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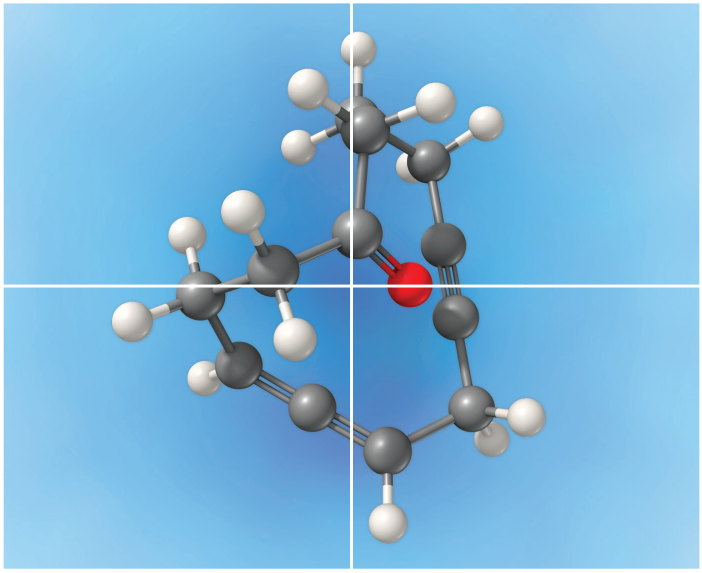

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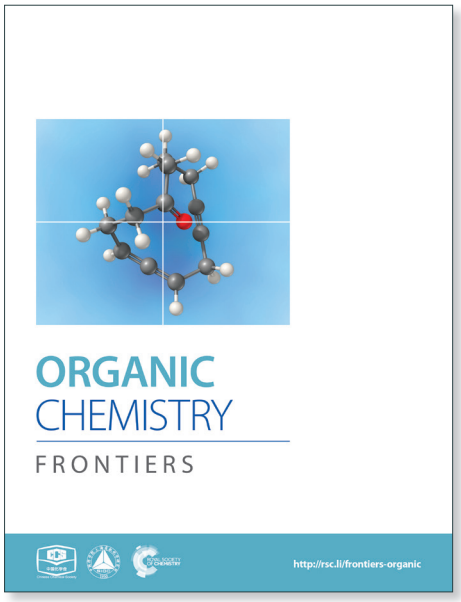


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ARTICLE TYPE

# Trienamine Catalysis with Linear Deconjugated 3,5-Dienones†

**Peng-Qiao Chen,[a] You-Cai Xiao,[a] Cai-Zhen Yue,[a] and Ying-Chun Chen*[a,b]**

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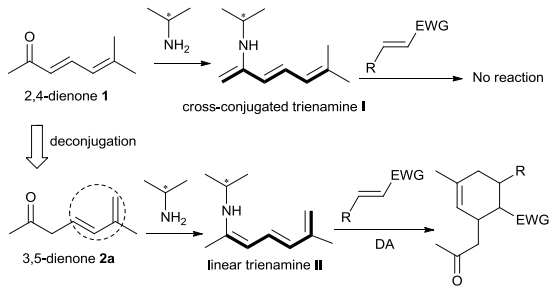
**An array of deconjugated linear 3,5-dienones with substantial substitutions have been successfully used in β,ε-regioselective Diels–Alder cycloadditions with 3-olefinic oxindole-based dienophiles via trienamine catalysis of cinchona-based primary amine, efficiently producing spirocyclic oxindole architectures with dense and diverse substitutions in high stereoselectivity (up to 99% ee, >19:1 d.r.).**

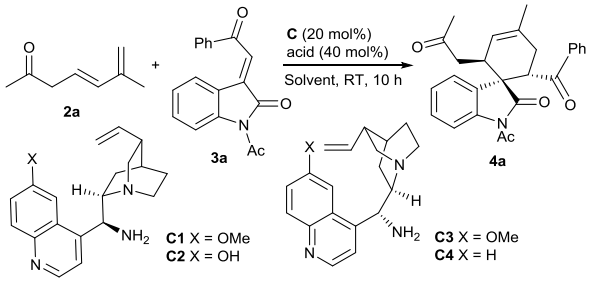
Asymmetric organocatalysis has been established as a powerful strategy for the development of stereoselective reactions of saturated or unsaturated carbonyl compounds via diverse catalytic modes, such as enamine, dienamine, iminium, or vinylogous iminium catalysis, leading to C-C or C-X bond formations at α, β, γ, or δ-sites.[1] Recently, trienamine catalysis has been reported as a new activation mode for 2,4-dienal substrates, furnishing more remote β,ε-regioselective Diels–Alder cycloaddition reactions with an array of electron-deficient dienophiles to construct multifunctional six-membered carbo- or heterocycles, generally in excellent stereoselectivity.[2] However, the similar catalytic strategy could not be simply switched to analogous 2,4-dienone substances, and only those with δ,δ-disubstituted and α′-aryl or styryl patterns could participate in the desired β,ε-regioselective cycloadditions via trienamine catalysis.[3]

In fact, almost no reaction occurred for the combination of linear 2,4-dienone **1** with an α′-enolizable methyl group and diverse dienophiles in the presence of primary amine catalyst, probably because the cross-conjugated trienamine intermediate **I** would be preferably generated, as outlined in Scheme 1. Very recently, we developed a new strategy, in which the previously positioned δ,ε-C=C bond could perform as an inducing group for the formation of linear trienamines from interrupted cyclic 2,5-dienones bearing α′-CH group.[4] Inspired by such observation, we envisaged that the similar inducing effect would be applicable to deconjugated linear 3,5-dienone **2a**, rendering the formation of requisite extended trienamine intermediate and facilitating the later β,ε-regioselective cycloaddition process.




**Scheme 1.** A deconjuagation strategy for linear trienamine catalysis with 3,5-dieone substrate.

**Table 1** Screening studies of Diels–Alder cycloaddition of 3,5-dienone **2a** and dienophile **3a**[a]



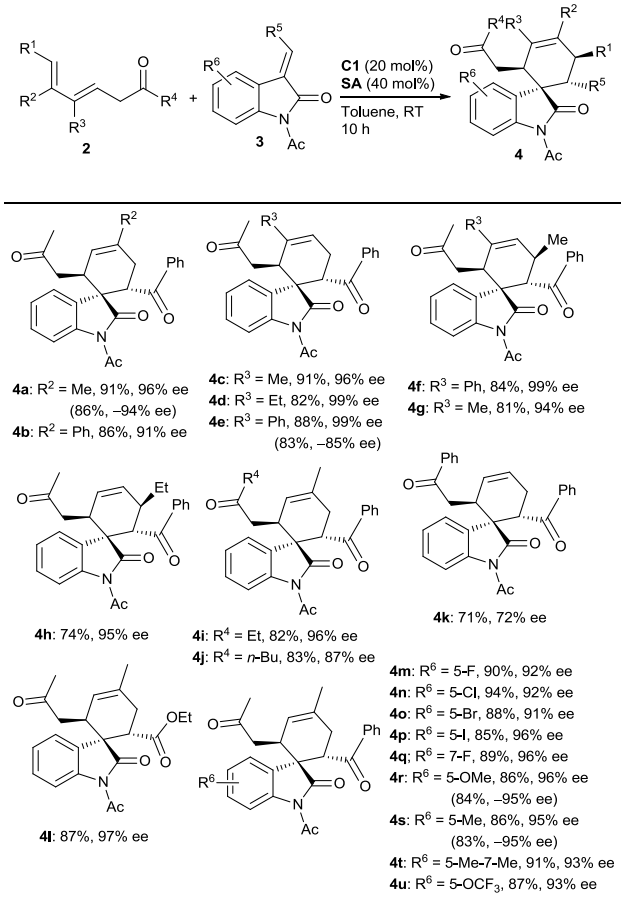

| Entry | 1 | Solvent | Acid | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **C1** | Toluene | SA | 91 | 96 |
| 2 | **C2** | Toluene | SA | 78 | 87 |
| 3 | **C3** | Toluene | SA | 86 | –94 |
| 4 | **C4** | Toluene | SA | 86 | –90 |
| 5 | **C1** | $CHCl_3$ | SA | 84 | 92 |
| 6 | **C1** | DCE | SA | 86 | 87 |
| 7 | **C1** | DCM | SA | 86 | 89 |
| 8 | **C1** | THF | SA | 91 | 90 |
| 9 | **C1** | Dioxane | SA | 84 | 92 |
| 10 | **C1** | MeCN | SA | 78 | 67 |
| 11 | **C1** | Toluene | BA | 84 | 87 |
| 12 | **C1** | Toluene | OFBA | 89 | 89 |
| 13[d] | **C1** | Toluene | SA | 86 | 87 |
| 14[e] | **C1** | Toluene | SA | 89 | 87 |

[a] Unless noted otherwise, reactions were performed with 3,5-dienone **2a** (0.2 mmol), 3-olefinic oxindole **3a** (0.1 mmol), amine **C** (20 mol%) and acid (40 mol%) in solvent (1.0 mL) at rt in 10 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral column; d.r. > 19:1 by $^1$H NMR analysis. [d] With 10 mol% of **C1** and 20 mol% SA for 18 h. [e] At 1.0 mmol scale for 12 h.

Based on the above-mentioned considerations, the initial investigation was set up for the model reaction of 6-methylhepta-4,6-dien-2-one **2a**, which was effectively obtained by the deconjugation of 6-methylhepta-3,5-dien-2-one **1**,[5] with 3-olefinic oxindole **3a**,[6] in the presence of 9-amino-9-deoxyepiquinine (**C1**, 20 mol%) and salicylic acid (SA, 40 mol%).[7] To our gratification, the desired Diels–Alder reaction occurred smoothly in toluene at room temperature, and the spirocyclic oxindole **4a** was produced in remarkable

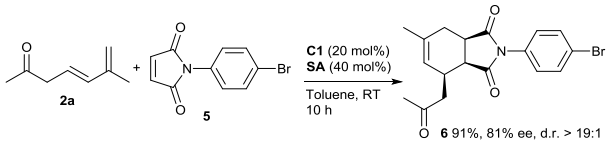
stereoselectivity and with good yield (Table 1, entry 1).[8] It should be pointed out that the cycloaddition reaction did not occur in the absence of primary amine catalyst, indicating the HOMO-activation of β,γ,δ,ε-diene moiety by the formation of conjugated enamine intermediate is necessary. Consequently, other catalytic parameters were briefly screened. Amine **C2** with a free OH group provided a decreased ee value and lower yield (entry 2). In addition, both 9-amino-9-deoxyepiquinidine (**C3**) and 9-amino-9-deoxyepicinchonine (**C4**) delivered the product with an opposite configuration, also in high stereoselectivity (entries 3 and 4). The cycloaddition could take place in an array of solvents, though diminished enantioselectivity was generally observed (entries 5–10). Lower enantiocontrol was also produced when benzoic acid (BA) or *o*-fluorobenzoic acid (OFBA) was used (entries 11 and 12). In addition, the reaction proceeded smoothly with 10 mol% of catalyst, while the enantiocontrol was slightly reduced (entries 13). The similar inferior data were observed at a larger scale under the optimized conditions (entry 14).

**Table 2** Substrate scope and limitations of cycloadditions of deconjugated 3,5-dienones **2** and 3-olefinic oxindoles **3**[a,b,c]




[a] Unless noted otherwise, reactions were performed with 3,5-dienone **2** (0.2 mmol), dienophile **3** (0.1 mmol), amine **C1** (20 mol%) and **SA** (40 mol%) in toluene (1.0 mL) at rt for 10 h. [b] Isolated yield. [c] Ee was determined by chiral HPLC analysis; d.r. >19:1. [d] The absolute configuration of **4i** was determined by X-ray analysis, see SI. The other products were assigned by analogy. [e] Data in parentheses were obtained with amine **C3**.

With the optimal reaction conditions in hand, we then investigated a variety of 3,5-dienones and 3-olefinc oxindoles catalyzed by amine **C1** (20 mol%) and **SA** (40 mol%) in toluene at room temperature. The results are summarized in Table 2. At first, an array of deconjugated 3,5-dienones **2** with diverse substituted patterns were investigated in the reaction with dienophile **3a**. Both aliphatic and aromatic substituents could be well compatible in the γ- or δ-position of 3,5-dienones **2**, delivering the corresponding cycloadducts **4a**–**4e** without apparent influence on the reaction outcome. It was gratifying that γ,ε-disubstituted 3,5-dienones exhibited good reactivity, and products **4f** and **4g** were obtained in good yield and with excellent diastereo- and enantioselectivity. When a single ethyl group was introduced at the ε-position of a 3,5-dienone, the desired cycloadduct **4h** was received in moderate yield but still with outstanding enantioselectivity. Notably, other 3,5-dienones carrying a larger α′-alkyl group could also be successfully employed and provided cycloadducts **4i** and **4j** in good results. A 3,5-dienone with an α′-phenyl group without substitution on the backbone still exhibited acceptable reactivity, though modest yield and enantioselectivity was attained for product **4k**. Unfortunately, simple hepta-4,6-dien-2-one showed much lower reactivity, and very poor yield with bad stereoseletivity was observed. Moreover, the results seemed reasonable when the benzoyl group was replaced by an ethoxycarbonyl group, and cycloadduct **4l** was produced in high yield and with prominent enantioselectivity; but 3-olefinic oxindole with a β-phenyl group ($R^5$ = Ph) showed no reactivity. On the other hand, a spectrum of oxindole-based dienophiles **3** with diverse electron-withdrawing or donating- substituents were tested in the reaction with 6-methylhepta-4,6-dien-2-one **2a**. Pleasingly, the corresponding cycloadducts **4m**–**4u** were generally delivered with the similar good results. A few substrates were further explored by the catalysis of amine **C3**, generally affording the cycloadducts with an opposite configuration in excellent enantioselectivity (see more data in parentheses). It should be pointed out that remarkably diastereoselectivity (d.r. > 19:1) was universally achieved in the illustrated reactions.




**Scheme 2.** Asymmetric Diels–Alder reaction of maleimide.

To further expand the utility of this strategy, more electron-deficient dienophiles were explored in the reactions with 3,5-dienone **2a** under the similar catalytic conditions. It was found that a good ee value with a high yield could be obtained by using maleimide **5** with an *N*-aryl group. However, attempt to improve the stereocontrol at lower temperature resulted in no success. On the other hand, other potential dienophiles, such as β-nitrostyrene, were further investigated, but generally failed to give the desired cycloadducts, and decomposition or other transformations of 3,5-dienone **2a** were observed when harsher conditions were applied.[9] Therefore, more explorations remain to be conducted to

expand the application of current catalytic protocol.

In conclusion, we have successfully accomplished the trienamine catalysis of linear polyunsaturated ketones with substantial substitutions by using deconjugated 3,5-dienones as the substrates, which is previously not feasible with conjugated 2,4-dienone analogues. Highly stereoselective and β,ε-regioselective Diels−Alder cycloadditions were developed with 3-olefinic oxindole-based dienophiles under the catalysis of readily available cinchona-based primary amine, efficiently producing a spectrum of spirocyclic oxindole architectures with dense and diverse substitutions. Currently, more investigation is conducted to develop asymmetric reactions with polyunsaturated carbonyl substances via aminocatalysis in this laboratory.

We are grateful for the financial support from the National Natural Science Foundation of China (21125206, 21372160 and 21321061) and the National Basic Research Program of China (973 Program, 2010CB833300)

## Notes and references

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[b] *College of Pharmacy, Third Military Medical University, Chongqing 400038, China.*

† Electronic Supplementary Information (ESI) available: Experimental procedures, structural proofs, CIF file of enantiopure product **4i** (CCDC 992018). See DOI: 10.1039/b000000x/

‡ Footnotes should appear here.

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9 For more details, see the Supplentary Information.

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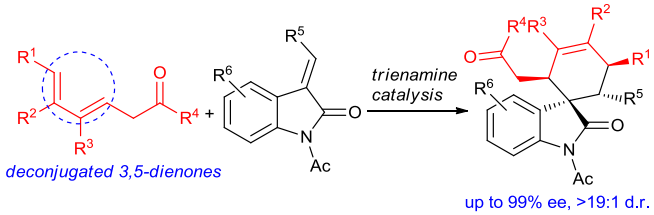
Deconjugated linear 3,5-dienones with substantial substitutions were used in β,ε-regioselective Diels–Alder cycloadditions with 3-olefinic oxindoles via trienamine catalysis of cinchona-based primary amine.



# Trienamine Catalysis with Linear Deconjugated 3,5-Dienones

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**Supporting Information**

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## 1. General methods

NMR data were obtained for $^{1}H$ at 400 MHz, and for $^{13}C$ at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. In each case, enantiomeric ratio was determined by HPLC analysis on a chiral column in comparison with authentic racemate, using a Daicel Chiralcel OD-H Column (250 x 4.6 mm), Chiralpak AD-H Column (250 x 4.6 mm) or Chiralpak IC Column (250 x 4.6 mm). UV detection was monitored at 220 nm or 254 nm. Optical rotation was examined in $CHCl_3$ solution at 20 °C. Column chromatography was performed on silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and $I_2$ were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted.

## 2. Preparation of 3,5-dienone substrates

**Procedure A**: The 3,5-dienone substrates **2** were synthesized according to the literature procedures from *α,β*-unsaturated aldehydes.[1,2]

(1) Y. Zou, D. Garayalde, Q. Wang, C. Nevado and A. Goeke, *Angew. Chem., Int. Ed*., 2008, **47**, 10110.

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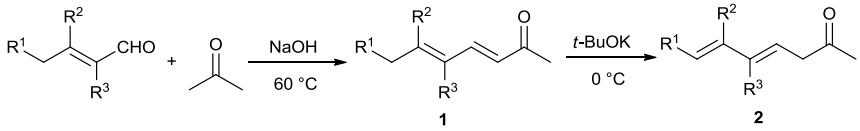
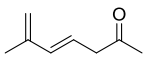
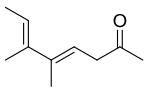



To a solution of *α,β*-unsaturated aldehyde in acetone was added NaOH. The mixture was stirred at 60 °C for 1.5 h, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 50:1) gave 2,4-dienone **1** as a yellow oil. To a solution of *t*-BuOK in DMSO was added **1** in an ice bath. After 5 min, the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether /EtOAc = 50:1) gave **2** as a colorless oil.

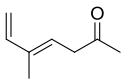



**6-Methylhepta-4,6-dien-2-one**: $^{1}H$ NMR (400 MHz, $CDCl_3$): δ = 6.15 (d, *J* = 15.6 Hz, 1H), 5.73-5.65 (m, 1H), 4.90 (s, 1H), 4.88 (s, 1H), 3.18 (d, *J* = 7.2 Hz, 2H),

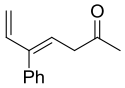
2.12 (s, 3H), 1.80 (s, 3H) ppm.



**5,6-Dimethylocta-4,6-dien-2-one**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.06 (d, *J* = 15.6 Hz, 1H), 5.64-5.59 (m, 1H), 5.46 (t, *J* = 7.2 Hz, 1H), 3.19 (d, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.69 (s, 3H) ppm.

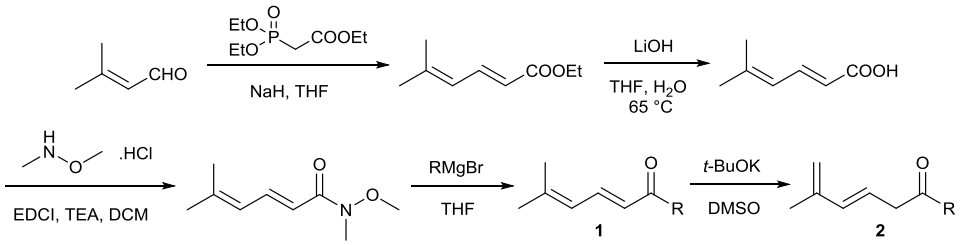


**Methylhepta-4,6-dien-2-one**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.42 (dd, *J* = 17.6 Hz, *J* = 10.4 Hz, 1H), 5.67 (t, *J* = 7.2 Hz, 1H), 5.27-5.20 (m, 1H), 5.05-5.01 (m, 1H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.76 (s, 3H) ppm.



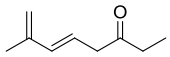
**5-Phenylhepta-4,6-dien-2-one**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.34 (m, 3H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.61 (dd, *J* = 17.2 Hz, *J* = 10.4 Hz, 1H), 5.89 (t, *J* = 7.2 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 17.2 Hz, 1H), 3.08 (d, *J* = 7.2 Hz, 2H), 2.05 (s, 3H) ppm.

**Procedure B:** 3,5-Dienones **2** with other α′-group were synthesized from 3-methylbut-2-enal.



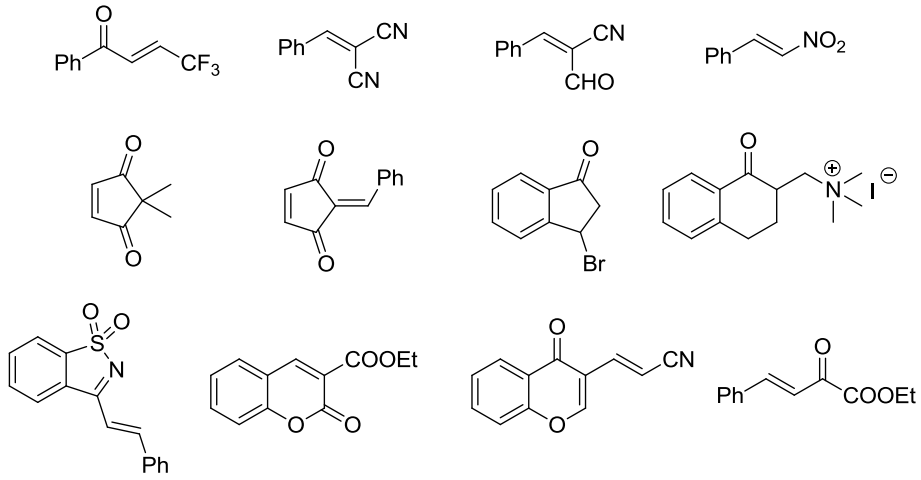

To a solution of ethyl 2-(diethoxyphosphoryl)acetate in dry THF was added NaH in an ice bath. The mixture was stirred at rt for 10 min, then 3-methylbut-2-enal was added. After a specific time, the reaction was quenched by cool water, and the mixture was extracted with EtOAc. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude ester was stirred with LiOH at 65 °C in a mixed solution of THF and $H_2O$ overnight. After completion, the mixture was extracted with EtOAc and the organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel gave the acid as a white solid. To a solution of acid was added EDCI, TEA and *N*,*O*-Dimethylhydroxylamine hydrochloride in DCM. The mixture was stirred at rt for 8 h, and extracted with EtOAc. The organic layer was collected, dried over anhydrous sodium

sulfate and concentrated under reduced pressure. Flash chromatography on silica gel gave Wenreib amind as a colorless oil. To a solution of RMgBr in try THF was added amide in an ice bath. After 10 min, the reaction was quenched with cool water, and the mixture was extracted with EtOAc. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography on silica gel gave **1** as a yellow oil. Then a similar deconjugation procedure as outlined above was conducted to give **2** as a colorless oil.

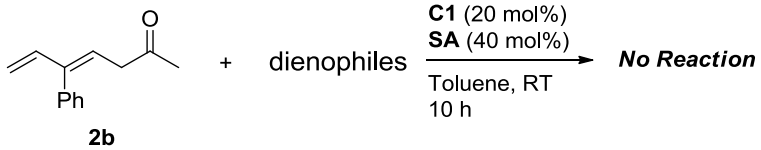


**7-Methylocta-5,7-dien-3-one**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.21 (d, *J* = 15.2 Hz, 1H), 5.79-5.71 (m, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 3.22 (d, *J* = 7.2 Hz, 2H), 2.48 (q, *J* = 7.2 Hz, 2H), 1.85 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

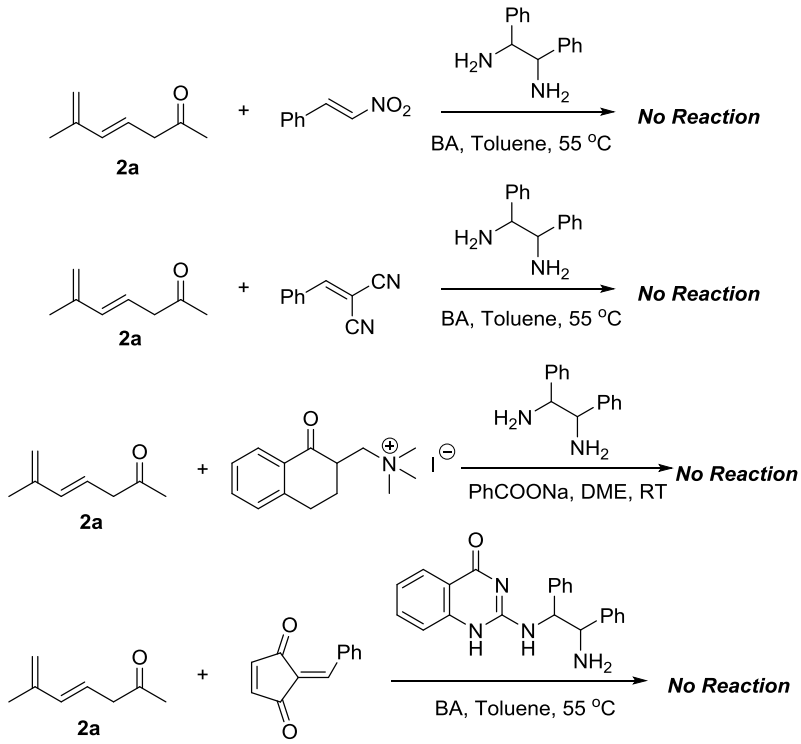
### 3. More screening studies on different electron-deficient dienophiles



To further expand the utility of this strategy, more electron-deficient dienophiles were explored in the reaction with 3,5-dienone **2a** under the similar catalytic conditions. Unfortunately, the dienophiles as outlined in the above scheme did not react with 3,5-dienone **2a** and failed to give the desired cycloadducts.



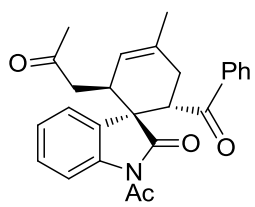

More reactive 3,5-dienone **2b** was applied to the Diels–Alder reaction but also failed.




Other catalytic parameters were briefly screened. But almost no reaction was observed in the presence of different primary amine.

## 4. General procedure for the Diels–Alder reaction of 3,5-dienones

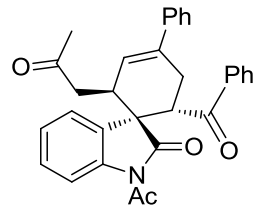
The reaction was performed with 3-olefinic oxindole **3** (0.10 mmol), 3,5-dienone **2** (0.20 mmol), catalyst **C1** (0.02 mmol) and SA (0.04 mmol) in toluene (1 mL) at room temperature. After completion, product **4** was obtained by flash chromatography on silica gel (petroleum ether/EtOAc = 8:1).



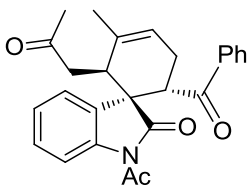

**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4-methyl-2-(2-oxopropyl)spiro[cyclohex [3]ene-1,3'-indolin]-2'-one (4a): 4a** was obtained as a colorless oil in 91% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralcel OD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.03 min, $t_{minor}$ = 5.43 min; $[\alpha]_D^{20}$ = -19.6 (*c* = 1.45 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 5.43(d, *J* = 4.0 Hz, 1H), 4.25 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.28

(dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), 2.96 (s, 1H), 2.60 (dd, *J* = 18.4 Hz, *J* = 5.6 Hz, 1H), 2.46 (s, 3H), 2.43-2.38 (m, 2H), 2.14 (s, 3H), 1.83 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.6, 200.2, 181.1, 170.8, 139.8, 136.1, 133.6, 133.2, 132.7, 128.7, 128.4, 127.9, 124.6, 123.7, 122.8, 116.4, 49.2, 45.7, 45.0, 39.6, 31.9, 29.9, 26.5, 23.0 ppm; ESI HRMS: calcd. for $C_{26}H_{25}NO_4$+$Na^+$ 438.1676, found 438.1679.

Enantiomer of **4a** was obtained as a colorless oil in 86% yield after flash chromatography and the enantiomeric excess was determined to be –94% by HPLC analysis on Chiralcel OD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 6.76 min, $t_{minor}$ = 6.12 min; $[\alpha]_D^{20}$ = +21.5 (*c* = 3.82 in $CHCl_3$).

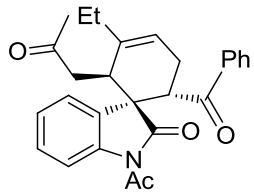



**(1*S*,2*S*,3*S*)-1'-Acetyl-3-benzoyl-1-(2-oxopropyl)-5-phenylspiro[cyclohex[5]ene-2,3'-indolin]-2'-one (4b): 4b** was obtained as a white semisolid in 86% yield after flash chromatography and the enantiomeric excess was determined to be 91% by HPLC analysis on Chiralpak IC-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 20.52 min, $t_{minor}$ = 15.00 min; $[\alpha]_D^{20}$ = -39.4 (*c* = 0.65 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46-7.26 (m, 8H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.14 (d, *J* = 5.2 Hz, 1H), 4.36 (dd, *J* = 12.4 Hz, *J* = 5.6 Hz, 1H), 3.98 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 3.22 (s, 1H), 3.13 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.92-2.85 (m, 1H), 2.54 (d, *J* = 18.0 Hz, 1H), 2.48 (s, 3H), 2.19 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.2, 200.0, 181.0, 170.8, 140.0, 139.6, 136.4, 136.0, 133.4, 132.5, 128.8, 128.7, 128.5, 128.1, 128.0, 126.2, 125.2, 124.9, 122.7, 116.5, 49.2, 45.8, 44.8, 40.2, 29.9, 29.4, 26.5 ppm; ESI HRMS: calcd. for $C_{31}H_{27}NO_4$+$Na^+$ 500.1832, found 500.1839.

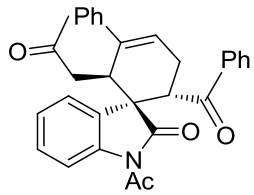



**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-3-methyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4c): 4c** was obtained as a white semisolid in 91% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 5.90 min, $t_{minor}$ = 10.73 min; $[\alpha]_D^{20}$ = -49.9 (*c* = 0.87 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.6 Hz,

2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 5.73(s, 1H), 4.18 (dd, *J* = 12.4 Hz, *J* = 6.4 Hz, 1H), 3.34 (dd, *J* = 18.8 Hz, *J* = 10.0 Hz, 1H), 2.80-2.75 (m, 2H), 2.50-2.45 (m, 5H), 2.19 (s, 3H), 1.69 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.6, 200.4, 181.2, 170.8, 139.9, 136.0, 135.1, 133.1, 132.5, 128.6, 128.4, 127.8, 124.7, 122.8, 121.7, 116.5, 49.5, 44.8, 43.4, 43.2, 29.8, 27.6, 26.4, 22.4 ppm; ESI HRMS: calcd. for $C_{26}H_{25}NO_4$+$Na^+$ 438.1676, found 438.1684.



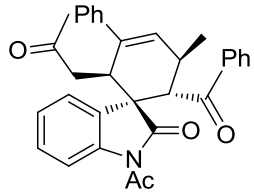

**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-3-ethyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4d): 4d** was obtained as a white semisolid in 82% yield after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.49 min, $t_{minor}$ = 9.43 min; $[\alpha]_D^{20}$ = -41.6 (*c* = 1.59 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (td, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.08 (td, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H), 5.73(s, 1H), 4.23 (dd, *J* = 12.8 Hz, *J* = 6.4 Hz, 1H), 3.26 (dd, *J* = 18.8 Hz, *J* = 10.0 Hz, 1H), 2.86-2.78 (m, 2H), 2.48-2.41 (m, 5H), 2.18 (s, 3H), 2.11-2.05 (m, 1H), 1.85-1.80 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.7, 200.4, 181.1, 170.8, 140.7, 139.9, 136.0, 133.1, 132.4, 128.6, 128.4, 127.8, 124.5, 123.0, 120.1, 116.4, 49.4, 44.9, 43.7, 41.7, 29.8, 28.0, 27.4, 26.4, 12.5 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_4$+$Na^+$ 452.1832, found 452.1834.



