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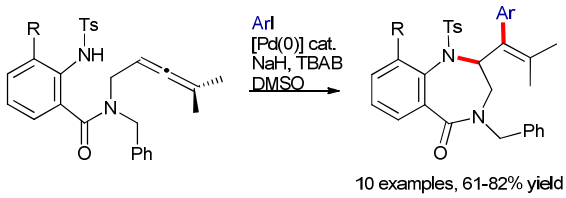

10 examples, 61-82% yield

Graphical Abstract

Synthesis of 1,4-benzodiazepinones via palladium-catalysed allene carbopalladation / amination domino sequence

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N-allenyl anthranyl amides and aryl iodides react to give vinyl-substituted benzodiazepinones. This new Pd-catalyzed domino sequence involves a C-C followed by an N-C bond formation.

Highlights

Aryl iodides are required for a successful outcome of the reaction.
This Pd-catalysed domino sequence involves a C-C and an N-C bond formation.
The protection of the amino group was necessary for the Pd-catalysed domino reaction.

Synthesis of 1,4-benzodiazepinones via palladium-catalysed allene carbopalladation / amination domino sequence

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Dedication

Dedicated to Professor Maria José Calhorda in occasion of her 65th birthday.

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Abstract

Vinyl-substituted 1,4-benzodiazepinones were obtained in good yields (10 examples, 61-82% yield) via the reaction between *N*-allenyl anthranyl amides and aryl iodides under Pd(0) catalysis. This new single cycle catalytic domino transformation involves a C-C followed by an N-C bond formation.

Keywords

palladium

allene

domino reactions

carbopalladation

amination

1,4-benzodiazepinones

1. Introduction

Since the discovery of chlordiazepoxide, by L. Sternbach, in the mid fifties, 1,4-benzodiazepines became one of the most popular heterocyclic structures in the history of drugs [1]. The benzodiazepine motif, found incorporated into a number of pharma molecules such as CNS drugs [2], antibiotics [3], antithrombotics [4], anti-HIV drugs [5], as well as peptidomimetics [6] is nowadays considered as a privileged structure [7].

In particular, the sub-set of 1,4-benzodiazepin-5-ones occupies an important role in medicinal chemistry [8]. For example, tri- as well as tetra-cyclic systems containing the 1,4-diazepin-5-one motif proved to be useful candidates for a wide array of therapeutic applications [9,10]. The antihistaminic property of tarpane [11], the antibiotic activity of abbeymycin [12], the anti-anxiety effect of flumazenil [13] and the anti-neurodegenerative activity of bretazenil [14] represent remarkable examples (Figure 1).

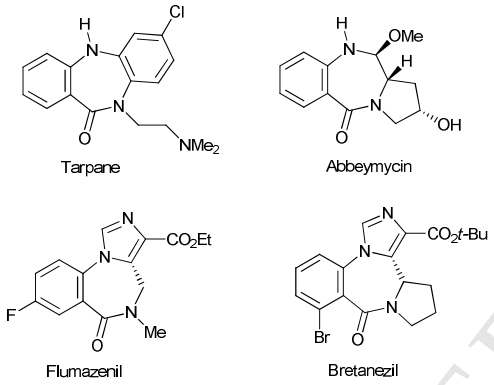


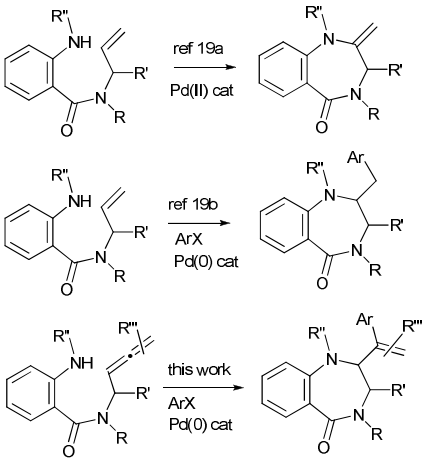
Figure 1. Some examples of pharmacologically active polycyclic 1,4-benzodiazepinones.

Appropriate structural modifications of the above structures may lead to new analogues endowed with interesting biological activities. Accordingly, the search for novel synthetic approaches toward such heterocyclic structures is highly desirable.

Most of the reported methods to prepare 1,4-benzodiazepin-5-ones start from the readily available isatoic anhydride [15]. Although useful solid supported variants of this approach have been reported [16], these methods either require harsh pre-functionalisation conditions, or are not atom economical.

In the context of our ongoing research directed toward the synthesis of heterocycles via transition metal-catalysis, we recently directed our interest toward allenes [17]. These previous studies led us to envision *N*-allenyl anthranil amides as suitable substrates for the synthesis of α-styryl-substituted 1,4-benzodiazepin-5-ones via a pure domino [18] Pd(0)-

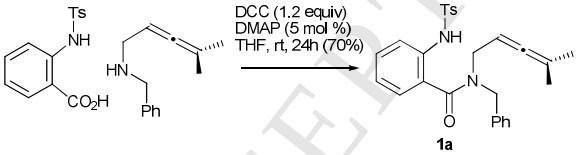
catalysed carbopalladation / allylic amination process. This plan proved successful and the present article describes details about this new strategy that widens the existing palladium-based approaches toward 1,4-benzodiazepin-5-ones (Scheme 1) [19].



Scheme 1. Previously reported Pd-catalysed syntheses of 1,4-benzodiazepin-5-ones and the present approach.

2. Results and discussion

The required *N*-allenyl amide cyclization precursor **1a** was first prepared by DCC promoted condensation between *N*-benzyl-(4-methylpenta-2,3-dienyl)-amine [17f] and *N*-tosyl anthranilic acid [20] under standard conditions (Scheme 2) [21].

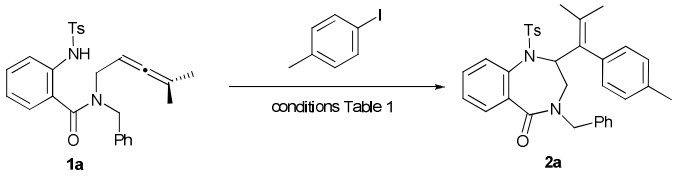


Scheme 2. Generation of the starting cyclization precursor.

Coupling between **1a** and 4-iodotoluene (1.2 equivalents) to give the benzodiazepine **2a** was chosen as model reaction to investigate the planned carbopalladation / amination sequence (Table 1).

Table 1

Optimization of the ring closing coupling between *N*-allenylamide **1a** and 4-iodotoluene to give 1,4-benzodiazepin-5-one **2a**.



Entry	Catalytic system[a]	Base	T (°C)	Additive (20%)	Solvent (0.05 M)	Ligand	Conversion (%)[b]	Yield (%)[c]
1	A	NaH (1.2 eq.)	rt,[d] 55[e]	TBAB	DMSO	-	84	46
2	B	NaH (1.2 eq.)	50	-	CH_3CN	dppf (10%)	75	27
3	A	Cs_2CO_3 (2 eq.)	50	TBAB	DMSO	-	6	n.i.[f]
4	A	K_2CO_3 (2 eq.)	50	TBAB	DMSO	-	20	n.i.
5	A	K_2CO_3 (2 eq.)	90	TBAB	DMSO	-	20	n.i.
6[g]	A	NaH (1.2 eq.)	50,[d] 90[e]	TBAB	DMSO	-	100	82
7	A	-	90	TBAB	DMSO	-	0	-

[a] Catalytic system A: $Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%); catalytic system B: $Pd(OAc)_2$ (5%). [b]Consumption of **1a** as determined by ^1H NMR spectroscopy. [c] Yields refer to isolated yields. [d]Temperature for deprotonation of 1. [e]Temperature for the cyclization reaction. [f]not isolated. [g]Flask 1: **1a** (1.0 equiv.)/NaH (1.2 equiv.), DMSO, 50°C, 10 min. Flask 2: a) $Pd(CH_3CN)_2Cl_2$ (5 mol%), DMSO, *n*-BuLi (10 mol %); b) ArI (1.2 equiv.), TBAB (20 mol%). Then, flask 2 into flask 1, 90 °C.

First, we investigated the feasibility of the reaction employing phosphine-free conditions. This protocol was recently reported by some of us for the synthesis of γ-lactams via carbopalladation / allylation of allenyl substrates [22, 17a]. Accordingly, the catalytically active palladium species was generated by the addition of BuLi (10 mol%) to a solution of $Pd(CH_3CN)_2Cl_2$ (5 mol%) in DMSO. Then, 4-iodotoluene (1.2 equiv.), tetrabutyl ammonium bromide (TBAB) (20 mol%) and a DMSO solution of the sodium amidate were added in sequence (Entry 1). Although the conversion of the substrate was satisfactory, the expected benzodiazepinone **2a** was isolated in only moderate yields. Switching to $Pd(OAc)_2$ / dppf as catalytic system in acetonitrile, decreased dramatically the substrate conversion (Entry 2). We thus decided to come back to the ligandless protocol, optimizing bases and temperatures. The use of Cs_2CO_3 or K_2CO_3 was nearly ineffective either at 50 °C or at 90°C (entries 3-5). Conversely, deprotonation of the allenylamide with NaH at 50 °C followed by heating at 90

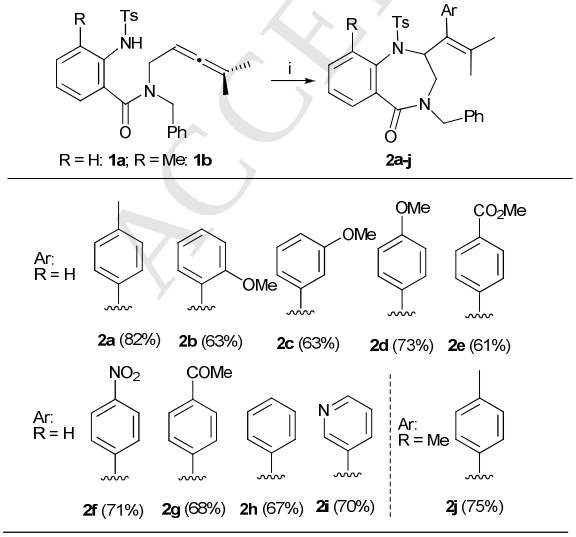
°C after the addition of the remaining reagents brought about a complete conversion together with a remarkable increase of the yield (entry 6). Finally, a blank experiment omitting NaH gave no product, thereby confirming the crucial role of that base for the success of the reaction (entry 7).

With the optimized ligandless conditions in hand, the scope of the domino sequence was next examined on 0.1 mmol scale reactions, reacting **1a** with various aryl iodides (Table 2). Electron-rich 2-, 3- and 4-iodoanisoles reacted smoothly, affording the expected corresponding benzodiazepinones **2b-d** in 63%, 63% and 73%, respectively. The reaction of electron poor aryl iodides such as those bearing *para* positioned methoxycarbonyl, nitro, and acetyl functions gave products **2e-g** in satisfactory yields (61%, 71% and 68%, respectively). The use of simple iodobenzene led to the expected benzodiazepinone **2h** in 67% yield. The heteroaromatic halide 3-iodopyridine afforded the expected product **2i** in 70% yield. Finally, the same protocol well sustained substitutions on the aromatic ring. Indeed, the *N*-allenyl 3-methyl anthranyl amide **1b** afforded uneventfully benzodiazepinone **2j** (75%) [23].

The formation of 1,4-benzodiazepin-5-ones can be rationalized according to the mechanism depicted in Scheme 3. First, the Pd(0) complex **I** [24] is generated from $Pd(CH_3CN)_2Cl_2$ and *n*-BuLi. After oxidative addition of the iodoarene to **I**, the thus formed PhPdI complex **II** undergoes carbopalladation to give the η^3-allyl complex **IV** *via* **III**. 7-*Exo* nucleophilic attack by the sodium salt of the sulfonamide (or carbamate) nitrogen atom forms the benzodiazepinone **2a** and regenerates a Pd(0)-species, thereby closing the catalytic cycle.

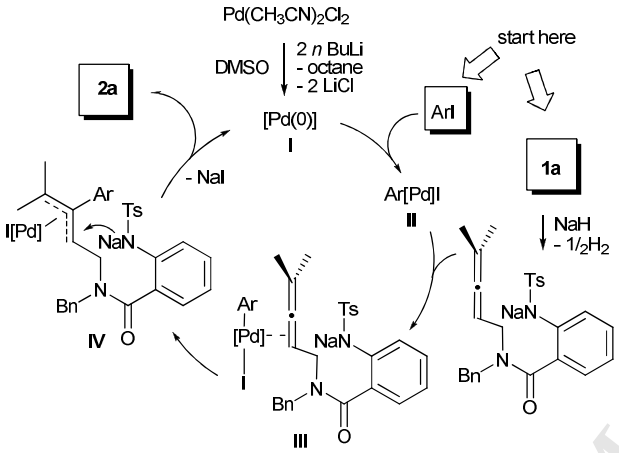
Table 2

Scope of the domino sequence.[a]



[a]For the reaction conditions, see entry 6, Table 1. Yields refer to isolated products.

Not surprisingly, in all the cases studied, the carbopalladation / amination sequence was totally regioselective, always yielding the desired 1,4-benzodiazepin-5-ones as the sole products. Indeed, a 9-*endo* type attack on the unsubstituted terminus of the allyl moiety to produce a benzo[1,5]diazoninone ring is expected to be much more disfavoured (Scheme 3).

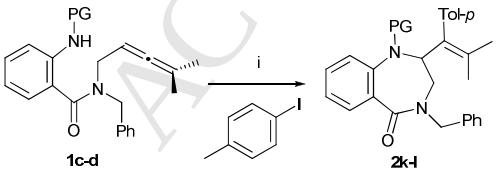


Scheme 3. Mechanistic proposal for the carbopalladation/allylic amination domino sequence.

Finally, to ascertain that the above cyclization strategy could be satisfactorily carried out with an *N*-protecting group synthetically more attractive than the tosyl function, the *N*-Boc **1c** and the *N*-nosyl analogs **1d** [25] were synthesized and submitted to the same domino protocol as above. Although the former derivative gave only a moderate yield of benzodiazepine, the *N*-nosyl one smoothly cyclised in high yield (Table 3) [26].

Table 3

Validation of the domino process on the *N*-Boc and *N*-Ns derivatives.[a]



Entry	PG	Substrate	Product	Yield (%)
1	BOC	**1c**	**2k**	48
2	Ns	**1d**	**2l**	80

[a]For the rection conditions, see entry 6, Table 1. Yields refer to isolated products.

3. Conclusion

We have developed an original approach to 1,4-benzodiazepin-5-ones starting from *N*-allenamides of anthranilic acid. This was obtained designing a catalytic sequence wherein a C-C and C-N carbon bond are created in a single synthetic operation. Besides their intrinsic pharmacological interest, the obtained scaffolds represent an interesting DOS-compatible platform [27] amenable to modular synthesis (*via* the use of differently substituted anthranilic acids and/or allenyl moieties) as well as orthogonal protections. Furthermore, the vinyl moiety of the products lends itself to easy post-cyclisation modifications.

4. Experimental section

4.1. General information

DMSO was distilled over CaH_2 under reduced pressure. All other solvents were dried on a MBraun solvent purification system MB SPS-800. Chemicals were purchased from Sigma Aldrich and Acros Organics and used as received, unless stated.

All reactions were conducted under argon and glassware was flame-dried before use. Flash chromatography was conducted on silica gel (0.040-0.063 mm). Analytical Thin Layer Chromatography (TLC) were performed on Merck precoated 60 F_{254} plates. Melting points were measured using a Stuart Scientific SMP3 apparatus. IR spectra were recorded on a Bruker Tensor 27 (Pike) apparatus and only the strongest or the structurally most important peaks were listed.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Avance 400 spectrometer (BBFO probe). Chemical shifts are reported in ppm relative to residual peak of deuterated chloroform as internal standard. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the DEPT pulse sequence.

High resolution mass spectrometry was performed on a Thermo Fisher Scientific LTQ-Orbitrap (ESI).

4.2. General procedure for the synthesis of N-protected allenyl amides

To a solution of *N*-benzyl-(4-methylpenta-2,3-dienyl)-amine [17f] (187 mg, 1 mmol, 1 equiv.) in THF (9.3 mL, 0,1 M) were rapidly added under argon atmosphere the appropriate *N*-protected-anthranylic acid (1.2 equiv.), DCC (248 mg, 1.2 equiv.) and DMAP (6.1 mg, 0.05 equiv.). The resulting mixture was stirred at room temperature overnight. The completion of the reaction was verified by TLC. Cyclohexane (28 mL) was then added, the mixture was

filtered over a celite pad and then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane/AcOEt 7:3.

