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Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

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The synthesis of various polycyclic systems containing a C^{3a}-N^{i} bond between a hexahydropyrrolo[2,3-*b*]indole and an indole tryptophan is described here. A series of experiments was run to determine the best combination of five orthogonal protecting groups and the best reaction conditions for formation of said bond, which is a common feature among many recently discovered marine natural products.

Introduction

The tricyclic motif hexahydropyrrolo[2,3-*b*]indole (HPI) is present in many natural compounds with important bioactivities.[1] These compounds all feature a substituent at the 3a-position of the HPI, such as a methyl group, in (–)-physostigmine;[2] a prenyl, in flustramines,[3] brevicompanines[4] and roquefortines;[5] and a newly discovered HPI linked by one aromatic carbon, in idiospermuline,[6] psychotridine[7] and quadrigemine.[8] Recently isolated natural compounds such as psychotrimine,[9] chaetomin and the chaetocochins[10] contain an unusual bond between the 3a-position of the HPI and the indole nitrogen of either a tryptamine or a tryptophan (Figure 1). Kapakahines are natural products with a bond between the C^{4a} of an α-carboline and the indole nitrogen of an *N*-Trp.[11]

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To date, four total syntheses of psychotrimine have been reported.[12] Takayama *et al.* were the first to synthesize this compound,[12a] assembling the HPI motif from a phenylacetonitrile that contains an indoline at the appropriate α-nitrile position. In contrast, Newhouse and Baran[12b] prepared psychotrimine via simultaneous formation of the HPI and the *N*-C^{3a} bond. They later employed the same strategy to prepare kapakahines B and F[13], and (+)-psychotetramine.[14]

During the course of the present work, Rainier *et al.* published a study on *N*-C^{3a} bond formation via bromo-displacement of 3a-bromo-HPIC with the *N*-anion of indole.[15] The same group harnessed this chemistry to prepare kapakahines E and F,[16] and more recently, described a mechanism for the substitution.[17]

Compound **1**, which contains a bond between the C^{3a} of HPI and the *N* of an indole, could be used as a scaffold for the synthesis of many natural products and analogs. In the work reported here, **1** was synthesized via nucleophilic substitution of the bromine at position 3a of 3a-bromo-HPI with an *N*-indole anion (Figure 2). To ensure chemoselectivity during this chemistry, five orthogonal protecting groups were required. Studies to determine the best protecting groups and conditions for this bond formation were then performed and are described herein.

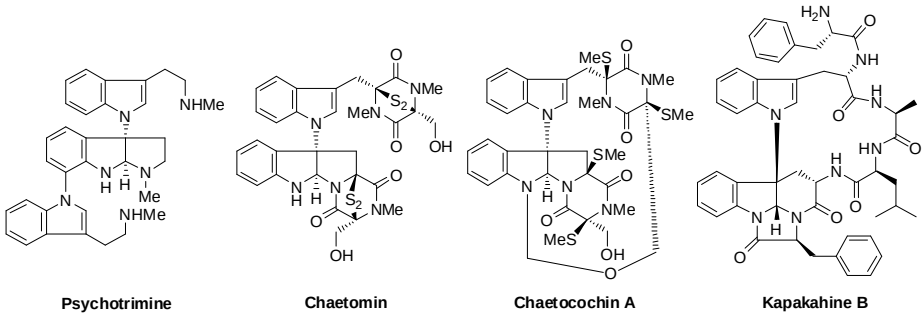


Figure 1. Natural products containing a bond between the C^{3a} of an HPI, or the C^{4a} of an α-carboline, and the indole nitrogen of either a tryptamine or a tryptophan.

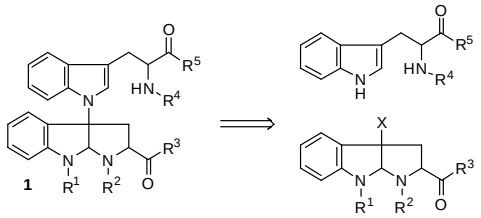


Figure 2. Retrosynthesis of compound **1**.

Results and Discussion

First of all, various bromo analogs of 3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3a-Br-HPI; **3**) were synthesized using two different procedures, which were subsequently compared for performance (Table 1). The first one follows the route described by Taniguchi and Hino,[18] based on cyclization of a protected Trp in acidic medium, followed by aniline protection and subsequent benzylic bromination of HPI-2-carboxylate. The second procedure is an one-step bromination-cyclization of a totally protected Trp using *N*-bromosuccinimide (NBS) and pyridinium *p*-toluenesulfonate (PPTS).[19] The resulting products **3** and their stereochemistries (*endo/exo*) are listed in Table 1. Although a three (two amino and one carboxylic protecting groups) orthogonal systems is desirable, the use of the same amino protecting groups (R^1 = R^2) for both amino groups were also studied (Table 1, Entries 2, 3, and 16) having in mind the different nucleophilicity of both amino functions. For the carboxylic protection, common esters such as methyl, *t*-butyl, and allyl were tested. On the other hand, for the amino function both alkoxycarbonyl, i.e., *tert*-butoxycarbonyl (Boc), allyloxycarbonyl (Alloc), benzyloxycarbonyl (Cbz), 2,2,2-trichloroetoxycarbonyl (Troc), and metoxycarbonyl (Moc), and and sulfonyl, i.e., 2-nitrobenzenesulfonyl (Nosyl) and SO_2Ph were tested. Additionally, , protected amino acids (R^2 and R^3 Table 1, Entries 14-16) were assayed with the idea of studying the size and/or the electronic properties of protecting groups.

The overall transformation of L-Trp-OMe (the starting material) into **3** was highly demanding, as illustrated by the yields, which ranged from poor to moderate. Method B, which is shorter, gave better yields for the same set of protecting groups (Table 1: Entries 7, 12 and 13) and has the important additional advantage of being amenable to use of various protecting groups for the α-amino group (R^2). Cyclization with H_3PO_4 (Method A) gave better yields when methoxycarbonyl (R^2=Moc) was used as N^{α}-Trp protecting group compared to when trichloroethoxycarbonyl (R^2=Troc) was used (see Table 1: Entries 12 and 7, respectively).

Despite various attempts in diverse conditions, we were unable to remove the Moc group from the N^1 of HPI-2-carboxylate.[21] Furthermore, to the best of our knowledge,[1] to date there have not been any reports of the Moc group being removed from the N^8 of HPI-2-carboxylate; instead, this group typically is reduced to obtain the desired *N*-Me product.[12b,22]

Compounds **3b** and **3c** possess two Boc groups at positions N^1 and N^8 which could be cleaved simultaneously; however, the amine of N^1 is more reactive than the aniline of N^8, which enabled chemoselective acylation of N^1 as reported by Danishefsky *et al.*.[23]

The ^{1}H-NMR signals corresponding to the protecting groups of R^2—namely, the signals for the CH_2 of Cbz or Troc, and for the CH_3 of Moc—are broad or split, because the protons are diastereotopic.

The difference in stereochemistry of the products **3** obtained from each method is noteworthy. Comparison of the ^{1}H-NMR spectra of the products **3g** obtained from Method A and from Method B revealed significant differences in the signals for the proton at position 2 (δ 4.67 vs. 3.98 ppm, respectively) and for the methyl ester (δ 3.21 vs. 3.74 ppm, respectively). Based on these data, the stereochemistry of the product from Method A was determined to be ***endo*-3g**, and that of the product from Method B, ***exo*-3g** (see Figure 3). The diamagnetic anisotropy of the phenyl ring shields the *endo*-methyl group (δ 3.21 ppm) and the *exo*-H2 (δ 3.98 ppm).[24] The same phenomenon occurred with the *endo/exo* **3l** and **3m** obtained with the appropriate method (see Supporting Information).

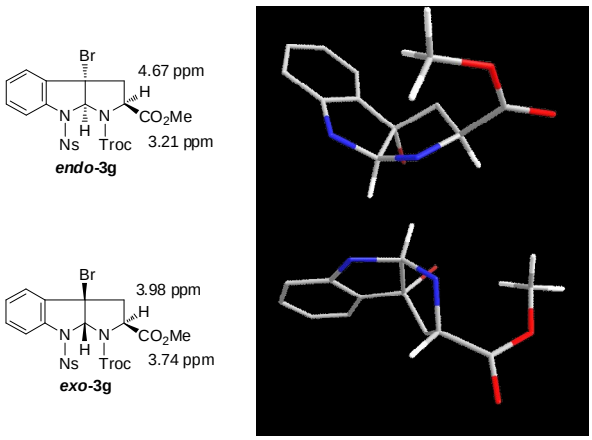
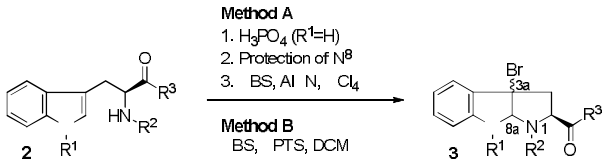


Figure 3. Comparison of the ^{1}H-NMR data for *endo* and *exo* **3g** (left). Three-dimensional models of the corresponding tricyclic systems (right).[25]

Compounds **3a**, **3b**, **3d**, **3k**, **3n**-**3p** (Table 1: Entries 1, 2, 4, 11, 14-16) only showed one diastereomer on NMR data. Their stereochemistry assignments were determined by comparing the chemical shifts of proton and substituent at C^2 of HPI.

To obtain a more versatile intermediate during synthesis of **3n**, **3o** and **3p** via Method B, protected Ala or Ile were used as N^{α}- and *O*-protecting groups respectively. However, the synthesis of compound **6** required an indirect route (see Table 1, footnote d), because subjecting dipeptide **4**, which was N^{α}-Alloc-Ala protected, to the acidic conditions for cyclization furnished the dimer **5** (Figure 4). Formation of **5** could be explained based on electrophilic substitution between **4** and the indoline that had formed after its protonation.

Table 1. Synthesis of the bromo compounds **3a-p**.



#	Comp.	R^1	R^2	R^3	Method (Yield %)	*endo*:*exo*
1	3a	Boc	Alloc	OMe	B (83)	*exo*
2	3b	Boc	Boc	OAllyl	B (30)[a]	*exo*
3	3c	Boc	Boc	OMe	B (86)	4:96[b]
4	3d	Boc	Cbz	OMe	B (78)	*exo*
5	3e	Boc	Troc	OMe	B (77)	11:89[c]
6	3f	Nosyl	Cbz	OtBu	B (80)	7:93[c]
7	3g	Nosyl	Troc	OMe	A (9) B (57)	*endo* 8:92[c]
8	3h	Nosyl	Troc	OtBu	B (59)	6:94[b]
9	3i	SO_2Ph	Boc	OMe	B (92)	7:93[b]
10	3j	SO_2Ph	Cbz	OMe	B (82)	4:96[b]
11	3k	SO_2Ph	Cbz	OtBu	B (83)	*exo*
12	3l	SO_2Ph	Moc	OMe	A (37) B (96)	*endo* 5:95[b]
13	3m	SO_2Ph	Moc	O*t*Bu	A (28) B (58)	91:9[c] 25:75[c]
14	3n	Boc	N^{α}-Alloc-Ala	OMe	B (47)	*exo*
15	3o	Boc	Alloc	Ile-OMOM	B (47)[d]	*exo*
16	3p	Boc	Boc	Ile-OAllyl	B (41)[d]	*exo*

[a] **3b**, **3o** and **3p** were synthesized from **3c**, **3a** and **3c**, respectively, after hydrolysis and subsequent esterification or coupling with the protected Ile (see Supporting Information). [b] Ratio determined by HPLC.[20] [c] Ratio determined by ^{1}H-NMR. [d]

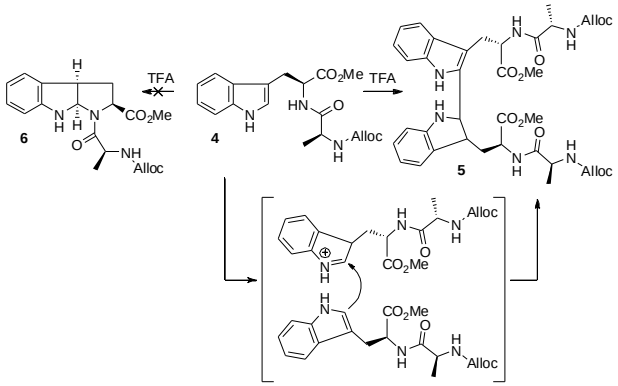


Figure 4. Dimerization of **4** under acidic conditions.

Consequently, in the first step of the HPI formation in Method A, working with an N^{α}-carbamate protecting group at this position, instead an amide bond, is rather important.

The second part of this work comprised formation of the bond between the C^{3a} of the HPI and the N^{i} of the Trp. Several pairs of base and solvent were tested to generate the indole anion that would drive the substitution to give compound **1**.[26] The best conditions found comprised NaH in DMF at 70 °C for 1.5 h. Every bromo derivative (**3a-p**) was tested with several protected Trp's. A distinguishing data point in the ^{13}C-NMR data for compounds **1** and **3** is the chemical shift of the quaternary C^{3a}, which is less shielded in **1** (δ 72.4 to 82.2 ppm) than in **3** (δ 53.7 to 67.9 ppm). The results of these substitutions are summarized in Table 2.

The best yields of **1** in the nucleophilic substitution were found using **3a**, **3l**, **3m** and **3p** (Table 2: Entries 1 and 7-10, respectively). Moderate yields were obtained for the substitutions with bromides **3c**, **3d** and **3g** (Entries 3-6). However, very poor yields (< 10%, data not shown) were observed when bromides **3b**, **3e**, **3f**, **3h-k** and **3n** were reacted with different protected versions of **7**, which contains two additional protecting groups.

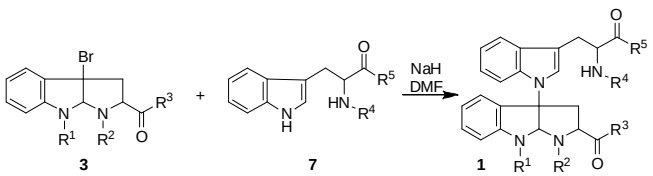


Table 2. Nucleophilic substitution at the C3a of 3a-Br-HPI

#	3[a]	R^4	R^5	3[b]	7[b]	1[b]	Comp (%)[c]
1	**exo-3a**	Phth	OMe	39	18	43	**1a** (41)
2	**3c**	Moc	OMe	49	22	29	**1b** (20)
3	**3c**	Phth	OMe	66	11	24	**1c** (21)
4	**exo-3d**	Phth	OMe	28	14	58	**1d** (26)
5	**endo-3g**	Alloc	OMe	24	21	48	**1e** (29)
6	**exo-3g**	Alloc	OtBu	62	22	15	**1f** (22)
7	**endo-3l**	Alloc-Ile	OtBu	-	24	50	**1g** (41)
8	**endo-3l**	Moc	OMe	-	1	91	**1h** (77)
9	**endo-3m**	Boc-Ile	OAllyl	29	20	48	**1i** (30)
10	**3p**	Phth	OMe	13	42	11	**1j** (30)

[a] See Table 1 for the protecting groups used in each compound **3**. [b] Percentage of each compound in the reaction crude (as measured by HPLC).[20]. [c] Yield of isolated compound.

The phthalamide (Phth) was introduced as R^4 because it is orthogonal to all protecting groups used in the first reactions (Table 2: Entries 1, 3, 4 and 10), as it eliminates all the N^{α} acid protons in **7.** The wide range of yields in the resulting substitution (from 21 to 41%) demonstrates the importance of the protecting groups in the starting bromide. The bromides **3l** and **3m** have the same protecting groups in both amino groups of HPI (R^1 = SO_2Ph, R^2 = Moc). Interestingly, the yield was lower when the group at R^5 was *tert*-butyl ester (**1g**, Entry 7) compared to methyl ester (**1h**, Entry 8). Likewise, the yield was lower when R^3 was *tert*-butyl ester (**1i**, Entry 9) compared to methyl ester (**1h**, Entry 8). The same trend was observed for **1f** (Entry 6) and **1e** (Entry 5), although to a lesser extent: the *tert*-butyl in **1f** is more sterically hindered than the methyl ester in **1e**. The results obtained with a protected Ile-Trp dipeptide as nucleophile (Entries 7 and 9), and with a Br-HPI and a protected Ile (Entry 10), are interesting, as they can serve as the stepping stone to synthesis of peptides found in natural compounds. Additionally, owing to this Ile protection, **1j** (R^3= Ile-OAllyl, Entry 10) was obtained in higher yield than was **1c** (R^3= OMe, Entry 3), whose protecting groups are the same, except for at R^3.

Reaction of bromide **3n** and N^{α}-Phth-Trp-OMe unexpectedly gave compound **8**. The product was characterized by mono- and bi-dimensional NMR and by HRMS (see Supporting Information). Important spectroscopy data for compound **8** are the lack of Br, the α-proton of the Trp, and the fact that the two protons of the cyclopropane CH_2 (2d, J = 15.4 Hz, at δ 3.43 and 3.91 ppm) only exhibit a geminal coupling constant. The significant difference in the chemical shift of the α-proton of the Ala in **3n** (δ 5.02 ppm) and that of the Ala in **8** (δ 4.11 ppm) could be justified by the different electronic effects in each compound. One hypothetical mechanism for formation of **8** begins with deprotonation of the C^2 of the HPI, made possible by the basic conditions, followed by intramolecular bromine displacement and subsequent formation of cyclopropane, to afford intermediate **B** (see Figure 5). The high strain in **B** could drive opening of the aminal and subsequent cyclization, to give a more relaxed cyclohexane (see Figure 5).

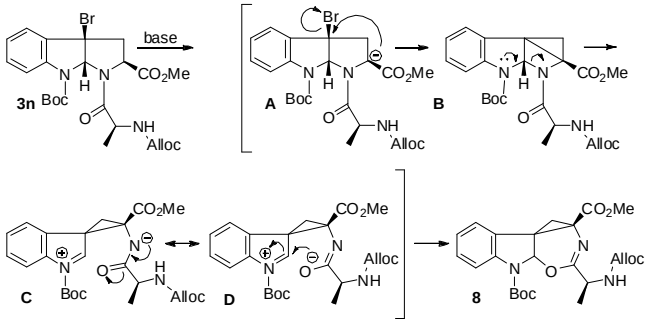


Figure 5. Hypothetical mechanism for formation of **8**.

This is the first time that the authors of this paper have isolated a compound such as **8** after the nucleophilic substitution reaction with the aforementioned conditions. Recently, J.D. Rainier *et al.* have reported the behavior of **3c** under basic conditions of KO*t*Bu and have isolated a tetracycle-containing compound that resembles **B**.[27]

Conclusions

In conclusion, various analogs of 3a-bromo-1,2,3,4,4a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (**3**), protected with different combinations of three orthogonal protecting groups, were prepared by two different routes. The routes were then compared for performance. Method A, based on sequential cyclization, protection and bromination, provided the thermodynamic *endo*-compound; whereas Method B, based on *one pot* bromination-cyclization of a fully protected Trp, afforded mainly the kinetic *exo*-bromide. The influence of the protecting groups on formation of the *N*-C^{3a} bond between the Trp and HPI to give compounds **1f**, **1g**, and **1i** (containing five orthogonal protecting groups) and compounds **1a**, **1d**, **1e** and **1j** (containing four orthogonal protecting groups) also was evaluated. Some of these compounds contain a protected Ile as the R^4 to protect the α-amino Trp; the orthogonal protecting groups enable synthetic versatility for constructing more structurally complex molecules. The protecting groups in the bromides **3** determined the yields of compounds **1a**, **1c**, **1d** and **1j**, whose starting N^{α}-Phth-Trp-OMe **7** is the same. Moreover, the importance of the carbamate protecting group at R^2 should be emphasized: unexpectedly, compound **5** was obtained from an attempted cyclization of **4** in acidic medium (using an Ala amide bond for protecting the N in **4**) and compound **8** was obtained from an attempted nucleophilic substitution of the bromine at C^{3a} of **3n**.