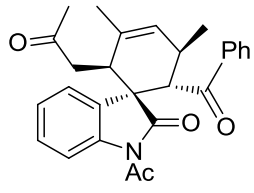

**(1*S*,2*S*,3*S*)-1'-Acetyl-1-benzoyl-3-(2-oxopropyl)-4-phenylspiro[cyclohex[4]ene-2,3'-indolin]-2'-one (4e): 4e** was obtained as a white semisolid in 88% yield after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.47 min, $t_{minor}$ = 10.92 min; $[\alpha]_D^{20}$ = +54.3 (*c* = 1.55 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.29-7.21 (m, 6H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.22(s, 1H), 4.32 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.37 (dd, *J* = 18.4 Hz, *J* = 10.4 Hz, 1H), 3.00 (dt, *J* = 19.2 Hz, *J* = 5.6 Hz, 1H), 2.70 (dd, *J* = 18.4 Hz, *J* = 12.8 Hz, 1H), 2.48 (s, 3H), 2.28 (d, *J* = 18.8 Hz, 1H), 2.08 (s, 3H) ppm; $^{13}$C NMR

(100 MHz, $CDCl_3$): δ = 206.5, 200.2, 181.0, 170.9, 140.2, 140.0, 136.0, 133.3, 132.4, 128.7, 128.5, 128.0, 127.9, 126.3, 124.9, 124.4, 122.8, 116.6, 49.6, 44.8, 43.9, 41.5, 29.7, 28.2, 26.4 ppm; ESI HRMS: calcd. for $C_{31}H_{27}NO_4$+$Na^+$ 500.1832, found 500.1833.

Enantiomer of **4e** was obtained as a white semisolid in 83% yield after flash chromatography and the enantiomeric excess was determined to be 85% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 11.58 min, $t_{minor}$ = 5.60 min; $[\alpha]_D^{20}$ = -68.4 (*c* = 1.08 in $CHCl_3$).

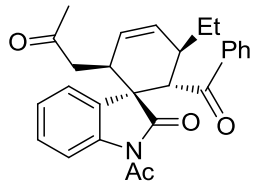



**(1*S*,2*S*,3*S*,6*R*)-1'-Acetyl-1-benzoyl-6-methyl-3-(2-oxopropyl)-4-phenylspiro[cyclohex[4]ene-2,3'-indolin]-2'-one (4f): 4f** was obtained as a white semisolid in 84% yield after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 6.65 min, $t_{minor}$ = 12.17 min; $[\alpha]_D^{20}$ = -125.0 (*c* = 0.26 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.47-7.43 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.29-7.28 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.11(s, 1H), 4.04 (d, *J* = 10.8 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 3.46 (dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), 3.12 (s, 1H), 2.30 (d, *J* = 18.8 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.7, 201.4, 179.5, 170.5, 140.0, 139.1, 138.7, 138.4, 133.3, 132.0, 131.7, 128.7, 128.5, 128.4, 128.3, 127.9, 126.5, 125.2, 123.7, 116.4, 51.8, 49.2, 44.1, 40.7, 33.1, 29.7, 26.3, 20.1 ppm; ESI HRMS: calcd. for $C_{32}H_{29}NO_4$+$Na^+$ 514.1989, found 514.1993.

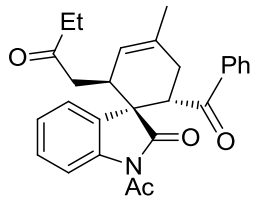



**(1*S*,2*S*,5*R*,6*S*)-1'-Acetyl-6-benzoyl-3,5-dimethyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4g): 4g** was obtained as a white semisolid in 81% yield after flash chromatography and the enantiomeric excess was determined to be 94% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 4.52 min, $t_{minor}$ = 6.81 min; $[\alpha]_D^{20}$ = -262.2 (*c* = 1.56 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.44-7.42 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 5.63(s, 1H), 3.92 (d, *J* = 10.8 Hz, 1H), 3.43 (dd, *J* = 19.2 Hz, *J* = 10.0 Hz, 1H),

2.89 (s, 1H), 2.83 (d, *J* = 10.4 Hz, 1H), 2.51 (d, *J* = 18.8 Hz, 1H), 2.20 (s, 3H), 2.16 (s, 3H), 1.74 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.0, 201.7, 180.0, 170.5, 139.0, 138.8, 133.2, 133.0, 131.8, 129.5, 128.5, 128.3, 128.1, 125.0, 123.7, 116.2, 51.7, 49.3, 43.4, 42.8, 32.7, 29.8, 26.3, 22.2, 20.3 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_4$+$Na^+$ 452.1832, found 452.1831.

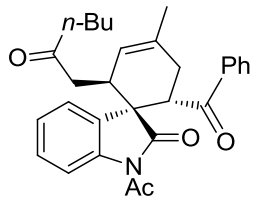



**(1*S*,2*S*,5*R*,6*S*)-1'-Acetyl-6-benzoyl-5-ethyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4h): 4h** was obtained as a colorless oil in 74% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Chiralpak AD-H column (10% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 6.79 min, $t_{minor}$ = 10.94 min; $[\alpha]_D^{20}$ = -231.9 (*c* = 0.52 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.49-7.41 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.01 (d, *J* = 10.0 Hz, 1H), 5.81-5.77 (m, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.43 (dd, *J* = 18.8 Hz, *J* = 9.6 Hz, 1H), 3.04-3.01 (m, 1H), 2.92-2.87 (m, 1H), 2.43 (dd, *J* = 18.8 Hz, *J* = 2.8 Hz, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 1.46-1.41 (m, 1H), 1.28-1.21 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 201.0, 179.3, 170.5, 138.8, 138.6, 133.2, 131.7, 130.9, 128.5, 128.4, 128.3, 125.1, 124.0, 116.2, 51.3, 47.1, 45.2, 38.7, 38.1, 29.9, 26.3, 25.9, 10.4 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_4$+$Na^+$ 452.1832, found 452.1833.

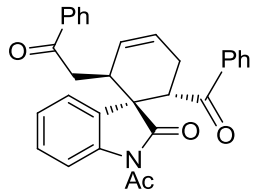



**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4-methyl-2-(2-oxobutyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4i): 4i** was obtained as a white semisolid in 82% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralcel OD-H column (10% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 7.15 min, $t_{minor}$ = 8.41 min; $[\alpha]_D^{20}$ = -21.3 (*c* = 1.56 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 5.44 (d, *J* = 3.2 Hz, 1H), 4.23 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.23 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 3.00 (s, 1H), 2.59 (dd, *J* = 18.4 Hz, *J* = 5.6 Hz, 1H), 2.54-2.36 (m, 7H), 1.84 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ =

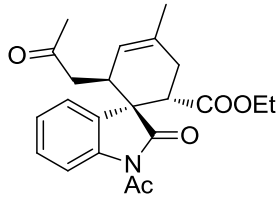
209.1, 200.2, 181.1, 170.8, 139.9, 136.1, 133.5, 133.2, 132.7, 128.7, 128.4, 127.9, 124.6, 123.9, 122.8, 116.4, 49.3, 45.7, 43.9, 39.5, 35.7, 32.0, 26.5, 23.0, 7.6 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_4$+$Na^+$ 452.1832, found 452.1837.



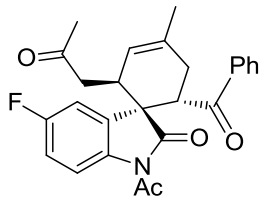

**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4-methyl-2-(2-oxohexyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4j): 4j** was obtained as a colorless oil in 83% yield after flash chromatography and the enantiomeric excess was determined to be 87% by HPLC analysis on Chiralpak AD-H column (10% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 7.57 min, $t_{minor}$ = 8.37 min; $[\alpha]_D^{20}$ = -23.0 (*c* = 1.59 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 6.8 Hz, 1H), 5.44(d, *J* = 4.0 Hz, 1H), 4.23 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.23 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.96 (s, 1H), 2.59 (dd, *J* = 18.4 Hz, *J* = 5.6 Hz, 1H), 2.46-2.35 (m, 7H), 1.84 (s, 3H), 1.56-1.48 (m, 2H), 1.33-1.26 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 208.8, 200.2, 181.0, 170.8, 139.9, 136.1, 133.4, 133.2, 132.8, 128.6, 128.4, 127.8, 124.6, 123.9, 122.8, 116.4, 49.3, 45.7, 44.2, 42.4, 39.4, 32.0, 26.5, 25.6, 23.0, 22.3, 13.8 ppm; ESI HRMS: calcd. for $C_{29}H_{31}NO_4$+$Na^+$ 480.2145, found 480.2146.



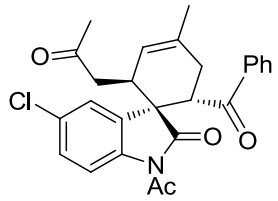

**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-2-(2-oxo-2-phenylethyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4k): 4k** was obtained as a white semisolid in 71% yield after flash chromatography and the enantiomeric excess was determined to be 72% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 10.13 min, $t_{minor}$ = 8.97 min; $[\alpha]_D^{20}$ = +42.7 (*c* = 0.82 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.58-7.35 (m, 7H), 7.29-7.26 (m, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.06 (s, 1H), 5.87 (s, 1H), 4.25 (dd, *J* = 12.0 Hz, *J* = 5.6 Hz, 1H), 3.88 (dd, *J* = 18.8 Hz, *J* = 9.2 Hz, 1H), 3.24 (s, 1H), 2.95 (d, *J* = 18.4 Hz, 1H), 2.85-2.80 (m, 1H), 2.59-2.51 (m, 1H), 2.38 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 200.2, 197.6, 180.7, 170.9, 140.0, 136.6, 136.1, 133.2, 133.1, 132.8, 129.8, 128.7, 128.6, 128.4, 128.0, 127.9, 126.2, 124.7, 123.0, 116.5, 49.5, 45.2, 40.1, 39.5, 27.5, 26.4 ppm; ESI HRMS: calcd. for $C_{30}H_{25}NO_4$+$Na^+$ 486.1676, found 486.1681.



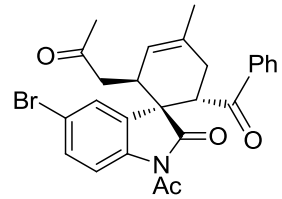

**(1*S*,2*S*,6*S*)-Ethyl 1'-acetyl-4-methyl-2'-oxo-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate (4l): 4l** was obtained as a colorless oil in 87% yield after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC analysis on Chiralpak AD-H column (40% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.62 min, $t_{minor}$ = 4.28 min; $[\alpha]_D^{20}$ = -15.4 (*c* = 1.7 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.4 Hz, 1H), 7.30 (td, *J* = 8.8 Hz, *J* = 1.6 Hz, 1H), 7.11-7.04 (m, 2H), 5.37 (d, *J* = 3.6 Hz, 1H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.33 (dd, *J* = 11.6 Hz, *J* = 6.8 Hz, 1H), 3.18 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.91 (s, 1H), 2.63 (dd, *J* = 18.4 Hz, *J* = 6.4 Hz, 1H), 2.54 (s, 3H), 2.49-2.48 (m, 1H), 2.28 (dd, *J* = 18.8 Hz, *J* = 2.4 Hz, 1H), 2.15 (s, 3H), 1.86 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.6, 180.9, 171.8, 170.9, 139.8, 133.1, 131.5, 128.2, 124.7, 123.0, 122.9, 116.2, 60.9, 48.7, 45.1, 42.0, 39.0, 30.1, 29.8, 26.5, 22.9, 13.7 ppm; ESI HRMS: calcd. for $C_{22}H_{25}NO_5$+$Na^+$ 406.1625, found 406.1633.




**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-5'-fluoro-4-methyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4m): 4m** was obtained as a white semisolid in 90% yield after flash chromatography and the enantiomeric excess was determined to be 92% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.03 min, $t_{minor}$ = 5.54 min; $[\alpha]_D^{20}$ = -13.1 (*c* = 2.01 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 9.2 Hz, *J* = 4.8 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.03 (td, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 5.44(d, *J* = 4.0 Hz, 1H), 4.24 (dd, *J* = 12.8 Hz, *J* = 6.4 Hz, 1H), 3.28 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.94 (s, 1H), 2.61 (dd, *J* = 18.4 Hz, *J* = 5.6 Hz, 1H), 2.44 (s, 3H), 2.40-2.31 (m, 2H), 2.16 (s, 3H), 1.84 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 200.2, 180.8, 170.6, 159.9 (d, $^1J_{C,F}$ = 240.6 Hz), 136.2, 135.8, 134.5 (d, $^3J_{C,F}$ = 8.4 Hz), 133.7, 133.4, 128.7, 128.4, 123.5, 117.5 (d, $^3J_{C,F}$ = 8.3 Hz), 114.0 (d, $^2J_{C,F}$ = 22.0 Hz), 110.5 (d, $^2J_{C,F}$ = 25.4 Hz), 49.3, 45.7, 44.9, 39.5, 31.8, 29.9, 26.3, 22.9 ppm; ESI HRMS: calcd. for $C_{26}H_{24}FNO_4$+$Na^+$ 456.1582, found 456.1583.

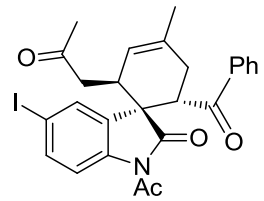


**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-5'-chloro-4-methyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4n): 4n** was obtained as a colorless oil in 94% yield after flash chromatography and the enantiomeric excess was determined to be 92% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 4.94 min, $t_{minor}$ = 5.34 min; $[\alpha]_D^{20}$ = -41.2 (*c* = 2.29 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.31 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 5.44(d, *J* = 4.0 Hz, 1H), 4.23 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 3.28 (dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), 2.93 (s, 1H), 2.61 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.45 (s, 3H), 2.40-2.31 (m, 2H), 2.15 (s, 3H), 1.85 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 206.6, 200.2, 180.6, 170.7, 138.4, 135.8, 134.6, 133.7, 133.4, 129.9, 128.7, 128.4, 127.7, 123.5, 123.1, 117.4, 49.2, 45.8, 44.9, 39.5, 31.8, 29.8, 26.3, 22.9 ppm; ESI HRMS: calcd. for $C_{26}H_{24}Cl^{35}NO_4$+$Na^+$ 472.1286, found 472.1292 ($Cl^{35}$), 474.1276 ($Cl^{37}$).

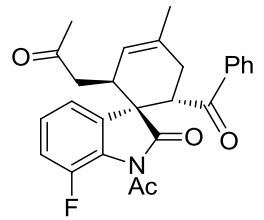


**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-5'-bromo-4-methyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4o): 4o** was obtained as a white semisolid in 88% yield after flash chromatography and the enantiomeric excess was determined to be 91% by HPLC analysis on Chiralpak IC-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 9.01 min, $t_{minor}$ = 10.41 min; $[\alpha]_D^{20}$ = -43.1 (*c* = 2.76 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46-7.42 (m, 3H), 7.10 (d, *J* = 1.6 Hz, 1H), 5.43(d, *J* = 4.4 Hz, 1H), 4.22 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 3.26 (dd, *J* = 18.8 Hz, *J* = 10.0 Hz, 1H), 2.91 (s, 1H), 2.60 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.44 (s, 3H), 2.39-2.30 (m, 2H), 2.14 (s, 3H), 1.84 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 206.5, 200.1, 180.4, 170.6, 138.9, 135.8, 135.0, 133.7, 133.3, 130.7, 128.7, 128.4, 125.9, 123.5, 117.9, 117.7, 49.2, 45.9, 44.9, 39.5, 31.8, 29.8, 26.3, 22.9 ppm; ESI HRMS: calcd. for $C_{26}H_{24}Br^{79}NO_4$+$Na^+$ 516.0781, found 516.0790 ($Br^{79}$), 518.0775 ($Br^{81}$).

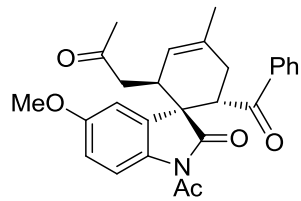
**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-5'-iodo-4-methyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4p): 4p** was obtained as a white semisolid in 85% yield after flash chromatography



and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralpak AD-H column (5% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 21.54 min, $t_{minor}$ = 19.78 min; $[\alpha]_D^{20}$ = -58.4 (*c* = 2.00 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.65 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 1.6 Hz, 1H), 5.44(d, *J* = 4.0 Hz, 1H), 4.21 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 3.26 (dd, *J* = 18.8 Hz, *J* = 10.0 Hz, 1H), 2.92 (s, 1H), 2.60 (dd, *J* = 18.4 Hz, *J* = 5.6 Hz, 1H), 2.44 (s, 3H), 2.39-2.29 (m, 2H), 2.15 (s, 3H), 1.85 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 200.1, 180.3, 170.7, 139.6, 136.8, 135.8, 135.2, 133.7, 133.4, 131.6, 128.7, 128.4, 123.5, 118.3, 88.7, 49.0, 45.9, 44.9, 39.4, 31.9, 29.8, 26.4, 22.9 ppm; ESI HRMS: calcd. for $C_{26}H_{24}INO_4$+$Na^+$ 564.0642, found 564.0641.



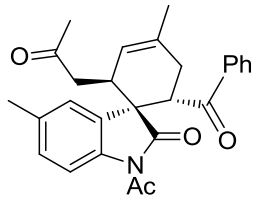
**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-7'-fluoro-4-methyl-2-(2-oxopropyl)spiro [cyclohex[3]ene-1,3'-indolin]-2'-one (4q): 4q** was obtained as a white semisolid in 89% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 7.51 min, $t_{minor}$ = 9.36 min; $[\alpha]_D^{20}$ = -18.3 (*c* = 1.27 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.13-7.06 (m, 2H), 6.83 (dd, *J* = 6.8 Hz, *J* = 2.0 Hz, 1H), 5.43(d, *J* = 4.0 Hz, 1H), 4.21 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.26 (dd, *J* = 18.8 Hz, *J* = 10.0 Hz, 1H), 2.96 (s, 1H), 2.60 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.49 (s, 3H), 2.44-2.39 (m, 2H), 2.16 (s, 3H), 1.83 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.5, 200.1, 180.1, 168.5, 149.9 (d, $^1J_{C,F}$ = 251.6 Hz), 136.4, 136.3, 135.9, 133.6, 133.3, 128.7, 128.4, 125.8 (d, $^3J_{C,F}$ = 7.2 Hz), 123.6, 118.6 (d, $^4J_{C,F}$ = 3.0 Hz), 116.5 (d, $^2J_{C,F}$ = 21.0 Hz), 50.4, 46.0, 44.9, 39.4, 31.9, 29.8, 25.8, 23.0 ppm; ESI HRMS: calcd. for $C_{26}H_{24}FNO_4$+$Na^+$ 456.1582, found 456.1586.



**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-5'-methoxy-4-methyl-2-(2-oxopropy l)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4r): 4r** was obtained as a colorless oil in 86% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 6.06 min,

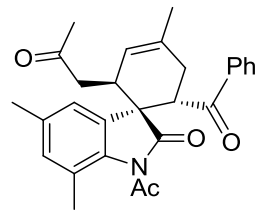
$t_{minor}$ = 6.87 min; $[\alpha]_D^{20}$ = -30.8 (*c* = 2.45 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 6.84 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 5.44(d, *J* = 4.0 Hz, 1H), 4.23 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.26 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.96 (s, 1H), 2.59 (dd, *J* = 18.0 Hz, *J* = 5.6 Hz, 1H), 2.44 (s, 3H), 2.40-2.38 (m, 2H), 2.15 (s, 3H), 1.83 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 206.4, 200.2, 181.0, 170.5, 156.6, 136.0, 134.1, 133.5, 133.2, 128.7, 128.4, 123.7, 123.6, 116.9, 110.8, 110.7, 55.3, 49.3, 45.7, 45.0, 39.5, 31.8, 29.9, 26.3, 23.0 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_5$+$Na^+$ 468.1781, found 468.1787.

Enantiomer of **4r** was obtained as a colorless oil in 84% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 6.78 min, $t_{minor}$ = 6.03 min; $[\alpha]_D^{20}$ = +10.2 (*c* = 1.39 in $CHCl_3$).

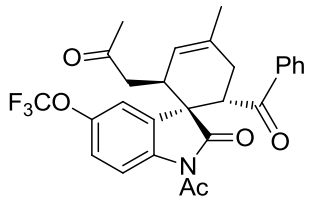



**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4,5'-dimethyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4s): 4s** was obtained as a white semisolid in 86% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 5.73 min, $t_{minor}$ = 6.26 min; $[\alpha]_D^{20}$ = -31.0 (*c* = 1.18 in $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 5.45(d, *J* = 4.0 Hz, 1H), 4.22 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 3.25 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.95 (s, 1H), 2.58 (dd, *J* = 18.0 Hz, *J* = 6.0 Hz, 1H), 2.45 (s, 3H), 2.43-2.36 (m, 2H), 2.29 (s, 3H), 2.15 (s, 3H), 1.84 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 206.6, 200.3, 181.2, 170.7, 137.5, 136.1, 134.0, 133.5, 133.2, 132.6, 128.6, 128.4, 128.3, 123.7, 123.6, 116.1, 49.3, 45.7, 45.1, 39.6, 31.9, 29.9, 26.4, 23.0, 21.6 ppm; ESI HRMS: calcd. for $C_{27}H_{27}NO_4$+$Na^+$ 452.1832, found 452.1835.

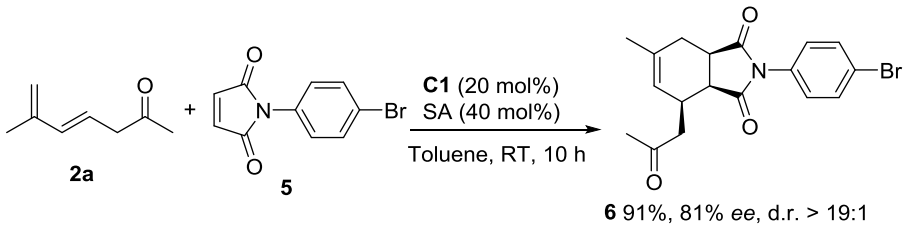
Enantiomer of **4s** was obtained as a white semisolid in 83% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 5.98 min, $t_{minor}$ = 5.48 min; $[\alpha]_D^{20}$ = +18.8 (*c* = 0.87 in $CHCl_3$).



**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4,5',7'-trimethyl-2-(2-oxopropyl)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4t): 4t** was obtained as a white semisolid in 91% yield after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC analysis on Chiralpak IC-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 10.94 min, $t_{minor}$ = 14.19 min; $[\alpha]_D^{20}$ = +10.4 (*c* = 1.56 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.97 (s, 1H), 6.67 (s, 1H), 5.43(d, *J* = 4.0 Hz, 1H), 4.18 (dd, *J* = 12.0 Hz, *J* = 6.4 Hz, 1H), 3.24 (dd, *J* = 18.4 Hz, *J* = 9.6 Hz, 1H), 2.95 (s, 1H), 2.53 (d, *J* = 6.0 Hz, 1H), 2.45 (s, 3H), 2.43-2.38 (m, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H), 1.83 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.7, 200.3, 181.8, 170.1, 136.2, 135.8, 134.2, 134.0, 133.4, 133.0, 131.6, 128.6, 128.4, 125.8, 123.8, 121.1, 50.1, 45.9, 45.1, 39.5, 31.9, 29.9, 26.2, 23.0, 21.5, 21.3 ppm; ESI HRMS: calcd. for $C_{28}H_{29}NO_4$+$Na^+$ 466.1989, found 466.1993.

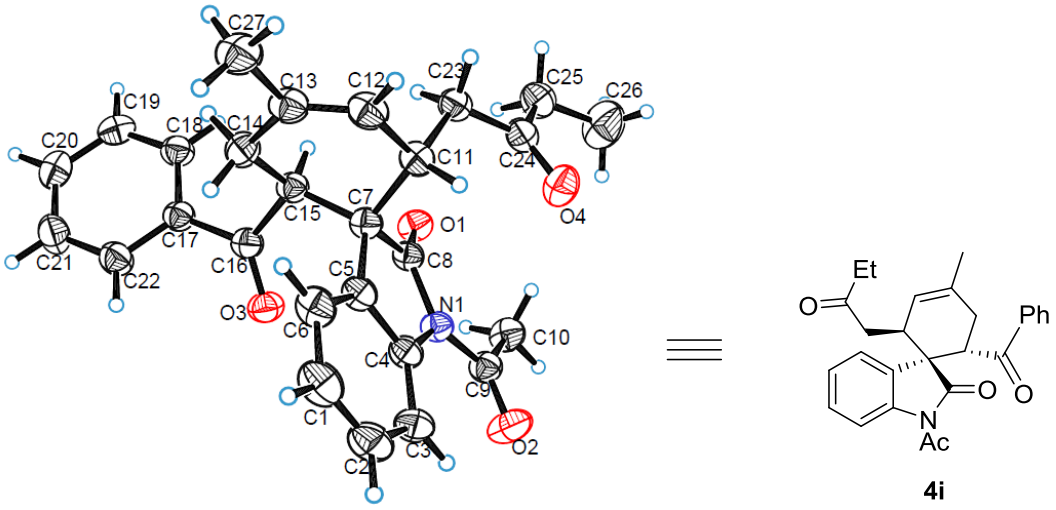


**(1*S*,2*S*,6*S*)-1'-Acetyl-6-benzoyl-4-methyl-2-(2-oxopropyl)-5'-(trifluoromethoxy)spiro[cyclohex[3]ene-1,3'-indolin]-2'-one (4u): 4u** was obtained as a colorless oil in 87% yield after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC analysis on Chiralpak IC-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 220 nm, $t_{major}$ = 6.32 min, $t_{minor}$ = 6.94 min; $[\alpha]_D^{20}$ = -14.7 (*c* = 2.73 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.19 (dd, *J* = 8.8 Hz, *J* = 1.6 Hz, 1H), 6.89 (s, 1H), 5.46(d, *J* = 4.4 Hz, 1H), 4.25 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 3.29 (dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), 2.94 (s, 1H), 2.63 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.46 (s, 3H), 2.41-2.28 (m, 2H), 2.16 (s, 3H), 1.84 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 206.6, 200.1, 180.7, 170.7, 145.9, 138.3, 136.1, 135.7, 134.4, 133.9, 133.4, 128.7, 128.4, 123.4, 120.4 (q, $J_{C,F}$ = 255.6 Hz), 117.2, 115.9, 49.2, 45.8, 44.8, 39.4, 31.9, 29.8, 26.3, 22.7 ppm; ESI HRMS: calcd. for $C_{27}H_{24}F_3NO_5$+$Na^+$ 522.1499, found 522.1499.




3,5-Dienone **2a** (0.20 mmol), maleimide **5** (0.1 mmol), catalyst **C1** (0.02 mmol) and **SA** (0.04 mmol) were stirred in toluene (1 mL) at rt. After 10 h, the reaction was directly purified by flash chromatography on silica gel to give product **6**. 91% yield; $[\alpha]_D^{20}$ = -14.1 (*c* = 1.84 in $CHCl_3$); 81% ee, determined by HPLC analysis on Chiralpak AD-H column (20% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, $t_{major}$ = 16.09 min, $t_{minor}$ = 12.49 min; $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.30 (s, 1H), 3.45-3.41 (m, 1H), 3.32-3.22 (m, 2H), 2.87 (d, *J* = 2.4 Hz, 1H), 2.78 (dd, *J* = 18.4 Hz, *J* = 6.0 Hz, 1H), 2.67 (d, *J* = 14.8 Hz, 1H), 2.31 (dd, *J* = 14.4 Hz, *J* = 6.4 Hz, 1H), 2.24 (s, 3H), 1.77 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 207.9, 178.5, 177.2, 137.5, 132.2, 130.7, 127.9, 124.7, 122.3, 44.5, 41.5, 40.5, 31.1, 30.4, 29.5, 23.1 ppm; ESI HRMS: calcd. for $C_{18}H_{18}Br^{79}NO_3$+$Na^+$ 398.0362, found 398.0363 ($Br^{79}$), 400.0352 ($Br^{81}$). *The absolute and relative configuration of* ***6*** *was assigned on the basis of the similar catalytic mechanism to that of cycloadducts* ***4****.*

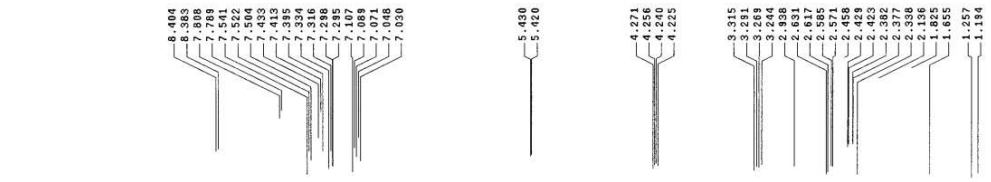
## 5. Crystal data and structure refinement for enantiopure cycloadduct 4i

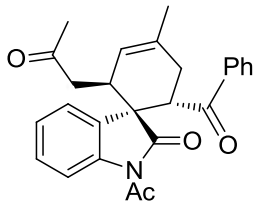



| | |
|---|---|
| Identification code | **4i** |
| Empirical formula | $C_{27}H_{27}NO_4$ |

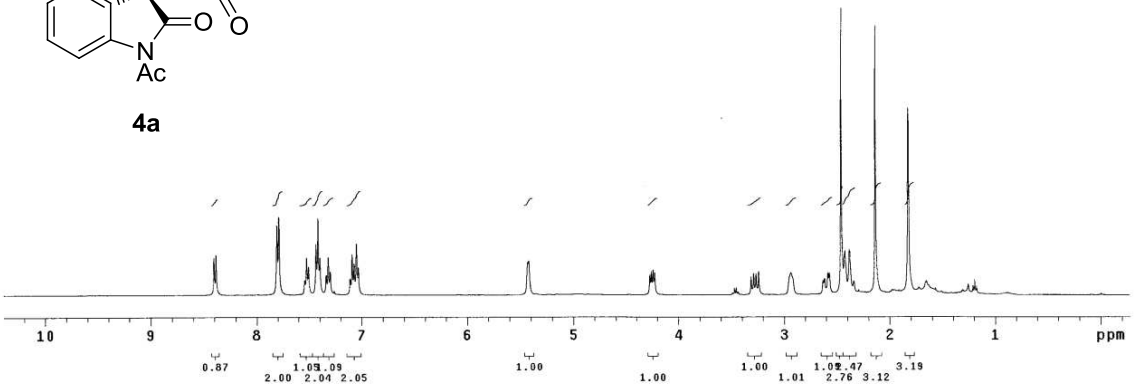
| | |
|---|---|
| Formula weight | 429.50 |
| Temperature/K | 291(2) |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| a/Å | 10.30150(10) |
| b/Å | 11.24590(10) |
| c/Å | 19.9126(2) |
| α/° | 90.00 |
| β/° | 90.00 |
| γ/° | 90.00 |
| Volume/$Å^3$ | 2306.87(4) |
| Z | 4 |
| $\rho_{calc}mg/mm^3$ | 1.237 |
| $m/mm^{-1}$ | 0.665 |
| F(000) | 912.0 |
| Crystal size/$mm^3$ | 0.42 × 0.39 × 0.32 |
| 2Θ range for data collection | 8.88 to 139.56° |
| Index ranges | $-11 \le h \le 12$, $-13 \le k \le 13$, $-23 \le l \le 24$ |
| Reflections collected | 20156 |
| Independent reflections | 4300[R(int) = 0.0232] |
| Data/restraints/parameters | 4300/0/292 |
| Goodness-of-fit on $F^2$ | 1.080 |
| Final R indexes [I>=2σ (I)] | $R_1 = 0.0328$, $wR_2 = 0.0906$ |
| Final R indexes [all data] | $R_1 = 0.0332$, $wR_2 = 0.0912$ |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.11/-0.16 |
| Flack parameter | 0.03(16) |

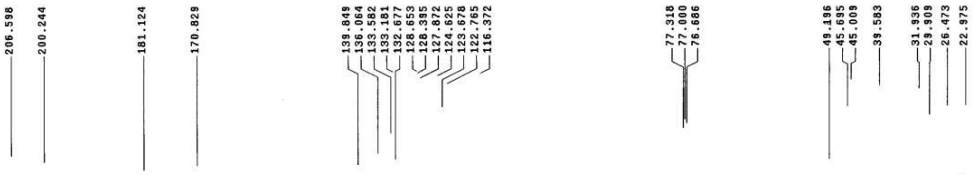
## 6. NMR spectra and HPLC chromatograms