4.2.1. *N*-Benzyl-*N*-(4-methylpenta-2,3-dienyl)-2-(4-methylphenylsulfonamido)benzamide (**1a**) - White solid. (Yield: 70%). M.p.: 107-109 °C. IR (neat) 1620, 1597, 1337, 1164, 737 cm^{-1}. Mixture of two rotamers in a 3.1:1 ratio. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.75 (6H, s), 2.20-2.50 (3H, m), 3.13 (2H, s br), 4.64 (2H, s br), 4.73-4.90 (1H, m), 6.70-7.80 (13H, m), 8.41 (1H, s br) (major rotamer); 1.75 (6H, s), 2.20-2.50 (3H, m), 3.96 (2H, s br), 4.17 (2H, s br), 4.85-5.10 (1H, m), 6.70-7.80 (13H, m), 8.57 (1H, s br) (minor rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.6 (q), 21.6 (q), 47.0 (t), 47.4 (t), 85.1 (d), 98.7 (s), 124.3 (d), 126.2 (d), 126.9 (s), 127.3 (d), 127.8 (d), 128.1 (d), 129.1 (d), 129.7 (d), 130.2 (d), 131.3 (d), 134.9 (s), 136.6 (s), 143.7 (s), 153.8 (s), 170.1 (s), 203.2 (s) (major rotamer); 20.6 (q), 21.9 (q), 47.0 (t), 47.4 (t), 85.1 (d), 98.7 (s), 123.9 (d), 126.2 (d), 126.9 (s), 127.3 (d), 127.8 (d), 128.2 (d), 129.1 (d), 129.7 (d), 130.2 (d), 131.5 (d), 134.9 (s), 136.4 (s), 144.8 (s), 153.8 (s), 167.6 (s), 203.2 (s) (minor rotamer). HRMS (ESI +): Calcd. for $C_{27}H_{28}N_2NaO_3S_1$ (M+Na^+): 483.17128, found: 483.17051.

4.2.2.N-Benzyl-3-methyl-*N*-(4-methylpenta-2,3-dienyl)-2-(4-methylphenylsulfonamido)benzamide (**1b**) - Colorless oil. (Yield: 60%). IR (neat) 1614, 1451, 1164 cm^{-1}. Mixture of two rotamers in a 2.5:1 ratio. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.74 (6H, d, J = 2.7 Hz), 2.30 (3H, s), 2.33 (3H, s), 3.45 (2H, d, J = 4.7), 4.62 (2H, s), 4.92 (1H, dddd, J = 4.7, 4.7, 2.7, 2.7 Hz), 7.00 (2H, d, J = 8.0 Hz), 7.01-7.50 (8H, m), 7.54 (2H, d, J = 8.0 Hz), 7.96 (1H, s br) (major rotamer); 1.65 (6H, d, J = 2.5 Hz), 2.29 (3H, s), 2.46 (3H, s), 3.96 (2H, d, J = 5.8 Hz), 4.38 (2H, s), 4.99-5.09 (1H, m), 7.01-7.50 (10H, m), 7.75 (2H, d, J = 8.0 Hz), 7.86 (1H, s br) (minor rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.6 (q), 20.9 (q), 21.7 (q), 47.9 (t), 48.3 (t), 85.5 (d), 98.2 (s), 125.4 (d), 126.6 (d),127.2 (d), 127.9 (d), 128.9 (d), 129.6 (d), 129.7 (d), 133.6 (d), 133.7 (s), 134.0 (s), 136.9 (s), 137.4 (s), 139.8 (s), 143.7 (s), 170.8 (s), 203.3 (s) (major rotamer); 19.6 (q), 20.6 (q), 21.9 (q), 45.5 (t), 52.7 (t), 84.6 (d), 96.5 (s), 124.6 (d), 126.9 (d), 127.2 (d), 127.9 (d), 129.2 (d), 129.6 (d), 129.9 (d), 133.6 (d), 133.7 (s), 134.0 (s), 136.9 (s), 137.4 (s), 139.8 (s), 144.0 (s), 171.3 (s), 203.7 (s) (minor rotamer). HRMS (ESI +): Calcd. for $C_{28}H_{30}N_2NaO_3S_1$ (M+Na^+): 497.18693, found: 497.18587.

4.2.3. Tert-butyl 2-[benzyl(4-methylpenta-2,3-dienyl)carbamoyl]phenylcarbamate (**1c**) - White solid (Yield: 58%). M.p.: 98-100 °C. IR (neat) 1728, 1626, 1516, 1157 cm^{-1}. Mixture of two rotamers in a 2:1 ratio. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.52 (9H, s), 1.75 (6H, s), 3.74 (2H, s br), 4.80 (2H, s br), 4.85-5.00 (1H, m), 6.80-7.40 (8H, m), 7.70-8.25 (2H, m) (major rotamer); 1.52 (9H, s), 1.75 (6H, s), 4.04 (2H, s br), 4.57 (2H, s br), 5.00-5.20 (1H, m), 6.80-7.40 (8H, m), 7.70-8.25 (2H, m) (minor rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.7 (q), 28.7 (q), 47.4 (t), 48.0 (t), 80.7 (s), 85.4 (d), 98.6 (s), 121.4 (d), 122.3 (d), 124.6 (s), 126.9 (d), 127.9 (d), 128.4 (s), 129.0 (d), 130.9 (d), 137.2 (s), 153.2 (s), 170.8 (s), 203.0 (s). HRMS (ESI +): Calcd. for $C_{25}H_{30}N_2NaO_3S$ (M+Na^+): 429.21486, found: 429.21436.

4.2.4. N-Benzyl-*N*-(4-methylpenta-2,3-dienyl)-2-(4-nitrophenylsulfonamido)benzamide (**1d**) - Yellow solid. (Yield: 62%). M.p.: 70-72 °C. IR (neat) 1619, 1531, 1348, 1170 cm^{-1}. Mixture of two rotamers in a 3.9:1 ratio. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.75 (6H, s br), 3.20 (2H, s br), 4.62 (2H, s br), 4.70-4.90 (1H, m), 7.00-8.40 (13H, m), 8.80 (1H, s br) (major rotamer); 1.75 (6H, s br), 3.96 (2H, s br), 4.29 (2H, s br), 4.85-5.05 (1H, m), 7.00-8.40 (13H, m), 9.0 (1H, s br) (minor rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.6 (q), 47.0 (t), 47.6 (t), 84.8 (d), 99.4 (s), 124.2 (d), 124.6 (d), 125.1 (d), 126.9 (s), 127.6 (d), 128.6 (d), 129.3 (d), 130.0 (d), 131.7 (d), 134.6 (d), 135.6 (s), 136.6 (s), 145.2 (s), 150.2 (s), 169.7 (s), 203.3 (s). HRMS (ESI +): Calcd. for $C_{26}H_{25}N_3NaO_5S_1$ (M+Na^+): 514.14071, found: 514.13935

4.3. General procedure for the Pd-catalysed domino sequence

NaH (4.8 mg, 0.12 mmol, 1.2 equiv., 60% dispersion in mineral oil) was added to a solution of the appropriate *N*-protected allenyl amide (0.1 mmol, 1 eq.) in freshly distilled DMSO (1.6 mL) under Ar atmosphere. The resulting mixture was stirred at 50 °C for 10 min. In another flask, *n*-butyllithium (10 mL, 0.02 mmol, 20 mol%, 2.0 M solution in hexanes) was added dropwise to a solution of $PdCl_2(CH_3CN)_2$ in freshly distilled DMSO under argon atmosphere. The resulting solution, initially yellow, became dark orange. The appropriate aromatic iodide (0.12 mmol, 1.2 equiv.) and tetrabutylammonium bromide (6.4 mg, 0.02 mmol, 20 mol%) were then successively added, and the solution containing the deprotonated amide was added via cannula. The resulting mixture was stirred at 90 °C. The completion of the reaction was monitored by TLC (about 2 h) and the reaction was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with a saturated solution of NaCl, dried on $MgSO_4$ and concentrated in vacuo. The

crude product was purified by flash chromatography on silica gel eluting with cyclohexane/AcOEt 8:2.

4.3.1. 4-Benzyl-2-(2-methyl-1-*p*-tolylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2a**) - Colorless oil. Yield: 82%. IR (neat) 1650, 1351, 1161, 716, 660 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.41 (3H, s), 1.80 (3H, s), 2.33 (3H, s), 2.43 (3H, s), 3.06 (1H, dd, *J* = 15.3, 4.3), 3.33 (1H, dd, *J* = 15.3, 12.5), 3.74 (1H, A part of AB system, *J* = 14.7 Hz), 3.81 (3H, s), 4.62 (1H, B part of AB system, *J* = 14.7 Hz),5.38 (1H, dd, *J* = 12.5, 4.3), 6.33 (1H, d, *J* = 8.0, 0.9 Hz), 6.60-6.95 (1H, m), 7.03 (1H, ddd, *J* = 8.0, 7.8, 1.7 Hz), 7.10-7.17 (2H, m), 7.22 (1H, ddd, *J* = 7.8, 7.8, 0.9 Hz), 7.27-7.37 (7H, m), 7.42-7.47 (2H, m), 7.54 (1H, dd, *J* = 7.8, 1.7 Hz), 7.67-7.87 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4 (q), 21.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 64.3 (d), 127.6 (d), 128.2 (d), 128.3 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.1 (d), 131.3 (s), 133.6 (d), 133.7 (s), 134.1 (s), 134.2 (s), 136.6 (s), 136.7 (s), 137.0 (s), 143.9 (s), 168.0 (s).HRMS (ESI +): Calcd. for $C_{34}H_{34}N_2NaO_3S_1$ (*M*+H^+): 551.23629, found: 551.23544.

4.3.2. Tert-butyl 4-benzyl-2-(2-methyl-1-*p*-tolylprop-1-enyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-1-carboxylate (**2k**) - Colorless oil (Yield: 48%). IR (neat) 1725, 1630, 1156 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.33 (9H, s), 1.49 (3H, s), 1.69 (3H, s), 2.34 (3H, s), 3.19-3.24 (1H, m), 3.41-3.49 (1H, m), 4.70 (1H, A part of AB system, *J* = 14.2 Hz), 5.03 (1H, B part of AB system, *J* = 14.2 Hz), 5.35-5.42 (1H, m), 5.52-5.60 (1H, m), 6.30-6.40 (1H, m), 6.70-7.50 (10H, m), 7.55-7.61 (1H, m). ^{13}C-NMR: (100 MHz, $CDCl_3$): 21.4 (q), 22.7 (q), 28.5 (q), 49.5 (t), 50.4 (t), 63.1 (d), 80.8 (s), 126.6 (d), 128.2 (d), 128.6 (d), 128.7 (d), 129.1 (d), 129.2 (d), 130.0 (d), 130.6 (d), 133.4 (s), 136.7 (s), 137.5 (s), 147.5 (s), 156.1 (s), 168.0 (s). HRMS: Calcd. For $C_{32}H_{36}N_2NaO_3$ (*M*+Na^+): 519.26181, found: 519.26114.

4-Benzyl-2-(2-methyl-1-*p*-tolylprop-1-enyl)-1-(4-nitrophenylsulfonyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2l**) - Colorless oil. (Yield: 80%). IR (neat) 1652, 1530, 1350, 1176, 668, 616 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.44 (3H, s), 1.87 (3H, s), 2.35 (3H, s), 3.14 (1H, dd, *J* = 15.5, 4.4 Hz), 3.36 (1H, dd, *J* = 15.5, 12.3 Hz), 3.88 (1H, A part of AB system, *J* = 14.5 Hz), 4.64 (B part of AB system, *J* = 14.5 Hz), 5.48 (1H, dd, *J* = 12.3, 4.4 Hz), 6.31 (1H, dd, *J* = 8.1, 1.0 Hz), 6.25-6.50 (1H, s br), 6.60-6.90 (1H, s br), 6.56 (1H, d, *J* = 9.0 Hz), 7.06 (1H, ddd, *J* = 8.1, , 7.8, 1.7 Hz), 7.13-7.18 (2H, m), 7.23-7.41 (6H, m), 7.50 (1H, dd, *J* = 7.8, 1.7 Hz), 15.2 (2H, d, *J* = 8.9 Hz), 8.28 (2H, d, *J* = 8.9 Hz). ^{13}C-NMR (100

MHz, $CDCl_3$): 19.5 (q), 21.4 (q), 22.8 (q), 49.0 (t), 49.8 (t), 65.5 (d), 124.7 (d), 128.4 (d), 128.6 (d), 128.8 (d), 129.0 (d), 129.3 (d), 129.9 (d), 131.3 (d), 132.2 (s), 132.9 (s), 133.2 (d), 134.2 (s), 136.3 (s), 136.6 (s), 136.9 (s), 144.7 (s), 150.4 (s), 167.5 (s). HRMS (ESI +): Calcd. for $C_{33}H_{31}N_3NaO_5S$ (M+Na^+): 604.18766, found: 604.18677.

4.3.3. 4-Benzyl-2-(1-(2-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)one (**2b**) - Colorless oil (Yield: 73%). IR (neat) 1651, 1466, 1351, 1159, 718, 658 cm^{-1}. Mixture of two atropoisomers in a 1.1:1 ratio. H-NMR: (400 MHz, $CDCl_3$): 1.43 (3H, s), 1.80 (3H, s), 2.43 (3H, s), 3.07 (1H, dd, J = 15.3, 4.0 Hz), 3.34 (1H, dd, J = 15.3, 12.5 Hz), 3.52 (3H, s br, minor atropoisomer) 3.70-3.85 (1H, m), 3.94 (3H, s br, major atropoisomer), 4.63 (1H, d, J = 14.7 Hz),5.39 (1H, dd, J = 12.5, 4.0 Hz) 5.90-6.10 (1H, m), 6.35-6.40 (1H, m), 6.78 (1H, dd, J = 7.8, 1.8 Hz), 7.00-7.25 (5H, m), 7.27-7.57 (9H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): 19.3 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 55.5 (q, minor atropoisomer), 55.8 (q), major atropoisomer), 64.1 (d), 127.6 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.3 (s), 133.5 (d), 133.6 (d), 134.0 (s), 134.1 (s), 136.6 (s), 137.0 (s), 141.0 (s), 144.0 (s), 168.0 (s). HRMS (ESI +): Calcd. for $C_{34}H_{34}N_2NaO_4S_1$ (M+Na^+): 589.21315, found: 589.21208.

4.3.4. 4-Benzyl-2-(1-(3-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2c**)

Colorless oil. (Yield: 63%). IR (neat) 1651, 1351, 1159, 718, 658 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.40 (3H, s), 1.80 (3H, s), 2.42 (3H, s), 3.11 (1H, dd, J = 15.8, 4.5 Hz), 3.15 (3H, s), 3.49 (1H, dd, J = 15.8, 12.3 Hz), 3.66 (1H, A part of AB system, J = 14.7 Hz), 4.56 (B part of AB system, J = 14.7 Hz), 5.40 (1H, dd, J = 12.3, 4.5 Hz), 6.09 (1H, d, J = 8.1), 6.56 (1H, d, J = 9.0 Hz), 6.90-7.50 (m, 14H), 7.56 (1H, d, J = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 54.8 (q), 64.6 (d), 110.6 (d), 121.4 (d), 127.6 (d), 128.1 (d), 128.3 (d), 128.5 (s), 128.7 (d), 128.9 (d), 129.1 (d), 129.7 (d), 130.1 (d), 130.5 (s), 131.1 (d), 131.3 (s), 133.7 (d), 134.1 (s), 134.6 (d), 134.7 (s), 136.9 (s), 137.2 (s), 143.8 (s), 157.3 (s), 168.2 (s). HRMS (ESI +): Calcd. for $C_{34}H_{34}N_2NaO_4S_1$ (M+Na^+): 589.21315, found: 589.21202.

4.3.5. 4-Benzyl-2-(1-(4-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2d**) - Colorless oil (Yield: 63%). IR (neat) 1651, 1509, 1350, 1244, 1172 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.41 (3H, s), 1.80 (3H, s), 2.43 (3H, s),

3.06 (1H, dd, *J* = 15.3, 4.3), 3.32 (1H, dd, *J* = 15.3, 12.4), 3.75 (1H, A part of AB system, *J* = 14.7 Hz), 3.81 (3H, s), 4.62 (1H, B part of AB system, *J* = 14.7 Hz), 5.38 (1H, dd, *J* = 12.4, 4.3 Hz), 6.20-6.60 (2H, m), 6.41 (1H, dd, *J* = 7.9, 1.1 Hz), 6.80-7.10 (1H, m), 7.09 (1H, ddd, *J* = 7.9, 7.6, 1.7 Hz), 7.11-7.15 (2H, m), 7.23 (1H, ddd, *J* = 7.6, 7.6, 1.1 Hz), 7.27-7.37 (6H, m), 7.42-7.47 (2H, m), 7.55 (1H, dd, *J* = 7.6, 1.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 55.7 (q), 64.3 (d), 127.6 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.8 (s), 132.0 (s), 133.3 (s), 133.6 (d), 134.1 (s), 134.2 (s), 136.6 (s), 136.9 (s), 144.0 (s), 158.9 (s), 168.0 (s). HRMS (ESI +): Calcd. for $C_{34}H_{34}N_2NaO_4S_1$ (*M*+Na^+): 589.21315, found: 589.21188.

