SUPPORTING INFORMATION

γ-Lactam Synthesis via C-H Insertion: Elaboration of *N*-Benzyl Protecting Groups for High Regioselectivity toward the Total Synthesis of Rolipram

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1. Preparation of α-(phenylsulfonyl)acetamide from secondary amine

To a solution of a secondary amine (10 mmol) and TEA (1.7 mL, 12 mmol) in dry CH_2Cl_2 (20 mL, C = 0.5 M), was slowly added α-bromoacetyl bromide (0.96 mL, 11 mmol) at 0 °C. The mixture was stirred briefly at 0 °C and then at r.t. for 1 h. The reaction mixture was washed with 1 N HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with sat'd $NaHCO_3$ solution, followed by brine, dried over Na_2SO_4, filtered, and concentrated to give an α-bromoacetyl amide, which was used for the next reaction without further purification.

To a solution of a crude α-bromoacetyl amide (10 mmol) in DMF (50 mL, C = 0.2 M), was added benzenesulfinic acid sodium salt (1.8 g, 11 mmol). The reaction mixture was stirred for 1 h at r.t. and was poured into EtOAc. The mixture was washed three times with water, then once with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed to give α-(phenylsulfonyl)acetamide (combined yield 80 - 85%).

2. Diazo transfer reaction of α-(phenylsulfonyl) acetamide

To a mixture of a α-(phenylsulfonyl)acetamide (5.0 mmol) and *p*-acetamidobenzenesulfonyl azide (ABSA)[1] (1.3 g, 5.5 mmol) in dry CH_3CN (25 mL, C = 0.2 M), was slowly added DBU (1.7 mL, 11 mmol) at 0 °C. The resulting mixture was stirred for 30 min at r.t., and the solvent was evaporated. The residue was diluted with Et_2O, and the mixture was washed successively with 1 N NaOH, water, and brine. The yellow organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed to give α-diazo-α-(phenylsulfonyl)acetamide (85 - 90% yield).

3. General procedure for the C-H insertion reaction of α-diazo-α-(phenylsulfonyl)acetamide

1. For the preparation of ABSA, see: Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93.

To a solution of an α-diazo-α-(phenylsulfonyl)acetamide (1 mmol) in dry CH_2Cl_2 or $ClCH_2CH_2Cl$, was added $Rh_2(OAc)_4$ (11 mg, 2.5 mol%). The mixture was refluxed for 12 h under N_2, cooled to r.t., and concentrated. The residue was chromatographed to give β-lactam and/or γ-lactam.

4. Deprotection of 4-Methoxybenzyl group of β-lactam 30

A mixture of β-lactam **30** and cerium ammonium nitrate in CH_3CN and water was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed to give *N*-4-methoxybenzyl deported β-lactam.

5. Synthesis of Rolipram

[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-ethyl]-(2,4,6-trimethyl-benzyl)-amine (48): Anhydrous Na_2SO_4 (4 g) was added into a solution of primary amine **47** (2.0 g, 8.5 mmol) and mesitaldehyde (1.35 g, 9.0 mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 30 minutes, filtered and concentrated in vacuo to give crude imine compound. The crude imine was dissolved in MeOH (42 mL) and cooled to 0 °C. $NaBH_4$ (0.62 g, 17 mmol) was added in portions and the reaction was further stirred for 30 minutes. MeOH was removed in vacuo and the residue was portioned with EtOAc and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed to yield secondary amine **48** as colorless oil (2.34 g, 75%).

2-Benzenesulfonyl-N-[2-(3-cyclopentyloxy-4-methoxy-phenyl)-ethyl]-2-diazo-N-(2,4,6-trimethyl-benzyl)-acetamide (49): Following the general procedures, diazo compound **49** was obtained from **48** in 3 steps.

3-Benzenesulfonyl-4-(3-cyclopentyloxy-4-methoxy-phenyl)-1-(2,4,6-trimethyl-benzyl)-pyrrolidin-2-one (50): Following the general procedure, γ-lactam **50** was obtained from diazo compound **49** in 75% yield.

