI): calc'd for [$C_{23}H_{23}NO_3$ + H^+], 362.17507; found: 362.17487

Crude ^{1}H NMR, including 1,3,5-trimethoxybenzene (300 MHz, $CDCl_3$, 292K):

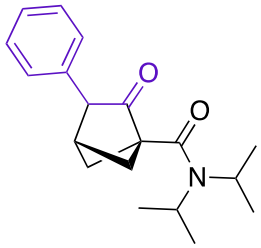


^{1}H NMR (500 MHz, $CDCl_3$, 292K): δ 7.33 (m, 6H), 7.00 (m, 2H), 6.89 (m, 2H), 4.02 – 3.92 (m, 1H), 3.76 (m, 6H), 3.38 (m, 2H), 2.83 (m, 1H), 2.75 – 2.53 (m, 3H).

Bicyclobutane peaks: 7.27 (m, 5H), 3.64 (m, 8H), 2.78 (t, J = 0.7 Hz, 2H), 1.62 (t, J = 0.7 Hz, 2H).



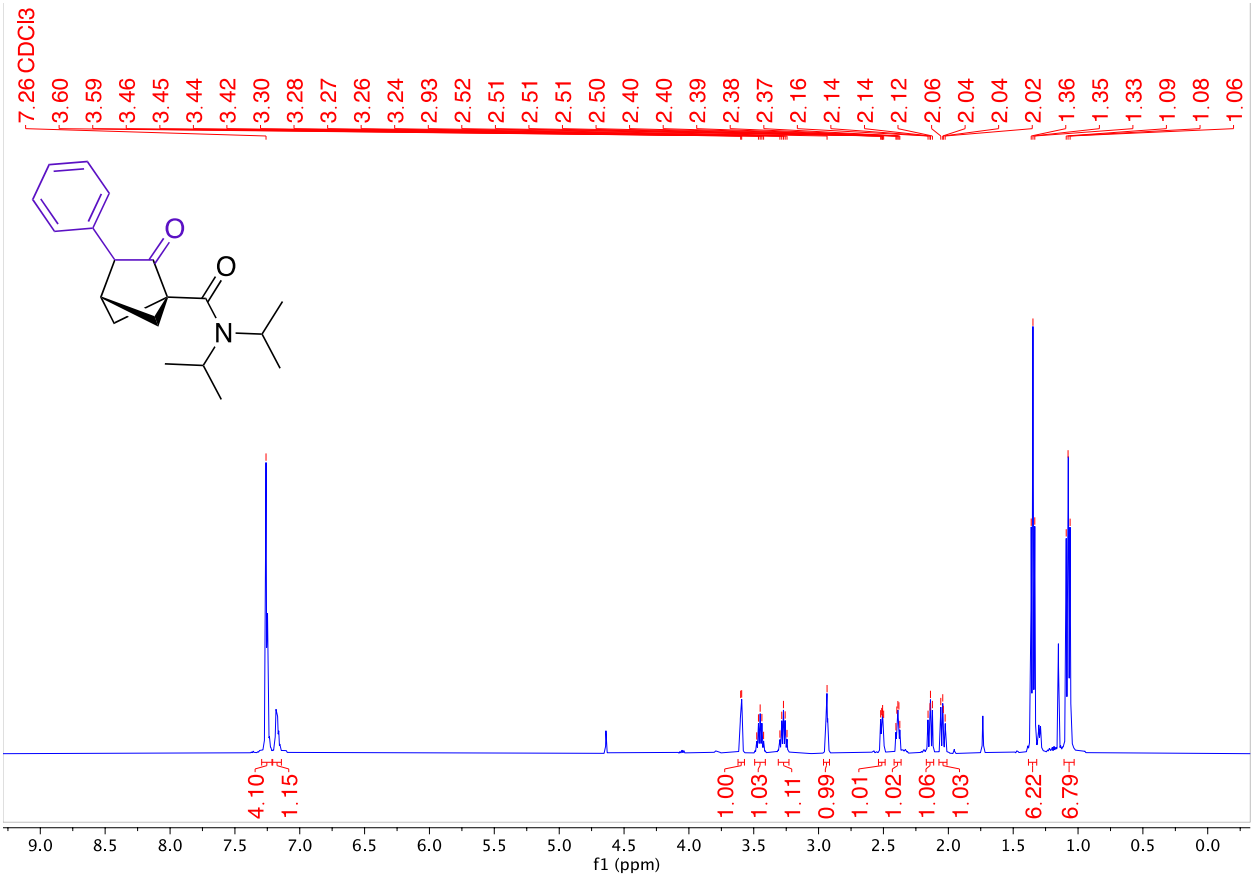
***N*,*N*-diisopropyl-2-oxo-3-phenylbicyclo[2.1.1]hexane-1-carboxamide (3m)**



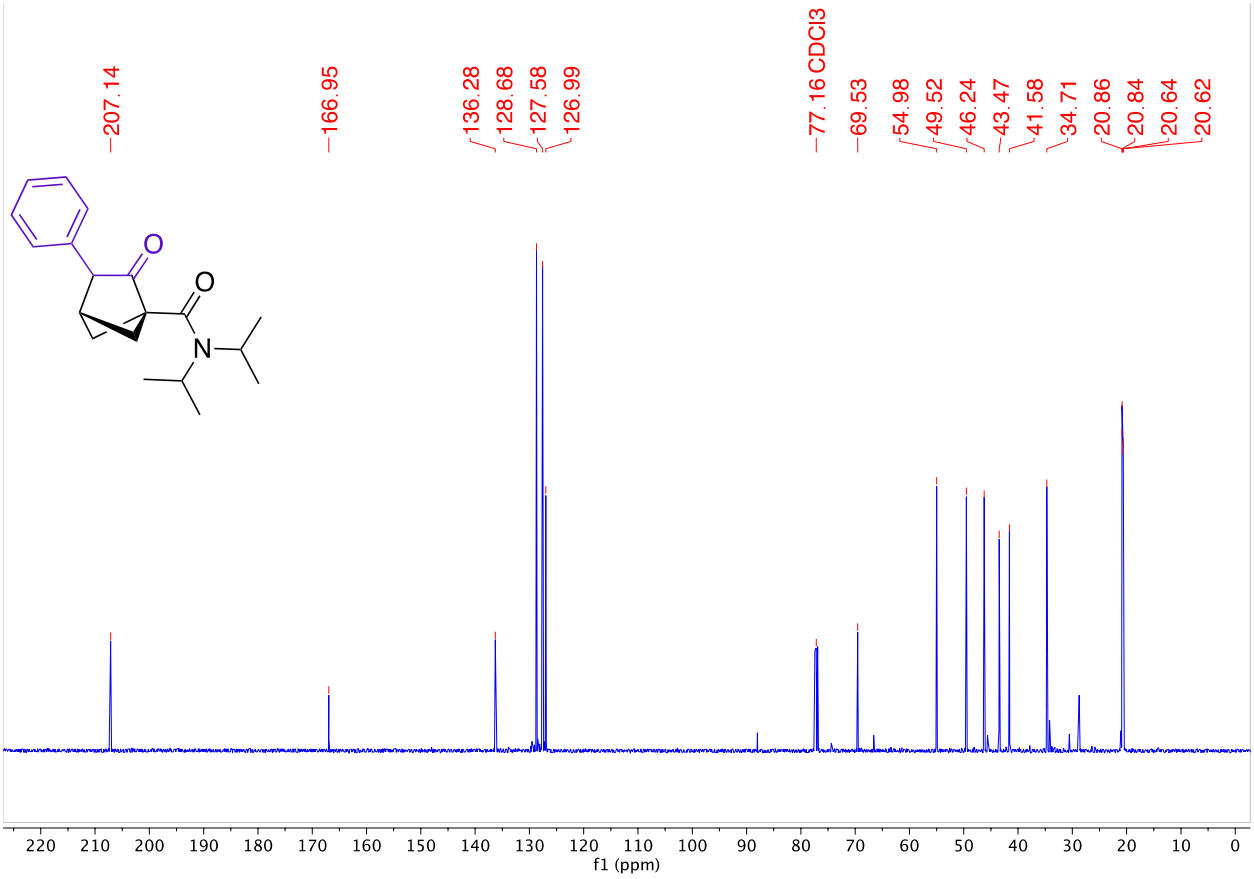
The product was prepared following the general procedure for bicyclohexane synthesis from **1m** and **2c** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 42% EtOAc). 39 mg of a clear colourless oil was obtained (43% Yield).

HRMS(ESI): calc'd for [$C_{19}H_{25}NO_2$ + H^+], 300.19581; found: 300.19577.