4.3.6. Methyl 4-[1-(4-benzyl-5-oxo-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin2-yl)-2-methylprop-1-enyl]benzoate (**2e**) - Colorless oil (Yield: 68%). IR (neat) 1722, 1651, 1276, 711, 659 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.38 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 3.10 (1H, dd, *J* = 15.3, 4.2), 3.34 (1H, dd, *J* = 15.3, 12.5 Hz), 3.79 (1H, A part of AB system, *J* = 14.7 Hz), 3.94 (3H, s), 4.61 (1H, B part of AB system, *J* = 14.7 Hz), 5.39 (1H, dd, *J* = 12.5, 4.2 Hz), 6.29 (1H, d, *J* = 8.0 Hz), 6.52 (1H, s br), 7.02 (1H, ddd, *J* = 8.0, 7.6, 1.7 Hz), 7.10-7.15 (2H, m), 7.22 (1H, ddd, *J* = 7.7, 7.6, 1.0 Hz), 7.27-7.37 (5H, m), 7.40-7.47 (2H, m), 7.54 (1H, dd, *J* = 7.7, 1.7 Hz), 7.50-7.85 (2H, m), 8.05-8.35 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4 (q), 21.9 (q), 22.7 (q), 48.9 (t), 49.5 (t), 52.4 (q), 64.0 (d), 127.6 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.0 (s), 129.2 (d), 130.1 (d), 130.2 (d), 131.4 (d), 132.1 (s), 133.1 (s), 133.2 (d), 133.8 (s), 134.0 (s), 136.3 (s), 136.8 (s), 144.2 (s), 144.9 (s), 167.4 (s), 167.9 (s). HRMS (ESI +): Calcd. for $C_{35}H_{34}N_2NaO_4S$ (*M*+Na^+): 617.20806, found: 617.20659.

4.3.7. 4-Benzyl-2-(2-methyl-1-(4-nitrophenyl)prop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2f**) - Colorless oil. (Yield: 61%). IR (neat) 1652, 1518, 1346 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.39 (3H, s), 1.81 (3H, s), 2.44 (3H, s), 3.12 (1H, dd, *J* = 15.3, 4.2 Hz), 3.33 (1H, dd, *J* = 15.3, 12.6 Hz), 3.82 (1H, A part of AB system, *J* = 14.7 Hz), 4.61 (B part of AB system, *J* = 14.7 Hz), 5.39 (1H, dd, *J* = 12.6, 4.2 Hz), 6.30 (1H, dd, *J* = 8.0, 1.0 Hz), 6.38-6.95 (1H, m), 7.05 (1H, ddd, *J* =8.0, 7.6, 1.6 Hz), 7.11-7.15 (2H, m), 7.21-7.45 (6H, m), 7.40-7.45 (2H, m), 7.57 (1H, dd, *J* = 7.6, 1.6 Hz), 7.59-8.65 (3H, m) ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5 (q), 22.0 (q), 22.8 (q), 48.8 (t), 49.6 (t), 63.9 (d), 127.6 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.3 (d), 130.2 (d), 130.4 (d), 131.4 (d), 132.3 (s), 132.8 (d), 133.1 (s), 133.7 (s), 134.1 (s), 136.0 (s), 136.7 (s), 144.4 (s), 147.3 (s), 167.7 (s). HRMS (ESI +): Calcd. for $C_{33}H_{31}N_3NaO_5S$ (*M*+Na^+): 604.18766, found: 604.18638.

4.3.8. 2-[1-(4-Acetylphenyl)-2-methylprop-1-enyl]-4-benzyl-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2g**) - Colorless oil (Yield: 71%). IR (neat) 1682, 1650, 1350, 1158, 714, 660 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.39 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 2.62 (3H, s), 3.11 (1H, dd, *J* = 15.2, 4.2 Hz), 3.34 (1H, dd, *J* = 15.2, 12.5 Hz), 3.79 (1H, A part of AB system, *J* = 14.6 Hz), 4.61 (1H, B part of AB system, *J* = 14.6 Hz), 5.39 (1H, dd, *J* = 12.5, 4.2 Hz), 6.26 (1H, dd, *J* = 8.1, 0.9 Hz), 6.40-6.75 (1H, br s), 6.99 (1H, ddd, *J* = 8.1, 7.6, 1.7 Hz), 7.13 (2H, m), 7.22 (1H, ddd, *J* = 7.6, 7.6, 0.9 Hz), 7.27-7.38 (5H, m), 7.41-7.46 (2H, m), 7.55 (1H, dd, *J* = 7.6, 1.7 Hz), 7.55-7.80 (2H, br s), 7.80-8.30 (1H, s br). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4 (q), 21.9 (q), 22.7 (q), 27.0 (q), 48.9 (t), 49.5 (t), 64.0 (d), 127.6 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.2 (d), 130.1 (d), 130.2 (d), 131.2 (d), 132.1 (s), 133.1 (d), 133.8 (s), 134.1 (s), 136.0 (s), 136.3 (s), 144.2 (s), 145.2 (s), 167.8 (s), 198.2 (s). HRMS (ESI +): Calcd. for $C_{35}H_{34}N_2NaO_4S$ (*M*+Na^+): 601.21315, found: 601.21187.

4.3.9. 4-Benzyl-2-(2-methyl-1-phenylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2h**) - White oil. (Yield: 67%). IR (neat) 1651, 1351, 1160, 703, 658 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): 1.40 (3H, s), 1.82 (3H, s), 2.43 (3H, s), 3.08 (1H, dd, *J* = 15.3, 4.2), 3.35 (1H, ddd, *J* = 15.3, 12.4, 0.8), 3.75 (1H, A part of AB system, *J* = 14.7 Hz), 4.62 (1H, B part of AB system, *J* = 14.7 Hz), 5.40 (1H, dd, *J* = 12.4, 4.2 Hz), 6.30 (2H, dd, *J* = 8.1, 1.1 Hz), 6.45 (1H, s br), 6.90-7.05 (1H, m), 7.03 (1H, ddd, *J* = 8.1, 7.6, 1.7 Hz), 7.11-7.16 (2H, m), 7.18-1.25 (1H, m), 7.21 (1H, ddd, *J* = 7.6, 7.6, 1.1),7.27-7.37 (5H, m), 7.42-7.60 (4H, m), 7.54 (1H, dd, *J* = 7.6, 1.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 64.2 (d), 127.0 (d), 127.6 (d), 128.2 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.4 (s), 133.5 (d), 133.8 (s), 134.0 (s), 136.6 (s), 137.0 (s), 139.7 (s), 144.0. (s), 168.0 (s). HRMS (ESI +): Calcd. for $C_{33}H_{32}N_2NaO_3S_1$ (*M*+Na^+): 559.20258, found: 559.20159.

4.3.10. 4-Benzyl-2-(2-methyl-1-pyridin-2-yl)prop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2i**) - Colorless oil. (Yield: 70%) IR (neat) 1651, 1351, 1159, 712, 658 cm-1. ^{1}H-NMR: (400 MHz, CDCl3): 1.40 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 3.10 (1H, dd, *J* = 15.3, 4.2), 3.25-3.33 (1H, m), 3.86 (1H, A part of AB system, *J* = 14.7 Hz), 4.59 (1H, B part of AB system, *J* = 14.7 Hz), 5.34-5.40 (1H, m), 6.32 (1H, s br), 7.08-7.14 (3H, m), 7.17-7.40 (8H, m), 7.41-7.48 (2H, m), 7.51-7.58 (1H, m), 7.60-8.40 (1H, m), 8.52 (1H, d, *J* = 4.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5 (q), 21.9 (q), 22.9 (q), 48.7 (t), 49.6

(t), 63.9 (d), 127.6 (d), 128.3 (d), 128.2 (d), 128.8 (d), 129.1 (s), 129.3 (d), 130.2 (d), 130.3 (d), 130.4 (d), 131.2 (s), 131.5 (d), 132.8 (s), 133.0 (s), 133.7 (d), 134.0 (s), 134.4 (s), 136.1 (s), 136.7 (s), 144.3 (s), 167.8 (s). HRMS (ESI +): Calcd. for $C_{32}H_{31}N_3NaO_3S_1$ (M+Na+): 560.19783, found: 560.19650.

4.3.11. 4-Benzyl-9-methyl-2-(2-methyl-1-*p*-tolylprop-1-enyl)-1-tosyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (**2j**) - Colorless oil (Yield: 75%). IR (neat) 1651, 1351, 1162, 700, 658 cm-1.^{1}H-NMR: (400 MHz, $CDCl_3$): 1.48 (3H, s), 1.57 (3H, s), 1.95 (3H, s), 2.32 (3H, s), 2.46 (3H, s), 3.00 (1H, dd, *J* = 15.2, 3.7), 3.18 (1H, A part of AB system, *J* = 14.9 Hz), 3.59 (1H, dd, *J* = 15.2, 12.2 Hz), 4.69 (1H, A part of AB system, *J* = 14.9 Hz), 5.36 (1H, dd, *J* = 12.2, 3.6 Hz), 6.40-6.80 (1H, m), 6.90-7.05 (2H, m), 7.10-7.15 (2H, m), 7.16-7.22 (1H, m), 7.23-7.35 (6H, m), 7. 38 (2H, d, *J* = 8.2 Hz), 7.50-7.55 (1H, m), 7.63 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR (100 MHz, CDCl3): 18.7 (q), 20.2 (q), 21.4 (q), 21.9 (q), 23.6 (q), 48.8 (t), 49.8 (t), 64.6 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.7 (d), 129.1 (d), 130.2 (d), 132.3 (s), 133.8 (s), 134.1 (s), 134.6 (d), 135.0 (s), 136.1 (s), 136.8 (s), 137.0 (s), 143.5 (s), 144.1 (s), 168.5 (s). HRMS (ESI +): Calcd. for $C_{35}H_{36}N_2NaO_3S_1$ (M+Na+): 587.23388, found: 587.23221.

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Appendix A. Supplementary data

^{1}H-NMR and ^{13}C-NMR spectra of compounds **1a-d** and **2a-j** can be found at DOI:

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[21] We exclusively worked with gem-dimethyl substituted allenes, as in our previous related study concerning Pd-catalyzed allene cyclizations (ref 17a) only this type of allenes gave clean and reliable results.

[22] This protocol, found after a thorough study, is a superior method to obtain a very active underligated Pd(0) species and in our hands favorably compared with all the other tested methods to generate zerovalent palladium.

[23] Not unexpectedly, use of aryl bromides for this protocol was not effective. See for example reaction 1 → 12 in ref 17a.

[24] Square brackets around the metal atom are intended to render implicit the dative ligands. For example, complex I will likely form surrounded by some loosely coordinated DMSO molecules.

[25] Contrary to the too robust tosyl function, the nosyl function is known to be easily cleaved under nucleophilic aromatic substitution conditions (i.e. mercaptoethanol / DBU).

[26] Attempted preparation of the corresponding N-SES derivative failed.

[27] DOS: Diversity oriented Organic Synthesis: S.L. Schreiber, Science 287 (2000) 1964-1969.

Synthesis of 1,4-benzodiazepinones via palladium-catalysed allene carbopalladation / amination domino sequence

Micol Rigamonti,[a,b] Guillaume Prestat,[a†] Gianluigi Broggini,[b*] and Giovanni Poli,[a*]

Contents

General information:

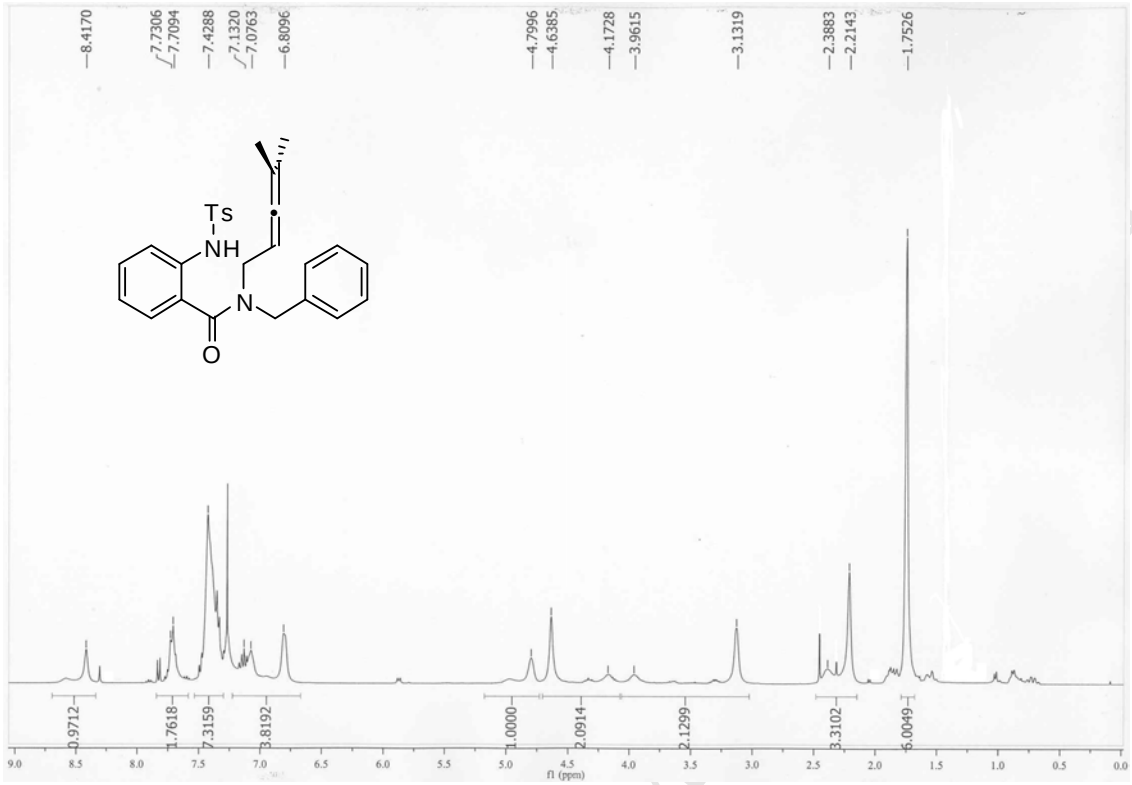
DMSO was distilled over CaH_2 under reduced pressure. All other solvents were dried on an MBraun solvent purification system MB SPS-800. Chemicals were purchased from Sigma Aldrich and Acros Organics and used as received, unless stated.

All reactions were conducted under argon and glassware was flame-dried before use. Flash chromatography was conducted on silica gel (0.040-0.063 mm). Analytical Thin Layer Chromatography (TLC) were performed on Merck precoated 60 F_{254} plates. Melting points were measured using a Stuart Scientific SMP3 apparatus. IR spectra were recorded on a Bruker Tensor 27 (Pike) apparatus and only the strongest or the structurally most important peaks were listed.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Avance 400 spectrometer (BBFO probe). Chemical shifts are reported in ppm relative to residual peak of deuterated chloroform as internal standard. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the DEPT pulse sequence.

High resolution mass spectrometry was performed on a Thermo Fisher Scientific LTQ-Orbitrap (ESI).