Experimental Section

General procedure for the synthesis of 1: A solution of **6** (3.0 mmol) in dry DMF (10 mL) was added to a suspension of 60% NaH in mineral oil (1.2 eq.) in dry DMF (20 mL), and the resulting mixture was stirred at room temperature for 15 min. A solution of **3** (3.0 mmol) in dry DMF (10 mL) was then added. The mixture was stirred at 70 °C for 1.5 h. The reaction mixture was then cooled to room temperature and quenched with H_2O. The aqueous phase was saturated with NaCl and extracted with EtOAc. The organic solution was dried over anhyd. Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel to afford **1**.

Compound 1a: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50), *endo*:*exo* (57:43) mixture. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48 and 1.49 (2s, 9H); 2.82 and 2.92 (2d, J = 13.0 Hz, 1H); 3.17 and 3.21 (2s, 3H); 3.33-3.45 (m, 1H); 3.49-3.68 (m, 2H); 3.76 (s, 3H); 4.59-4.74 (m, 2H); 4.88 (t, J = 9.8 Hz, 1H); 5.08-5.16 (m, 1H); 5.17-5.31 (m, 2H); 5.85-5.99 (m, 1H); 6.62-6.88 (m, 3H); 6.95-7.14 (m, 4H); 7.30 (dd, J = 7.4 and 14.8 Hz, 1H); 7.57 (t, J = 6.8 Hz, 1H); 7.68 (dd, J = 3.1 and 5.5 Hz, 1H); 7.71 (dd, J = 3.0 and 5.6 Hz, 1H); 7.73-7.79 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.1 (3q); 38.1 (t); 52.2 (q); 52.3 (d); 52.5 and 52.8 (q); 53.4 (s); 59.3 and 59.4 (d); 66.6 (t); 79.6 (d); 82.2 (2s); 110.6 (s); 111.2 and 111.3 (d); 117.6 and 117.7 (t); 119.2 and 119.3 (d); 120.0 (d); 122.3 and 122.4 (d); 123.4 (4d); 124.4 and 124.7 (d); 129.7 (s); 129.8 (s); 130.9 (d); 131.6 (s); 131.7 (s); 132.5 (d); 134.0 (3d); 134.7 (s); 143.3 (s); 143.4 (s); 151.8 (s); 151.9 (s); 167.2 (s); 167.4 (s); 169.4 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 2952, 1716, 1390, 1255, 1158, 1019, 721. HRMS (ESI) calculated for $C_{41}H_{40}N_4O_{10}Na$ *m/z* ($M+Na^+$) 771.2642, found 771.2634.

Compound 1b: Purified by flash chromatography (hexane/EtOAc, from 80:20 to 50:50). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.50 (s, 9h); 1.52 (s, 9H); 2.98-3.20 (m, 3H); 3.23 (s, 3H); 3.54-3.65 (m, 7H); 4.60 (m, 1H); 4.90 (bs, 1H); 5.19 (t, J = 8.3 Hz, 1H); 6.69 (d, J = 7.3 Hz, 1H); 6.75 (s, 1H); 7.07-7.33 (m, 5H); 7.35-7.42 (m, 1H); 7.52 (t, J = 7.5 Hz, 1H); 7.67 (bs, 1H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.6 (t); 28.2 (3q); 28.3 (3q); 38.4 (t); 52.2 (q); 52.3 (q); 52.4 (q); 54.5 (d); 59.4 (d); 72.5 (s); 79.8 (d); 81.6 (s); 82.4 (s); 109.3 (s); 111.6 (d); 119.4 (d); 120.2 (2d); 122.5 (d); 123.6 (d); 124.9 (d); 125.3 (d); 130.2 (s); 131.0 (d); 131.1 (s); 134.8 (s); 143.5 (s); 152.2 (s); 156.6 (s); 164.3 (s); 171.5 (s); 172.3 (s). IR (KBr): ν (cm^{-1}) 3352, 2978, 1719, 1394, 1368, 1158, 740. HRMS (ESI+) calculated for $C_{36}H_{45}N_4O_{10}$ *m/z* ($M+H^+$) 693.3130, found 693.3118.

Compound 1c: Purified by flash chromatography ($MeCN/H_2O$, from 30:70 to 90:10). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.46 and 1.48 (2s, 9H); 1.50 and 1.52 (2s, 9H); 2.77 and 2.90 (2d, *J* = 12.9 Hz, 1H); 3.17 and 3.21 (2s, 3H); 3.38 (dd, *J* = 9.3 and 12.9 Hz, 1H); 3.50-3.66 (m, 2H); 3.76 (s, 3H); 4.83 (bs, 1H); 5.08-5.18 (m, 1H); 6.64-6.75 (m, 3H); 6.82 (t, *J* = 7.6 Hz, 1H); 7.03-7.14 (m, 4H); 7.24-7.31 (m, 1H); 7.57 (dd, *J* = 7.6 and 7.8 Hz, 1H); 7.66-7.79 (m, 4H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.2 (3q); 28.3 (3q); 38.8 (t); 52.1 (q); 52.6 (d); 52.8 (q); 59.3 (d); 72.4 (s); 79.6 (d); 79.7 (s); 82.0 (s); 110.4 (s); 111.4 (d); 119.2 (d); 119.9 (d); 122.3 (d); 123.1 (d); 123.4 (2d); 124.4 (d); 124.7 (d); 125.0 (d); 128.9 (s); 129.7 (s); 130.8 (d); 131.7 (s); 134.0 (s and 2d); 134.7 (s); 143.5 (s); 151.8 (2s); 167.2 (s); 167.4 (s); 169.4 (s); 171.0 (s). IR (KBr): ν (cm^{-1}) 2977, 1716, 1390, 1255, 1158, 1019, 739, 721. HRMS (ESI+) calculated for $C_{42}H_{45}N_4O_{10}$ *m/z* ($M+H^+$) 765.3130, found 765.3091.

Compound 1d: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50), *endo*:*exo* (69:31) mixture. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H); 2.80 (d, *J* = 13.0 Hz, 1H); 3.16 and 3.20 (2s, 3H); 3.37 (dt, *J* = 9.3 and 13.0 Hz, 1H); 3.49-3.68 (m, 2H); 3.76 (s, 3H); 4.88 (t, *J* = 10.6 Hz, 1H); 5.07-5.30 (m, 3H); 6.62-6.89 (m, 3H); 7.02-7.10 (m, 4H); 7.26-7.36 (m, 6H); 7.54-7.61 (m, 1H); 7.66 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.70 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.74 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.76 (dd, *J* = 3.1 and 5.5 Hz, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.1 (3q); 38.3 (t); 52.2 (q); 52.5 (d); 52.8 (q); 59.4 (d); 67.5 (t); 72.4 (s); 79.7 (d); 82.2 (s); 110.5 (s); 111.3 (d); 119.2 (d); 120.0 (d); 122.4 (2d); 123.4 (4d); 124.6 (d); 127.8 (d); 128.0 (d); 128.4 (3d); 129.7 (s); 130.9 (d); 131.6 (s); 134.0 (2d); 134.7 (s); 136.2 (s); 143.2 (s); 143.4 (s); 151.8 (s); 167.2 (s); 167.3 (s); 169.4 (s); 169.4 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 2952, 1716, 1389, 1255, 1158, 1020, 721. HRMS (ESI) calculated for $C_{45}H_{42}N_4O_{10}Na$ *m/z* ($M+Na^+$) 821.2799, found 821.2804.

Compound 1e: Purified by flash chromatography (hexane/EtOAc, from 70:30 to 60:40). ^{1}H-RMN (500 MHz, $CDCl_3$): δ (ppm) 2.81-2.95 (m, 1H); 2.98 (d, *J* = 13.4 Hz, 1H); 3.07 (ddd, *J* = 5.0, 5.4 and 14.8 Hz, 1H); 3.27 (s, 3H); 3.57 and 3.63 (2s, 3H); 3.62-3.68 (m, 1H); 4.06-4.17 and 4.59-4.67 (2m, 1H); 4.74-4.82 and 5.27-5.33 (2m, 1H); 4.50-4.57 (m, 3H); 4.96-5.08 (m, 1H); 5.09-5.30 (m, 3H); 5.80-5.96 (m, 1H); 6.32 and 6.43 (2s, 1H); 6.80 and 6.93 (2d, *J* = 13.7 Hz, 1H); 7.10 (dd, *J* = 7.6 and 8.1 Hz, 1H); 7.12-7.18 (m, 2H); 7.21 (bs, 1H); 7.37 (bs, 1H); 7.39-7.49 (m, 4H); 7.52-7.59 (m, 1H); 7.62 (dd, *J* = 2.9 and 8.1 Hz, 1H); 7.86 (bs, 1H). ^{13}C-RMN (125 MHz, $CDCl_3$): δ (ppm) 27.7 and 27.8 (t); 37.9 (t); 52.3 (q); 52.6 (q); 54.1 and 54.4 (d); 59.4 and 60.1 (d); 65.8 (t); 72.9 and 74.0 (s); 74.6 and 75.3 (t); 81.0 and 81.7 (d); 94.8 and 95.3 (s); 109.3 (s); 110.9 (d); 117.8 and 117.9 (t); 119.7 (d); 119.8 (d); 120.5 (d); 122.8 (d); 124.0 and 124.2 (d); 124.8 (d); 125.8 (d); 126.2 (d); 126.5 (s); 129.7 (d); 130.2 (s); 130.5 (s); 131.5 (d); 132.1 (d); 132.6 (d); 133.3 (d); 133.8 and 133.9 (s); 143.0 and 143.1 (s); 147.3 (s); 151.6 and 152.6 (s); 155.4 and 155.5 (s); 169.9 (s); 171.9 and 172.0 (s). IR (KBr): ν (cm^{-1}) 3369, 2953, 1733, 1545, 1402, 1368, 1231, 1174, 1055, 852, 740, 580. HRMS (ESI+) calculated for $C_{37}H_{35}N_5O_{12}SCl_3$ *m/z* ($M+H^+$) 878.1063, found 878.1059.

Compound 1f: Purified by flash chromatography ($MeCN/H_2O$, from 0:100 to 70:30). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.22 and 1.34 (2s, 9H); 2.74-3.11 (m, 3H); 3.27 (s, 3H); 3.49-3.68 (m, 1H); 4.45 (bs, 1H); 4.49-4.58 (m, 2H); 4.59-4.84 (m, 2H); 5.02 (bs, 1H); 5.09-5.33 (m, 3H); 5.79-5.96 (m, 1H); 6.36 and 6.46 (2s, 1H); 6.82 and 6.94 (2d, *J* = 18.7 Hz, 1H); 7.04-7.25 (m, 4H); 7.29-7.58 (m, 6H); 7.62 (d, *J* = 8.3 Hz, 1H); 7.75-7.97 (m, 1H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.8 and 28.0 (3q); 27.9 (t); 37.9 (t); 52.6 (q); 54.4 and 54.6 (d); 59.4 (d); 65.7 (t); 74.6 (s); 75.3 (t); 81.6 (s); 82.2 (d); 109.5 (s); 110.8 (d); 117.8 (t); 119.8 (d); 120.2 (d); 120.5 (d); 122.7 (d); 124.2 (d); 124.6 (d); 125.8 (d); 126.3 (s); 126.7 (d); 129.7 (d); 130.5 (s); 131.7 (d); 132.1 (d); 132.7 (d); 133.3 (d); 133.7 (s); 137.9 (s); 143.1 (s); 147.4 (s); 155.6 (s); 155.7 (s); 169.9 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 3419, 2979, 1733, 1545, 1368, 1230, 1173, 1129, 1055, 740, 581. HRMS (ESI+) calculated for $C_{40}H_{41}N_5O_{12}SCl_3$ *m/z* ($M+H^+$) 920.1538, found 920.1578.

Compound 1g: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.81-0.88 (m, 6H); 1.00-1.12 (m, 1H); 1.31 (s, 9H); 1.39 (bs, 1H); 1.72-1.82 (m, 1H); 2.67 (dd, J = 4.7 and 14.7 Hz, 1H); 2.82 (d, J = 13.3 Hz, 1H); 3.08 (dd, J = 5.9 and 14.7 Hz, 1H); 3.21 (s, 3H); 3.50 (m, 1H); 3.83 (s, 3H); 3.89 (dd, J = 6.6 and 8.4 Hz, 1H); 4.54 (m, 2H); 4.64 (m, 1H); 4.92 (bs, 1H); 5.21 (d, J = 10.5 Hz, 1H); 5.26-5.34 (m, 2H); 5.83 (bs, 1H); 5.84-5.96 (m, 1H); 6.10 (d, J = 7.7 Hz, 1H); 6.70 (bs, 1H); 6.90 (t, J = 7.8 Hz, 2H); 7.15 (bs, 2H); 7.16-7.22 (m, 2H); 7.23-7.35 (m, 4H); 7.50 (t, J = 7.3 Hz, 2H); 7.77 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.4 (q); 15.3 (q); 24.7 (t); 27.6 (t); 28.0 (3q); 37.2 (t); 37.8 (d); 52.3 (q); 53.3 (q and d); 59.2 (d); 59.5 (d); 65.8 (t); 73.4 (s); 81.9 (s); 82.1 (d); 109.2 (s); 110.9 (d); 117.7 (t); 119.9 (2d); 120.5 (d); 122.7 (d); 124.3 (d); 125.7 (d); 126.4 (2d); 126.7 (d); 128.5 (2d); 130.3 (s); 130.6 (s); 131.7 (d); 132.2 (d); 132.7 (d); 133.5 (s); 138.2 (s); 143.2 (s); 154.8 (s); 155.9 (s); 170.1 (s); 170.5 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 3367, 2954, 1721, 1447, 1363, 1170 cm^{-1}. HRMS (ESI) calculated for $C_{45}H_{54}N_5O_{11}S$ *m/z* ($M+H^+$) 872.3541, found 872.3557.

Compound 1h: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 2.66 (dd, *J* = 9.5 and 5.3 Hz, 1H); 2.79 (d, *J* = 13.3 Hz, 1H); 3.03-3.14 (m, 1H); 3.20 (s, 3H); 3.42-3.54 (m, 1H); 3.58-3.68 (m, 6H); 3.84 (s, 3H); 4.42-4.57 (m, 1H); 4.91 (bs, 1H); 5.10 (d, *J* = 8.1 Hz, 1H); 5.73 (s, 1H); 6.71 (bs, 1H); 6.87 (t, *J* = 7.5 Hz, 2H); 7.12-7.35 (m, 5H); 7.43-7.58 (m, 3H); 7.80 (bd, *J* = 7.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.0 (t); 37.5 (t); 52.5 (3q); 53.5 (q); 54.8 (d); 59.4 (d); 73.6 (s); 82.1 (d); 109.4 (s); 111.2 (d); 119.8 (d); 120.2 (d); 120.7 (d); 123.0 (d); 124.3 (d); 124.5 (s); 125.8 (s); 126.6 (2d); 126.8 (d); 128.7 (2d); 130.5 (s); 132.1 (2d); 132.4 (d); 133.7 (s); 138.3 (s); 143.5 (s); 156.5 (s); 170.6 (s); 172.3 (s). IR (KBr): ν (cm^{-1}) 3328, 2964, 1722, 1676, 1448, 1368, 1170. HRMS (ESI) calculated for $C_{34}H_{35}N_4O_{10}S$ *m/z* ($M+H^+$) 691.2074, found 691.2079.

Compound 1i: Purified by flash chromatography ($MeCN/H_2O$, from 30:70 to 50:50). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.84 (m, 6H); 1.07 (m, 1H); 1.18 (s, 9H); 1.40 (s, 10H); 1.80 (m, 1H); 2.80 (m, 2H); 3.10 (dd, *J* = 5.9 and 14.6 Hz, 1H); 3.50 (dd, *J* = 10.1 and 13.4, 1H); 3.81 (s, 3H); 3.85 (m, 1H); 4.41 (dd, *J* = 5.7 and 13.2 Hz, 1H); 4.51 (dd, *J* = 5.7 and 13.2 Hz, 1H); 4.70-4.87 (m, 2H); 5.10 (bs, 1H); 5.20 (m, 2H); 5.70 (m,1H); 5.78 (bs, 1H); 6.20 (d, *J* = 7.0 Hz, 1H) 6.65 (bs, 1H); 6.85 (t, *J* = 7.6, 2H); 7.25 (m, 8H); 7.50 (m, 2H); 7.80 (d, *J* = 7.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.6 (q); 15.4 (q); 24.7 (t); 27.7 (3q); 28.2 (t); 28.4 (3q); 31.5 (q); 36.6 (q); 37.3 (t); 37.7 (d); 53.2 (d); 59.1 (d); 60.0 (d); 66.0 (t); 79.8 (s); 82.1 (d); 82.3 (s); 109.0 (d); 111.1 (d); 118.8 (t); 119.6 (d); 120.1 (s); 120.6 (d); 122.8 (d); 124.4 (d); 126.0 (d); 126.5 (d); 126.6 (d); 128.6 (2d); 130.4 (d); 131.0 (s); 131.4 (d); 131.7 (d); 132.3 (d); 133.7 (s); 138.3 (s); 141.7 (s); 143.2 (s); 145.0 (s); 155.6 (s); 162.7 (s); 168.8 (s); 171.0 (s); 171.3 (s). IR (KBr): ν (cm^{-1}) 3323, 2965, 2929, 1716, 1448, 1367, 1171. HRMS (ESI) calculated for $C_{48}H_{60}N_5O_{11}S$ *m/z* ($M+H^+$) 914.4010, found 914.3986.

Compound 1j: Purified by flash chromatography (hexane/EtOAc 70:30) ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.85-1.03 (m, 6H); 1.13 (dd, *J* = 3.2 and 6.7 Hz, 2H); 1.54 (s, 9H); 1.56 (s, 9H); 2.52 (bs, 1H); 2.68-2.90 (m, 1H); 2.97-3.15 (m, 1H); 3.54-3.66 (m, 2H); 3.77 (s, 3H); 3.94-4.07 (m, 1H); 4.49-4.73 (m, 3H); 5.08-5.31 (m, 3H); 5.75-5.90 (m, 1H); 6.50 (d, *J* = 7.7 Hz, 1H); 6.65 (d, *J* = 11.2 Hz, 1H); 6.75 (d, *J* =9.2 Hz, 1H); 6.87-7.18 (m, 5H); 7.33-7.41 (m, 1H); 7.61 (dd, *J* = 6.1 and 7.4 Hz, 1H); 7.66-7.83 (m, 5H); 7.87-8.01 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 10.7 and 11.3 (q); 15.8 and 16.8 (q); 24.3 (t); 25.8 and 27.4 (t); 28.2 (6q); 34.1 and 34.4 (d); 39.9 (t); 52.2 and 52.3 (d); 52.8 (q); 56.8 and 58.2 (d); 61.2 (d); 61.5 (s); 66.3 (t); 78.4 (d); 78.7 (s); 83.1 (2s); 109.7 (s); 110.7 (d); 111.0 (d); 116.0 and 116.1 (d); 118.8 (t); 119.4 (d); 120.3 (d); 122.8 (d); 123.3 (d); 123.4 (d); 123.5 and 123.6 (s); 124.5 (2d); 126.4 (s); 129.9 (s); 131.4 (d); 131.5 (d); 131.7 (s); 134.1 (2d); 134.3 (s); 134.4 (s); 151.2 (s); 167.1 (s); 167.3 (s); 168.0 (s); 168.1 (s); 169.3 (2s). IR (KBr): ν (cm^{-1}) 3413, 2969, 1718, 1483, 1455, 1388, 1253, 1162, 1019, 739, 720. HRMS (ESI+) calculated for $C_{46}H_{49}N_5O_{11}$ *m/z* (M–*t*Bu) 847.3429, found 847.3658.

Supporting Information (see footnote on the first page of this article)

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[20] Column: Waters XBridge C_{18} (75 x 4.6 mm, 2.5 μm); eluent and gradient: MeCN/H_2O (from 30:70 to 100:0 in 8 minutes).

[21] Several reaction conditions were tested to remove the Moc group from methyl N^1-(methoxycarbonyl)-N^8-(phenylsulphonyl)HPI-2-carboxylate (**S6**, see Supporting Information): the reagents comprised LiOH, LiSBn, $LiSCH_2CH_2OH$ or TMSI; the solvents tested were THF, H_2O, 1,4-dioxane, MeOH and HMPA; and the temperatures, from rt to solvent reflux temperature. Several of these tests were performed on MW.