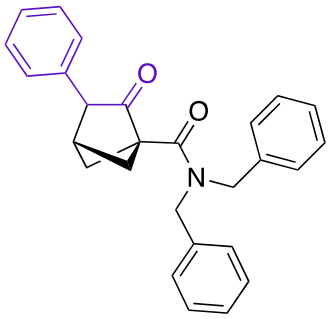
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.29 – 7.21 (m, 4H), 7.21 – 7.14 (m, 1H), 3.60 (d, J = 4.0 Hz, 1H), 3.45 (p, J = 6.6 Hz, 1H), 3.27 (p, J = 6.8 Hz, 1H), 2.93 (s, 1H), 2.54 – 2.49 (m, 1H), 2.39 (dt, J = 7.8, 3.8 Hz, 1H), 2.14 (dd, J = 9.5, 7.7 Hz, 1H), 2.04 (dd, J = 9.5, 7.5 Hz, 1H), 1.35 (t, J = 6.8 Hz, 6H), 1.11 – 1.03 (m, 6H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.14, 166.95, 136.28, 128.68, 127.58, 126.99, 69.53, 54.98, 49.52, 46.24, 43.47, 41.58, 34.71, 20.86, 20.84, 20.64, 20.62.



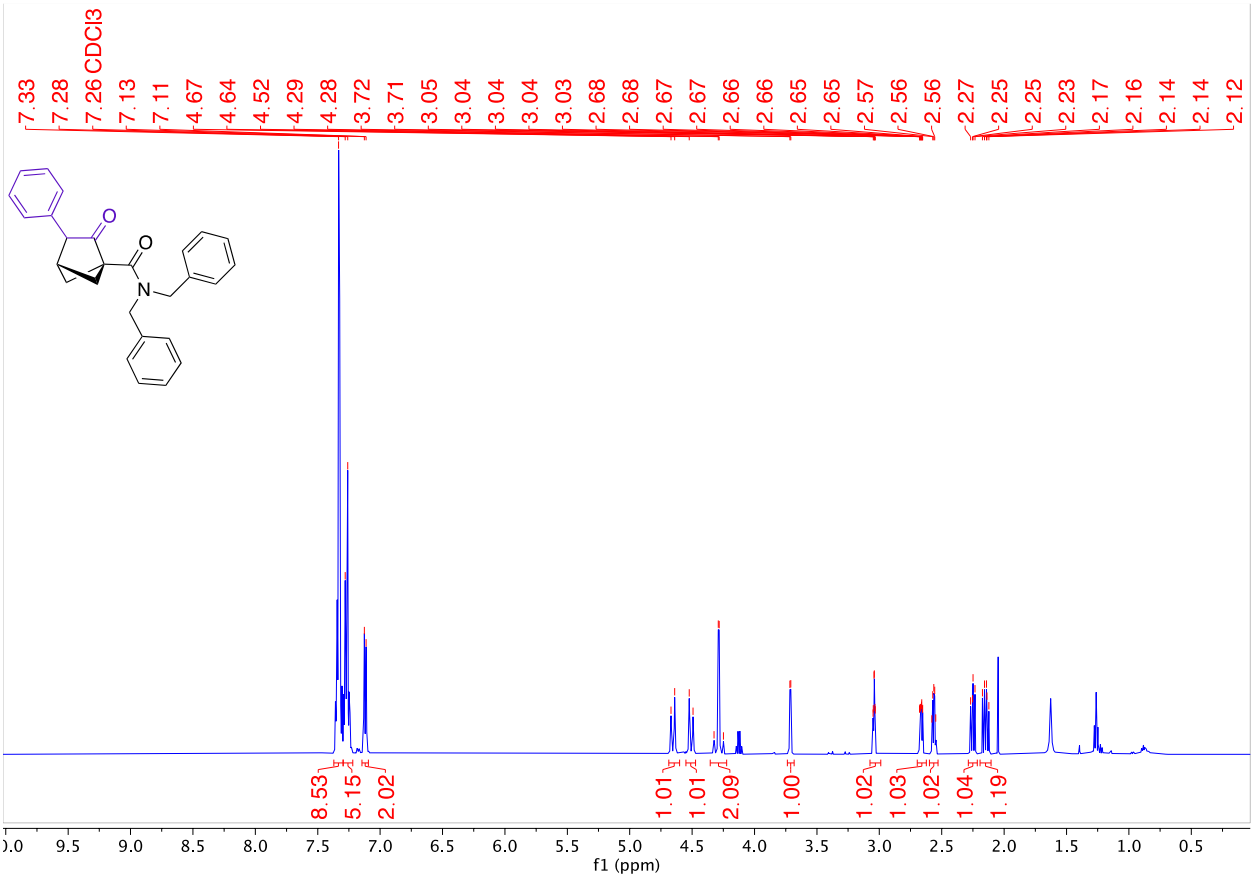
***N*,*N*-Dibenzyl-2-oxo-3-phenylbicyclo[2.1.1]hexane-1-carboxamide (3n)**



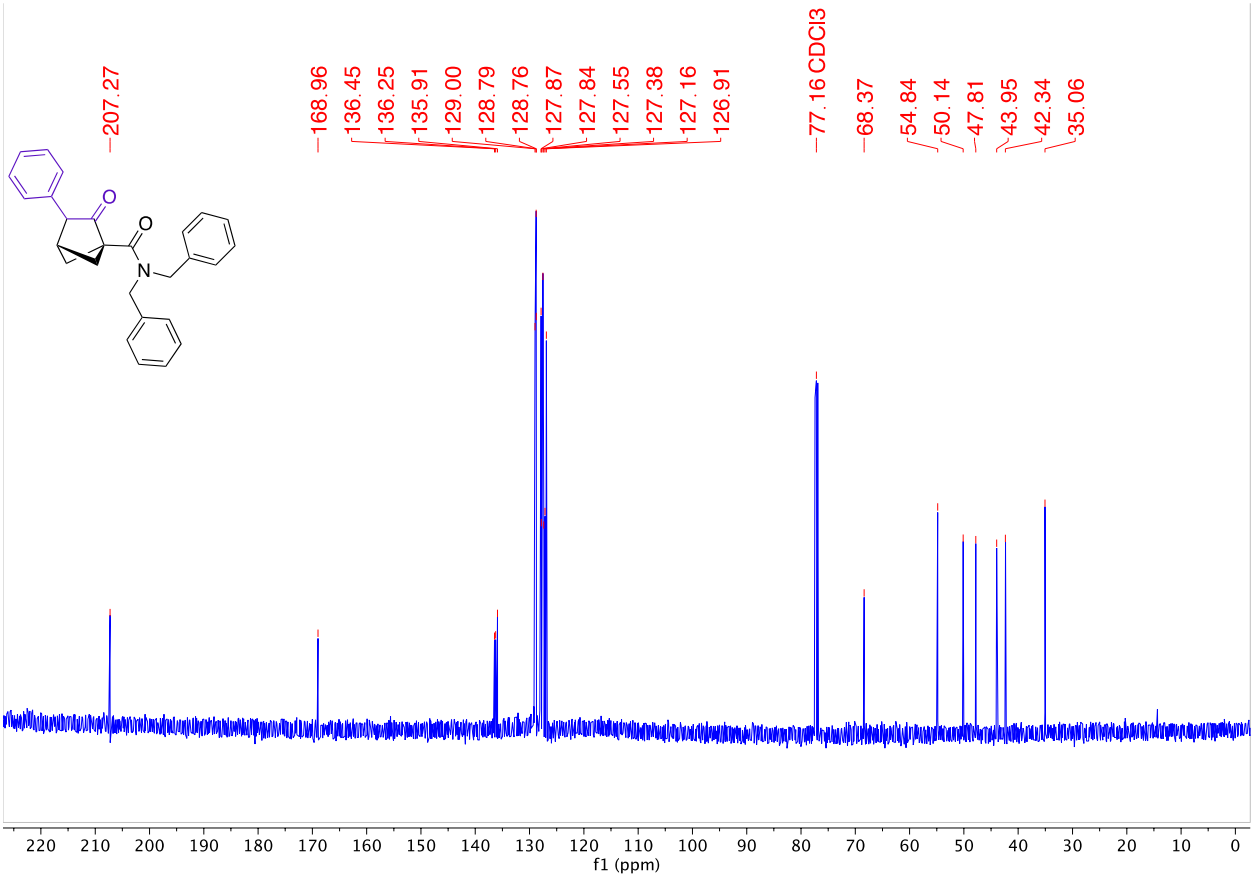
The product was prepared following the general procedure for bicyclohexane synthesis from **1n** and **2c** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 36% EtOAc). 81 mg of a clear colourless oil was obtained (68% Yield).