^{1}H spectrum of compound **1a**



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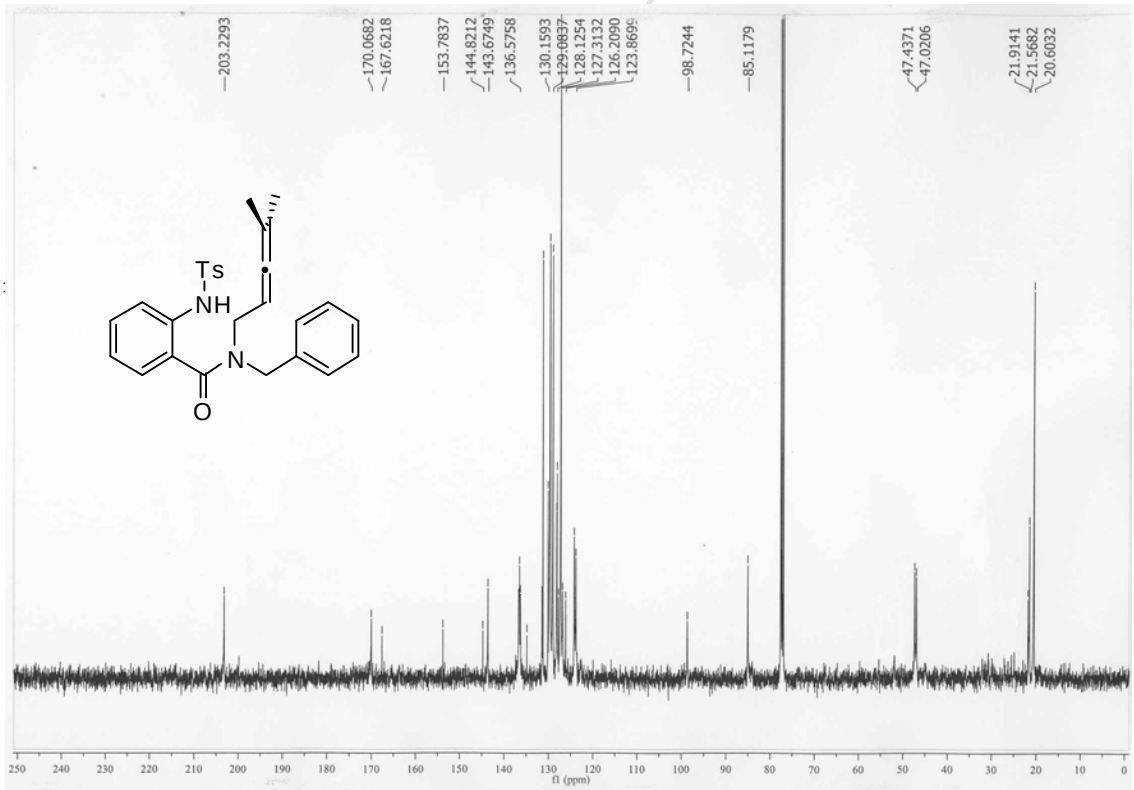

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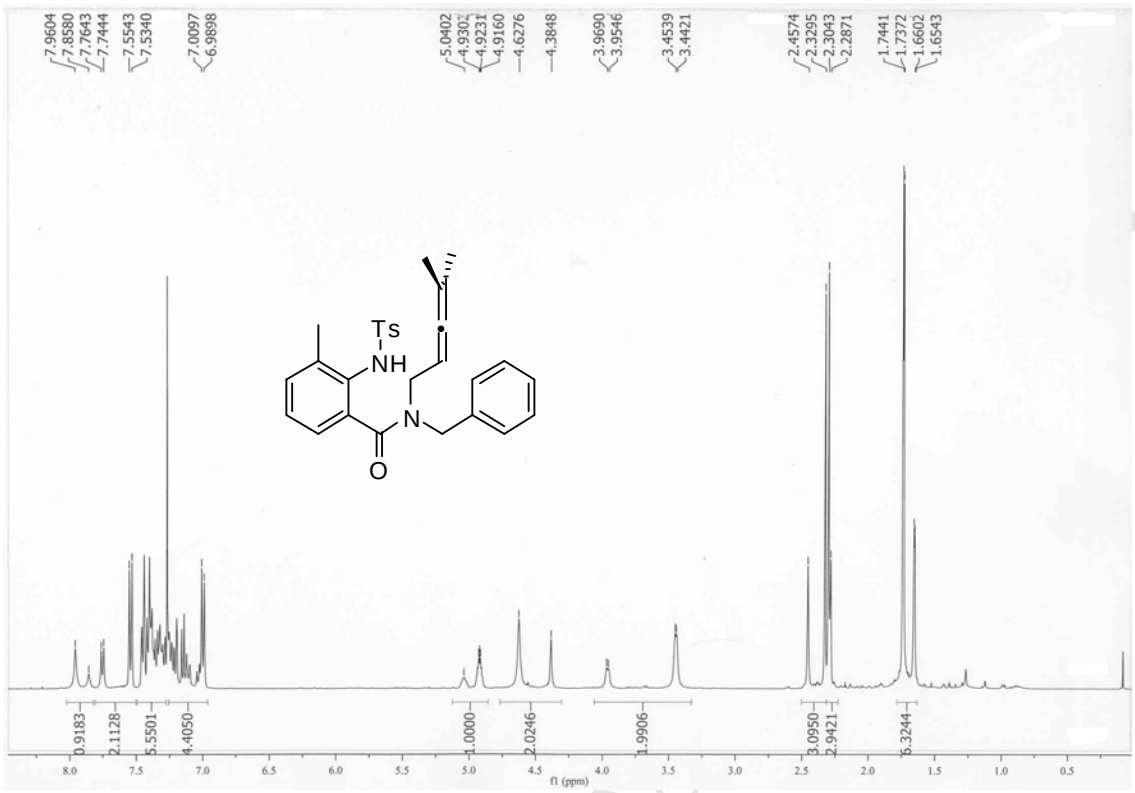

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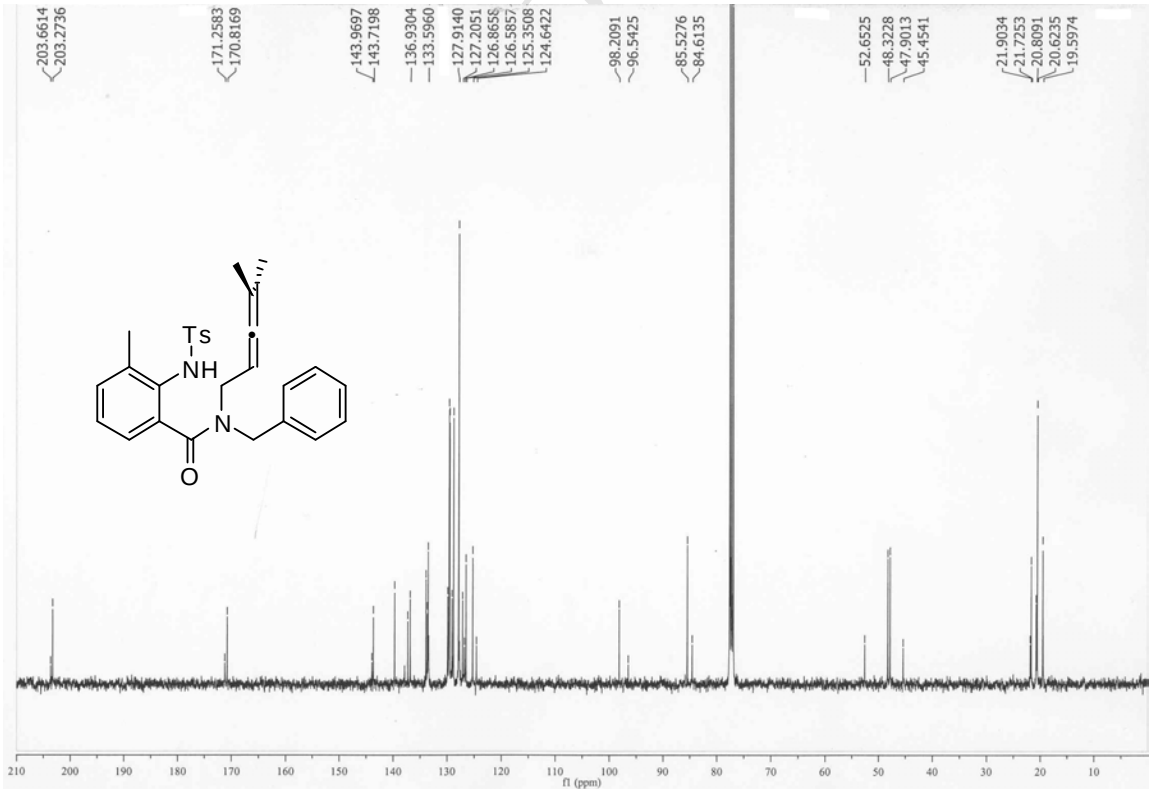

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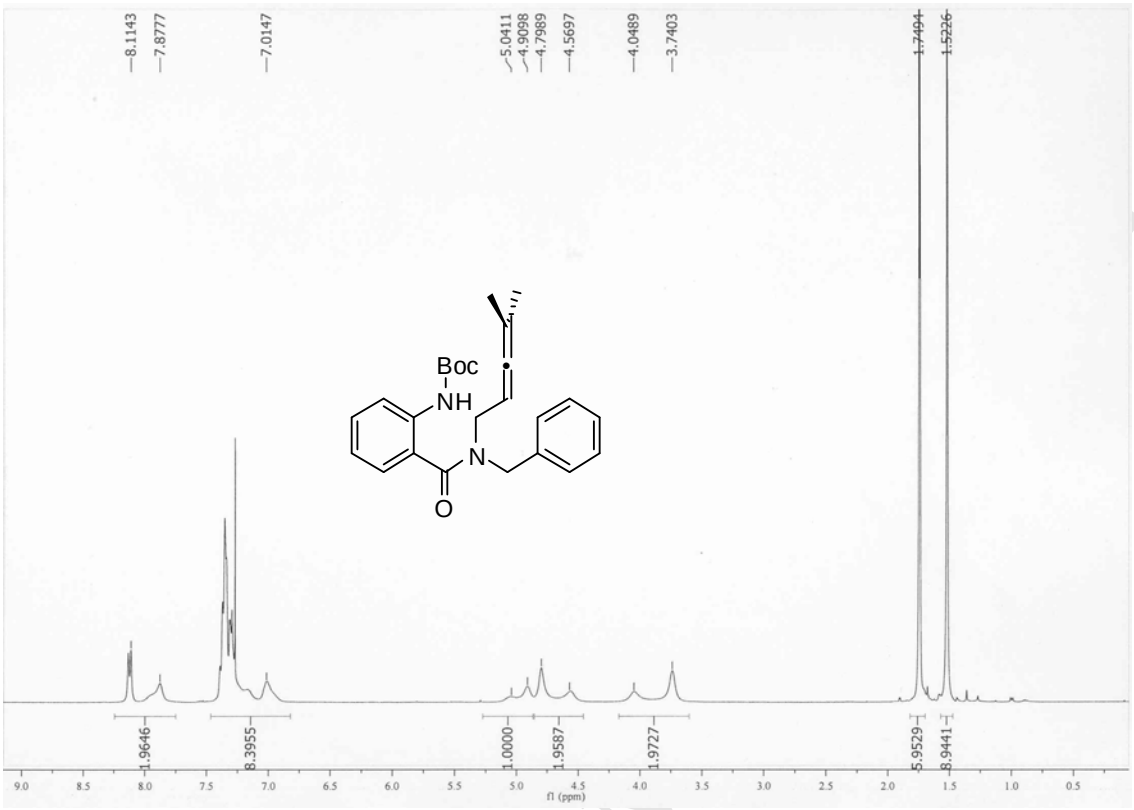

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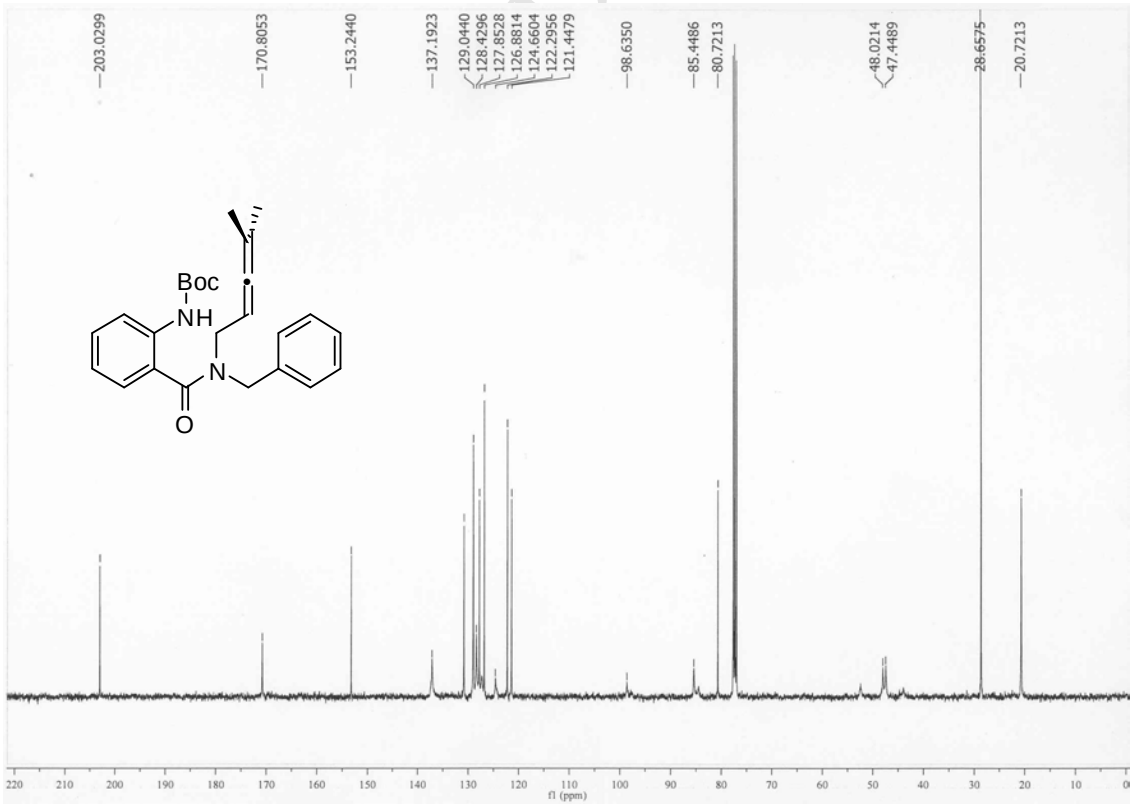

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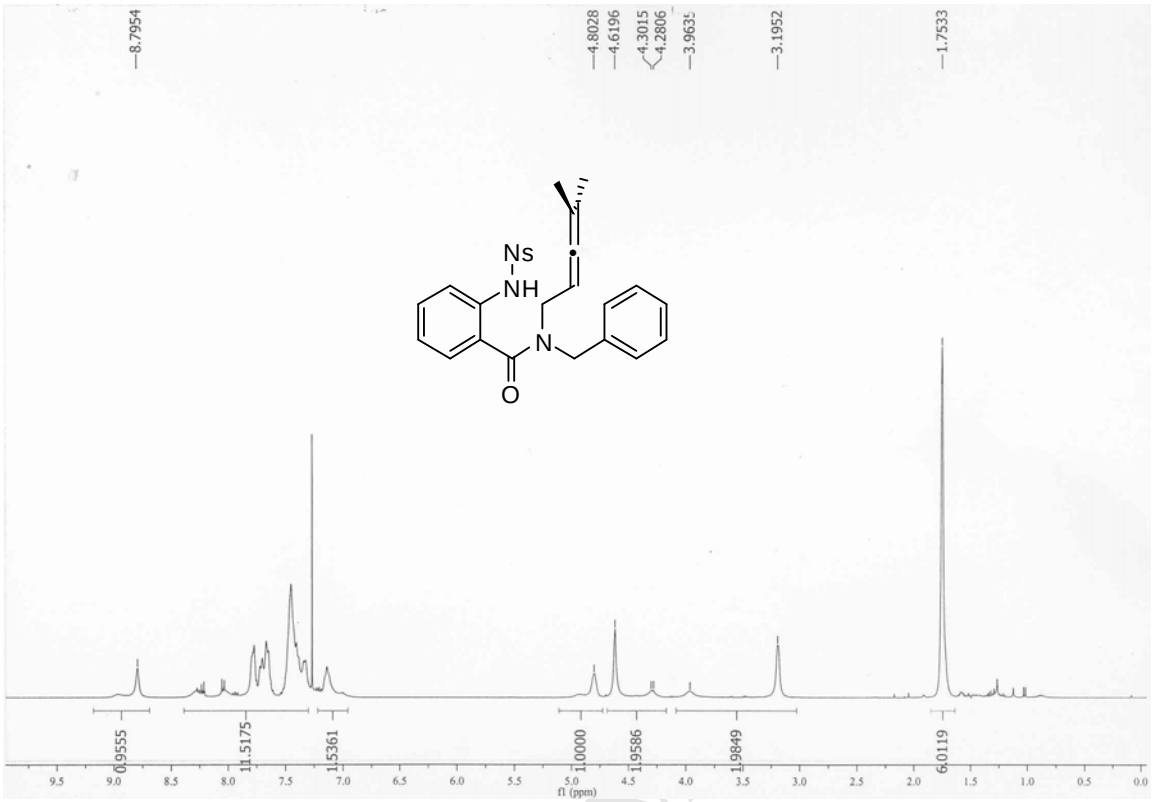

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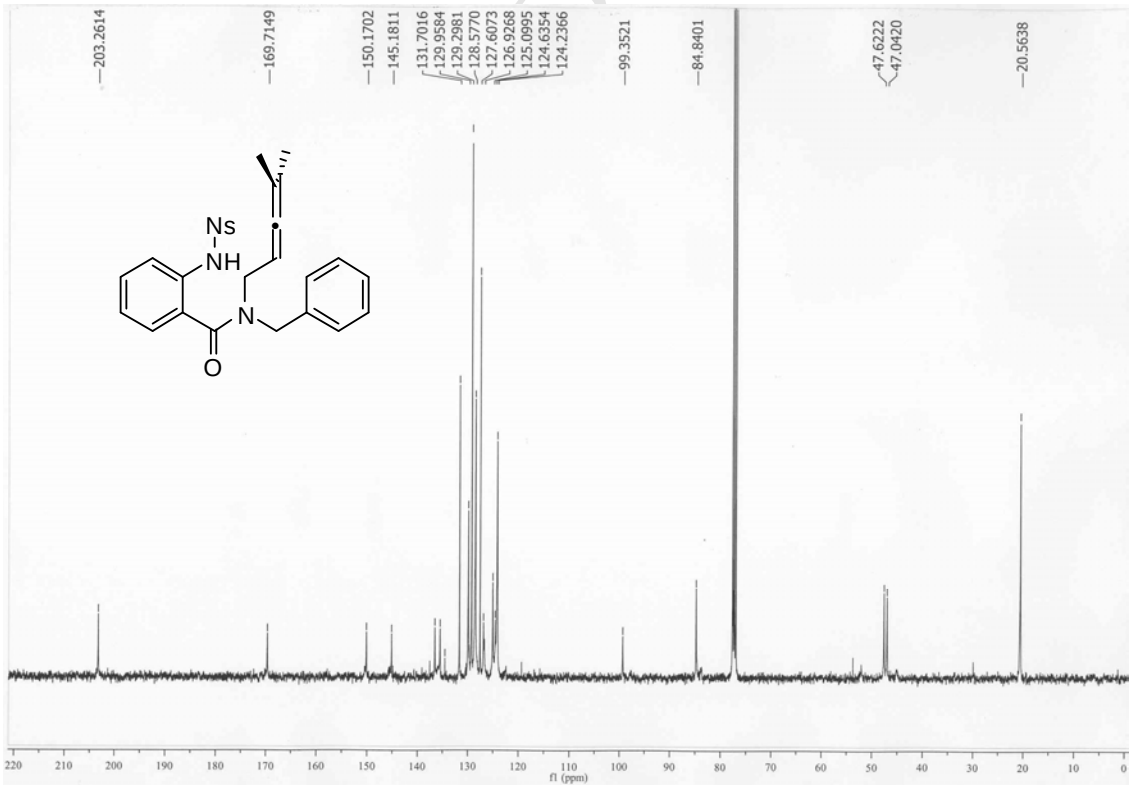

