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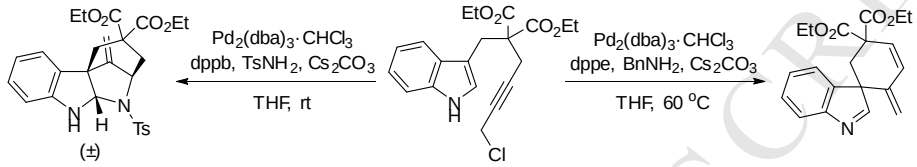

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Convenient synthesis of spiroindole derivatives via palladium-catalyzed cyclization of propargyl chlorides

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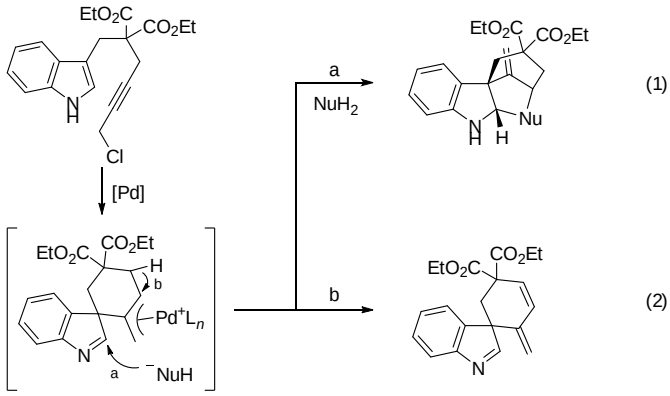
ABSTRACT

Herein, we report the palladium-catalyzed cyclization reactions of indoles bearing a propargyl chloride side chain at their 3-position. In the presence of an external nucleophile, such as a sulfonamides or malonate, indoles bearing a propargyl group at their 3-position gave fused tetracyclic spiroindolines preferentially. However, in the absence of an external nucleophile, the same substrates afforded spiroindoles. Our attempts to develop a catalytic asymmetric spirocyclization onto a propargylpalladium species are also presented in this paper.

1. Introduction

The palladium-catalyzed reactions of propargyl compounds provide efficient approaches for the formation of carbon-carbon and carbon-heteroatom bonds.[1] The pioneering work of Tsuji and co-workers revealed that double nucleophilic additions proceeded at the central and terminal carbons of the propargylic moiety when soft carbon- or oxo-nucleophiles were employed.[2] This chemistry is particularly useful for the construction of carbo- and heterocyclic frameworks, including furans,[3] cyclobutanes,[4] indenes,[5] cyclopentanones,[6] cyclic carbonates,[7] benzofurans,[8] and indoles,[9] especially when it is used in combination with an inter- or intramolecular nucleophilic addition reaction as the terminating step.

Spirocyclic compounds are currently attracting considerable interest in organic chemistry because of their unique molecular structure and diverse biological activities.[10] In particular, enantio-enriched spiroindoles and spiroindolines represent important structural motifs that can be found in a wide range of biologically active natural products and synthetic compounds.[11] As part of our ongoing efforts towards the construction of heterocyclic frameworks based on the palladium-catalyzed reactions of propargyl/allenic compounds, we recently became interested in the intramolecular nucleophilic addition reactions of indoles as a strategy for the synthesis of spiroindoles. It was envisaged that this strategy would provide facile access to tetracyclic spiroindolines when it was used in combination with the intermolecular nucleophilic cyclization of an external nucleophile (Scheme 1, eq. 1, path a). We also expected that running the same reaction without using an external nucleophile would promote β-hydride elimination (path b) to produce spiroindoles bearing a conjugated diene moiety (eq. 2).



Scheme 1. Our concept: palladium-catalyzed spirocyclization of indole-based propargyl compounds

In 2013, Hamada and co-workers reported the development of a palladium-catalyzed intramolecular spirocyclization of phenol-based propargylic carbonates (Scheme 2, eq. 3).[12] When tryptamine-derived carbonates were used, this reaction produced spiroindoles bearing an azepine moiety. Immediately after our communication in 2014,[13] the groups of Rawal[14a] and You[14b]

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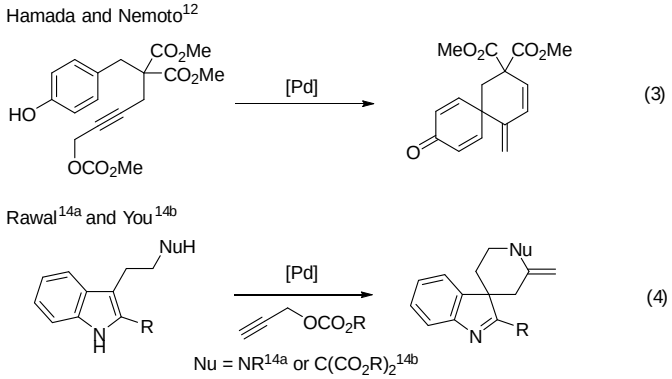
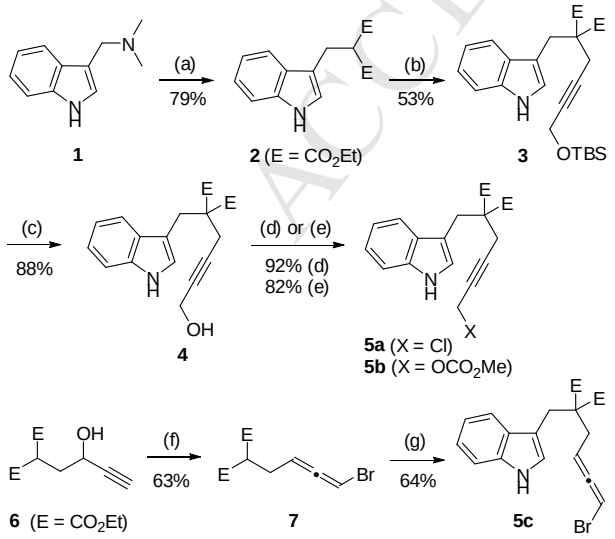
independently reported the intermolecular reactions of indole-based dual nucleophiles and propargyl carbonates as general strategies for the synthesis of spiroindoles (eq. 4). In this paper, we report the full details of our recent investigations into construction of tetracyclic spiroindolines (eq. 1) and conjugated diene-type spiroindoles (eq. 2) via the palladium-catalyzed cyclization of propargyl chlorides. Our attempts to achieve a catalytic asymmetric spirocyclization onto a propargylpalladium species have also been presented.



Scheme 2. Related palladium-catalyzed spirocyclization reaction using propargyl compounds

2. Results and discussion

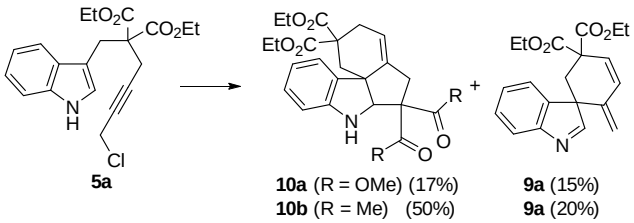
The route used for the preparation of substrates **5a**–**c** is shown in Scheme 3. In accordance with a literature procedure,[15] gramine (**1**) was converted to the corresponding malonate **2**. The subsequent alkylation of **2** followed by a desilylation reaction afforded propargyl alcohol **4**. Substrates **5a** and **5b** were obtained by the reaction of **4** with NCS/PPh_3 or $ClCO_2Me$/pyridine, respectively. Bromoallene **5c** was prepared from propargyl alcohol **6** using an established procedure for the formation of bromoallenes.[16] The treatment of **6** with TrisCl (Tris = 2,4,6-triisopropylbenzenesulfonyl) and DMAP gave the corresponding sulfonate, which was converted to bromoallene **7** by treatment with $CuBr\cdot SMe_2$ in the presence of LiBr. Finally, the introduction of the indole unit to **7** was achieved by its reaction with gramine (**1**) in the presence of ethyl propiolate to give bromoallene **5c**. The other substrates were also prepared in the same manner (see Supplementary material).



Scheme 3. Preparation of substrates **5a**–**c**. (a) diethyl malonate, ethyl propiolate, Et_2O, rt; (b) $BrCH_2C{\equiv}CCH_2OTBS$, NaH, THF, 0 °C to rt; (c) TBAF, THF, 0 °C; (d) NCS, PPh_3, CH_2Cl_2, rt; (e) $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C; (f) TrisCl, DMAP, CH_2Cl_2, then $CuBr\cdot Me_2S$, LiBr, THF, 50 °C; (g) **1**, ethyl propiolate, Et_2O, rt.

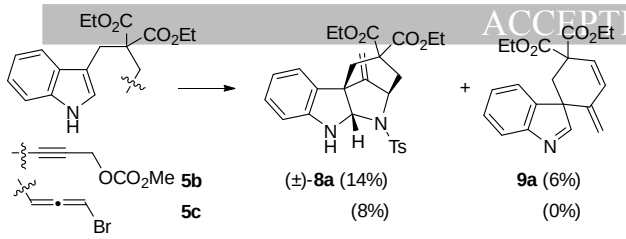
Our studies began with a series of screening experiments to identify the optimal reaction conditions using propargyl chloride **5a** as a model substrate (Table 1). The reaction of **5a** with 5 mol % $Pd(PPh_3)_4$, $TsNH_2$ and Cs_2CO_3 in THF gave spiroindole **9a**, the β-hydride elimination product, in only 20% yield (entry 1). When the reaction was conducted in the presence of 5 mol % $Pd(dba)_2$ and the bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf), the desired reaction proceeded smoothly to afford the tetracyclic spiroindoline **8a** in 47% yield (entry 2). A variety of different inorganic bases (entries 3–5), ligands (entries 6–10) and solvents (entries 11–13) were also screened against the reaction, and the results revealed that the use of 1,4-bis(diphenylphosphino)butane (dppb) as the ligand with Cs_2CO_3 as the base in THF gave the best results, with compound **8a** being isolated in *ca*. 72% yield (entry 9). However, the main problem with these conditions was found to be poor reproducibility. Operating under the assumption that the poor reproducibility of these conditions was related to the purity of $Pd(dba)_2$, we investigated the use of $Pd_2(dba)_3\cdot CHCl_3$ following its recrystallization from $CHCl_3$.[17] This change afforded the desired product **8a** in 72% yield reproducibly (entry 14).

With the optimized conditions in hand, we proceeded to examine the performance of the reaction in the presence of a variety of different nucleophiles. The results are summarized in Table 1 (entries 15–19) and Scheme 4. The reaction with sulfonamides (e.g., $PhSO_2NH_2$, $MtsNH_2$, $NsNH_2$, and $MsNH_2$) gave the corresponding tetracyclic spiroindolines **8b**–**e** in moderate yields (entries 15–18). In contrast, benzylamine was found to be inert as the external nucleophile, with the β-hydride elimination product **9a** being isolated as the major product (entry 19). Interestingly, the use of dimethyl malonate as the nucleophile resulted in the formation of the regioisomeric spiroindoline **10a** (17%) and spiroindole **9a** (15%) as shown in Scheme 4. The use of acetyl acetone, which is a more acidic carbon nucleophile than dimethyl malonate, led to an increase in the yield of spiroindoline **10b** (50%), along with spiroindole **9a** (20%).



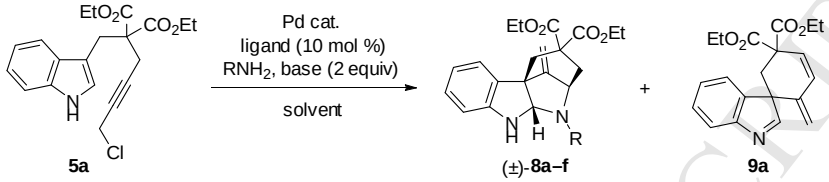
Scheme 4. Reaction with carbon nucleophiles. Reaction conditions: $Pd_2(dba)_3\cdot CHCl_3$ (2.5 mol %), dppb (10 mol %), Cs_2CO_3 and $CH_2(COR)_2$ in THF at rt.

It is well known that bromoallenes are the synthetic equivalents of propargyl compounds including chlorides and carbonates in palladium-catalyzed transformations.[18] With this in mind, we examined the reactions of propargyl carbonate **5b** and bromoallene **5c** (Scheme 5). Unfortunately, these reactions gave the desired spiroindoline **8a** in only 8–14% yield. These results therefore demonstrated that substrates of this type are less effective for this reaction than propargyl chloride **5a**.



Scheme 5. Reaction of carbonate **5b** and bromoallene **5c**. Reaction conditions: $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), dppb (10 mol %), $TsNH_2$ and Cs_2CO_3 in THF at rt.

Table 1. Optimization of the reaction conditions and the reaction with various nitrogen nucleophiles.



entry	Pd (mol %)	ligand	RNH_2 (equiv)	Base	solvent (M)	temp (°C)	time (h)	% yield[a] (product) 8		% yield[a] (product) 9a
1	$Pd(PPh_3)_4$ (5)	(PPh_3)	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	24	0		20
2	$Pd(dba)_2$ (5)	dppf[b]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	0.5	47	(**8a**)	5
3	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	K_2CO_3	THF (0.1)	50	3	15	(**8a**)	6
4	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	$CaCO_3$	THF (0.1)	60	24	0		0
5	$Pd(dba)_2$ (5)	dppf	$TsNH_2$ (1)	$NaHCO_3$	THF (0.1)	60	24	0		0
6	$Pd(dba)_2$ (5)	dppm[c]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	24	0		17
7	$Pd(dba)_2$ (5)	dppe[d]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	60	7	22	(**8a**)	62
8	$Pd(dba)_2$ (5)	dppp[e]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	1	29	(**8a**)	6
9	$Pd(dba)_2$ (5)	dppb[f]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	rt	2.5	*ca.* 72	(**8a**)	3
10	$Pd(dba)_2$ (5)	dpppe[g]	$TsNH_2$ (1)	Cs_2CO_3	THF (0.1)	50	5	37	(**8a**)	2
11	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	dioxane (0.1)	70	20	*ca.* 13	(**8a**)	3
12	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	DMF (0.1)	rt	2.5	*ca.* 59	(**8a**)	1
13	$Pd(dba)_2$ (5)	dppb	$TsNH_2$ (1)	Cs_2CO_3	CH_3CN (0.1)	40	2	*ca.* 54	(**8a**)	1
14	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$TsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	rt	3	72	(**8a**)	5
15	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$PhSO_2NH_2$ (1.5)	Cs_2CO_3	THF (0.067)	rt	5	64	(**8b**)	6
16	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$MtsNH_2$[h] (1.5)	Cs_2CO_3	THF (0.067)	rt	3.5	55	(**8c**)	9
17	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$NsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	2	43	(**8d**)	15
18	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$MsNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	24	68	(**8e**)	10
19	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	$BnNH_2$ (1.5)	Cs_2CO_3	THF (0.067)	60	7	0	(**8f**)	54

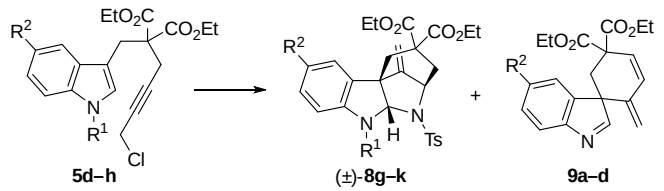
[a] Isolated yields. [b] 1,1'-bis(diphenylphosphino)ferrocene [c] bis(diphenylphosphino)methane. [d] 1,2-bis(diphenylphosphino)ethane. [e] 1,3-bis(diphenylphosphino)propane. [f] 1,4-bis(diphenylphosphino)butane. [g] 1,5-bis(diphenylphosphino)pentane. [h] Mts = 2,4,6-trimethylbenzenesulfonyl.

We next examined the scope and limitations of the reaction using a series of different indole substrates (Table 2). *N*-Substituted indoles **5d** and **5e** did not produce the spirocyclic products (entries 1 and 2). In contrast, indoles bearing an electron-withdrawing fluorine group (**5f**) or electron-donating methoxy group (**5h**) at their 5-position reacted smoothly under the optimized conditions to give the desired products **8i** and **8k** in good yields (entries 3 and 5). However, when compound **5g** bearing a bromine group at the 5-position of the indole was used as a substrate, a slightly lower yield (43%) of spiroindoline **8j** was observed. The lower yield observed in this case was attributed to side reaction(s) involving the aryl bromide moiety of the substrate, as well as the aryl bromide of the product **8j**.

We then turned our attention to the selective synthesis of the β-elimination product **9** (Table 3). It was envisaged that **9** could be efficiently produced under the same reaction conditions in the absence of an external nucleophile. This assumption was based on the results of our previous reaction, where the use of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand afforded spiroindole **9a** as the major product in 62% yield (Table 1, entry 7). Contrary to our expectation, the treatment of **5a** with $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %) and dppe (10 mol %) in the

presence of Cs_2CO_3 (2 equiv) at 70 °C afforded the desired product **9a** in only 7% yield (Table 3, entry 1). Based on this disappointing result, we carefully examined the reaction parameters and screened a series of bases against the reaction (entries 2–6), including Cs_2CO_3, Et_3N, $(i\text{-Pr})_2NEt$ (DIPEA) and $BnNH_2$ at 50–55 °C. Among them, a combination of $BnNH_2$ and Cs_2CO_3 gave a better result (33%, entry 6) than the reaction using Cs_2CO_3 alone (entry 1). Furthermore, the reaction temperature had a significant impact on the yield of **9a**. For example, the reaction reached completion within 3 h at a slightly elevated temperature (60 °C) to afford the desired product in 68% yield (Table 3, entry 7). Lowering the loading of $BnNH_2$ (entry 8, 45%) or increasing the loading of the catalyst (entry 9, 64%) did not improve the yield of **9a**. It is noteworthy that the reaction involving the use of $BnNH_2$ as the only base afforded only a trace amount of **9a** (entry 10). Under the optimized conditions, substituted indoles **5f** and **5h** afforded spiroindoles **9b** and **9d**, respectively, in moderate to good yields (entries 11 and 13). Furthermore, the brominated substrate **5g** reacted under these conditions to **9c**, albeit in a lower yield (40%, entry 12).

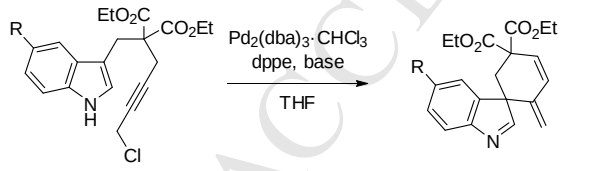
Table 2. Reaction of various indoles.[a]



entry	subst.	R^1	R^2	temp (°C)	time (h)	% yield (product)[b] 8	9
1	**5d**	Boc	H	60	24	0 (**8g**)	0 (**9a**)
2	**5e**	Me	H	60	24	0 (**8h**)	0 (**9a**)
3	**5f**	H	F	rt	3	71 (**8i**)	5 (**9b**)
4	**5g**	H	Br	60	3	43 (**8j**)	6 (**9c**)
5	**5h**	H	OMe	rt	2.5	71 (**8k**)	20 (**9d**)

[a] Reactions were carried out using propargyl chloride **5d–h** with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), dppb (10 mol %), Cs_2CO_3 (2 equiv) and $TsNH_2$ (1.5 equiv) in THF (0.067 M). [b] Isolated yields.

Table 3 Synthesis of spiroindoles **9a–d.**



entry	subst.	[Pd]/dppe (mol %)	base (equiv)	temp (°C)	time (h)	% yield[a] (product)
1	**5a**	5/10	Cs_2CO_3 (2)	70	4	7 (**9a**)
2	**5a**	5/10	Et_3N (2)	55	24	3 (**9a**)
3	**5a**	5/10	DIPEA (2)	55	24	4 (**9a**)
4	**5a**	5/10	Et_3N (1.5)/ Cs_2CO_3 (2)	55	24	11 (**9a**)
5	**5a**	5/10	DIPEA (1.5)/ Cs_2CO_3 (2)	55	20	21 (**9a**)
6	**5a**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	55	24	33 (**9a**)
7	**5a**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	68 (**9a**)
8	**5a**	5/10	$BnNH_2$ (0.2)/ Cs_2CO_3 (2)	60	4	45 (**9a**)
9	**5a**	10/20	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	64 (**9a**)
10	**5a**	10/20	$BnNH_2$ (2)	60	24	trace (**9a**)
11	**5f**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	56 (**9b**)
12	**5g**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	40 (**9c**)
13	**5h**	5/10	$BnNH_2$ (1.5)/ Cs_2CO_3 (2)	60	3	74 (**9d**)

[a] Isolated yields.

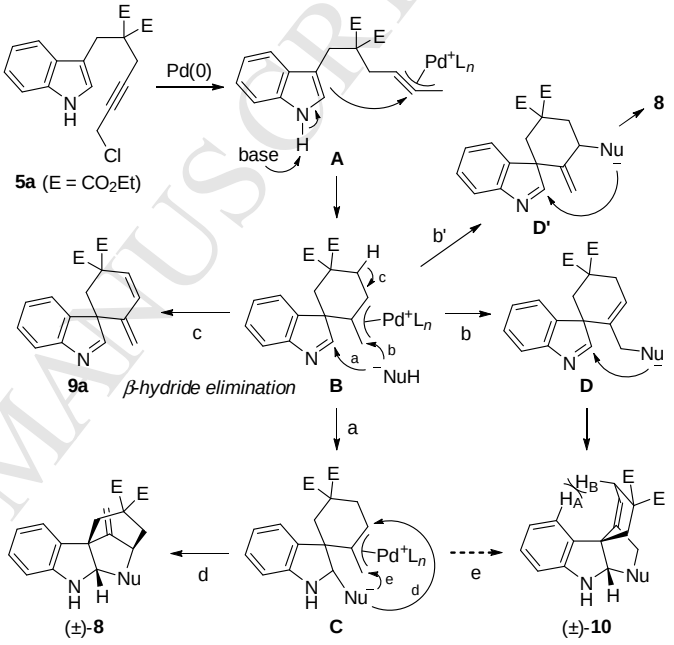


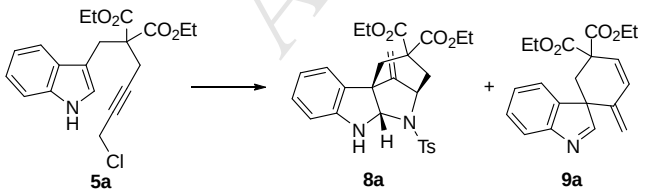
Figure 1. Proposed mechanism for palladium-catalyzed cascade cyclization.

A plausible mechanism for the cascade cyclization is shown in Figure 1. Briefly, propargyl chloride would initially react with a palladium catalyst to give the η^3-propargylpalladium complex **A**.[1c,18] Intramolecular nucleophilic addition of the indole to the central carbon atom of the η^3-propargylpalladium **A** would give η^3-allylpalladium complex **B**.[19] Deprotonation at the indole nitrogen would be necessary for this step, considering that the *N*-substituted substrates **5d** and **5e** did not react under the optimized reaction conditions (Table 2, entries 1 and 2). The tetracyclic spiroindolines **8** and **10** would then be formed by the intermolecular nucleophilic attack of the external nucleophile via path a and/or b. Path a represents the first intermolecular nucleophilic attack on the imine carbon, which would be followed by the allylic substitution reaction of intermediate **C**. Depending on which carbons of the allylic moiety in **C** participated in the cyclization (path d vs. e), the regioisomeric products **8** and **10** would be formed. Path b would occur to give intermediate **D** if the intermolecular allylic substitution reaction dominated over the addition of the nucleophile to the imine, with spiroindoline **10** being formed as the major product. In this step, the occurrence of an intermolecular reaction at the more hindered

carbon (path b') would be another possible pathway. In contrast, β-hydride elimination from **B** would produce diene **9a** (path c). When a sulfonamide was used as the external nucleophile, tetracyclic spiroindoline **8** was obtained without producing any of the regioisomeric spiroindoline **10**. This regioselectivity was most likely affected by steric hindrance during the reactions involved in path a, in that the product **10** as well as the transition state from **C** to **10** would be destabilized by unfavorable steric interactions between the indole proton at the 4-position (H_A) and the flagpole hydrogen (H_B) of the cyclohexene moiety. In contrast, the reaction using carbon nucleophile would favor the formation of regioisomer **10** (Scheme 4). This can be explained by considering both the sterically congested and soft characteristics of the carbon nucleophiles. Thus, the sterically hindered imine carbon (having a quaternary carbon at the neighboring position) would induce the nucleophilic attack of the soft carbon nucleophiles at the η^3-allylpalladium moiety of **B** to form **10** via intermediate **D** (path b).[20]

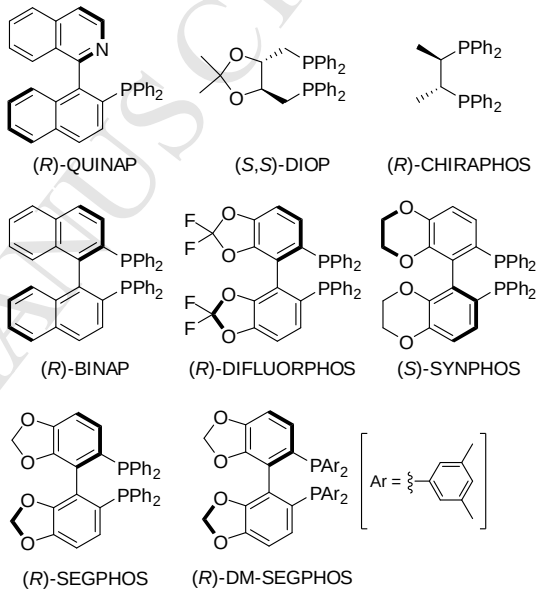
Finally, we attempted to carry out a catalytic asymmetric version of the current reaction. To the best of our knowledge, only two catalytic asymmetric reactions have been reported to date for the propargylpalladium chemistry. Rawal et al.[14a] reported an asymmetric version of the aforementioned intermolecular spirocyclization of a tryptamine-derived substrate (Scheme 2, eq 4) and obtained the spiroindole (Nu = NR) in 16% ee using (*R*)-BINAP. You et al.[14b] found that (*R*)-SEGPHOS showed more efficient asymmetric induction, affording the corresponding spiroindole [Nu = $C(CO_2Et)_2$] in 52% ee. The enantio-determining step in these reactions would be the allylic substitution step, where the chiral spirocenter would be formed by the nucleophilic reaction of the indole moiety. We screened a series of chiral ligands against β-hydride elimination reaction to produce spiroindole **9a** (Table 4, entries 1–8). When (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS were used, these reactions produced spiroindole **9a** with better enantioselectivities (51–53% ee, entries 6 and 7), although the yields of **9a** were unsatisfactory (12–24%). We thus proceeded to examine the synthesis of tetracyclic spiroindoline **8a** using (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS. Fortunately, the palladium-catalyzed reaction of **5a** with $TsNH_2$ in the presence of H_2O (1 equiv) using (*R*)-SEGPHOS gave the tetracyclic spiroindoline **8a** (38% yield) and spiroindole **9a** (15% yield) with moderate enantioselectivities (65–71% ee, entry 10). It should be noted that the addition of H_2O to the reaction was necessary for a high level of reproducibility. This result therefore highlights the great potential of a propargylpalladium complex in terms of its use in catalytic asymmetric reactions.