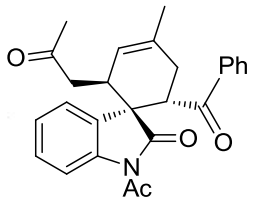




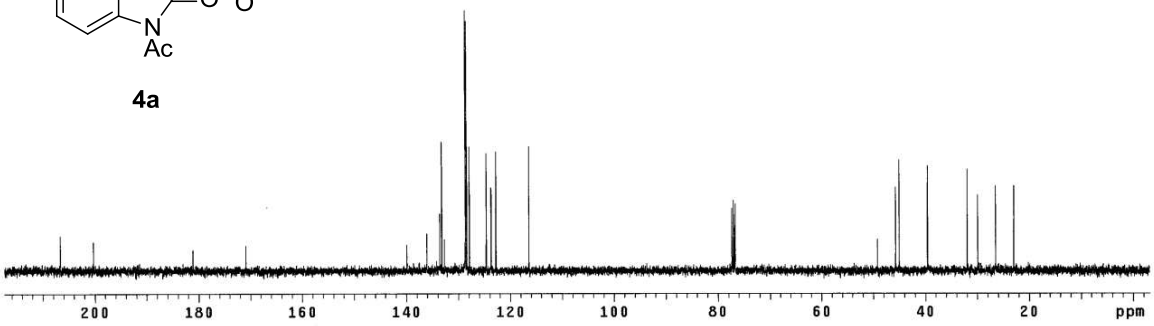

**4a**

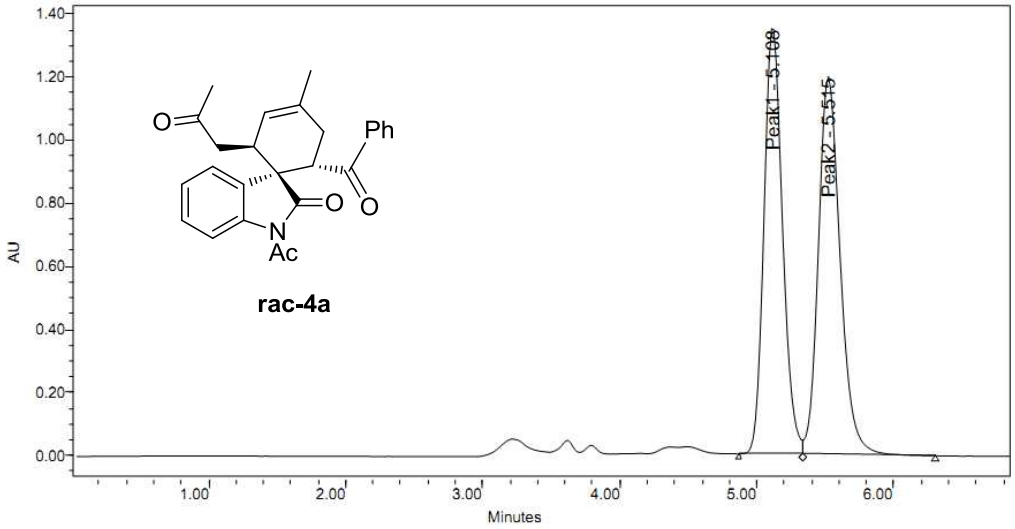




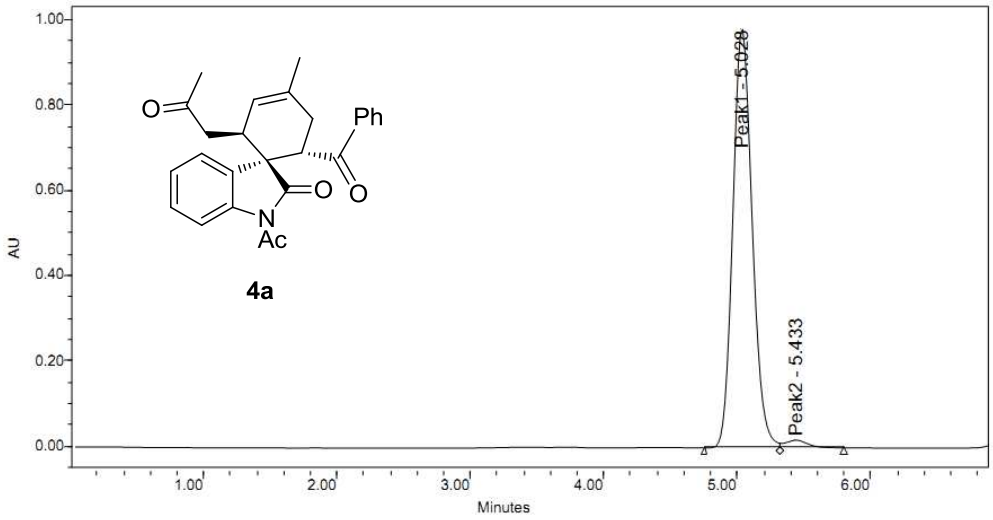

**4a**





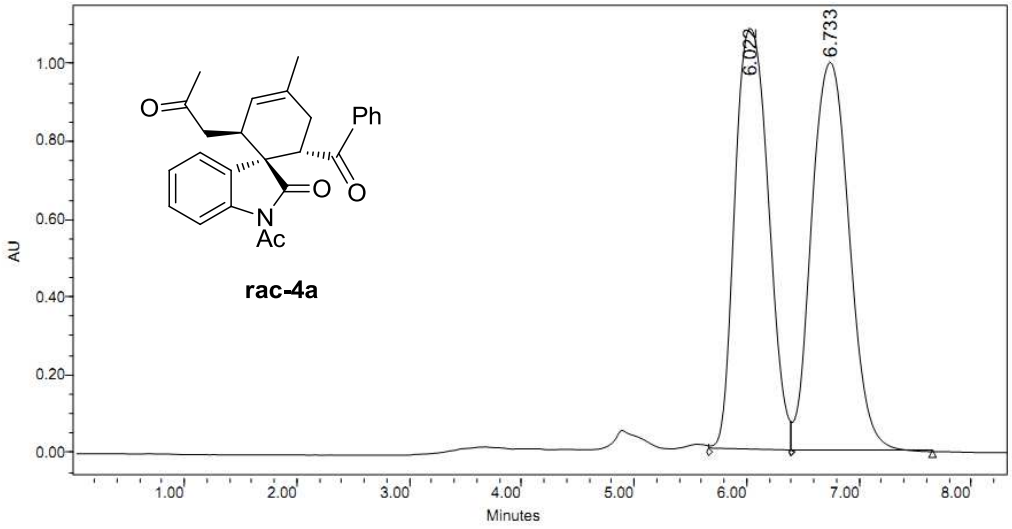

**rac-4a**

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.108 | 12773063 | 49.01 | 1359061 | 53.13 |
| 2 | Peak2 | 5.515 | 13288884 | 50.99 | 1199062 | 46.87 |



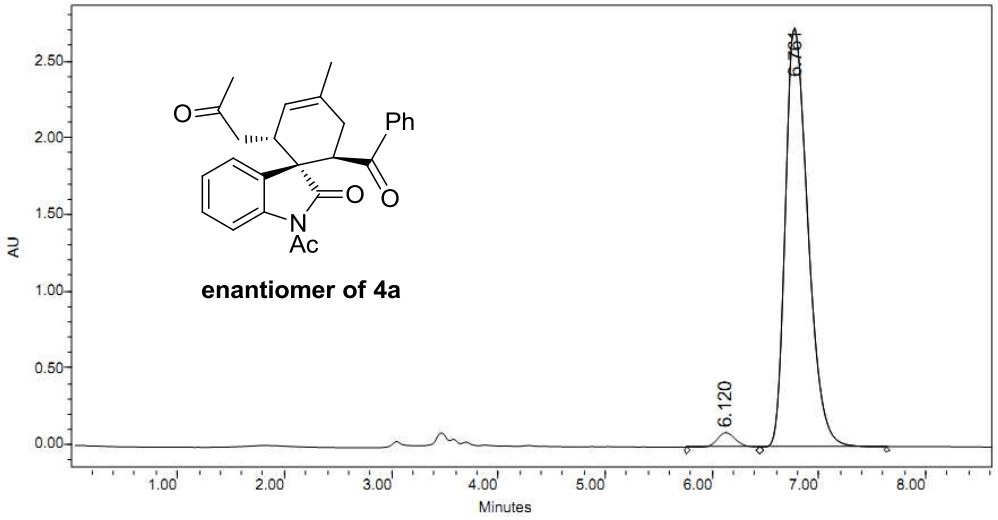

**4a**

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.028 | 9898334 | 97.93 | 984111 | 98.21 |
| 2 | Peak2 | 5.433 | 209173 | 2.07 | 17923 | 1.79 |



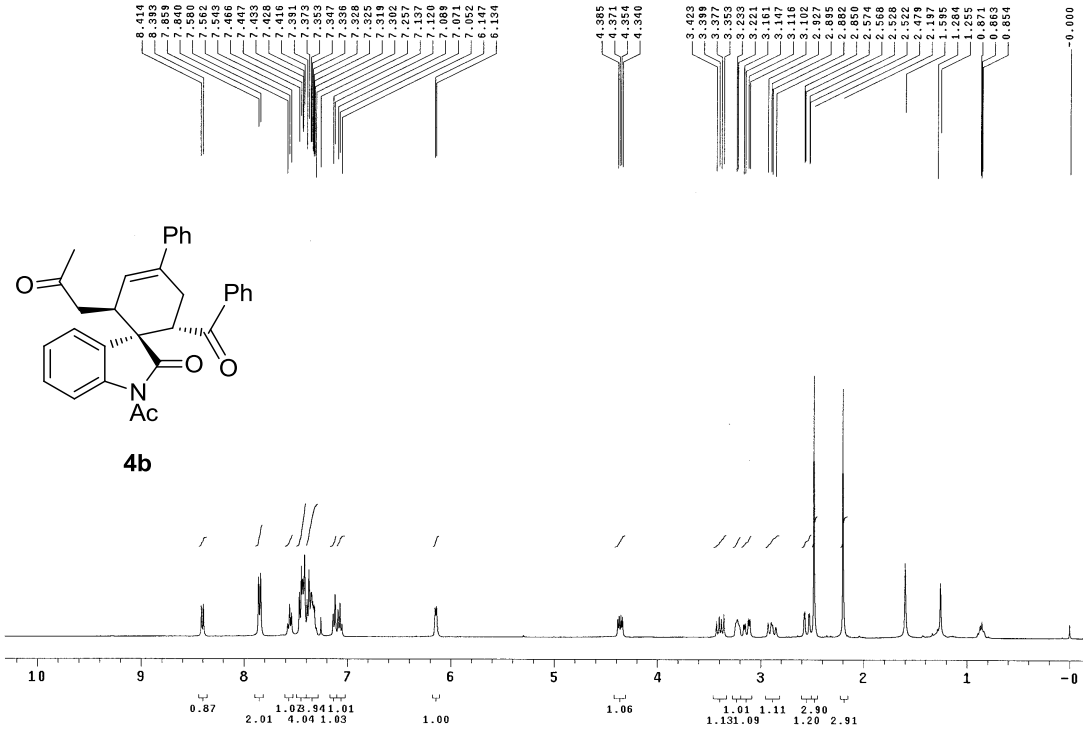

**rac-4a**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.022 | 22544182 | 49.21 | 1083712 | 52.05 |
| 2 | 6.733 | 23268055 | 50.79 | 998463 | 47.95 |




**enantiomer of 4a**

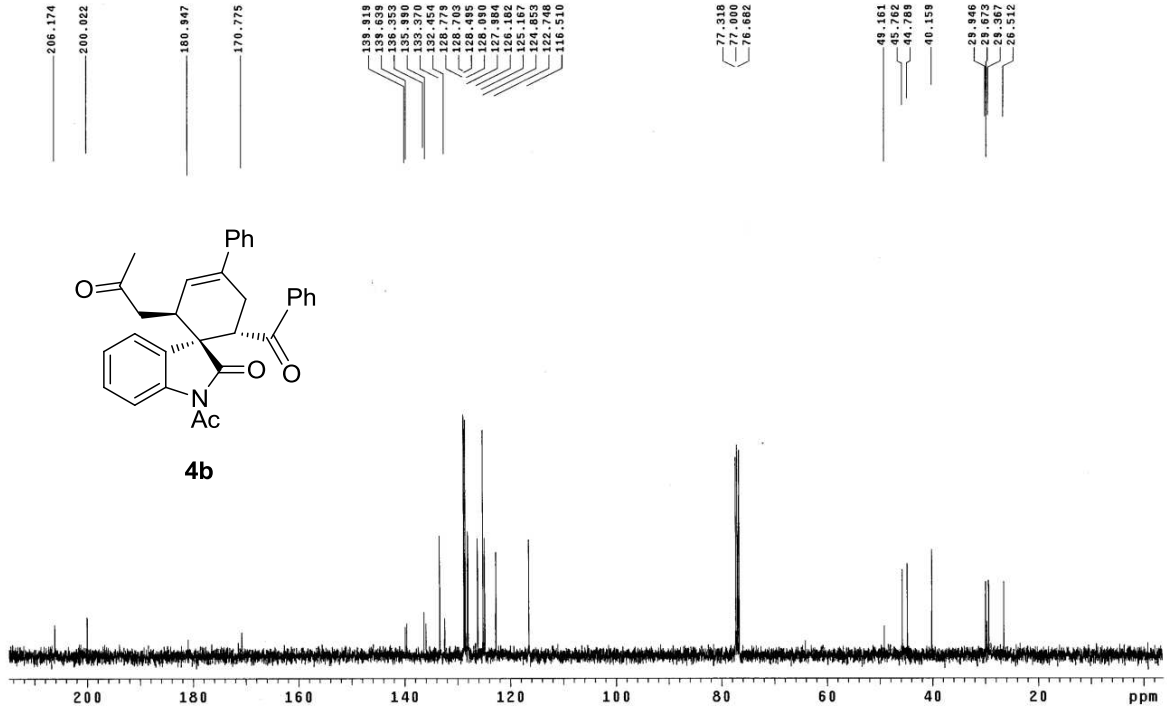
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.120 | 1142951 | 2.76 | 94946 | 3.36 |
| 2 | 6.761 | 40318384 | 97.24 | 2730932 | 96.64 |





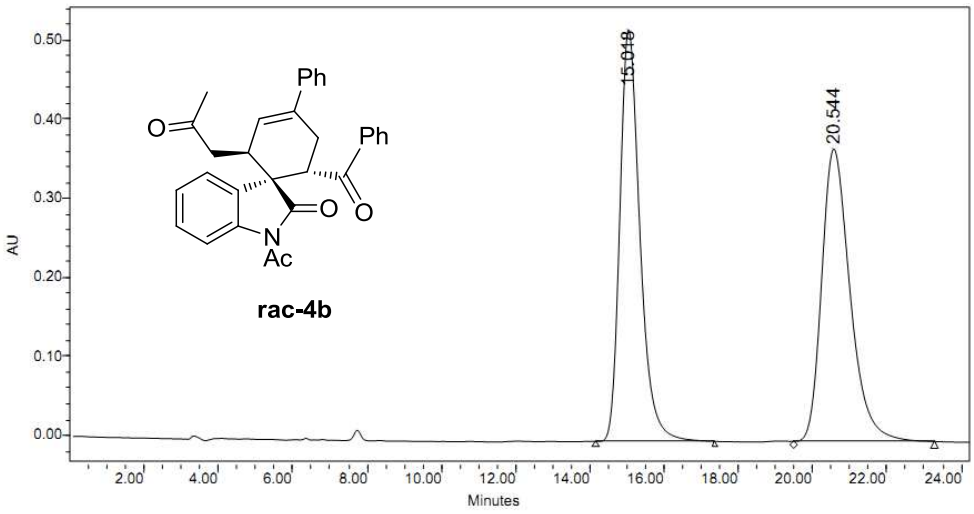
4b





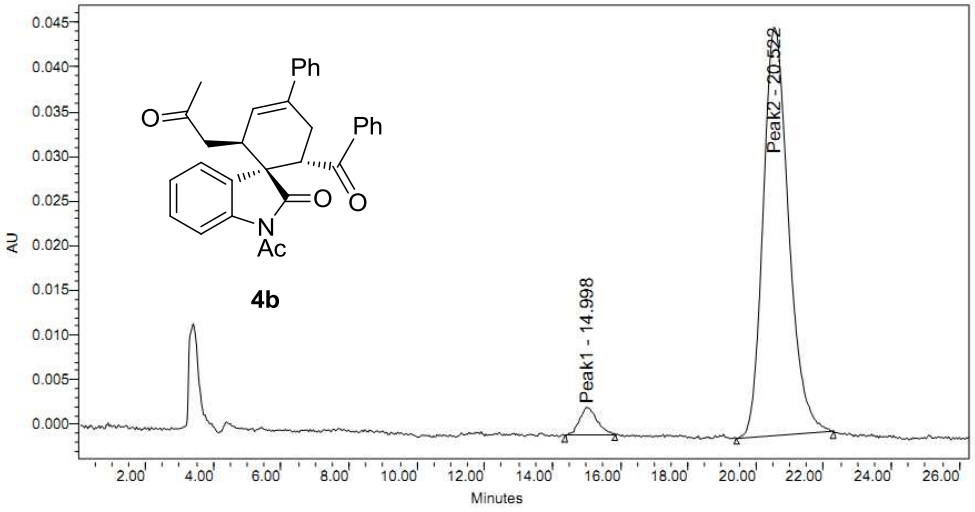


4b



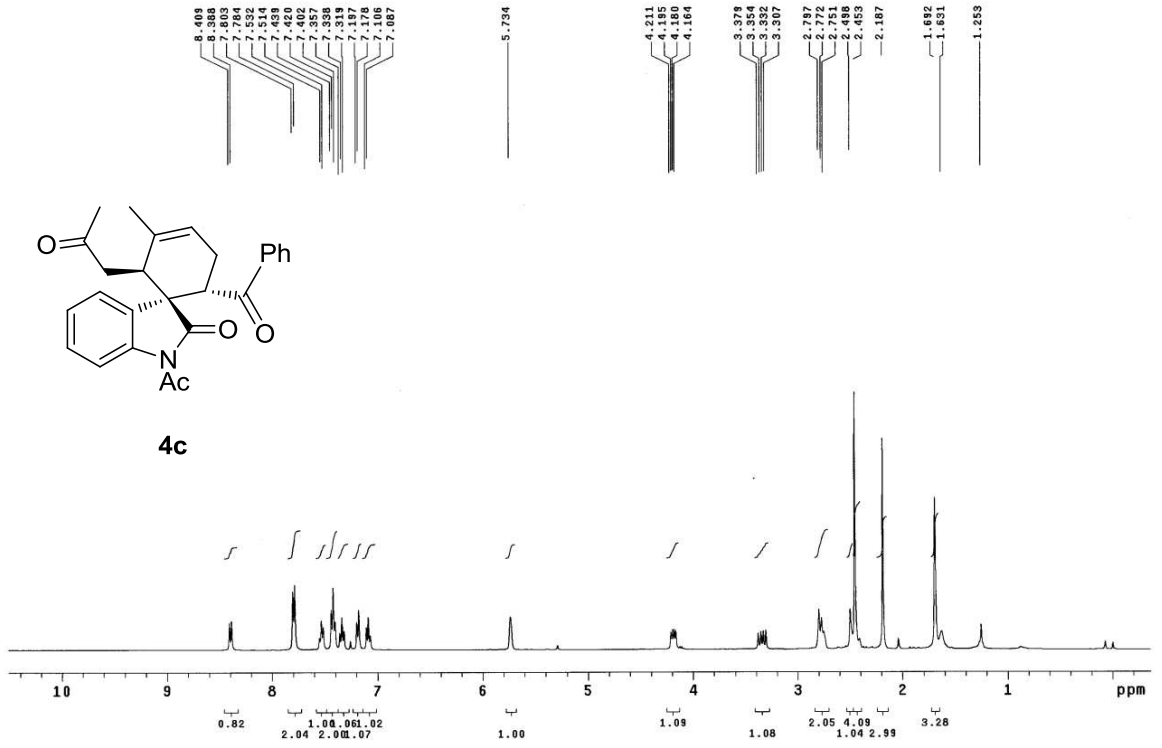

**rac-4b**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 15.018 | 19628961 | 49.82 | 521207 | 58.44 |
| 2 | 20.544 | 19768443 | 50.18 | 370653 | 41.56 |

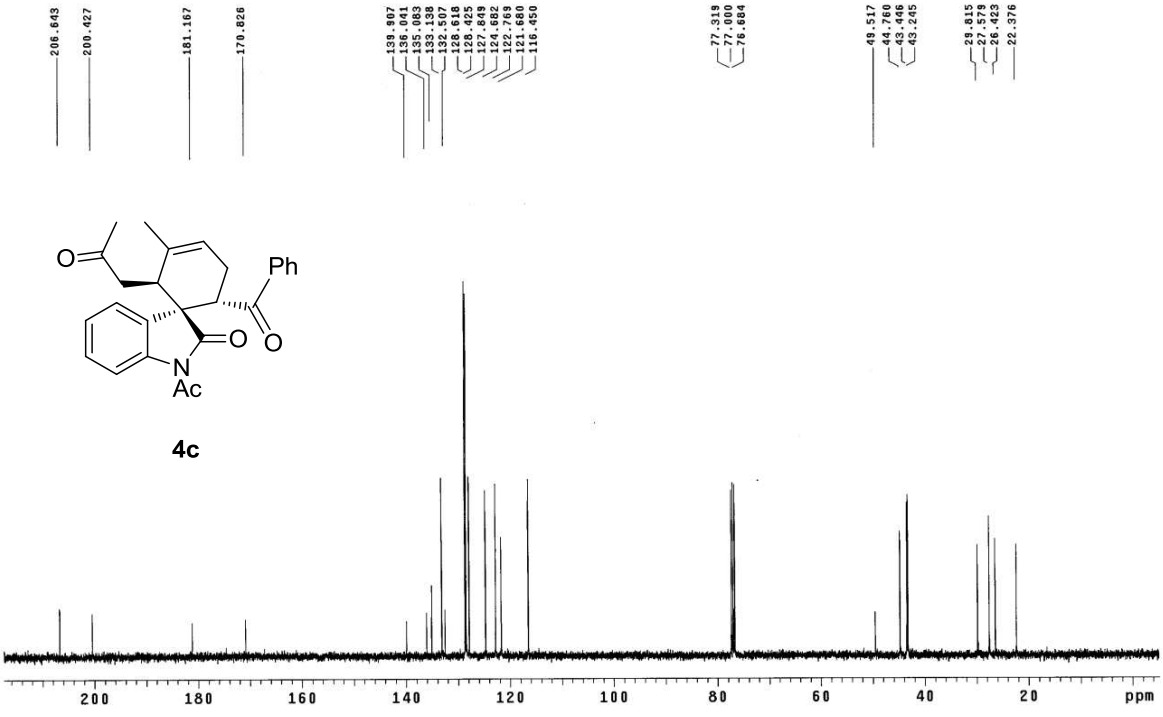



**4b**

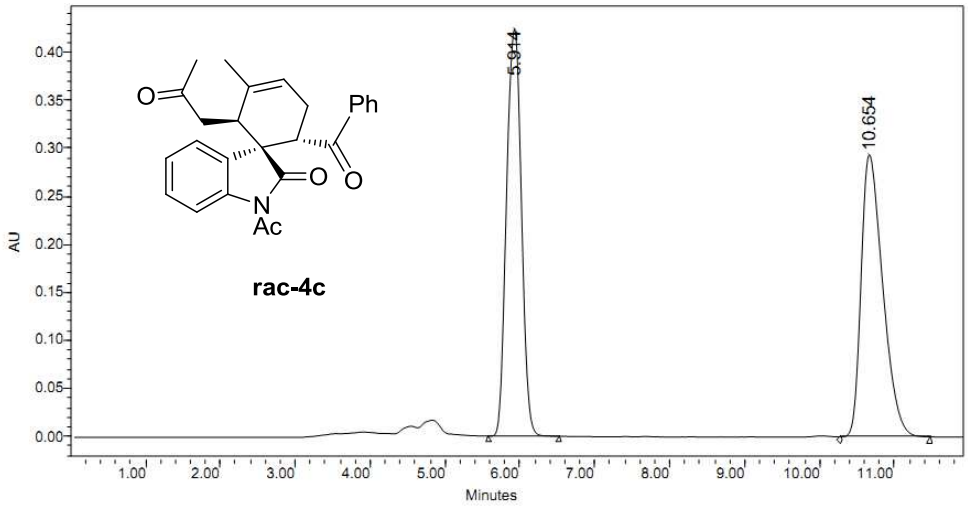
| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 14.998 | 118487 | 4.69 | 3164 | 6.46 |
| 2 | Peak2 | 20.522 | 2408054 | 95.31 | 45785 | 93.54 |



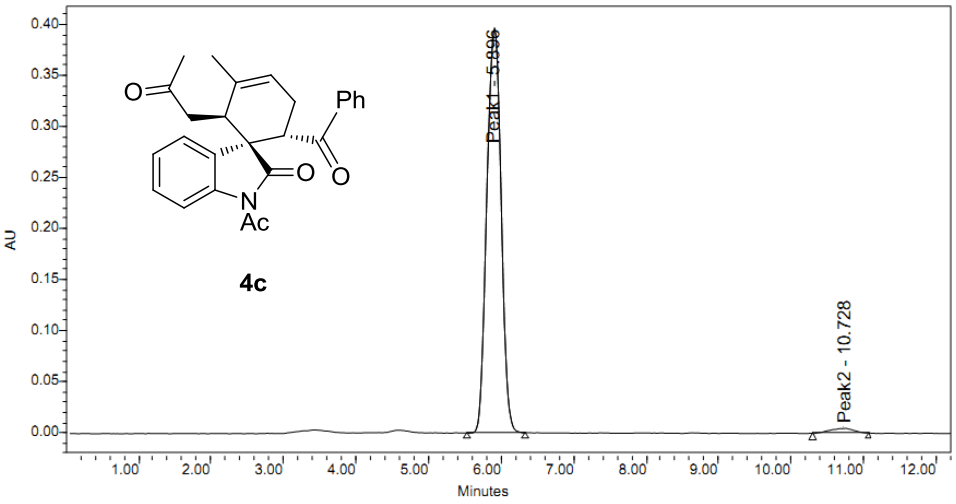

**4c**



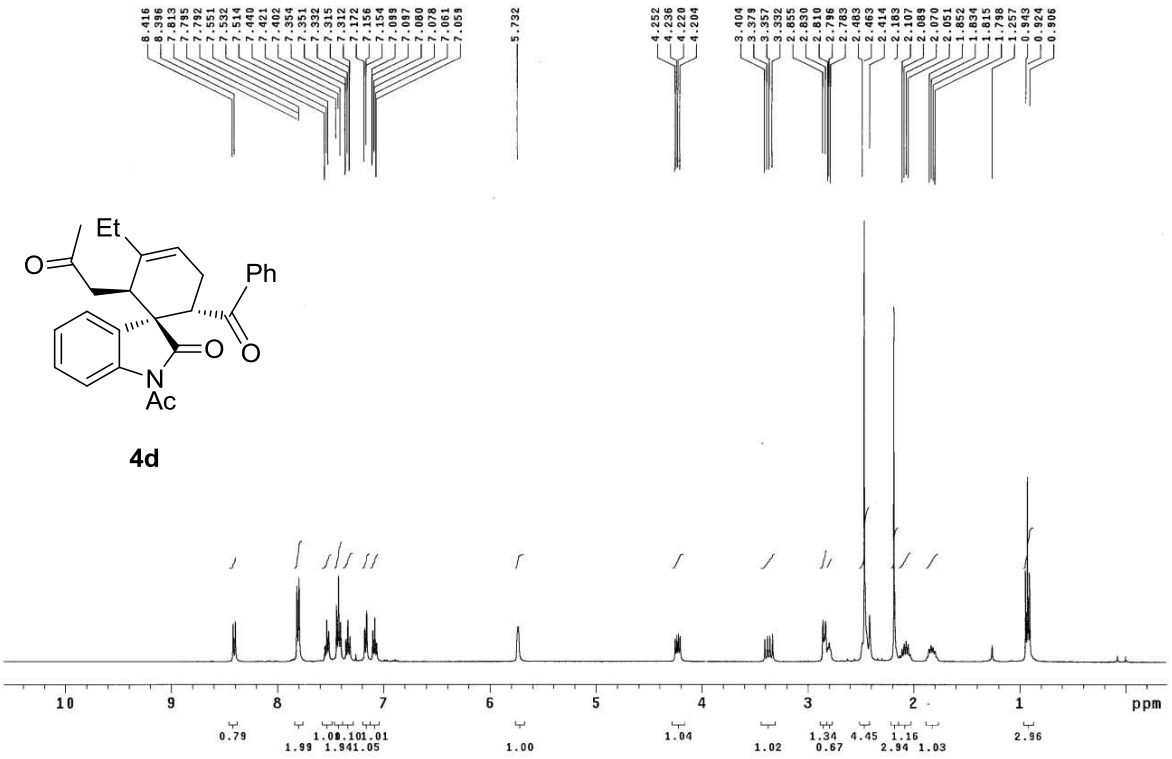

**4c**



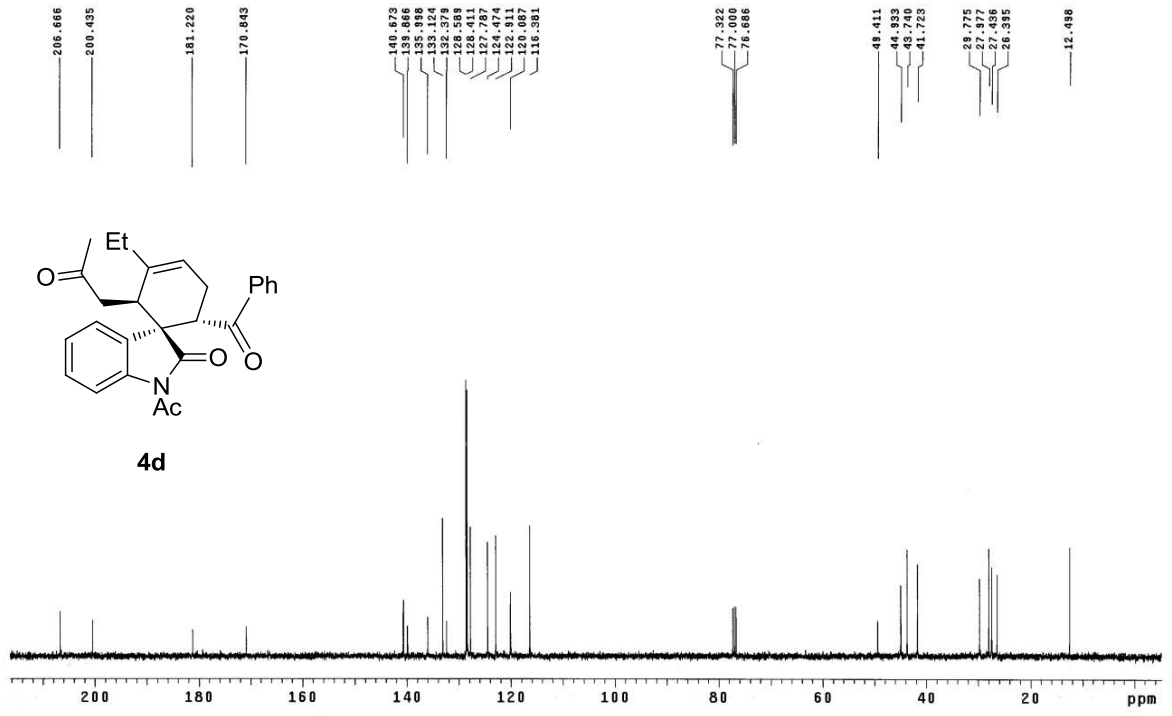

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.914 | 5867889 | 49.84 | 425073 | 59.08 |
| 2 | 10.654 | 5906676 | 50.16 | 294456 | 40.92 |




| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.896 | 5440332 | 97.97 | 396623 | 98.81 |
| 2 | Peak2 | 10.728 | 112550 | 2.03 | 4784 | 1.19 |