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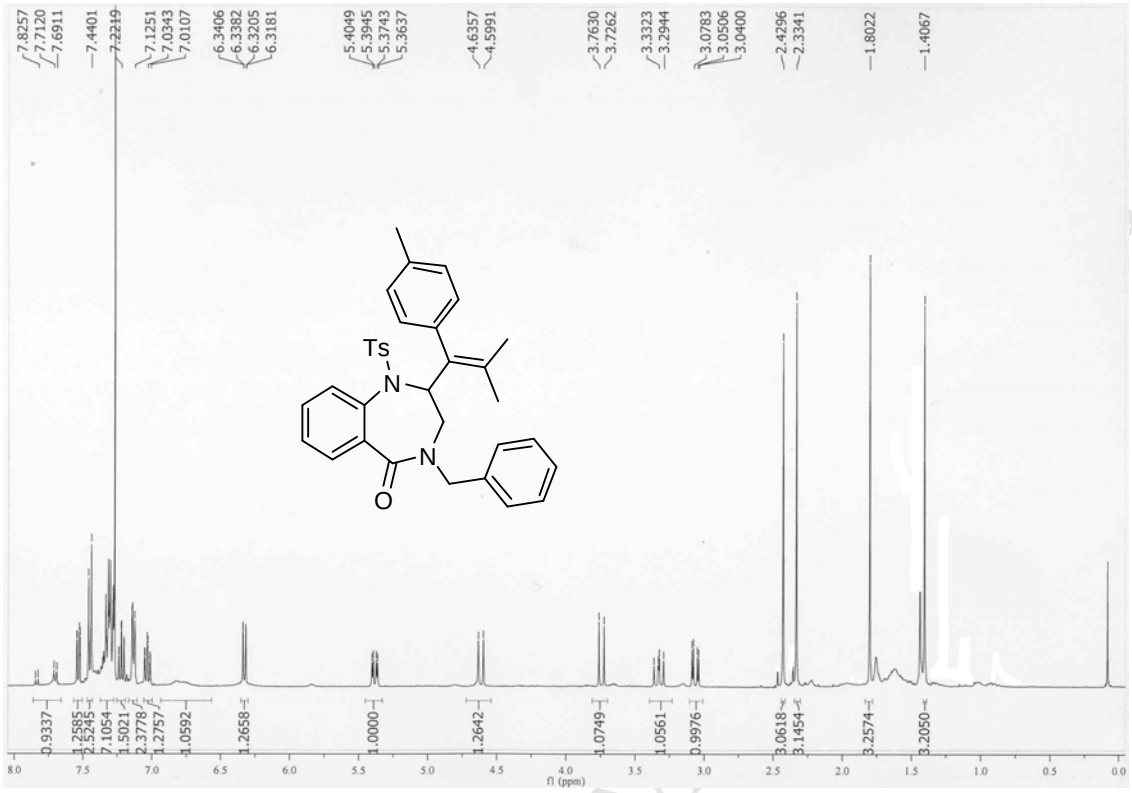

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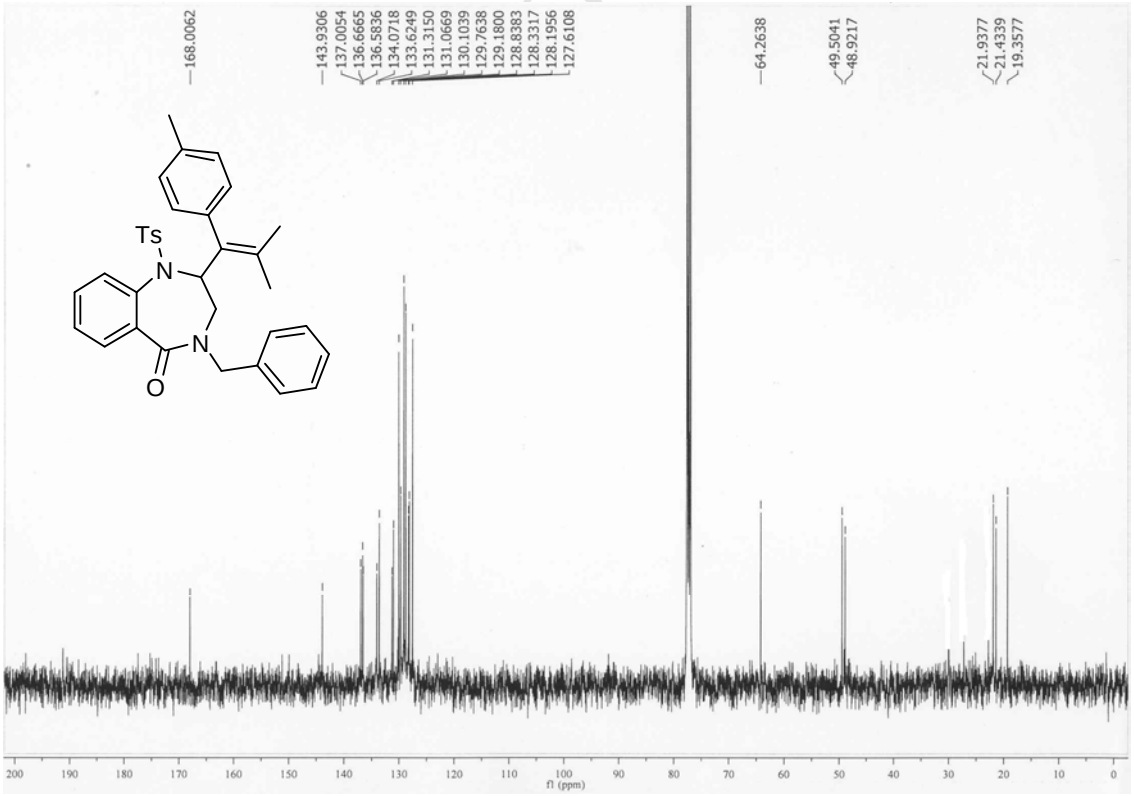

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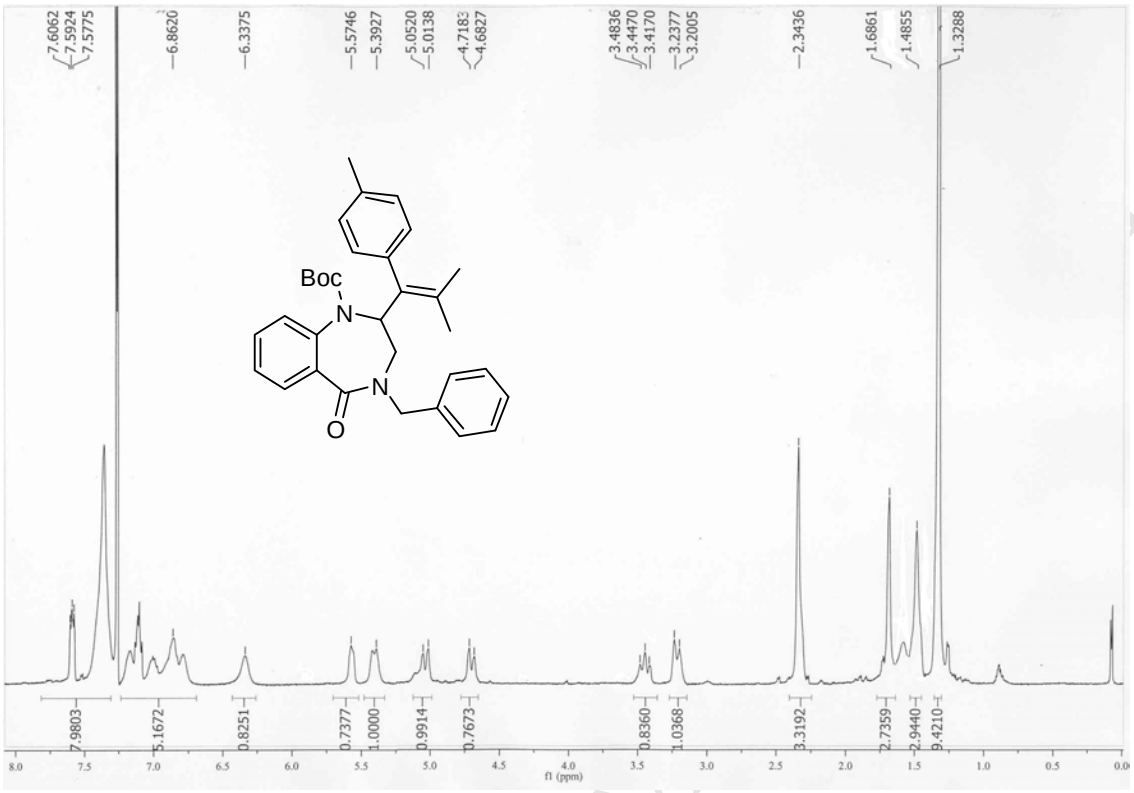

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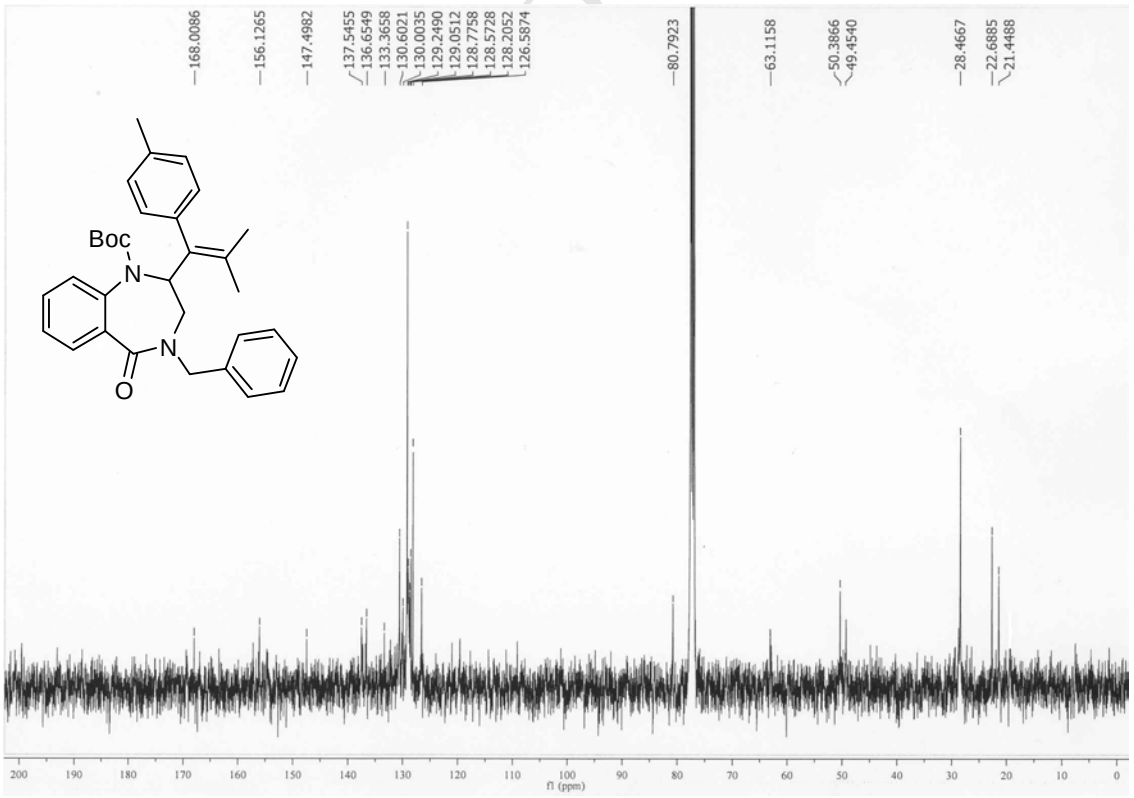

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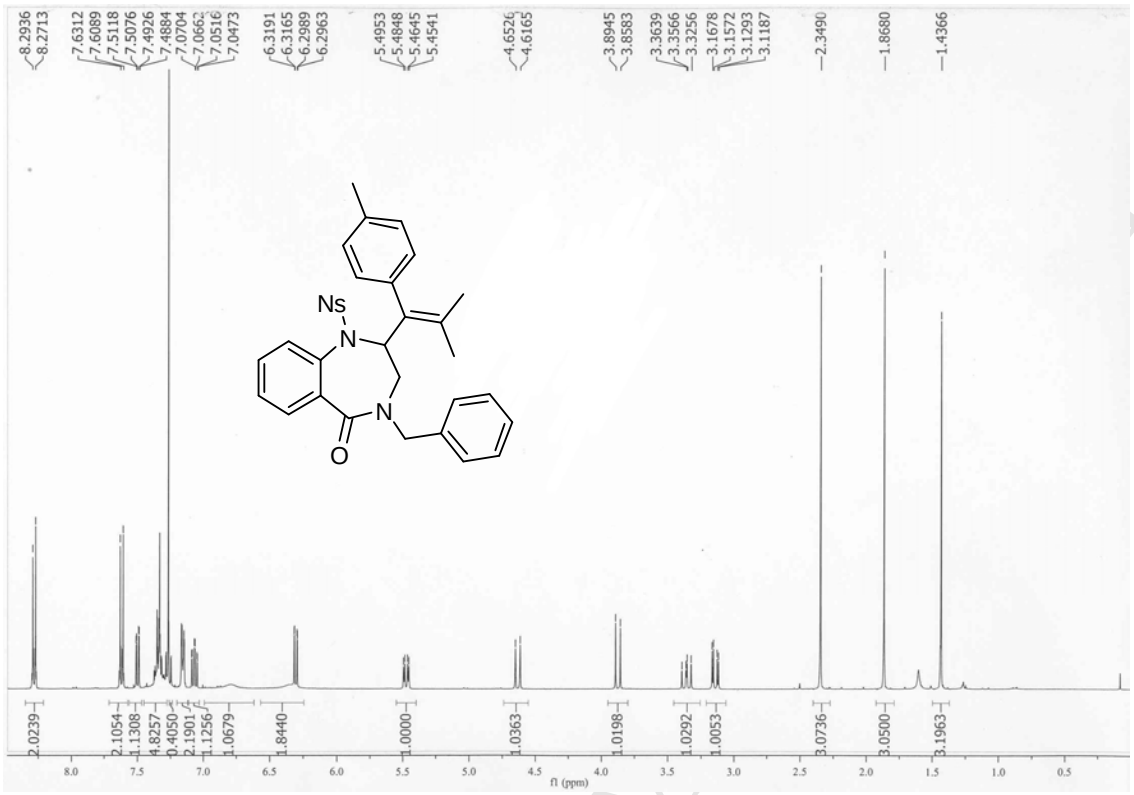

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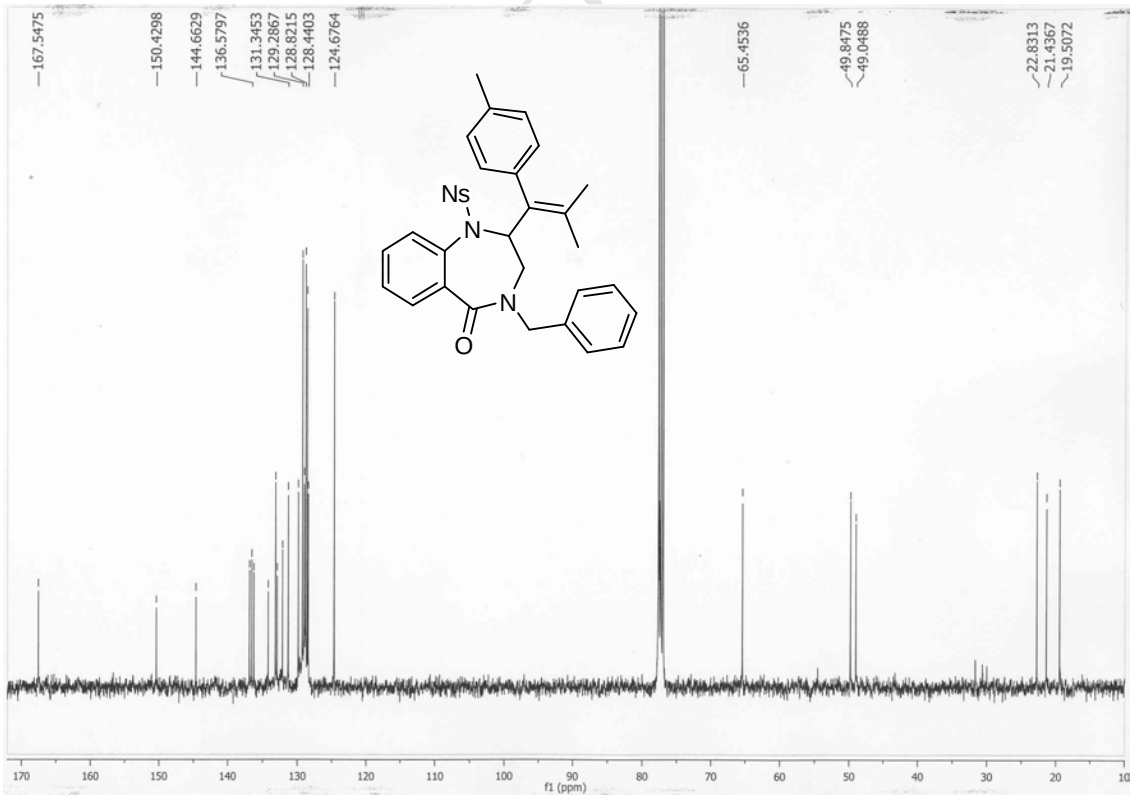