HRMS(ESI): calc'd for [$C_{27}H_{25}NO_2$ + H^+], 396.19581; found: 396.19583.

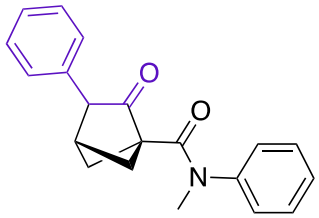
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.33 (m, 8H), 7.28 (m, 5H), 7.12 (d, J = 6.8 Hz, 2H), 4.65 (d, J = 15.1 Hz, 1H), 4.51 (d, J = 15.2 Hz, 1H), 4.29 (d, J = 3.7 Hz, 2H), 3.71 (d, J = 4.0 Hz, 1H), 3.04 (td, J = 3.7, 1.3 Hz, 1H), 2.67 (ddd, J = 7.6, 3.9, 1.0 Hz, 1H), 2.56 (dt, J = 7.8, 3.8 Hz, 1H), 2.25 (dd, J = 9.6, 7.9 Hz, 1H), 2.19 – 2.10 (m, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.27, 168.96, 136.45, 136.25, 135.91, 129.00, 128.79, 128.76, 127.87, 127.84, 127.55, 127.38, 127.16, 126.91, 68.37, 54.84, 50.14, 47.81, 43.95, 42.34, 35.06.



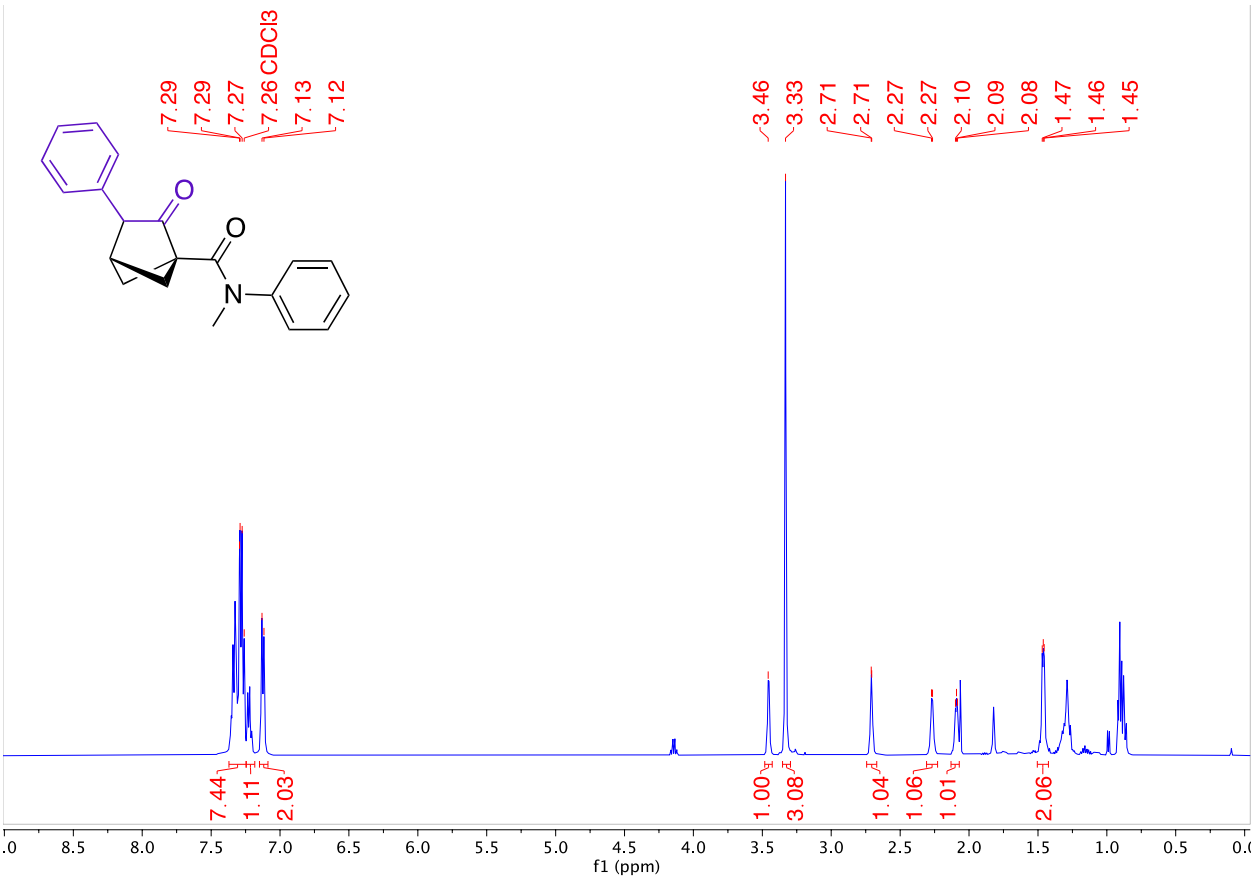
***N*-Methyl-2-oxo-N,3-diphenylbicyclo[2.1.1]hexane-1-carboxamide (3o)**



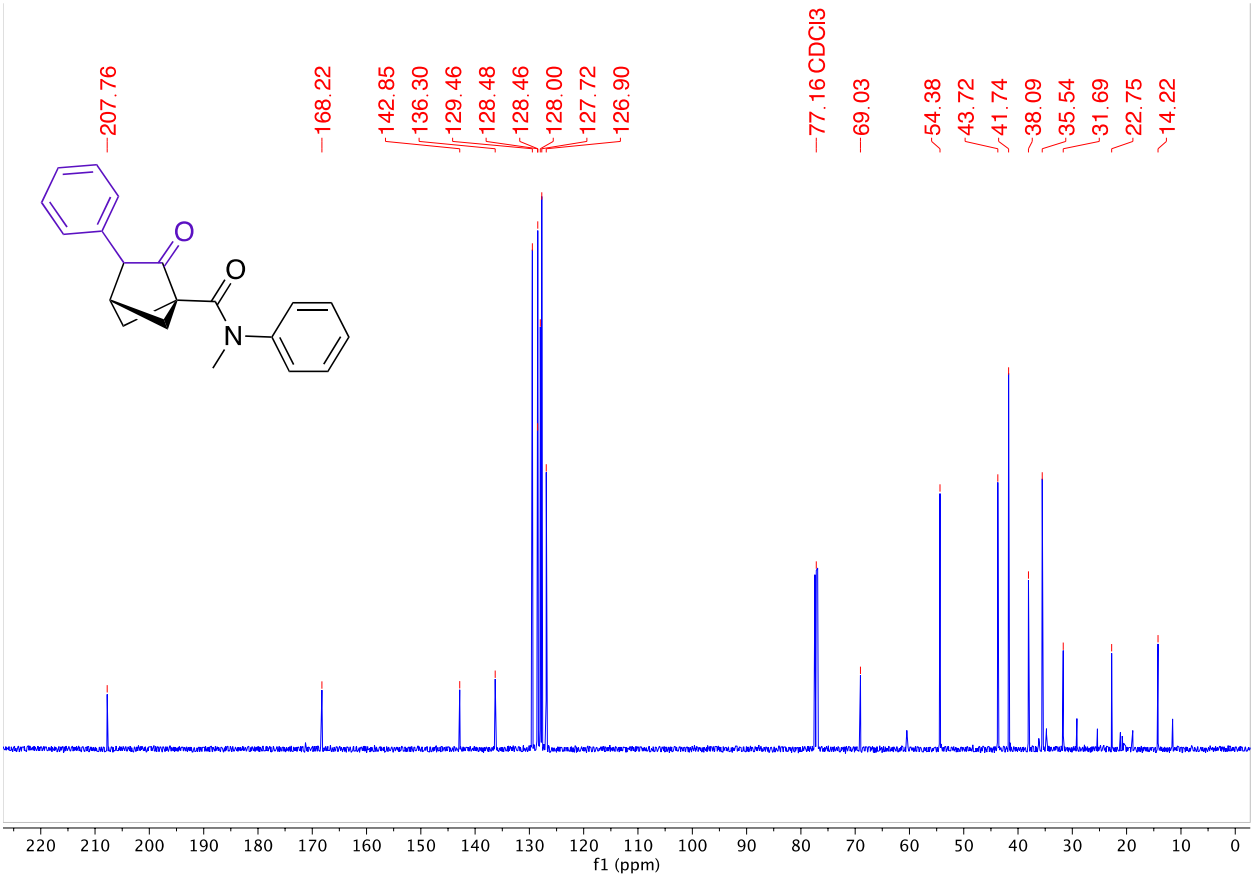
The product was prepared following the general procedure for bicyclohexane synthesis from **1o** and **2c** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 71% EtOAc). 42 mg of a clear colourless oil was obtained (46% Yield).