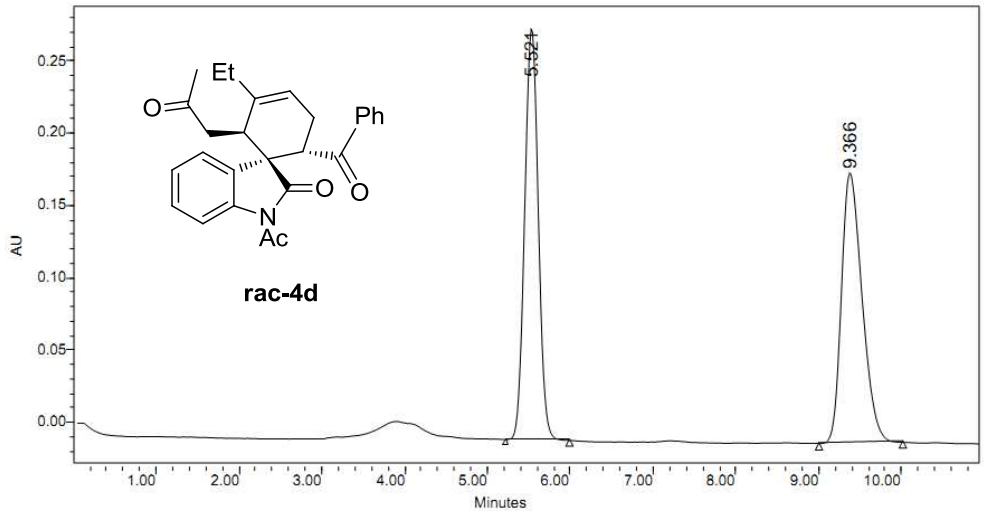



**4d**



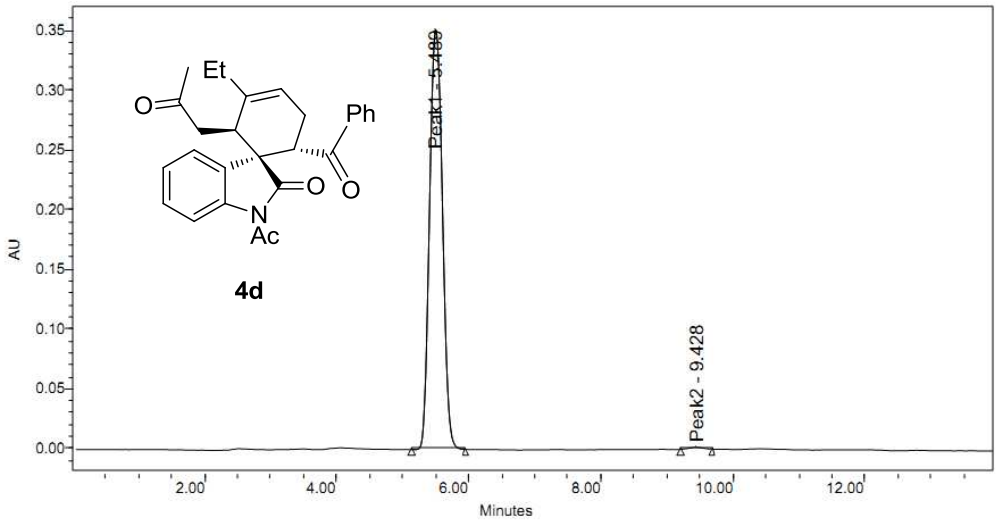



**4d**



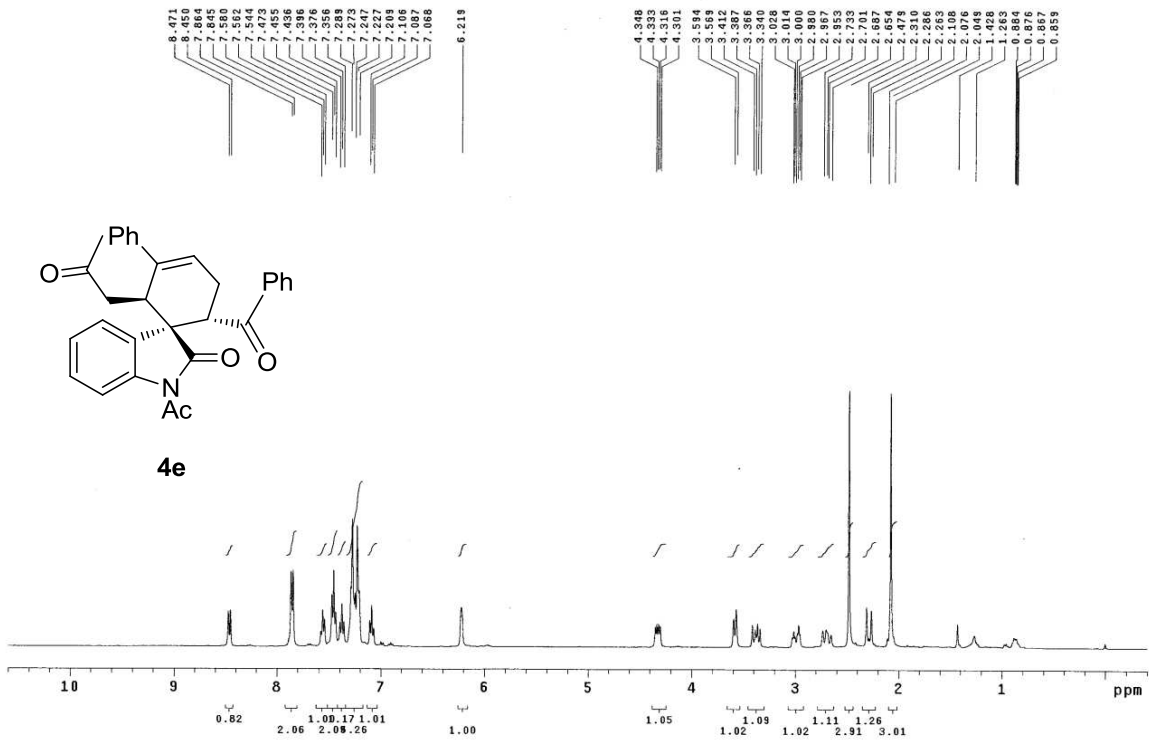

**rac-4d**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.521 | 3241883 | 50.03 | 284819 | 60.37 |
| 2 | 9.366 | 3237771 | 49.97 | 186952 | 39.63 |

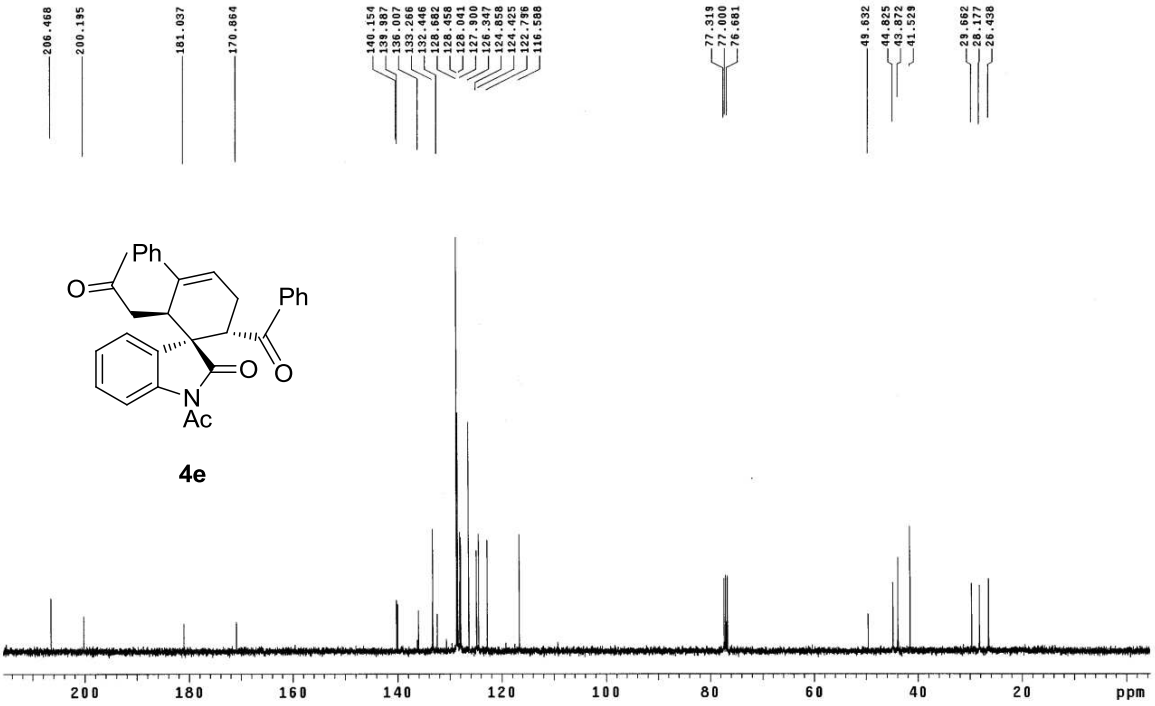



**4d**

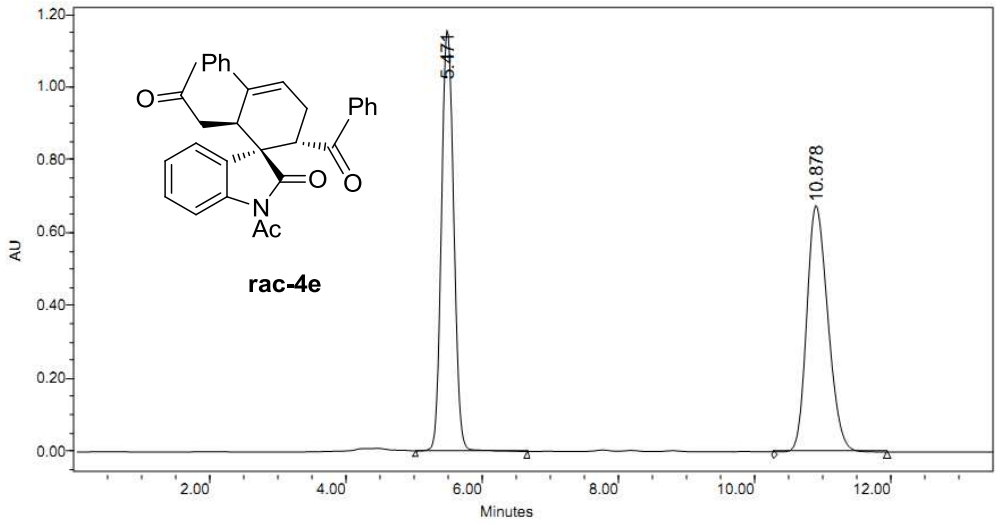
| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.489 | 4759242 | 99.53 | 352230 | 99.55 |
| 2 | Peak2 | 9.428 | 22599 | 0.47 | 1599 | 0.45 |



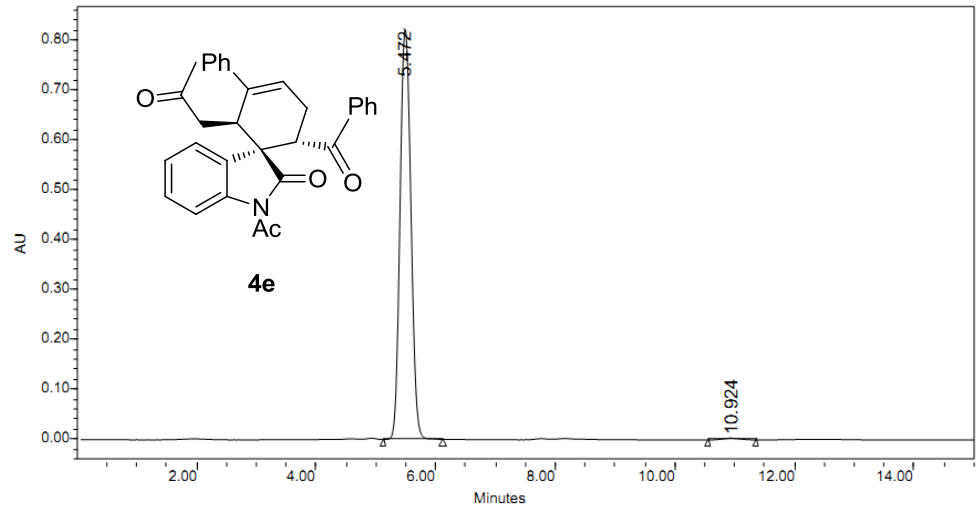

**4e**



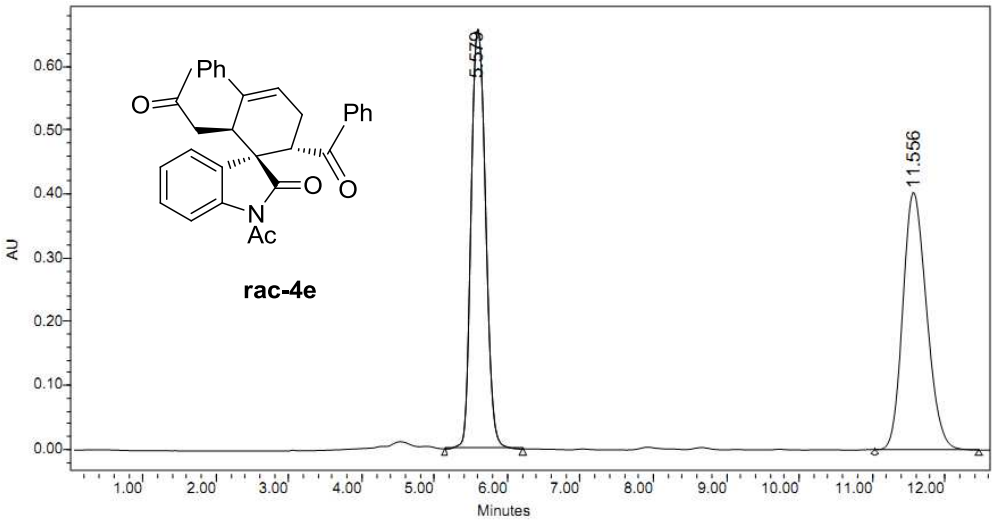

**4e**



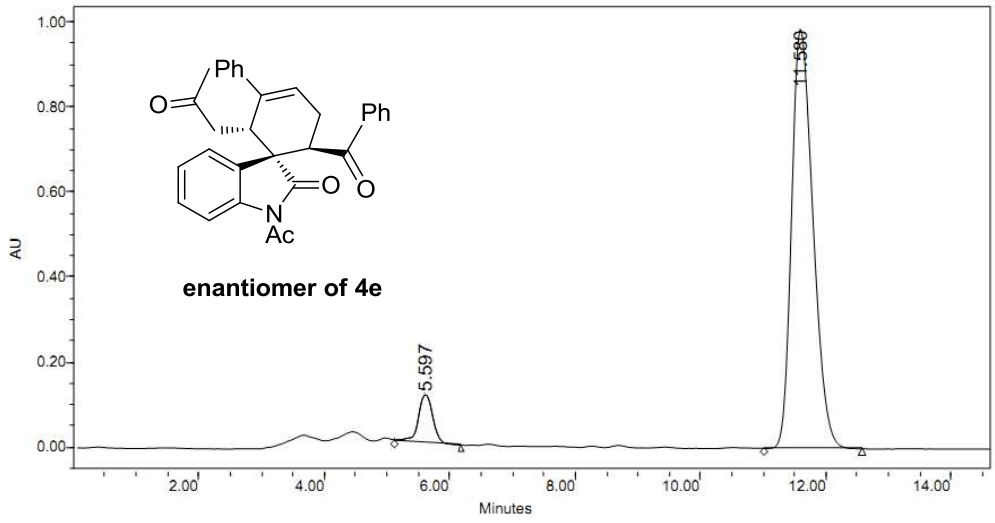

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.471 | 14537842 | 49.92 | 1156647 | 63.11 |
| 2 | 10.878 | 14582381 | 50.08 | 675965 | 36.89 |



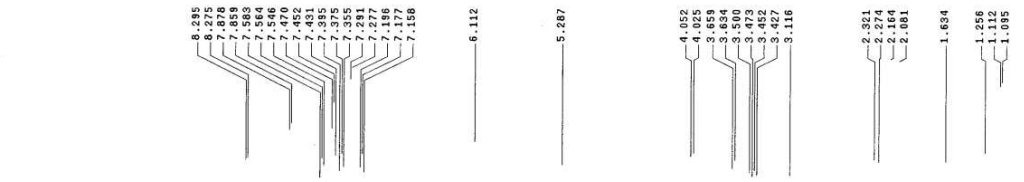

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.472 | 10392258 | 99.36 | 825125 | 99.60 |
| 2 | 10.924 | 67425 | 0.64 | 3341 | 0.40 |

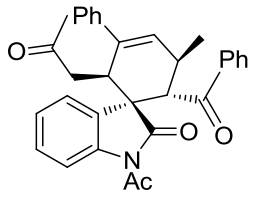



| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.579 | 9127188 | 49.83 | 658518 | 61.97 |
| 2 | 11.556 | 9188941 | 50.17 | 404115 | 38.03 |

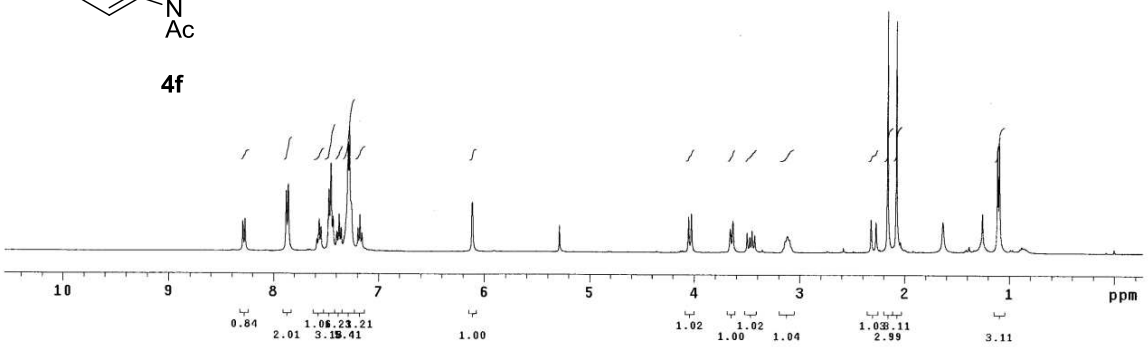


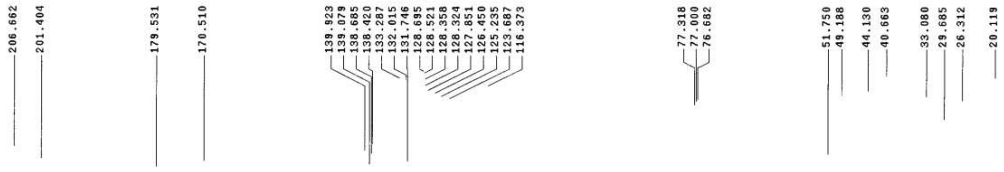

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.597 | 1918105 | 7.57 | 114463 | 10.40 |
| 2 | 11.580 | 23419569 | 92.43 | 986668 | 89.60 |

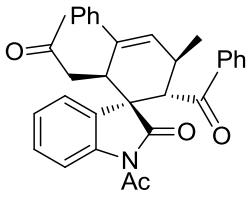


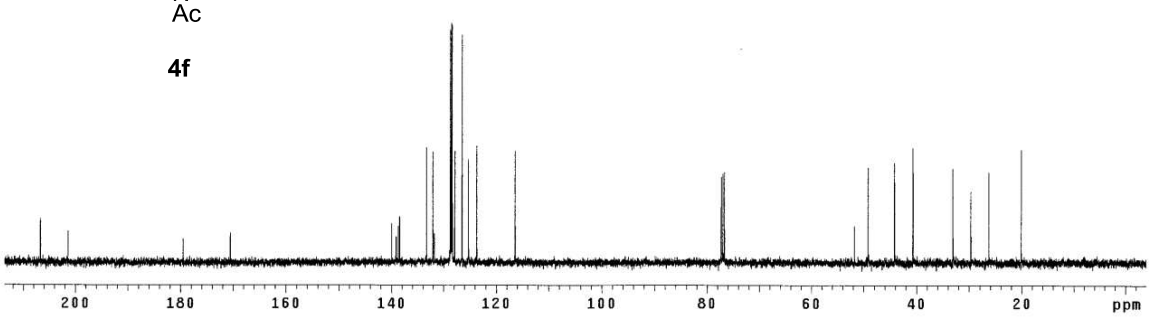

**4f**

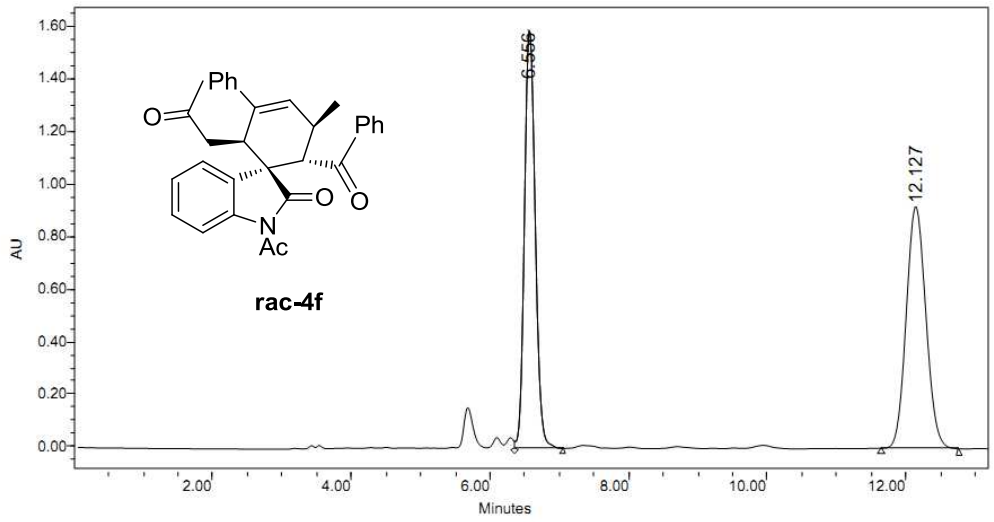


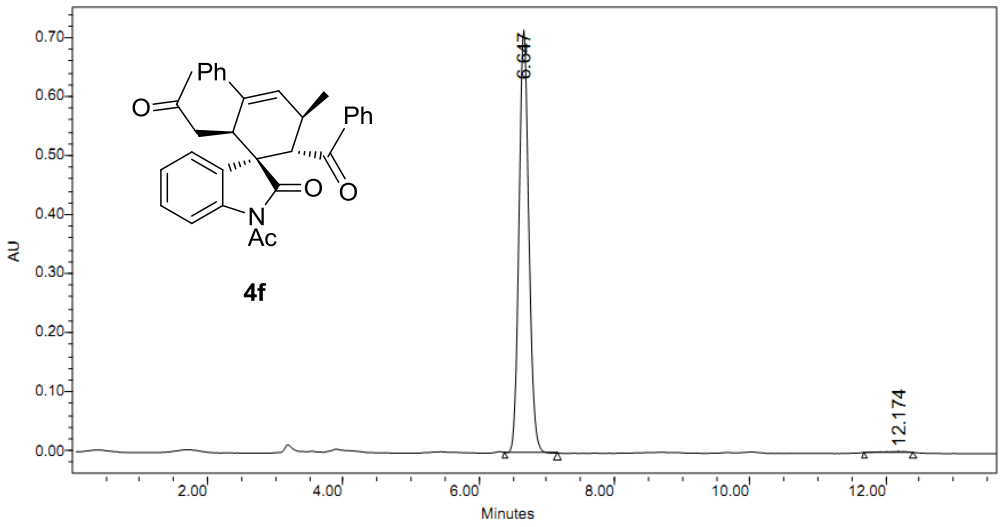

**4f**





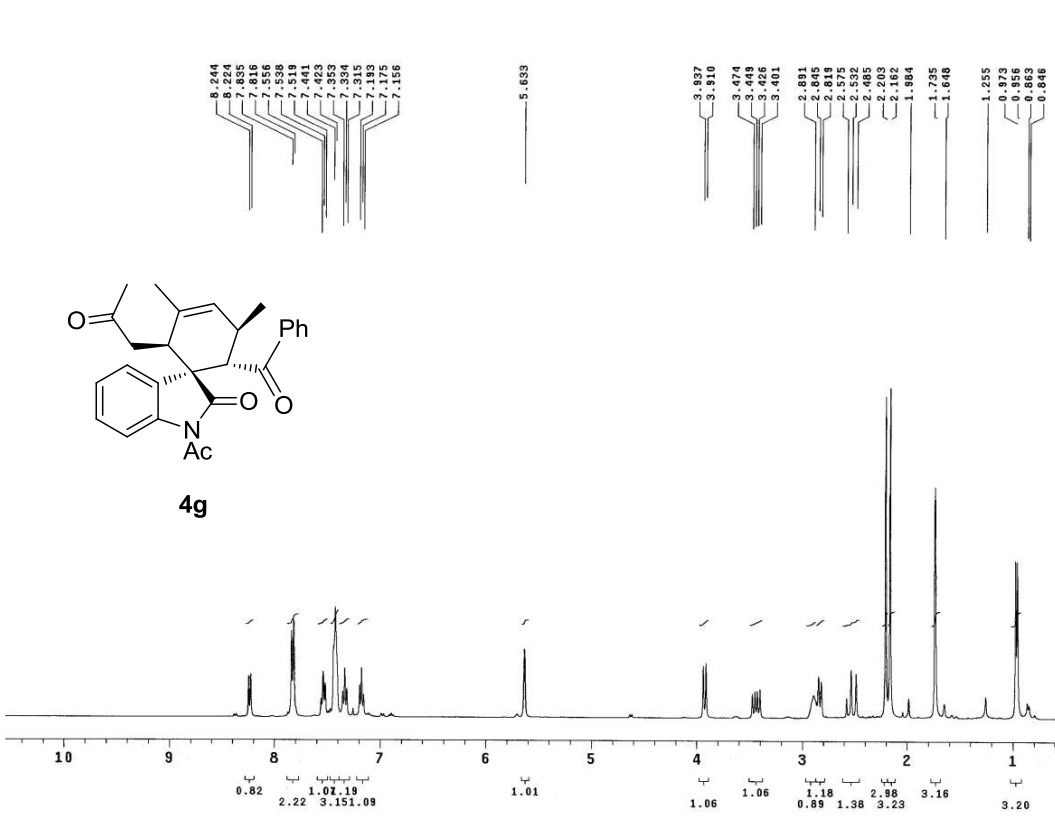

**rac-4f**

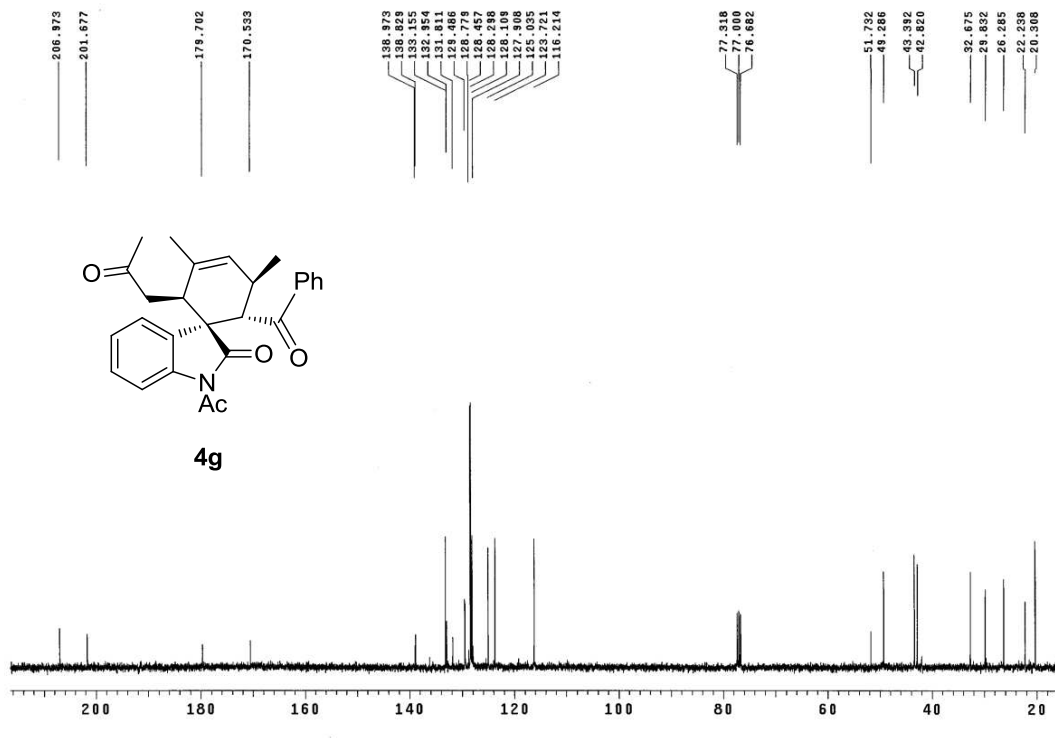
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.556 | 17143949 | 48.57 | 1595730 | 63.39 |
| 2 | 12.127 | 18152888 | 51.43 | 921495 | 36.61 |

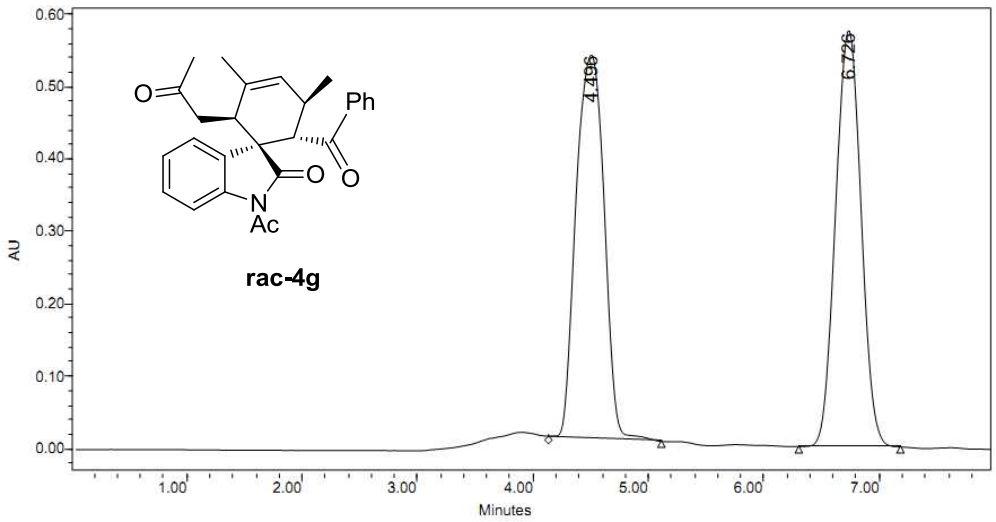



**4f**

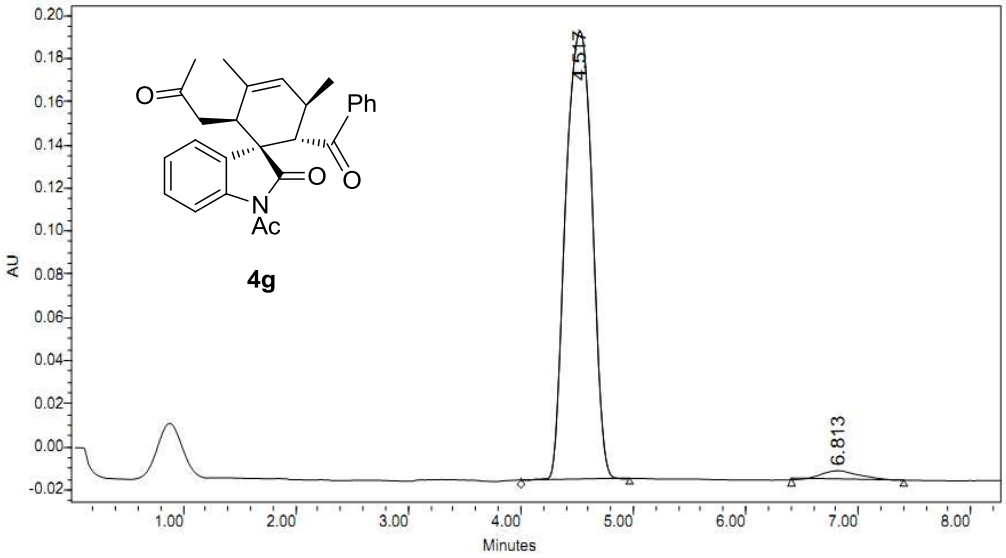
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.647 | 7232301 | 99.40 | 715426 | 99.76 |
| 2 | 12.174 | 43890 | 0.60 | 1718 | 0.24 |



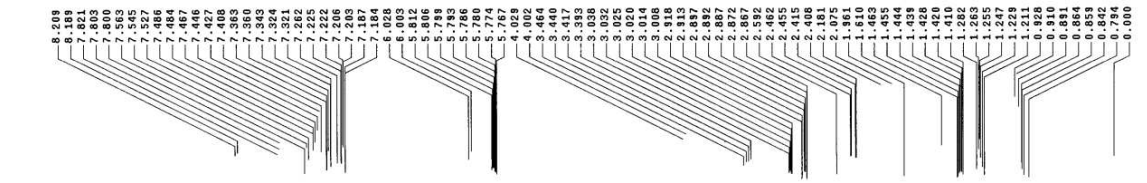



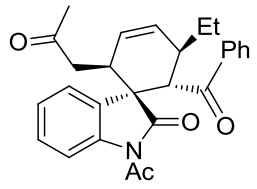



| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 4.496 | 8987730 | 50.47 | 530526 | 47.96 |
| 2 | 6.726 | 8820071 | 49.53 | 575676 | 52.04 |



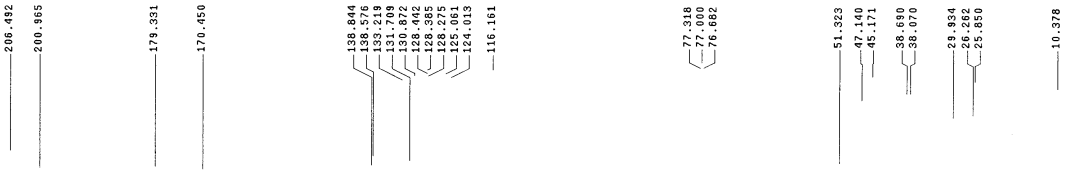

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 4.517 | 3418714 | 97.03 | 208219 | 97.99 |
| 2 | 6.813 | 104724 | 2.97 | 4268 | 2.01 |