Table 4. Optimization of the catalytic asymmetric reaction conditions. [a,b]



entry	chiral ligand	other reagent	time (h)	% yield[c] (% ee)[d]	
				8a	**9a**
1	(*R*)-QUINAP	$BnNH_2$	5	-	trace
2	(*S*,*S*)-DIOP	$BnNH_2$	3.5	-	mixture
3	(*R*)-CHIRAPHOS	$BnNH_2$	7	-	13 (13)
4	(*R*)-BINAP	$BnNH_2$	4	-	22 (34)
5	(*S*)-SYNPHOS	$BnNH_2$	6	-	*ca.* 34% (40)
6	(*R*)-SEGPHOS	$BnNH_2$	6	-	12 (53)
7	(*R*)-DM-SEGPHOS	$BnNH_2$	4	-	24 (51)
8	(*R*)-DIFLUORPHOS	$BnNH_2$	24	-	5.5 (34)
9	(*R*)-SEGPHOS	$TsNH_2$	24	24 (56)	14 (73)
10	(*R*)-SEGPHOS	$TsNH_2$, H_2O[e]	14	38 (65)	15 (71)
11	(*R*)-DM-SEGPHOS	$TsNH_2$, H_2O[e]	20	16 (30)	4 (77)

[a] Reactions were carried out using propargyl chloride **5a** with $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), chiral ligand (10 mol %), Cs_2CO_3 (2 equiv) and other reagent (1.5 equiv) in THF (0.067 M). [b] One of the enantiomers of **8a** is shown in the Scheme. [c] Isolated yields. [d] Determined by HPLC analysis (Chiralcel IC-3) [e] Reaction was carried out with addition of H_2O (1 equiv).



3. Conclusion

In conclusion, we have developed the palladium-catalyzed spirocyclization of propargyl chlorides using an external nucleophile for the divergent synthesis of tetracyclic spiroindolines. When this reaction was conducted in the absence of an appropriate external nucleophile, it gave the corresponding spiroindoles through β-hydride elimination. The regioselectivity of this reaction was found to be dependent on the external nucleophiles employed in the reaction. We have also investigated an asymmetric version of this reaction to produce spiroindole derivatives in 65–71% ee. This methodology would provide a novel approach to biologically active spiroindole derivatives.

4. Experimental

General Methods.

All reactions under argon atmosphere were performed using syringe-septum cap techniques and all glassware was dried in an oven at 80 °C for 2 h prior to use. For flash chromatography, silica gel (Wakosil C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was

performed on Merck TLC silica gel 60 F_{254} or Wako NH_2 silica gel 60 F_{254} plate (layer thickness 0.25 mm), which were developed using standard visualizing agents: UV fluorescence (254 nm) and anisaldehyde with heating. Melting points were measured by a hot stage melting point apparatus (uncorrected). ^{1}H NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

General procedure for the synthesis of tetracyclic spiroindolines (8).

To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $TsNH_2$ (20.5 mg, 0.12 mmol) in THF were added $Pd_2(dba)_3 \cdot CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppb (3.4 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at room temperature under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (8:1) to give **8a** (29.3 mg, 72% yield) and **9a** (1.4 mg, 5.2% yield).

General procedure for the synthesis of spiroindoles (9).

To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $BnNH_2$ (13 μL, 0.12 mmol) in THF were added $Pd_2(dba)_3 \cdot CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppe (3.2 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1 to 8:1) to give **9a** (18.5 mg, 68% yield).

Asymmetric synthesis of spiroindoline (8a) and spiroindole (9a).

To a stirred mixture of **5a** (30 mg, 0.080 mmol), $TsNH_2$ (20.5 mg, 0.12 mmol) and H_2O (1.4μl, 0.080) in THF were added $Pd_2(dba)_3 \cdot CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), (*R*)-SEGPHOS (4.9 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 14 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (10:1 to 8:1) to give **8a** (15.7 mg, 38% yield, 65% ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/*i*-PrOH at 0.75 mL/min, t_1 = 17.98 min (major enantiomer), t_2 = 26.74 min (minor enantiomer)]} and **9a** {4.1 mg, 15% yield and 71% ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/*i*-PrOH at 0.75 mL/min, t_1 = 16.03 min (major enantiomer), t_2 = 39.26 min (minor enantiomer)]}.

Diethyl 2-[(1*H*-indol-3-yl)methyl]-2-(4-chlorobut-2-yn-1-yl)malonate (5a).

Brown oil; IR (neat): 3409 (NH), 2242 (C≡C), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 6H), 2.83 (t, *J* = 2.2 Hz, 2H), 3.57 (s, 2H), 4.10-4.25 (m, 6H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.3, 30.8, 58.2, 61.7 (2C), 78.3, 82.9, 109.6, 111.0, 118.9, 119.5, 122.0, 123.4, 128.1, 135.8, 170.1 (2C). HRMS (FAB) calcd $C_{20}H_{21}ClNO_4$: $[M - H]^-$, 374.1165; found: $[M - H]^-$, 374.1168.

Diethyl 11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8a).

Colorless solid; mp 164–165 °C; IR (neat): 3361 (NH), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 2.40 (d, *J* = 13.7 Hz, 1H), 2.48 (d, *J* = 13.7 Hz, 1H), 3.22 (d, *J* = 13.7 Hz, 2H), 4.09-4.10 (m, 1H), 4.13-4.39 (m, 4H), 4.44 (s, 1H), 4.66 (d, *J* = 4.1 Hz, 1H), 4.76 (s, 1H), 6.05 (d, *J* = 4.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.07-7.15 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 21.4, 37.7, 39.9, 52.3, 57.7, 61.3, 62.1, 62.6, 84.0, 103.4, 110.7, 119.3, 122.9, 127.4 (3C), 129.0, 129.6 (2C), 137.6, 143.2, 148.8, 151.7, 170.9, 171.3. HRMS (FAB) calcd $C_{27}H_{30}N_2O_6S$: $[M^+]$, 510.1825; found: $[M^+]$, 510.1832.

Diethyl 2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9a).

Yellow oil; IR (neat): 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 6H), 2.37 (d, *J* = 14.3 Hz, 1H), 2.72 (d, *J* = 14.3 Hz, 1H), 4.16-4.30 (m, 4H), 4.56 (s, 1H), 4.87 (s, 1H), 6.18 (d, *J* = 10.3 Hz, 1H), 6.57 (d, *J* = 10.3 Hz, 1H), 7.27-7.35 (m, 2H), 7.37-7.43 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 35.0, 55.5, 60.8, 62.3 (2C), 114.8, 121.5, 122.9, 125.4, 126.5, 128.5, 131.6, 137.6, 141.3, 155.4, 169.8, 170.1, 173.9. HRMS (FAB) calcd $C_{20}H_{22}NO_4$: $[M + H]^+$, 340.1549; found: $[M + H]^+$, 340.1555.

2,2-Diethyl 6,6-dimethyl 3,5,6a,7-tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2,6,6-tetracarboxylate (10a).

Yellow oil; IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.23-1.28 (m, 3H), 2.53 (d, *J* = 14.9 Hz, 1H), 2.66-2.90 (m, 5H), 3.68 (s, 3H), 3.73 (s, 3H), 4.00-4.34 (m, 5H), 4.76 (s, 1H), 5.70-5.76 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 29.6, 29.7, 38.6, 39.9, 52.6, 52.9, 53.9, 54.7, 61.5, 65.6., 74.2, 109.4, 118.0, 119.4, 123.6, 128.2, 135.0, 140.9, 149.6, 169.3, 170.6, 171.0, 171.8. HRMS (FAB) calcd $C_{25}H_{29}NO_8$: $[M^+]$, 471.1893; found: $[M^+]$, 471.1901.

Diethyl 6,6-diacetyl 5,6,6a,7-tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2(3*H*)-dicarboxylate (10b).

Yellow oil; IR (neat): 3406 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.01 (s, 3H), 2.18 (s, 3H), 2.37 (d, *J* = 14.7 Hz, 1H), 2.64-2.73 (m, 3H), 2.84-2.91 (m, 2H), 4.04-4.20 (m, 4H), 4.43 (br s, 1H),

4.83 (s, 1H), 5.70-5.75 (m, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 8.0 Hz, 1H), 6.91 (dd, J = 8.0, 1.1 Hz, 1H), 7.00 (ddd, J = 8.0, 8.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 26.3, 28.8, 29.5, 36.3, 40.4, 54.2, 55.0, 61.6 (2C), 73.3., 79.5, 110.2, 117.6, 119.8, 123.4, 128.3, 136.0, 141.1, 149.4, 170.8, 171.7, 203.1, 204.8. HRMS (FAB) calcd $C_{25}H_{29}NO_6$: [M^+], 439.1995; found: [M^+], 439.2000.

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20. At present, formation of **10** through intermediate **C** (path e) cannot be completely excluded. We performed an additional experiment with a separately prepared propargyl tosylamide (S_N2 adduct from **5a**) to confirm that this reaction does not proceed via the first S_N2 reaction. In addition, the tetracyclic spiroindolines **8a** was not obtained from the elimination product **9a** under the reaction conditions.

Supplementary Material

Supplementary material was provided by the authors including further optimization of the reaction conditions, experimental procedures and characterization data for all new compounds.

Supplementary Material

Convenient synthesis of spiroindole derivatives via palladium-catalyzed cyclization of propargyl chlorides

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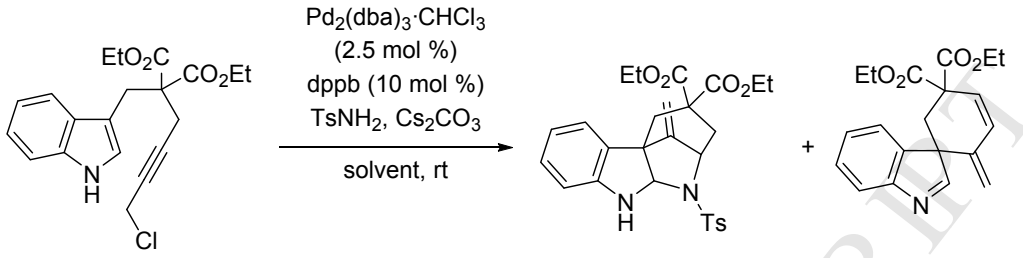
Optimization of reaction conditions
(Equivalents and concentrations of $TsNH_2$ and Cs_2CO_3)



5a **8a** **9a**

entry	$TsNH_2$ (equiv)	Cs_2CO_3 (equiv)	solvent (M)	% yield [a]	
				8a	**9a**
1	$TsNH_2$ (1)	Cs_2CO_3 (2)	THF (0.1)	59	7
2	$TsNH_2$ (1.5)	Cs_2CO_3 (2)	THF (0.1)	68	4
3	$TsNH_2$ (1.5)	Cs_2CO_3 (1)	THF (0.1)	69	5
4	$TsNH_2$ (1.5)	Cs_2CO_3 (2)	THF (0.067)	72	5
5	$TsNH_2$ (1.5)	Cs_2CO_3 (1)	THF (0.067)	61	9

[a] Isolated yields.

Experimental Section

Preparation of the substrates.

The known compounds **S2** (R = H,[1] Br,[2] OMe[1]), **S3** (R =H, Br, OMe),[3] **S4** (R =H, Br, OMe)[3] and **6**[3] were prepared according to the literature procedure.

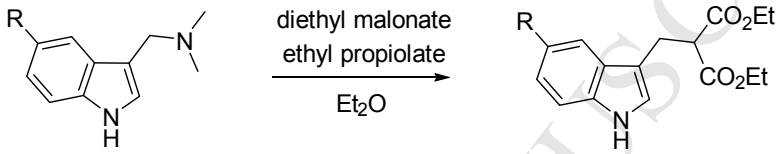
1 Jones, D. T.; Artman, G. D.; Williams, R. M. *Tetrahedron Lett.* **2007**, *48*, 1291.

2 Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed*. **2009**, *48*, 9533.

3 Cera, G.; Crispino, P.; Monari, M.; Bandini, M. *Chem. Commun.* **2011**, *47*, 7803.

4 Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 1758.

General procedure for the synthesis of malonates S2.



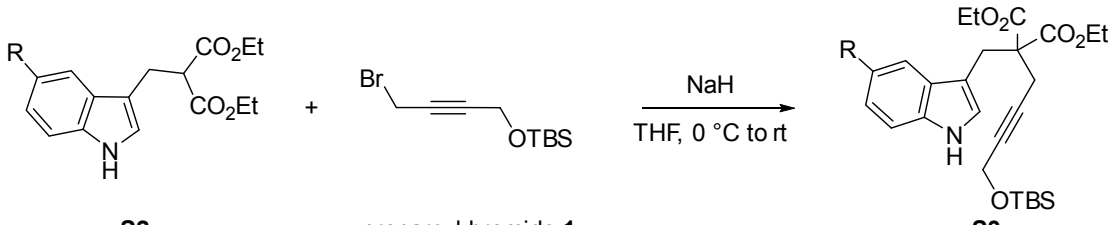
S1 **S2**

To a stirred mixture of **S1** (R = H, F, Br, or OMe; 5.20 mmol) and diethyl malonate (4.85 mmol) in Et_2O (2.6 mL) was added dropwise ethyl propiolate (5.20 mmol) at room temperature. The mixture was stirred for 45 min at this temperature, followed by quenching with H_2O. The whole was extracted with Et_2O. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:1) to give the corresponding **S2** as a pale yellow needle. The NMR spectra of the known compounds (R = H,[1] Br,[2] and OMe[1]) were identical with those of previous report.

Diethyl 2-[(5-fluoro-1*H*-indol-3-yl)methyl]malonate (S2; R = F).

Pale yellow needle (1.27 g, 77% yield): mp 60–61 °C; IR (neat): 3410 (NH), 1726 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 6H), 3.33 (d, J = 7.7 Hz, 2H), 3.72 (t, J = 7.7 Hz, 1H), 4.12-4.20 (m, 4H), 6.93 (ddd, J = 9.2, 9.2, 2.5 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 7.23-7.26 (m, 2H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 24.4, 52.9, 61.4 (2C), 103.5 (d, J = 24.0 Hz), 110.4 (d, J = 26.4 Hz), 111.8 (d, J = 9.6 Hz), 112.3 (d, J = 4.8 Hz) 124.4, 127.5 (d, J = 9.6 Hz), 132.6, 157.8 (d, J = 235 Hz), 169.2 (2C). *Anal*. Calcd for $C_{16}H_{18}FNO_4$: C, 62.53; H, 5.90; N, 4.56. Found: C, 62.41; H, 5.93; N, 4.50.

General procedure for the synthesis of malonates S3.



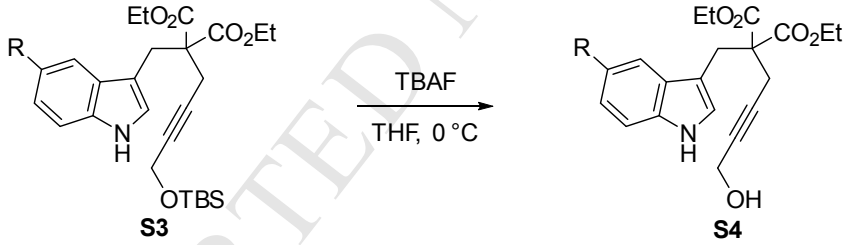
S2 propargyl bromide **1** **S3**

To a solution of **S2** (R = H, F, Br, or OMe; 3.71 mmol) in THF was added NaH (60% suspension in mineral oil; 7.42 mmol) at 0 °C. The suspension was stirred for 30 min at 0 °C, then propargyl bromide **1** (4.45 mmol) in THF was added dropwise. The reaction was warmed up to room temperature and stirred for 2 h, followed by quenching with H_2O. The whole was extracted with EtOAc. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) to give the corresponding **S3** as a colorless oil. The NMR spectra of the known compounds (R = H, Br, and OMe) were identical with those of previous report.[3]

Diethyl 2-{4-[(*tert*-butyldimethylsilyl)oxy]but-2-yn-1-yl}-2-[(5-fluoro-1*H*-indol-3-yl)methyl]malonate (S3; R = F).

Colorless oil (682 mg, 38%): IR (neat): 3387 (NH), 2332 (C≡C), 1736 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.92 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 6H), 2.81 (t, *J* = 2.1 Hz, 2H), 3.51 (s, 2H), 4.10-4.22 (m, 4H), 4.37 (t, *J* = 2.1 Hz, 2H), 6.90 (ddd, *J* = 9.0, 9.0, 2.5 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.29 (dd, *J* = 9.9, 2.5 Hz, 1H), 8.12 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2 (2C), 13.9 (2C), 18.3, 23.1, 25.8 (3C), 27.3, 51.8, 58.0, 61.6 (2C), 80.2, 82.4, 103.8 (d, *J* = 24.0 Hz), 110.0 (d, *J* = 4.8 Hz), 110.4 (d, *J* = 26.4 Hz), 111.6 (d, *J* = 9.6 Hz), 125.3, 128.5 (d, *J* = 9.6 Hz), 132.3, 157.9 (d, *J* = 234 Hz), 170.1 (2C). HRMS (FAB) calcd $C_{26}H_{36}FNO_5Si$: [M^+], 489.2347; found: [M^+], 489.2350.

General procedure for the synthesis of propargyl alcohols S4.



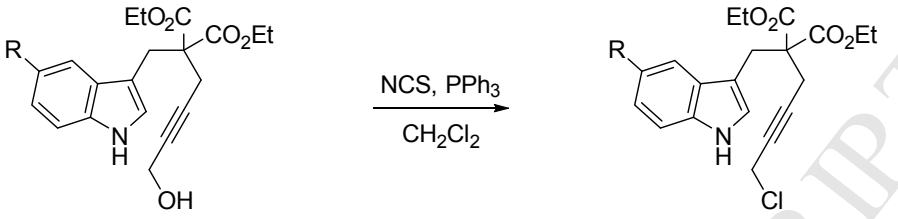
To a stirred solution of **S3** (1.30 mmol) in THF was added TBAF (1.00 M solution in THF; 1.43 mL, 1.43 mmol) at 0 °C. The mixture was stirred for 1.5 h at this temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give the corresponding **S4** as a pale yellow oil. The NMR spectra of the known compounds (R = H, Br, and OMe) were identical with those of previous report.[3]

Diethyl 2-[(5-fluoro-1*H*-indol-3-yl)methyl]-2-(4-hydroxybut-2-yn-1-yl)malonate (S4; R = F).

Yellow oil (485 mg, 99% yield): IR (neat): 3410 (NH), 3403 (OH), 2254 (C≡C), 1720 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 6H), 1.97 (s, 1H), 2.80 (s, 2H), 3.51 (s, 2H), 4.11-4.25 (m, 4H), 4.31 (s, 2H), 6.90 (ddd, *J* = 8.9, 8.9, 2.5 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.9, 4.4 Hz, 1H), 7.29 (dd, *J* = 10.0, 2.5 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.1, 27.3, 51.2, 58.0, 61.7 (2C), 81.4, 82.2, 103.7

(d, J = 23.0 Hz), 109.7 (d, J = 4.8 Hz), 110.4 (d, J = 25.9 Hz), 111.7 (d, J = 10.5 Hz), 125.4, 128.5 (d, J = 11.5 Hz), 132.3, 157.9 (d, J = 235 Hz), 170.2 (2C). HRMS (FAB) calcd $C_{20}H_{22}FNO_5$: [M^+], 375.1482; found: [M^+], 375.1478.

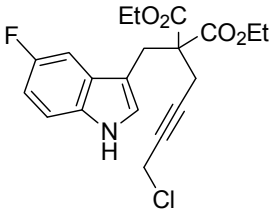
General procedure for the synthesis of propargyl chloride 5a and 5f-h.



S4

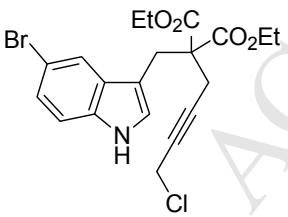
5a (R = H), **5f** (R = F)
5g (R = Br), **5h** (R = OMe)

To a stirred mixture of a propargyl alcohol **S4** (1.0 equiv) and PPh_3 (1.5 equiv) in CH_2Cl_2 was added NCS (1.2 equiv) in CH_2Cl_2 at room temperature. The mixture was stirred for 1.5–3 h at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel to give the corresponding propargyl chloride **5**.



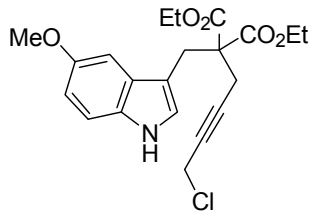
5f

Diethyl 2-(4-chlorobut-2-yn-1-yl)-2-[(5-fluoro-1*H*-indol-3-yl)methyl]malonate (5f).
Brown oil. Flash chromatography: *n*-hexane–EtOAc = 5:1. Yield = 87%.
IR (neat): 3407 (NH), 2238 (C≡C), 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.4 Hz, 6H), 2.82 (t, J = 2.3 Hz, 2H), 3.51 (s, 2H), 4.13-4.24 (m, 6H), 6.90 (ddd, J = 9.0, 9.0, 2.5 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.21 (dd, J = 9.0, 4.3 Hz, 1H), 7.29 (dd, J = 9.0, 2.5 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.1, 27.4, 30.7, 58.0, 61.8 (2C), 78.6, 82.7, 103.8 (d, J = 24.0 Hz), 109.7 (d, J = 4.8 Hz), 110.5 (d, J = 26.4 Hz), 111.7 (d, J = 9.6 Hz), 125.3, 128.5 (d, J = 9.6 Hz), 132.3, 157.9 (d, J = 235 Hz), 170.0 (2C). HRMS (FAB) calcd $C_{20}H_{21}ClFNO_4$: [M^+], 393.1143; found: [M^+], 393.1147.



5g

Diethyl 2-[(5-bromo-1*H*-indol-3-yl)methyl]-2-(4-chlorobut-2-yn-1-yl)malonate (5g).
Brown oil. Flash chromatography: *n*-hexane–EtOAc = 4:1. Yield = 73%.
IR (neat): 3384 (NH), 2238 (C≡C), 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6H), 2.80 (t, J = 2.3 Hz, 2H), 3.52 (s, 2H), 4.15-4.25 (m, 6H), 7.06 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 8.6, 1.9 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.2, 30.7, 57.8, 61.9 (2C), 78.7, 82.6, 109.3, 112.5, 112.9, 121.5, 124.8, 124.9, 129.7, 134.4, 169.9 (2C). HRMS (FAB) calcd $C_{20}H_{21}BrClNO_4$: [M^+], 453.0342; found: [M^+], 453.0345.

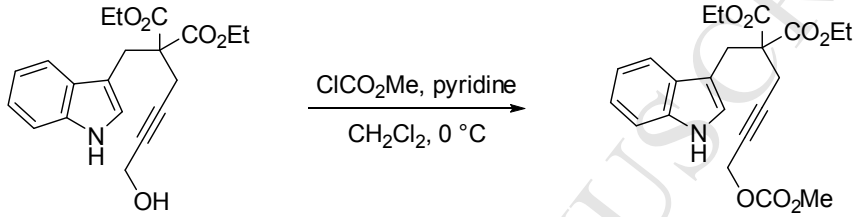


5h

Diethyl 2-(4-chlorobut-2-yn-1-yl)-2-[(5-methoxy-1*H*-indol-3-yl)methyl]malonate (5h).

Brown oil. Flash chromatography: *n*-hexane–EtOAc = 4:1. Yield = 70%.

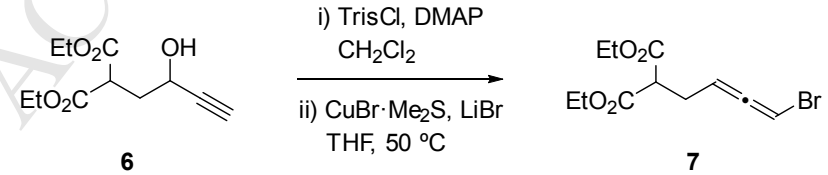
IR (neat): 3417 (NH), 2239 (C≡C), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 6H), 2.85 (t, J = 2.0 Hz, 2H), 3.53 (s, 2H), 3.86 (s, 3H), 4.14-4.24 (m, 6H), 6.83 (dd, J = 8.9, 2.5 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.4, 30.7, 55.9, 58.5, 61.7 (2C), 78.3, 83.1, 100.5, 109.4, 111.8, 112.6, 124.1, 128.6, 131.0, 154.2, 170.0 (2C). HRMS (FAB) calcd $C_{21}H_{24}ClNO_5$: [M^+], 405.1343; found: [M^+], 405.1345.



4 **5b**

Diethyl 2-[(1*H*-indol-3-yl)methyl]-2-{4-[(methoxycarbonyl)oxy]but-2-yn-1-yl}malonate (5b).

To a stirred mixture of **4** (50 mg, 0.135 mmol), pyridine (33 μL, 0.41 mmol) in CH_2Cl_2 (675 μL) was added $ClCO_2Me$ (14 μL, 0.20 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with Et_2O. The extract was washed with H_2O, 1 N HCl, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **5b** as a brown oil (47.5 mg, 82% yield): IR (neat): 3407 (NH), 2252 (C≡C), 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, J = 6.8 Hz, 6H), 2.82 (t, J = 2.3 Hz, 2H), 3.56 (s, 2H), 3.82 (s, 3H), 4.10-4.23 (m, 4H), 4.78 (t, J = 2.3 Hz, 2H), 7.01 (d, J = 2.3 Hz, 1H), 7.09 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.15 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.0, 27.3, 55.1, 55.9, 58.1, 61.6 (2C), 77.3, 83.7, 109.5, 110.0, 118.8, 119.4, 122.0, 123.5, 128.1, 135.8, 155.2, 170.0 (2C). HRMS (FAB) calcd $C_{22}H_{25}NO_7$: [M – H]$^-$, 414.1558; found: [M – H]$^-$, 414.1564.

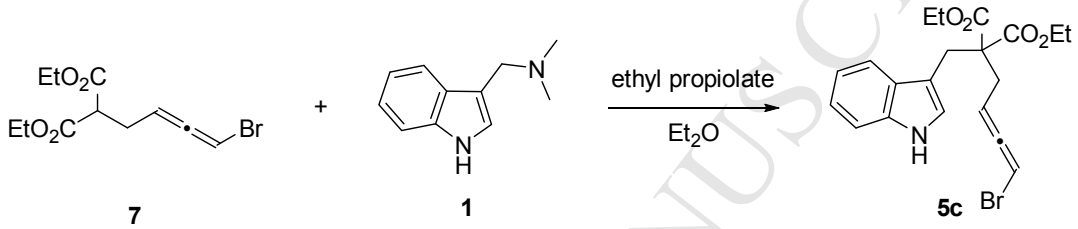


6 **7**

Diethyl 2-(4-bromobuta-2,3-dien-1-yl)malonate (7)

To a stirred mixture of **6** (410 mg, 1.8 mmol) and TrisCl (1.36 g, 4.5 mmol) in CH_2Cl_2 (41 mL) was added DMAP (770 mg, 6.3 mmol) at room temperature. The mixture was stirred for 3 h at this temperature. Concentration of the mixture under reduced pressure followed by rapid filtration through a short pad of silica gel with Et_2O to give a crude sulfonate, which was used without further purification. $CuBr{\cdot}SMe_2$ (1.10 g, 5.4 mmol) and LiBr (465 mg,

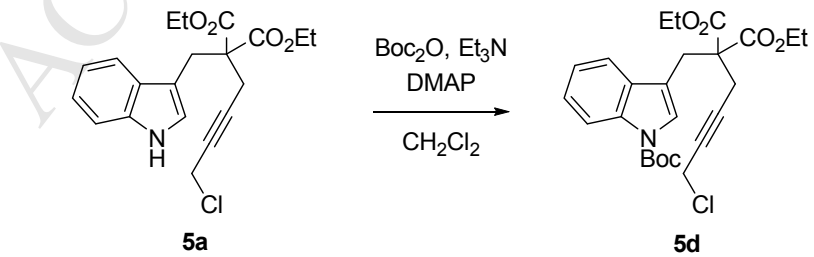
0.373 mmol) were dissolved in THF (18 mL) at room temperature under argon, and the mixture was stirred for 30 min at this temperature. To this mixture was added a solution of the above crude sulfonate in THF (26 mL) at room temperature. The mixture was allowed to warm to 50 °C and stirred at this temperature for 1.5 h, which was quenched by addition of saturated NH_4Cl and 28% NH_4OH. The whole was extracted with EtOAc. The extract was washed with H_2O and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (30:1) to give **7** as a colorless oil (330 mg, 63% yield): IR (neat): 1958 (C=C=C), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26-1.31 (m, 6H), 2.73-2.78 (m, 2H), 3.52 (t, J = 7.4 Hz, 1H), 4.18-4.27 (m, 4H), 5.45 (dd, J = 12.6, 5.7 Hz, 1H), 6.00 (ddd, J = 5.7, 2.4, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 21.2, 50.8, 61.7 (2C), 73.7, 97.3, 168.4, 168.5, 202.3; HRMS (FAB) calcd $C_{11}H_{16}BrNO_4$: $[M + H]^+$, 291.0232; found: $[M + H]^+$, 291.0227.