HRMS(ESI): calc'd for [$C_{20}H_{19}NO_2$ + H^+], 306.14886; found: 306.14879.

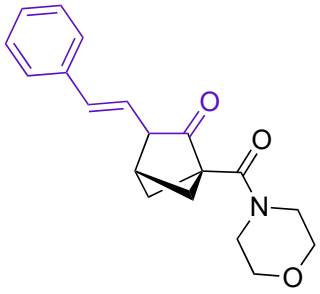
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.37 – 7.25 (m, 7H), 7.25 – 7.18 (m, 1H), 7.12 (d, J = 7.1 Hz, 2H), 3.46 (s, 1H), 3.33 (s, 3H), 2.74 – 2.67 (m, 1H), 2.27 (d, J = 3.5 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.50 – 1.42 (m, 2H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.76, 168.22, 142.85, 136.30, 129.46, 128.48, 128.46, 128.00, 127.72, 126.90, 69.03, 54.38, 43.72, 41.74, 38.09, 35.54, 31.69, 22.75, 14.22.



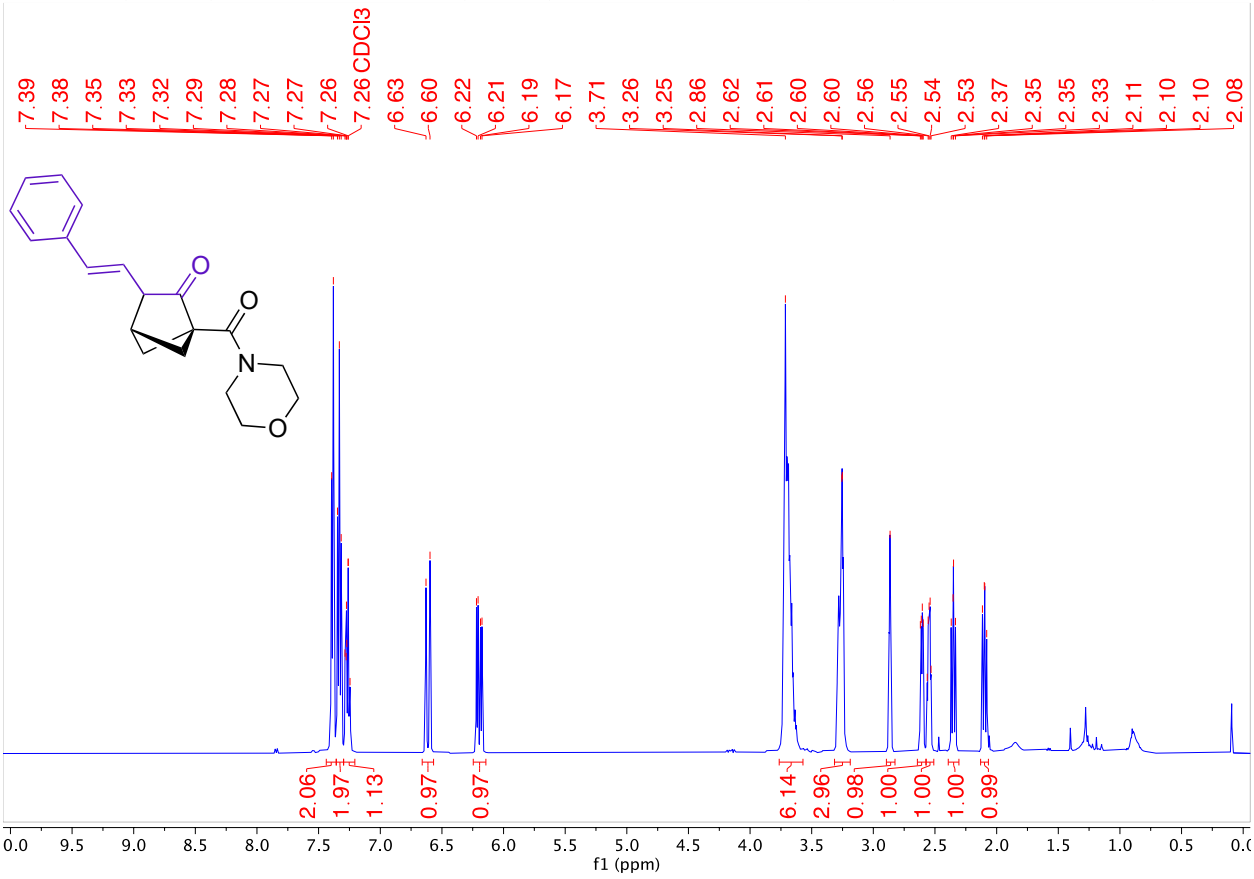
1-(Morpholine-4-carbonyl)-3-((E)-styryl)bicyclo[2.1.1]hexan-2-one (3p)



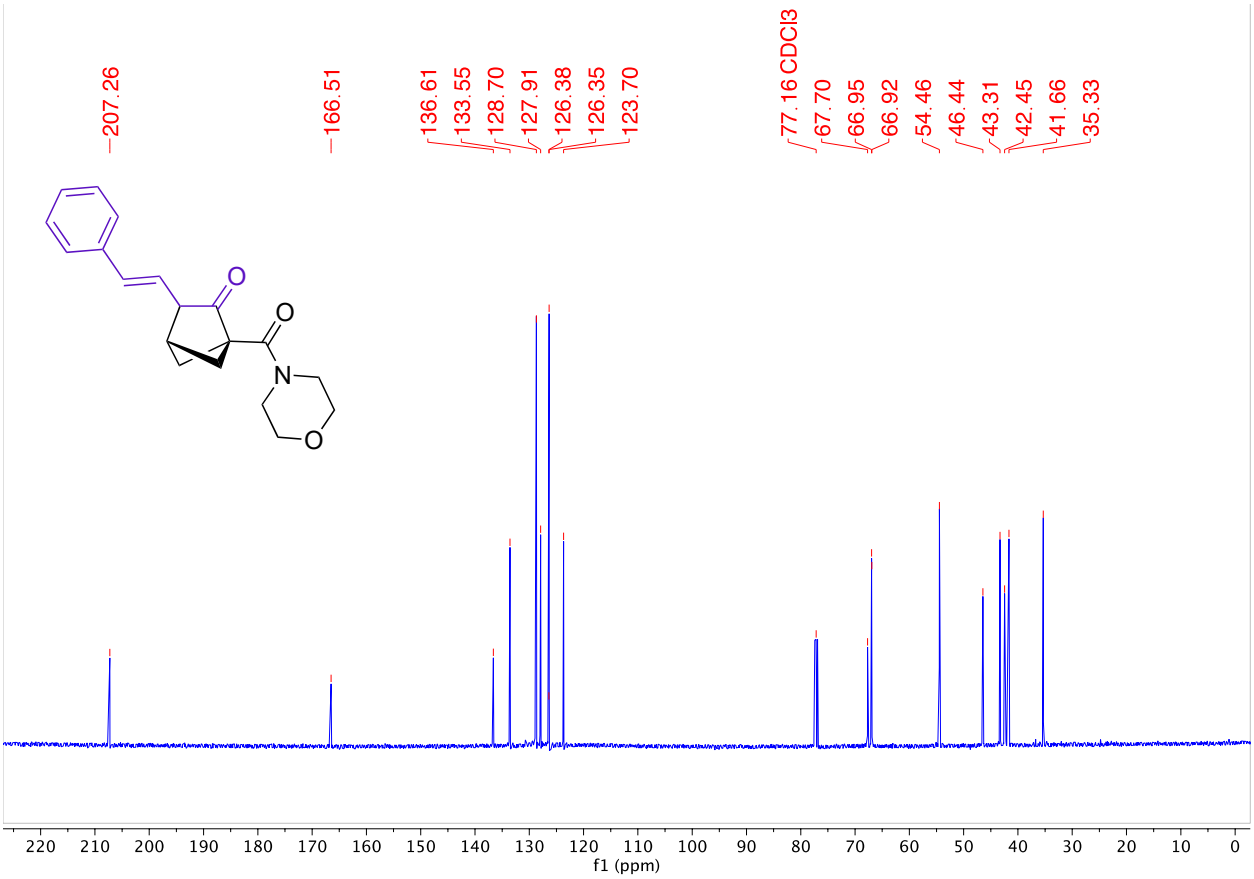
The product was prepared following the general procedure for bicyclohexane synthesis from **1a** and **2p** on a 0.30 mmol bicyclobutane scale. The compound was purified by column chromatography (Biotage® Sfär 5g Column, 0-100% EtOAc/hexanes, eluted at 50% EtOAc). 66 mg of a white solid was obtained (71% Yield).