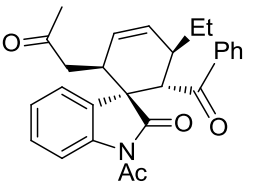




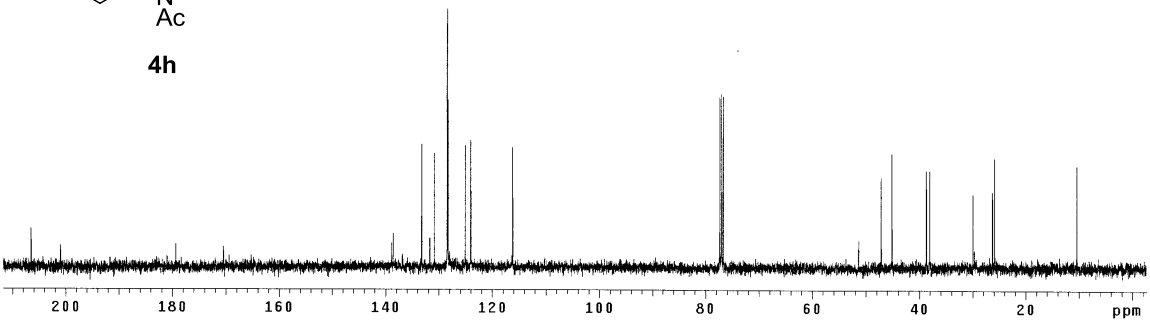

**4h**

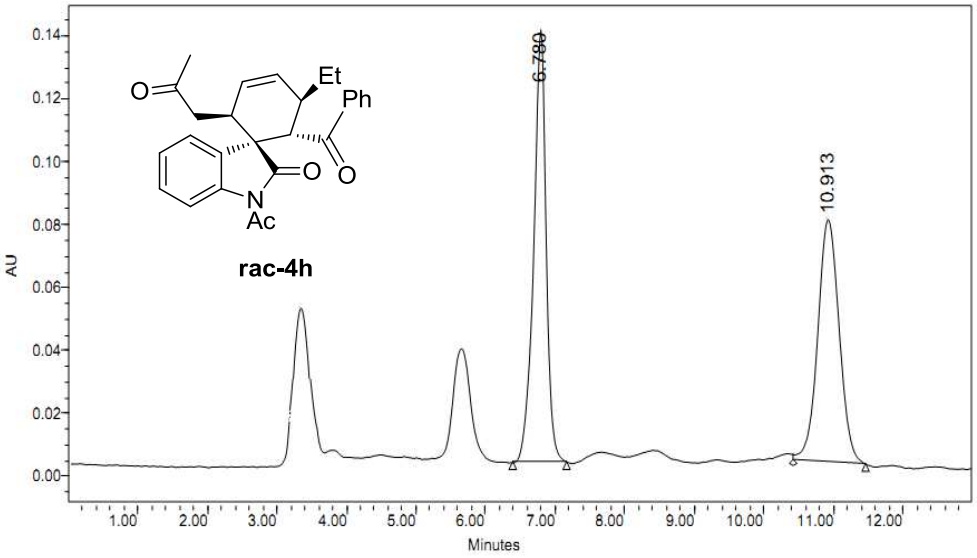




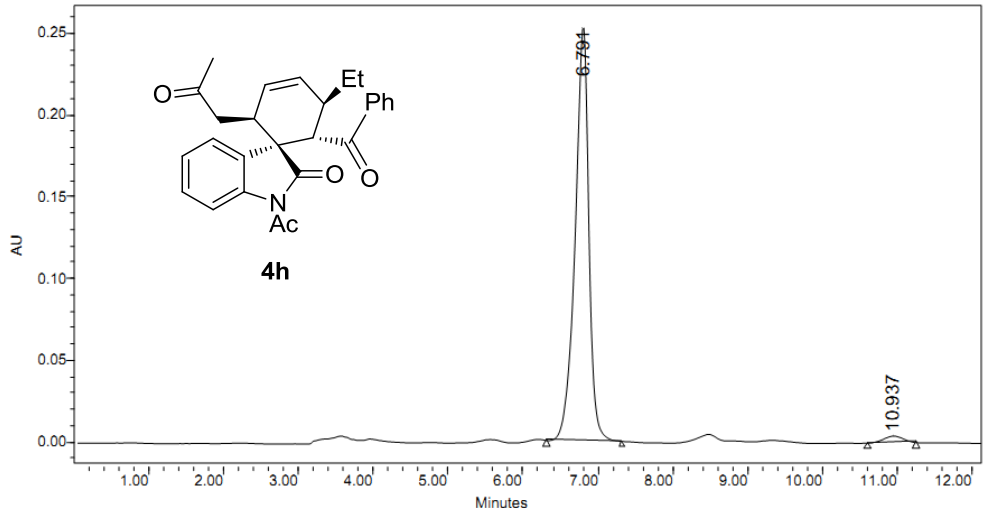

**4h**





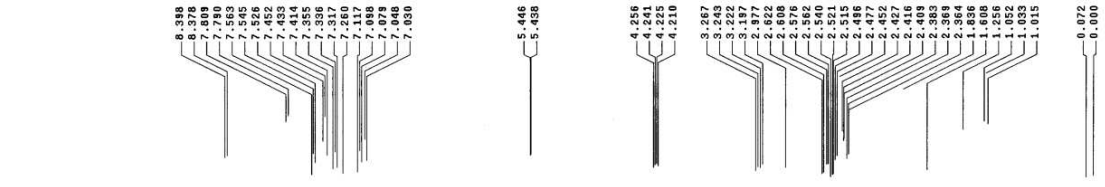

**rac-4h**

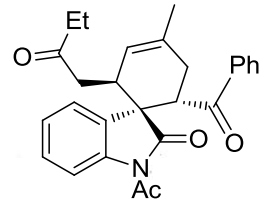
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.780 | 1710165 | 50.86 | 137537 | 64.07 |
| 2 | 10.913 | 1652659 | 49.14 | 77146 | 35.93 |



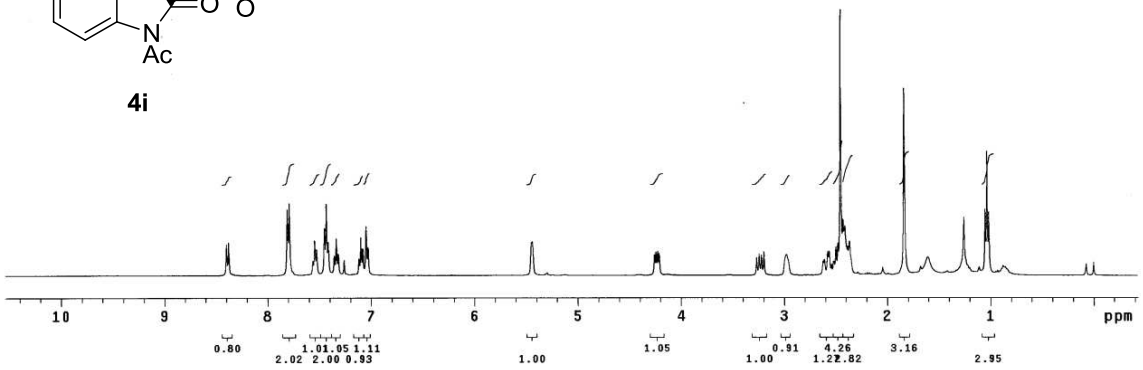

**4h**

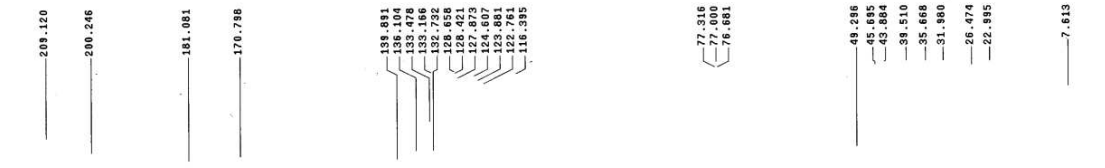
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.791 | 3216495 | 97.70 | 254222 | 98.39 |
| 2 | 10.937 | 75815 | 2.30 | 4169 | 1.61 |

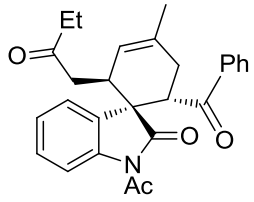




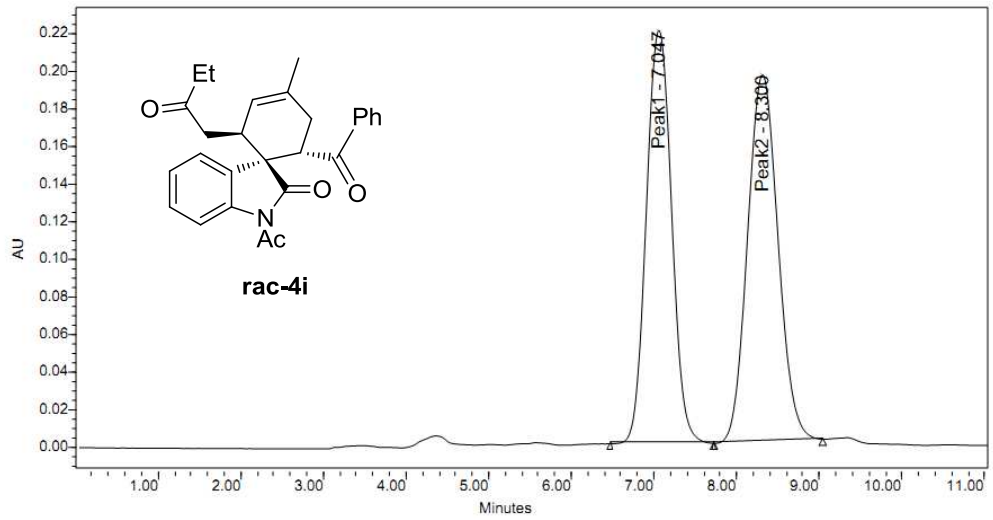

**4i**



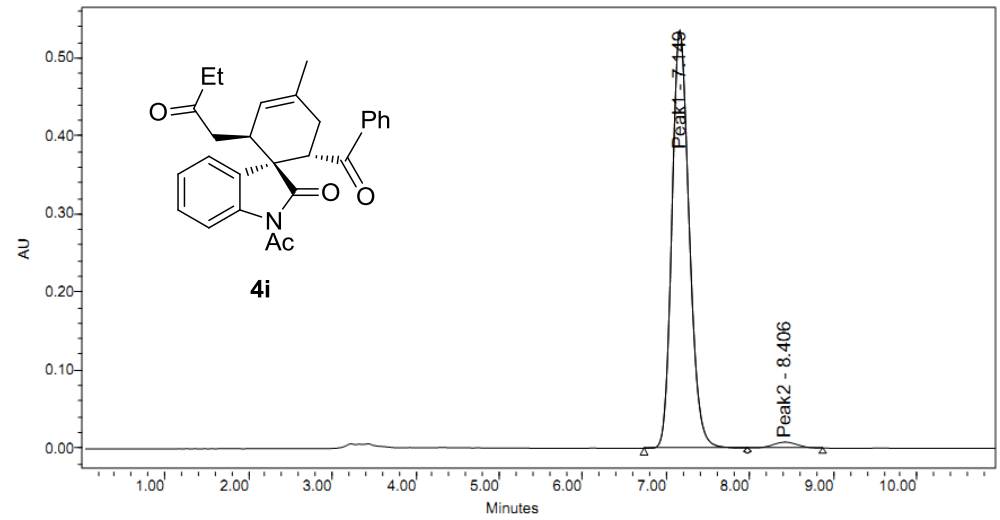





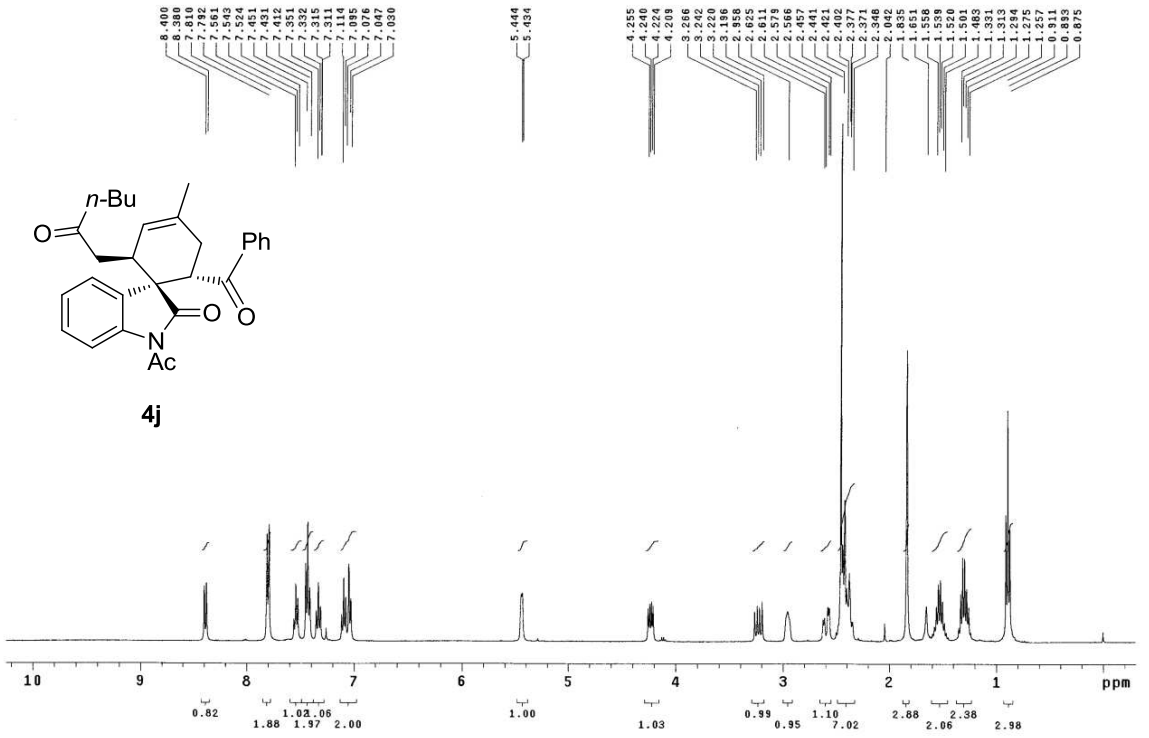

**4i**



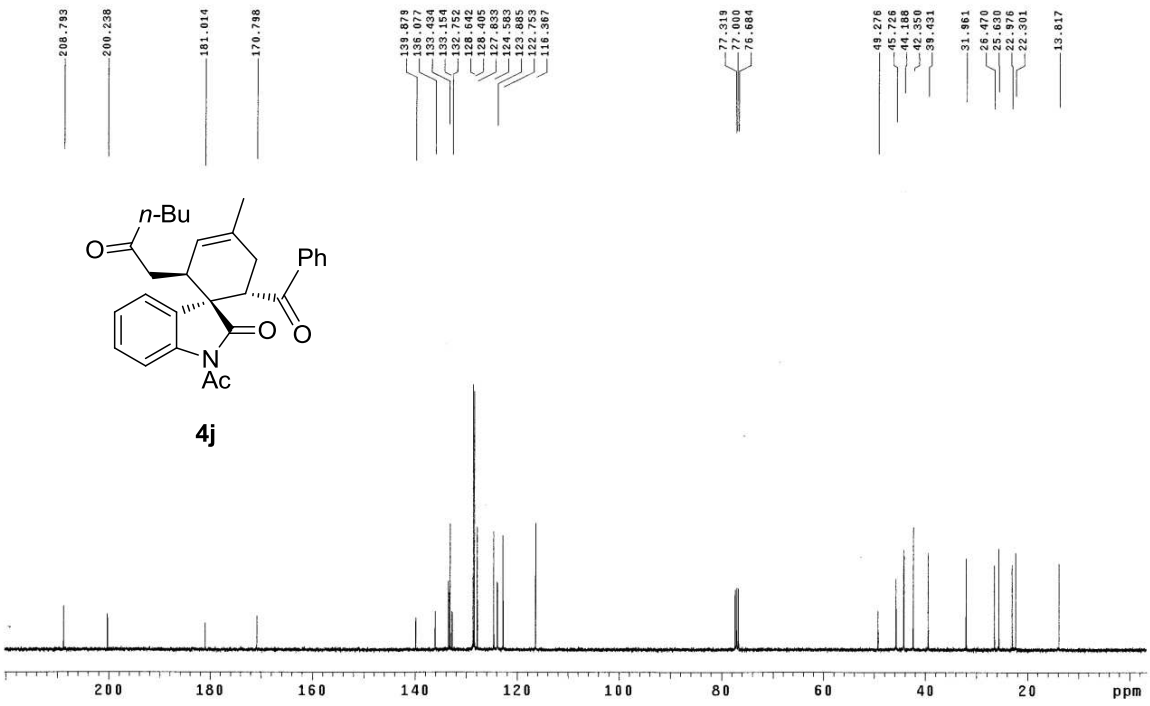

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 7.047 | 4672621 | 48.40 | 220051 | 52.96 |
| 2 | Peak2 | 8.300 | 4982238 | 51.60 | 195435 | 47.04 |



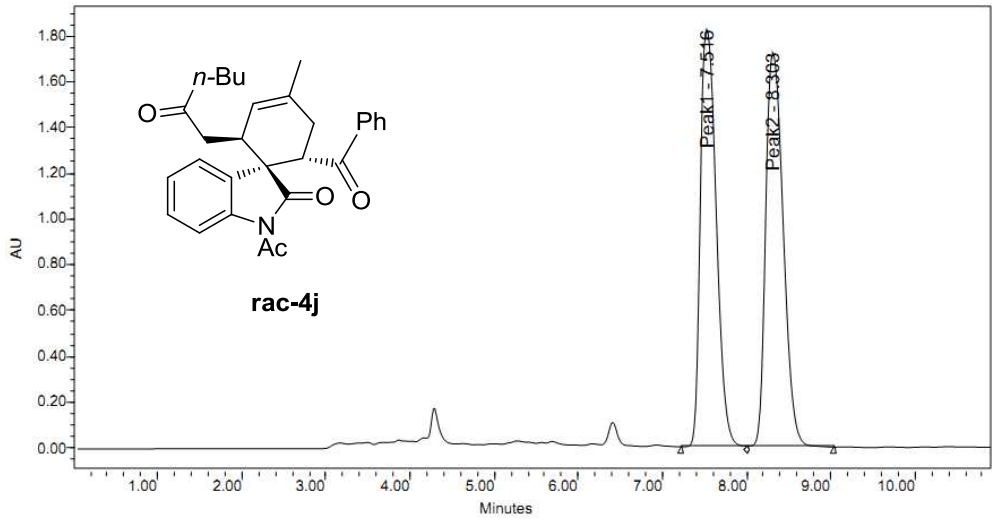

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 7.149 | 7705135 | 97.91 | 535843 | 98.57 |
| 2 | Peak2 | 8.406 | 164798 | 2.09 | 7766 | 1.43 |



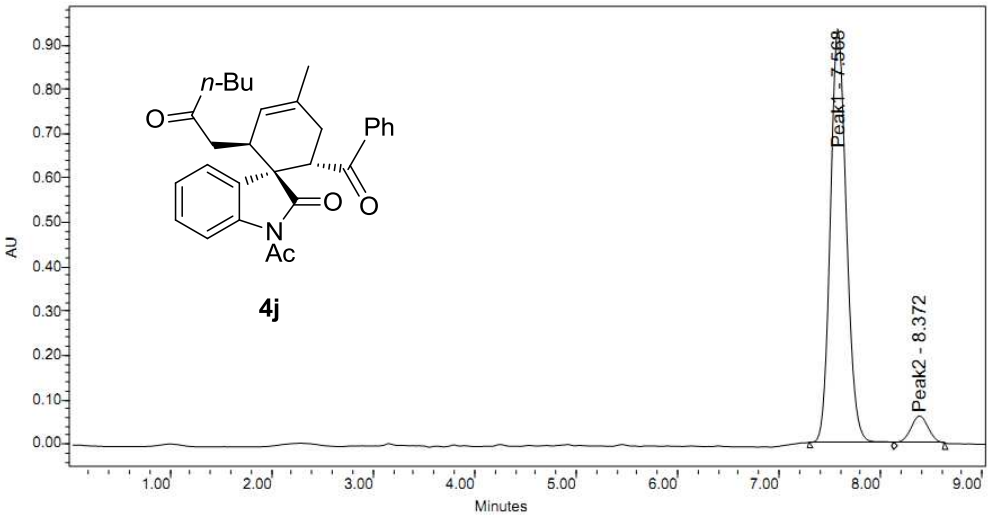

**4j**



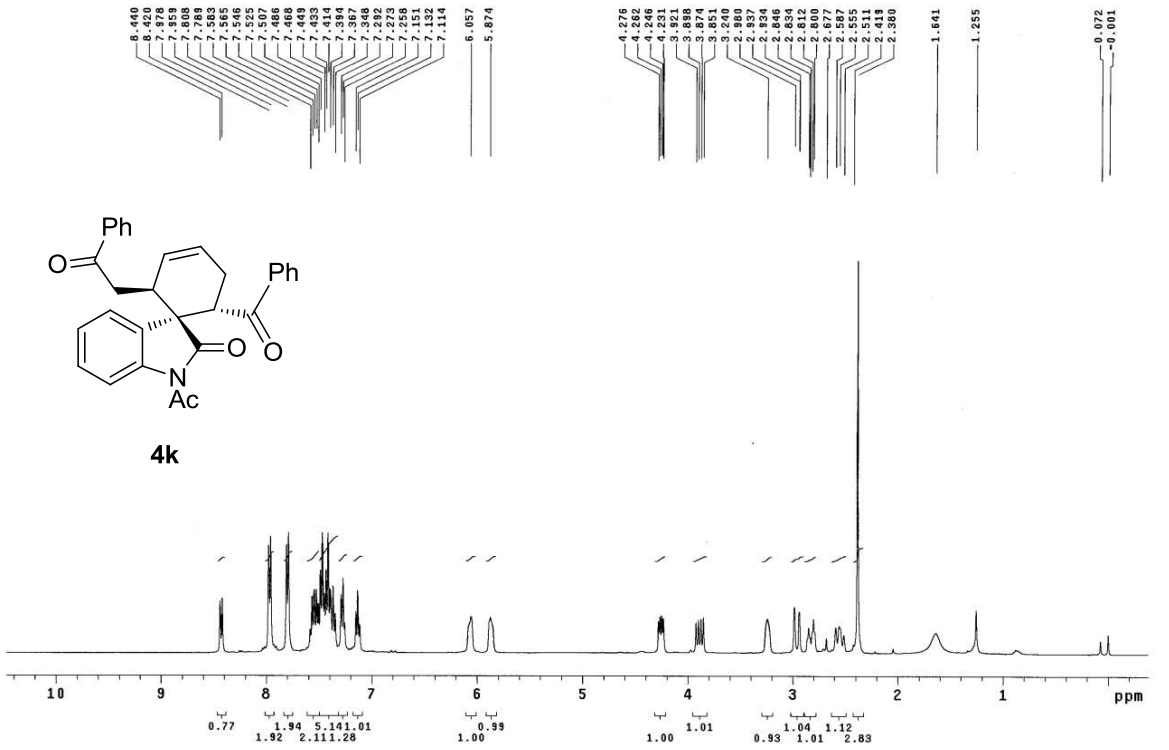

**4j**



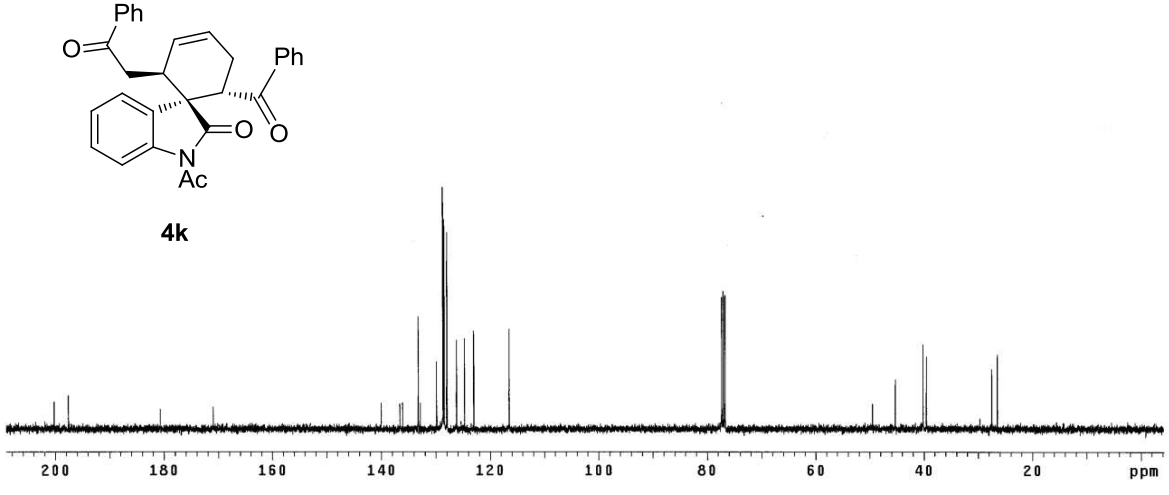

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 7.516 | 23983406 | 49.00 | 1825974 | 51.44 |
| 2 | Peak2 | 8.303 | 24962532 | 51.00 | 1723748 | 48.56 |



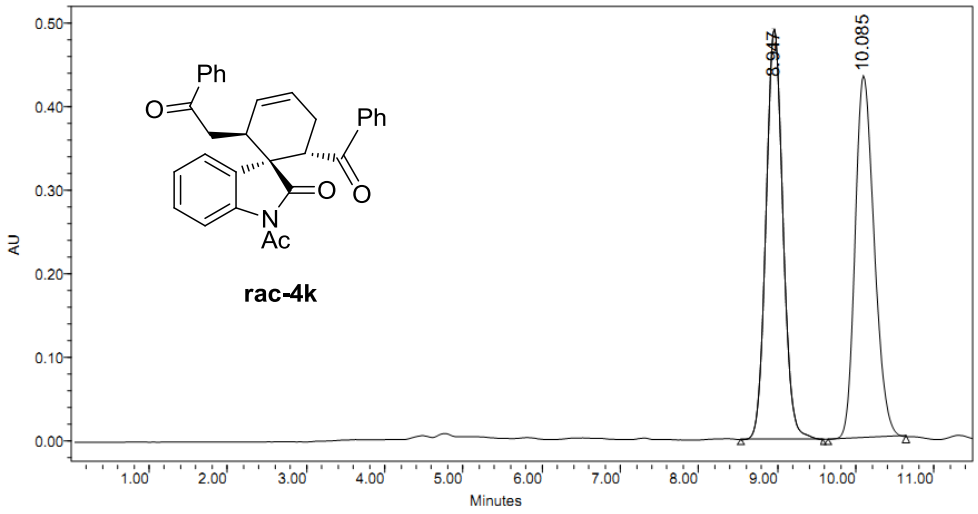

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 7.568 | 10269733 | 93.26 | 931942 | 93.83 |
| 2 | Peak2 | 8.372 | 742034 | 6.74 | 61259 | 6.17 |




**4k**

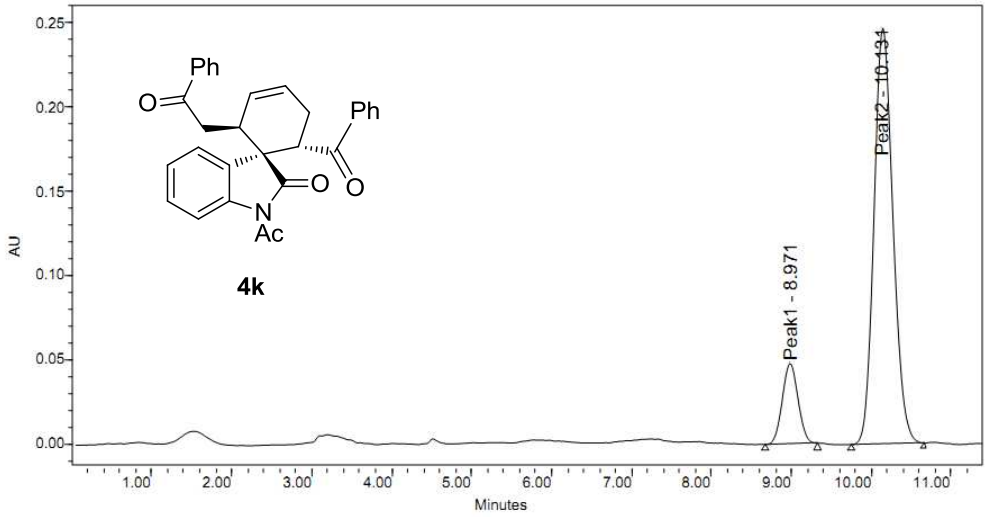



**4k**



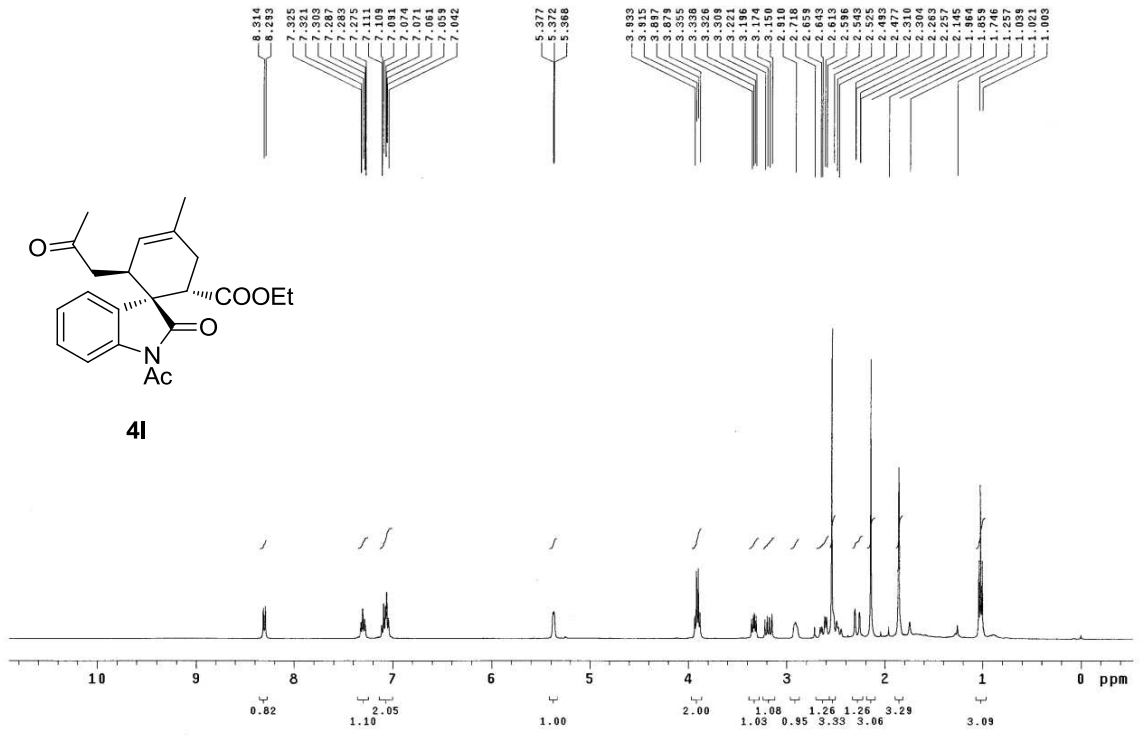

**rac-4k**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 8.947 | 7362425 | 50.03 | 491987 | 53.12 |
| 2 | 10.085 | 7353706 | 49.97 | 434190 | 46.88 |