[22] a) M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.* **1994**, *59*, 5543-5549; b) M. Kawahara, A. Nishida, M. Nakagawa, *Org. Lett.* **2000**, *2*, 675-678

[23] a) T.M. Kamenecka, S.J. Danishefsky *Angew. Chem. Int. Ed.* **1998**, *37*, 2993-2995; b) T.M. Kamenecka, S.J. Danishefsky *Angew. Chem. Int. Ed.* **1998**, *37*, 2995-2998

[24] N.H. Martin, N.W. Allen III, K.D. Moore, L. Vo, *J. Mol. Struct.* **1998**, *454*, 161-166

[25] The 3D model of Br-HPI ***endo*-** and ***exo*-3g** was calculated with Gaussian® 03W V 6.0 (Gaussian Inc.) and built with ChemBio3D V 11.0 (CambridgeSoft).

[26] Base-solvent pairs such as NaH/THF, NaHMDS/THF, K*t*BuO/MeCN or proton sponge/THF did not provide better yields.

[27] V.R. Espejo, X.-B. Li, J.D. Rainier, *J. Am. Chem. Soc.* **2010**, *132*, 8282-8284

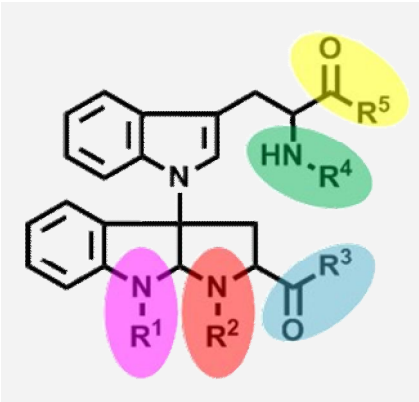
Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

Entry for the Table of Contents ((Please choose one layout.))

Layout 1:

Trp-HPI

Several Tryptophanyl-Hexahydropyrroloindoles (Trp-HPI) with four or five orthogonal protecting groups have been synthesized. This polyheterocyclic system is the scaffold of many natural products, recently isolated.



Pau Ruiz-Sanchis, Svetlana A. Savina, Gerardo A. Acosta, Fernando Albericio,* and Mercedes Álvarez*
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Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

Keywords: Natural products / Heterocycles / Amino acids / Protecting groups

Supporting Information

Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

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Fernando Albericio,*[a,c,d] and Mercedes Álvarez *[a,b,c]

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General data

Reagents and solvents were purified according to *Purification of Laboratory Chemicals* (Armarego, W. and Chai, C.; Elsevier; 2003). Automatic flash chromatography was done in an Isco Combiflash medium pressure liquid chromatograph with Redisep silica gel columns (47-60 μm). ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 MHz. Multiplicity of the carbons was assigned with DEPT and gHSQC experiments, although standard abbreviations according to off-resonance decoupling are used here: (s) singlet, (d) doublet, (t) triplet and (q) quartet. For ^{1}H-NMR, the following additional abbreviations are used: (m) multiplet, (bs) broad singlet and (bd) broad doublet. Spectra were referenced to the residual solvent peak of $CDCl_3$. IR spectra were obtained on a Thermo Nicolet FT-IR spectrometer. HRMS was performed on an Acquity UPLC Binary Sol MGR (Waters-Corporation) by the Mass Spectrometry Core Facility at the IRBB. Analytical HPLC was performed on a Waters Alliance 2695 separation module equipped with a Waters 996 PDA detector (λ = 254 nm) and Waters XBridge C_{18} column (75 x 4.6 mm, 2.5 μm), in runs of 8 min. Microwave-assisted reactions were carried out in a CEM Discover microwave oven.

Experimental section

N^{α}-Protection of L-Trp-OMe (R^2= Alloc, Boc, Cbz, Moc, Troc, N^{α}-Alloc-Ala)

A solution of L-Trp-OMe·HCl (5.4 g, 21.2 mmol) and Et_3N (2.9 mL, 21.2 mmol) in dry CH_2Cl_2 (85 mL) was added to a solution of either di-*tert*-butyldicarbonate (5.5 g, 25.4 mmol) or an appropriate chloroformate (1.5 eq) in CH_2Cl_2 (3 mL/mmol). The reaction mixture was stirred for 2 h at rt. The organic solution was washed with brine, and then dried over Na_2SO_4. The solvent was removed, and the crude was purified by flash chromatography (hexanes/EtOAc) to afford the desired product in 80 to 99% yield.

If R^2= N^{α}-Alloc-Ala. A solution of Alloc-Ala-OH dicyclohexylamine salt (4.1 g, 11.7 mmol), EDC·HCl (2.3 g, 11.9 mmol) and HOBt (1.6 g, 11.9 mmol) in dry CH_2Cl_2 (20 mL) was added to a solution of Trp-OMe (2.9 g, 11.5 mmol) and DIEA (4.2 mL, 24.1 mmol) in dry CH_2Cl_2 (16 mL). The mixture was stirred for 4 h at rt. The organic solution was washed with sat. NH_4Cl, 10% $NaHCO_3$, water and brine, dried over Na_2SO_4, and then concentrated. The resulting crude was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to obtain the desired product in 58% yield.

Syntheses of N^{α}-protected-Trp-O*t*Bu analogs (2f, 2h, 2k, 2m; R^1= H)

Hydrolysis of the methyl ester. N^{α}-protected-Trp-methyl ester (9.9 mmol) was dissolved in 10:1 THF/H_2O (168 mL) and 2M LiOH (15 mL, 30,0 mmol), and the solution was stirred at rt for 3 h. The solution was then diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous solution was saturated with NaCl and the phases were separated. The aqueous layer was extracted with THF. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the carboxylic acid in quantitative yield.

Formation of the tert-butyl ester. A mixture of N^{α}-protected-Trp (8.4 mmol), $BnEt_3NCl$ (1.9 g, 8.4 mmol) and K_2CO_3 (7.6 g, 54.7 mmol) in MeCN (25 mL) was vigorously stirred for 5 h. *t*-BuBr (9.9 mL, 88.4 mmol) was then added, and the solution was heated at 50 ºC for 2 h. The reaction mixture was treated with MeCN (13 mL), and then stirred for 24 h. The solvent was evaporated off and the resulting solid was dissolved in 2:1 EtOAc/H_2O. The aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to give the *tert*-butyl N^{α}-protected-Trp carboxylates **2f** (84%), **2k** (84%), **2h** (55%) or **2m** (58%).

Syntheses of N^{α},N^{i}-protected-Trp-alkyl esters (2a-2n)

Compounds **2c**[1] and **2l**[2] have previously been reported.

N^{α}-Protected-Trp alkyl ester (13.3 mmol), Bu_4NHSO_4 (0.4 g, 1.3 mmol) and crushed NaOH (1.6 g, 39.9 mmol) were mixed in CH_2Cl_2 (26 mL). Di-*tert*-butyl dicarbonate (4.3 g, 19.9 mmol) was then added slowly, and the resulting mixture was stirred for 15 h at rt. The solvent was evaporated off, the crude was dissolved in 1:1 sat. NH_4Cl/EtOAc and extracted with EtOAc. The organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was removed, and the crude was purified by flash chromatography (hexanes/EtOAc, 80:20 to 60:40) to give **2a** (68%), **2d** (32%), **2e** (42%) or **2n** (16%).

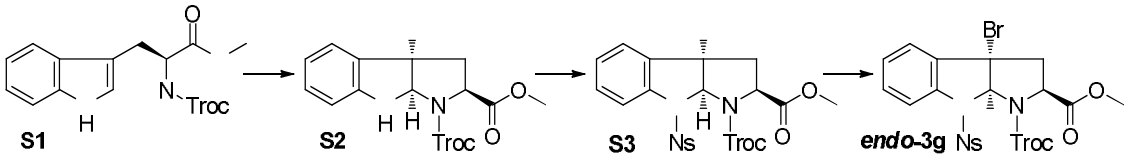
For Nosyl protection, either N^{α}-Cbz-Trp-OtBu, N^{α}-Troc-Trp-OMe or N^{α}-Troc-Trp-O*t*Bu (2.5 mmol) was treated with 2-nitrobenzenesulfonyl chloride (0.7 g, 3.1 mmol), which provided the corresponding 8-(2-nitrobenzenesulfonyl) analogs **2f** (80%), **2g** (43%) or **2h** (46%), respectively.

For SO_2Ph protection, either N^{α}-Boc-Trp-OMe, N^{α}-Cbz-Trp-OMe, N^{α}-Cbz-Trp-O*t*Bu, or N^{α}-Moc-Trp-O*t*Bu (23.9 mmol) was treated with $PhSO_2Cl$ (3.7 mL, 28.7 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred for 2 h to give **2i** (87%), **2j** (92%), **2k** (80%) or **2m** (93%), respectively.

Synthesis of 3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3)

Method A: three-step synthesis for *endo*-3g, *endo*-3l and *endo*-3m

*endo-(2S, 3aS, 8aS)-Methyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethylcarbonyl--1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3g**)*

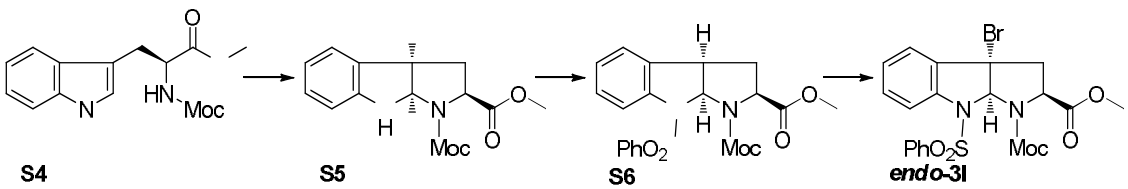


A solution of N^{α}-Troc-Trp-OMe (1.0 g, 2.5 mmol) and trifluoroacetic acid (6.3 mL) was stirred for 30 minutes at rt, and then slowly poured into a mixture of CH_2Cl_2 (30.5 mL) and 15% Na_2CO_3 (76.2 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was removed and the resulting residue was dried *in vacuo* to give **S2** in quantitative yield.

2-Nitrobenzenesulfonyl chloride (2.0 g, 9.2 mmol) was slowly added to a mixture of the previously **S2** (0.9 g, 2.3 mmol) and pyridine (3.0 mL) cooled to 0 ºC and the reaction mixture was stirred at rt for 2 h. The organic solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with 2M HCl, 15% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give **S3** (0.9 g, 65%).

AIBN (0.1 g, 0.7 mmol) was added to a solution of **S3** (0.9 g, 1.5 mmol) in dry CCl_4 (28 mL) under N_2. The solution was heated to reflux, and then treated with NBS (0.3 g, 1.5 mmol), the resulting mixture was stirred for 2 h. The crude was then cooled to rt and the precipitate was filtered off. The organic layer was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (hexanes/EtOAc, 80:20 to 60:40) to give ***endo*-3g** (0.1 g, 14%). The starting material was recovered.

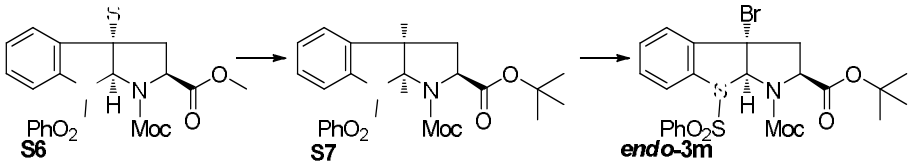
*endo-(2S, 3aS, 8aS)-Methyl 3a-bromo-1-methoxycarbonyl-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3l**).*



[1] S.P. Marsden, K.M. Depew, S.J. Danishefsky; *J. Am. Chem. Soc.*,**1994**, *116*, 11143-11144.
[2] D. Crich, X. Huang; *J. Org. Chem.*, **1999**, *64*, 7218-7223

A solution of N^{α}-Moc-Trp-OMe (1.0 g, 3.6 mmol) and 85% H_3PO_4 (11 mL) was stirred under N_2 at rt for 3 h. The reaction mixture was then slowly poured into a mixture of CH_2Cl_2 (43 mL) and 15% Na_2CO_3 (109 mL), and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give **S5** in quantitative yield.
Benzenesulfonyl chloride (0.8 mL, 6.4 mmol) was slowly added to a mixture of **S5** (0.9 g, 3.2 mmol) and pyridine (4 mL) cooled to 0 ºC and the reaction mixture was stirred at rt for 15 h. The organic solvent was then removed *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with 2M HCl, 15% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give **S6** (1.1 g, 80%).
***endo*-3l** was obtained with 49% yield from **S6** following the same reported method for ***endo*-3g**.

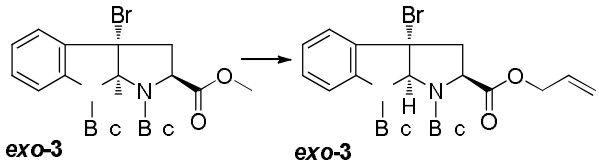
*endo-(2S, 3aS, 8aS)-tert-Butyl 3a-bromo-1-methoxycarbonyl-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3m**).*



To a solution of **S6** (5.0 g, 12.0 mmol) in 10:1 THF/H_2O (204 mL) was added 2M LiOH (12.0 mL, 24.0 mmol). The reaction mixture was stirred at reflux temperature for 2.5 h. The solution was diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous solution was saturated with NaCl and extracted with THF. The combined organic layers were dried over Na_2SO_4, and then concentrated *in vacuo* to give the carboxylic acid in quantitative yield.
Following the aforementioned method to generate a *tert*-butyl ester, **S7** was obtained with 81% yield.
***endo*-3m** was obtained in 46% yield from **S7** following the same method reported for ***endo*-3g**.

Method B: One-pot bromocyclization for *exo*-3a, *exo*-(3c-3n)
To a solution of PPTS (1.9 g, 7.4 mmol) and NBS (1.3 g, 7.4 mmol) was added N^{α}-N^{i}-protected-Trp alkyl ester (7.4 mmol) in anhydrous CH_2Cl_2 (67 mL) under N_2. The reaction mixture was stirred at rt for 4 h. The crude mixture was washed with 15% $NaHCO_3$, 10% $Na_2S_2O_4$ and brine, and then dried over Na_2SO_4. The solvent was evaporated off, and the crude was purified by flash chromatography (see the following section for yields and solvent systems).

Synthesis of *exo*-3b



2M LiOH (1.5 mL, 3.0 mmol) was added to a solution of ***exo*-3c** (0.5 g, 1.0 mmol) in 10:1 THF/H_2O (17 mL). The solution was stirred at reflux for 5 h. The solution was then diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous layer was saturated with NaCl and extracted with THF. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the carboxylic acid in quantitative yield.
To a solution of the aforementioned acid (0.7 g, 1.5 mmol) in MeOH (10 mL) was added Cs_2CO_3 (0.5 g, 1.6 mmol), and the solution was stirred for 30 min at rt. The reaction mixture was then concentrated, treated with dry DMF (5 mL) and AllylBr (0.25 mL, 3.0 mmol), and finally, stirred at rt for 4 h. The organic solution was diluted with EtOAc and washed with 5% $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 80:20 to 70:30) to give ***exo*-3b** (0.2 g, 30%).

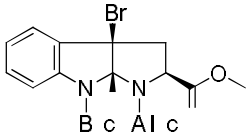
Synthesis of *exo*-3o and *exo*-3p
***exo*-3a** or ***exo*-3c** were hydrolyzed following the aforementioned method for hydrolysis of a methyl ester of ***exo*-3c**.
A solution of DIEA (0.63 mL, 3.6 mmol) and either Ile-OMOM (0.6 g, 3.6 mmol, for ***exo*-3o**) or Ile-OAllyl (0.6 g, 3.6 mmol, for ***exo*-3p**) in CH_2Cl_2 (14 mL) was added to a solution of the acid obtained (3.0 mmol) from either ***exo*-3a**

or ***exo*-3c**, respectively, in CH_2Cl_2 (23 mL). The mixture was stirred at -10 °C for 10 min, and then treated with HBTU (1.1 g, 3.0 mmol), and the resulting mixture was stirred at rt for 21 h. The mixture was washed with 5% $NaHCO_3$, sat. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude was purified by flash chromatography (hexanes/EtOAc, 70:30) to afford ***exo*-3o** (47%) or ***exo*-3p** (41%).

Compounds Characterization:

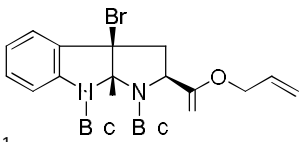
***endo*-3l**,[3] has been reported previously.

exo-Methyl 1-allyloxycarbonyl-3a-bromo-8-(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (_exo_-3a).



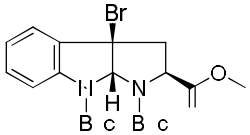
Purified by flash chromatography (hexanes:EtOAc 30:70) 83% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.59 (s, 9H); 2.86 (dd, *J* = 10.3 and 12.7 Hz, 1H); 3.26 (dd, *J* = 6.5 and 12.7 Hz, 1H); 3.74 (s, 3H); 3.97 (dd, *J* = 6.5 and 10.3 Hz, 1H); 4.43-4.70 (m, 2H); 5.14-5.29 (m, 2H); 5.75-5.94 (m, 1H); 6.40 (s, 1H); 7.13 (dd, *J* = 7.5 and 7.6 Hz, 1H); 7.33 (dd, *J* = 7.5 and 8.1 Hz, 1H); 7.37 (d, *J* = 7.6 Hz, 1H); 7.60 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.2 (3q); 41.8 (t); 52.6 (q); 59.5 (d); 59.7 (s); 66.4 (t); 82.3 (s); 83.8 (d); 117.7 (t); 118.4 (d); 123.2 (d); 124.5 (d); 130.8 (d); 132.2 (d); 132.5 (s); 141.3 (s); 152.0 (s); 171.1 (s).
IR (KBr): ν (cm^{-1}) 2978, 1717, 1479, 1405, 1334, 1156, 1017, 754.
HRMS (ESI+) calculated for $C_{21}H_{25}BrN_2O_6Na$ *m/z* ($M+Na^+$) 503.0794, found 503.0800.

exo-Allyl 3a-bromo-1,8-di-_tert_-butyloxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3b).



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H); 1.59 (s, 9H); 2.82 (dd, J = 10.3 and 12.6 Hz, 1H); 3.23 (dd, J = 6.4 and 12.6 Hz, 1H); 3.91 (dd, J = 6.4 and 10.3 Hz, 1H); 4.56-4.70 (m, 2H); 5.23-5.37 (m, 2H); 5.85-5.96 (m, 1H); 6.39 (s, 1H); 7.12 (t, J = 7.6 Hz, 1H); 7.32 (dd, J = 7.6 and 8.0 Hz, 1H); 7.36 (d, 7.6 Hz, 1H); 7.54 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.2 (6q); 41.9 (t); 59.5 (d); 59.7 (s); 66.0 (t); 82.3 (2s); 83.8 (d); 119.0 (t); 123.2 (2d); 124.4 (d); 130.6 (d); 131.5 (d); 133.1 (s); 141.5 (s); 152.2 (s); 171.0 (s).
IR (KBr): ν (cm^{-1}) 2979, 1722, 1604, 1479, 1395, 1333, 1256, 1161, 1017, 851, 752.
HRMS (ESI+) calculated for $C_{48}H_{62}Br_2N_4O_{12}Na$ *m/z* ($2M+Na^+$) 1067.2629, found 1067.2601.

exo-Methyl 3a-bromo-1,8-di(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3c)

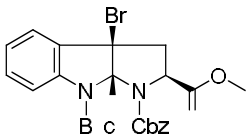


Purified by flash chromatography (hexanes:EtOAc 80:20); 86% yield; *endo*:*exo* 4:96.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H); 1.59 (s, 9H); 2.82 (dd, J = 10.3 and 12.6 Hz, 1H); 3.20 (dd, J = 6.3 and 12.6 Hz, 1H); 3.74 (s, 3H); 3.89 (dd, J = 6.3 and 10.3 Hz, 1H); 6.39 (s, 1H); 7.12 (dd, J = 7.5 and 7.6 Hz, 1H); 7.32 (dd, J = 7.5 and 8.1 Hz, 1H); 7.36 (d, J = 7.6 Hz, 1H); 7.56 (bs, 1H).

[3] M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.* **1994**, *59*, 5543-5549.