HRMS(ESI): calc'd for [$C_{19}H_{21}NO_3$ + H^+], 312.15942; found: 312.15937.

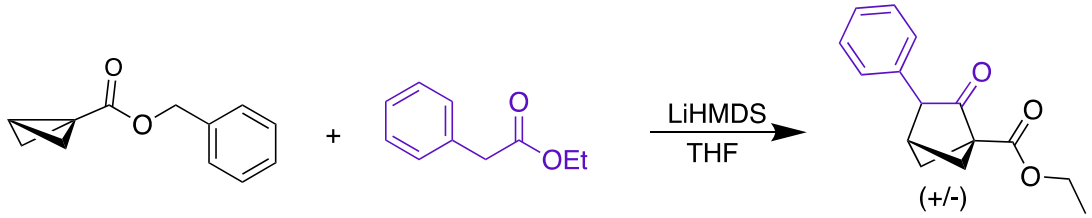
^{1}H NMR (500 MHz, $CDCl_3$, 292K) δ 7.39 (d, J = 7.3 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.27 (m, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.20 (dd, J = 16.1, 6.2 Hz, 1H), 3.71 (m, 6H), 3.25 (m, 3H), 2.86 (m, 1H), 2.61 (dd, J = 7.7, 3.8 Hz, 1H), 2.55 (dt, J = 7.7, 3.8 Hz, 1H), 2.35 (dd, J = 9.5, 7.8 Hz, 1H), 2.10 (dd, J = 9.5, 7.6 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 207.26, 166.51, 136.61, 133.55, 128.70, 127.91, 126.35, 123.70, 67.70, 66.95, 66.92, 54.46, 46.44, 43.31, 42.45, 41.66, 35.33.



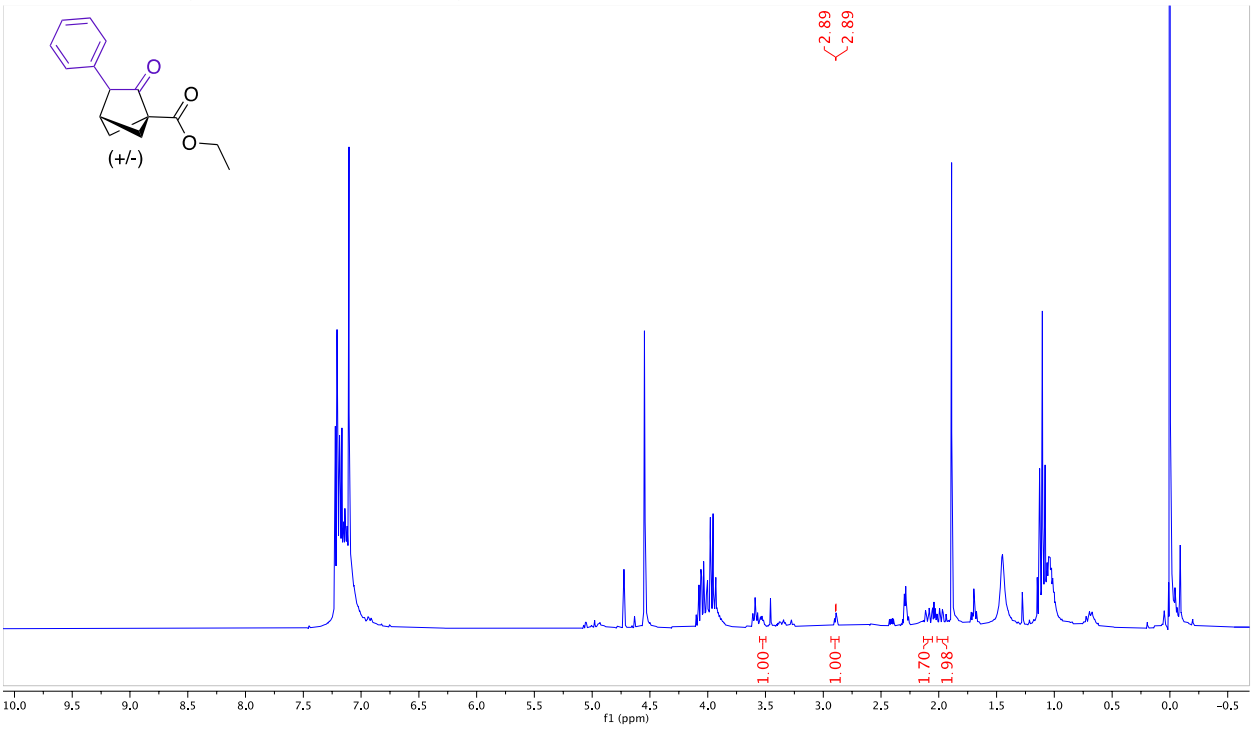
Synthesis of bicyclo[2.1.1]hexane with a benzyl ester bicyclobutane derivative



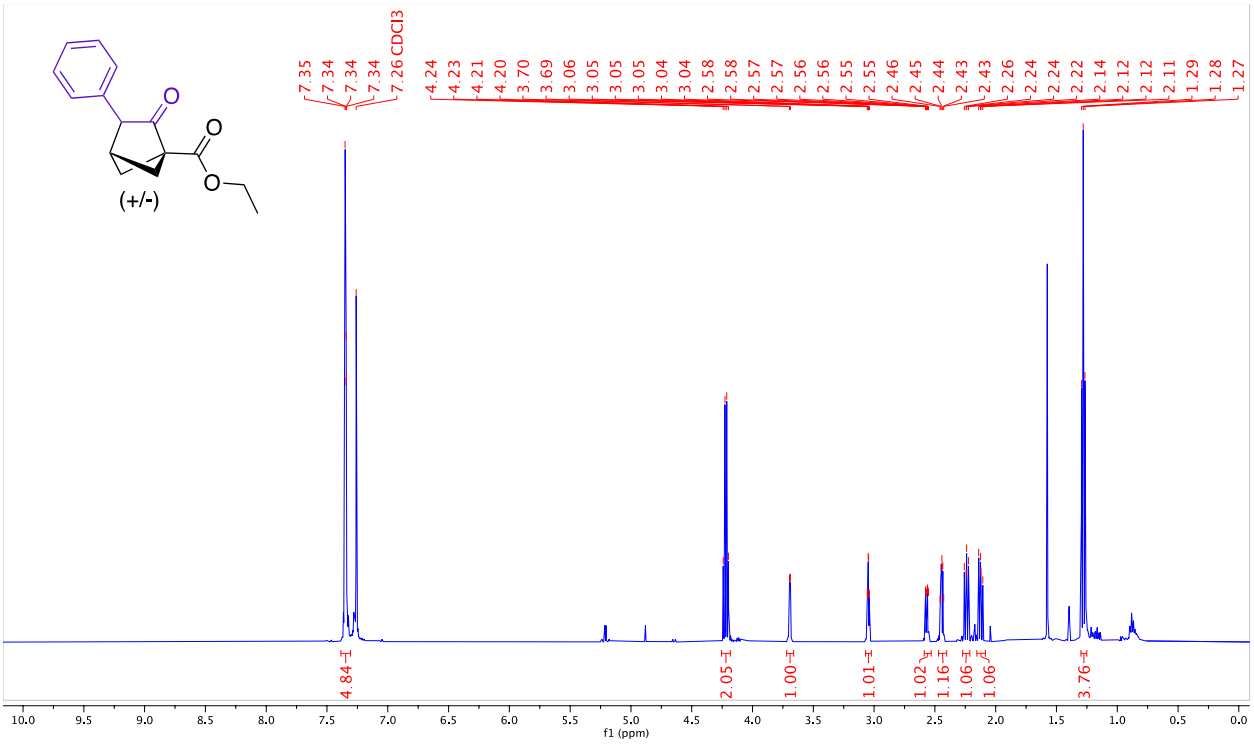
The benzyl ester bicyclobutane and aryl enolate were used following the general procedure for bicyclohexane synthesis from **1p a**nd **2c** on a 0.70 mmol bicyclobutane scale. With the ester on the bicyclobutane, side reactions with the enolate and intermediates resulted a low solution yield and formation of multiple products, with only the ethyl ester product shown (due to transesterification of the benzyl ester with the ethoxide byproduct of the reaction). The ethyl ester product was purified by column chromatography (Biotage® Sfär 10g Column, 0-100% EtOAc/hexanes, eluted at 8% EtOAc). 21 mg of a clear colourless oil was obtained (12% Yield).