7 1 5c

Diethyl 2-(4-bromobuta-2,3-dien-1-yl)-2-[(1*H*-indol-3-yl)methyl]malonate (5c).

To a stirred mixture of **7** (286 mg, 1.13 mmol) and **1** (306 mg, 1.05 mmol) in Et_2O (1.1 mL) was added dropwise ethyl propiolate (115 μL, 1.13 mmol) at room temperature. The mixture was stirred for 5 h at this temperature, followed by quenching with H_2O. The whole was extracted with EtOAc. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:1 to 5:1) to give **5c** as a brown oil (285 mg, 64% yield): IR (neat): 3393 (NH), 1957 (C=C=C), 1720 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.24 (m, 6H), 2.75-2.77 (m, 2H), 3.42-3.52 (m, 2H), 4.10-4.22 (m, 4H), 5.34-5.41 (m, 1H), 5.92-5.97 (m, 1H), 7.03 (d, J = 2.3 Hz, 1H), 7.10 (dd, J = 8.0, 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 8.05 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 28.0, 31.9, 58.6, 61.5 (2C), 72.4, 95.7, 109.5, 111.1, 118.7, 119.4, 121.9, 123.4, 128.0, 135.7, 170.7 (2C), 203.6. HRMS (FAB) calcd $C_{20}H_{22}BrNO_4$: $[M^+]$, 419.0732; found: $[M^+]$, 419.0724.

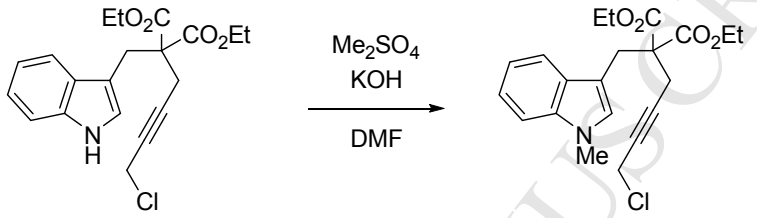


5a 5d

Diethyl 2-{[1-(*tert*-butoxycarbony)-1*H*-indol-3-yl]methyl}-2-(4-chlorobut-2-yn-1-yl)malonate (5d).

To a stirred mixture of **5a** (100 mg, 0.27 mmol), DMAP (3.2 mg, 0.027 mmol) and Et_3N (46 μL, 0.32 mmol) in CH_2Cl_2 (2.6 mL) was added Boc_2O (70 mg, 0.32 mmol) at room temperature. The mixture was stirred for 30 min

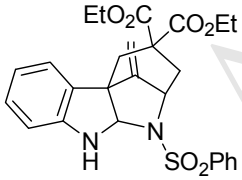
at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1) to give **5d** as a colorless oil (91.0 mg, 72% yield): IR (neat): 1733 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 6H), 1.66 (s, 9H), 2.83 (t, J = 2.2 Hz, 2H), 3.49 (s, 2H), 4.14-4.25 (m, 6H), 7.22 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.29 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.41 (s, 1H), 7.63 (dd, J = 7.6, 1.0 Hz, 1H), 8.05-8.14 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.2, 26.9, 28.2 (3C), 30.7, 57.9, 61.9 (2C), 78.7, 82.6, 83.7, 114.4, 115.2, 119.1, 122.5, 124.4, 124.9, 131.0, 135.1, 149.6, 169.7 (2C). HRMS (FAB) calcd $C_{25}H_{30}ClNO_6$: [M^+], 475.1762; found: [M^+], 475.1758.



5a **5e**

Diethyl 2-(4-chlorobut-2-yn-1-yl)-2-[(1-methyl-1*H*-indol-3-yl)methyl]malonate (5e).

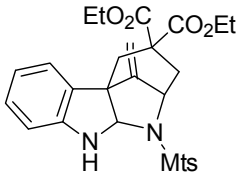
To a stirred mixture of **5a** (183 mg, 0.49 mmol) and KOH (64 mg, 0.97 mmol) in DMF (4.8 mL) was added Me_2SO_4 (92 μL, 0.32 mmol) at room temperature. The mixture was stirred for 3.5 h at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (6:1) to give **5e** as a pale yellow oil (100 mg, 53% yield): IR (neat): 2252 (C≡C), 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6H), 2.83 (t, J = 2.3 Hz, 2H), 3.54 (s, 2H), 3.72 (s, 3H), 4.11-4.24 (m, 6H), 6.87 (s, 1H), 7.08 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.18 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.23-7.26 (m, 1H), 7.63 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.3, 30.8, 32.7, 58.2, 61.6 (2C), 78.2, 83.0, 107.8, 109.1, 118.9 (2C), 121.5, 128.1, 128.6, 136.6, 169.7 (2C). HRMS (FAB) calcd $C_{21}H_{24}ClNO_4$: [M^+], 389.1394; found: [M^+], 389.1390.



8b

Diethyl 11-methylene-1-(phenylsulfonyl)-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8b).

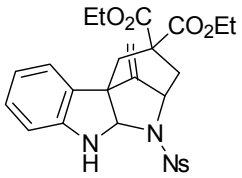
IR (neat): 3355 (NH), 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.41 (d, J = 13.6 Hz, 1H), 2.49 (d, J = 13.6 Hz, 1H), 3.21-3.27 (m, 2H), 4.10-4.12 (m, 1H), 4.13-4.40 (m, 4H), 4.46 (s, 1H), 4.67 (d, J = 4.0 Hz, 1H), 4.77 (s, 1H), 6.07 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.83 (dd, J = 7.7, 7.7 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 7.7 Hz, 1H), 7.43-7.55 (m, 3H), 7.99 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 37.7, 39.9, 52.3, 57.7, 61.3, 62.1, 62.6, 84.0, 103.6, 110.8, 119.4, 122.9, 127.3 (2C), 127.4, 128.9 (2C), 129.0, 132.5, 140.5, 148.8, 151.6, 170.9, 171.2. HRMS (FAB) calcd $C_{26}H_{28}N_2O_6S$: [M^+], 496.1668; found: [M^+], 496.1668.



8c

Diethyl 1-(mesitylsulfonyl)-11-methylene-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8c).

IR (neat): 3377 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 6H), 2.31 (s, 3H), 2.38 (d, J = 14.5 Hz, 1H), 2.64 (s, 6H), 2.73 (dd, J = 13.7, 2.9 Hz, 1H), 3.08 (dd, J = 14.5, 2.9 Hz, 1H), 3.21 (d, J = 13.7 Hz, 1H), 4.02 (d, J = 4.0 Hz, 1H), 4.10-4.33 (m, 4H), 4.37 (t, J = 2.9 Hz, 1H), 4.52 (s, 1H), 4.92 (s, 1H), 5.98 (d, J = 4.0 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 6.76 (dd, J = 8.0, 8.0 Hz, 1H), 6.95 (s, 2H), 7.03-7.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 13.9, 21.0, 23.1 (2C), 38.6, 39.4, 51.5, 58.0, 62.0, 62.3, 62.4, 82.8, 103.7, 109.9, 118.6, 122.8, 126.8, 128.9, 132.0 (2C), 133.9, 140.2 (2C), 142.6, 148.9, 151.4, 170.9, 171.5. HRMS (FAB) calcd $C_{29}H_{34}N_2O_6S$: [M^+], 538.2138; found: [M^+], 538.2142.

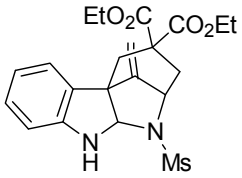


8d

Diethyl 11-methylene-1-[(2-nitrophenyl)sulfonyl]-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8d).

The reaction was performed for 2 h at 60 °C.

IR (neat): 3372 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 2.46-2.51 (m, 2H), 3.23-3.32 (m, 2H), 4.10-4.40 (m, 5H), 4.57 (s, 1H), 4.66 (d, J = 4.6 Hz, 1H), 4.95 (s, 1H), 6.07 (d, J = 4.6 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 7.4, 7.4 Hz, 1H), 7.12-7.17 (m, 2H), 7.59-7.71 (m, 3H), 8.18 (dd, J = 7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 37.8, 39.9, 52.3, 57.9, 62.3, 62.6, 62.8, 84.0, 104.3, 111.0, 119.8, 123.0, 124.4, 127.3, 129.1, 129.5, 132.1, 133.1, 134.6, 148.5, 148.9, 151.5, 170.8, 171.1. HRMS (FAB) calcd $C_{26}H_{27}N_3O_8S$: [M^+], 541.1519; found: [M^+], 541.1511.

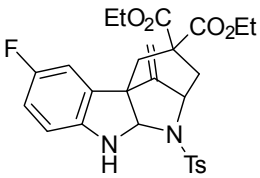


8e

Diethyl 11-methylene-1-(methylsulfonyl)-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8e).

The reaction was performed for 24 h at 60 °C.

IR (neat): 3345 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 2.43-2.48 (m, 2H), 2.98 (s, 3H), 3.20-3.26 (m, 2H), 4.11-4.33 (m, 4H), 4.35-4.37 (m, 1H), 4.50 (s, 1H), 4.55 (d, J = 4.6 Hz, 1H), 4.96 (s, 1H), 5.78 (d, J = 4.6 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 6.87 (dd, J = 7.4, 7.4 Hz, 1H), 7.10-7.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 37.5, 40.5, 40.6, 52.6, 58.2, 61.8, 62.2, 62.6, 84.0, 103.4, 111.2, 119.8, 122.9, 127.8, 129.1, 148.6, 152.1, 170.7, 171.2. HRMS (FAB) calcd $C_{21}H_{26}N_2O_6S$: [M^+], 434.1512; found: [M^+], 434.1512.

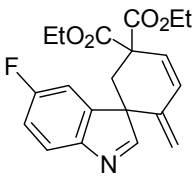


8i

Diethyl 7-fluoro-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8i).

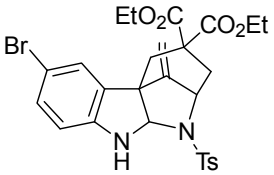
IR (neat): 3345 (NH), 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.7 Hz, 3H), 1.35 (t, J = 7.7 Hz, 3H), 2.32 (d, J = 13.7 Hz, 1H), 2.39 (s, 3H), 2.48 (d, J = 14.9 Hz, 1H), 3.20-3.23 (m, 2H), 4.09-4.11 (m, 1H), 4.13-4.41 (m, 4H), 4.46 (s, 1H), 4.55 (d, J = 4.0 Hz, 1H), 4.79 (s, 1H), 6.07 (d, J = 4.6 Hz, 1H), 6.55 (dd, J = 8.0, 4.3 Hz, 1H), 6.80-6.86 (m,

2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 21.5, 37.6, 39.9, 52.2, 57.7, 61.2, 62.2, 62.7, 84.4, 103.6, 110.6 (d, *J* = 22.8 Hz), 111.2 (d, *J* = 8.4 Hz), 115.1 (d, *J* = 25.2 Hz), 127.4 (2C), 128.9 (d, *J* = 10.8 Hz), 129.6 (2C), 137.5, 143.3, 144.7, 151.3, 157.1 (d, *J* = 243.5 Hz), 170.9, 171.11. HRMS (FAB) calcd $C_{27}H_{29}FN_2O_6S$: [M^+], 528.1730; found: [M^+], 528.1724.



9b

Diethyl 5'-fluoro-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9b). IR (neat): 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.30 (m, 6H), 2.39 (d, *J* = 14.3 Hz, 1H), 2.66 (d, *J* = 14.3 Hz, 1H), 4.18-4.30 (m, 4H), 4.58 (s, 1H), 4.90 (s, 1H), 6.19 (d, *J* = 9.7 Hz, 1H), 6.56 (d, *J* = 9.7 Hz, 1H), 7.02 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.08 (ddd, *J* = 8.6, 8.0, 2.2 Hz, 1H), 7.60 (dd, *J* = 8.6, 4.6 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 34.8, 55.3, 61.3, 62.4 (2C), 110.7 (d, *J* = 25.2 Hz), 115.0, 115.3 (d, *J* = 2.5 Hz), 122.4 (d, *J* = 9.6 Hz), 125.4, 131.4, 137.1, 143.4, 151.4, 161.7 (d, *J* = 245.9 Hz), 170.0 (2C), 173.8. HRMS (FAB) calcd $C_{20}H_{21}FNO_4$: [M + H]$^+$, 358.1455; found: [M + H]$^+$, 358.1447.

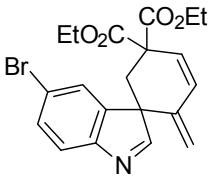


8j

Diethyl 7-bromo-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8j).

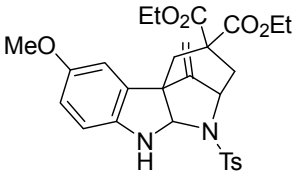
The reaction was performed for 3 h at 60 °C.

IR (neat): 3364 (NH), 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 2.32 (d, *J* = 13.7 Hz, 1H), 2.39 (s, 3H), 2.48 (d, *J* = 12.6 Hz, 1H), 3.17-3.23 (m, 2H), 4.10 (s, 1H), 4.12-4.38 (m, 4H), 4.49 (s, 1H), 4.65 (d, *J* = 4.6 Hz, 1H), 4.79 (s, 1H), 6.06 (d, *J* = 4.6 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 21.5, 37.5, 39.8, 52.2, 57.6, 61.2, 62.2, 62.6, 84.1, 103.7, 111.0, 119.3, 126.0, 127.3 (2C), 129.0, 129.6 (2C), 129.7, 137.4, 143.3, 147.9, 151.1, 170.8, 171.0. HRMS (FAB) calcd $C_{27}H_{29}BrN_2O_6S$: [M^+], 588.0930; found: [M^+], 588.0926.



9c

Diethyl 5'-bromo-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9c). IR (neat): 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.30 (m, 6H), 2.40 (d, *J* = 14.3 Hz, 1H), 2.65 (d, *J* = 14.3 Hz, 1H), 4.19-4.28 (m, 4H), 4.59 (s, 1H), 4.91 (s, 1H), 6.19 (d, *J* = 10.3 Hz, 1H), 6.56 (d, *J* = 10.3 Hz, 1H), 7.43-7.45 (m, 1H), 7.51-7.53 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 34.7, 55.3, 61.1, 62.4, 62.5, 115.1, 120.4, 122.9, 125.5, 126.4, 131.3, 131.7, 136.8, 143.6, 154.4, 169.6, 169.9, 174.4. HRMS (FAB) calcd $C_{20}H_{21}BrNO_4$: [M + H]$^+$, 418.0654; found: [M + H]$^+$, 418.0650.

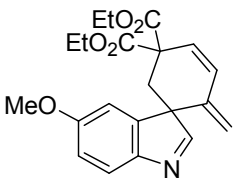


8k

Diethyl 7-methoxy-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8k).

IR (neat): 3352 (NH), 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.35 (d, *J* = 13.7 Hz, 1H), 2.38 (s, 3H), 2.46 (dd, *J* = 14.9, 1.7 Hz, 1H), 3.20-3.26 (m, 2H), 3.77 (s, 3H), 4.08-4.11 (m, 1H), 4.13-4.39 (m, 4H),

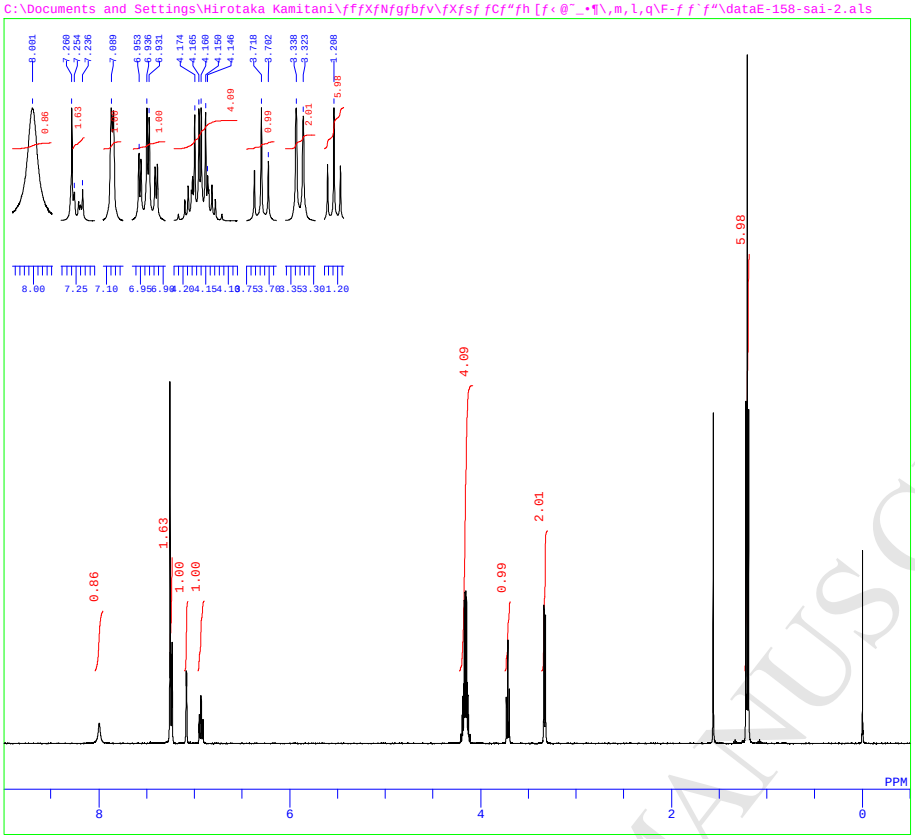
4.44 (d, *J* = 5.2 Hz, 1H), 4.47 (s, 1H), 4.77 (s, 1H), 6.03 (d, *J* = 5.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.67-6.71 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 21.5, 37.7, 40.0, 52.3, 56.0, 57.9, 61.3, 62.1, 62.6, 84.3, 103.4, 110.1, 111.2, 113.6, 127.4 (2C), 128.8, 129.6 (2C), 137.6, 142.4, 143.1, 151.6, 153.7, 170.9, 171.3. HRMS (FAB) calcd $C_{28}H_{32}N_2O_7S$: $[M^+]$, 540.1930; found: $[M^+]$, 540.1935.



9d

Diethyl 5'-methoxy-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9d).

IR (neat): 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.30 (m, 6H), 2.38 (d, *J* = 14.3 Hz, 1H), 2.68 (d, *J* = 14.3 Hz, 1H), 3.84 (s, 3H), 4.19-4.27 (m, 4H), 4.58 (s, 1H), 4.89 (s, 1H), 6.17 (d, *J* = 10.3 Hz, 1H), 6.56 (d, *J* = 10.3 Hz, 1H), 6.86 (d, *J* = 2.6 Hz, 1H), 6.90 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 25.8, 35.2, 55.5, 55.7, 60.9, 62.3, 109.1, 113.6, 114.9, 121.9, 125.3, 131.6, 137.8, 143.0, 149.0, 158.9, 169.8, 170.1, 171.9. HRMS (FAB) calcd $C_{21}H_{24}NO_5$: $[M + H]^+$, 370.1654; found: $[M + H]^+$, 370.1653.

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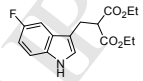
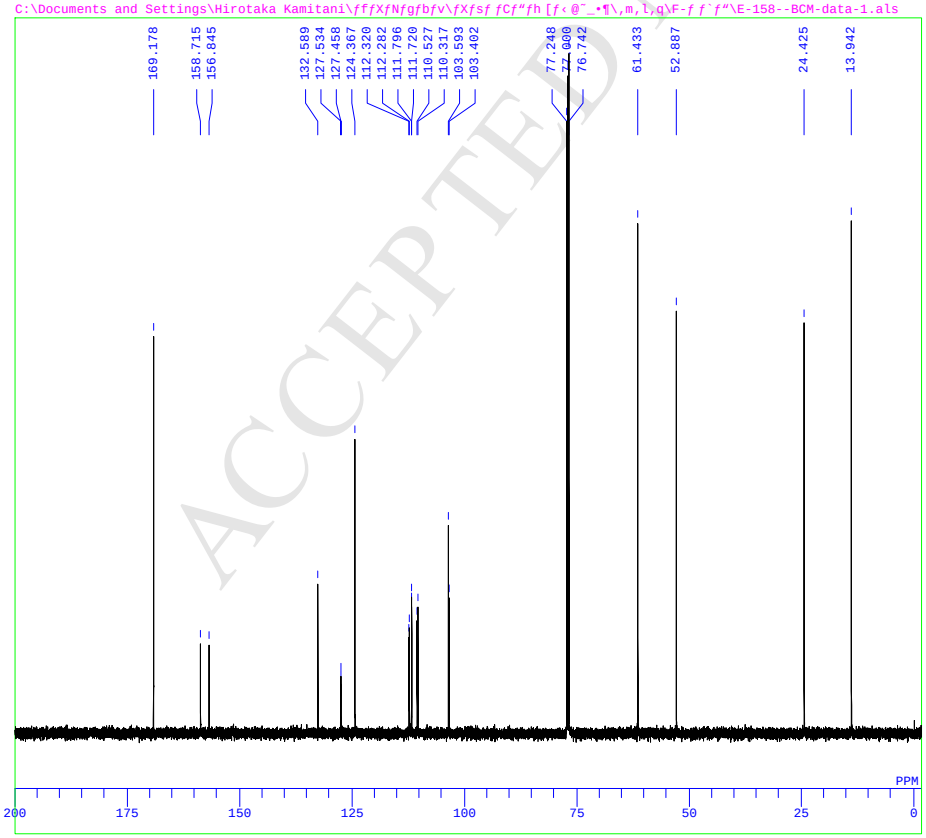


S2

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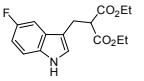
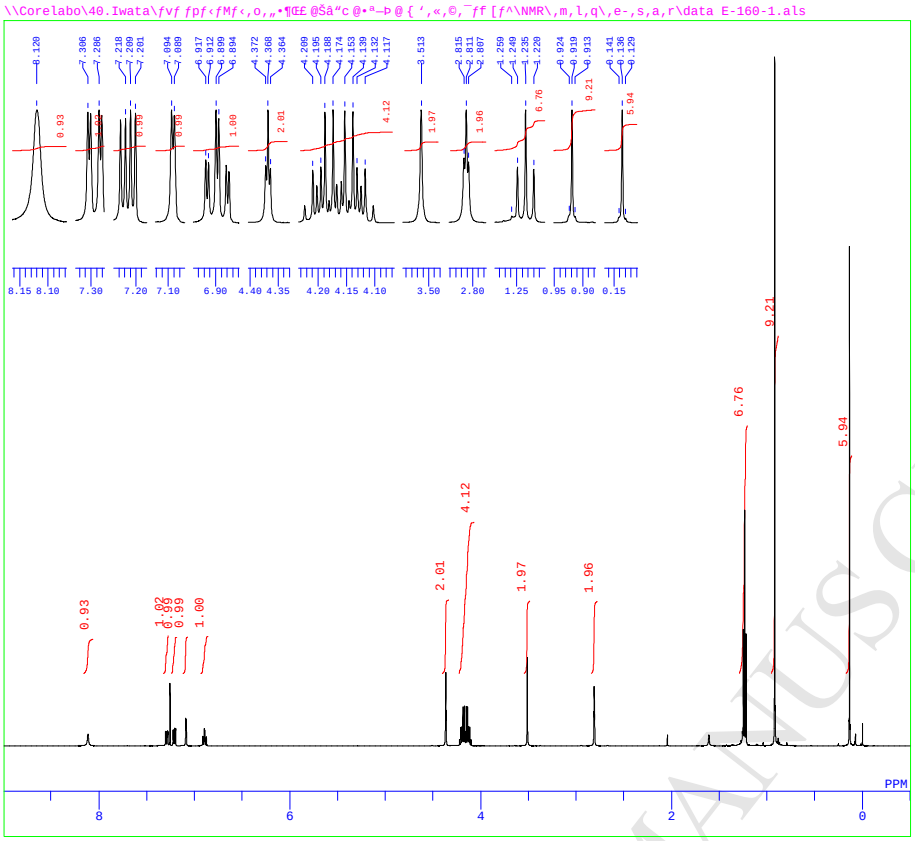


S2

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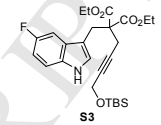
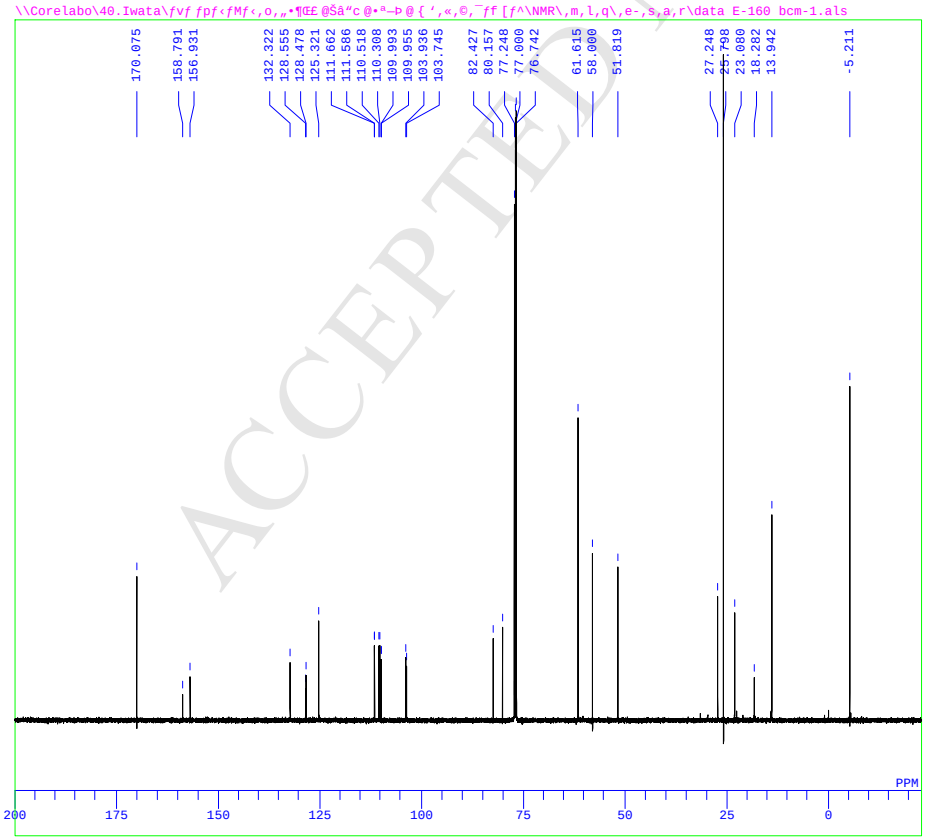
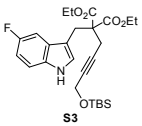