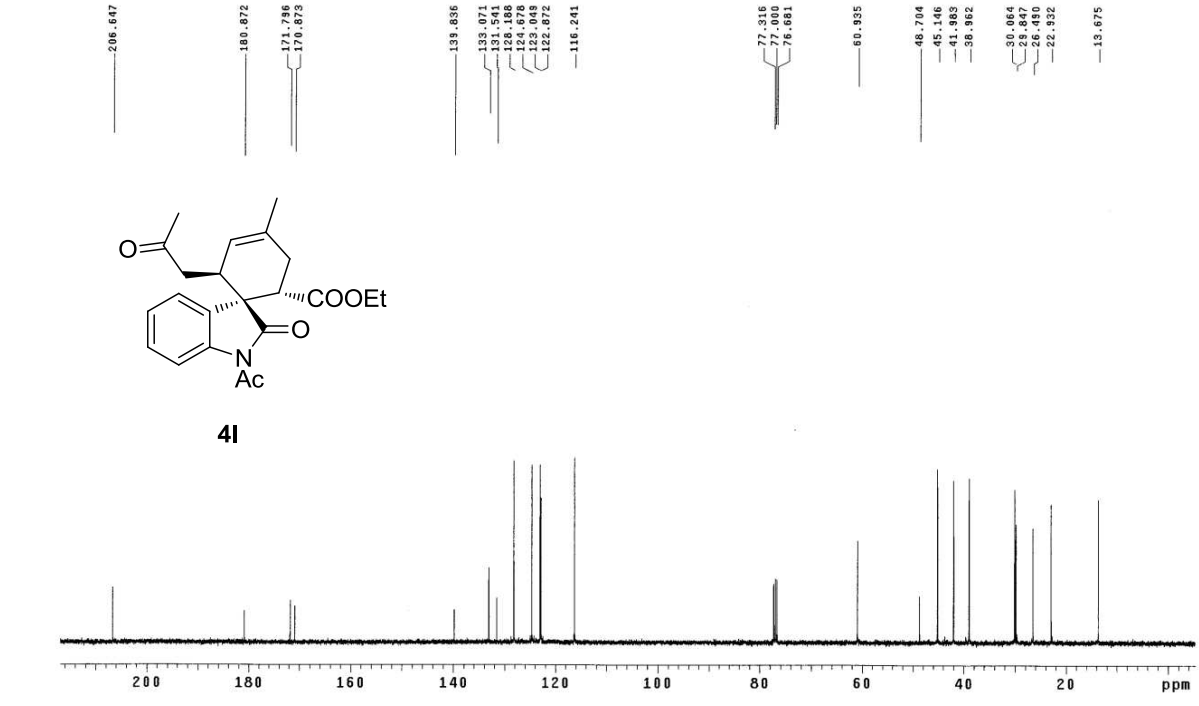



**4k**

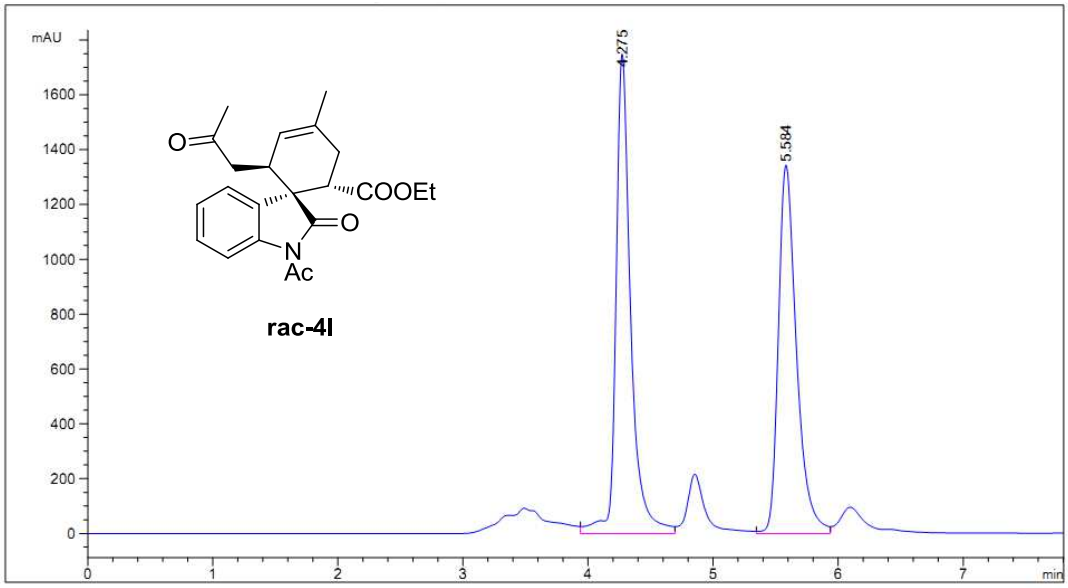
| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 8.971 | 652889 | 13.84 | 47728 | 16.21 |
| 2 | Peak2 | 10.131 | 4064297 | 86.16 | 246779 | 83.79 |




**4l**

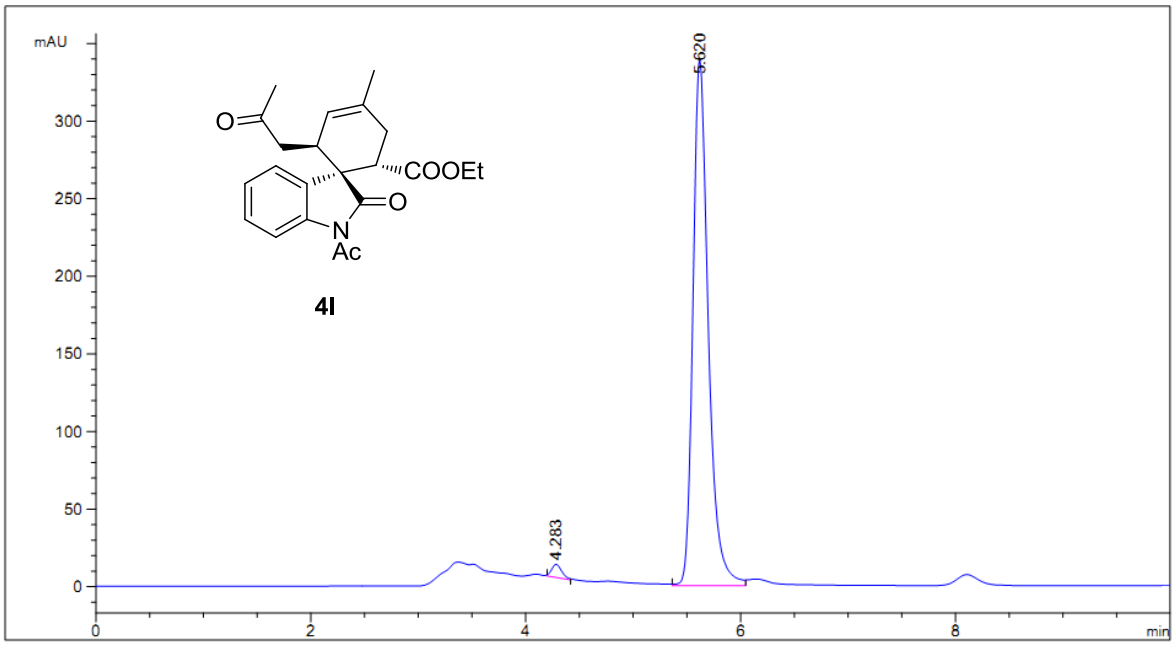



**4l**



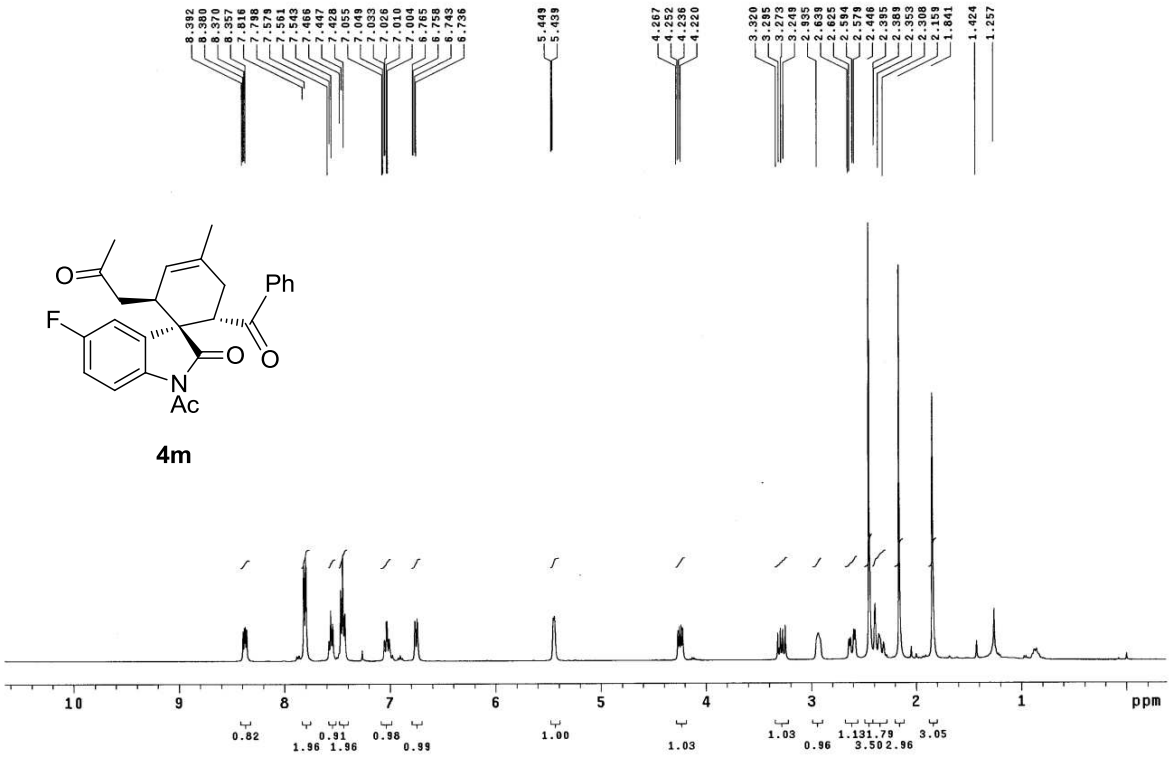

**rac-4l**

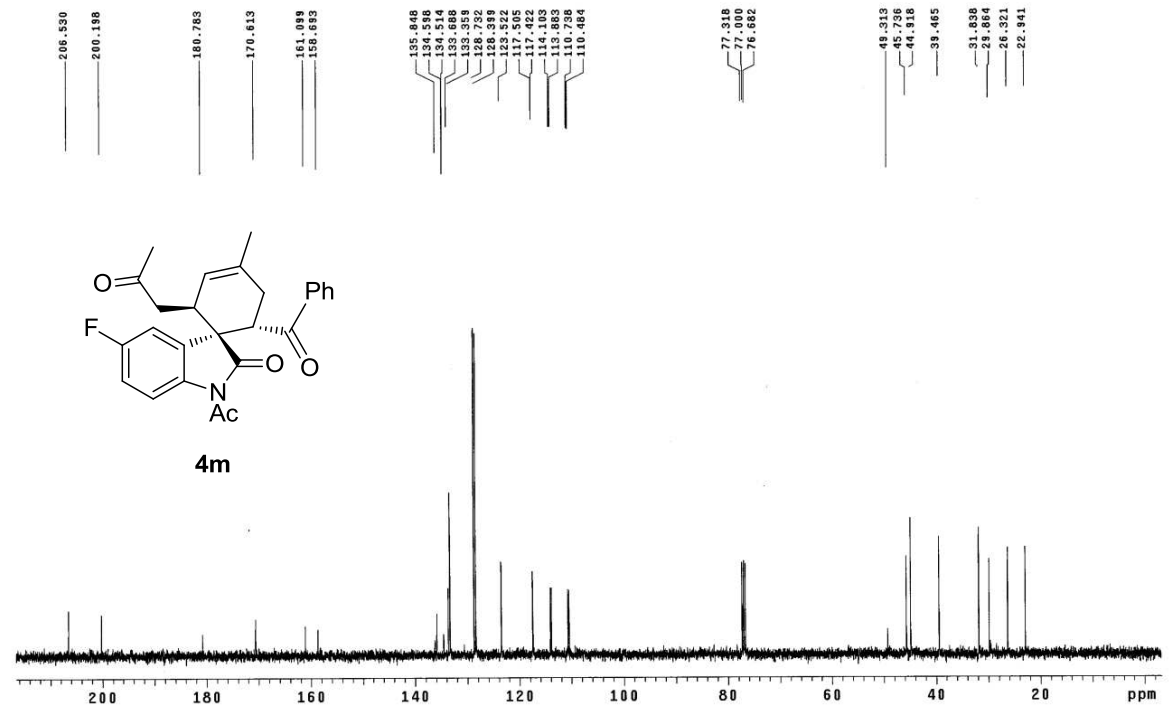
| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.275 | VV | 0.1256 | 1.43070e4 | 1730.41858 | 51.3838 |
| 2 | 5.584 | VV | 0.1527 | 1.35364e4 | 1340.61377 | 48.6162 |

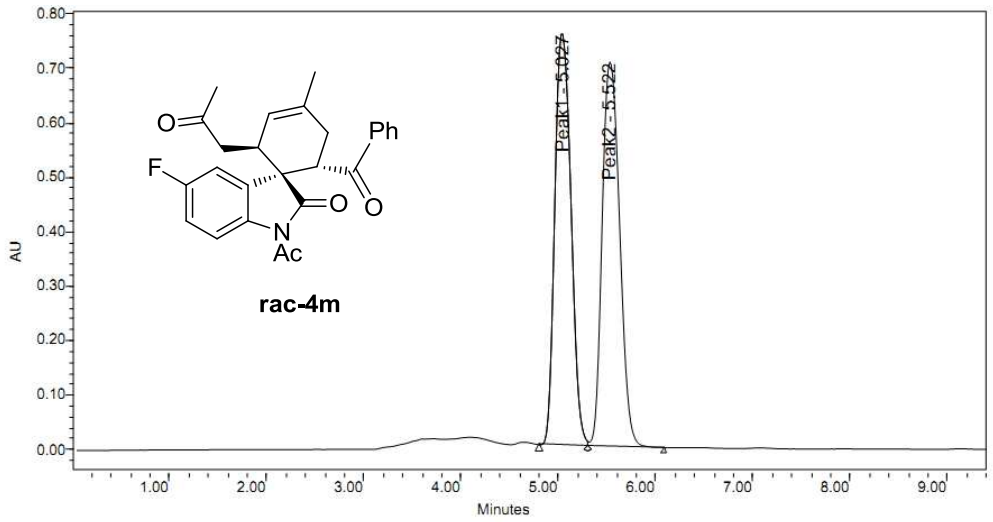



**4l**

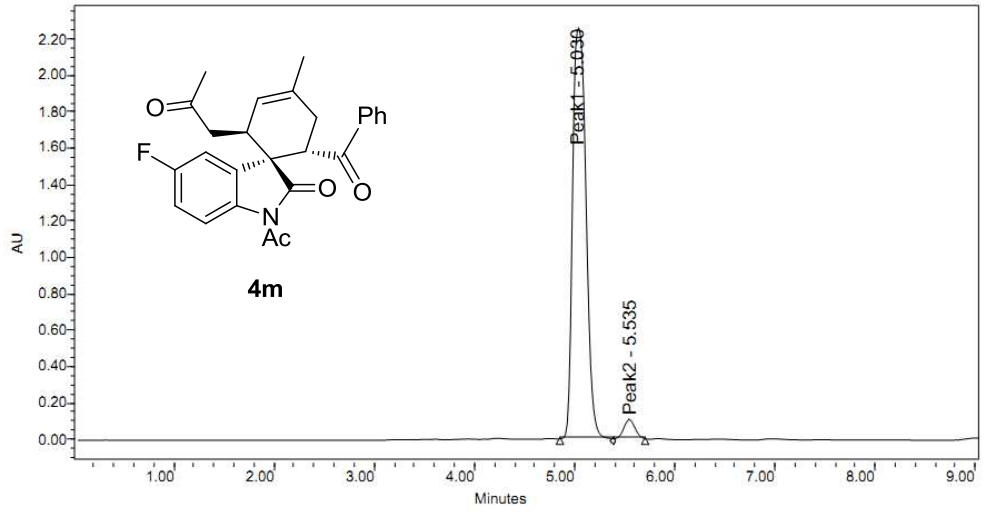
| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.283 | MM | 0.1085 | 54.84772 | 8.42430 | 1.6059 |
| 2 | 5.620 | VV | 0.1569 | 3360.59937 | 337.53897 | 98.3941 |



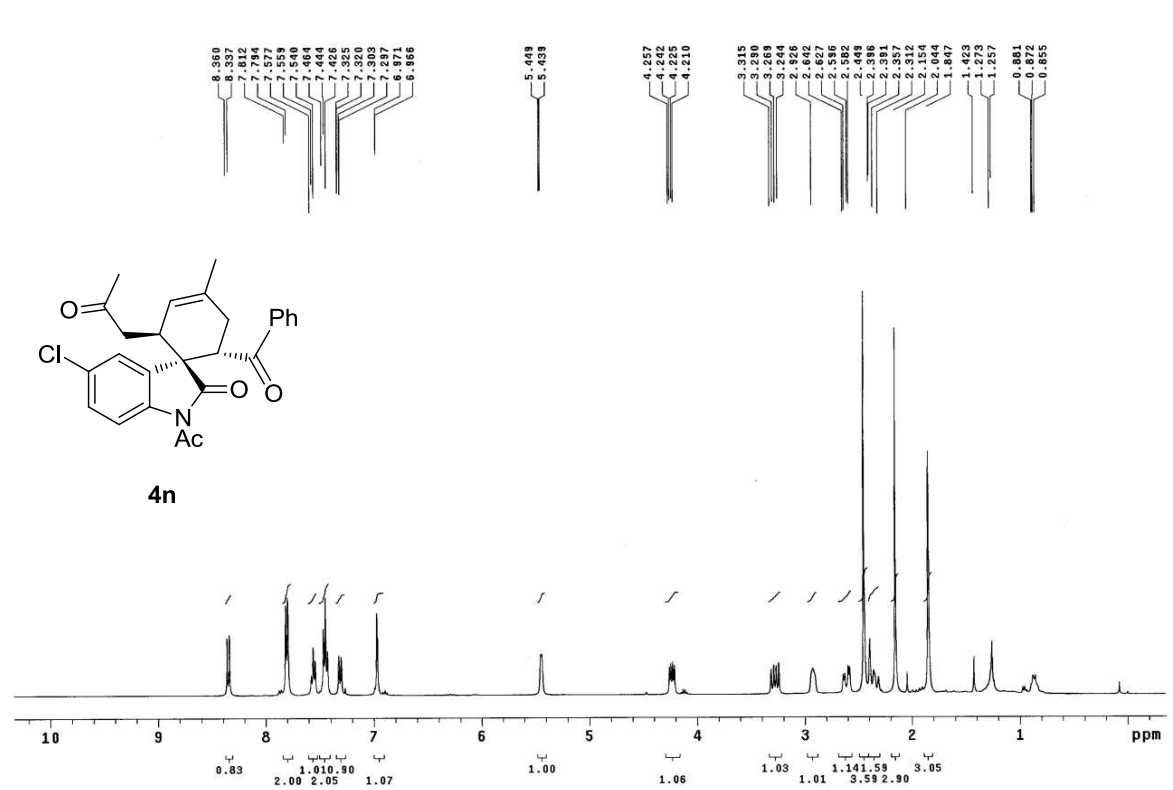





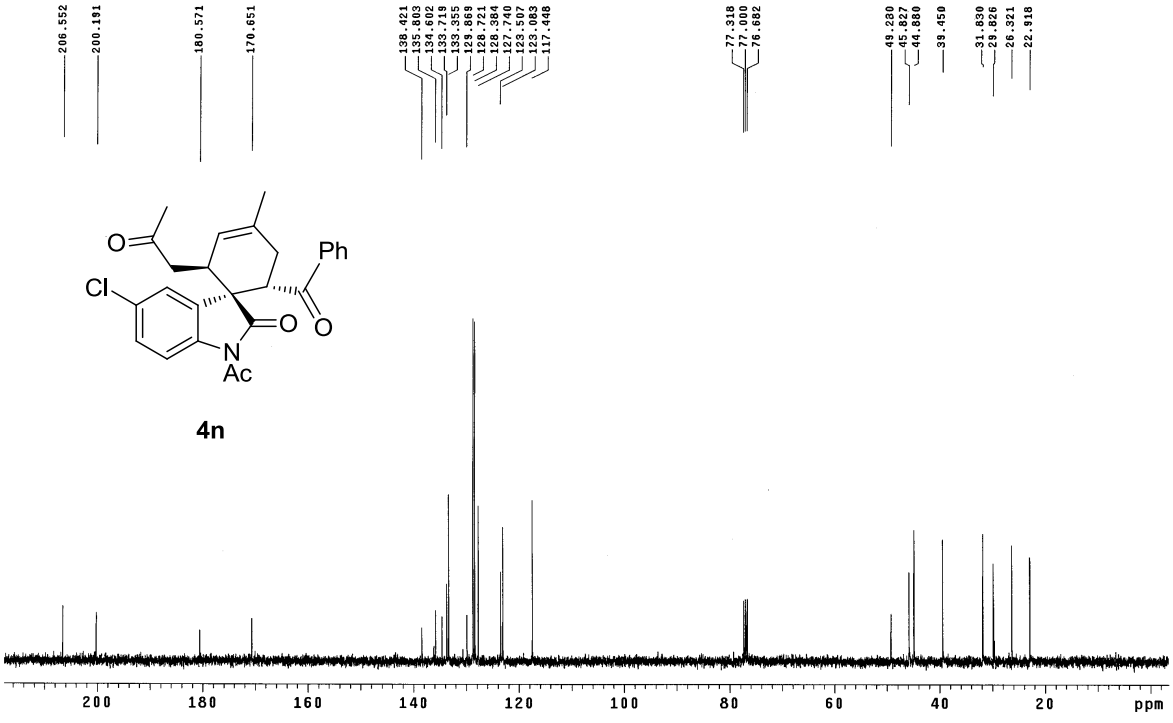

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.027 | 8804329 | 49.87 | 756942 | 51.72 |
| 2 | Peak2 | 5.522 | 8851394 | 50.13 | 706624 | 48.28 |



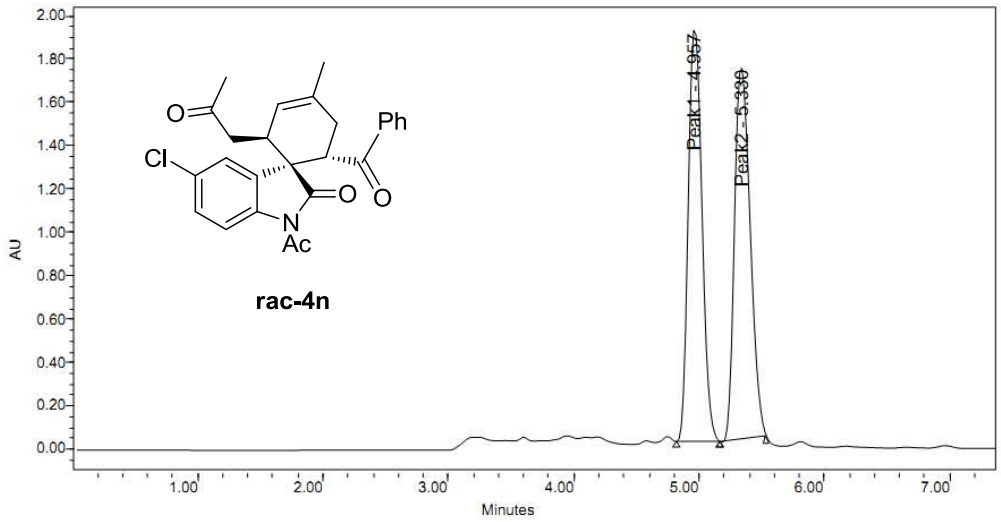

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.030 | 20988732 | 96.22 | 2263985 | 95.53 |
| 2 | Peak2 | 5.535 | 824595 | 3.78 | 106022 | 4.47 |



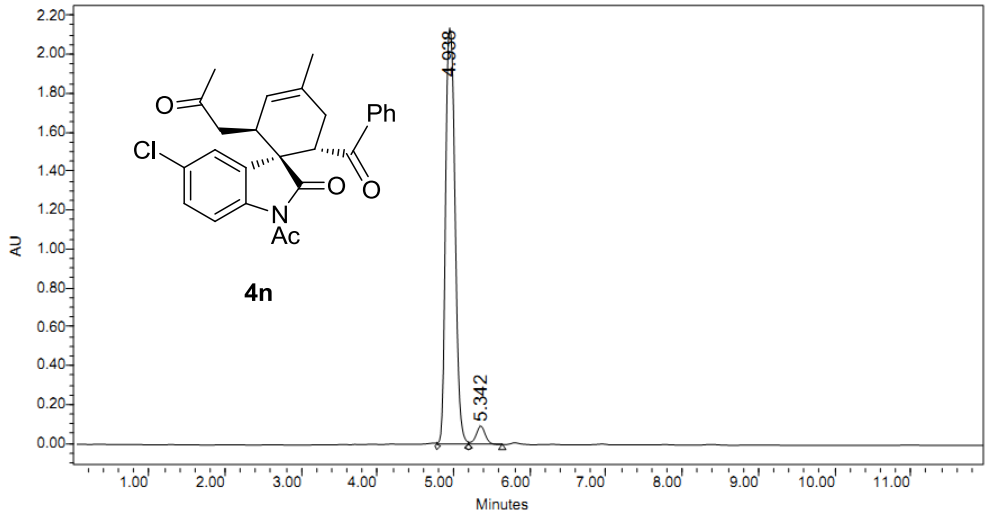

**4n**



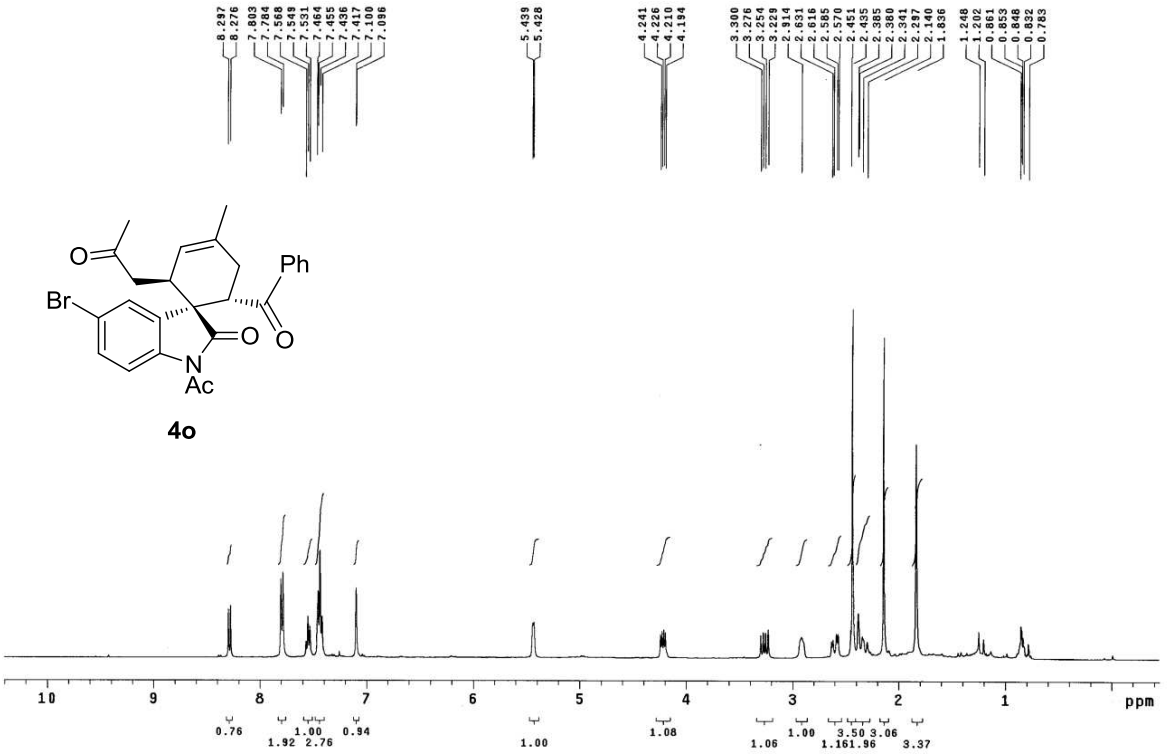

**4n**

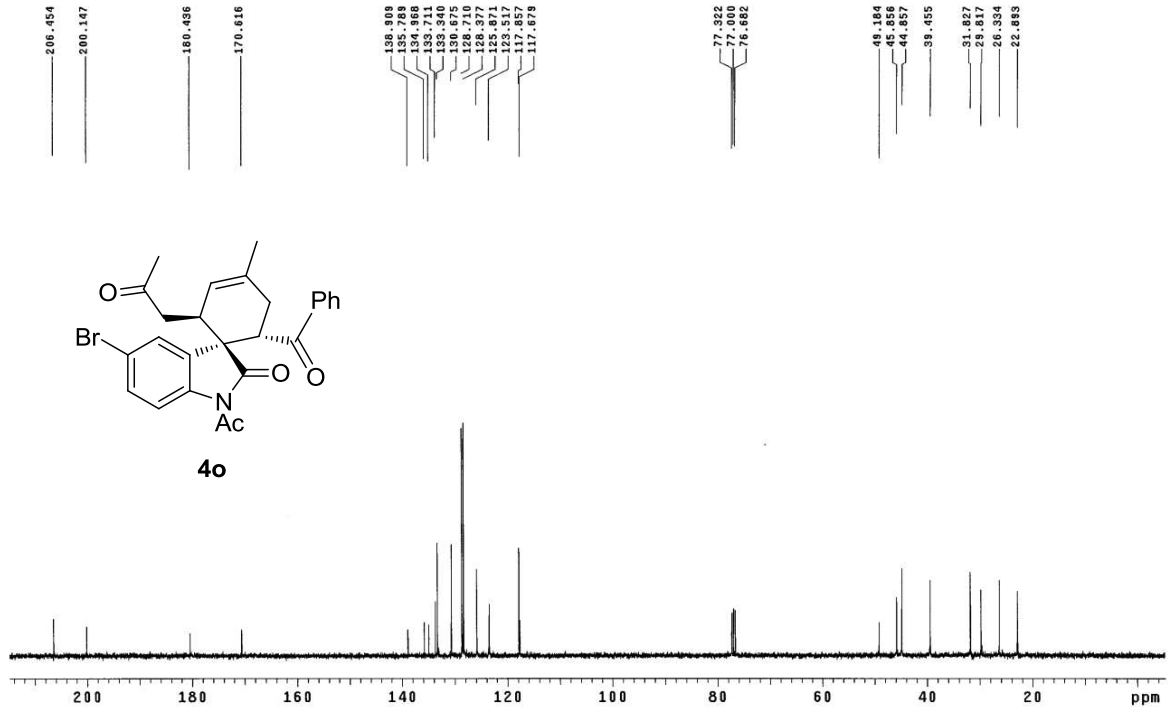


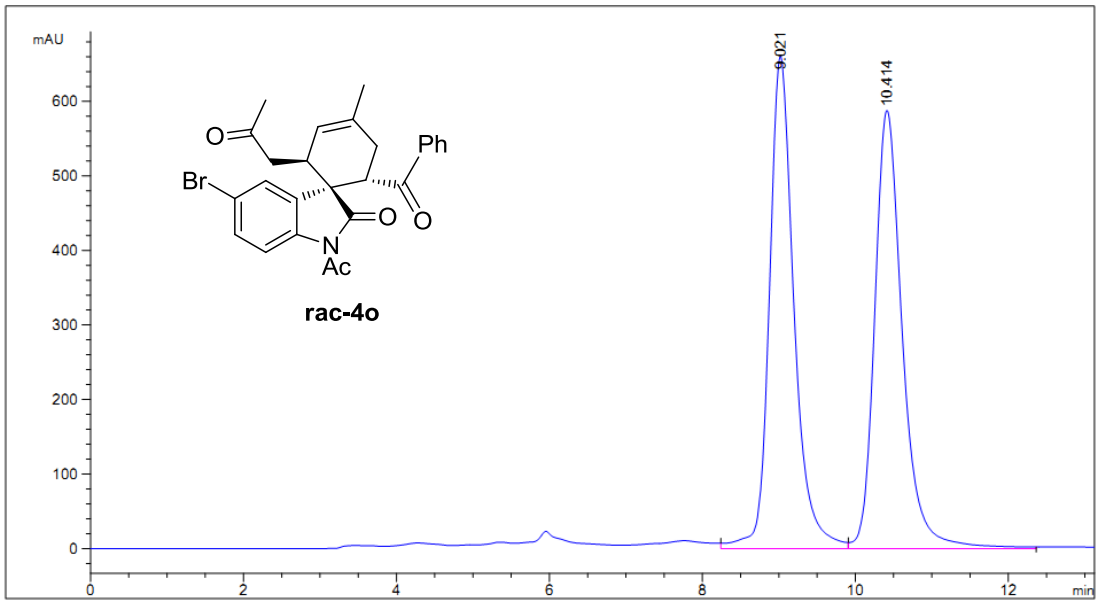

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 4.957 | 14539909 | 49.28 | 1916233 | 52.74 |
| 2 | Peak2 | 5.330 | 14966093 | 50.72 | 1717117 | 47.26 |




| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 4.938 | 18457891 | 95.83 | 2148241 | 95.80 |
| 2 | 5.342 | 802828 | 4.17 | 94179 | 4.20 |