HRMS(ESI): calc'd for [$C_{15}H_{16}O_3$ + Na^+], 267.09916; found: 267.09924.

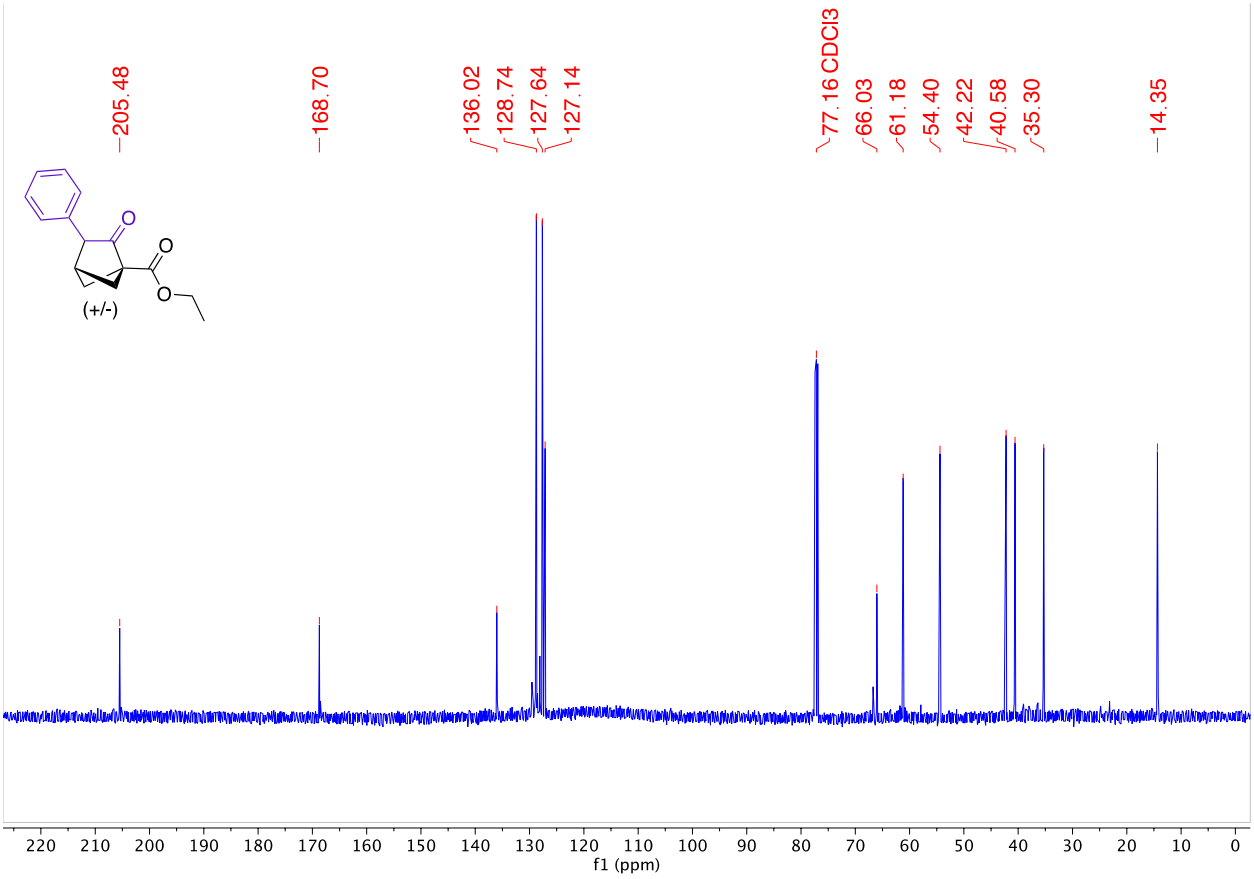
Crude ^{1}H NMR (300 MHz, $CDCl_3$, 292K):



^{1}H NMR (500 MHz, $CDCl_3$, 292K): δ 7.39 – 7.31 (m, 5H), 4.22 (q, J = 7.1 Hz, 2H), 3.69 (d, J = 3.6 Hz, 1H), 3.05 (td, J = 3.7, 1.4 Hz, 1H), 2.56 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 2.44 (dt, J = 7.7, 3.8 Hz, 1H), 2.24 (dd, J = 9.4, 7.8 Hz, 1H), 2.12 (dd, J = 9.4, 7.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 4H).

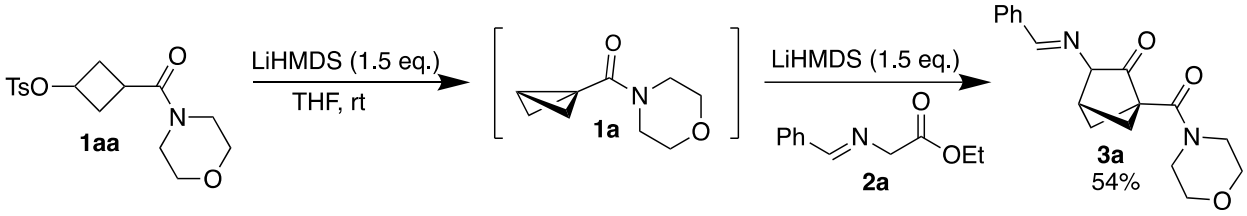


^{13}C NMR (126 MHz, $CDCl_3$, 292 K, ppm): δ 205.48, 168.70, 136.02, 128.74, 127.64, 127.14, 66.03, 61.18, 54.40, 42.22, 40.58, 35.30, 14.35.