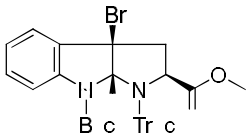
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.5 (3q); 28.6 (3q); 42.2 (t); 52.7 (q); 59.8 (d); 60.1 (s); 81.8 (s); 82.6 (s); 84.1 (d); 119.2 (d); 123.5 (d); 124.7 (d); 130.9 (d); 140.7 (s); 141.9 (s); 152.5 (s); 163.6 (s); 171.8 (s).
IR (KBr): v (cm^{-1}) 2979, 1720, 1394, 1333, 1161, 733.
HRMS (ESI+) calculated for $C_{22}H_{30}BrN_2O_6S$ *m/z* ($M+H^+$) 497.1282, found 497.1276.

exo-Methyl 1-benzyloxycarbonyl-3a-bromo-8-_tert_-butyloxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3d)



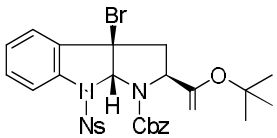
Purified by flash chromatography (hexanes:EtOAc from 90:10 to 70:30); 78% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.54 (bs, 9H); 2.85 (dd, *J* = 10.2 and 12.8 Hz, 1H); 3.26 (dd, *J* = 6.6 and 12.8 Hz, 1H); 3.65 (bs, 3H); 3.98 (dd, *J* = 6.6 and 10.2 Hz, 1H); 5.20 (bs, 2H); 6.43 (s, 1H); 7.13 (t, *J* = 7.5 Hz, 1H); 7.25-7.38 (m, 7H); 7.61 (m, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.1 (3q); 41.8 (t); 52.4 (q); 59.5 (d); 59.7 (s); 67.4 (t); 82.4 (s); 83.9 (d); 118.3 (d); 123.2 (d); 124.6 (d); 128.0 (s); 128.4 (4d); 130.8 (2d); 132.5 (s); 141.3 (s); 152.0 (s); 171.1 (s).
IR (KBr): v (cm^{-1}) 2978, 1717, 1478, 1410, 1335, 1157, 1018, 855, 753.
HRMS (ESI+) calculated for $C_{25}H_{27}BrN_2O_6Na$ *m/z* ($M+Na^+$) 553.0950, found 553.0950.

exo-Methyl 1-trichloroethoxycarbonyl-3a-bromo-8-(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3e).



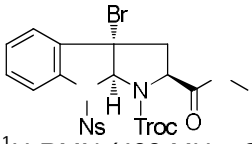
Purified by flash chromatography (hexanes:EtOAc 30:70) 77% yield; *endo:exo* (11:89).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.61 (s, 9H); 2.88 (dd, *J* = 10.0 and 13.0 Hz, 1H); 3.33 (dd, *J* = 6.5 and 13.0 Hz, 1H); 3.76 (s, 3H); 4.05-4.13 (m, 1H); 4.75 and 4.78 (2s, 2H); 6.45 (bs, 1H); 7.14 (t, *J* = 7.6 Hz, 1H); 7.34 (dd, *J* = 7.6 and 7.9, 1H); 7.38 (d, *J* = 7.6 Hz, 1H); 7.68 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 29.6 (q); 43.5 (t); 53.7 (s); 54.2 (q); 60.7 (d); 76.5 (t); 84.0 (s); 85.7 (d); 96.1 (s); 119.2 (d); 124.6 (d); 125.2 (s); 125.8 (d); 132.3 (d); 142.6 (s); 153.3 (2s); 172.2 (s).
IR (KBr): v (cm^{-1}) 2979, 1719, 1479, 1401, 1156, 1063, 754, 577.
HRMS (ESI+) calculated for $C_{20}H_{23}BrCl_3N_2O_6$ *m/z* ($M+H^+$) 570.9805, found 570.9791.

exo-tert-Butyl 1-benzyloxycarbonyl-3a-bromo-8-(2-nitrobenzenesulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3f).



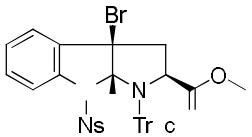
Purified by flash chromatography (hexanes:EtOAc 80:20) 80% yield; *endo:exo* (7:93).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.34 (s, 9H); 2.80 (dd, *J* = 10.5 and 12.2 Hz, 1H); 3.10-3.19 (m, 1H); 3.79 (bs, 1H); 4.90 and 4.93 (2s, 1H); 5.20 (bs, 1H); 6.54 (s, 1H); 7.25-7.47 (m, 10H); 7.55-7.65 (m, 3H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.9 (3q); 43.3 (t); 59.2 (s); 60.3 (d); 67.5 (t); 82.4 (d); 85.4 (s); 119.3 (d); 123.9 (2d); 124.2 (d); 127.0 (s); 128.1 (2d); 128.3 (2d); 128.4 (d); 129.9 (s); 131.1 (d); 131.4 (2d); 134.1 (d); 134.4 (s); 139.8 (s); 148.6 (s); 168.7 (s); 171.1 (s).
IR (KBr): v (cm^{-1}) 2978, 1719, 1546, 1463, 1370, 1217, 1152, 1063, 594.
HRMS (ESI+) calculated for $C_{29}H_{29}BrN_3O_8S$ *m/z* ($M+H^+$) 658.0859, found 658.0856.

***endo*-Methyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxilate (3g)**



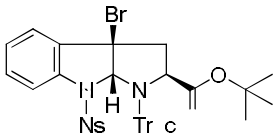
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 3.08-3.19 (m, 1H); 3.21 (s, 3H); 3.35 (d, *J* = 13.2 Hz, 1H); 4.50 (m, 2H); 4.67 (d, *J* = 8.6 Hz, 1H); 6.59 (s, 1H); 7.21 (t, *J* = 7.2 Hz, 1H); 7.33-7.50 (m, 3H); 7.57 (t, *J* = 7.6 Hz, 1H); 7.69 (t, *J* = 7.6 Hz, 1H); 7.79 (bd, *J* = 7.2 Hz, 1H); 8.03 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 44.5 (t); 52.5 (q); 58.8 (s); 59.6 (d); 75.0 (t); 86.5 (d); 94.6 (s); 117.9 (d); 121.0 (s); 124.4 (d); 124.8 (d); 125.9 (d); 129.6 (d); 131.4 (d); 132.1 (d); 132.6 (s); 133.6 (d); 134.0 (s); 141.3 (s); 148.0 (s); 169.4 (s); 175.6 (s).
IR (KBr): v (cm^{-1}) 2994, 1736, 1545, 1463, 1376, 1228, 1175, 1048, 852, 767, 583.
HRMS (ESI+) calculated for $C_{21}H_{18}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 655.9064, found 655.9041.

***exo*-Methyl 3a-Bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxilate (3g)**



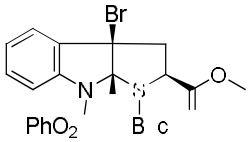
Purified by flash chromatography (DCM); 57% yield; *endo*:*exo* (8:92).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.90 (dd, *J* = 10.1 and 13.0 Hz, 1H); 3.20 (dd, *J* = 6.2 and 13.0 Hz, 1H); 3.74 (s, 3H); 3.93-4.02 (m, 1H); 4.55 and 4.58 (2s, 2H); 6.60 (s, 1H); 7.30 (dd, *J* = 7.4 and 7.6 Hz, 1H); 7.38 (d, *J* = 7.9 Hz, 1H); 7.43 (dd, *J* = 7.4 and 7.9 Hz, 1H); 7.48 (d, *J* = 7.6 Hz, 1H); 7.57 (d, *J* = 7.3 Hz, 1H); 7.64 (dd, *J* = 7.3 and 8.0 Hz, 2H); 7.73-7.83 (m, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.7 (t); 52.8 (q); 58.7 (s); 59.5 (d); 75.1 (t); 86.1 (d); 94.8 (s); 119.6 (d); 123.9 (d); 124.3 (d); 127.2 (d); 130.3 (d); 131.3 (d); 131.4 (d); 132.0 (s); 134.1 (s); 134.3 (d); 139.9 (s); 148.9 (s); 160.1 (s); 169.7 (s).
IR (KBr): v (cm^{-1}) 2955, 1750, 1545, 1464, 1373, 1208, 1177, 1061, 774, 595.
HRMS (ESI+) calculated for $C_{21}H_{18}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 655.9064, found 655.9045.

***exo*-*tert*-Butyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3h).**



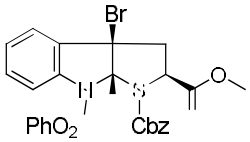
Purified by flash chromatography (hexanes:EtOAc from 80:20 to 70:30) 59% yield; *exo*.
^{1}HRMN (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H); 2.85 (dd, *J* = 10.5 and 12.4 Hz, 1H); 3.08-3.28 (m, 1H); 3.66-4.08 (m, 1H); 4.22-4.67 (m, 1H); 4.88-5.26 (m, 1H); 6.59 (s, 1H); 7.31 (dd, *J* = 7.4 and 7.5 Hz, 1H); 7.42-7.50 (m, 3H); 7.52-7.71 (m, 4H).
^{13}CRMN (400 MHz, $CDCl_3$): δ (ppm) 28.1 (3q); 43.8 (t); 59.1 (s); 60.7 (d); 74.9 (t); 83.1 (s); 85.5 (d); 95.2 (s); 119.9 (d); 124.2 (d); 124.4 (2d); 127.6 (d); 130.3 (s); 131.6 (2d); 134.5 (d); 137.9 (s); 140.0 (s); 149.0 (s); 167.8 (s); 168.6 (s).
IR (KBr): v (cm^{-1}) 2980, 1741, 1546, 1464, 1371, 1218, 1152, 1062, 851, 773, 595.
HRMS (ESI+) calculated for $C_{24}H_{24}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 697.9533, found 697.9526.

***exo*-Methyl 8-benzenesulfonyl-3a-bromo-1-*tert*-butoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3i)**



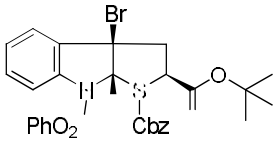
Purified by flash chromatography (hexanes:EtOAc 70:30); 92% yield.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.54 (bs, 9H); 2.77 (dd, *J* = 10.4 and 12.6 Hz, 1H); 3.06 (dd, *J* = 6.0 and 12.6 Hz, 1H); 3.73 (s, 3H); 3.83 (dd, *J* = 6.0 and 10.4 Hz, 1H); 6.32 (bs, 1H); 7.17 (dd, *J* = 7.5 and 8.0 Hz, 1H); 7.24-7.28 (m, 1H); 7.34 (dd, *J* = 7.1 and 7.5 Hz, 3H); 7.46 (t, J = 7.5 Hz, 1H); 7.57 (d, *J* = 8.0 Hz, 1H); 7.82 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.3 (3q); 43.2 (t); 52.5 (q); 58.6 (s); 59.5 (d); 86.7 (d); 88.9 (s); 118.8 (d); 123.9 (d); 126.4 (d); 128.3 (2d); 128.6 (2d); 129.3 (s); 130.9 (d); 133.4 (d); 134.1 (s); 140.3 (s); 170.8 (s).
IR (KBr): v (cm^{-1}) 2979, 1752, 1702, 1448, 1367, 1032, 1171, 733.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0689, found 537.0689.

***exo*-Methyl 8-benzenesulfonyl-1-benzyloxycarbonyl-3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3j)**



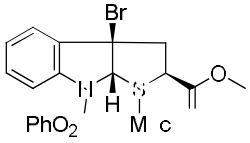
Purified by flash chromatography (hexanes:EtOAc 70:30); 82% yield.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.78 (dd, *J* = 10.1 and 12.8 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.8 Hz, 1H); 3.68 (bs, 3H); 3.88 (dd, *J* = 6.3 and 10.1 Hz, 1H); 5.13-5.45 (m, 2H); 6.33 (bs, 1H); 7.18 (dd, *J* = 7.4 and 8.0 Hz, 1H); 7.26 (d, *J* = 6.8 Hz, 2H); 7.29-7.40 (m, 6H); 7.47 (t, *J* = 7.4 Hz, 2H); 7.62 (d, *J* = 8.1 Hz, 1H); 7.79 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.3 (t); 52.4 (q); 59.3 (d); 59.5 (s); 67.9 (t); 86.7 (d); 118.9 (d); 123.8 (2d); 126.4 (d); 128.2 (2d); 128.3 (2d); 128.7 (2d); 128.8 (2d and s); 131.0 (d); 133.5 (d); 133.8 (s); 138.4 (s); 140.2 (s); 170.4 (s).
IR (KBr): v (cm^{-1}) 2953, 1749, 1711, 1408, 1366, 1172, 1029, 755.
HRMS (ESI+) calculated for $C_{26}H_{24}BrN_2O_6S$ *m/z* ($M+H^+$) 571.0533, found 571.0531.

***exo*-*tert*-Butyl 1-benzyloxycarbonyl-3a-bromo-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3k).**



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 83% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.35 (s, 9H); 2.73 (dd, *J* = 10.2 and 12.7 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.7 Hz, 1H); 3.78 (bs, 1H); 5.11 (d, *J* = 12.1, 1H); 5.37 (bs, 1H); 6.31 (bs, 1H); 7.17 (t, *J* = 7.6 Hz, 1H); 7.25-7.40 (m, 7H); 7.46 (t, *J* = 7.4 Hz, 2H); 7.47-7.51 (m, 1H); 7.60 (d, *J* = 8.1 Hz, 1H); 7.79 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.7 (3q); 43.3 (t); 59.3 (s); 60.2 (d); 67.6 (t); 82.2 (s); 86.9 (d); 118.8 (d); 123.9 (2d); 126.3 (d); 128.0 (d); 128.2 (d); 128.3 (2d); 128.7 (2d); 129.4 (s); 130.9 (2d); 133.4 (2d); 134.1 (s); 138.5 (s); 140.2 (s); 161.9 (s); 169.0 (s).
IR (KBr): v (cm^{-1}) 2978, 1715, 1463, 1368, 1216, 1172, 1041, 595.
HRMS (ESI+) calculated for $C_{29}H_{30}BrN_2O_6S$ *m/z* ($M+H^+$) 613.1008, found 613.1002.

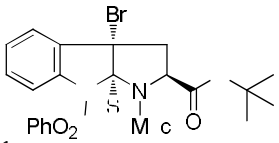
***exo*-Methyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3l).**



Purified by flash chromatography (hexanes:EtOAc 70:30); 96% yield.

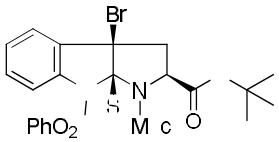
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.81 (dd, *J* = 10.4 and 12.7 Hz, 1H); 3.11 (dd, *J* = 6.0 and 12.7 Hz, 1H); 3.75 (s, 3H); 3.81 (bs, 3H); 3.87 (dd, *J* = 6.0 and 10.4 Hz, 1H); 6.29 (s, 1H); 7.18 (dd, *J* = 7.4 and 7.7 Hz, 1H); 7.27 (bd, J = 7.7 Hz, 1H); 7.31-7.39 (m, 3H); 7.48 (dd, *J* = 7.4 and 7.5 Hz, 1H); 7.60 (d, *J* = 8.2 Hz, 1H); 7.80 (d, *J* = 7.4 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.4 (t); 52.7 (q); 53.0 (q); 59.1 (s); 59.2 (d); 86.7 (d); 118.8 (d); 123.8 (d); 126.4 (d); 128.1 (2d); 128.8 (2d); 131.0 (d); 133.5 (d); 133.7 (s); 138.4 (s); 140.2 (s); 149.3 (s); 170.4 (s).
IR (KBr): v (cm^{-1}) 2954, 1714, 1447, 1366, 1173, 1092, 1027, 733.
HRMS (ESI+) calculated for $C_{20}H_{20}BrN_2O_6S$ *m/z* ($M+H^+$) 495.0220, found 495.0219.

endo-tert-Butyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3m)



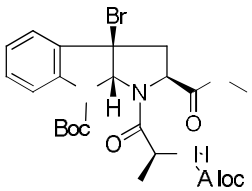
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.08 (s, 9H); 3.04 (dd, *J* = 9.6 and 13.2 Hz, 1H); 3.23 (d, *J* = 13.2 Hz, 1H); 3.65 (s, 3H); 4.49 (d, *J* = 9.6 Hz, 1H); 6.35 (s, 1H); 7.12 (dd, *J* = 7.5 and 7.8 Hz, 1H); 7.27-7.35 (m, 2H); 7.41 (t, *J* = 7.6 Hz, 2H); 7.47-7.55 (m, 2H); 7.86 (d, *J* = 7.6 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.5 (3q); 44.3 (t); 52.7 (s); 52.9 (q); 60.2 (d); 82.0 (s); 87.2 (d); 118.2 (d); 124.5 (d); 125.9 (d); 127.4 (2d); 128.9 (2d); 129.1 (s); 131.0 (d); 133.2 (d); 133.6 (s); 141.6 (s); 157.2 (s); 160.0 (s).
IR (KBr): v (cm^{-1}) 2979, 1721, 1600, 1447, 1369, 1172, 1092, 975, 850, 756, 735.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0689, found 537.0687.

exo-tert-Butyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3m).



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 58% yield; *endo:exo* (25:75).
^{1}H-RMN (400 MHz, $CDCl_3$): *exo* product δ (ppm) 1.45 (s, 9H); 2.75 (dd, *J* = 10.3 and 12.7 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.7 Hz, 1H); 3.75 (dd, *J* = 6.3 and 10.3 Hz, 1H); 3.78 (bs, 3H); 6.28 (s, 1H); 7.18 (t, *J* = 7.6 Hz, 1H); 7.29 (t, *J* = 7.0 Hz, 1H); 7.32-7.40 (m, 3H); 7.42-7.51 (m, 1H); 7.58 (d, *J* = 8.1 Hz, 1H); 7.79 (bd, *J* = 6.9 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): *exo* product δ (ppm) 27.8 (q); 43.6 (t); 52.8 (q); 59.2 (s); 60.1 (d); 82.3 (s); 86.9 (d); 118.7 (d); 123.9 (d); 125.1 (s); 126.3 (d); 128.1 (2d); 128.7 (d); 129.4 (d); 130.9 (d); 133.4 (d); 138.5 (s); 140.2 (s); 169.6 (s); 171.5 (s).
IR (KBr): v (cm^{-1}) 2979, 1725, 1447, 1369, 1172, 595.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0695, found 537.0681.

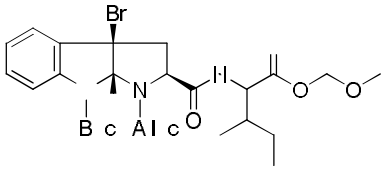
exo-Methyl 2-(_N^α^_-allyloxycarbonyl-Ala-O-yl)-3a-bromo-1-(_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3n)



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 47% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.50 (d, *J* = 6.8 Hz, 3H); 1.62 (s, 9H); 2.79 (dd, *J* = 10.9 and 12.5 Hz, 1H); 3.26 (dd, *J* = 6.2 and 12.5 Hz, 1H); 3.73 (s, 3H); 4.03 (dd, J = 6.2 and 10.9 Hz, 1H); 4.46-4.57 (m, 2H); 5.02 (t, 6.8 Hz, 1H); 5.13-5.29 (m, 2H); 5.43 (bs, 1H); 5.82-5.94 (m, 1H); 6.41 (s, 1H); 7.18 (dd, *J* = 7.3 and 7.4 Hz, 1H); 7.32-7.40 (m, 2H); 7.50 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 19.3 (q); 28.1 (3q); 40.6 (t); 47.9 (d); 52.5 (q); 60.0 (d); 65.3 (t); 67.9 (s); 84.0 (s); 84.5 (d); 117.3 (t); 120.5 (d); 122.8 (d); 125.6 (d); 128.1 (s); 130.8 (d), 132.9 (d); 133.4 (s); 154.9 (s); 170.3 (s); 173.8 (s).