Rolipram (8): A solution of γ-lactam **50** (100 mg, 0.18 mmol) was dissolved in anhydrous THF and cooled to −78 °C under N_2 atmosphere. NH_3 was then bubbled through the flask till 10 mL was collected. Excess lithium was added into the reaction mixture and stirred until the dark blue color was regained. Reaction was quenched with solid NH_4Cl. NH_3 was removed by allowing the reaction to warm to room temperature. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed to give rolipram **(8)** as white solid (45 mg, 90%).

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Ph
Ph
PhO2S

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Ph
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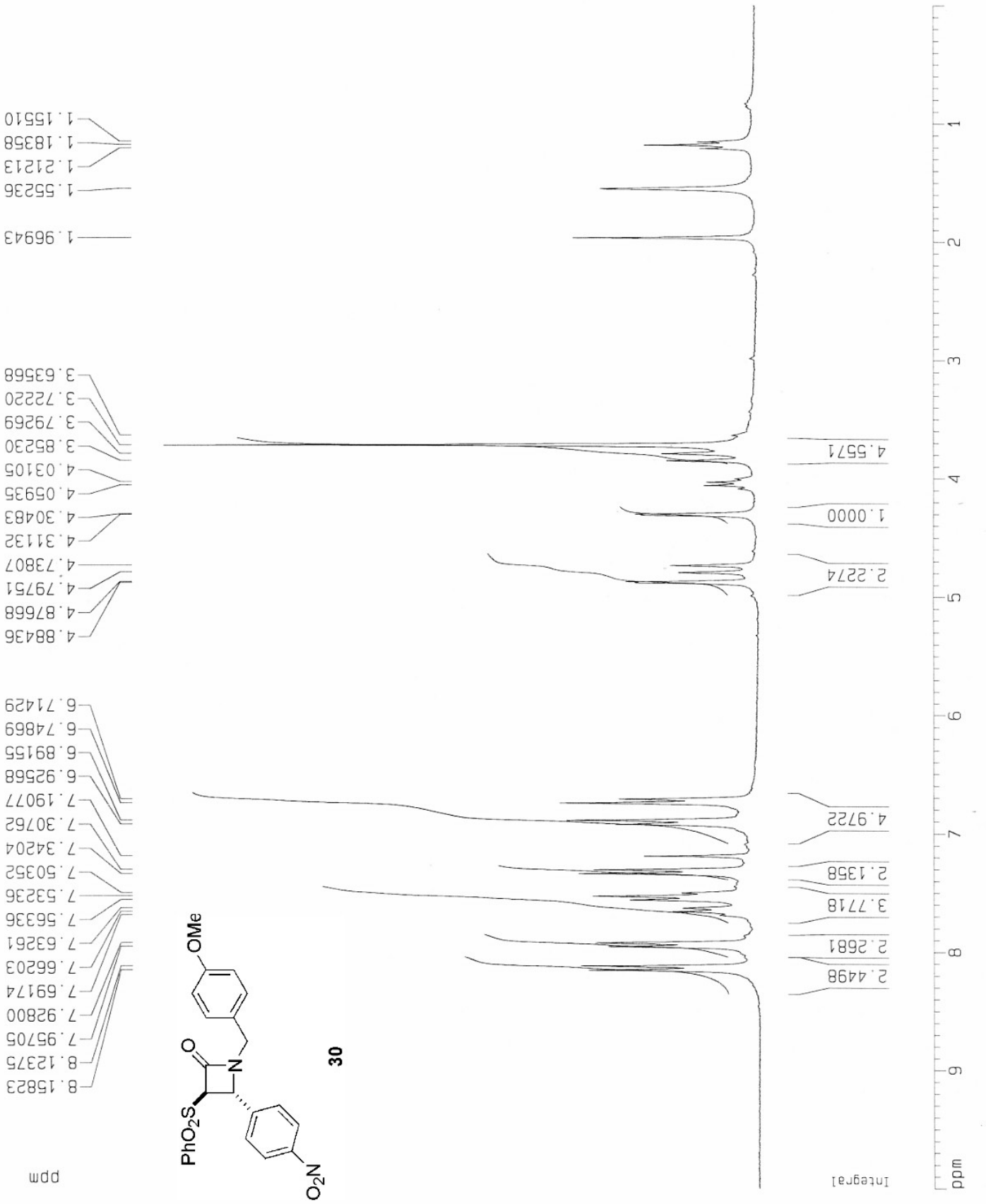
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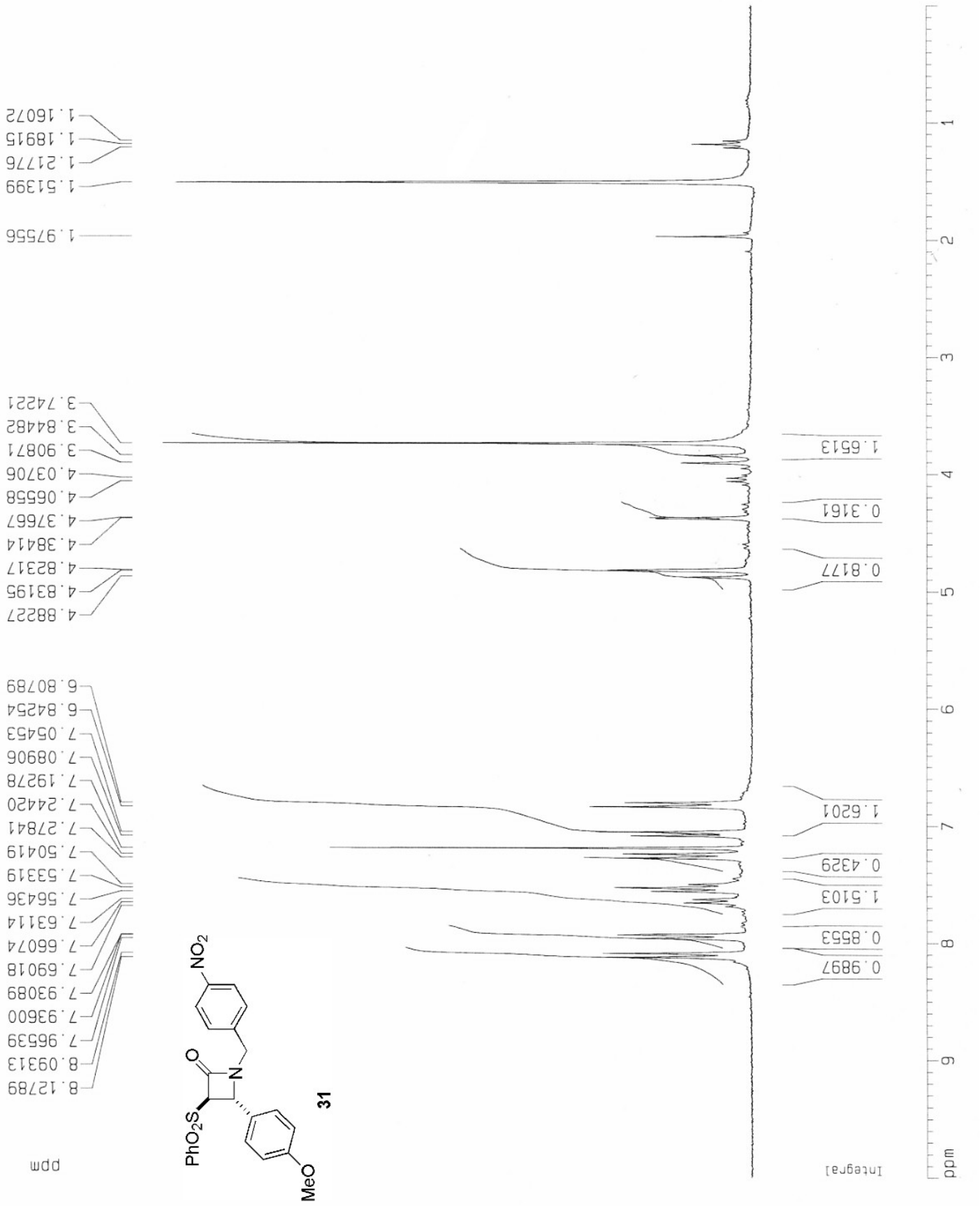
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ppm
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