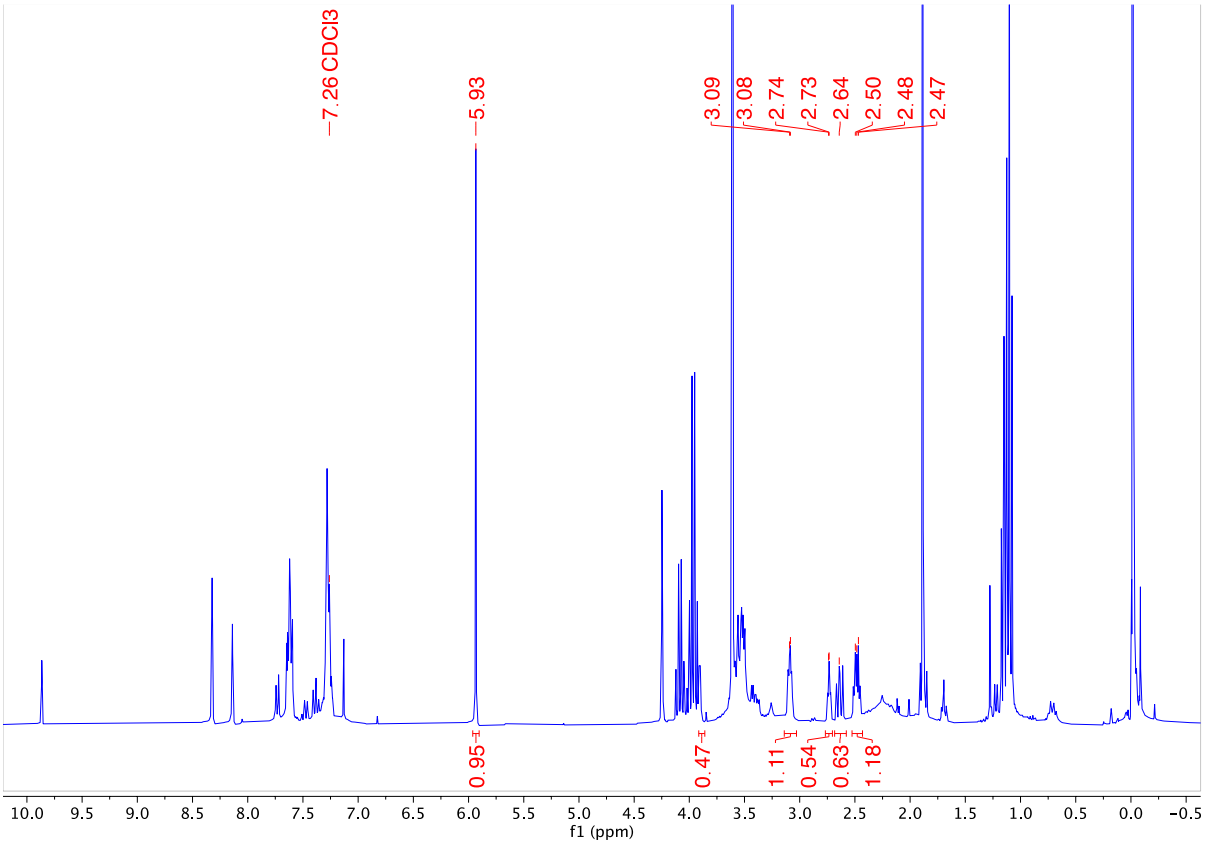


VI: Additional Reactions

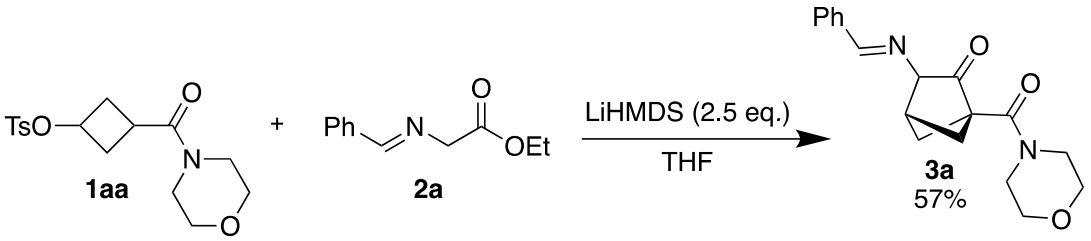
Telescoped synthesis of bicyclohexane 3a:



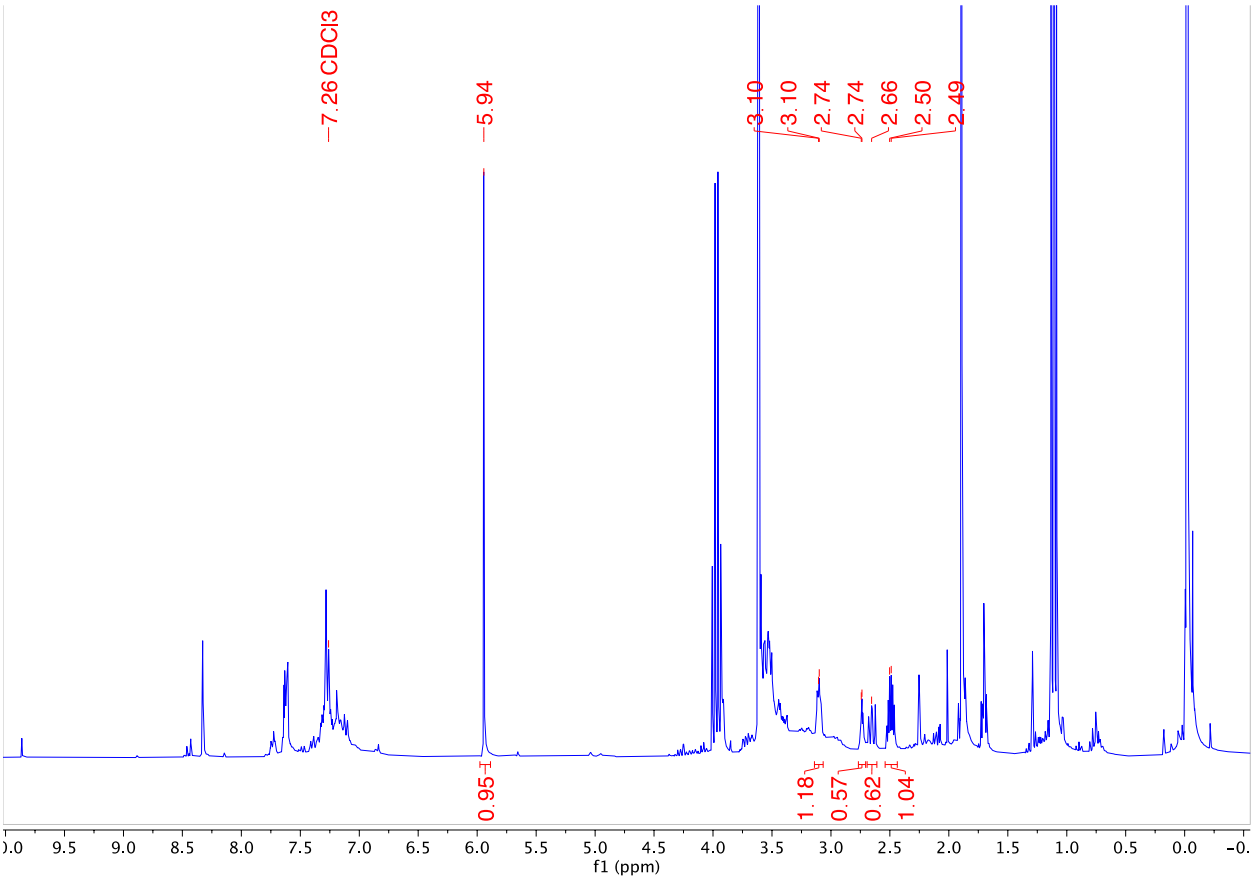
In one vial, 3-(morpholine-4-carbonyl)cyclobutyl 4-methylbenzenesulfonate (33.9 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (5.6 mg, 0.33 eq.) were added and dissolved in 50% of the THF solvent (1 mL total, 0.10 M) under a nitrogen atmosphere. LiHMDS (1.0M in THF, 0.15 mL, 1.5 eq.) was added to the vial and it was left to stir for 15 minutes at room temperature. In another vial, the imine **2a** (68.8 mg, 1.2 eq.) was dissolved in 50% of the THF solvent. LiHMDS (1.0M in THF, 0.15 mL, 1.5 eq.) was added to the imine vial and left to stir for 10 minutes at room temperature. The two vials were then cooled in the freezer for 10 minutes followed by a dropwise addition of the BCB vial to the enolate vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate 3 times. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 54% product (2.74 ppm peak).



All-at-once one pot synthesis of bicyclohexane 3a:

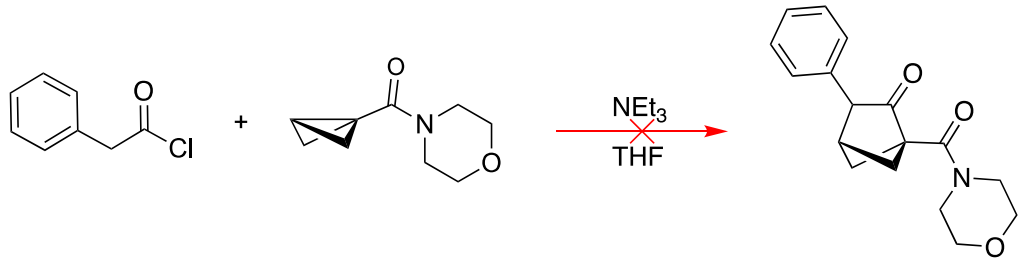


In one vial, the 3-(morpholine-4-carbonyl)cyclobutyl 4-methylbenzenesulfonate (101.8 mg, 0.30 mmol) and 1,3,5-trimethoxybenzene (16.8 mg, 0.33 eq.) were added. In another vial, the imine **2a** (68.8 mg, 1.2 eq.), was added and the vials were put under a nitrogen atmosphere in the glovebox. 50% of the THF solvent (2 mL total, 0.15 M) was added to the tosylated cyclobutane and 50% of the THF was added to the imine vial. LiHMDS (1.0M in THF, 0.75 mL, 2.5 eq.) was added to the imine vial and left to stir for 10 minutes at room temperature. The two vials were then cooled in the freezer for 10 minutes followed by a dropwise addition of the tosylated cyclobutane to the enolate vial. The reaction was left to stir for 24 hours at room temperature. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate 3 times. The organic layers were dried with Mg_2SO_4, filtered and the solvent was evaporated. The amounts of product and starting materials were determined by NMR relative to the internal standard (1,3,5-trimethoxybenzene). 57% product (2.74 ppm peak).