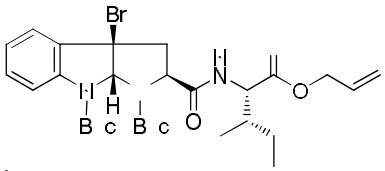
IR (KBr): v (cm^{-1}) 3325, 2979, 1724, 1663, 1478, 1414, 1370, 1333, 1254, 1155, 852, 754.
HRMS (ESI+) calculated for $C_{24}H_{31}BrN_3O_7$ *m/z* ($M+H^+$) 552.1340, found 552.1338.

exo-Methoxymethyloxyisoleucinyl 2-allyloxycarbonyl-3a-bromo-1-(_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carbonylate (3o)



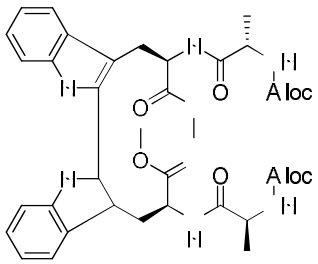
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.91 (t, *J* = 7.5 Hz, 3H); 0.93 (d, *J* = 6.9 Hz, 3H); 1.14-1.24 (m, 1H); 1.39-1.49 (m, 1H); 1.57 (s, 9H); 1.88-1.98 (m, 1H); 2.93 (dd, *J* = 10.1 and 12.8 Hz, 1H); 3.22 (dd, *J* = 6.4 and 12.8 Hz, 1H); 3.47 (s, 3H); 3.85 (dd, *J* = 6.4 and 10.1 Hz, 1H); 4.48-4.65 (m, 3H); 5.12-5.24 (m, 2H); 5.20 (d, *J* = 5.9 Hz, 1H); 5.33 (d, *J* = 5.9 Hz, 1H); 5.76-5.88 (m, 1H); 6.23 (d, *J* = 8.5 Hz, 1H); 6.39 (s, 1H); 7.12 (dd, *J* = 7.5 and 8.3 Hz, 1H); 7.31 (dd, *J* = 7.2 and 8.3 Hz, 1H); 7.36 (d, *J* = 7.5 Hz, 1H); 7.58 (bd, *J* = 7.2 Hz, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 11.6 (q); 15.3 (q); 25.0 (t); 28.2 (3q); 37.8 (d); 41.9 (t); 56.6 (d); 57.9 (q); 59.8 (s); 61.2 (d); 66.3 (t); 82.3 (s); 84.1 (d); 91.1 (t); 117.5 (t); 118.3 (d); 123.2 (d); 124.4 (d); 130.6 (d); 132.3 (d); 132.8 (s); 141.2 (s); 152.0 (s); 169.7 (s); 171.4 (2s).
IR (KBr): v (cm^{-1}) 3333, 2967, 2934, 1718, 1540, 1478, 1369, 1335, 1161, 927, 755.
HRMS (ESI+) calculated for $C_{28}H_{38}BrN_3O_8Na$ *m/z* ($M+Na^+$) 646.1740, found 646.1730.

exo-Allyloxyisoleucinyl 3a-bromo-1,8-(di-_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carbonylate (3p)



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.88-0.94 (m, 6H); 1.15-1.26 (m, 1H); 1.39 (s, 9H); 1.41-1.49 (m, 1H); 1.58 (s, 9H); 1.86-1.93 (m, 1H); 2.84-2.95 (m, 1H); 3.18 (dd, *J* = 6.3 and 12.8 Hz, 1H); 3.77 (dd, *J* = 6.3 and 10.1 Hz, 1H); 4.58 (dd, *J* = 3.6 and 4.9 Hz, 1H); 4.59-4.63 (m, 2H); 5.26 (ddd, *J* = 1.1 , 2.5 and 10.4 Hz, 1H); 5.33 (ddd, *J* = 1.4 , 2.5 and 17.2, 1H); 5.84-5.95 (m, 1H); 6.28 (d, *J* = 8.5 Hz, 1H); 6.36 (s, 1H); 7.12 (t, *J* = 7.6 Hz, 1H); 7.30 (dd, *J* = 7.6 and 7.9 Hz, 1H); 7.35 (bd, *J* = 7.6 Hz, 1H); 7.50 (bd, *J* = 7.9 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 11.5 (q); 15.4 (q); 25.1 (t); 28.2 (3q); 28.3 (3q); 38.1 (d); 41.9 (t); 56.5 (d); 59.9 (s); 61.3 (d); 65.8 (t); 81.6 (s); 82.4 (s); 84.1 (d); 118.7 (d); 119.0 (t); 123.3 (d); 124.5 (d); 130.5 (d); 131.5 (d); 133.3 (s); 141.4 (s); 152.3 (s); 169.9 (s); 171.4 (2s).
IR (KBr): v (cm^{-1}) 3343, 2975, 2933, 1721, 1532, 1478, 1394, 1368, 1331, 1165, 853, 751.
HRMS (ESI+) calculated for $C_{30}H_{42}BrN_3O_7$ *m/z* (M) 635.2206, found 635.2628.

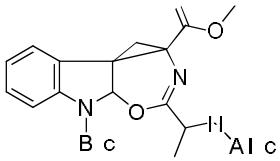
Compound 5



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.18 (s, 3H); 1.20 (s, 3H); 2.17-2.36 (m, 2H); 3.24-3.41 (m, 2H); 3.62 (s, 3H); 3.63 (s, 3H); 3.78 (bs, 1H); 4.09 (t, *J* = 7.1 Hz, 1H); 4.22-4.51 (m, 5H); 4.70 (dd, *J* = 7.6 and 12.0 Hz, 1H); 4.92 (dd, *J* = 6.7 and 12.8 Hz, 1H); 5.13-5.28 (m, 5H); 5.31 (d, *J* = 6.9 Hz, 1H); 5.49 (d, *J* = 6.0 Hz, 1H); 5.76-5.90 (m, 2H); 6.63 (bs, 1H); 6.95 (bd, *J* = 6.4 Hz, 1H); 7.03-7.20 (m, 5H); 7.22 (d, *J* = 8.0 Hz, 1H); 7.31 (t, *J* = 4.4 Hz, 1H); 7.45 (d, *J* = 7.9 Hz, 2H); 9.42 (s, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 17.4 (q); 18.0 (q); 27.1 (t); 35.8 (t); 46.1 (d); 50.2 (d); 50.3 (2d); 52.6 (q); 52.7 (q); 52.9 (d); 60.6 (d); 66.0 (t); 66.2 (t); 109.2 (s); 111.7 (d); 116.0 (d); 118.1 (2t); 118.8 (d); 119.9 (d); 122.8 (s);

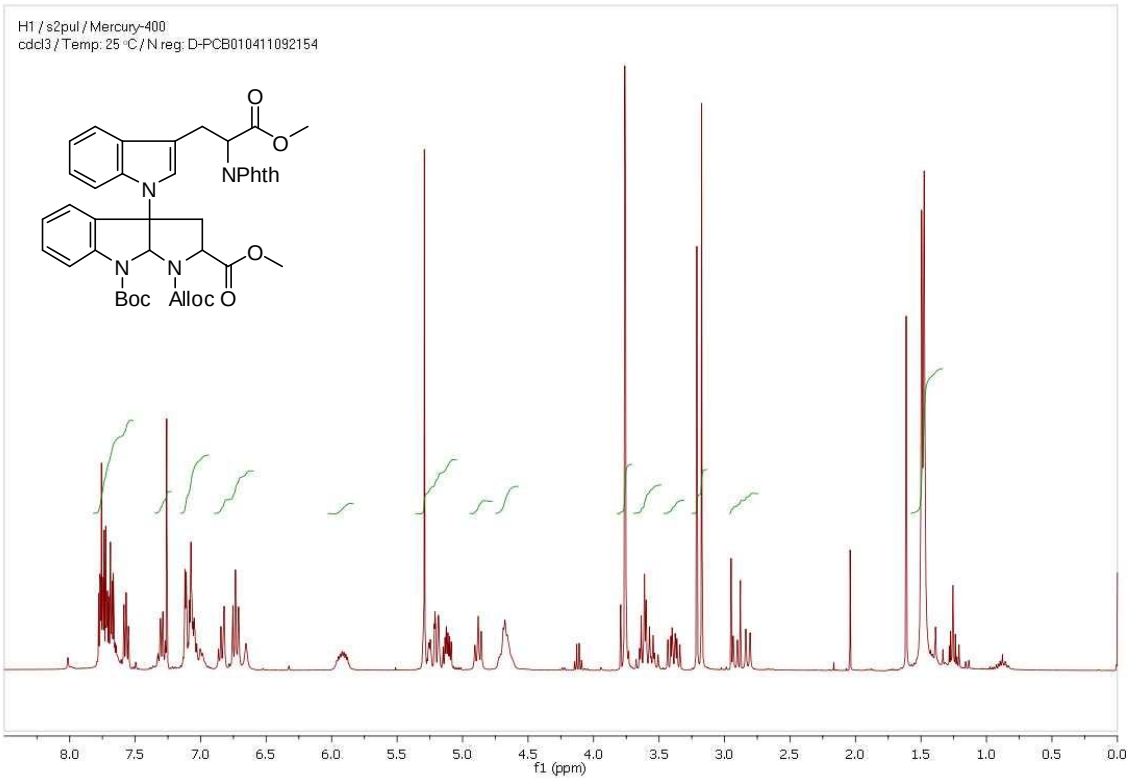
123.2 (d); 124.7 (d); 126.1 (d); 127.6 (s); 127.9 (s); 129.1 (d); 132.1 (d); 132.3 (d); 136.1 (s); 156.4 (s); 160.9 (s); 161.2 (s); 171.8 (s); 172.9 (s); 173.1 (2s).
MS (ESI+) *m/z* = 747 ($M+H^+$, 100%), 374 ($½M+H^+$, 30%).
HPLC (MeCN:H_2O des de 40:60 fins 50:50 en 8 minuts): t_R= 5.52 min.

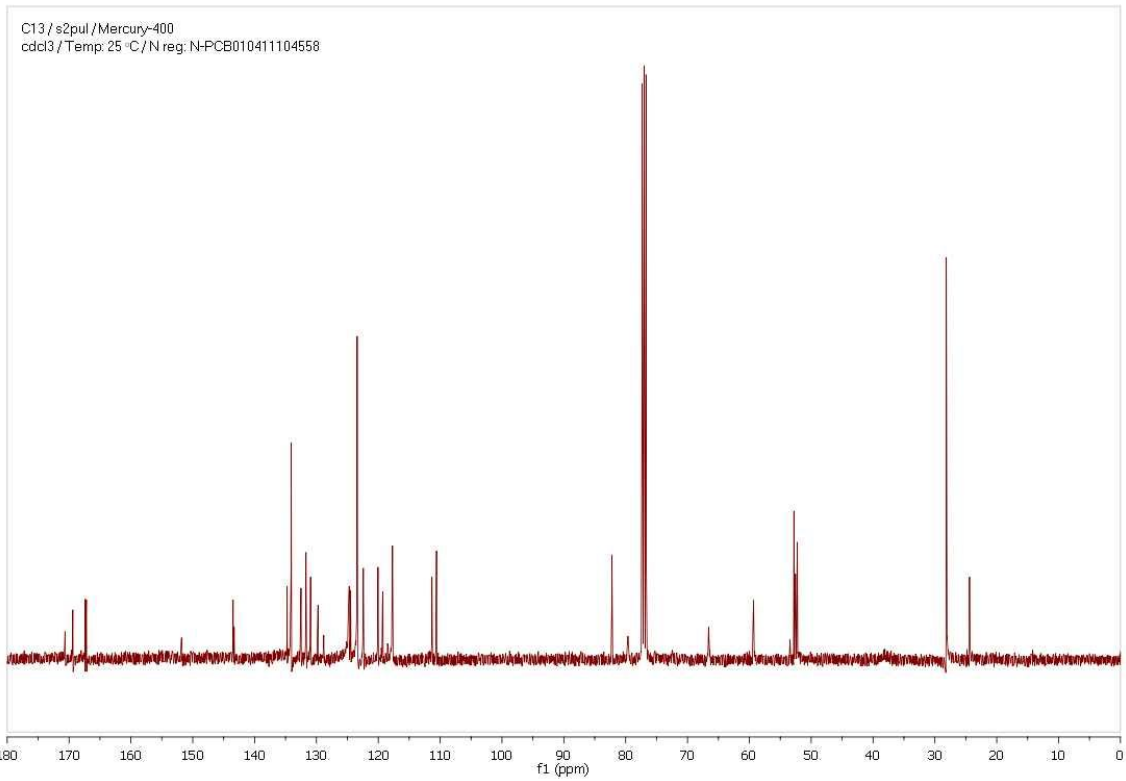
Compound 8



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.66 and 0.77 (2d, *J* = 6,6 Hz, 3H); 1.64 (s, 9H); 3.43 (d, *J* = 15.4 Hz, 1H); 3,81 (s, 3H); 3.91 (d, *J* = 15.4 Hz, 1H); 4.04-4.19 (m, 1H); 4.54-4.77 (m, 2H); 5.15-5.44 (m, 2H); 5.84-5.99 (m, 1H); 7.08 (bs, 1H); 7.14 (dd, *J* = 7.2 and 7.6 Hz, 1H); 7.27 (dd, *J* = 7.2 and 8.2 Hz, 1H); 7.43-7.52 (m, 2H); 8.08 (d, *J* = 8.2 Hz, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 17.0 (q); 28.1 (3q); 28.9 (t); 53.3 (q); 54.9 (d); 66.4 (t); 77.9 (s); 83.8 (s); 113.3 (s); 115.1 (d); 118.1 (t); 119.1 (d); 122.6 (d); 124.4 (d); 125.9 (d); 132.0 (s); 135.0 (s);149.6 (s); 154.0 (s); 170.2 (s); 172.9 (s).
IR (KBr): v (cm^{-1}) 3283, 2931, 1735, 1452, 1370, 1257, 1158, 1082, 747.
HRMS (ESI+) calculated for $C_{48}H_{58}N_6O_{14}Na$ *m/z* ($2M+Na^+$) 965.3909, found 965.3934.

1a.





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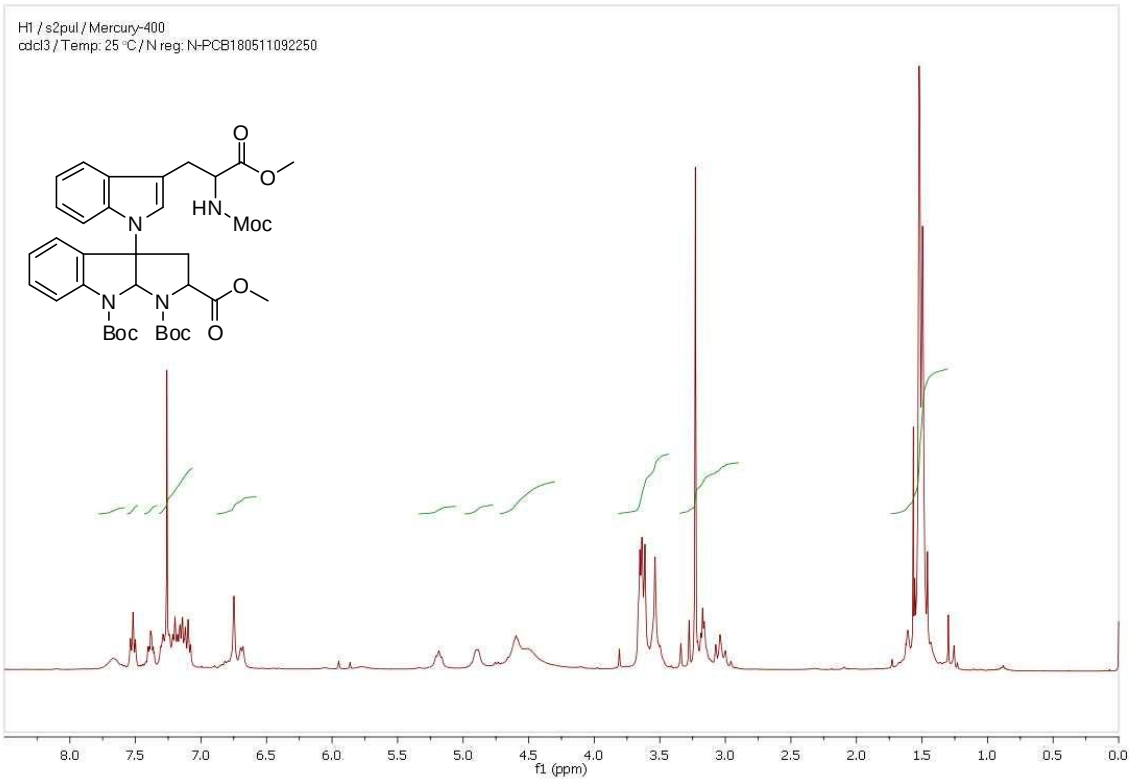

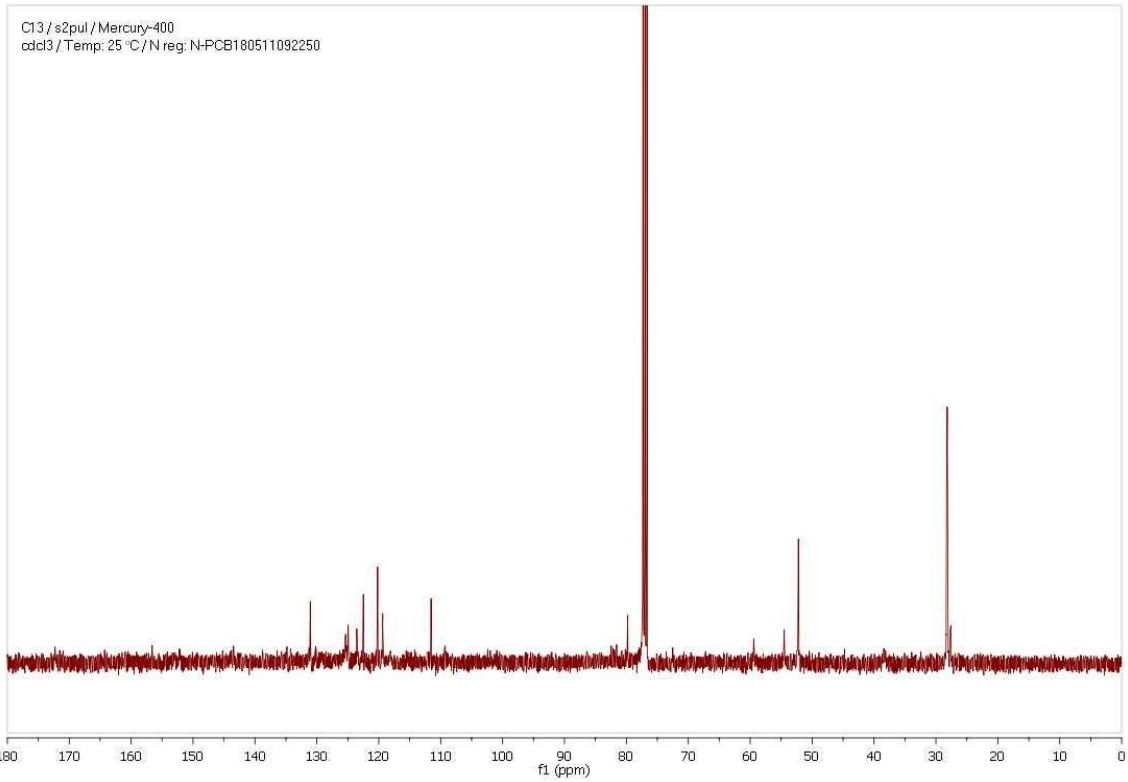

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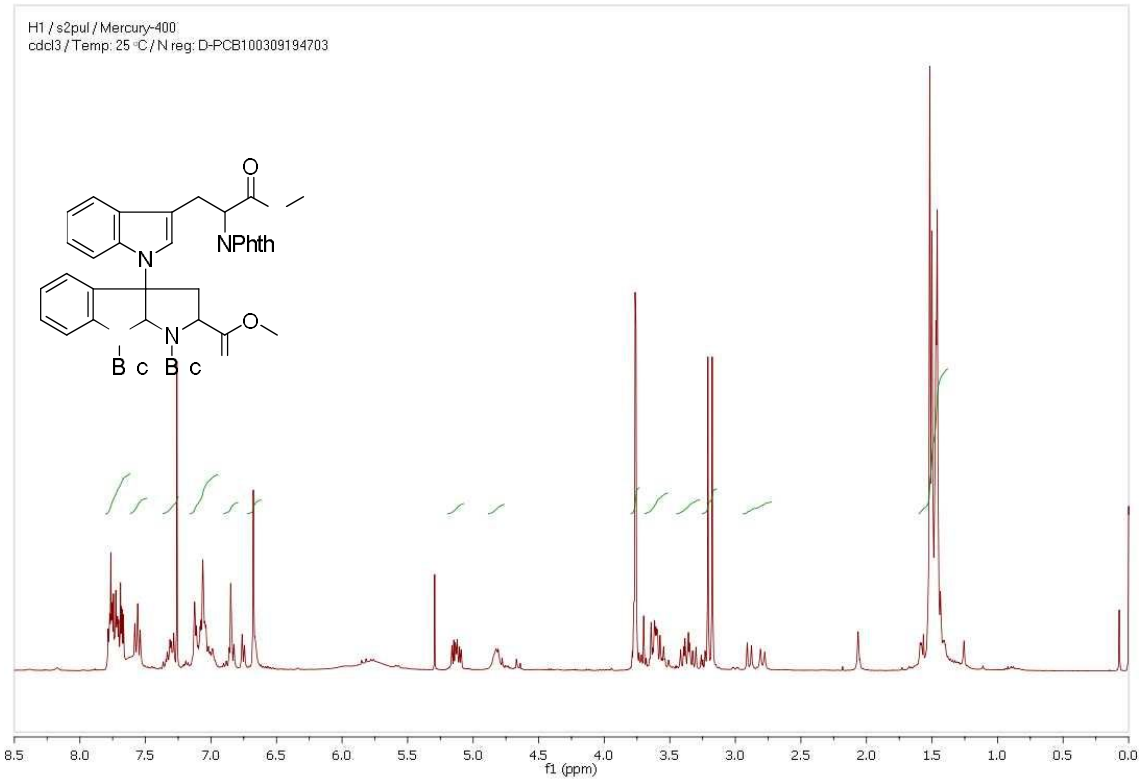