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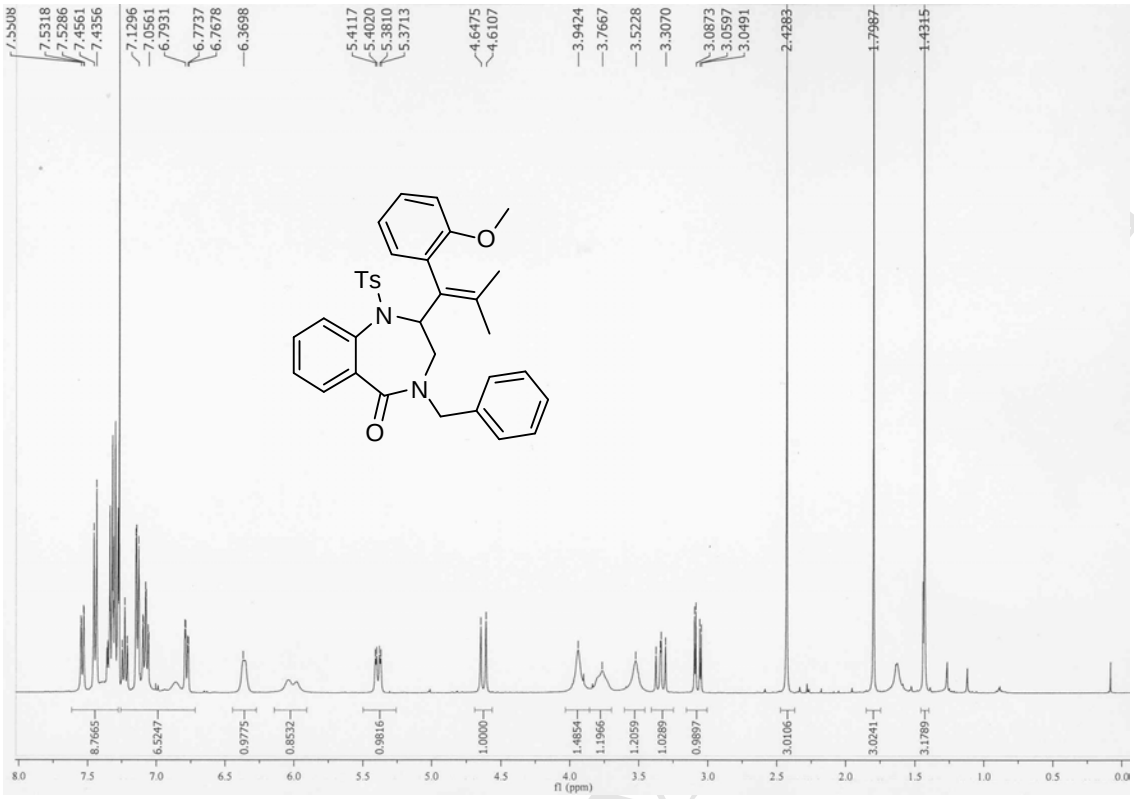

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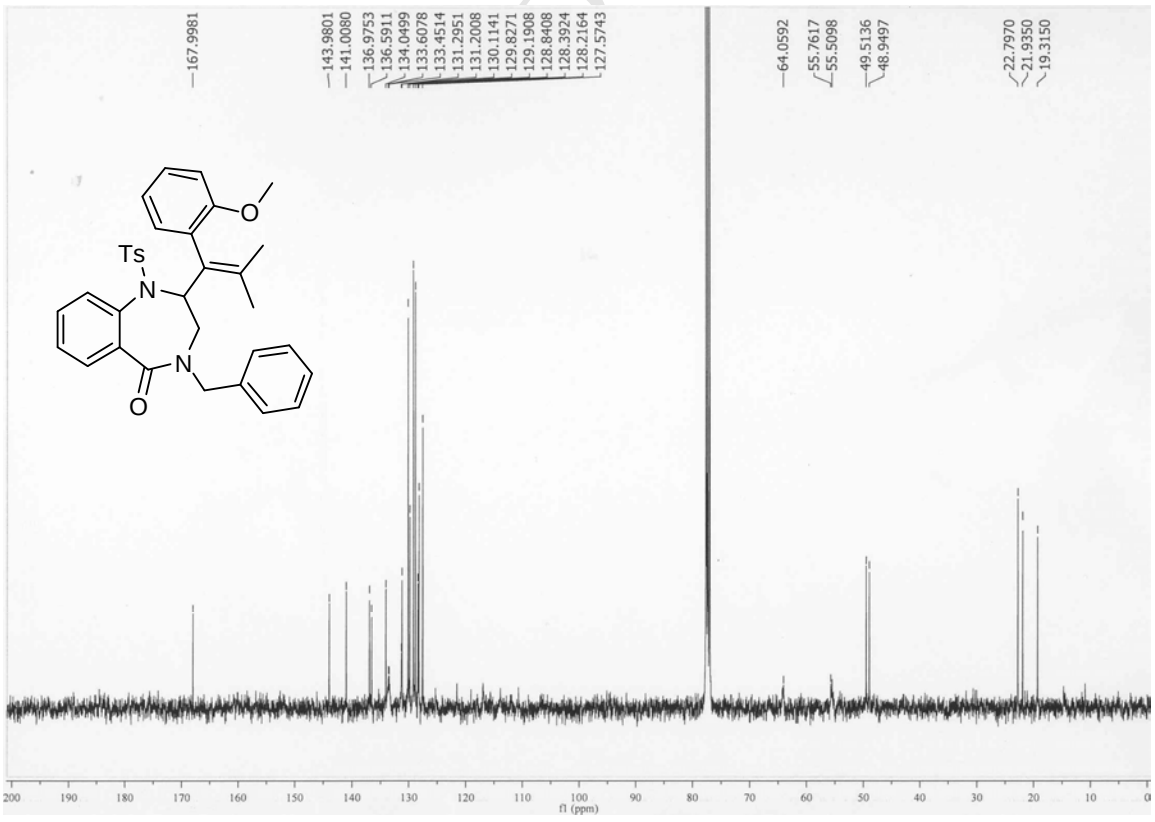

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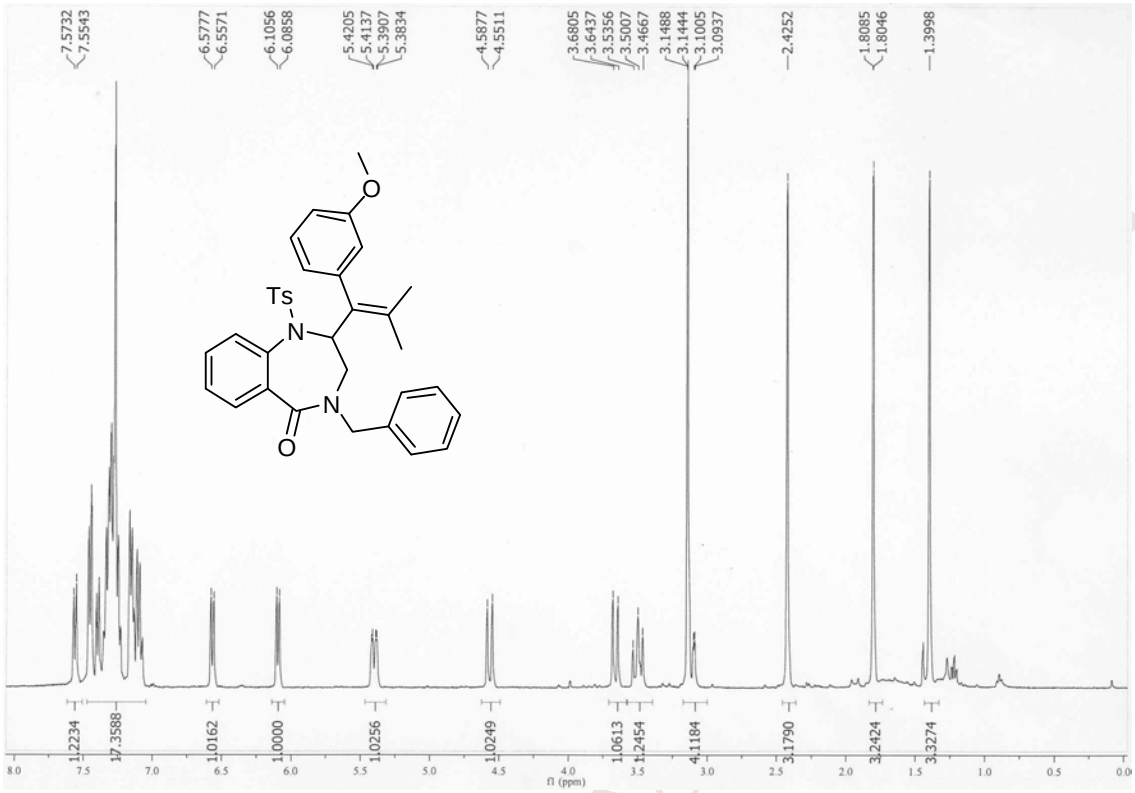

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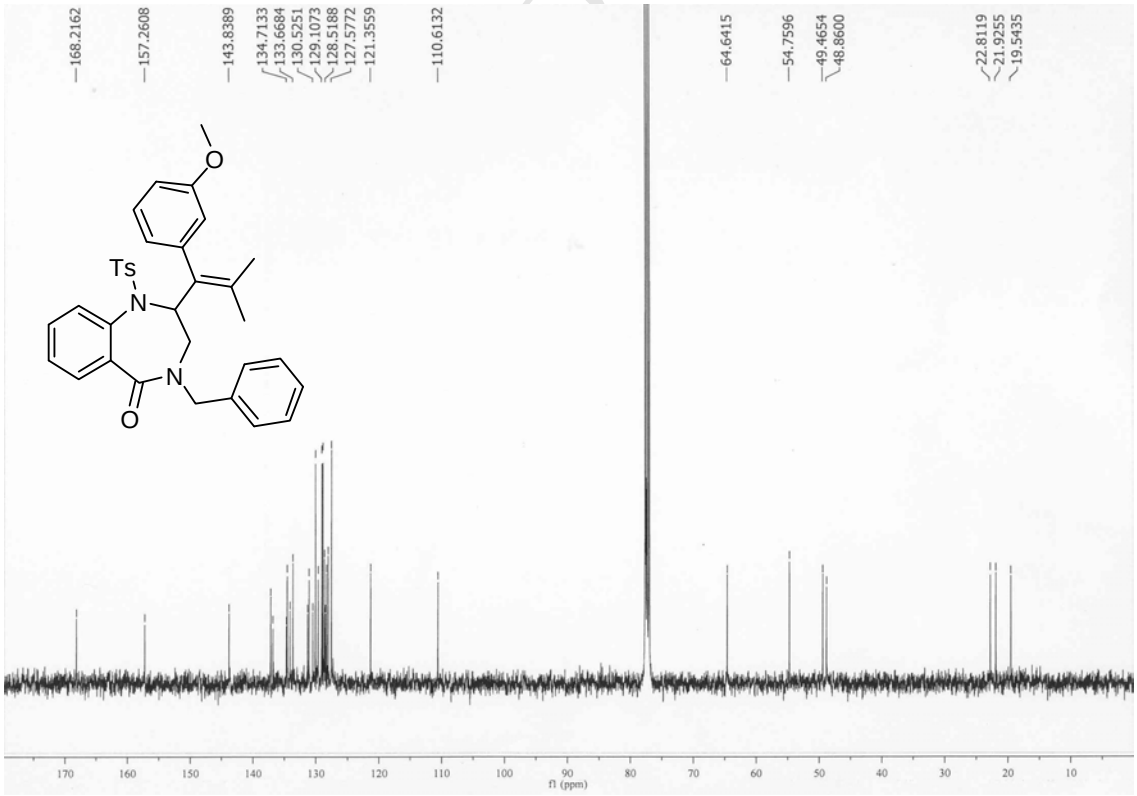

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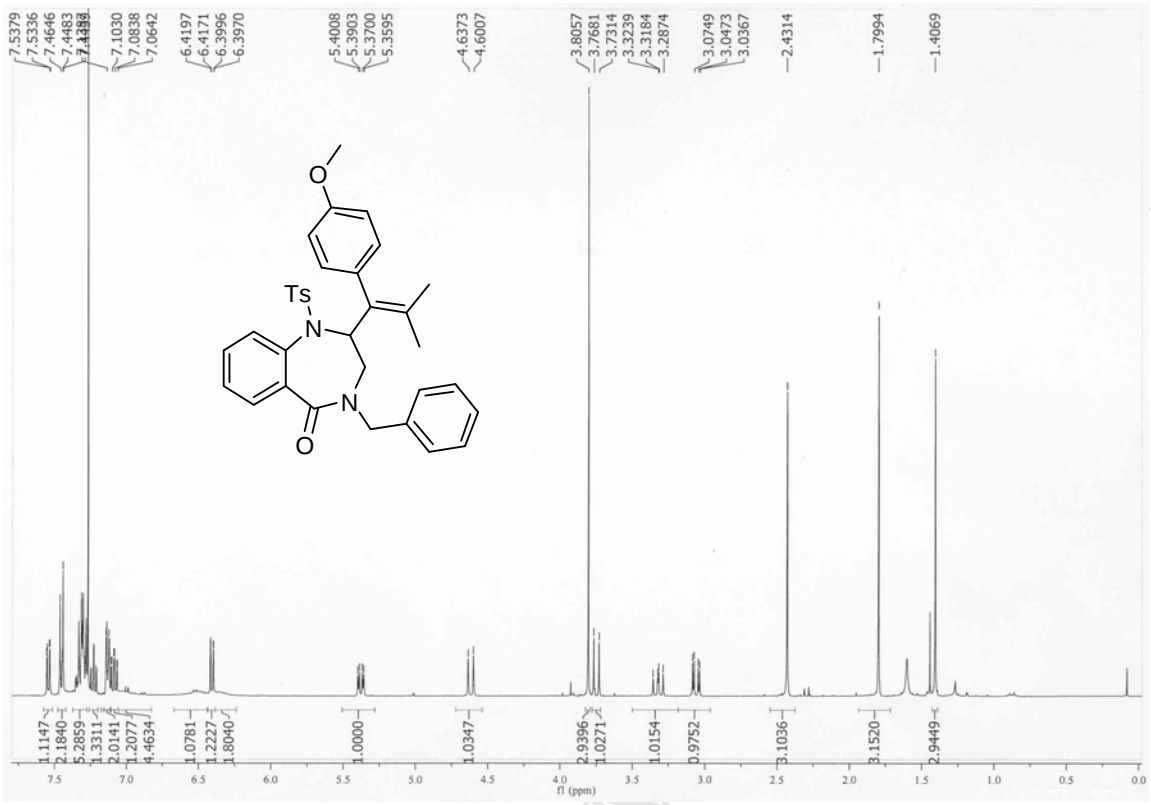