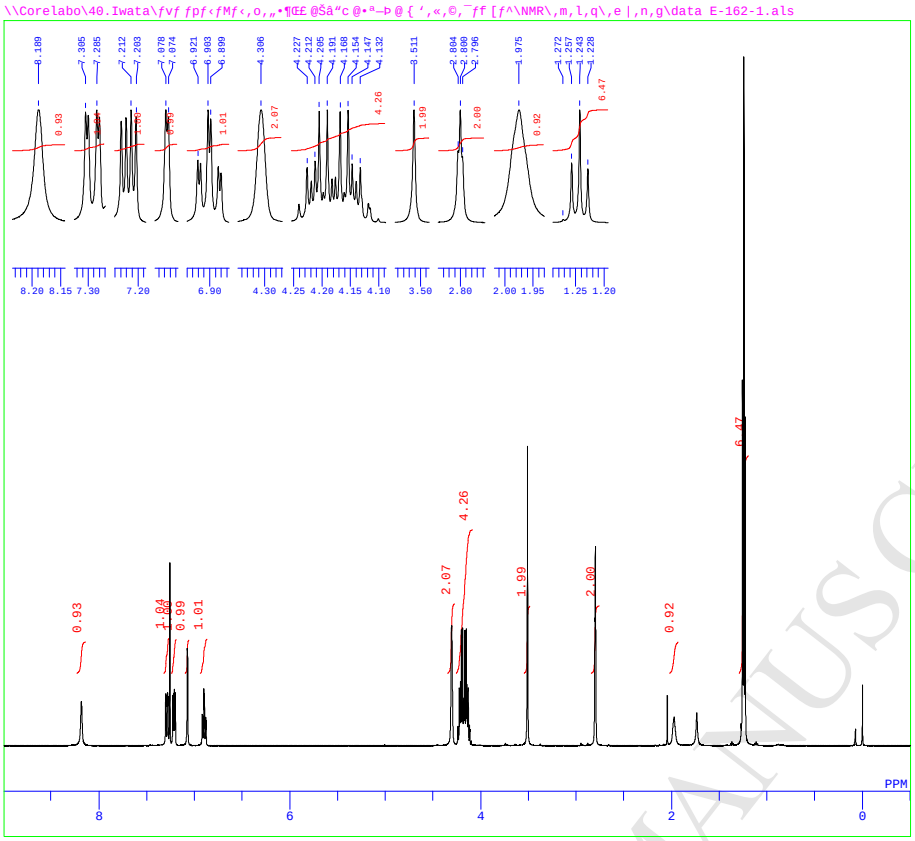
S3



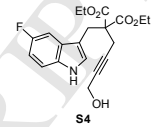

```
DFILE  data E-160 bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-05 03:04:19
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          4048
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          25.6 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            58
```



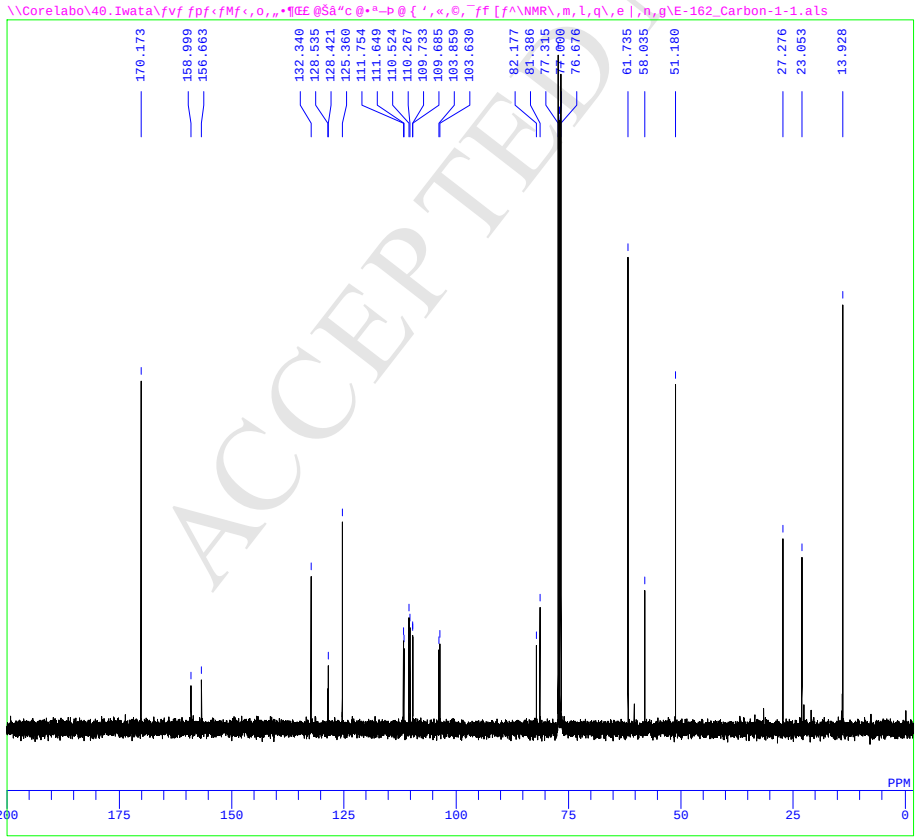
S3



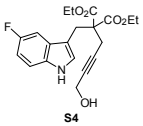
DFILE data E-162-1.als
COMNT single_pulse
DATIM 2013-04-04 09:27:30
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 52428
FREQU 7507.39 Hz
SCANS 8
ACQTM 6.9835 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 25.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 42



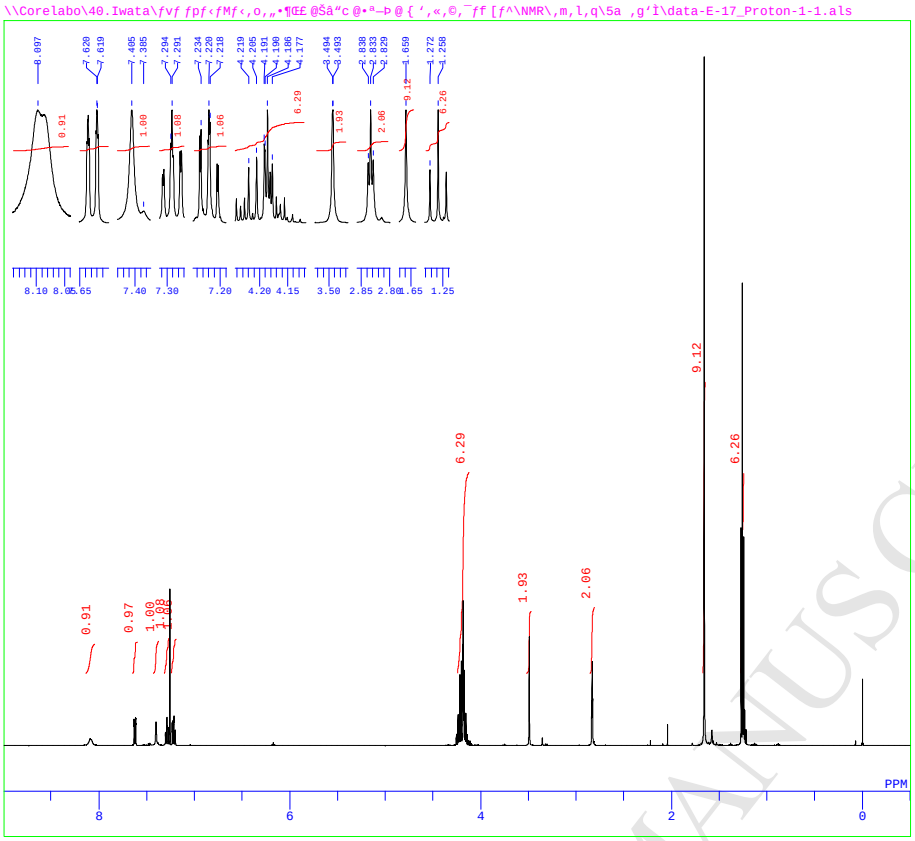
S4



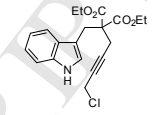
DFILE E-162_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2013-01-17 10:23:53
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 400
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 3.00 usec
IRNUC 1H
CTEMP 26.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60



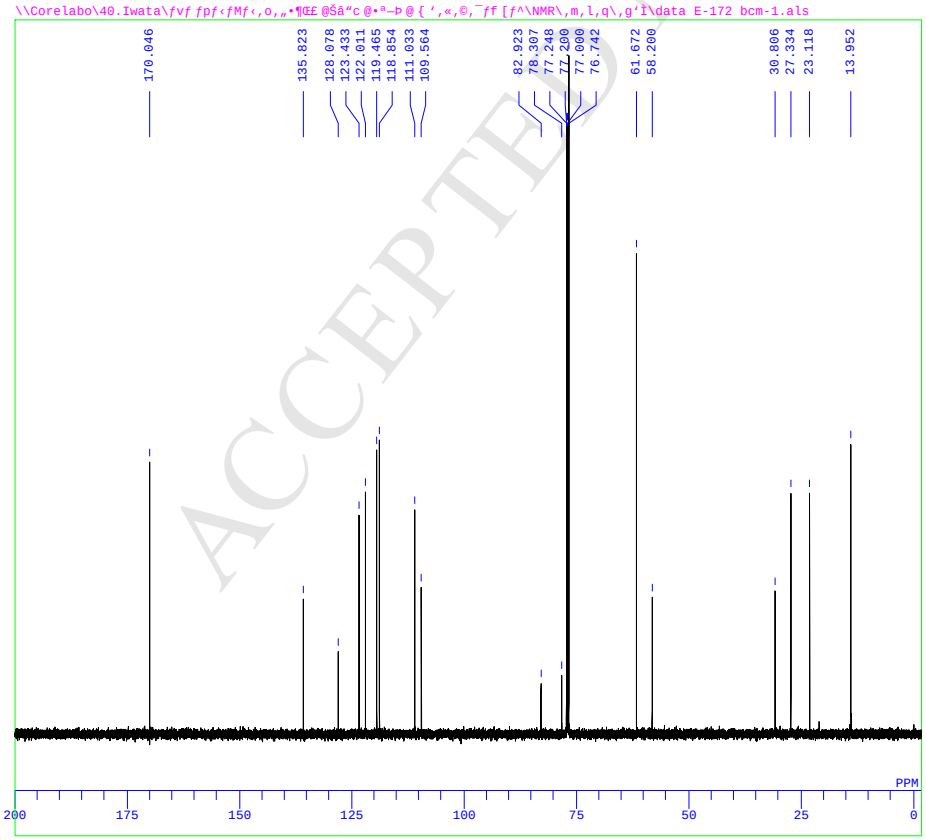
S4



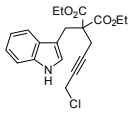
DFILE data-E-17_Proton-1-1.als
COMNT single_pulse
DATIM 2013-04-03 13:30:43
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 52428
FREQU 7507.39 Hz
SCANS 8
ACQTM 6.9835 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 24.8 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 40



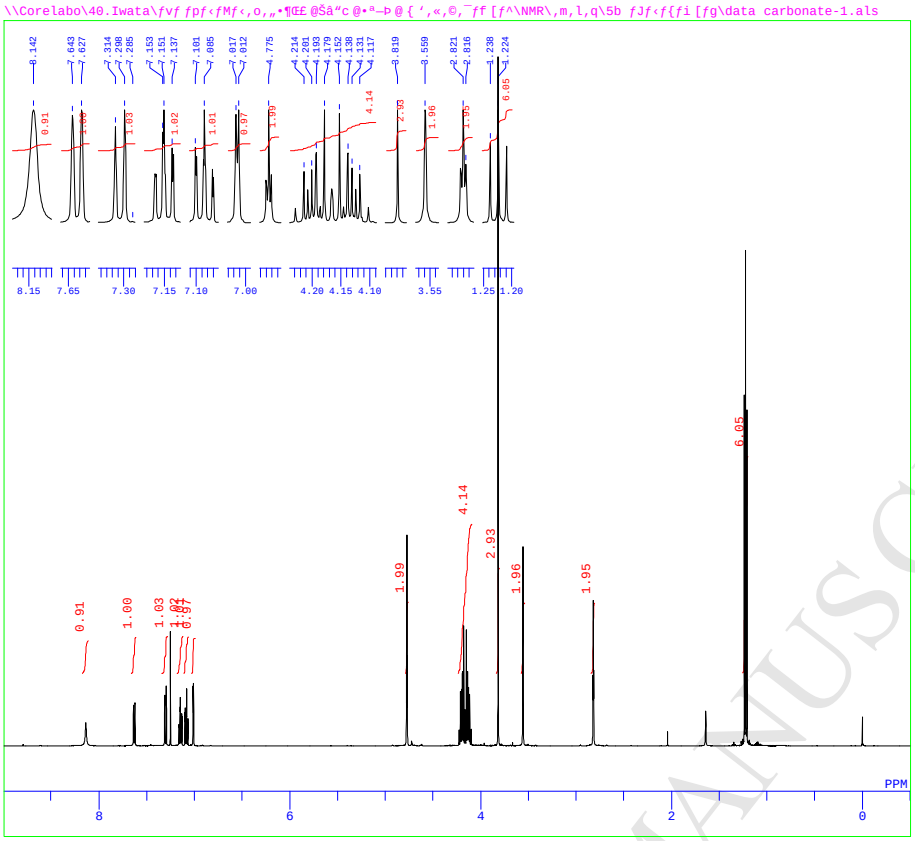
5a



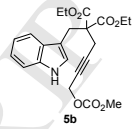
DFILE data E-172 bcm-1.als
COMNT single pulse decoupled gated NOE
DATIM 2013-04-02 15:41:46
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 883
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 25.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 56



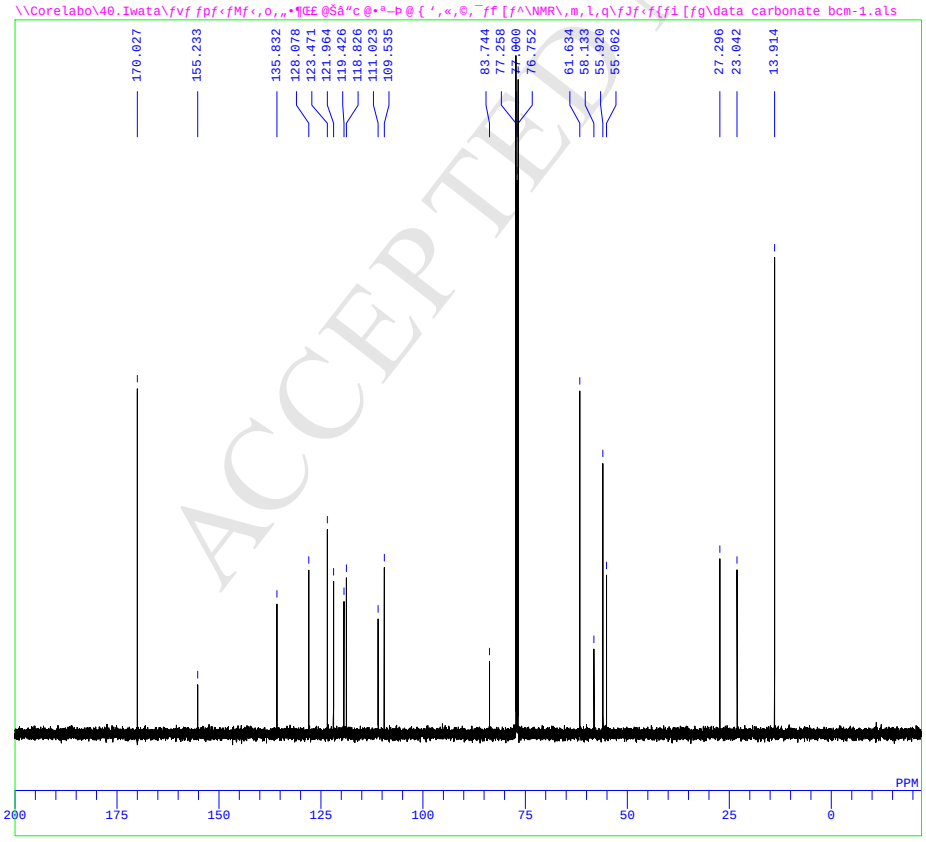
5a



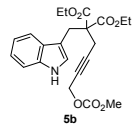

```
DFILE  data carbonate-1.als
COMNT  single_pulse
DATIM  2013-05-10 15:29:01
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP          25.5 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            38
```



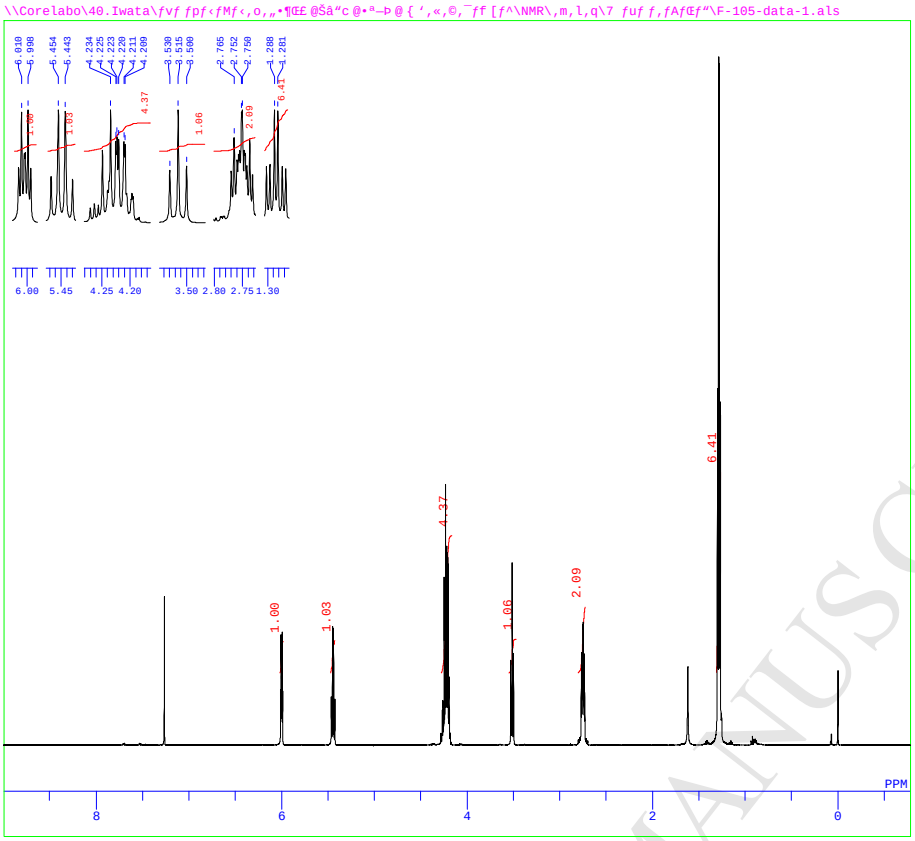
5b



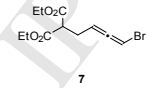

```
DFILE  data carbonate bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-05-10 15:58:49
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           616
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          26.2 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            56
```



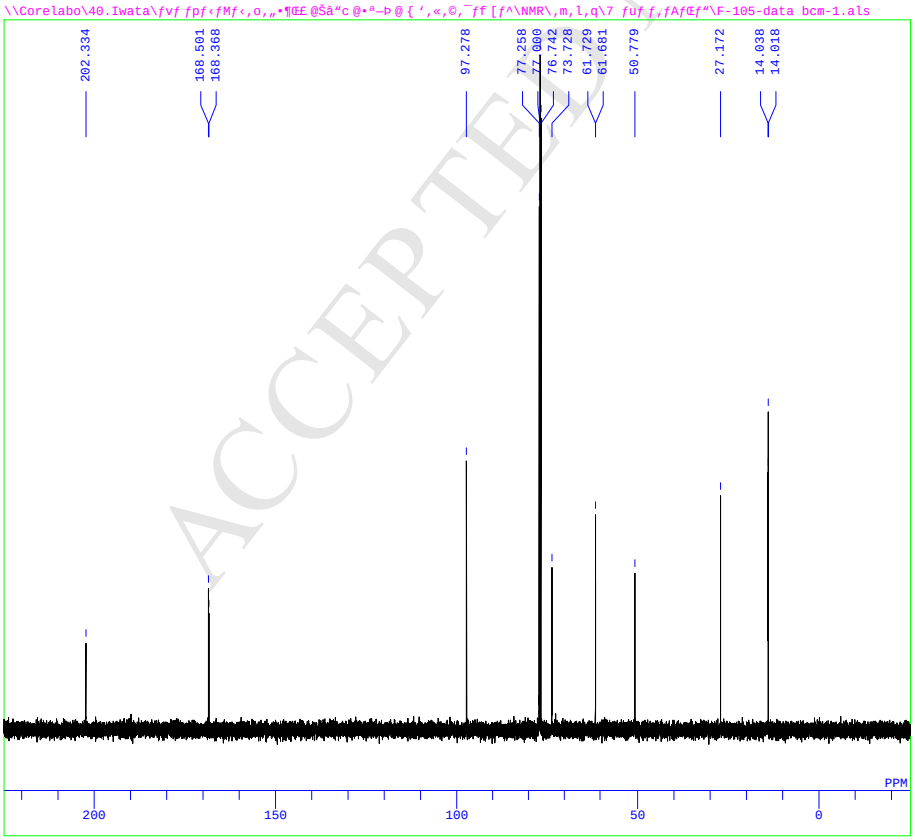
5b



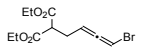

```
DFILE  F-105-data-1.als
COMNT  single_pulse
DATIM  2013-07-13 13:25:56
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         52428
FREQU       7507.39 Hz
SCANS             4
ACQTM         6.9835 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP          25.0 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             40
```



7

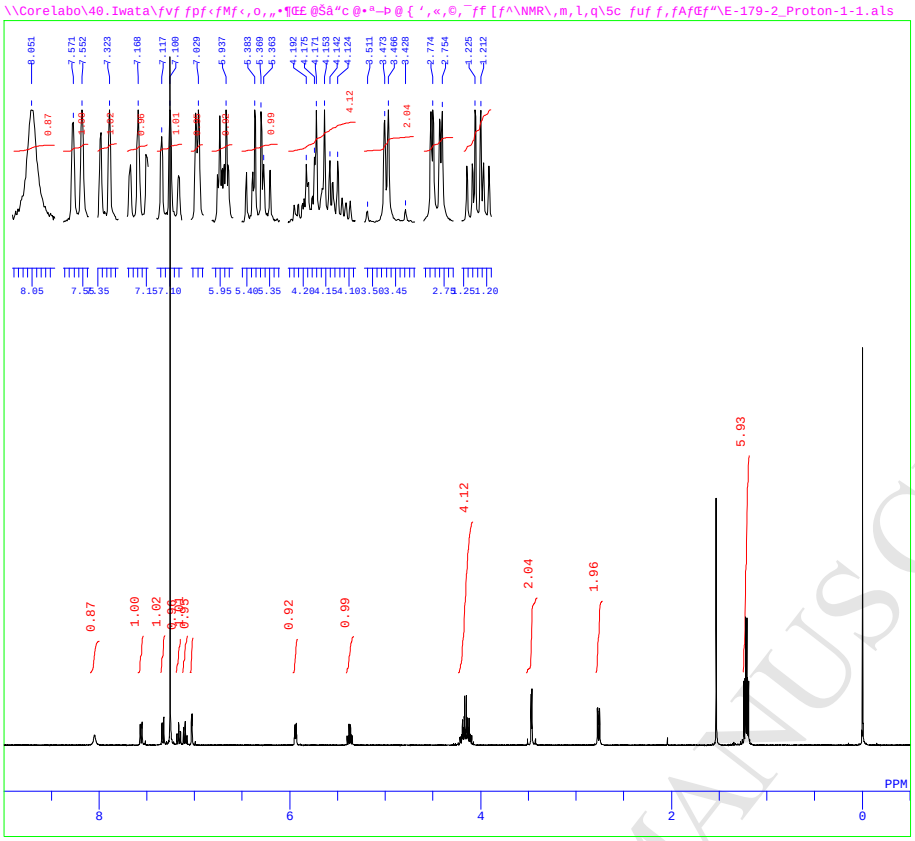



```
DFILE  F-105-data bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-07-13 13:42:20
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           333
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          25.4 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            52
```

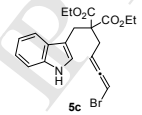


7

\\Corelabo\40.Iwata\ƒvƒ fpƒ‹ƒMƒ‹,o,„•¶ŒÊ @Ša“c @•ª—Þ @{ ',«,©,¯ƒf [ƒ^\NMR\,m,l,q\5c ƒuƒ ƒ,ƒAƒŒƒ"\E-179-2_Proton-1-1.als

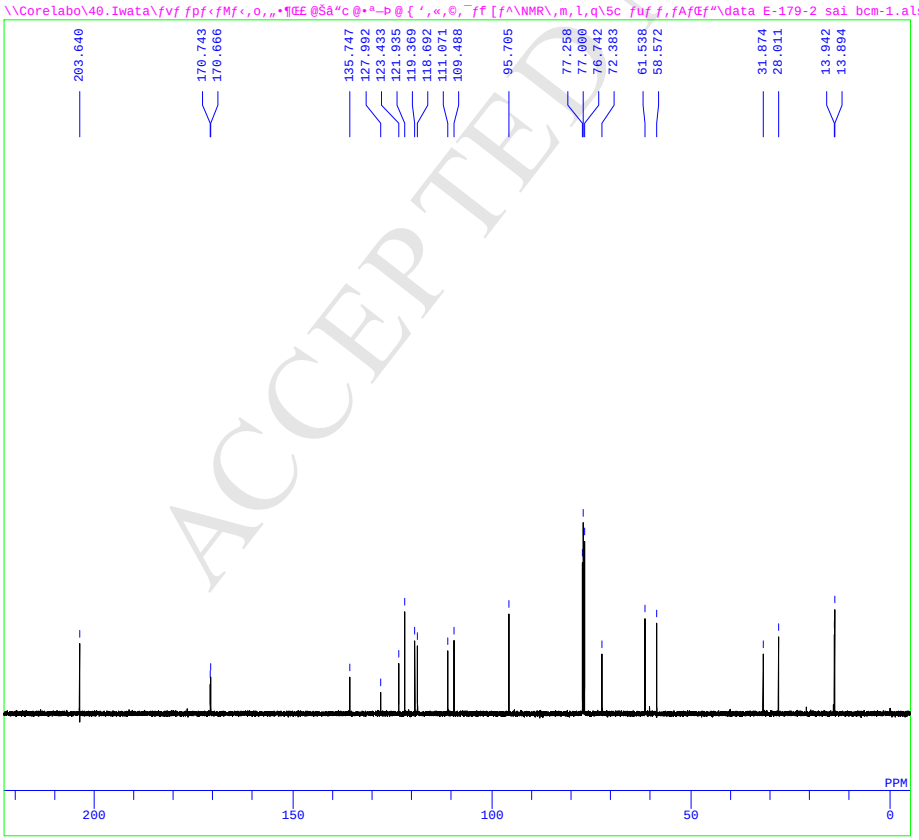



```
DFILE  E-179-2_Proton-1-1.als
COMNT  single_pulse
DATIM  2013-02-07 10:02:40
OBNUC  1H
EXMOD  proton.jxp
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         13107
FREQU       7598.78 Hz
SCANS            8
ACQTM        1.7249 sec
PD           5.0000 sec
PW1            4.65 usec
IRNUC  1H
CTEMP         25.2 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            52
```