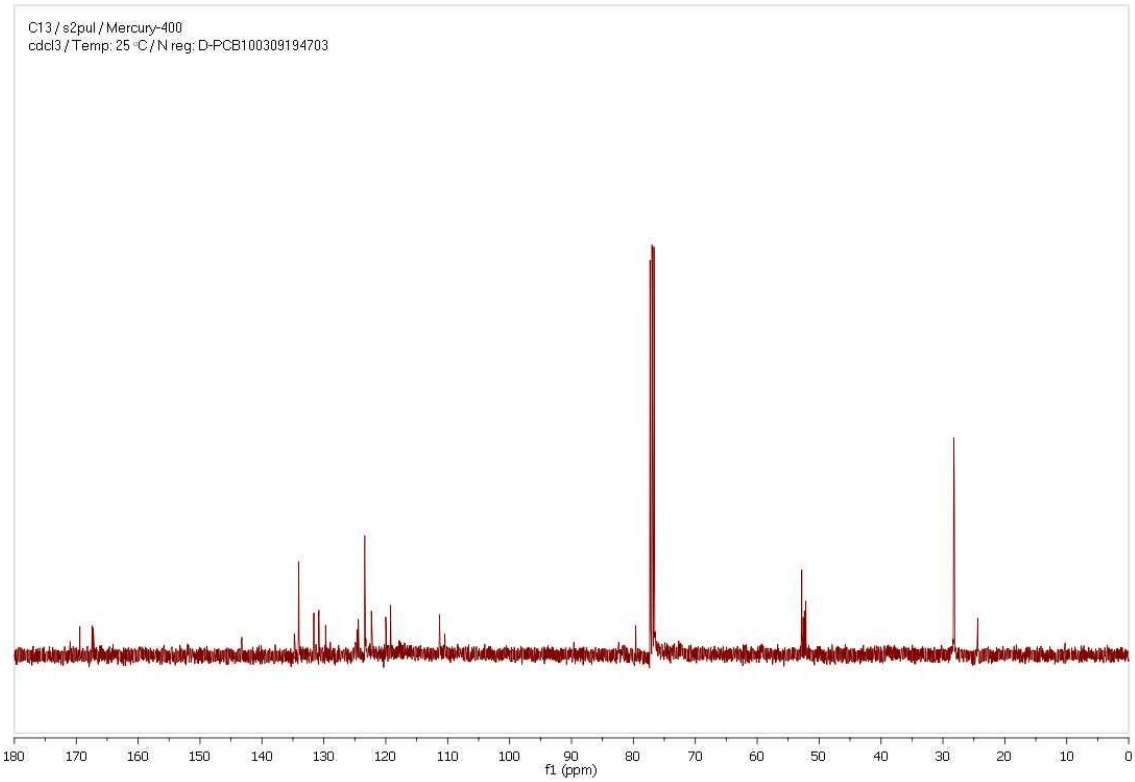

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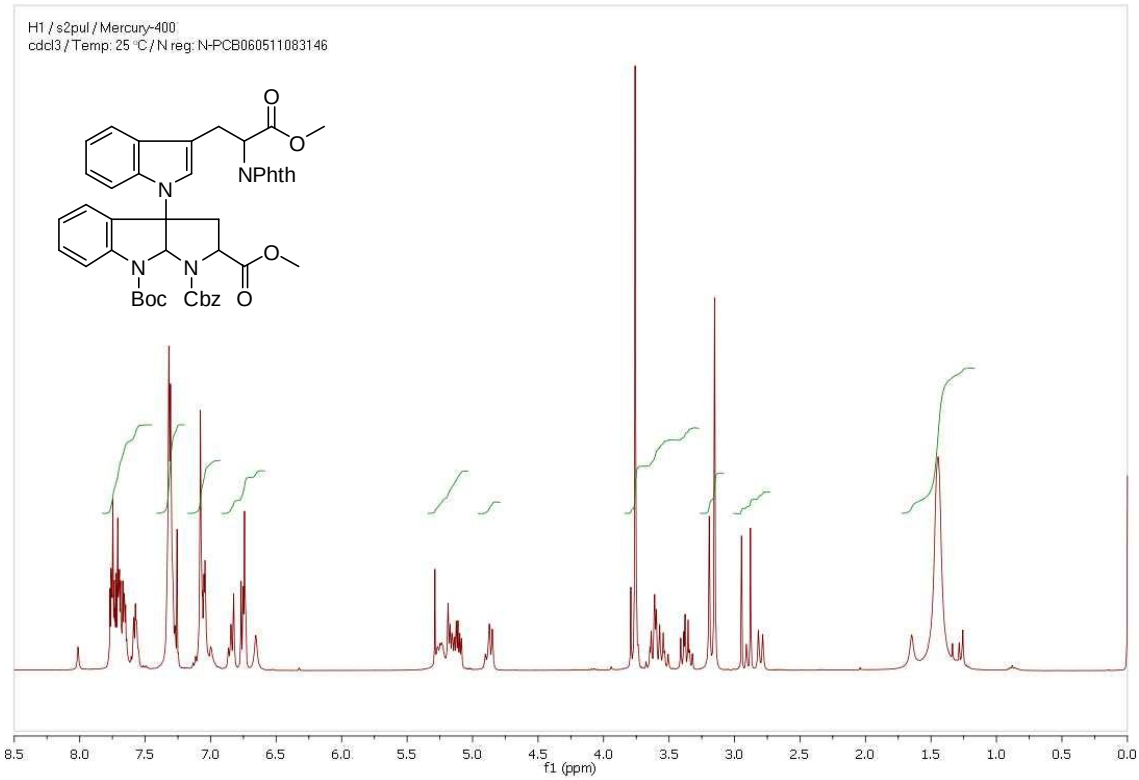

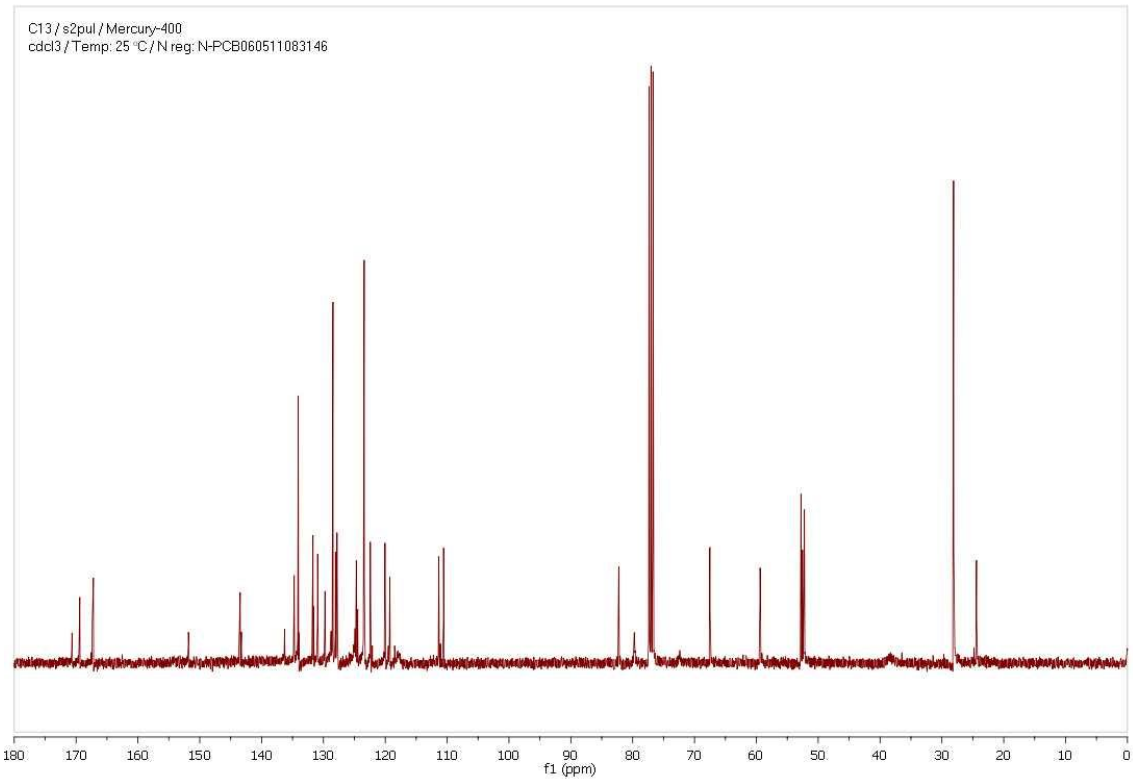

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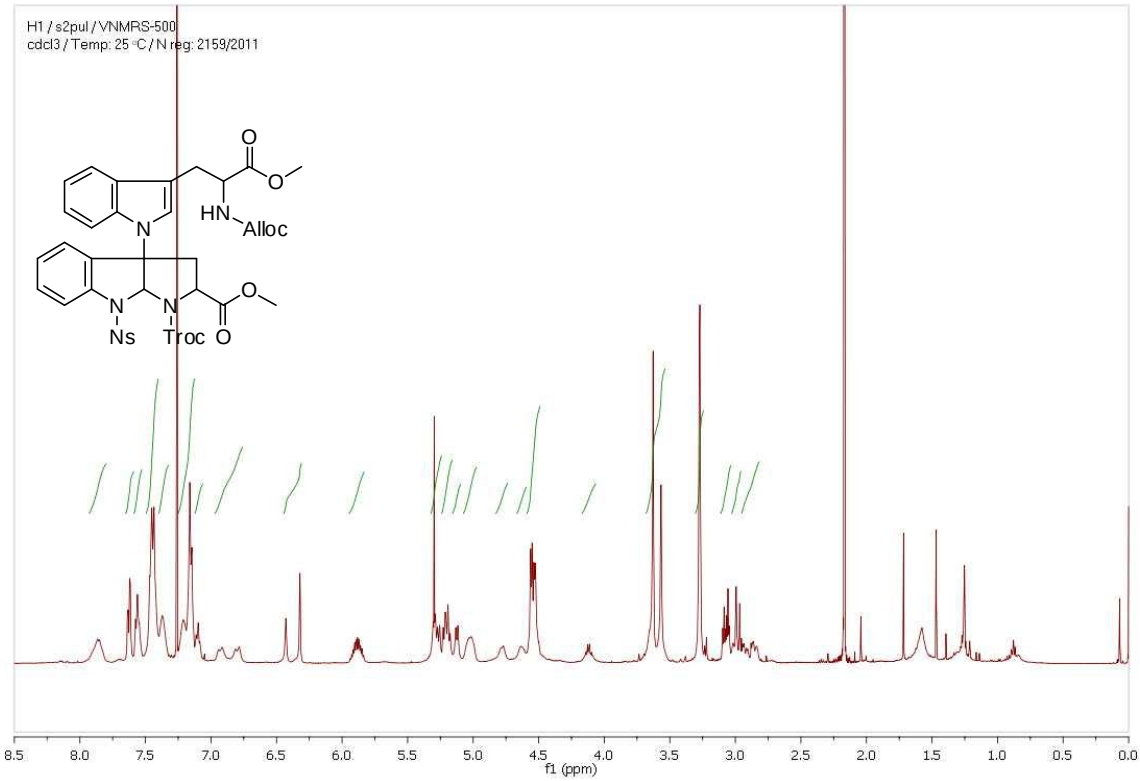