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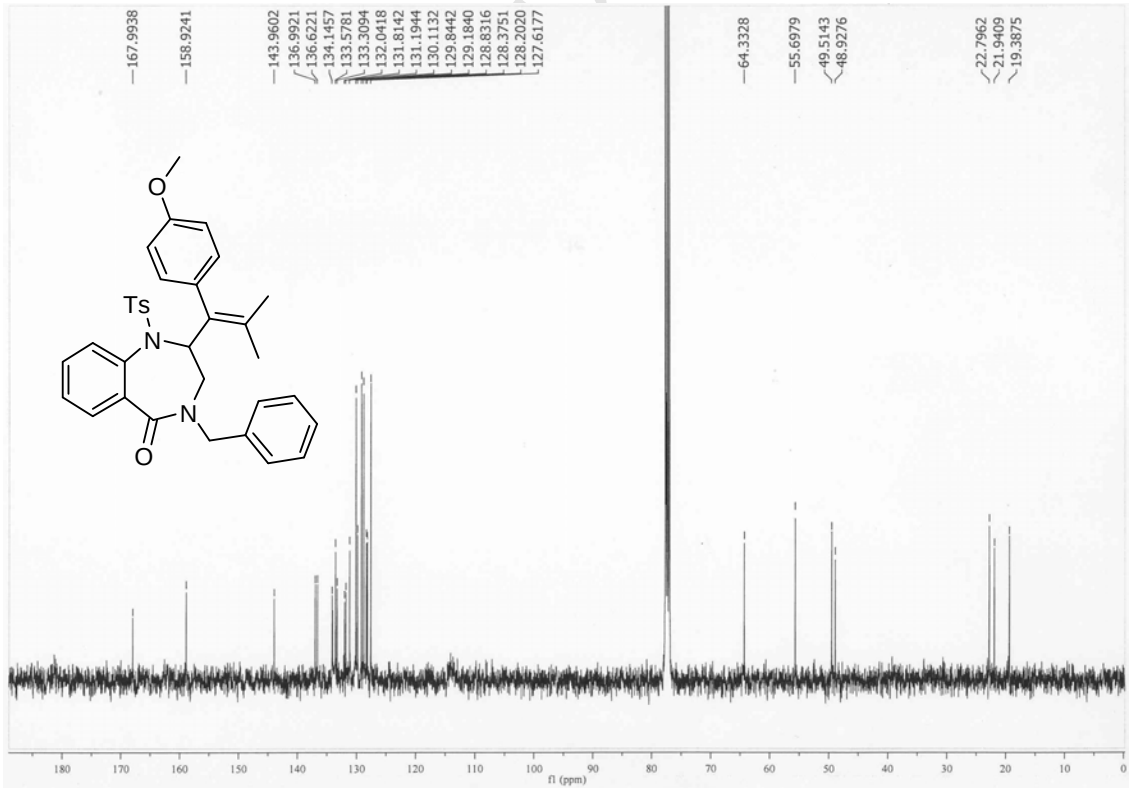

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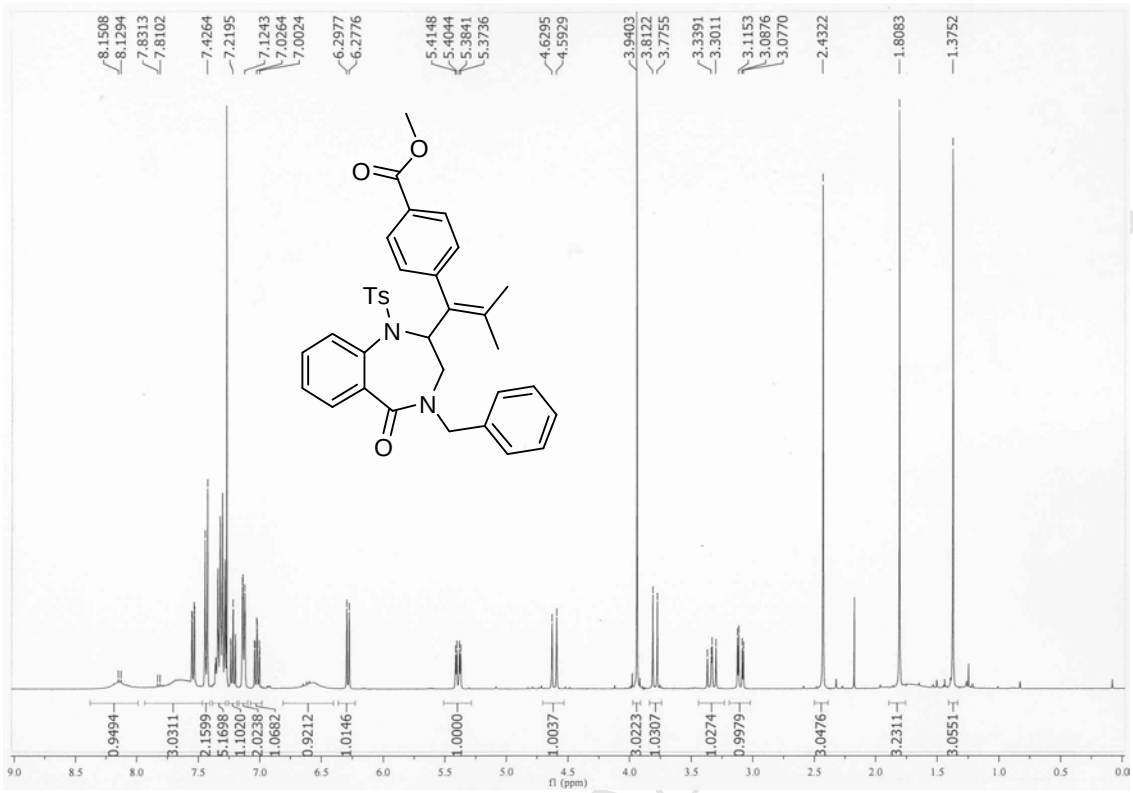

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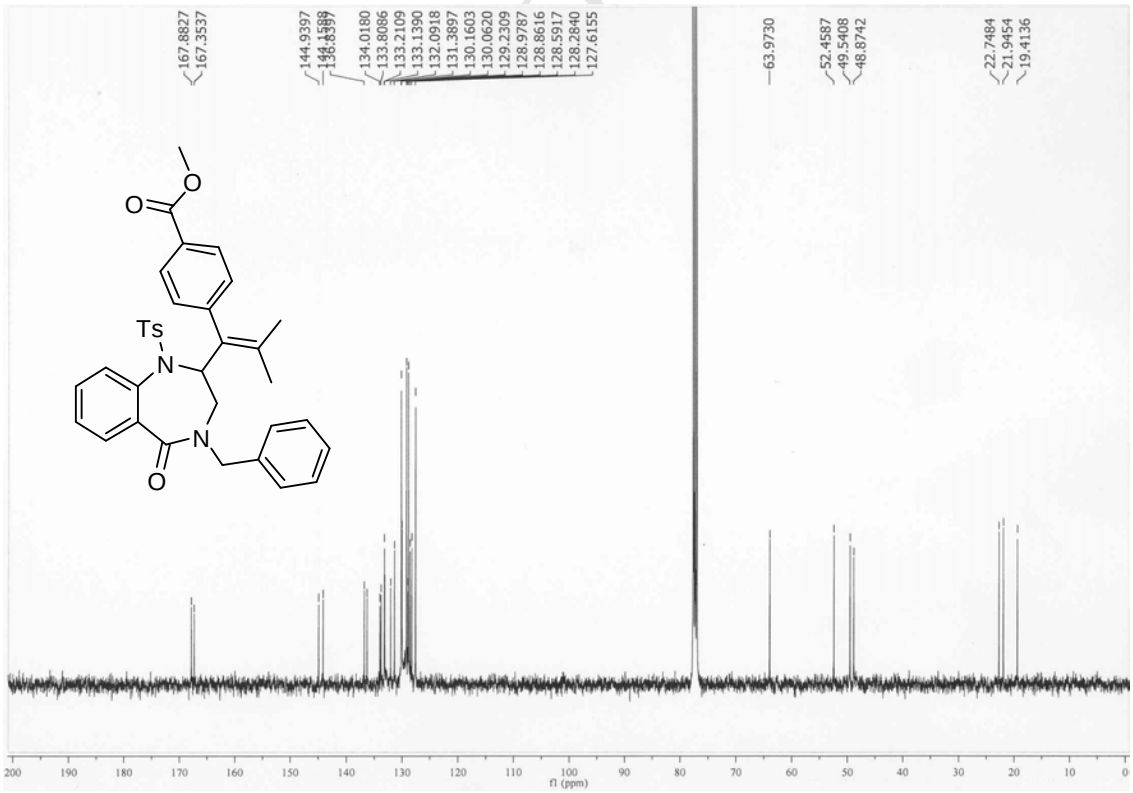

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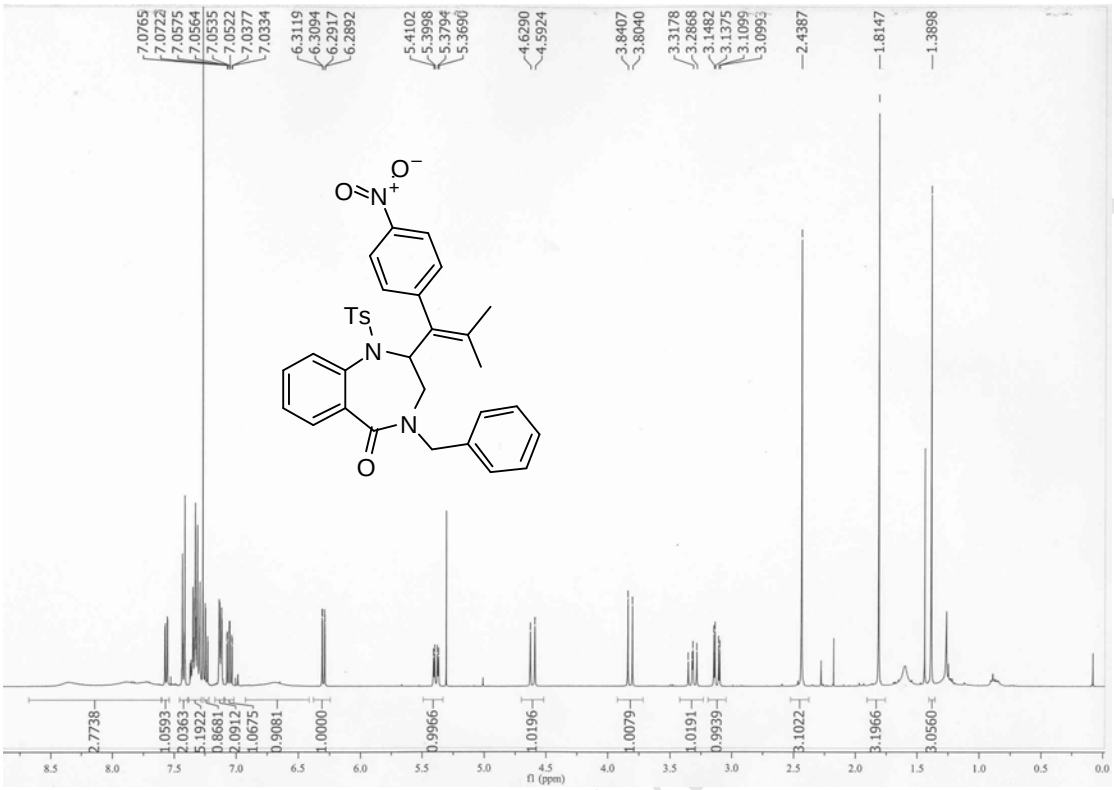

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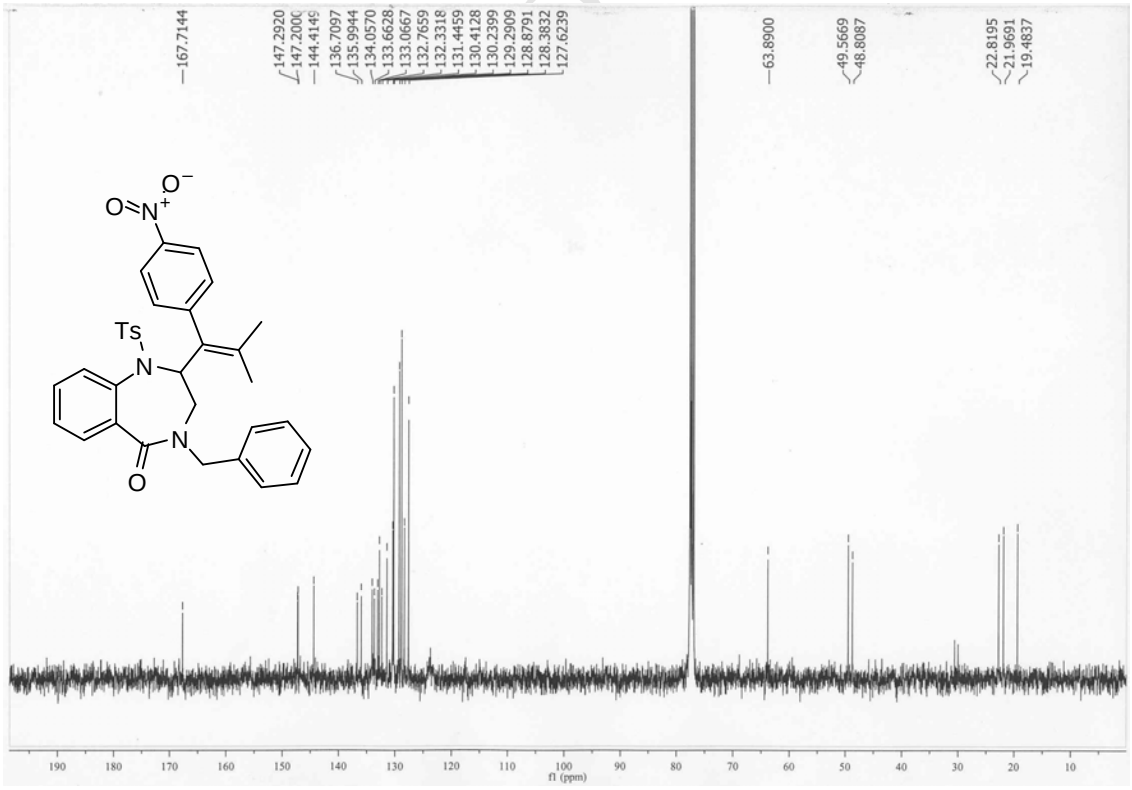

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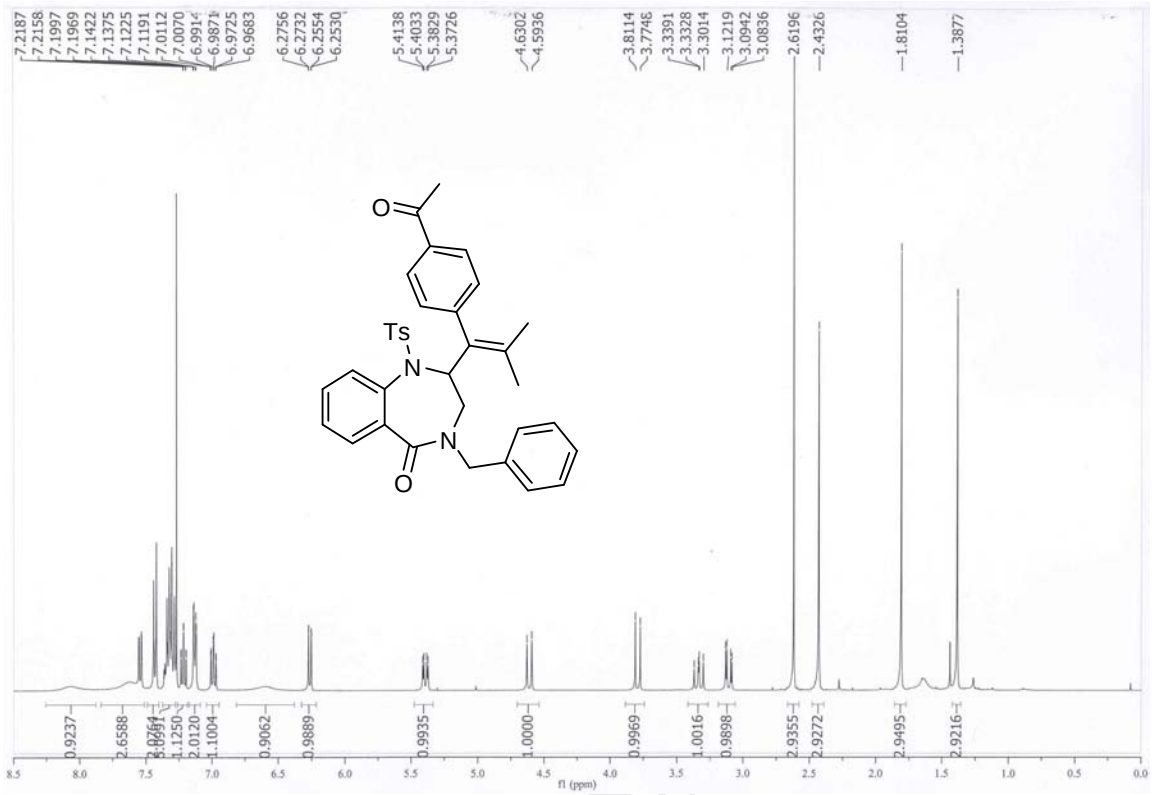