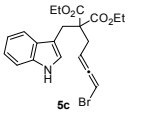


5c

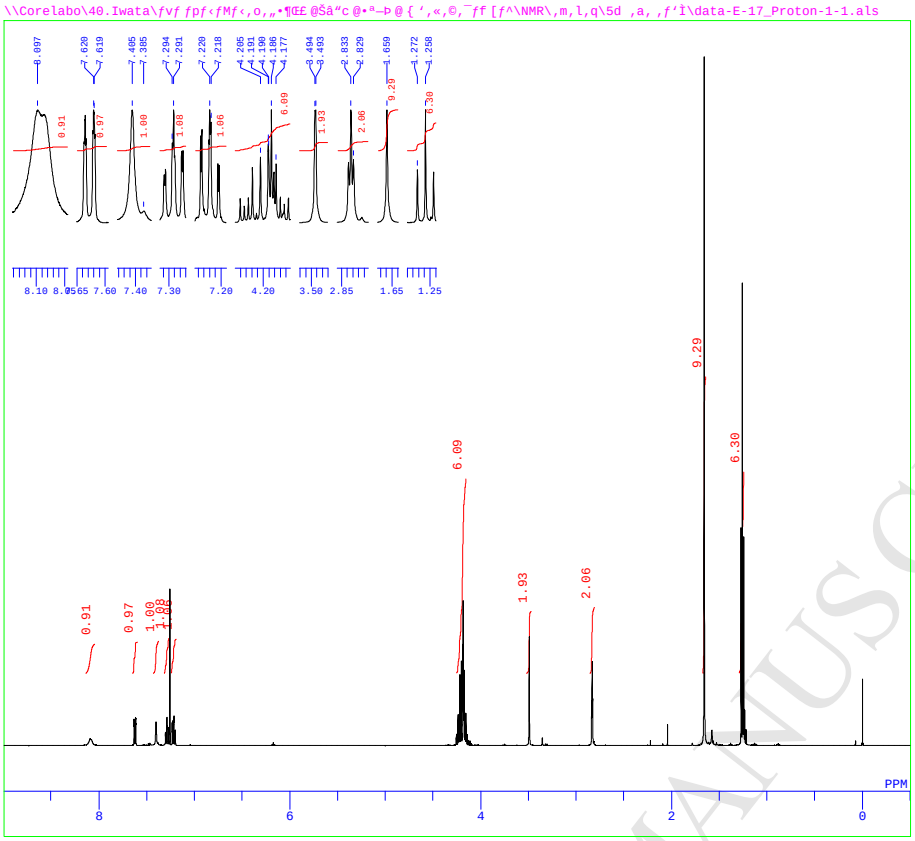
\\Corelabo\40.Iwata\ƒvƒ fpƒ‹ƒMƒ‹,o,„•¶ŒÊ @Ša“c @•ª—Þ @{ ',«,©,¯ƒf [ƒ^\NMR\,m,l,q\5c ƒuƒ ƒ,ƒAƒŒƒ"\data E-179-2 sai bcm-1.als



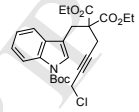

```
DFILE  data E-179-2 sai bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-05-11 14:08:34
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           344
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          25.8 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            56
```



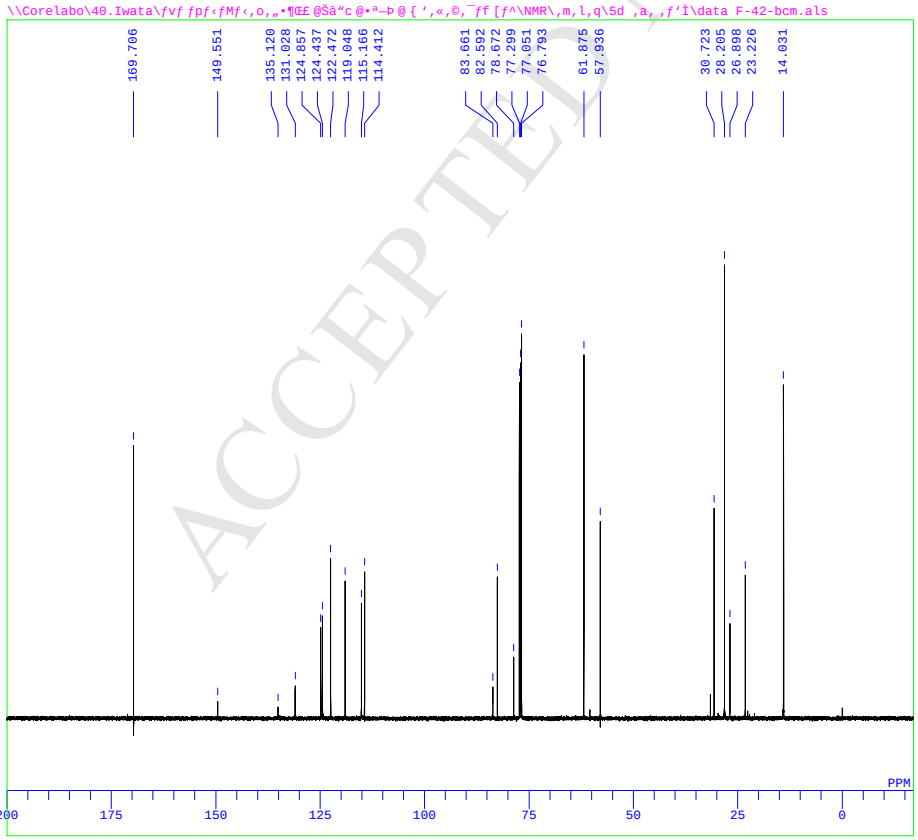
5c



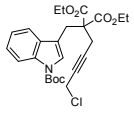

```
DFILE  data-E-17_Proton-1-1.als
COMNT  single_pulse
DATIM  2013-04-03 13:30:43
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         52428
FREQU       7507.39 Hz
SCANS              8
ACQTM         6.9835 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP           24.8 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             40
```



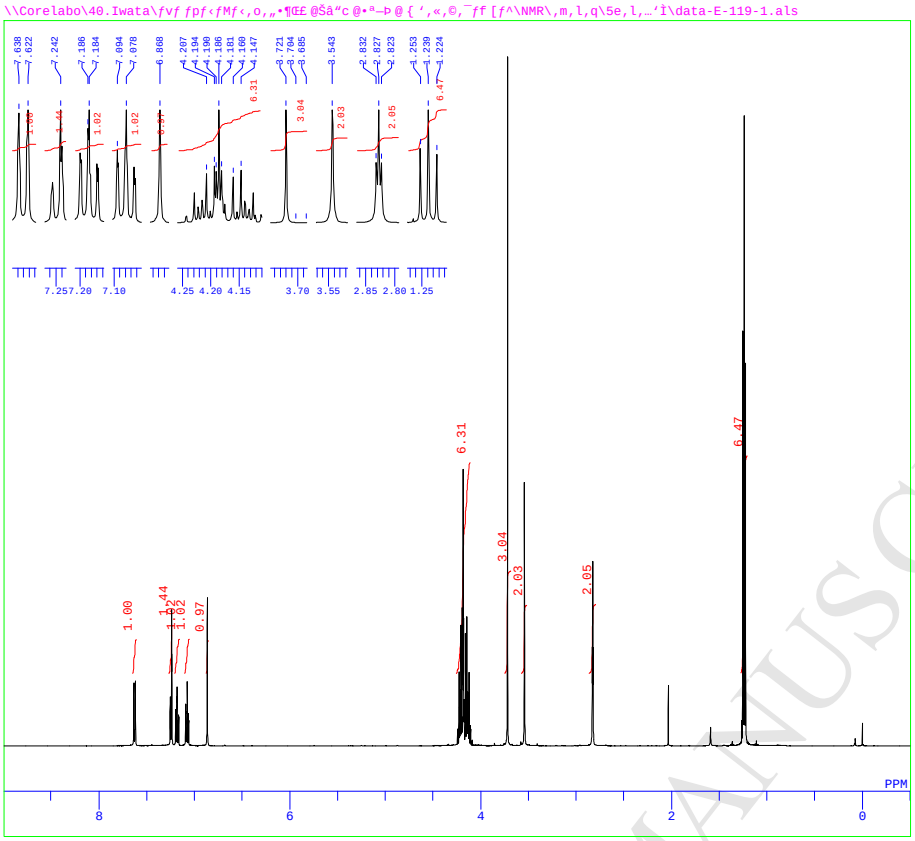
5d



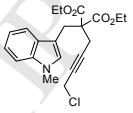

```
DFILE  data F-42-bcm.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-17 08:00:08
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          2400
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP           25.7 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             60
```



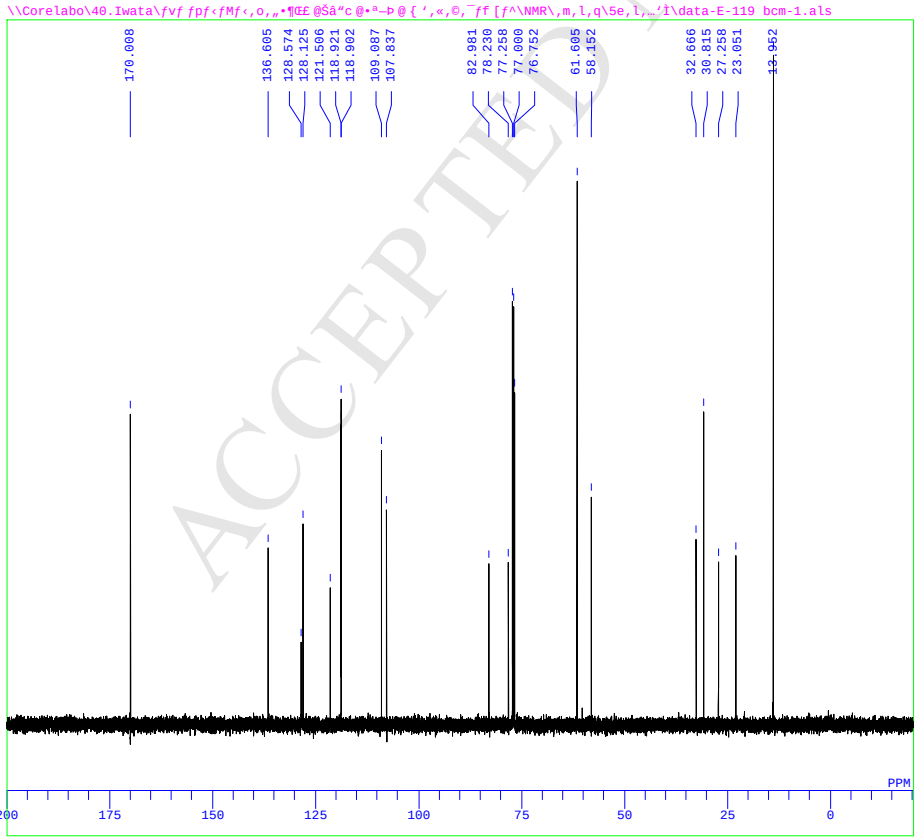
5d



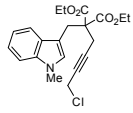
DFILE data-E-119-1.als
COMNT single_pulse
DATIM 2013-04-03 19:01:25
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 24.9 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 34



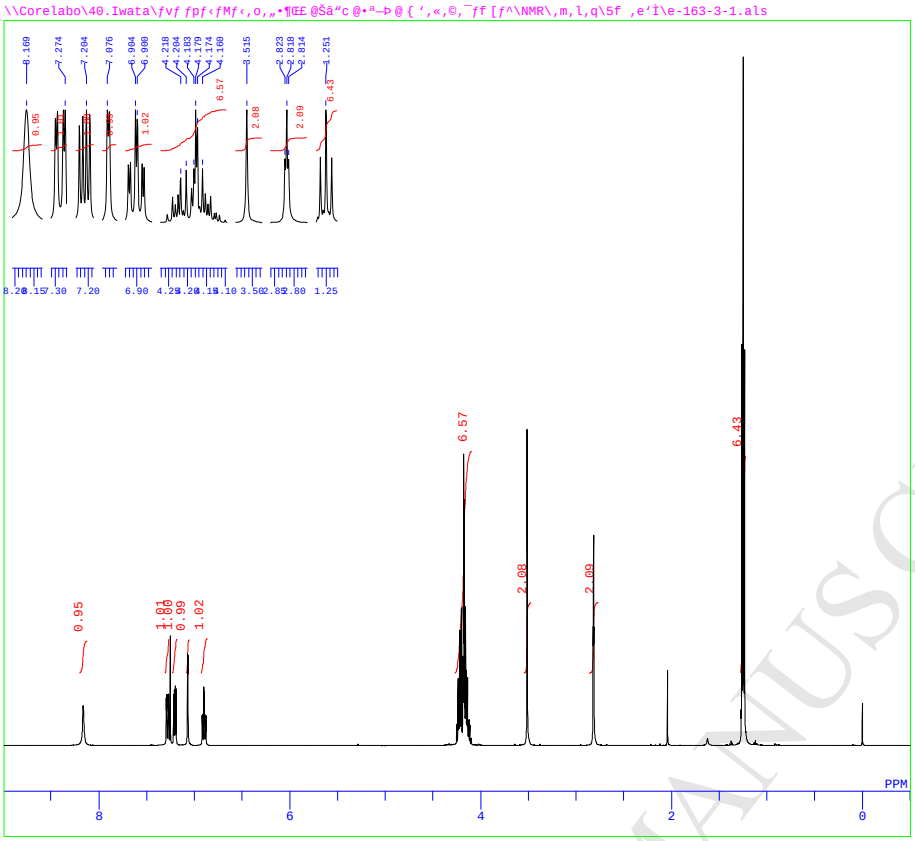
5e



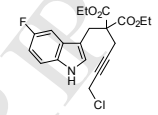
DFILE data-E-119 bcm-1.als
COMNT single pulse decoupled gated NOE
DATIM 2013-04-03 19:08:42
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 142
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 25.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 54



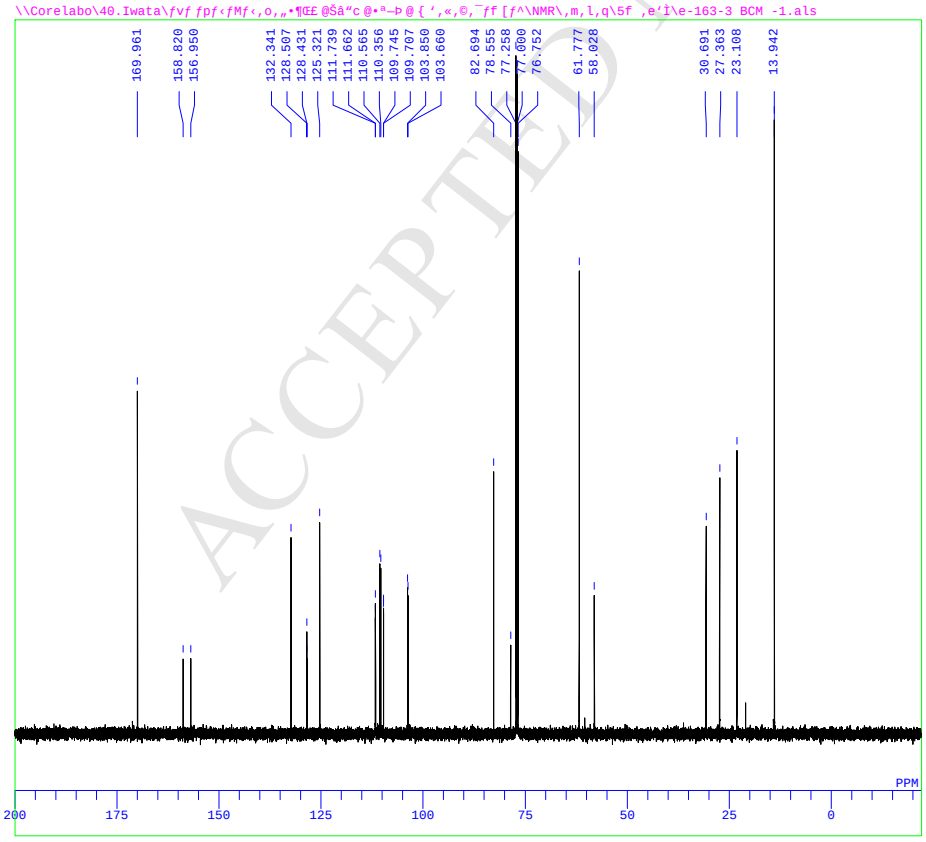
5e



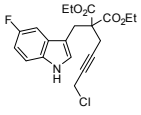

```
DFILE  e-163-3-1.als
COMNT  single_pulse
DATIM  2013-01-23 15:50:46
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1             6.90 usec
IRNUC  1H
CTEMP           27.3 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             30
```



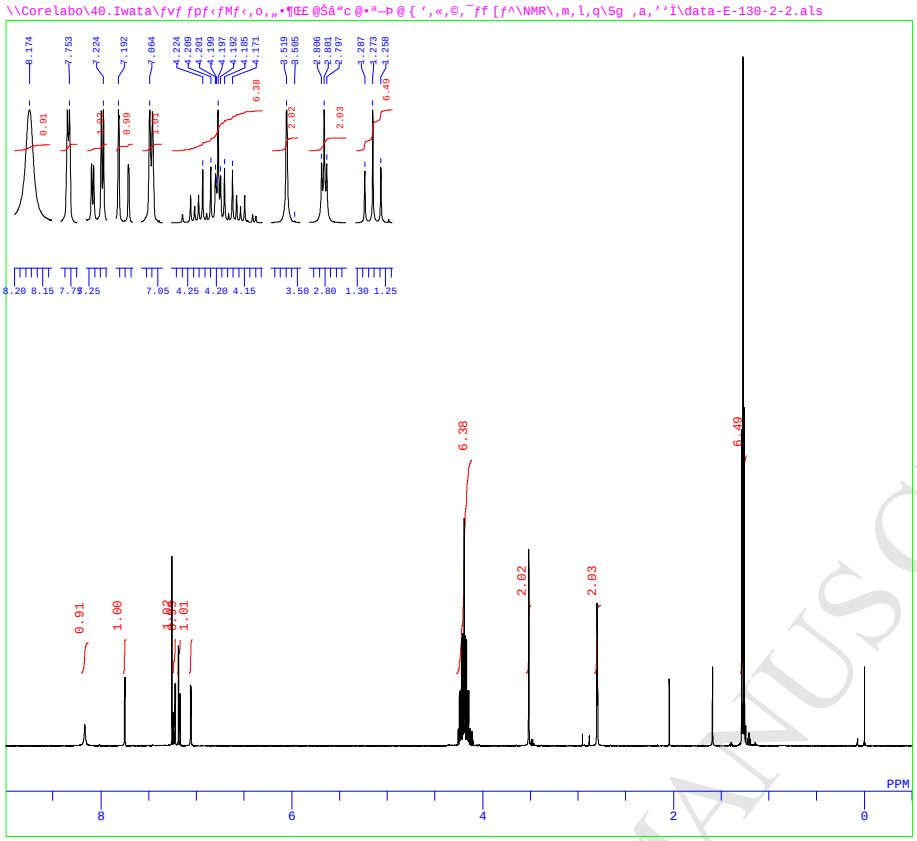
5f



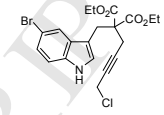

```
DFILE  e-163-3 BCM -1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-01-23 16:13:22
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           466
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP           27.7 c
SLVNT  CDCL3
EXREF          77.00 ppm
BF              0.12 Hz
RGAIN             54
```



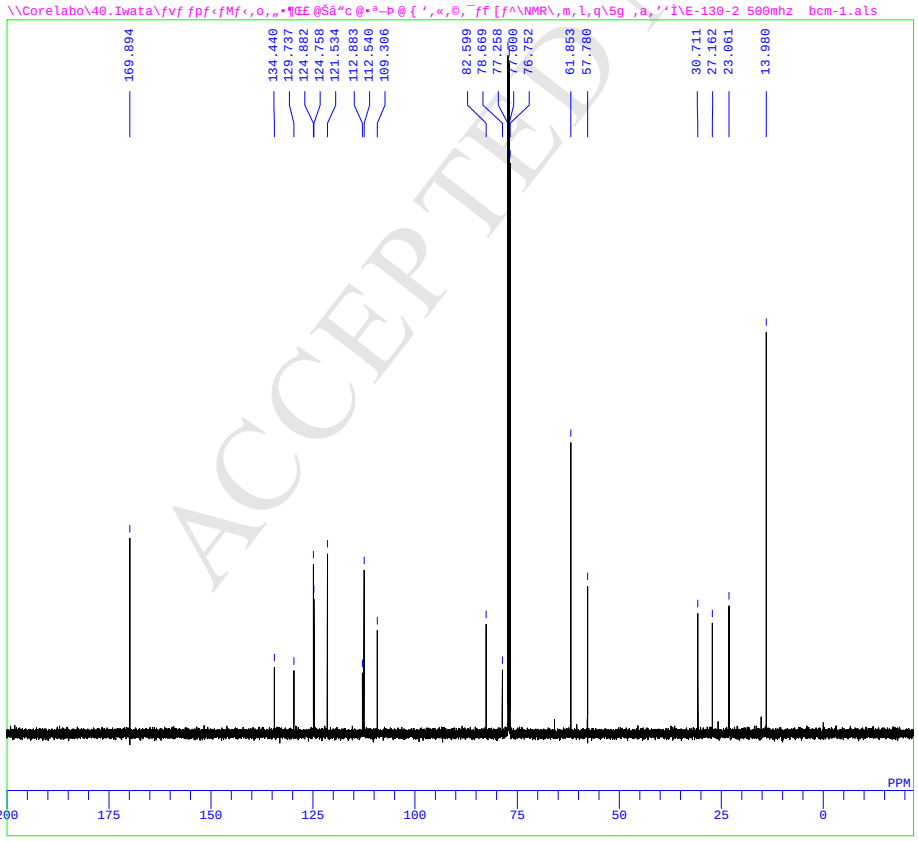
5f



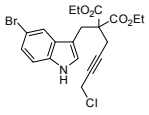

```
DFILE  data-E-130-2-2.als
COMNT  single_pulse
DATIM  2013-04-03 10:19:53
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         52428
FREQU       7507.39 Hz
SCANS             8
ACQTM         6.9835 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP          25.1 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            42
```



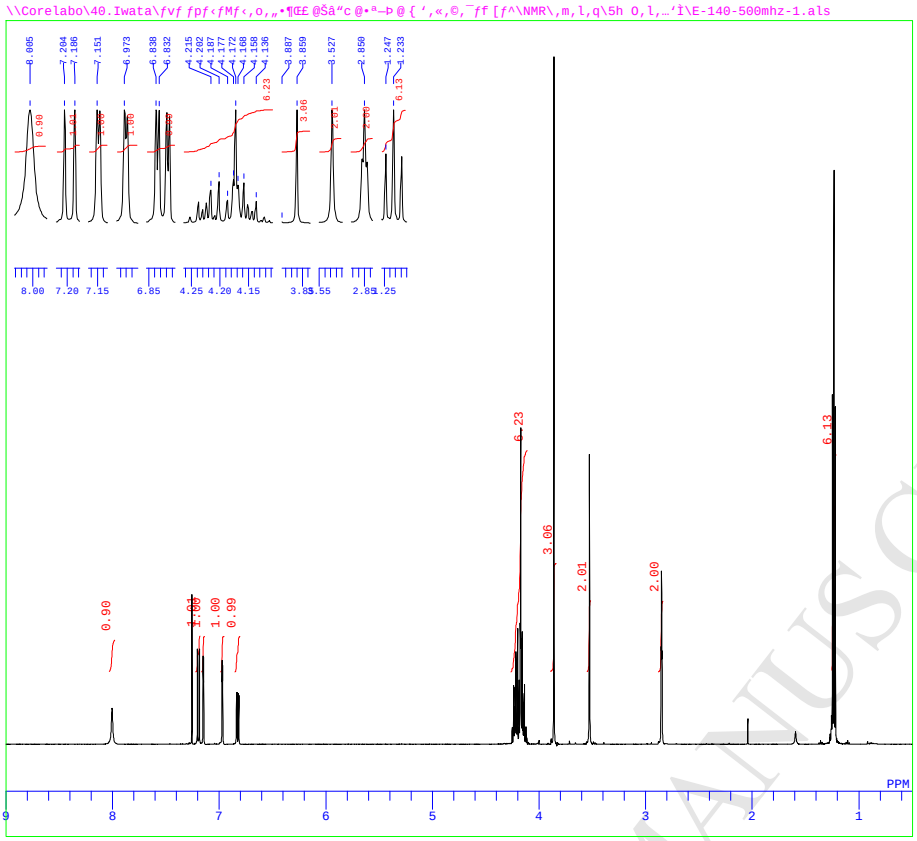
5g



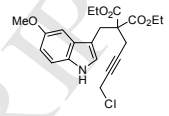

```
DFILE  E-130-2 500mhz  bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2012-12-03 19:23:44
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          1024
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          27.7 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            54
```



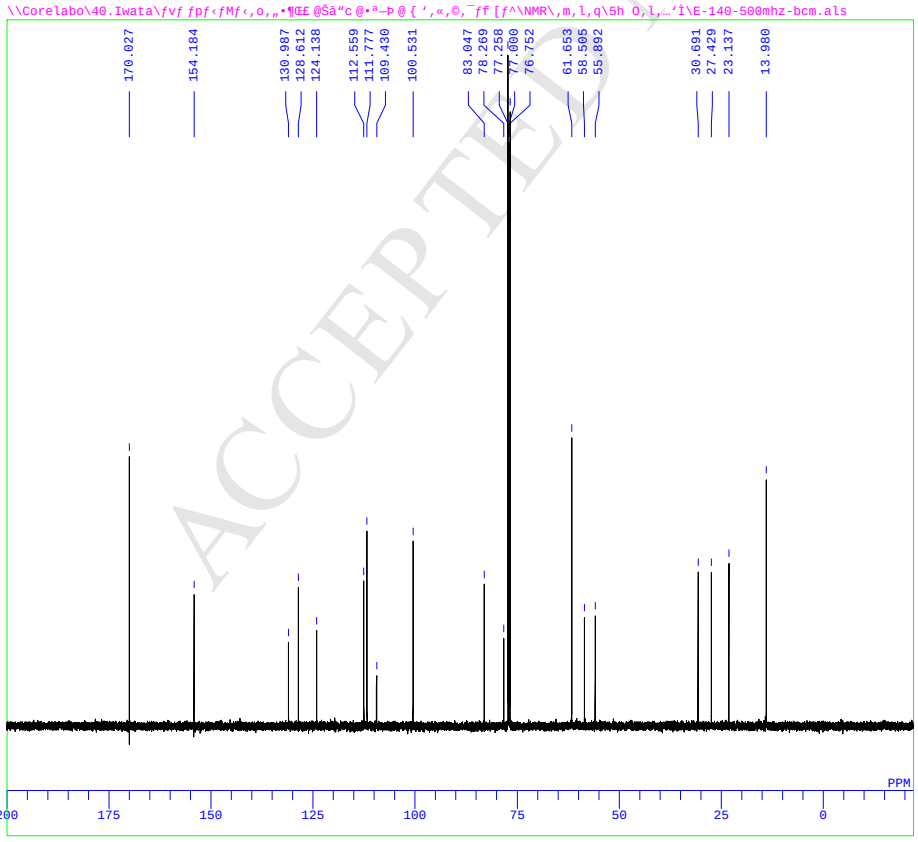
5g



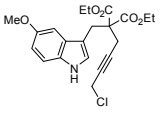

```
DFILE  E-140-500mhz-1.als
COMNT  single_pulse
DATIM  2012-12-10 09:49:60
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP          28.0 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             40
```