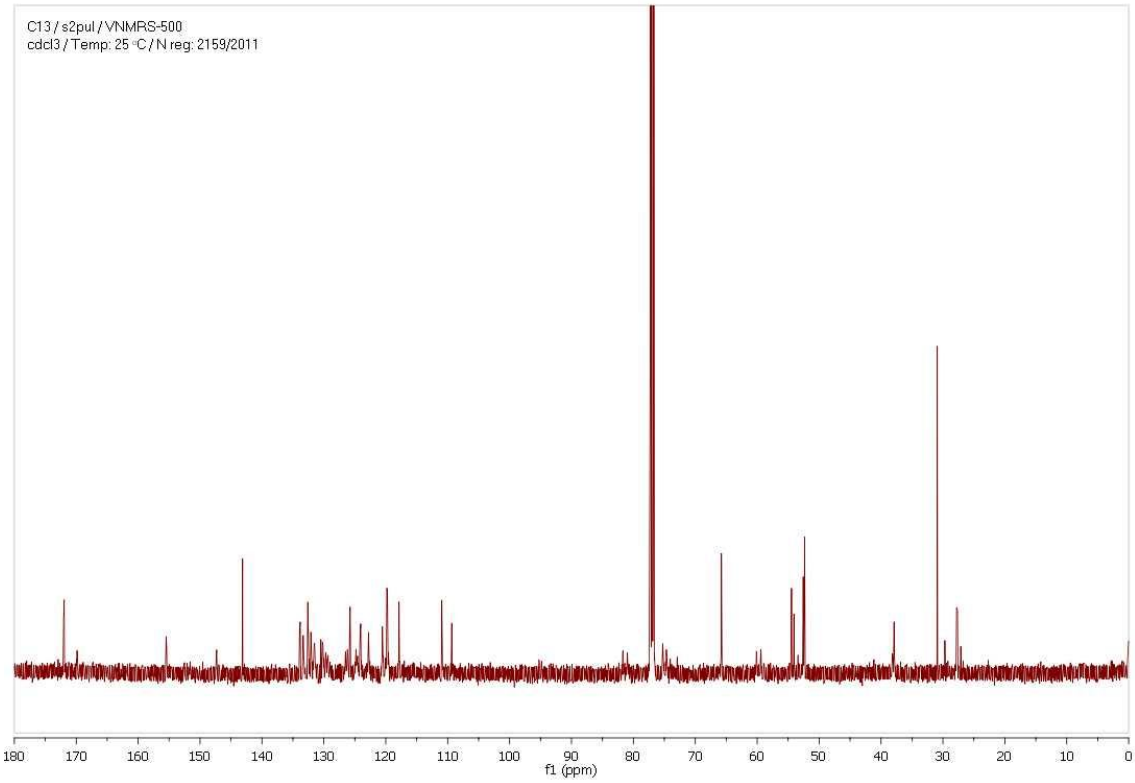

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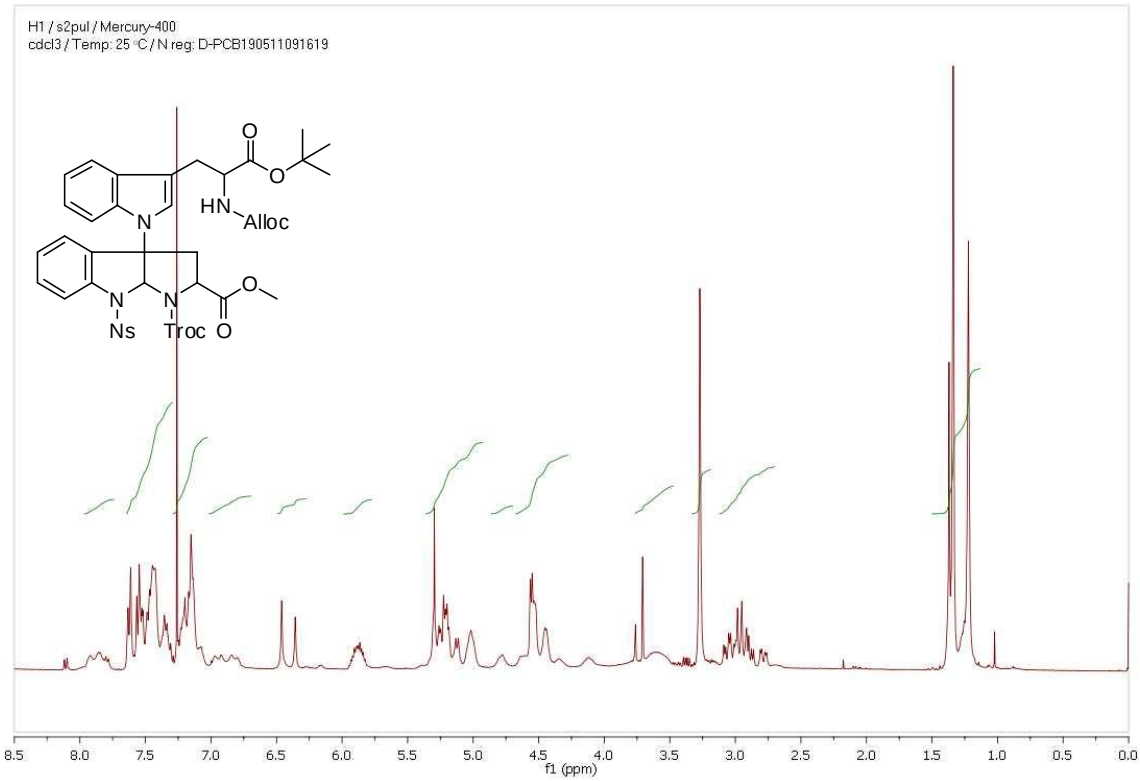
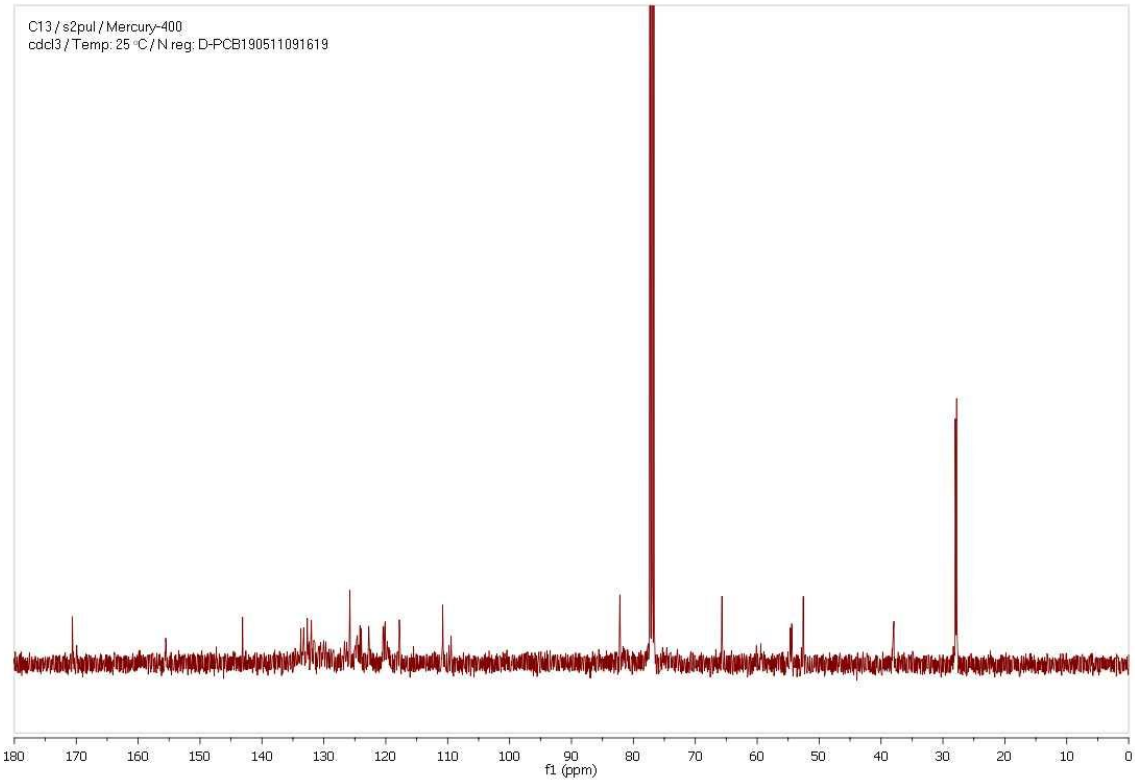
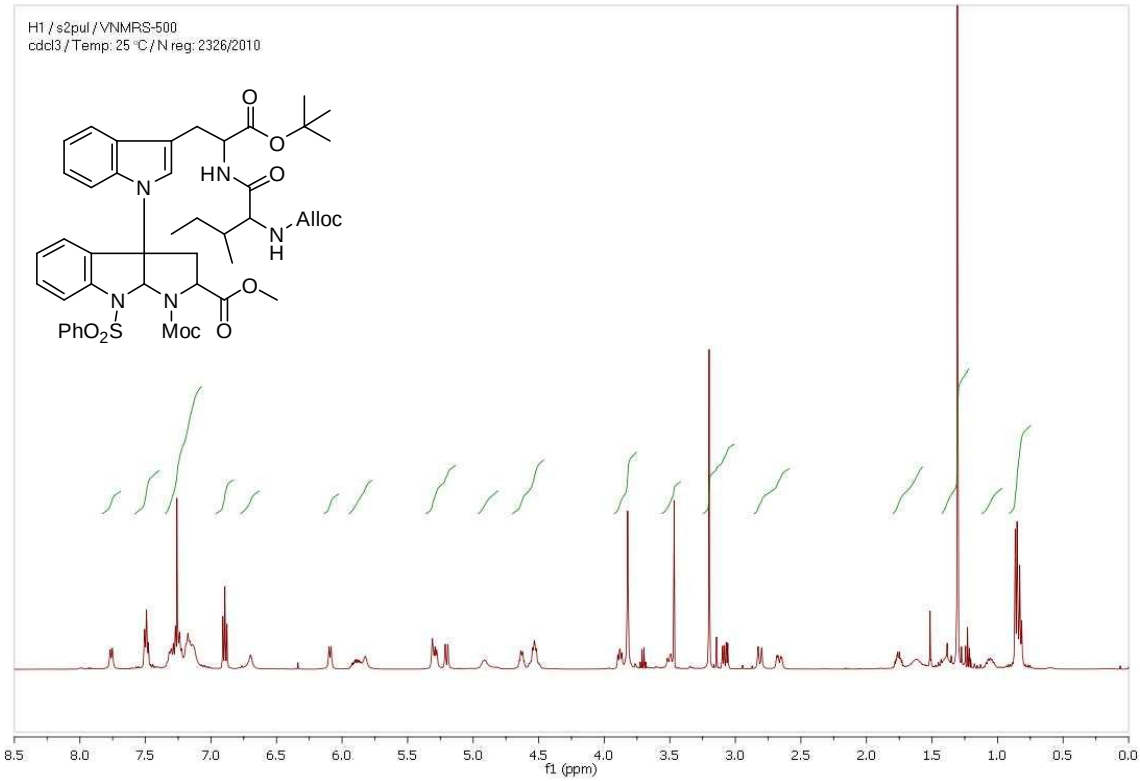
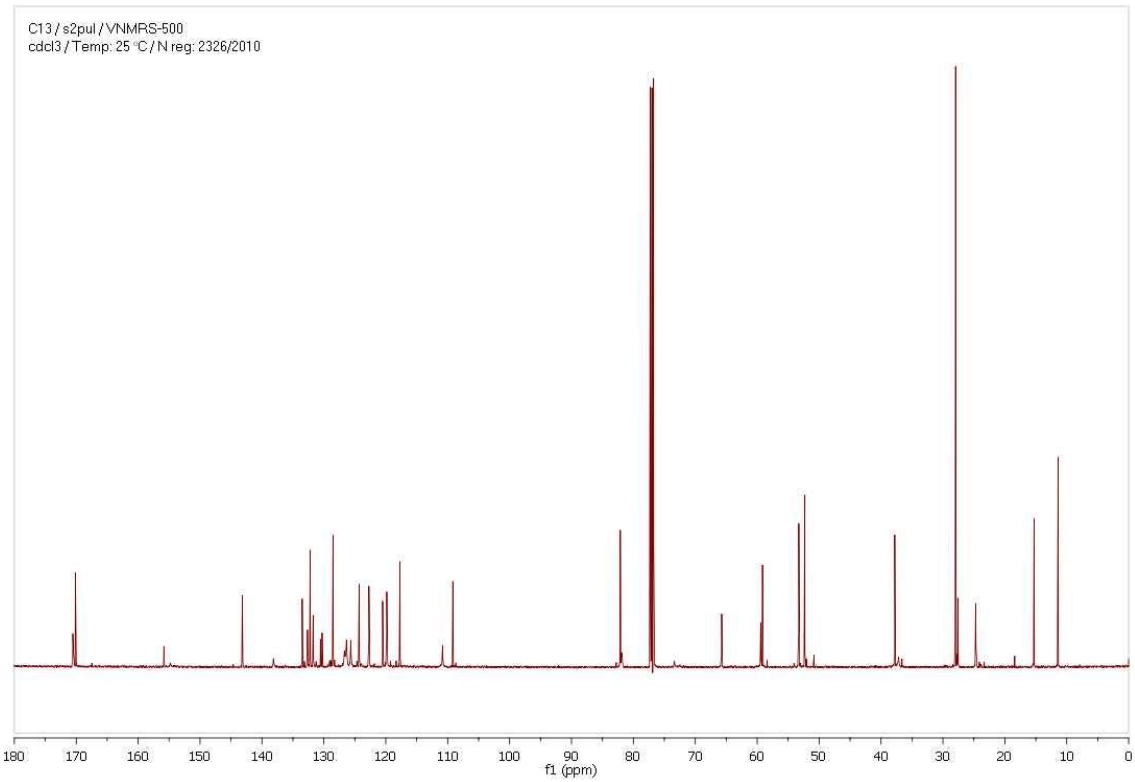




1g.





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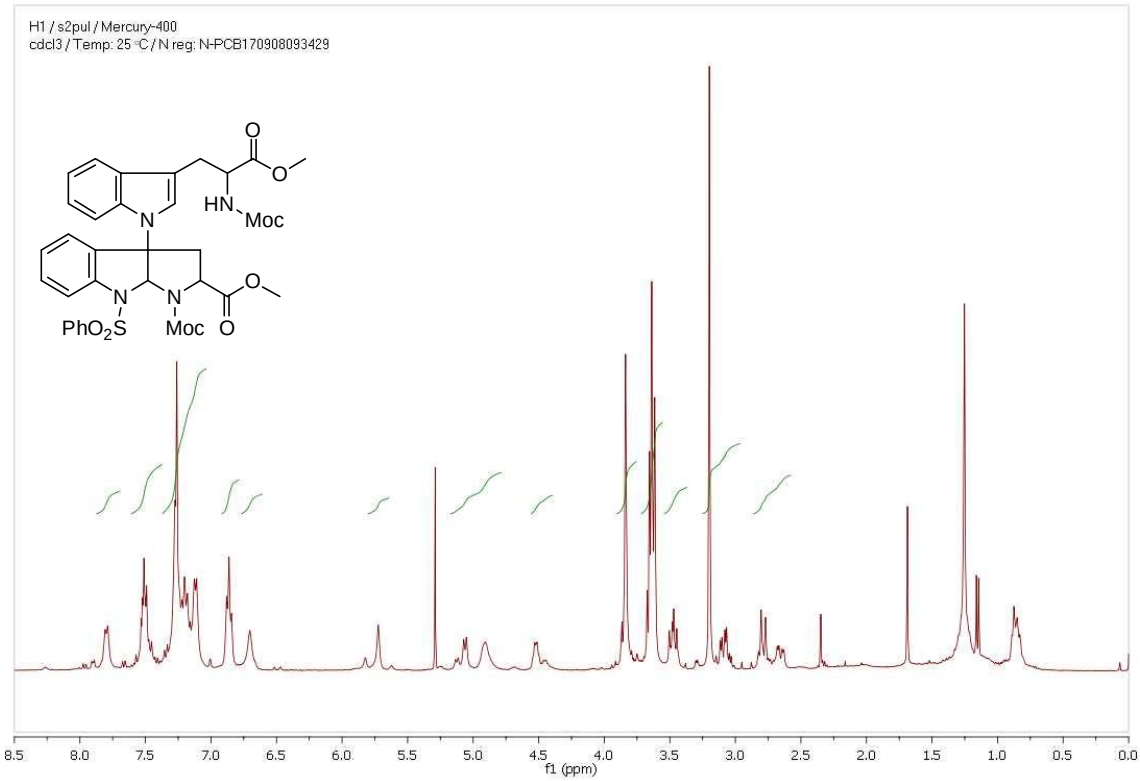

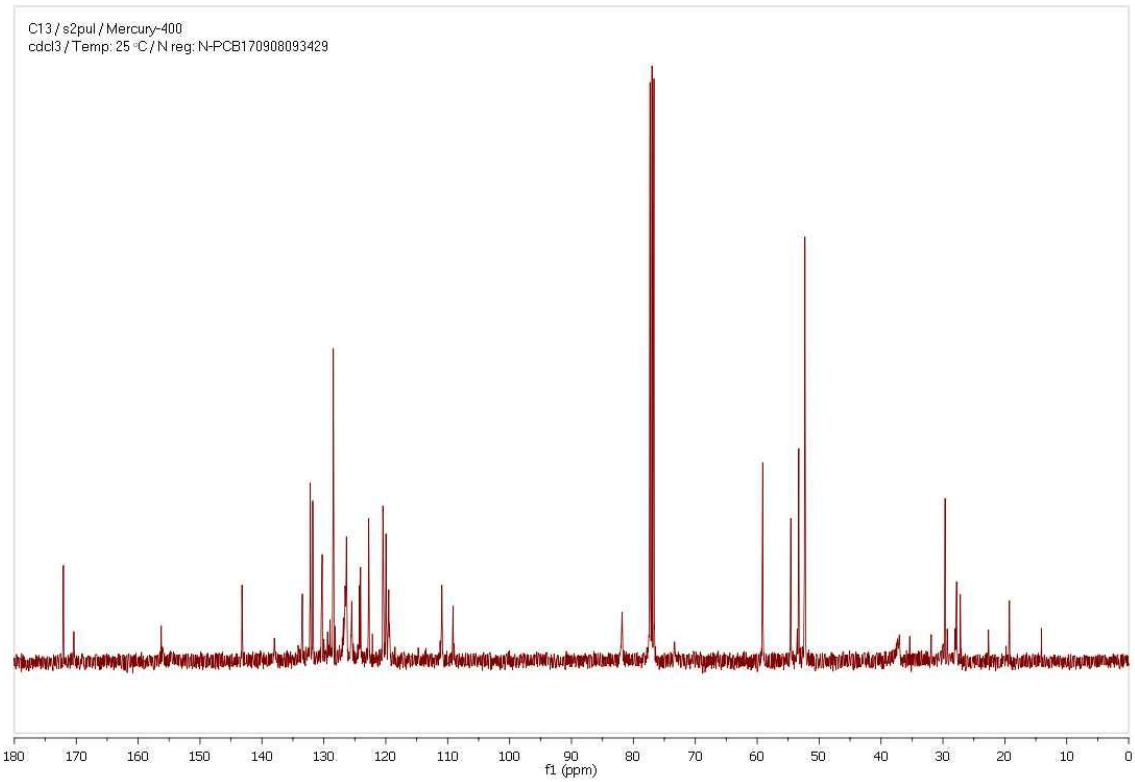

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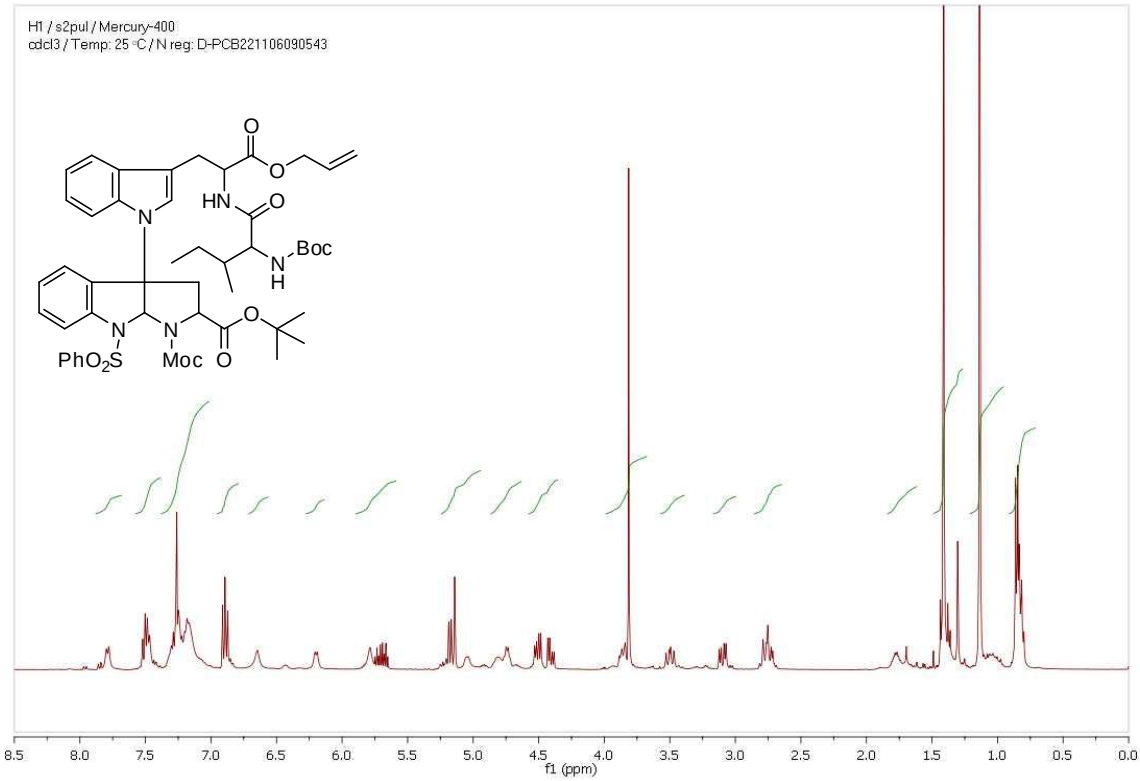
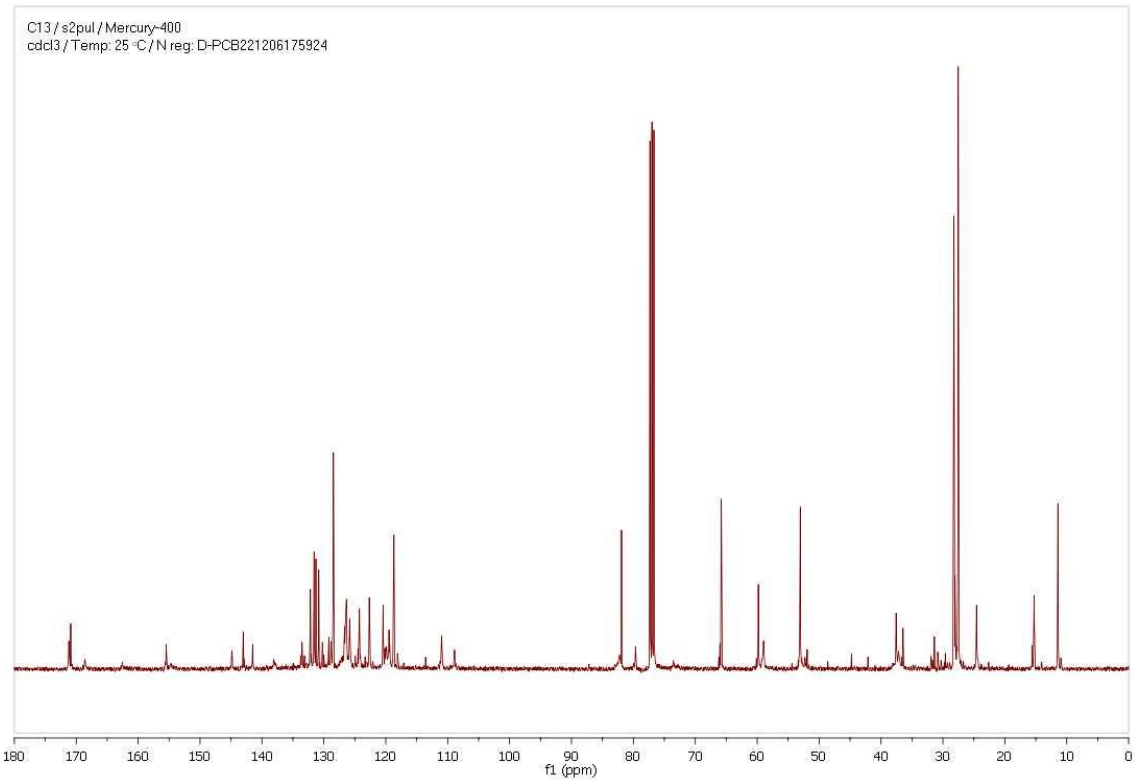
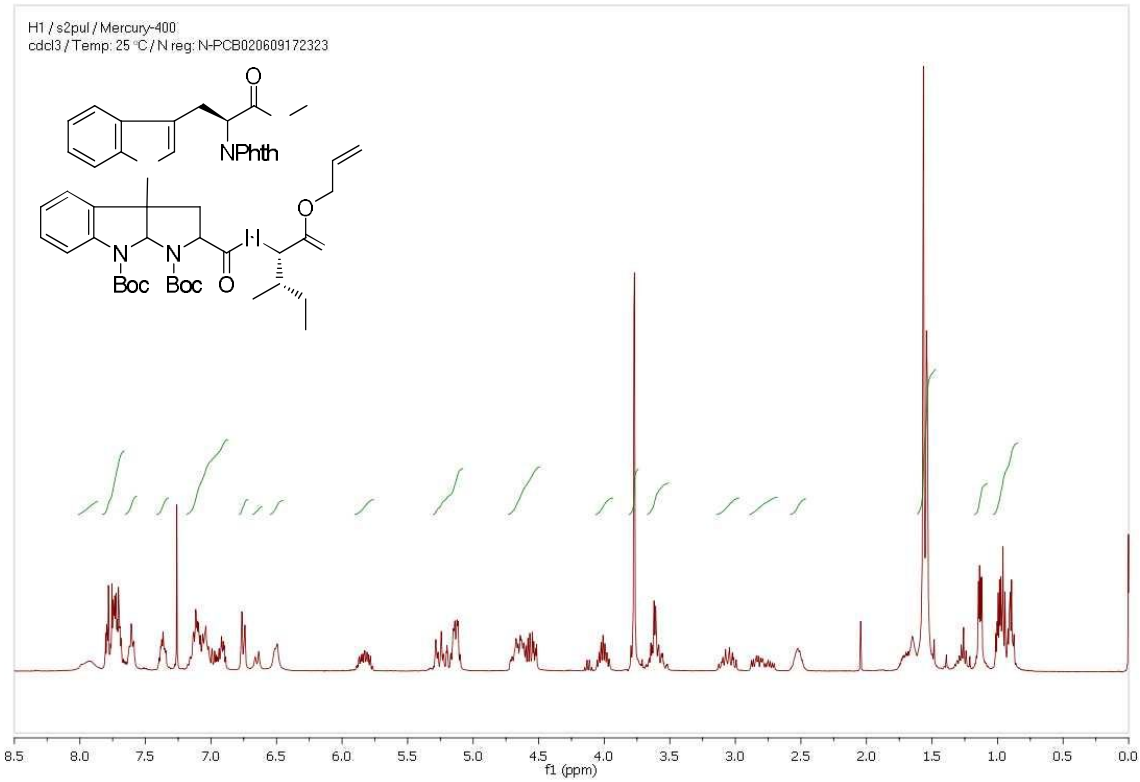
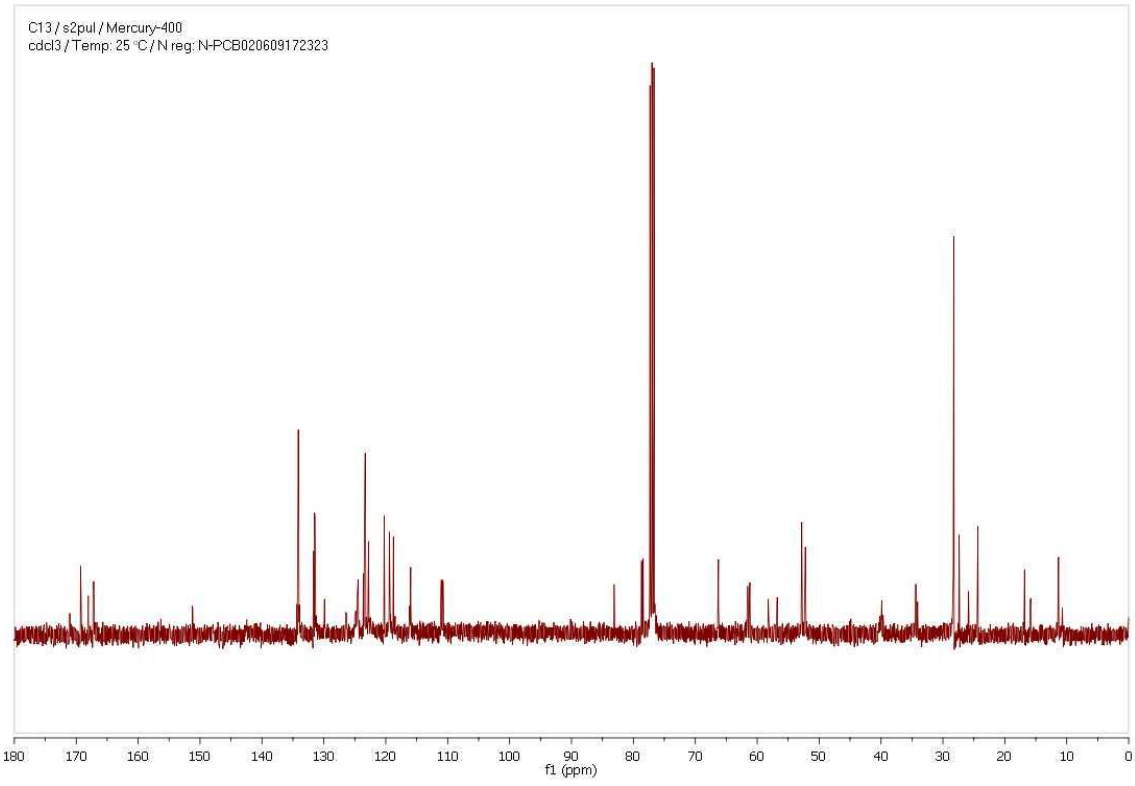