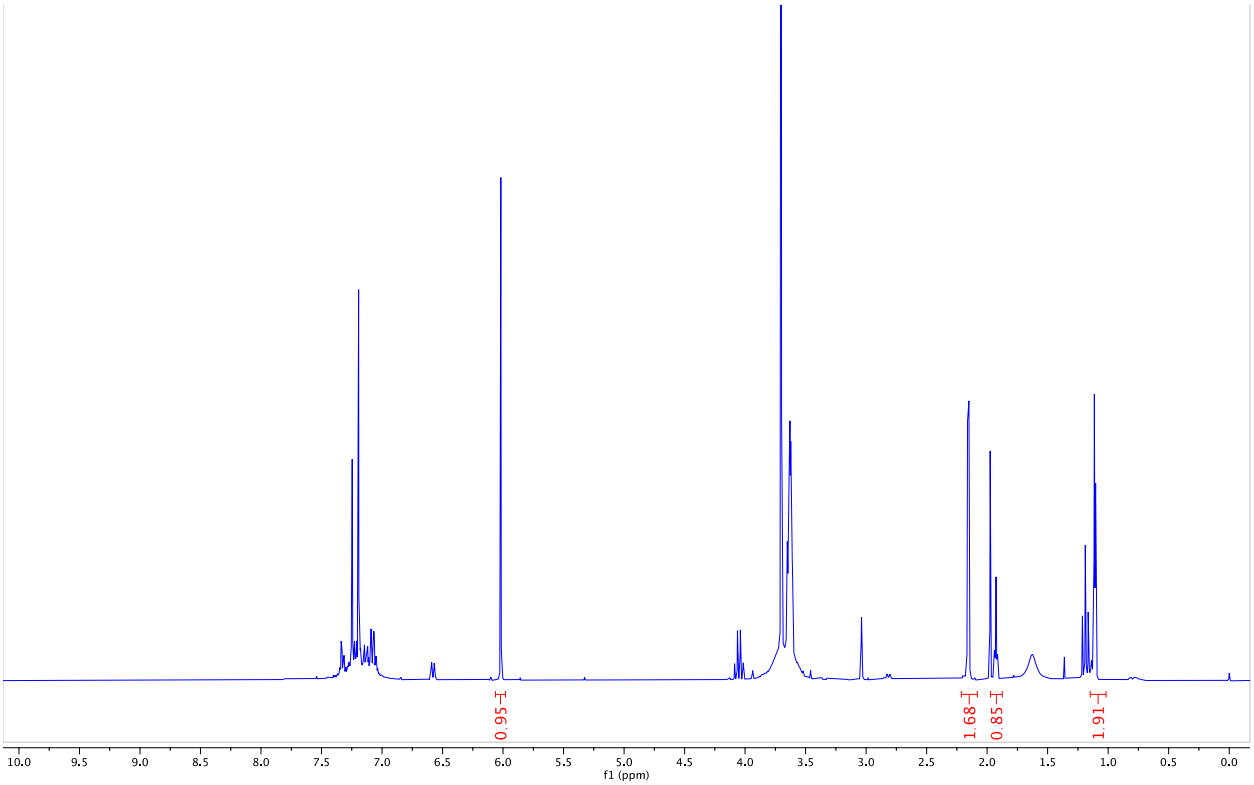


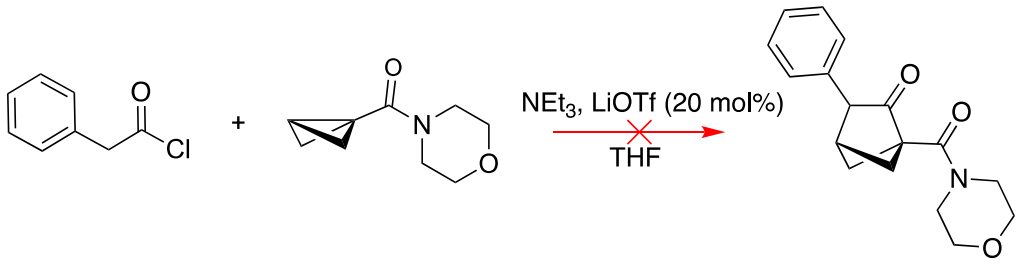
Test for ketene addition to bicyclobutanes:

To test if the mechanism proceeds through a ketene addition to the bicyclobutane, phenyl acetyl chloride was reacted with triethylamine and the bicyclobutane with or without the presence of LiOTf in THF at room temperature as follows:

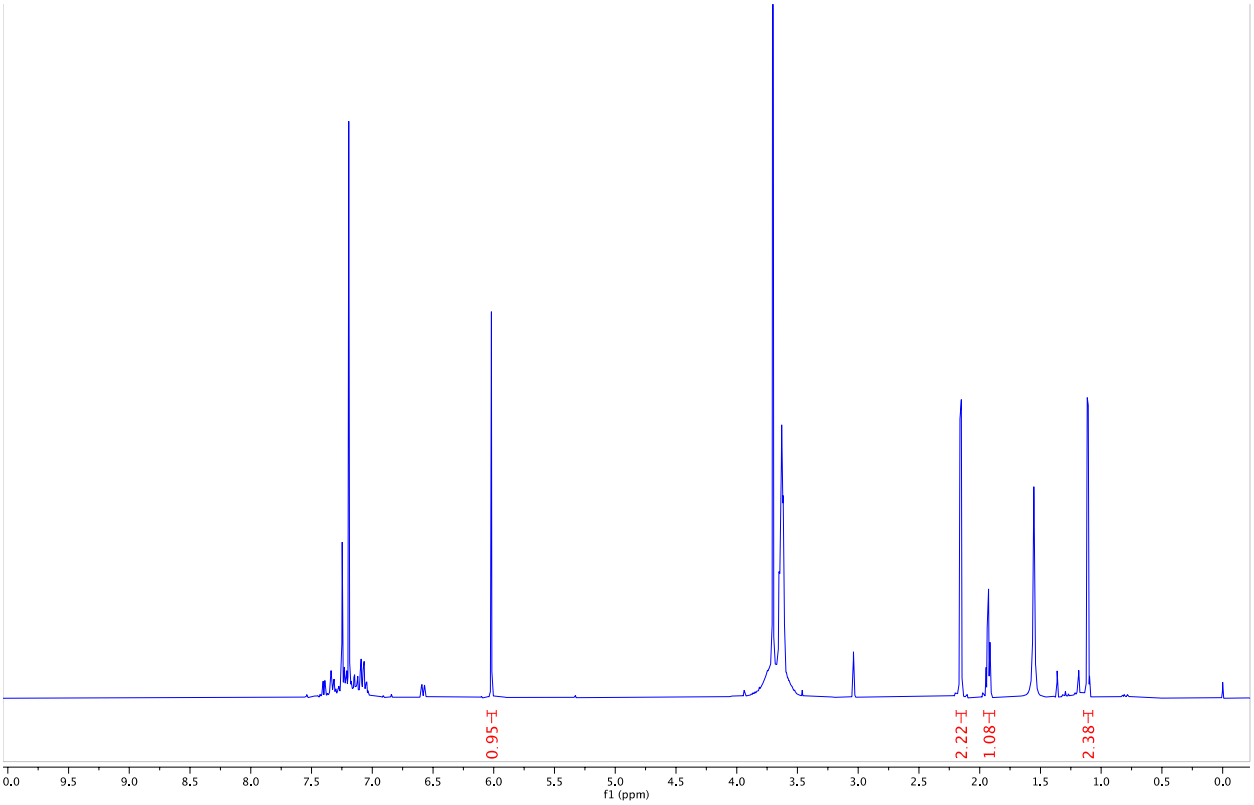


In one vial, phenyl acetyl chloride (7.9 μL, 1.2 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and dissolved in 50% of the THF solvent (0.17 mL total, 0.30 M) under a nitrogen atmosphere. Triethylamine (10.5 μL, 1.5 eq.) was added to the vial and it was left to stir for 5 minutes at room temperature. In another vial, the bicyclobutane **1a** (8.4 mg, 1 eq., 0.05 mmol) was dissolved in 50% of the THF solvent. The two vials were then cooled in the freezer for 10 minutes followed by a dropwise addition of the BCB vial to the ketene vial. The reaction was left to stir overnight at room temperature. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried with Mg_2SO_4, filtered and the solvent was evaporated. Decomposition of the phenyl acetyl chloride was observed and no bicyclohexane product was formed.





In one vial, phenyl acetyl chloride (7.9 μL, 1.2 eq.) and 1,3,5-trimethoxybenzene (2.8 mg, 0.33 eq.) were added and dissolved in 33% of the THF solvent (0.26 mL total, 0.2 M) under a nitrogen atmosphere. Triethylamine (10.5 μL, 1.5 eq.) was added to the vial and it was left to stir for 5 minutes at room temperature. In another vial, the bicyclobutane **1a** (8.4 mg, 1 eq., 0.05 mmol) was dissolved in 33% of the THF solvent. The two vials were then cooled in the freezer for 10 minutes followed by a dropwise addition of the BCB vial to the ketene vial. LiOTf was dissolved in 33% of the THF solvent and then added to the reaction mixture. The reaction was left to stir overnight at room temperature. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried with Mg_2SO_4, filtered and the solvent was evaporated. Decomposition of the phenyl acetyl chloride was observed and no bicyclohexane product was formed.



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