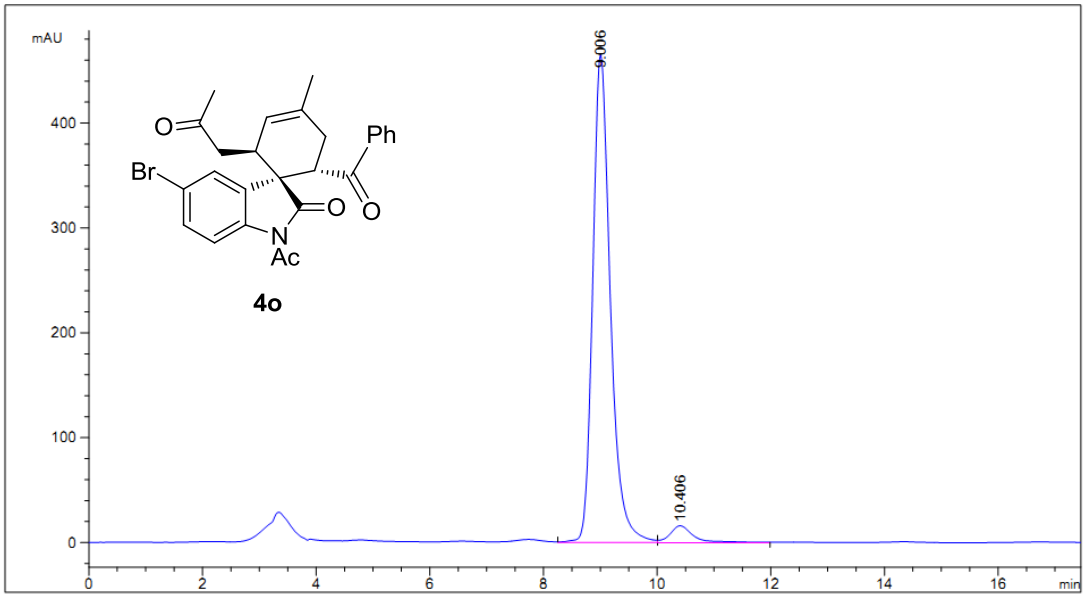




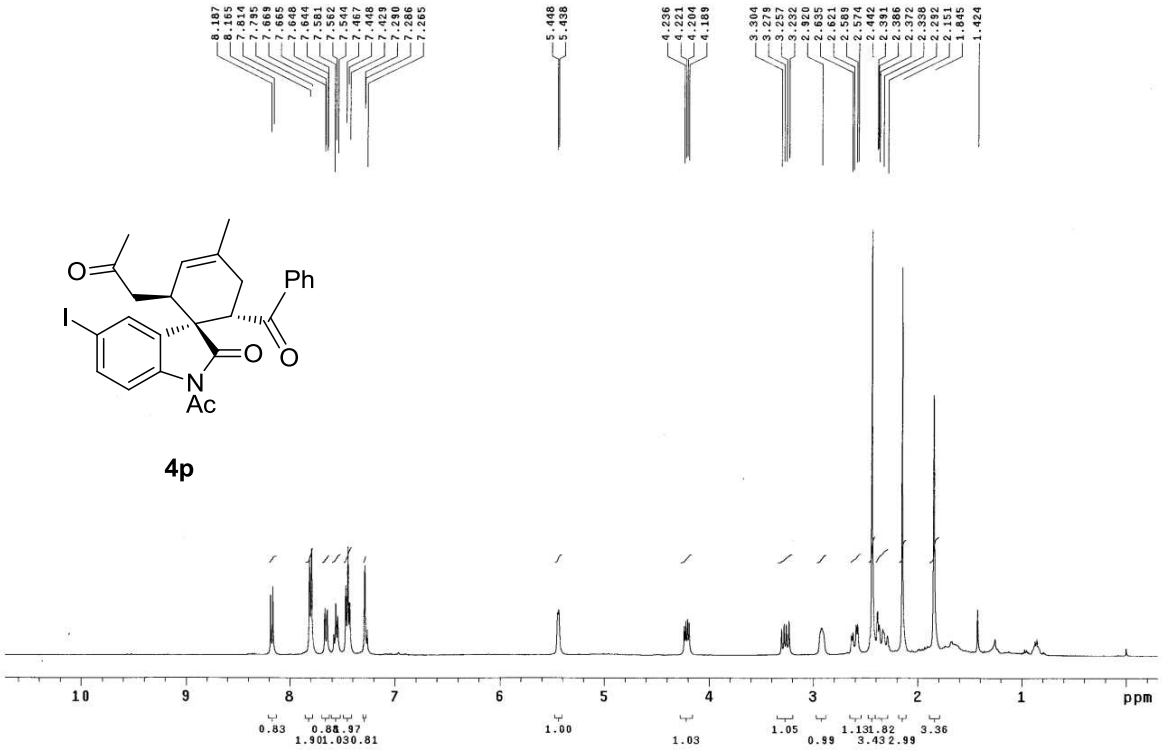

rac-4o

| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.021 | VV | 0.3371 | 1.47894e4 | 660.08008 | 50.0021 |
| 2 | 10.414 | VV | 0.3810 | 1.47882e4 | 587.57233 | 49.9979 |

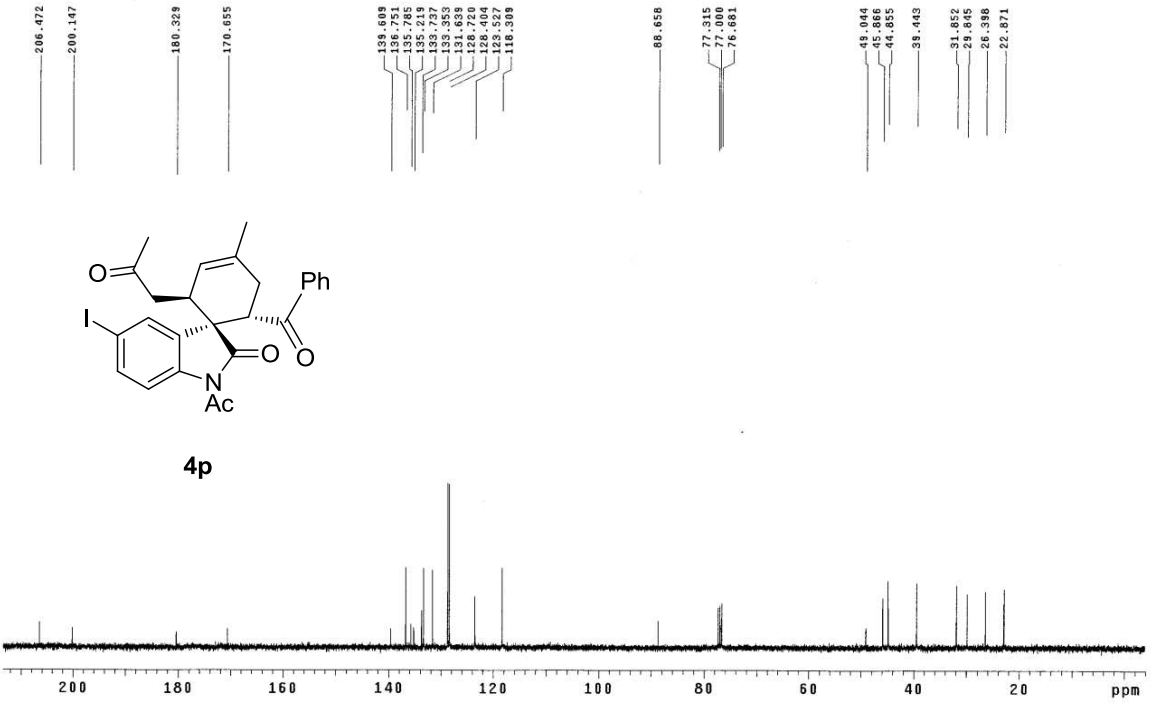



4o

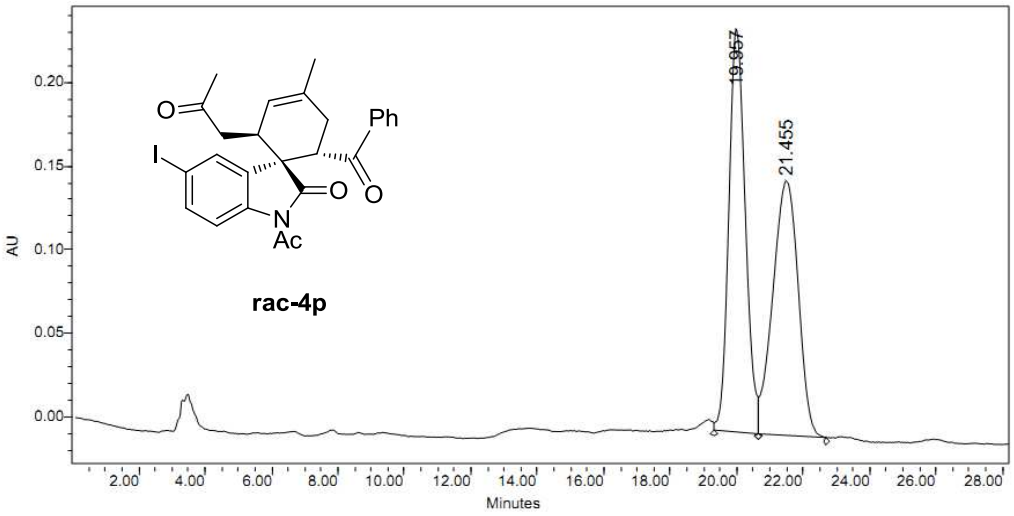
| Peak # | RetTime [min] | Type | Width [min] | Area mAU *s | Height [mAU ] | Area % |
|---|---|---|---|---|---|---|
| 1 | 9.006 | VV | 0.3332 | 1.00172e4 | 464.39960 | 95.5457 |
| 2 | 10.406 | VB | 0.4298 | 466.99796 | 16.18357 | 4.4543 |




**4p**

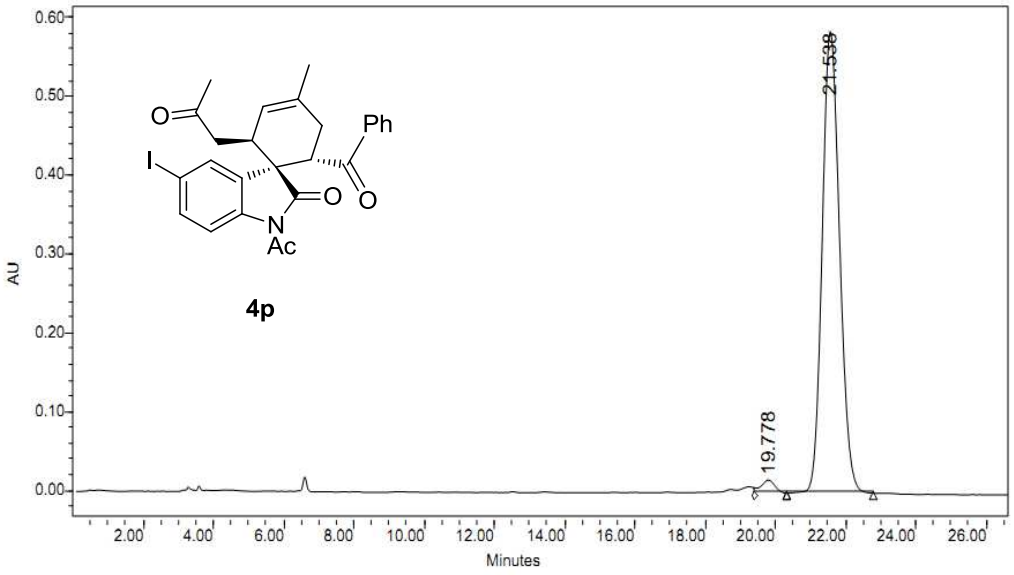



**4p**



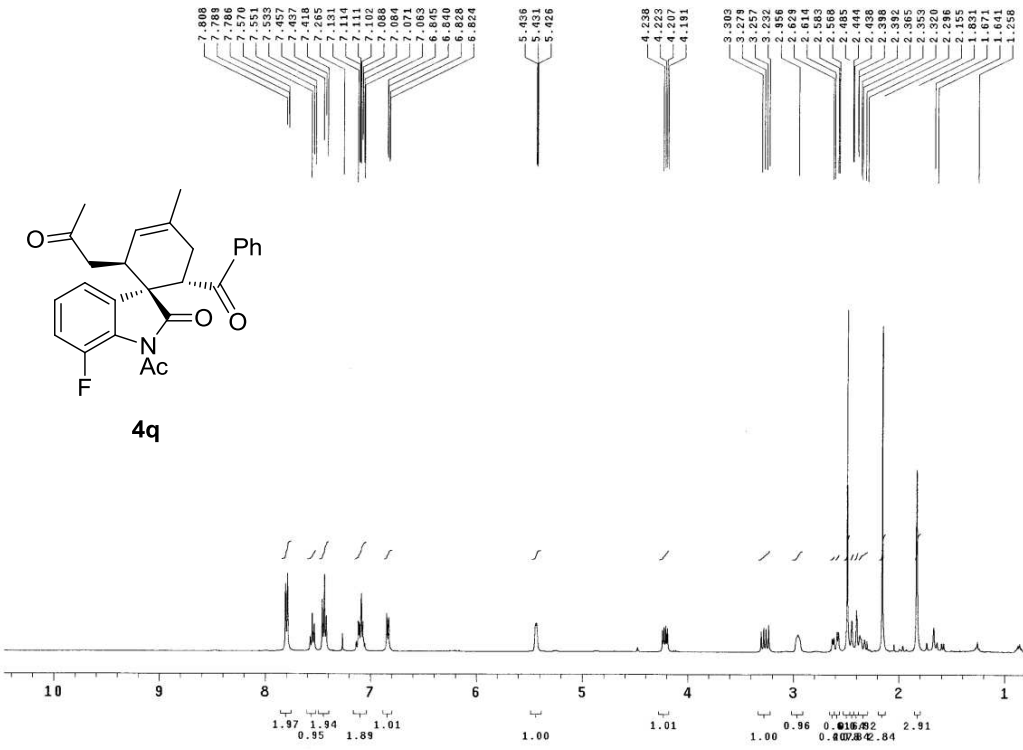

**rac-4p**

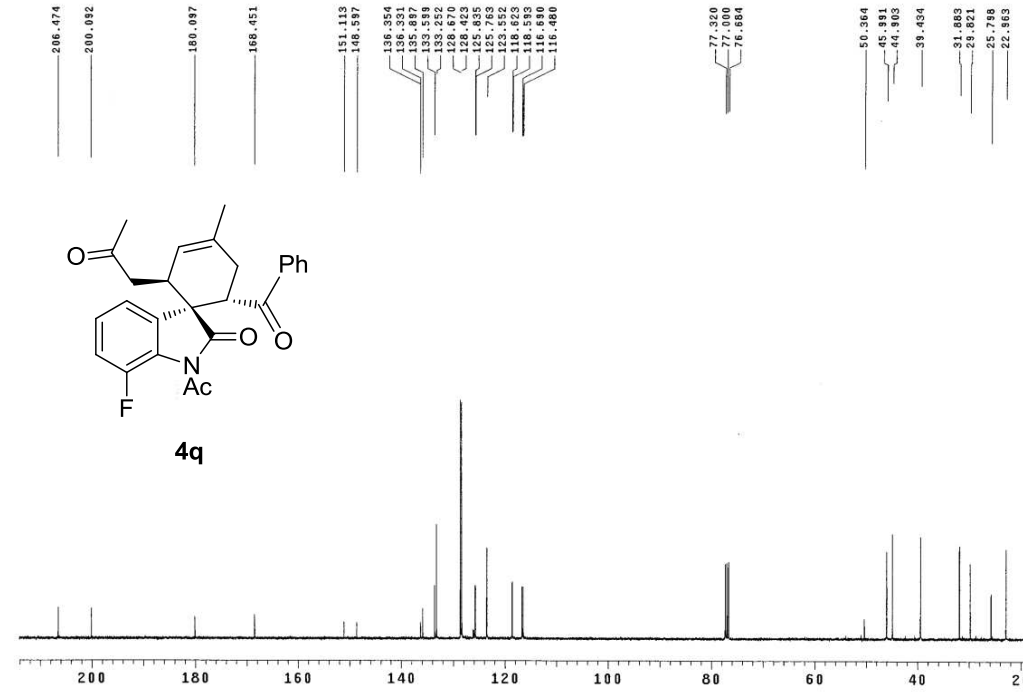
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 19.957 | 8376559 | 50.67 | 241587 | 61.26 |
| 2 | 21.455 | 8155940 | 49.33 | 152769 | 38.74 |

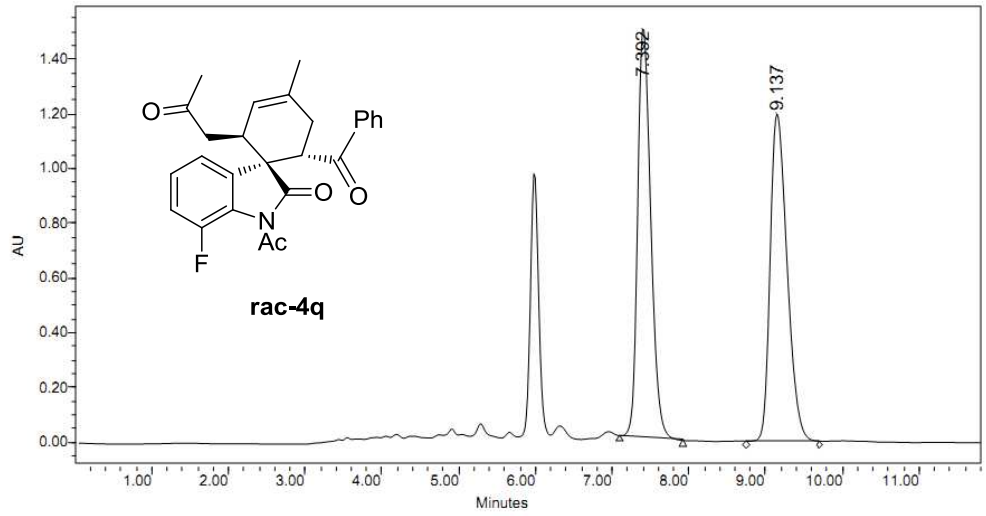



**4p**

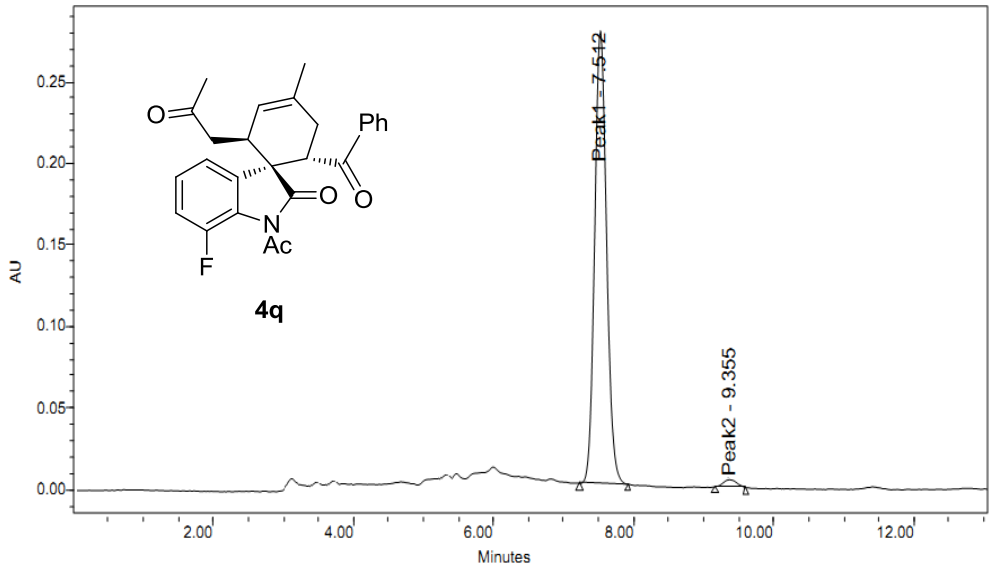
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 19.778 | 431703 | 2.10 | 16126 | 2.68 |
| 2 | 21.538 | 20151951 | 97.90 | 585499 | 97.32 |



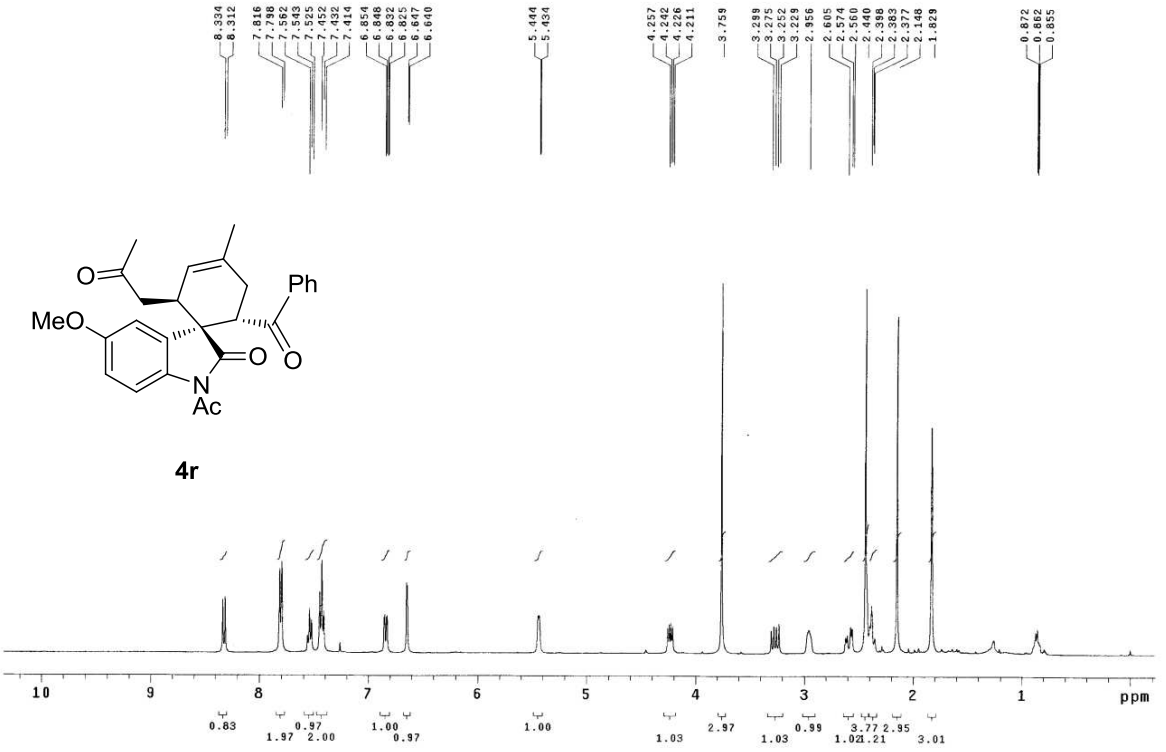



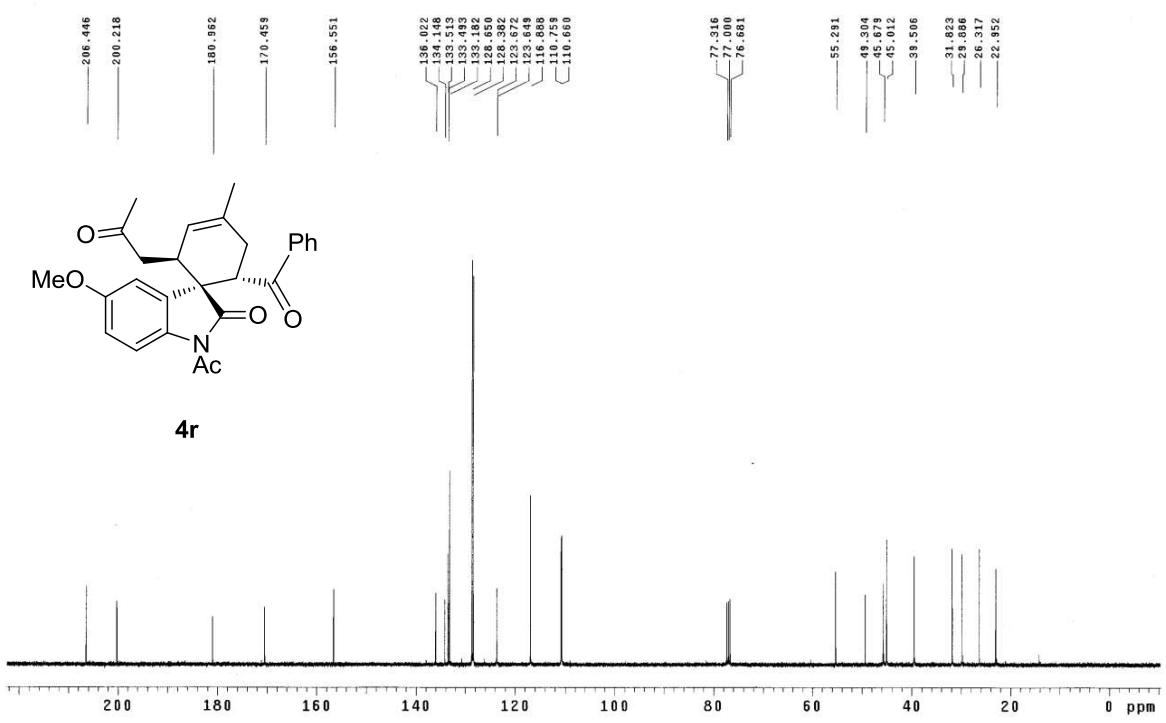


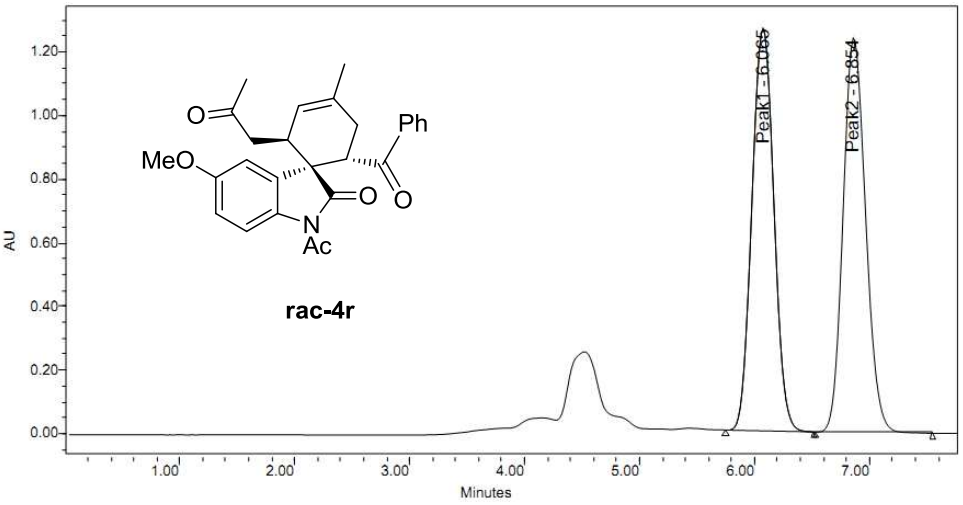

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 7.392 | 17775401 | 49.11 | 1500902 | 55.59 |
| 2 | 9.137 | 18419489 | 50.89 | 1198857 | 44.41 |




| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 7.512 | 3279779 | 98.23 | 277830 | 98.45 |
| 2 | Peak2 | 9.355 | 58987 | 1.77 | 4374 | 1.55 |

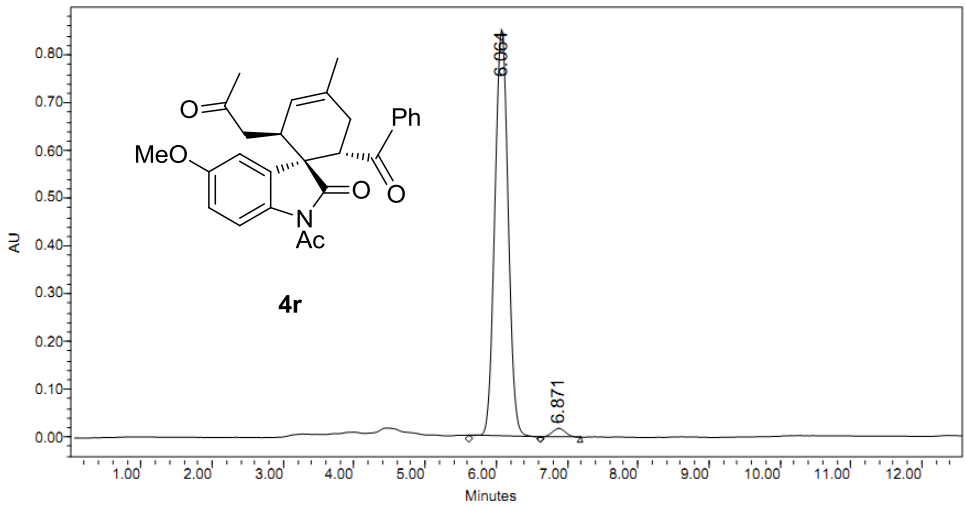




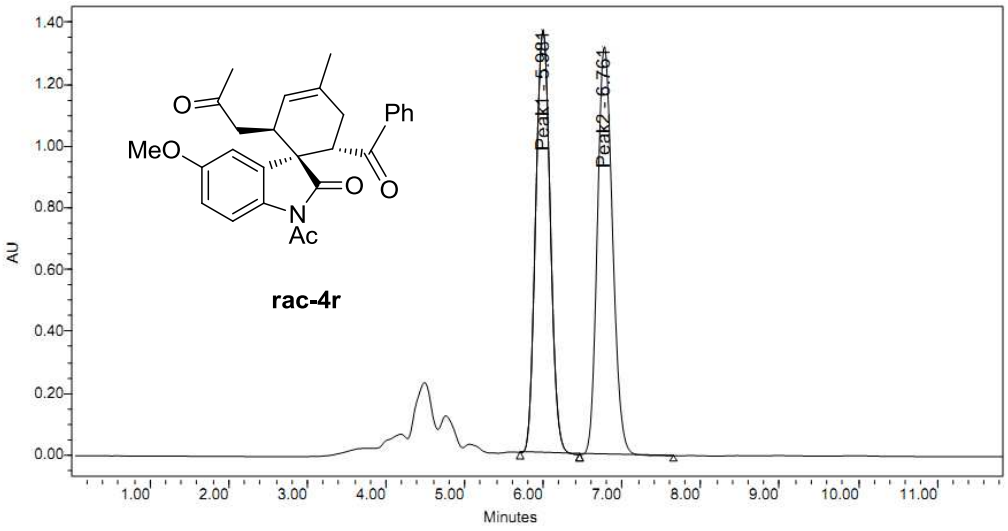

**rac-4r**

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 6.065 | 16762555 | 49.80 | 1264545 | 50.48 |
| 2 | Peak2 | 6.854 | 16897254 | 50.20 | 1240429 | 49.52 |



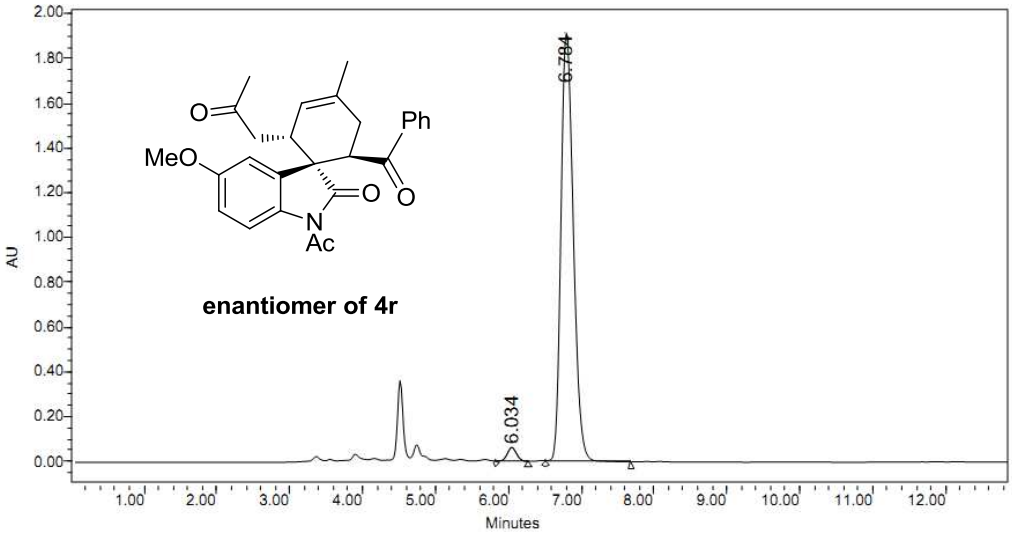

**4r**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.064 | 11160620 | 97.89 | 852772 | 97.91 |
| 2 | 6.871 | 240624 | 2.11 | 18245 | 2.09 |