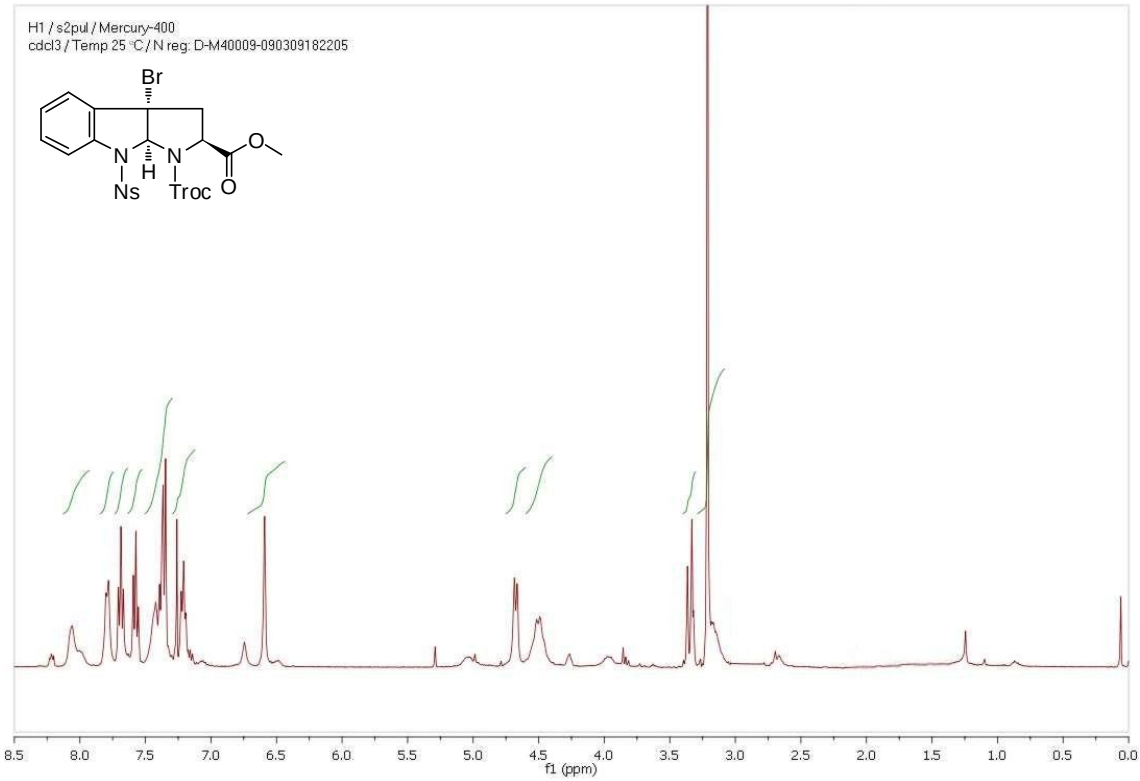


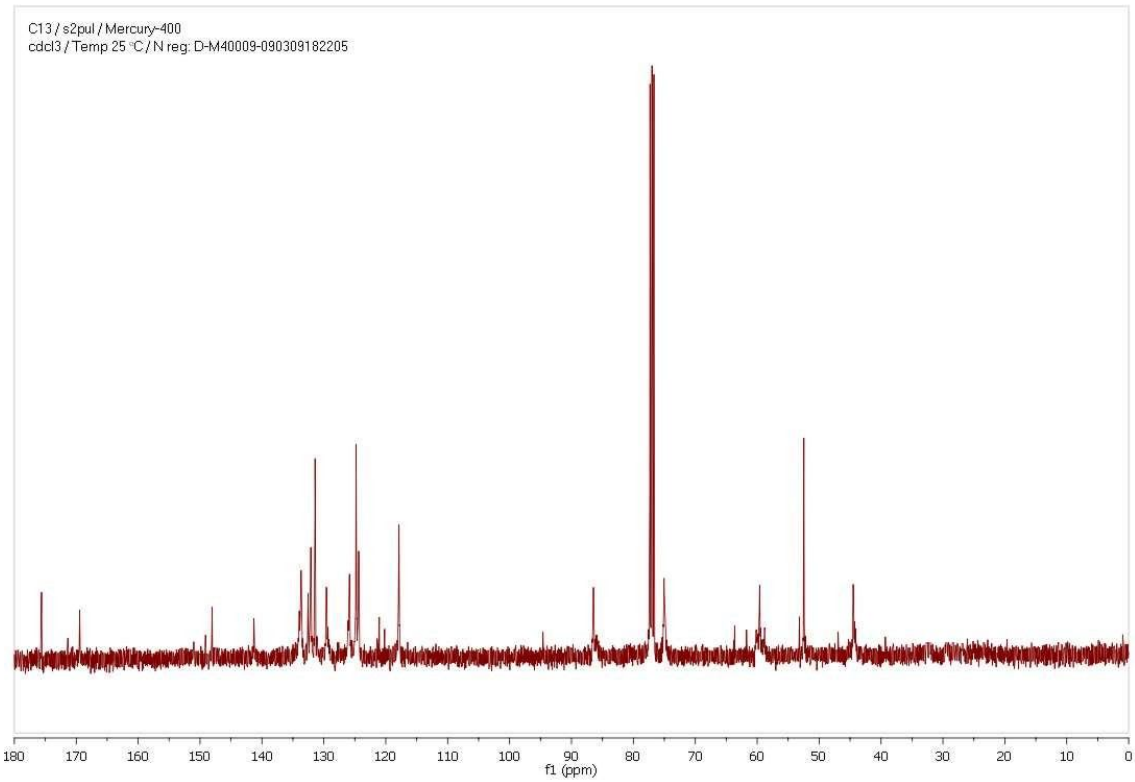
1j.





***endo*-3g.**





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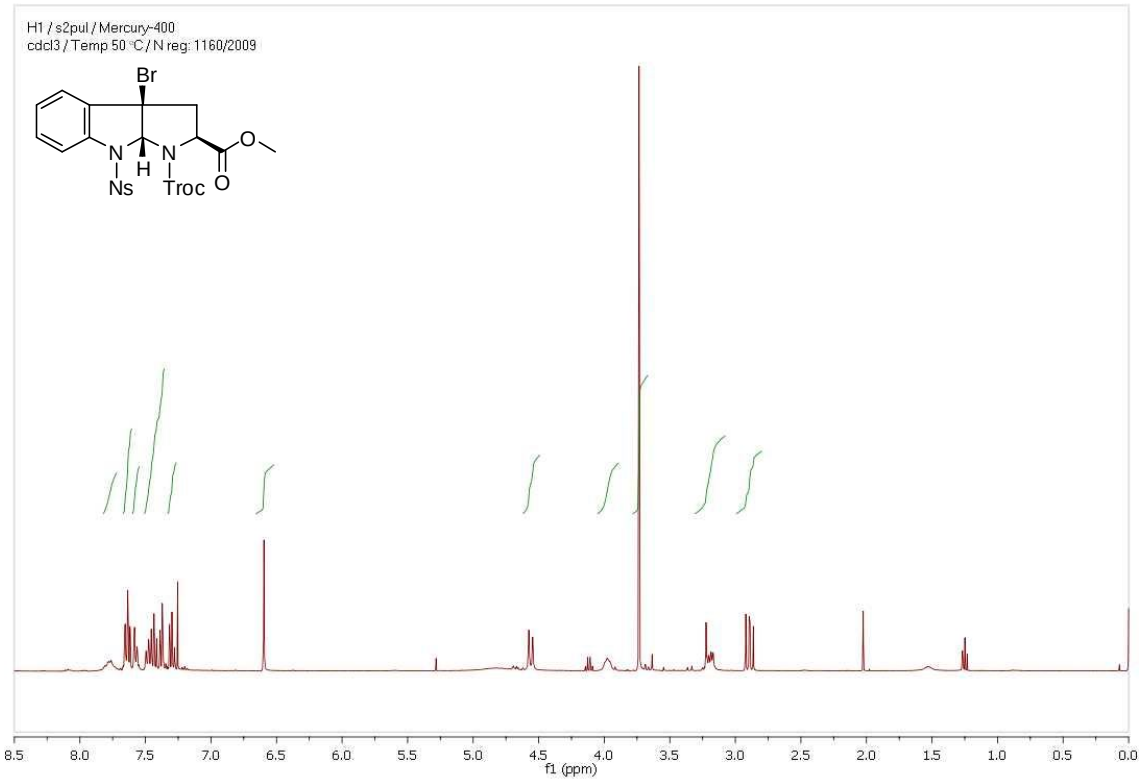
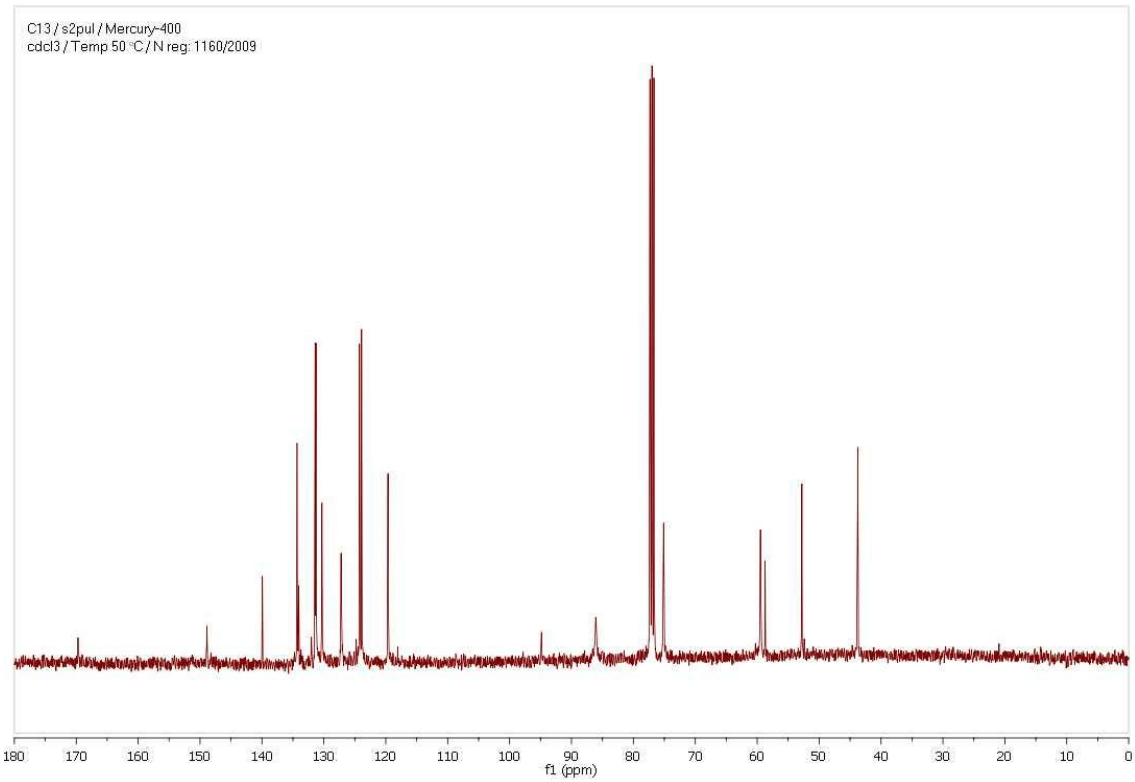
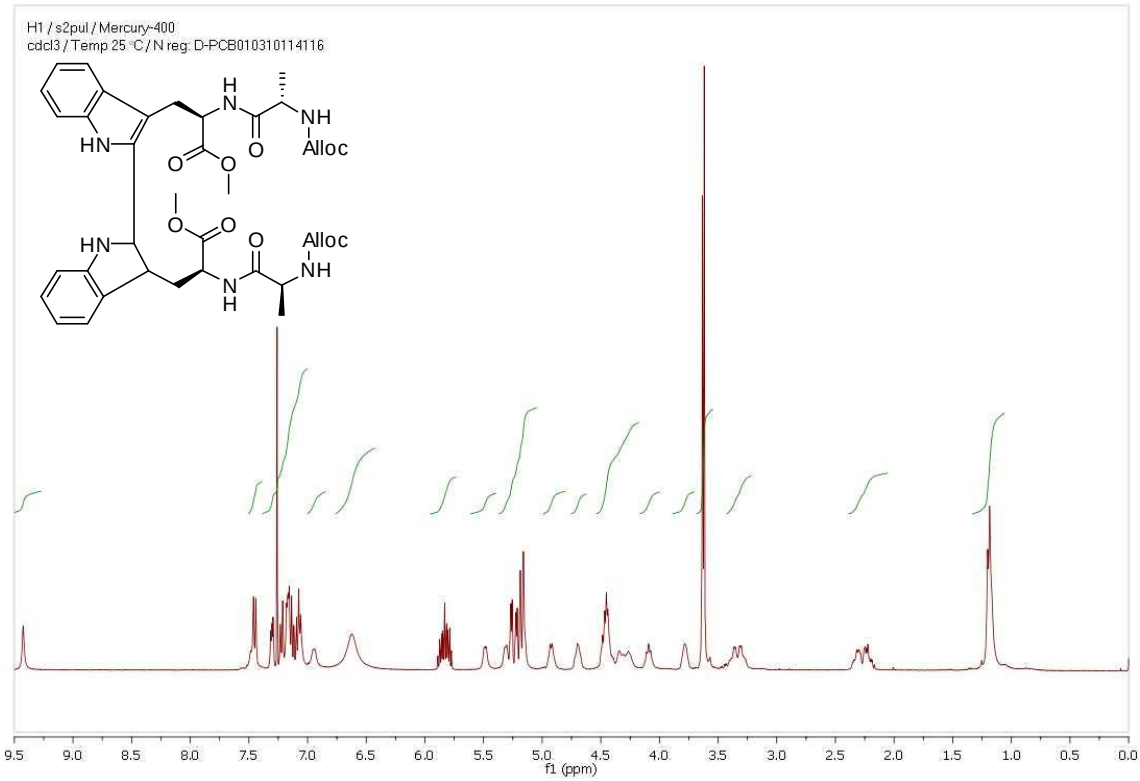
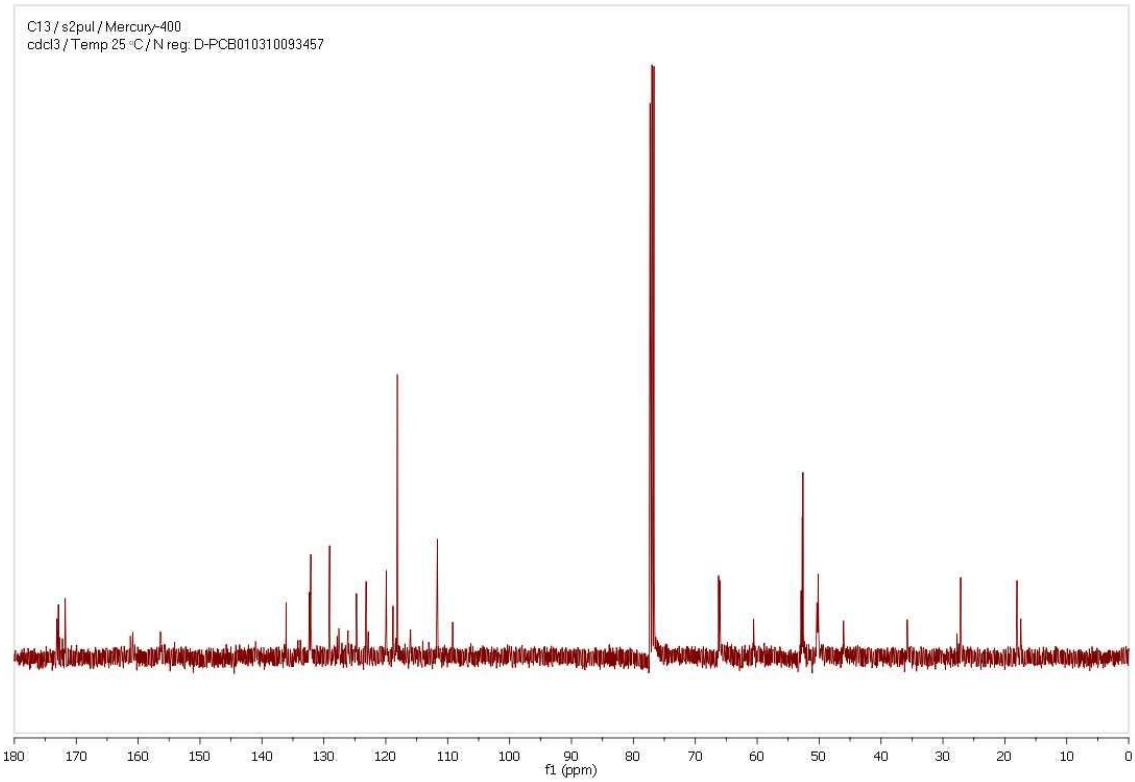




Compost 5





Compost 8