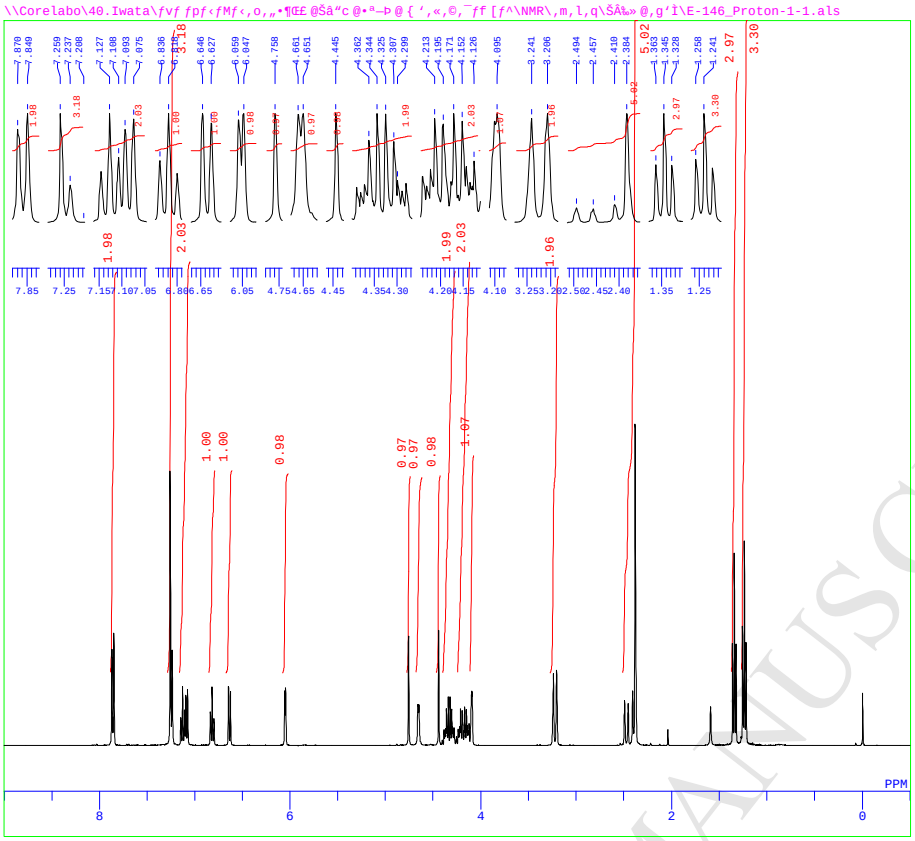
5h



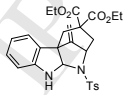

```
DFILE  E-140-500mhz-bcm.als
COMNT  single pulse decoupled gated NOE
DATIM  2012-12-10 10:39:54
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          1024
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          28.3 c
SLVNT  CDCL3
EXREF          77.00 ppm
BF              0.12 Hz
RGAIN             56
```



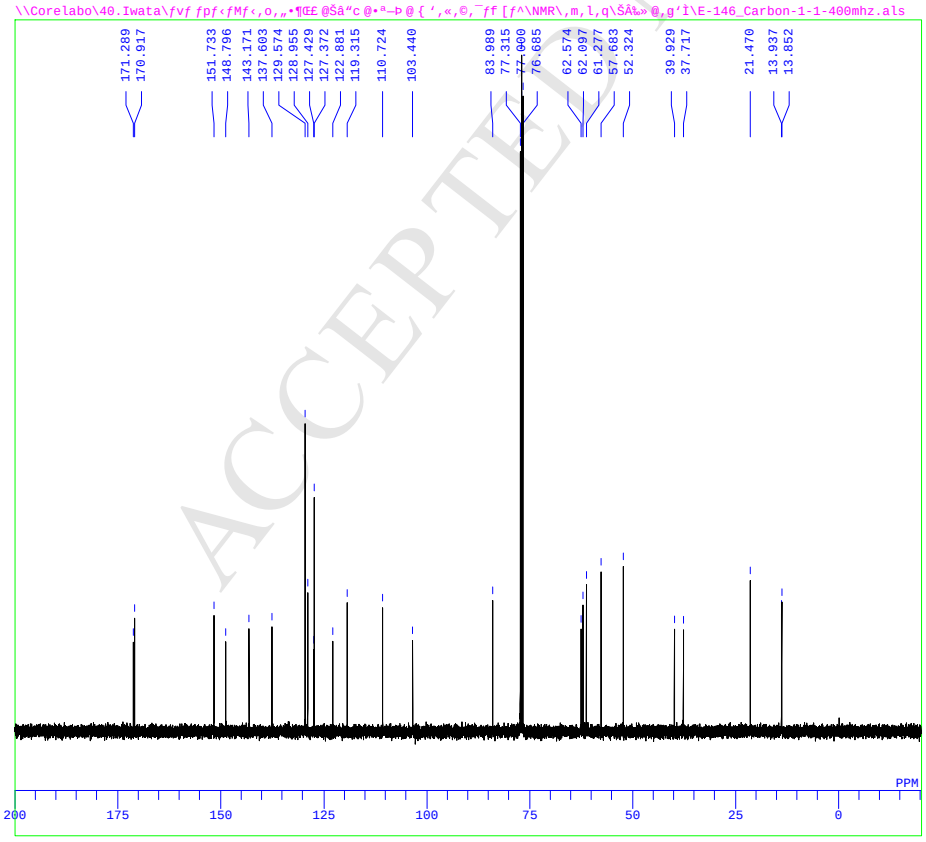
5h



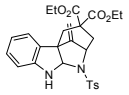

```
DFILE  E-146_Proton-1-1.als
COMNT  single_pulse
DATIM  2012-12-17 13:48:16
OBNUC  1H
EXMOD  proton.jxp
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         13107
FREQU       6002.40 Hz
SCANS             8
ACQTM         2.1837 sec
PD            5.0000 sec
PW1           4.65 usec
IRNUC  1H
CTEMP          25.4 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            38
```



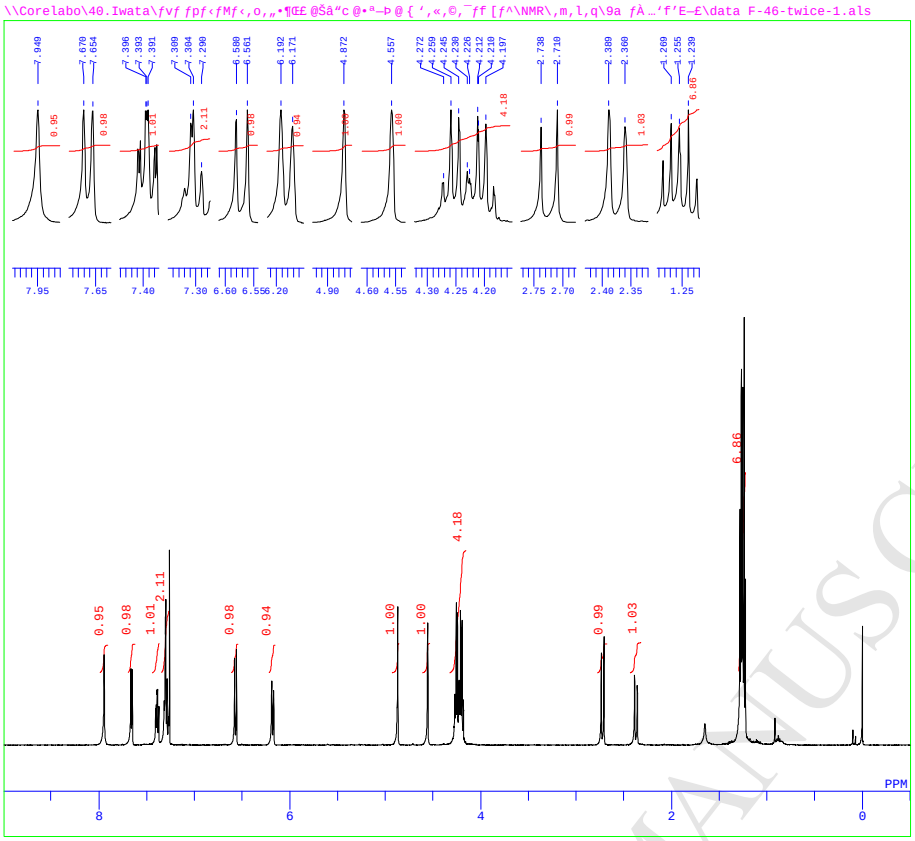
8a



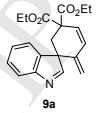

```
DFILE  E-146_Carbon-1-1-400mhz.als
COMNT  single pulse decoupled gated NOE
DATIM  2012-12-17 13:50:00
OBNUC  13C
EXMOD  carbon.jxp
OBFRQ        100.53 MHz
OBSET          5.35 KHz
OBFIN          5.86 Hz
POINT         26214
FREQU      25125.63 Hz
SCANS           512
ACQTM         1.0433 sec
PD            2.0000 sec
PW1             3.00 usec
IRNUC  1H
CTEMP          25.5 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            60
```



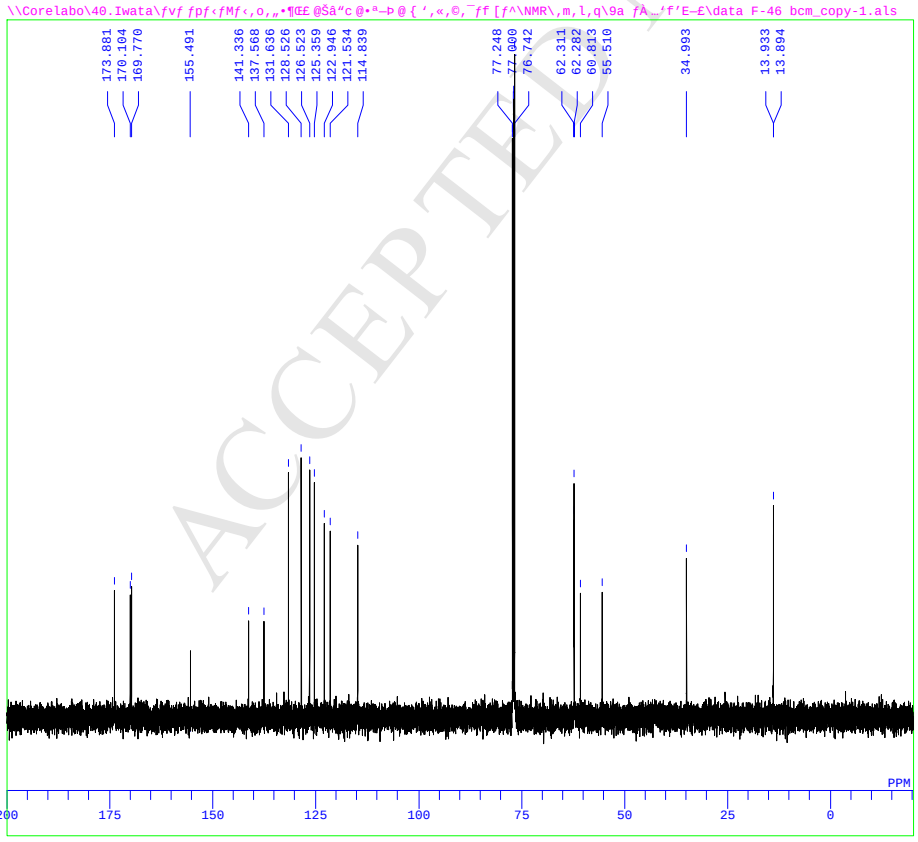
8a



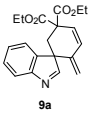
DFILE data F-46-twice-1.als
COMNT single_pulse
DATIM 2013-04-22 20:26:03
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 25.7 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 46



9a

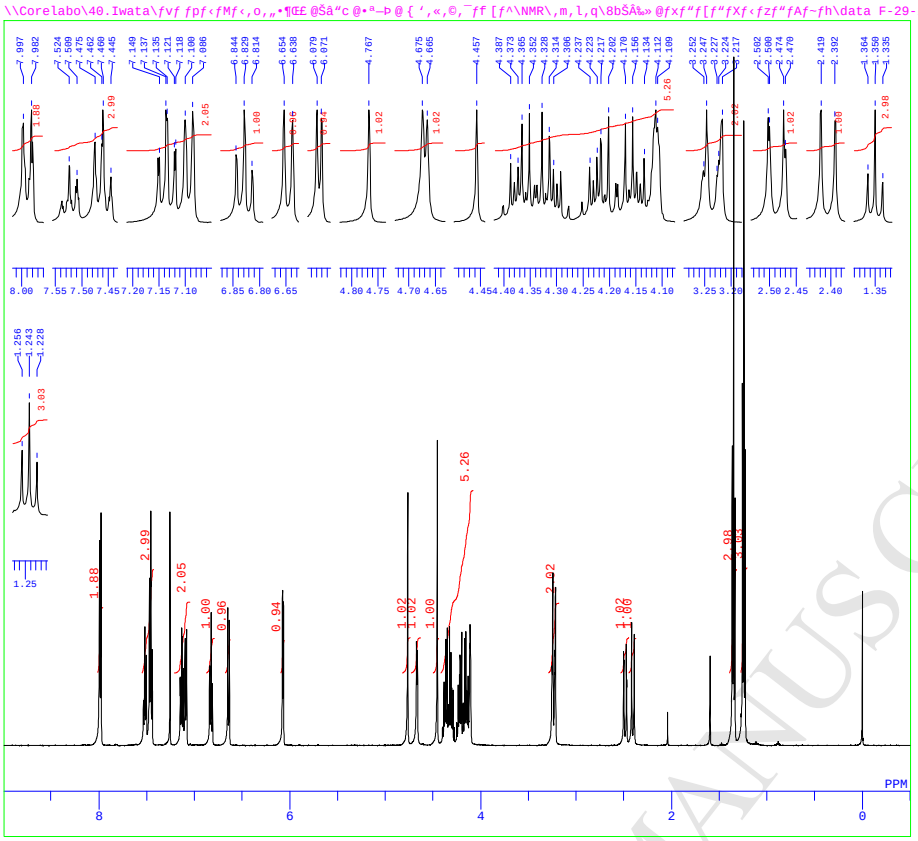


DFILE data F-46 bcm_copy-1.als
COMNT single pulse decoupled gated NOE
DATIM 2013-04-20 16:10:50
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 417
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 25.8 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 54

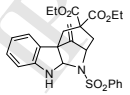


9a

\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @ŠÀ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\,m,l,q\8bŠÀ‰» @ƒxƒ“ƒ[ƒ“ƒXƒ‹ƒzƒ“ƒAƒ~ƒh\data F-29-2 RECRYSTALIZATION-2.als

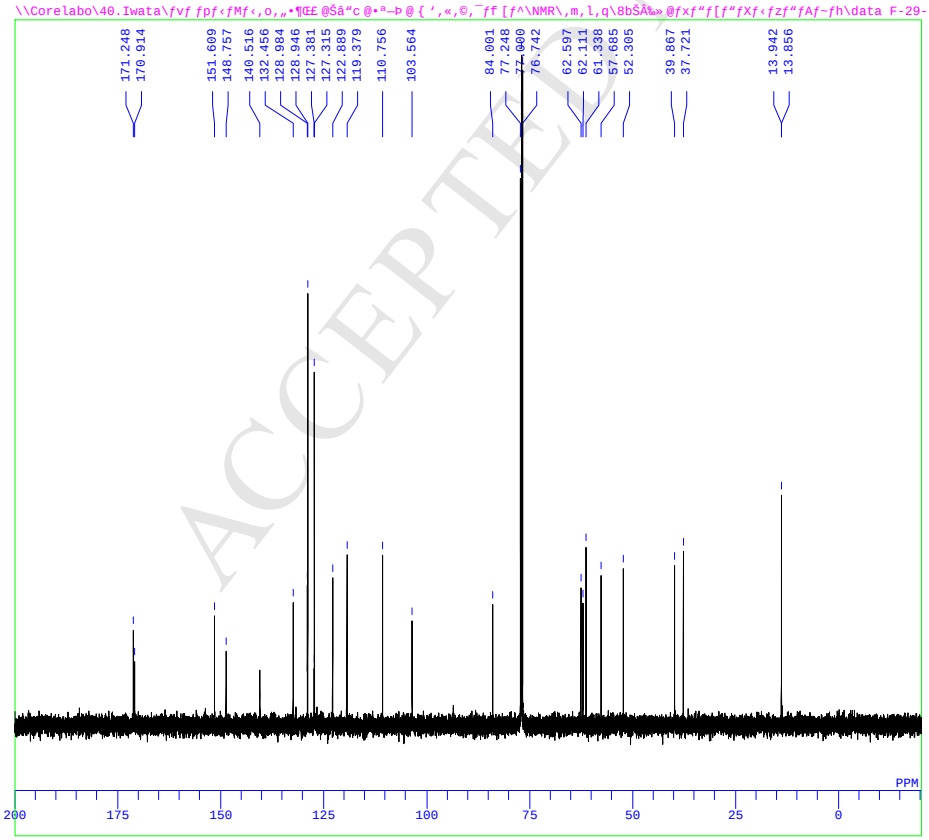



```
DFILE  data F-29-2 RECRYSTALIZATION-2.al
COMNT  single_pulse
DATIM  2013-04-09 16:22:05
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1           6.50 usec
IRNUC  1H
CTEMP          26.1 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            42
```

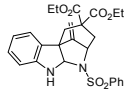


8b

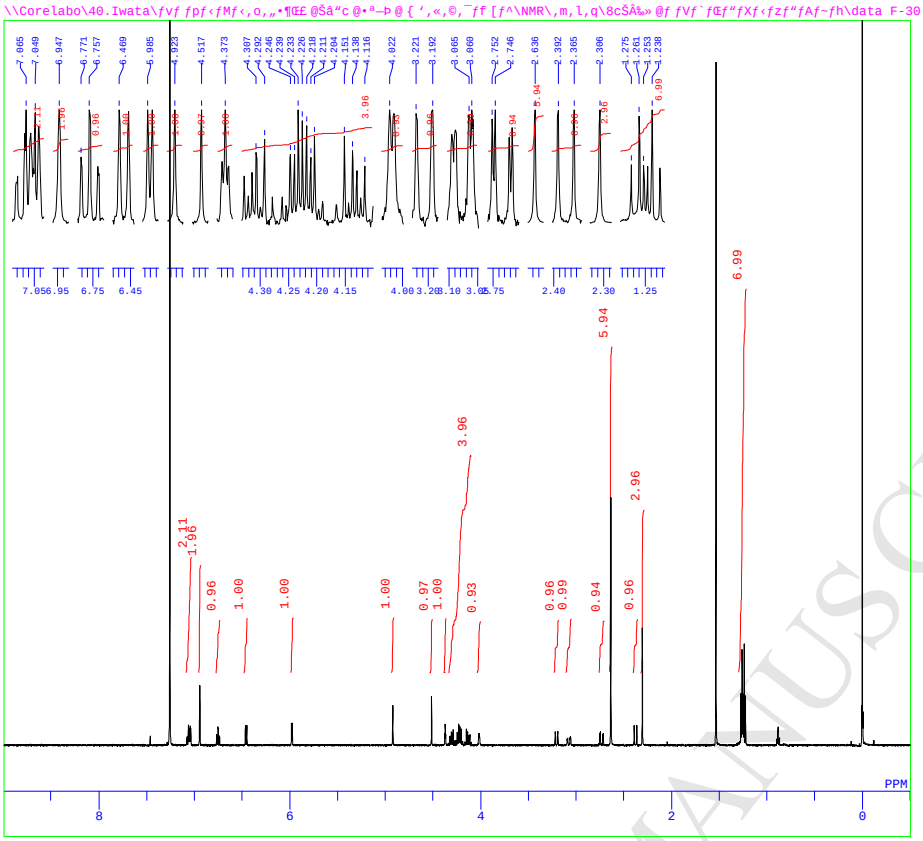
\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @ŠÀ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\,m,l,q\8bŠÀ‰» @ƒxƒ“ƒ[ƒ“ƒXƒ‹ƒzƒ“ƒAƒ~ƒh\data F-29-2 RECRYSTALIZATION BCM-1.als



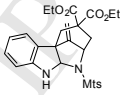

```
DFILE  data F-29-2 RECRYSTALIZATION BCM-
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-09 17:00:06
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS            792
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          26.5 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            54
```



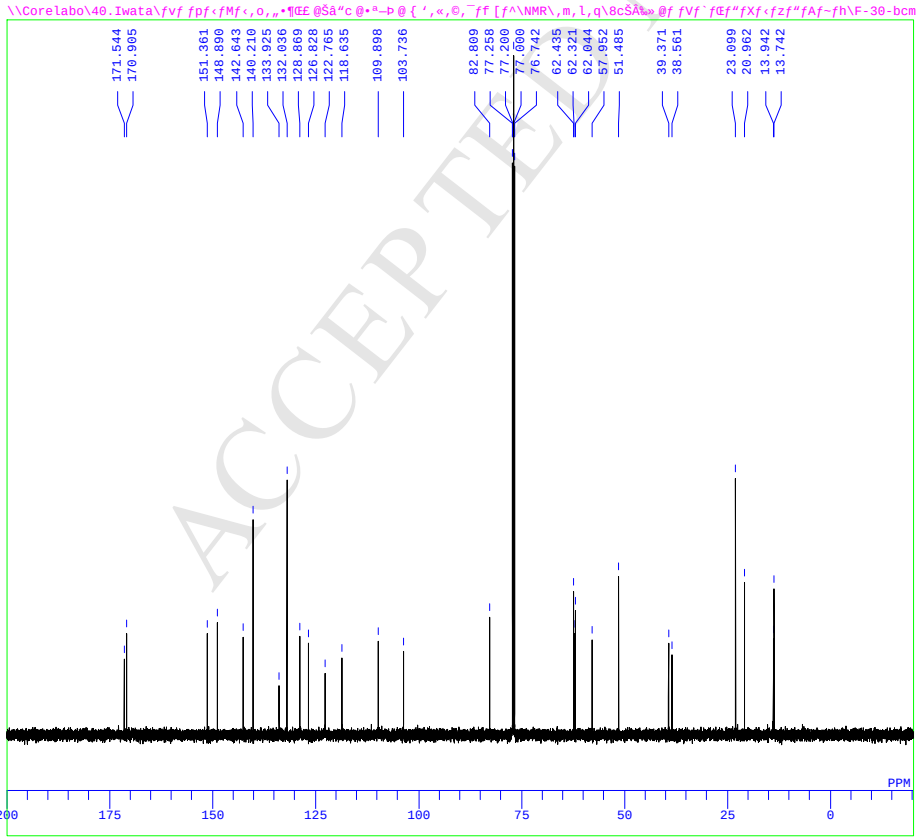
8b



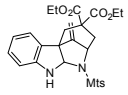

```
DFILE  data F-30-1-1.als
COMNT  single_pulse
DATIM  2013-04-16 22:45:43
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS            8
ACQTM        1.7459 sec
PD           5.0000 sec
PW1            6.50 usec
IRNUC  1H
CTEMP         25.5 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            54
```



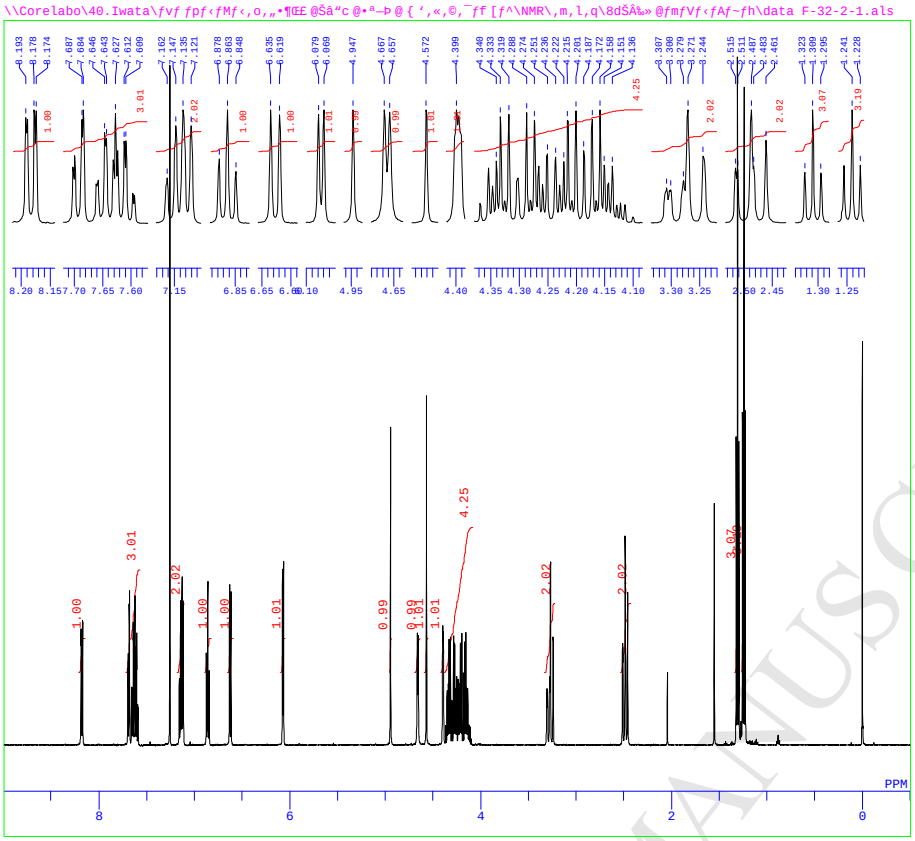
8c



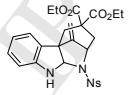

```
DFILE  F-30-bcm.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-03-14 15:52:37
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           570
ACQTM        0.8336 sec
PD           2.0000 sec
PW1            3.73 usec
IRNUC  1H
CTEMP          26.2 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            54
```



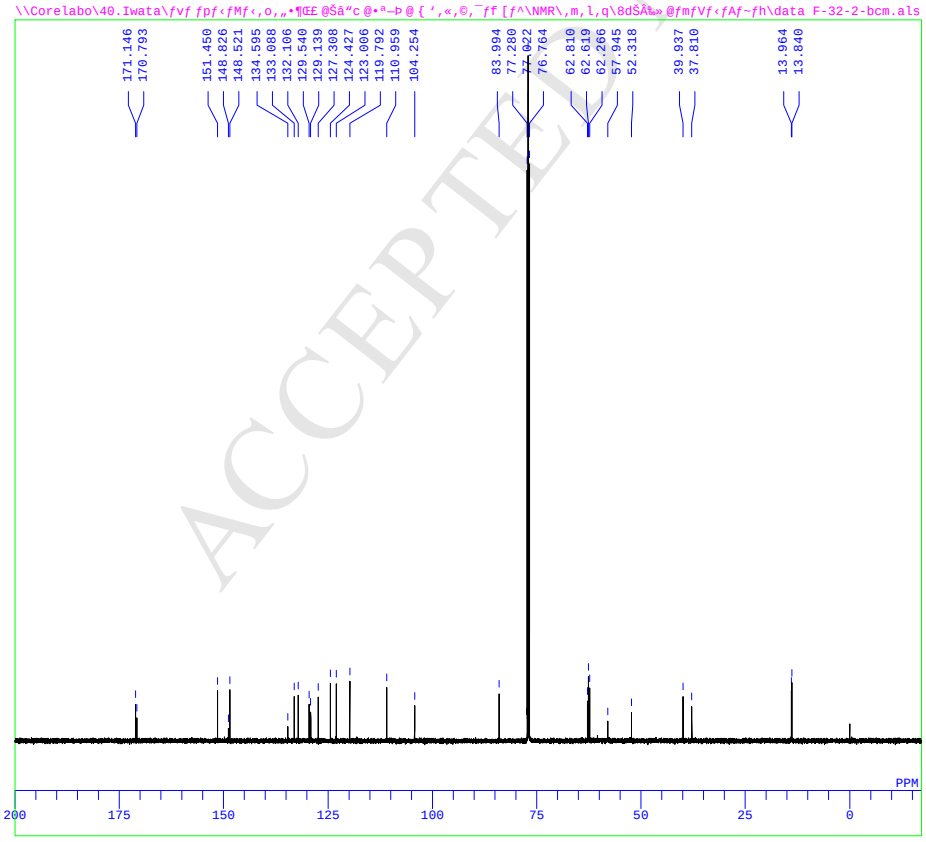
8c



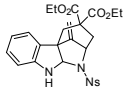

```
DFILE  data F-32-2-1.als
COMNT  single_pulse
DATIM  2013-04-17 02:30:45
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP         402.3 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             46
```