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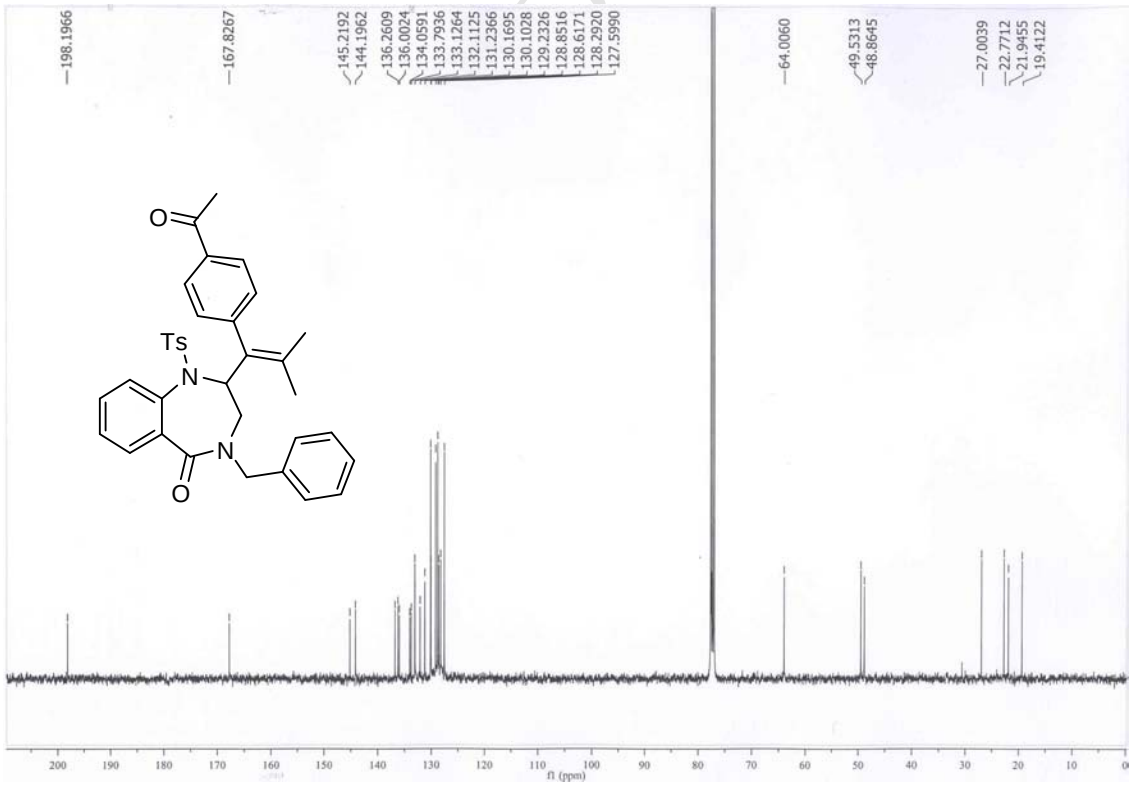

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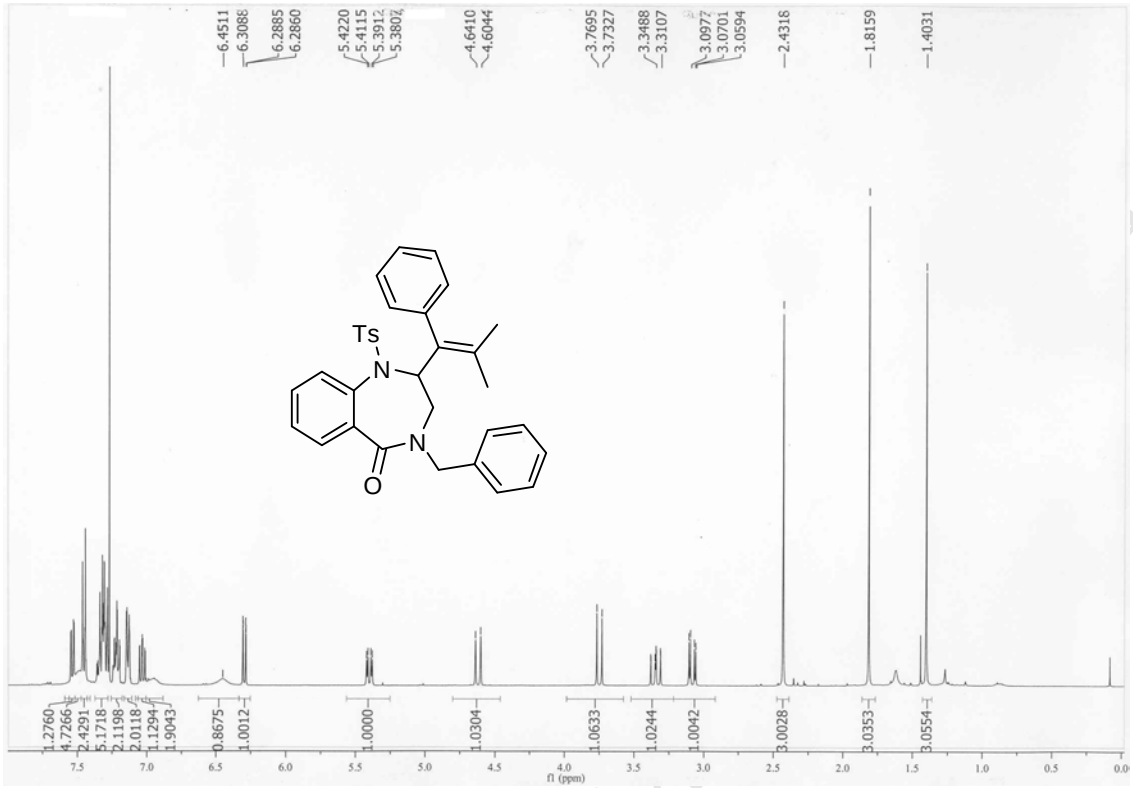

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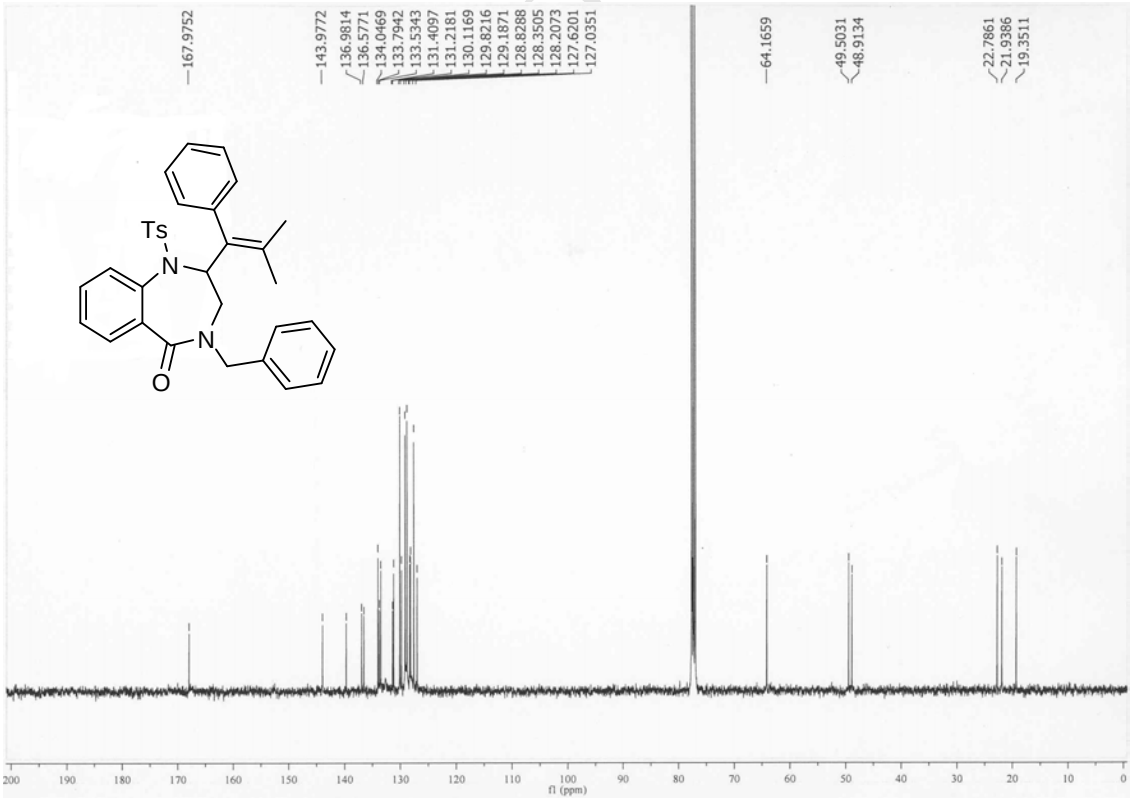

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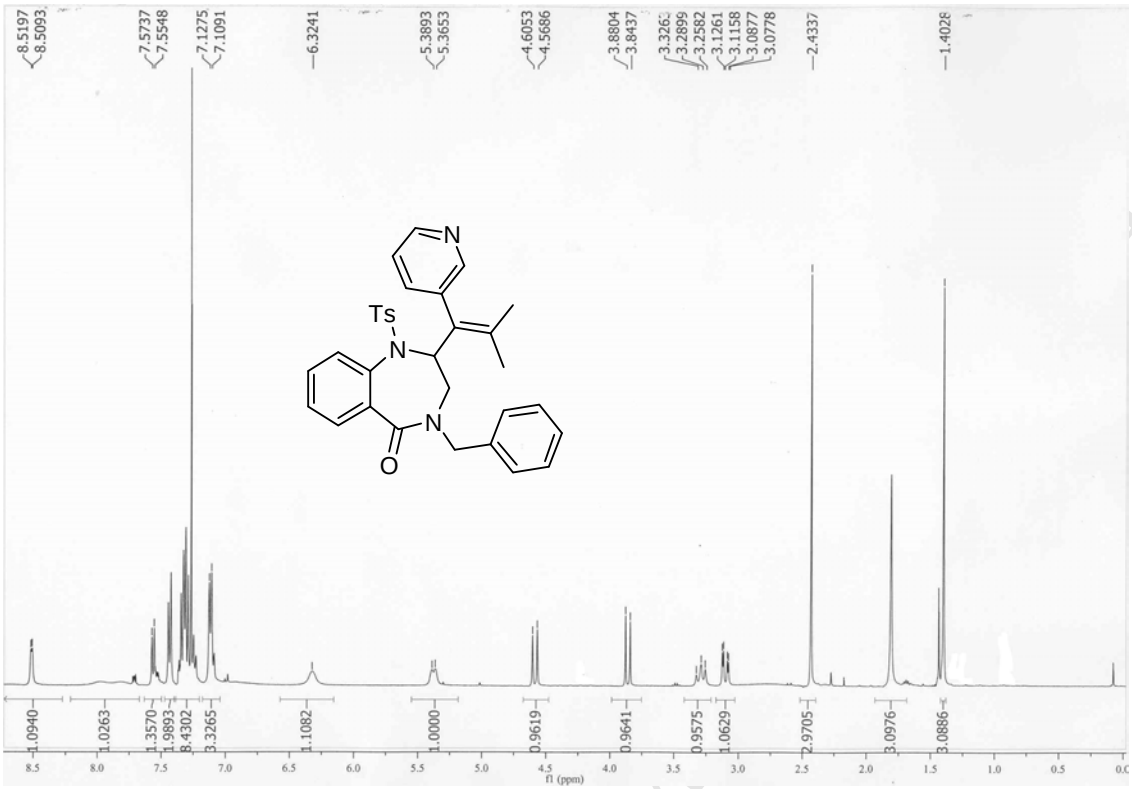
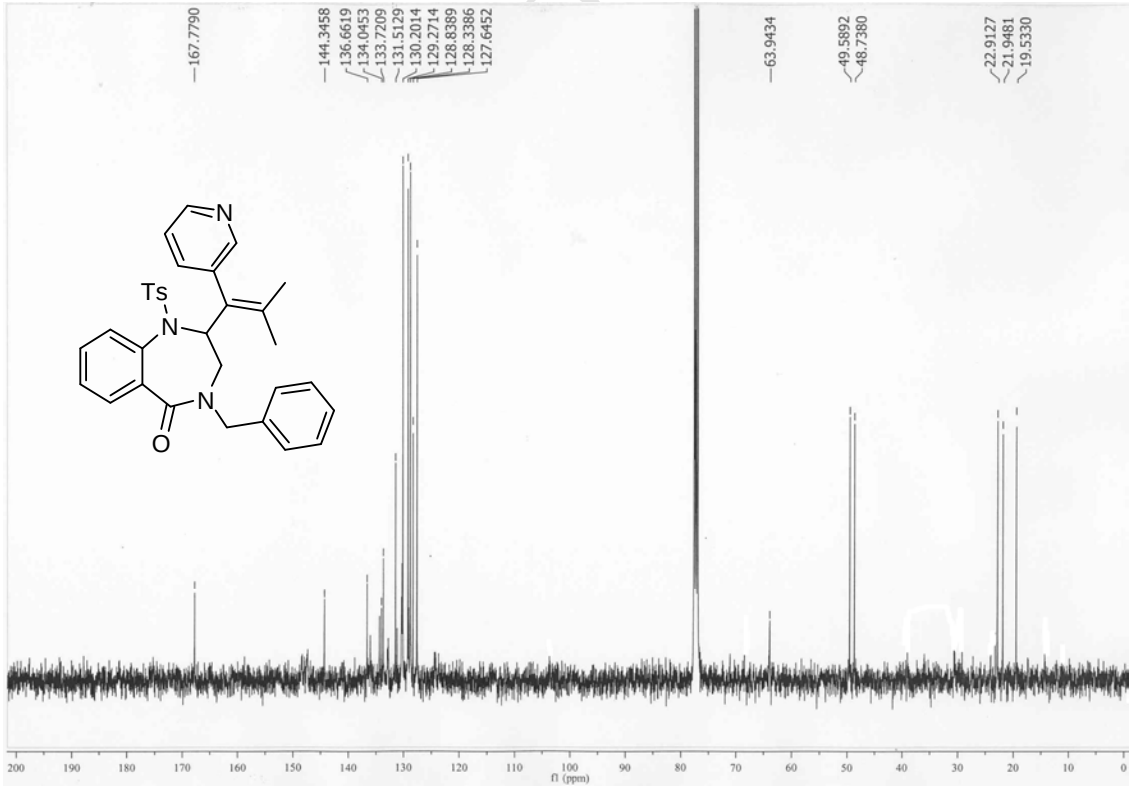
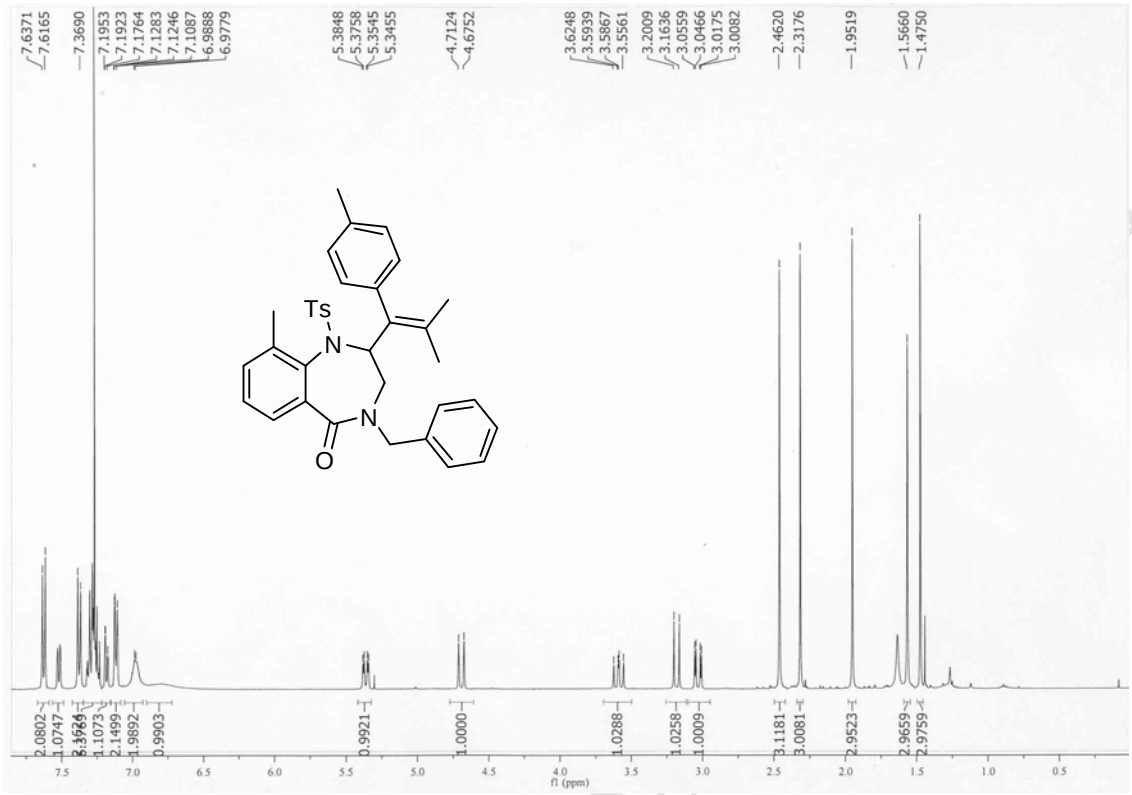


^{13}C spectrum of compound **2i**



^{1}H spectrum of compound **2j**



^{13}C spectrum of compound **2j**