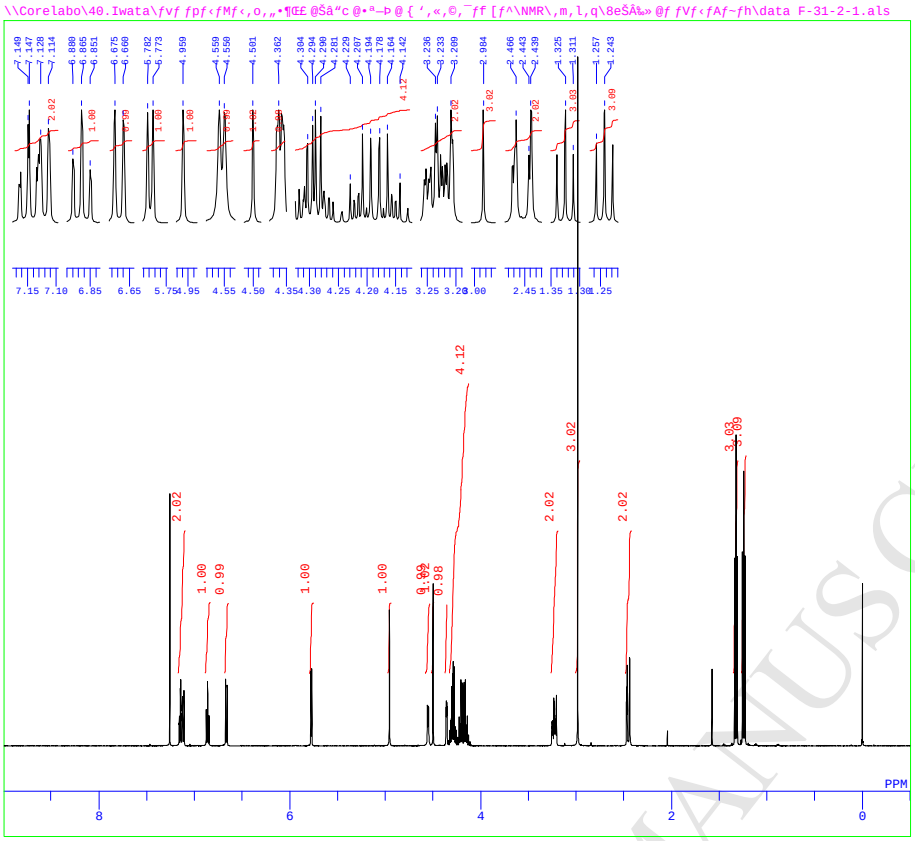
8d



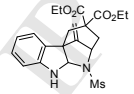

```
DFILE  data F-32-2-bcm.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-17 05:59:09
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          4400
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          25.5 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             60
```



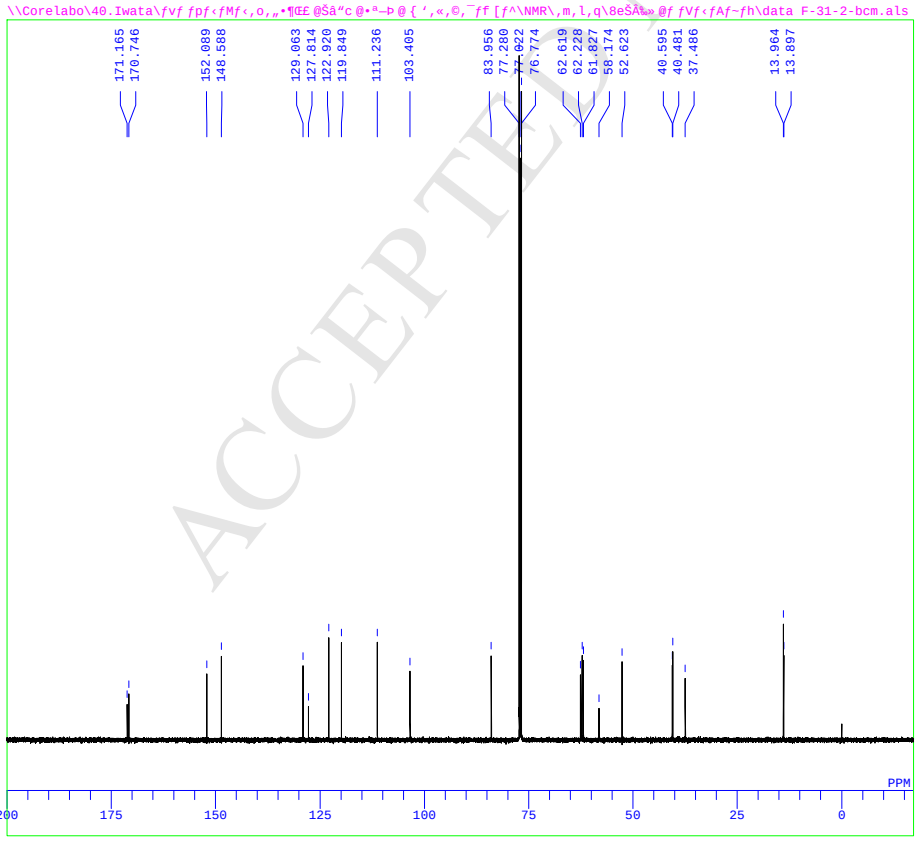
8d



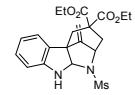
DFILE data F-31-2-1.als
COMNT single_pulse
DATIM 2013-04-16 22:53:32
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 402.1 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44



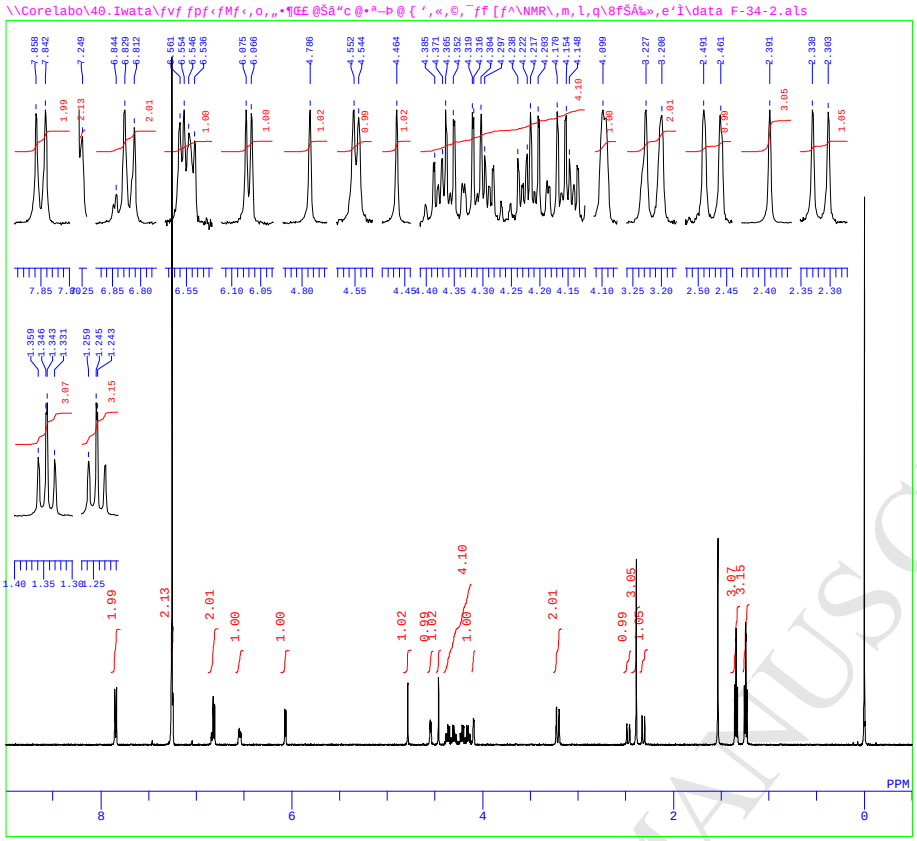
8e



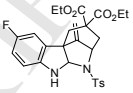
DFILE data F-31-2-bcm.als
COMNT single pulse decoupled gated NOE
DATIM 2013-04-17 02:21:55
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 4400
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 26.1 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 54



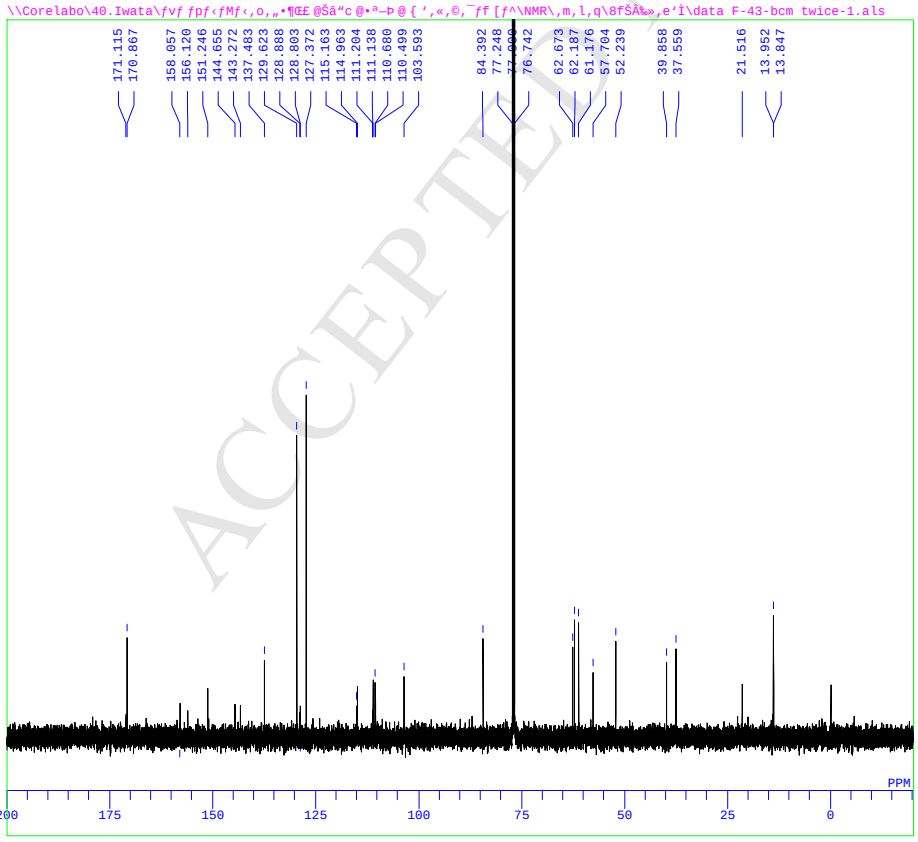
8e



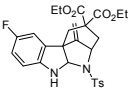

```
DFILE  data F-34-2.als
COMNT  single_pulse
DATIM  2013-04-09 16:16:58
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS            8
ACQTM        1.7459 sec
PD           5.0000 sec
PW1            6.50 usec
IRNUC  1H
CTEMP         26.1 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            54
```



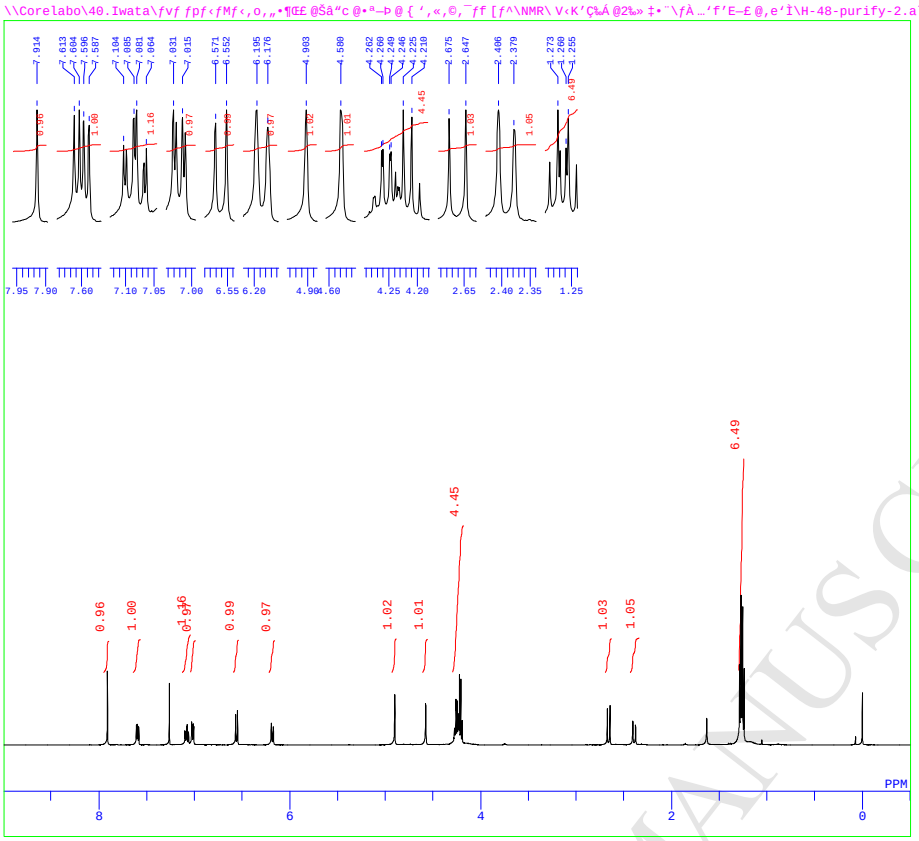
8i



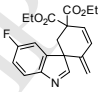

```
DFILE  data F-43-bcm twice-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-18 16:33:00
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          1024
ACQTM        0.8336 sec
PD           2.0000 sec
PW1            3.73 usec
IRNUC  1H
CTEMP        401.8 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            56
```



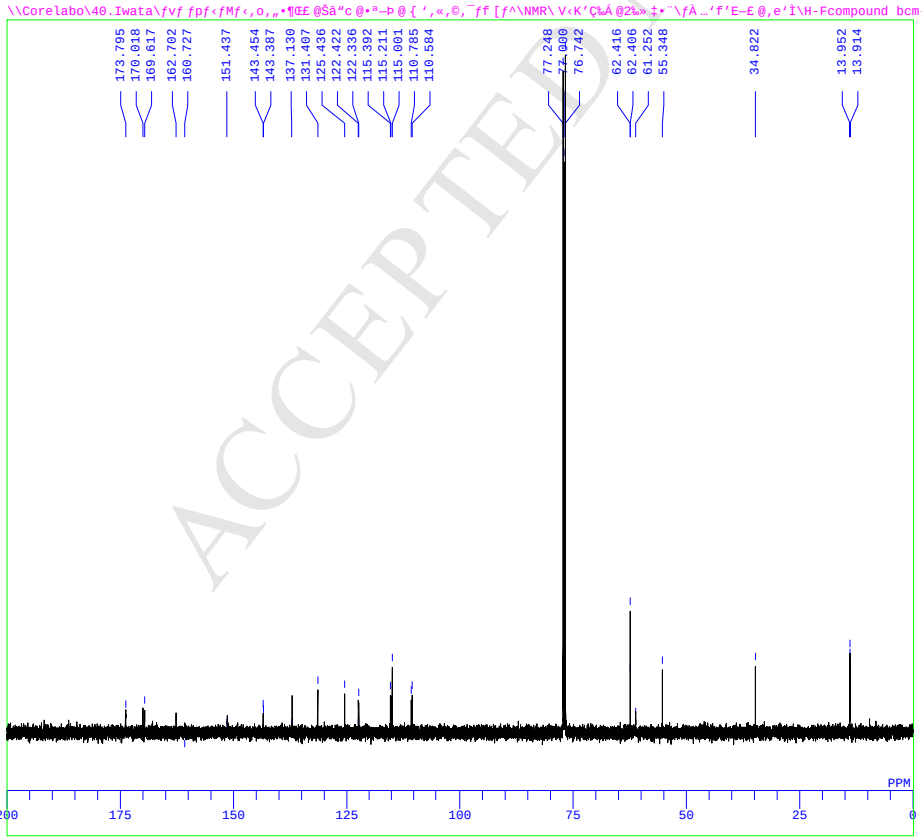
8i



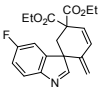
DFILE H-48-purify-2.als
COMNT single_pulse
DATIM 2015-01-17 10:08:22
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.82 usec
IRNUC 1H
CTEMP 20.8 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 48



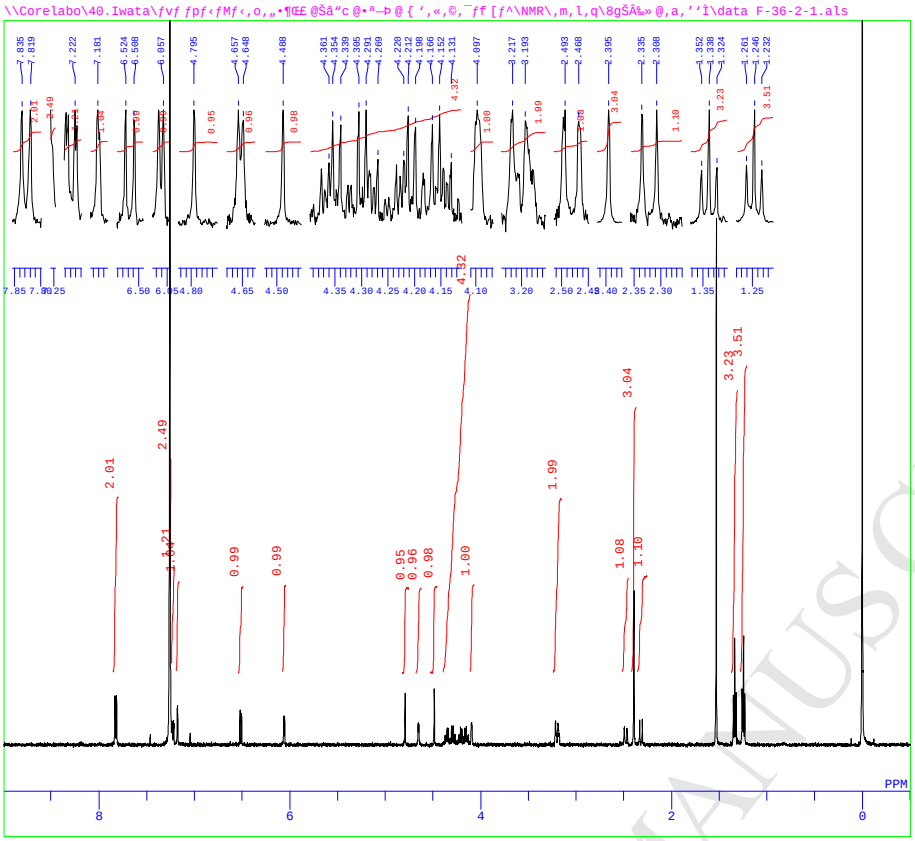
9b



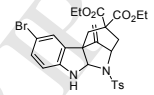
DFILE H-Fcompound bcm-1.als
COMNT single pulse decoupled gated NOE
DATIM 2015-01-16 14:03:37
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 1024
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.50 usec
IRNUC 1H
CTEMP 21.5 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 52



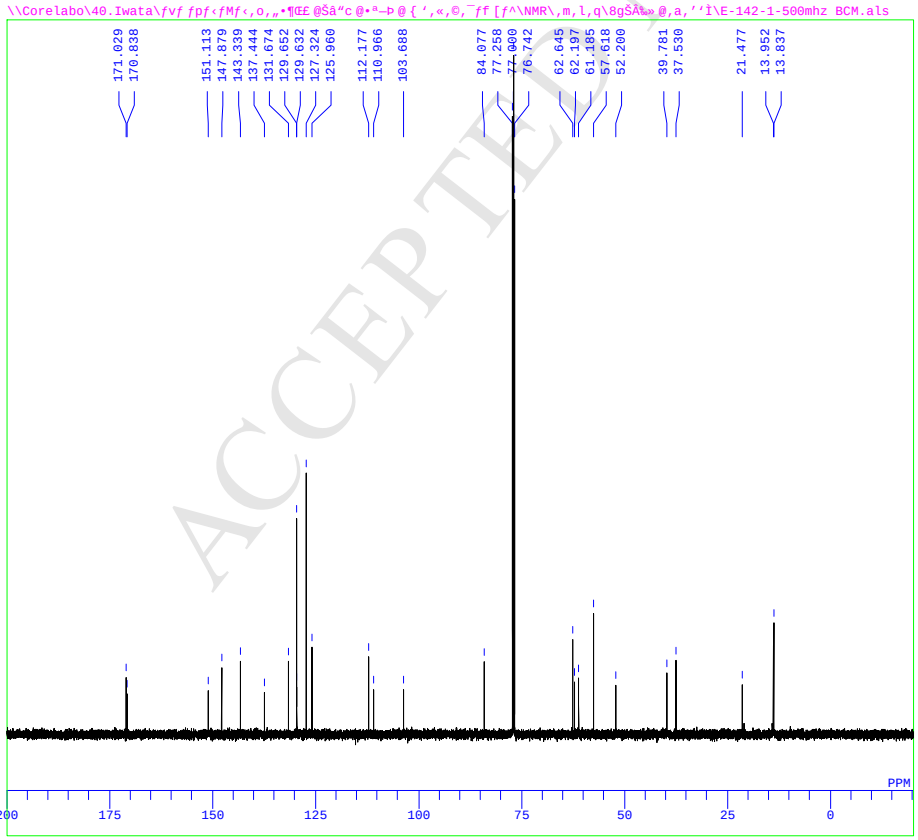
9b



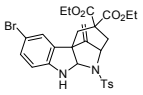
DFILE data F-36-2-1.als
COMNT single_pulse
DATIM 2013-04-12 11:19:40
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 137.3 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 56



8j

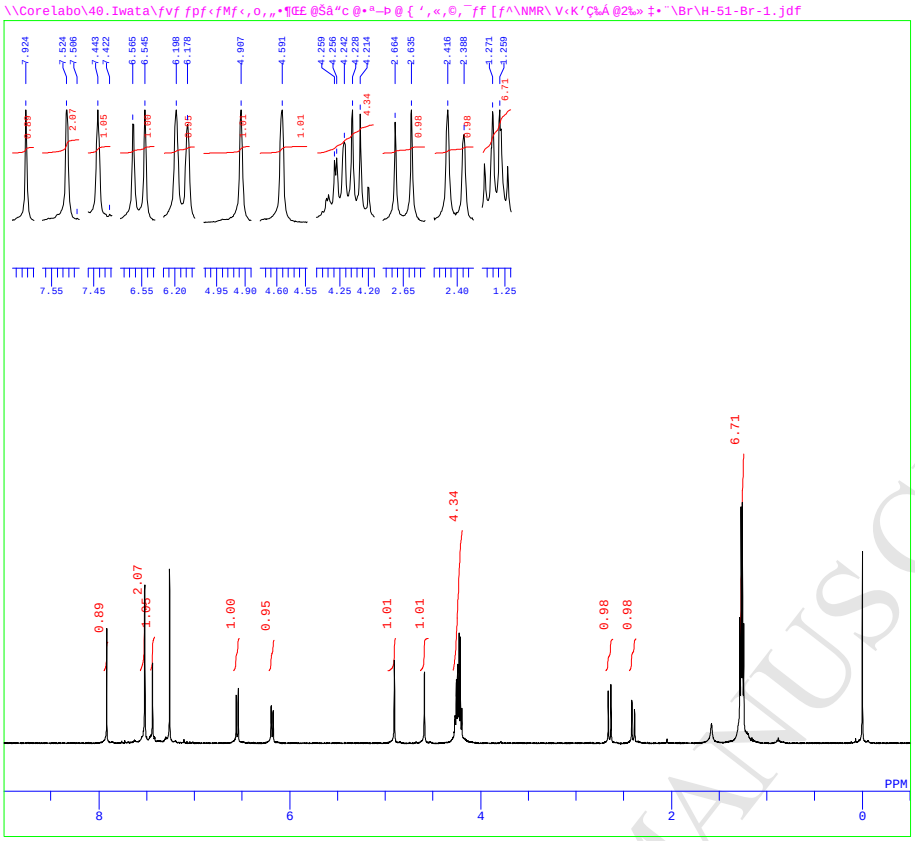


DFILE E-142-1-500mhz BCM.als
COMNT single pulse decoupled gated NOE
DATIM 2012-12-14 15:42:13
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 1024
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 27.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50

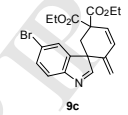


8j

\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @ŠÀ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\ V‹K’Ç‰Á @2‰» ‡•¨\Br\H-51-Br-1.jdf

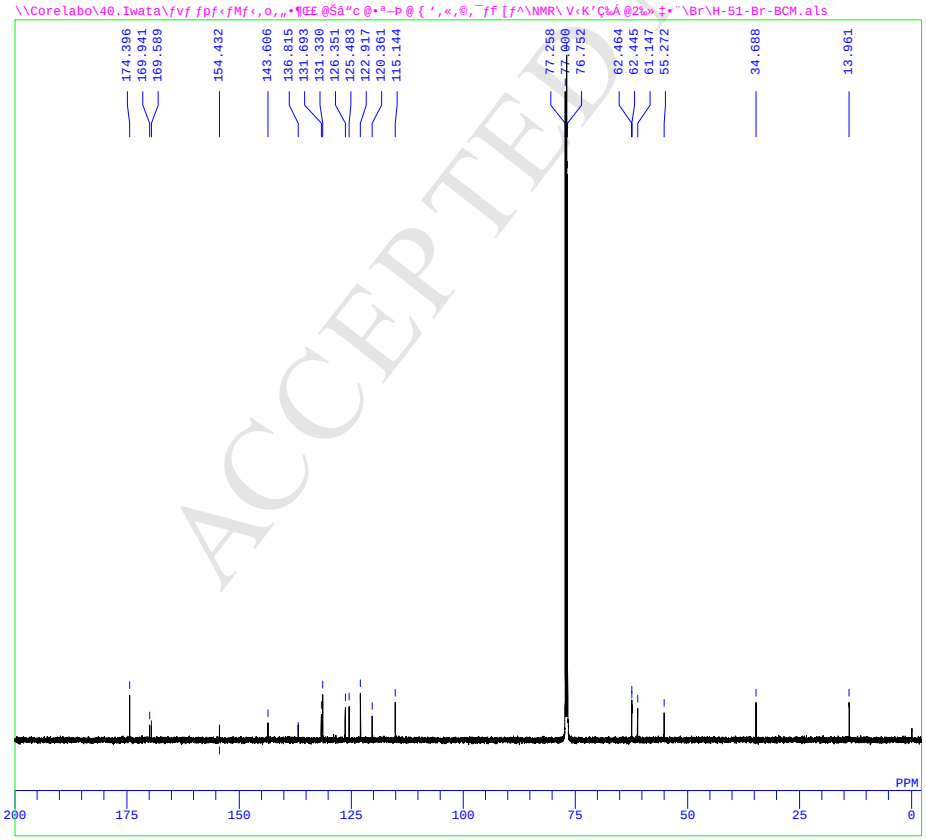


DFILE H-51-Br-1.jdf
COMNT single_pulse
DATIM 2015-03-12 21:21:56
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 16384
FREQU 9384.38 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.82 usec
IRNUC 1H
CTEMP 21.4 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 50

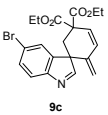


9c

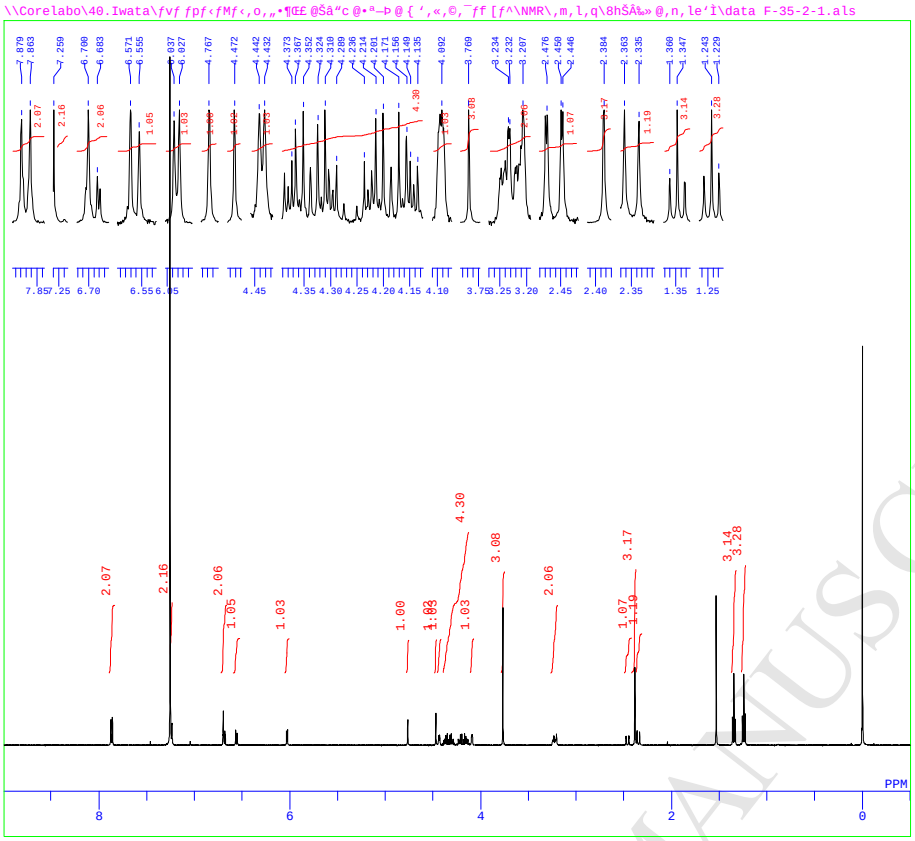
\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @ŠÀ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\ V‹K’Ç‰Á @2‰» ‡•¨\Br\H-51-Br-BCM.als



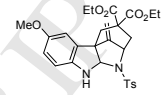
DFILE H-51-Br-BCM.als
COMNT single pulse decoupled gated NOE
DATIM 2015-03-13 06:50:26
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 32768
FREQU 39308.18 Hz
SCANS 12000
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.50 usec
IRNUC 1H
CTEMP 21.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50



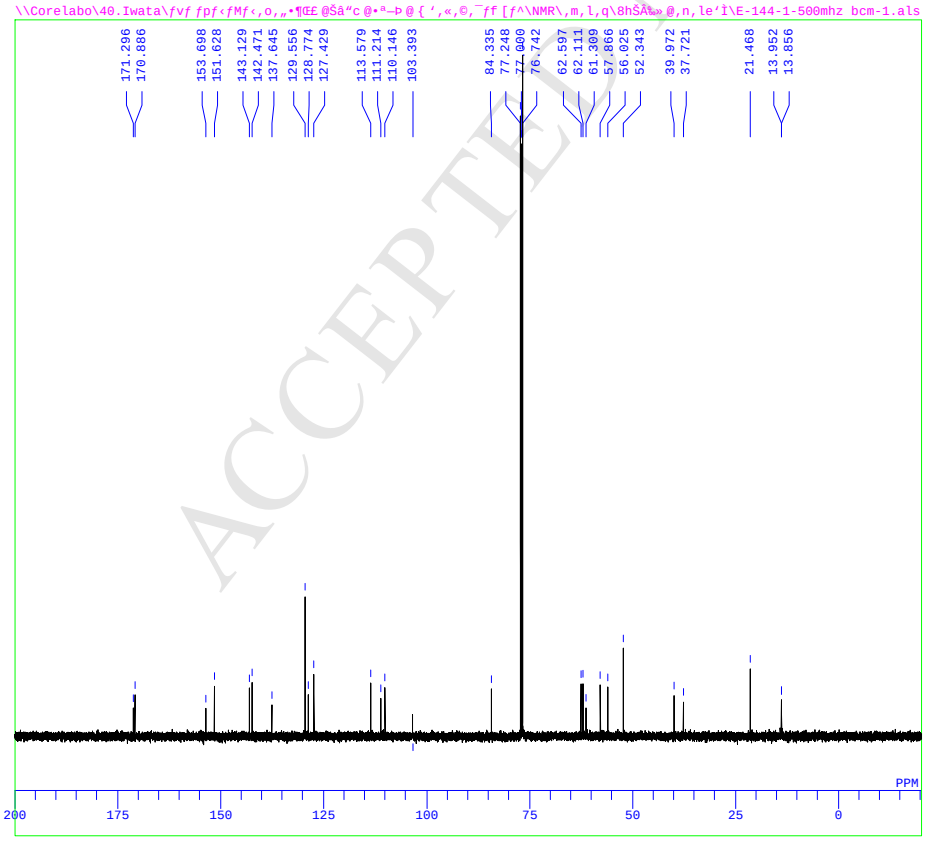
9c



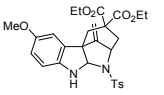

```
DFILE  data F-35-2-1.als
COMNT  single_pulse
DATIM  2013-04-12 11:15:53
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS            8
ACQTM        1.7459 sec
PD           5.0000 sec
PW1            6.50 usec
IRNUC  1H
CTEMP          117.5 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            54
```



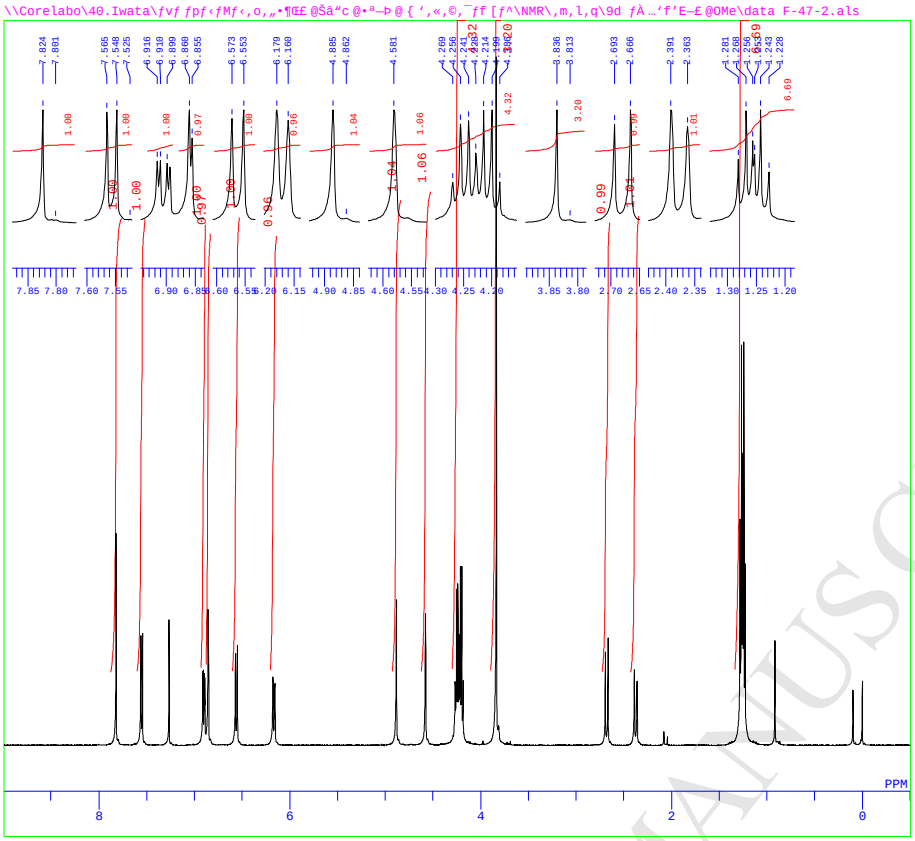
8k



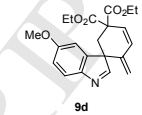

```
DFILE  E-144-1-500mhz bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2012-12-14 16:36:07
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          1024
ACQTM        0.8336 sec
PD           2.0000 sec
PW1            3.73 usec
IRNUC  1H
CTEMP          27.5 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            58
```



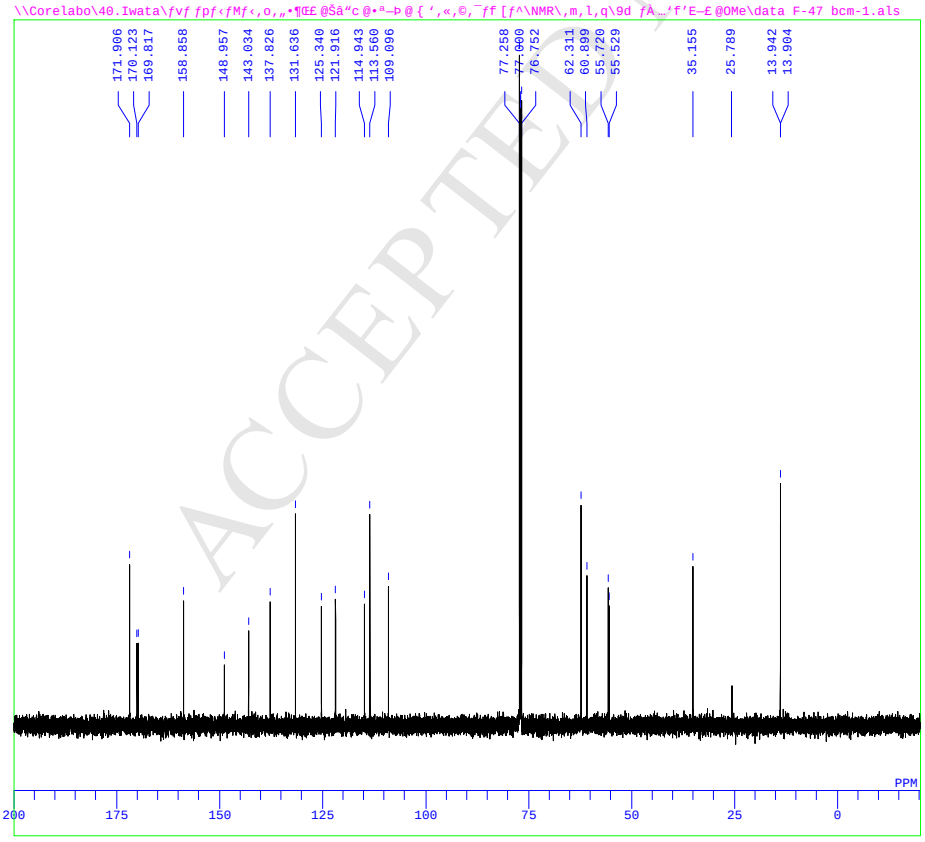
8k



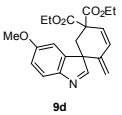

```
DFILE  data F-47-2.als
COMNT  single_pulse
DATIM  2013-04-20 14:35:47
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1             6.50 usec
IRNUC  1H
CTEMP          25.6 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            42
```



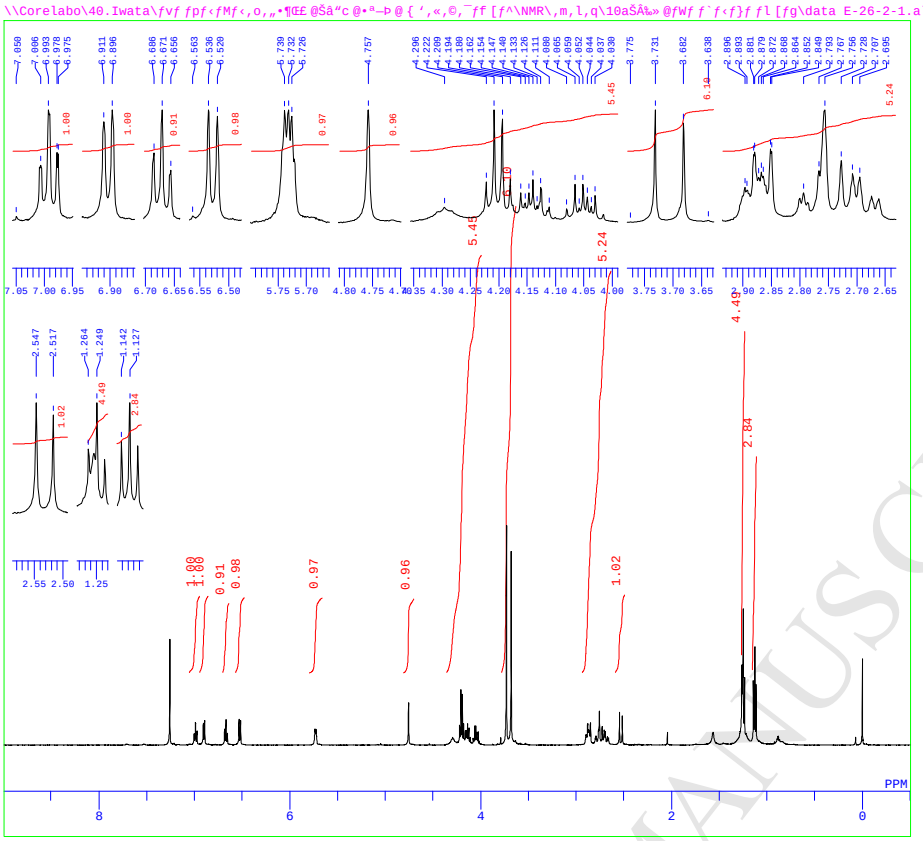
9d



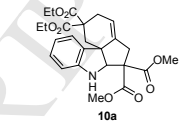

```
DFILE  data F-47 bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-20 14:32:47
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS           964
ACQTM         0.8336 sec
PD            2.0000 sec
PW1             3.73 usec
IRNUC  1H
CTEMP          25.4 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            54
```



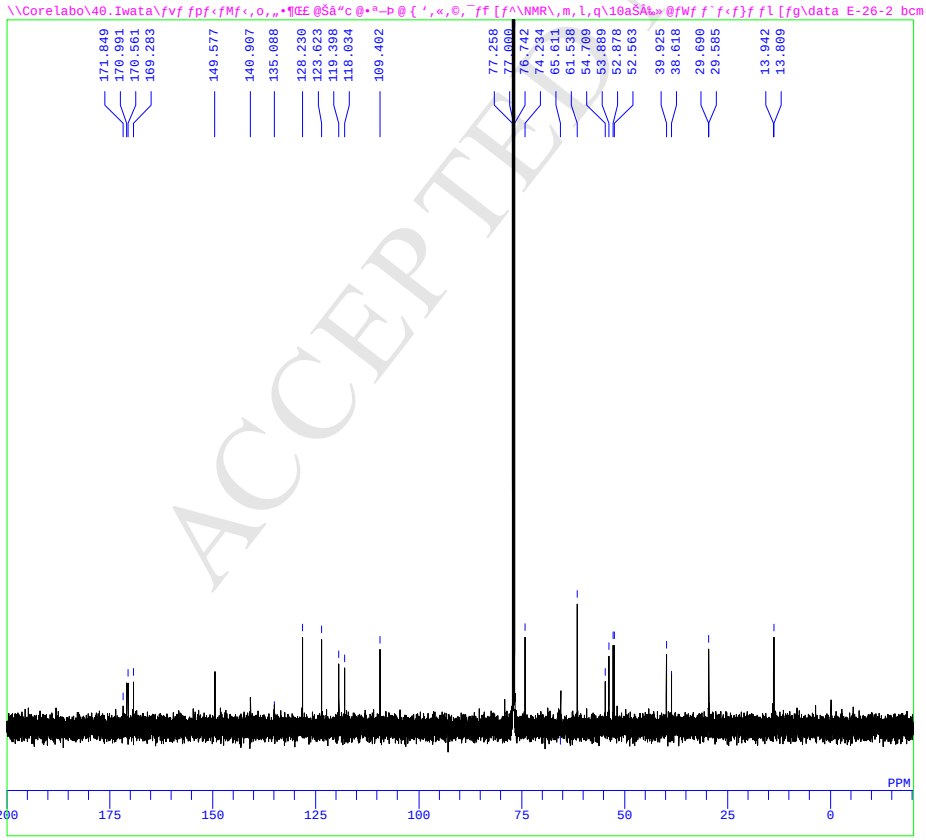
9d



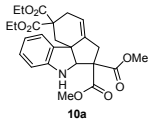
```
DFILE  data E-26-2-1.als
COMNT  single_pulse
DATIM  2013-04-23 09:43:28
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM         1.7459 sec
PD            5.0000 sec
PW1           6.50 usec
IRNUC  1H
CTEMP         25.3 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            46
```



10a

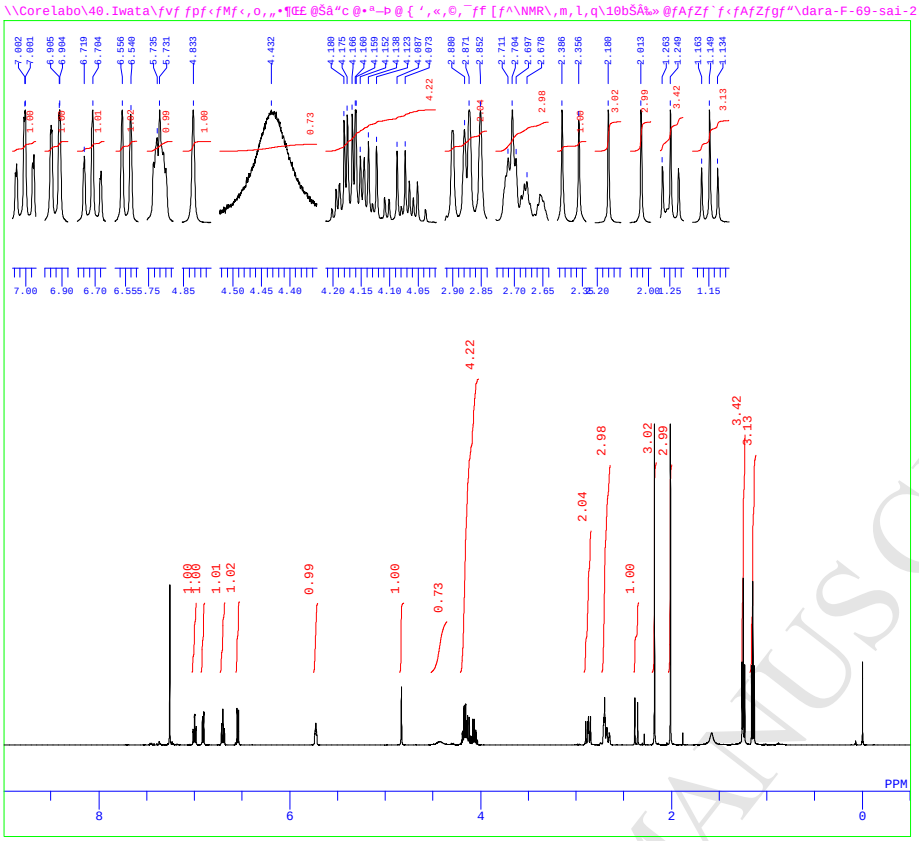


```
DFILE  data E-26-2 bcm-1.als
COMNT  single pulse decoupled gated NOE
DATIM  2013-04-23 10:33:34
OBNUC  13C
EXMOD  single_pulse_dec
OBFRQ        125.77 MHz
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS          1024
ACQTM         0.8336 sec
PD            2.0000 sec
PW1           3.73 usec
IRNUC  1H
CTEMP         25.4 c
SLVNT  CDCL3
EXREF         77.00 ppm
BF             0.12 Hz
RGAIN            54
```

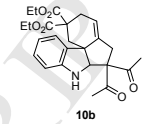


10a

\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @Šâ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\,m,l,q\10bŠÂ‰» @fAfZf`ƒ‹fAfZfgf“\dara-F-69-sai-2-1.als

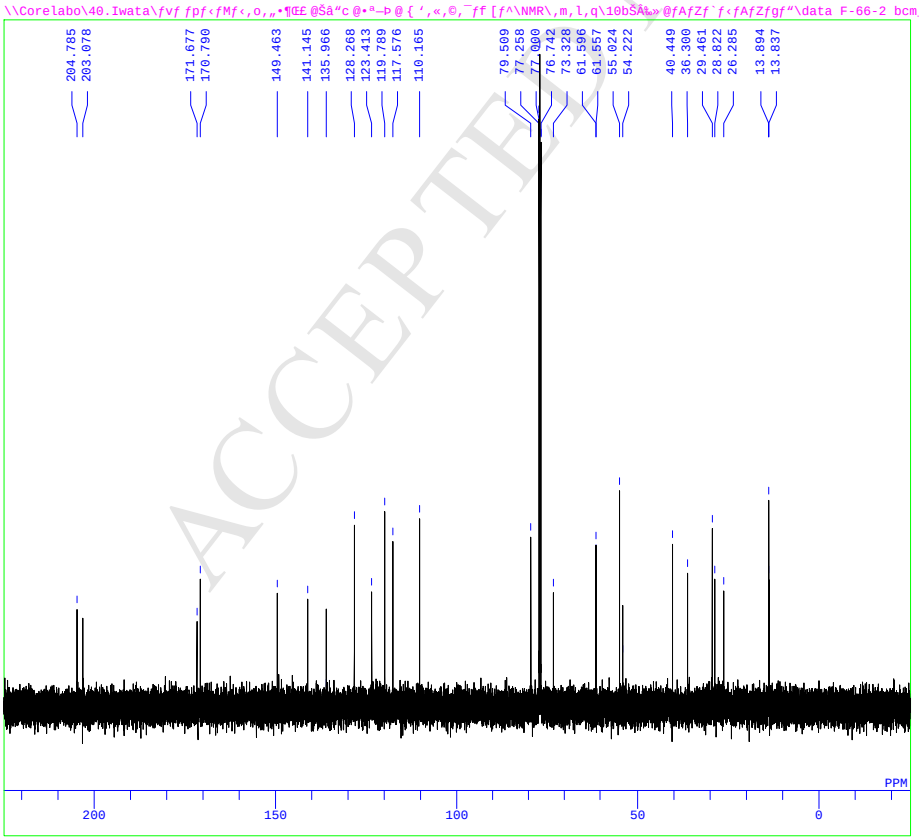


DFILE dara-F-69-sai-2-1.als
COMNT single_pulse
DATIM 2013-06-26 10:00:38
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 52428
FREQU 7507.39 Hz
SCANS 8
ACQTM 6.9835 sec
PD 5.0000 sec
PW1 6.50 usec
IRNUC 1H
CTEMP 26.4 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 46

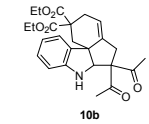


10b

\\Corelabo\40.Iwata\fvf fpf‹fMf‹,o,„•¶Œ£ @Šâ“c @•ª–Þ @ { ‘,«,©,¯ƒf [ƒ^\NMR\,m,l,q\10bŠÂ‰» @fAfZf`ƒ‹fAfZfgf“\data F-66-2 bcm_copy-1.als

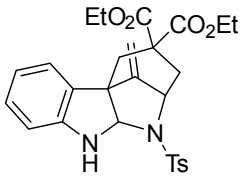


DFILE data F-66-2 bcm_copy-1.als
COMNT single pulse decoupled gated NOE
DATIM 2013-05-22 16:19:03
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 92
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.73 usec
IRNUC 1H
CTEMP 25.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50

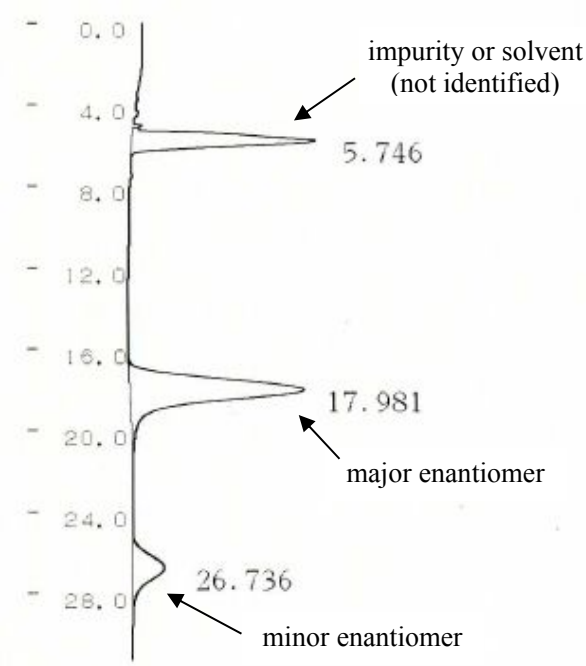


10b

HPLC chart



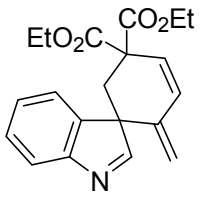
8a (65% ee)



H-69-2 (spiroindoline **8a**)
IC-3, 0.75ml/min, *n*-hexane : *i*-PrOH = 65 ; 35
254nm, (65% ee)

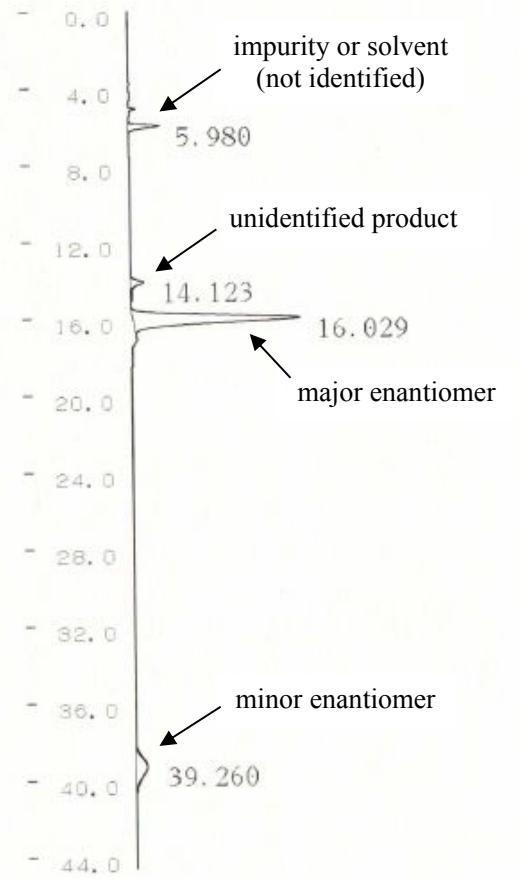
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	3	5.746	766457	20394	V		30.3347	
	18	17.981	1448693	19529			57.336	**65% ee**
	19	26.736	311522	3579			12.3293	
		TOTAL	2526671	43502			100	



9a (71% ee)

C-R8A CHROMATOPAC CH=1 Report No.=115 DATA=1:@CHRM1.C00 15/02/25 14:35:38



H-69-1 (spiroindole **9a**)
IC-3, 0.75ml/min, *n*-hexane : *i*-PrOH = 65 ; 35
UV 254nm, (71% ee)

** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	5	5.98	102623	7392			6.9899	
	27	14.123	62303	3023			4.2436	
	28	16.029	1113824	39399			75.8649	**71% ee**
	38	39.26	189418	2618			12.9017	
		TOTAL	1468168	52432			100	