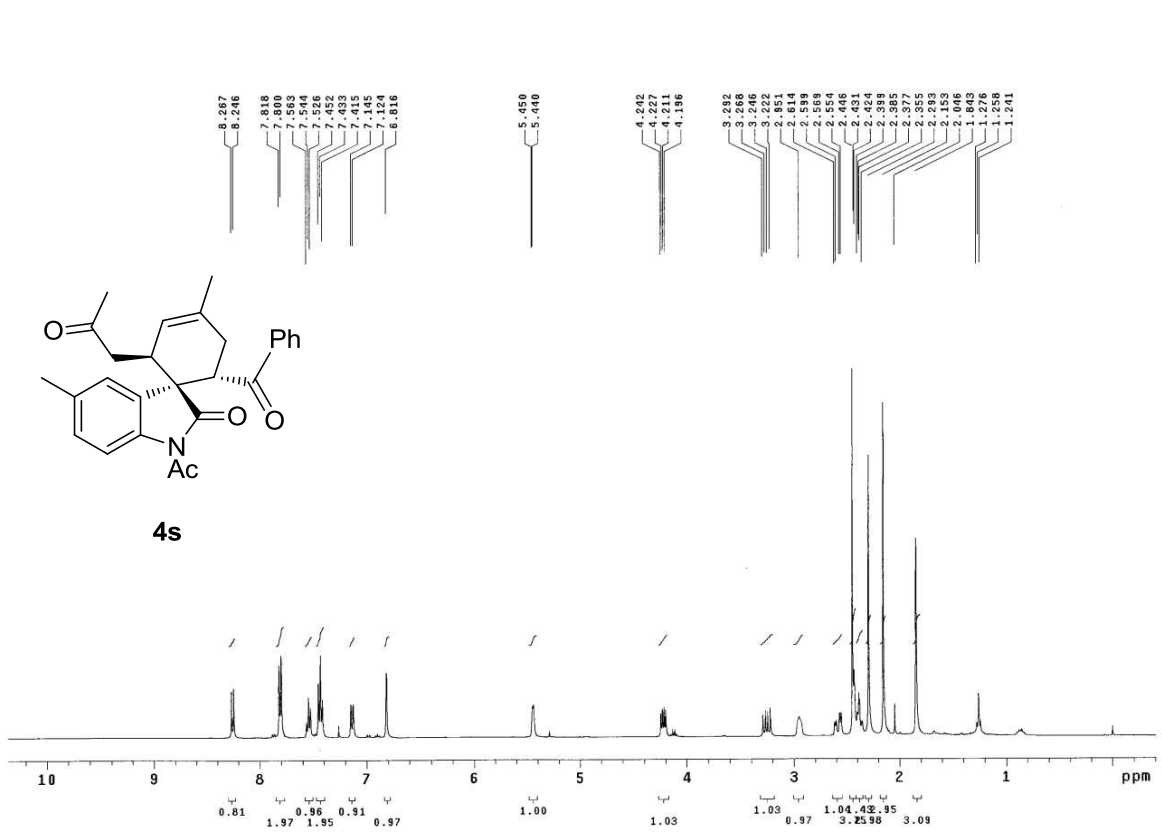

rac-4r

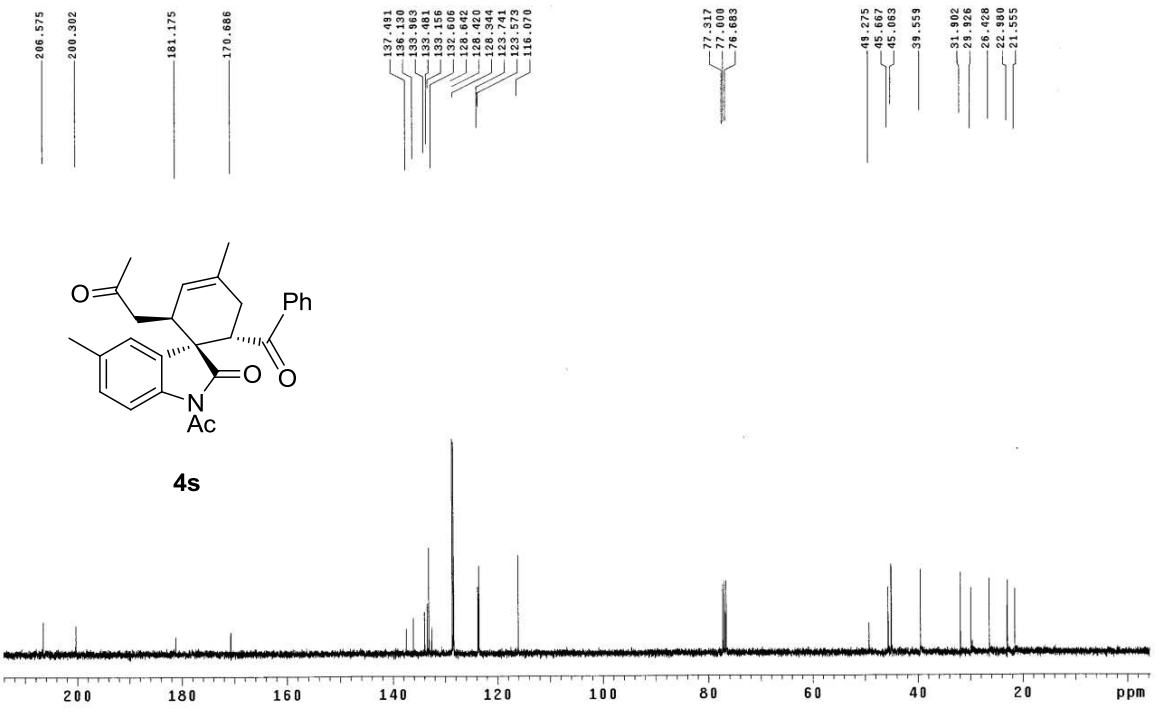
| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 5.981 | 17628527 | 49.81 | 1371635 | 50.89 |
| 2 | Peak2 | 6.761 | 17760537 | 50.19 | 1323870 | 49.11 |

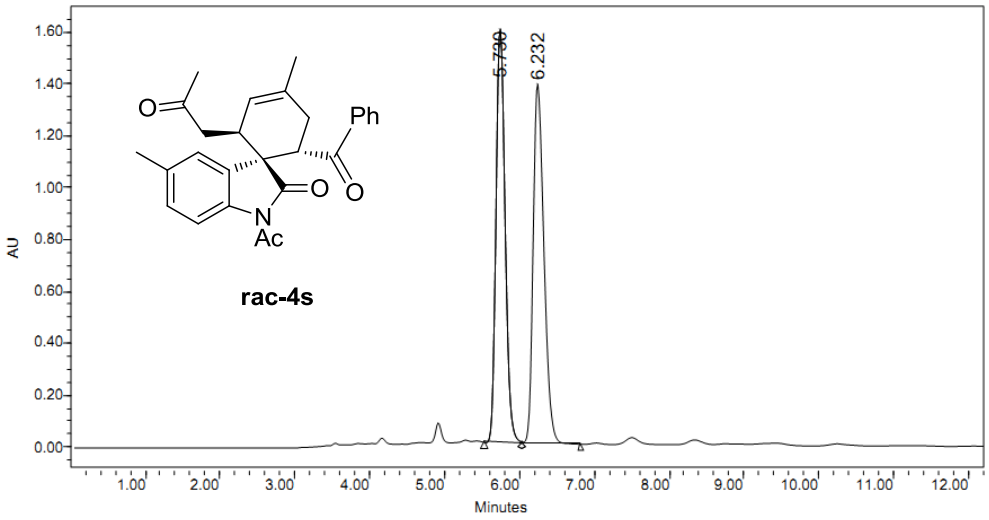



enantiomer of 4r

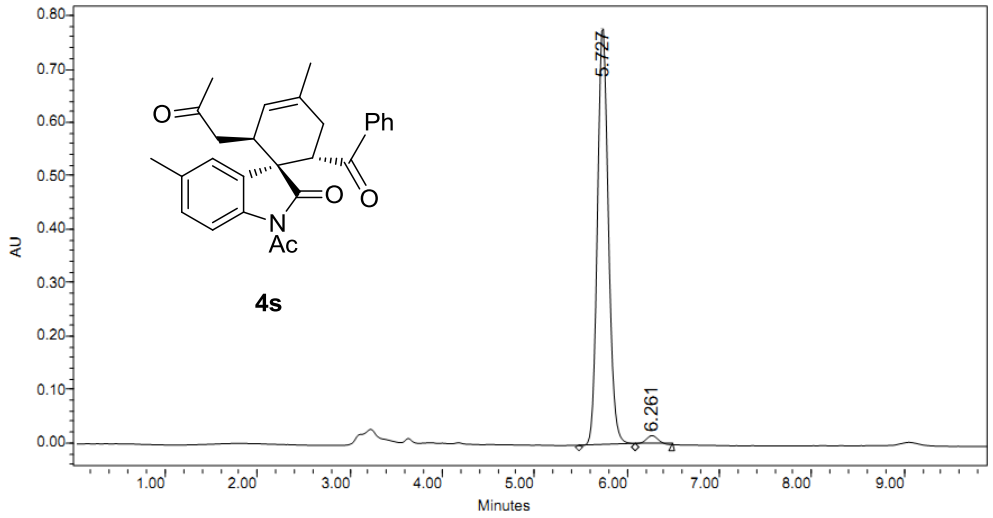
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 6.034 | 535712 | 2.31 | 61077 | 3.09 |
| 2 | 6.784 | 22620178 | 97.69 | 1914903 | 96.91 |



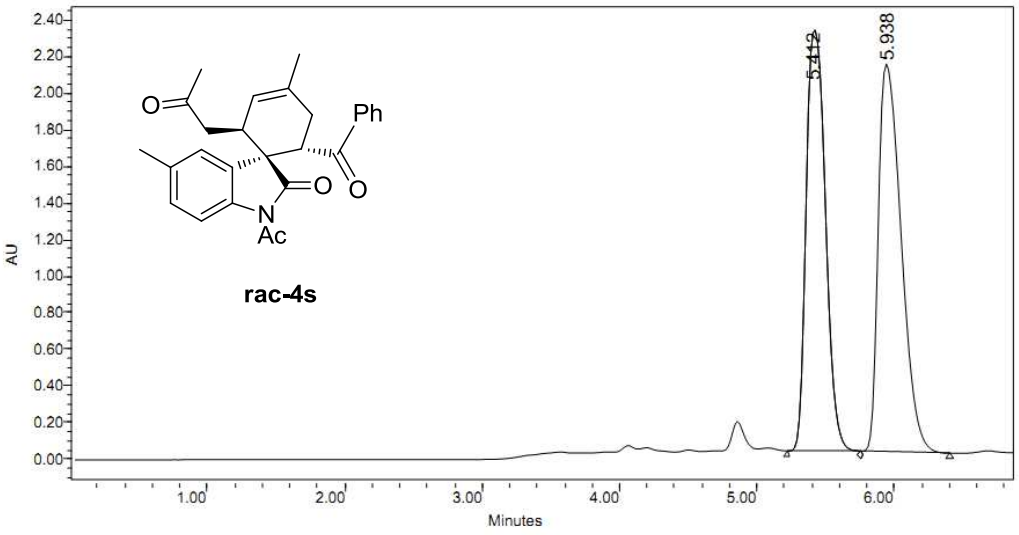






| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.730 | 13563327 | 49.47 | 1597168 | 53.52 |
| 2 | 6.232 | 13852330 | 50.53 | 1387123 | 46.48 |

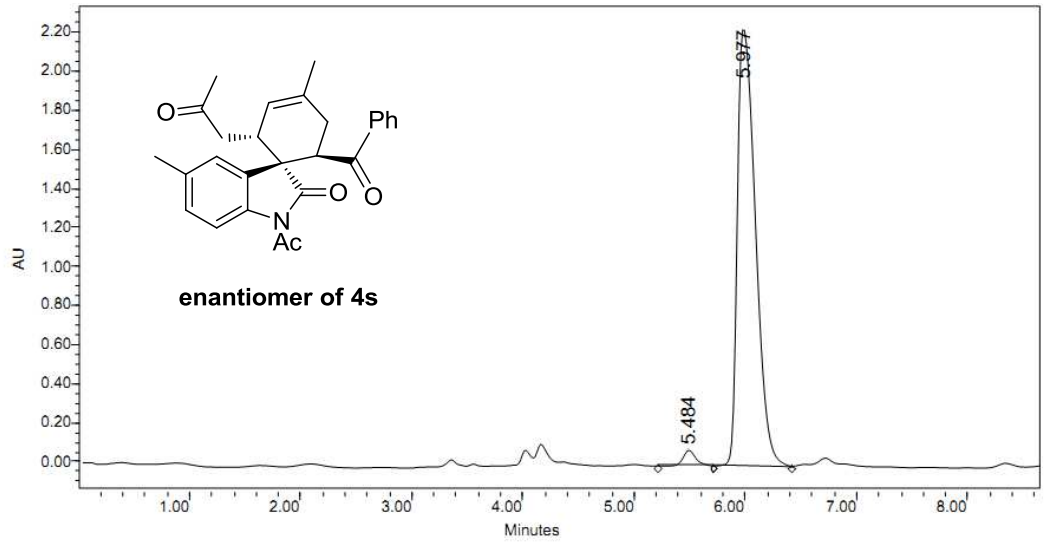



| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.727 | 6491143 | 97.45 | 783460 | 97.87 |
| 2 | 6.261 | 170120 | 2.55 | 17055 | 2.13 |



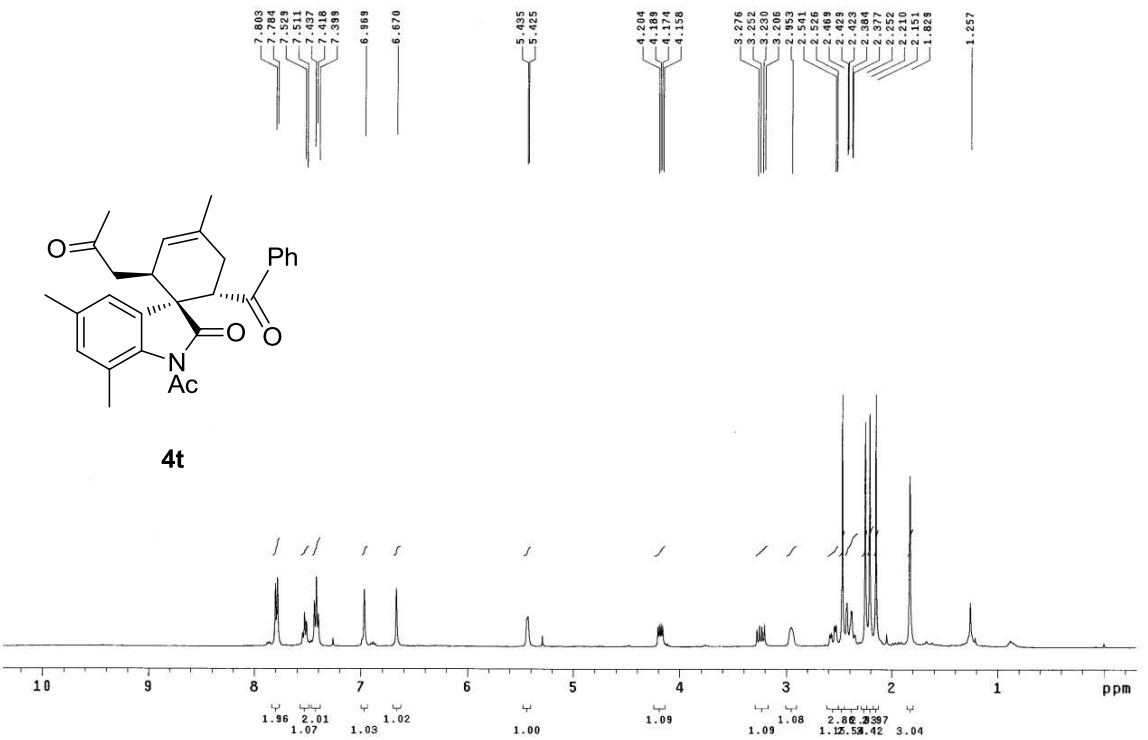

**rac-4s**

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.412 | 22572269 | 47.83 | 2307953 | 52.01 |
| 2 | 5.938 | 24624500 | 52.17 | 2129604 | 47.99 |

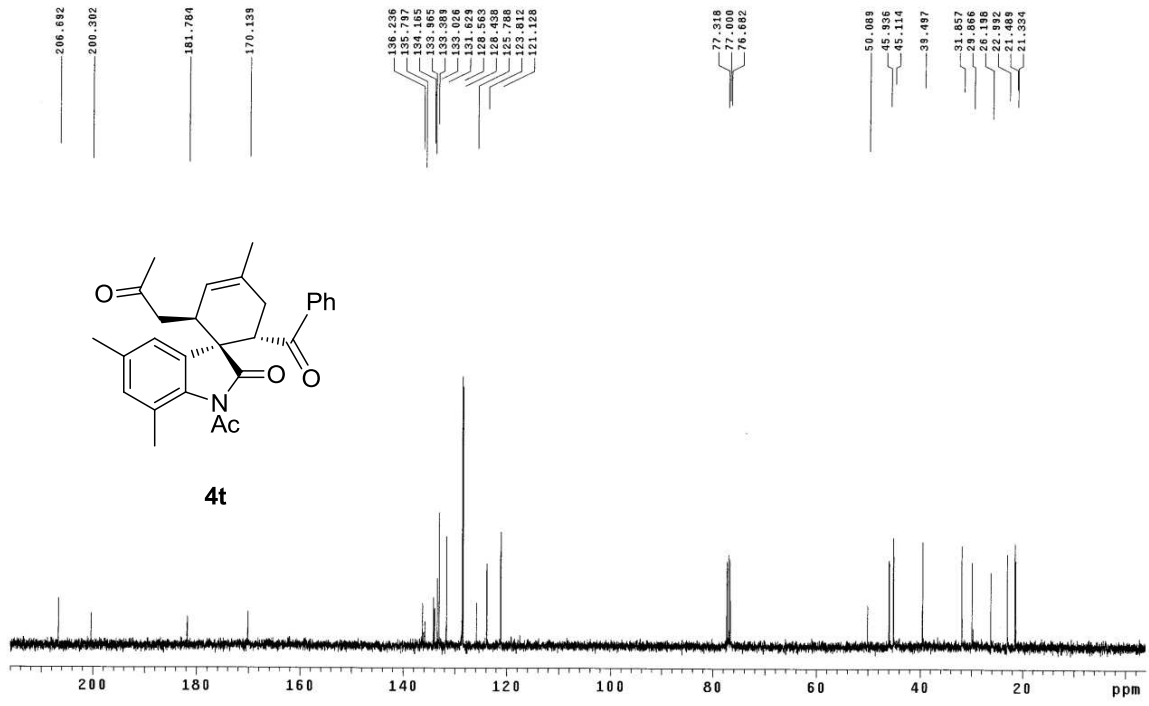



**enantiomer of 4s**

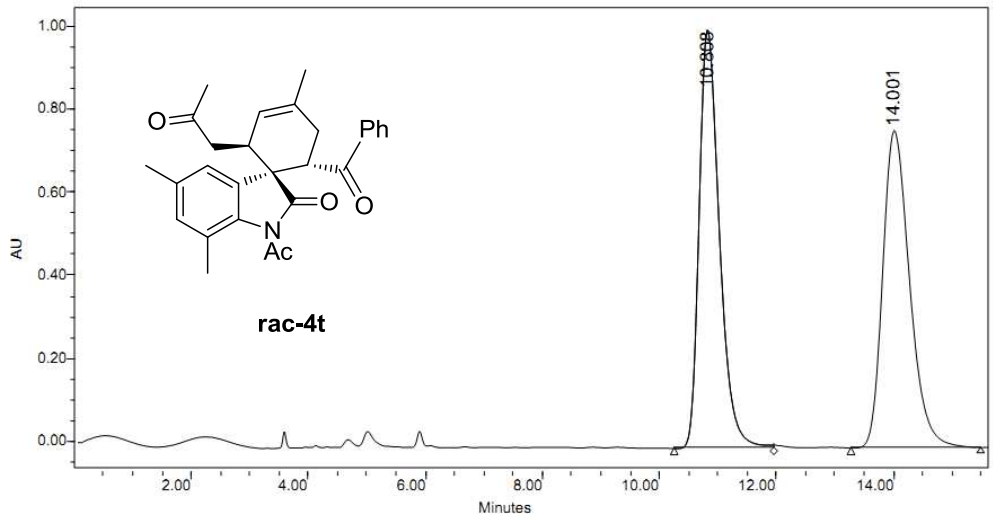
| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 5.484 | 720239 | 2.75 | 82621 | 3.51 |
| 2 | 5.977 | 25454859 | 97.25 | 2268161 | 96.49 |



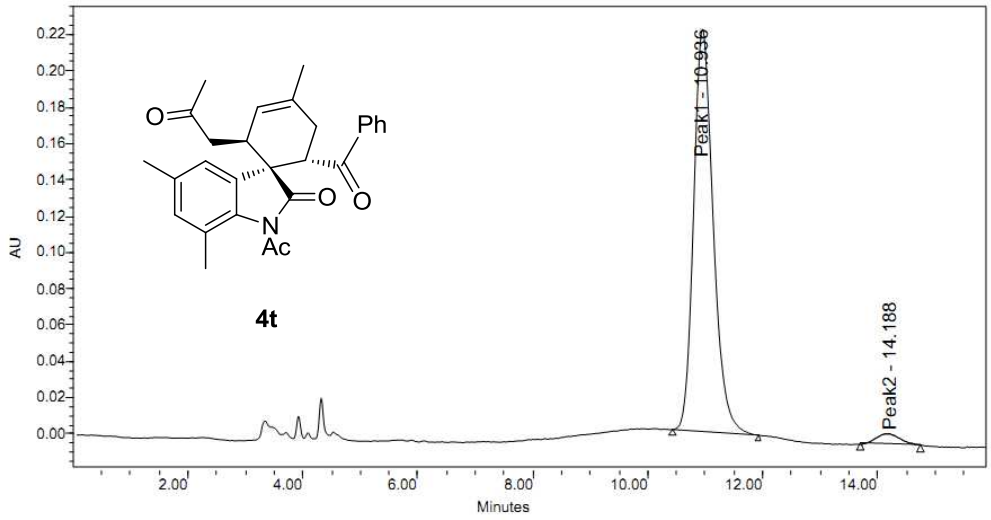

**4t**



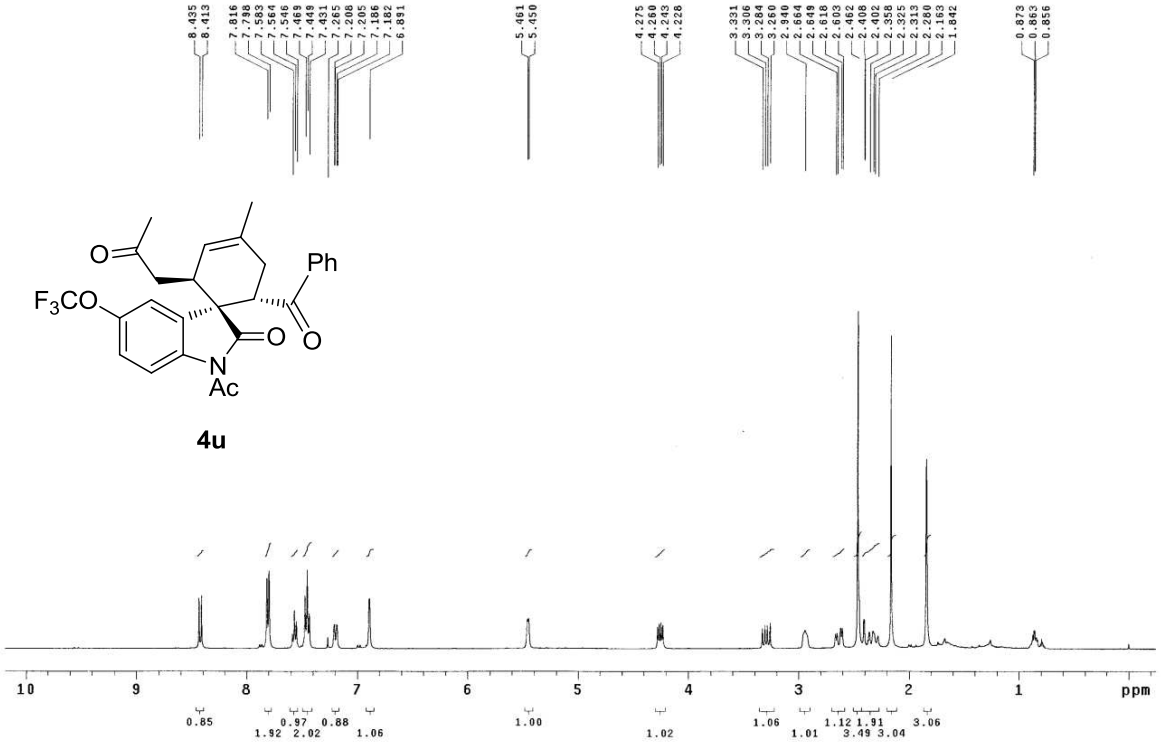

**4t**

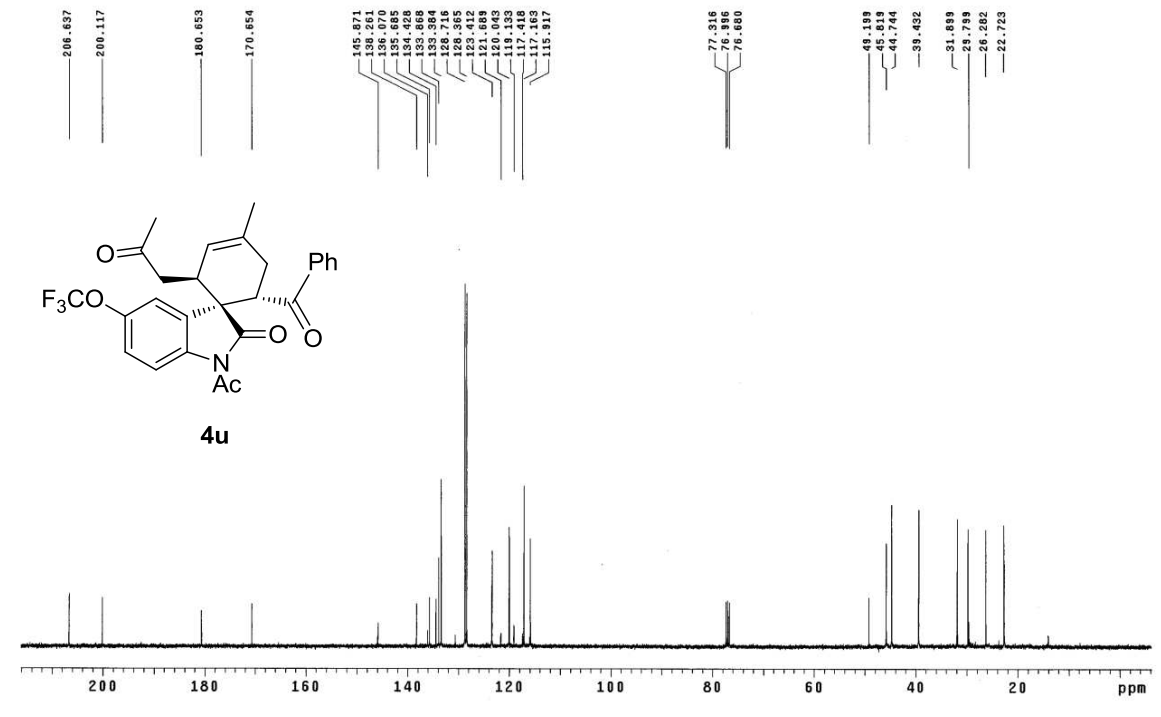


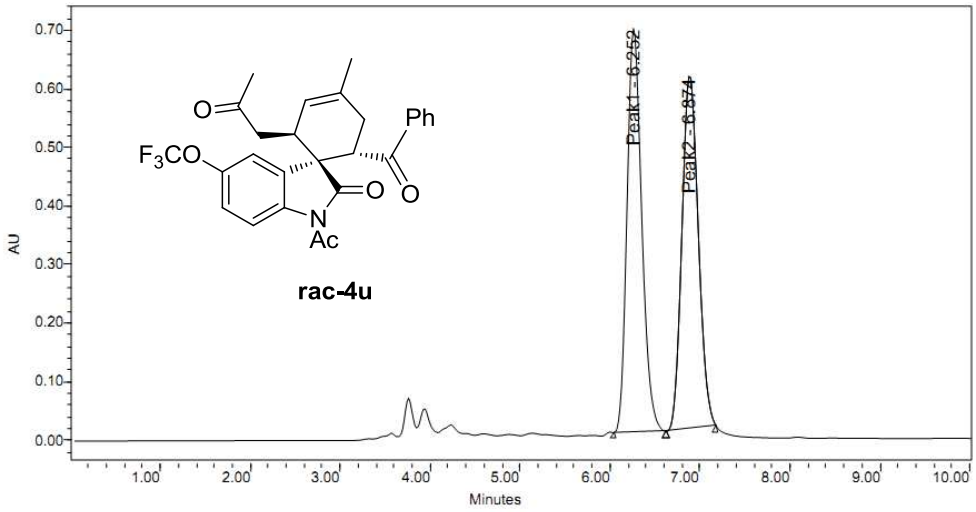

| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 10.808 | 24347158 | 49.98 | 1007031 | 56.90 |
| 2 | 14.001 | 24369080 | 50.02 | 762869 | 43.10 |



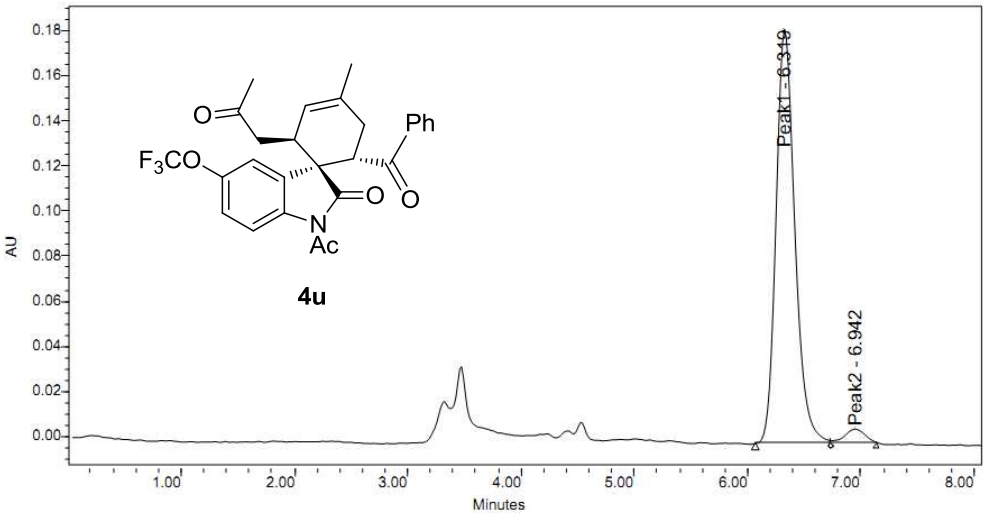

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 10.936 | 5248642 | 96.66 | 221720 | 97.33 |
| 2 | Peak2 | 14.188 | 181099 | 3.34 | 6074 | 2.67 |



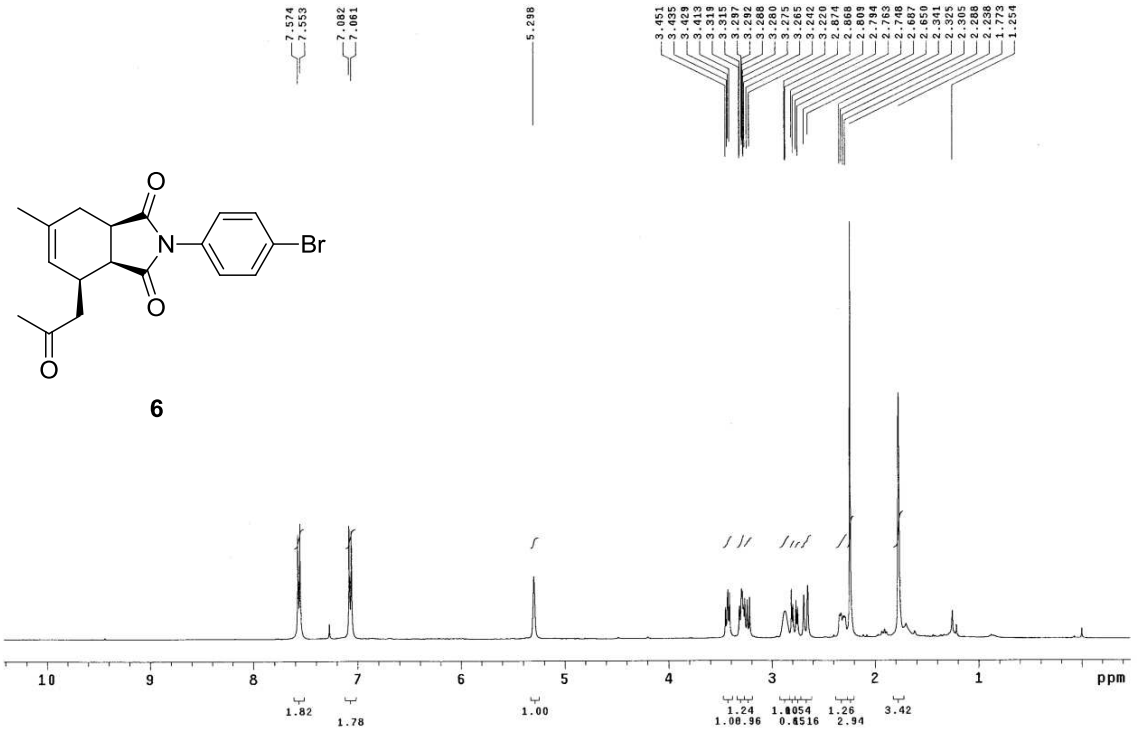



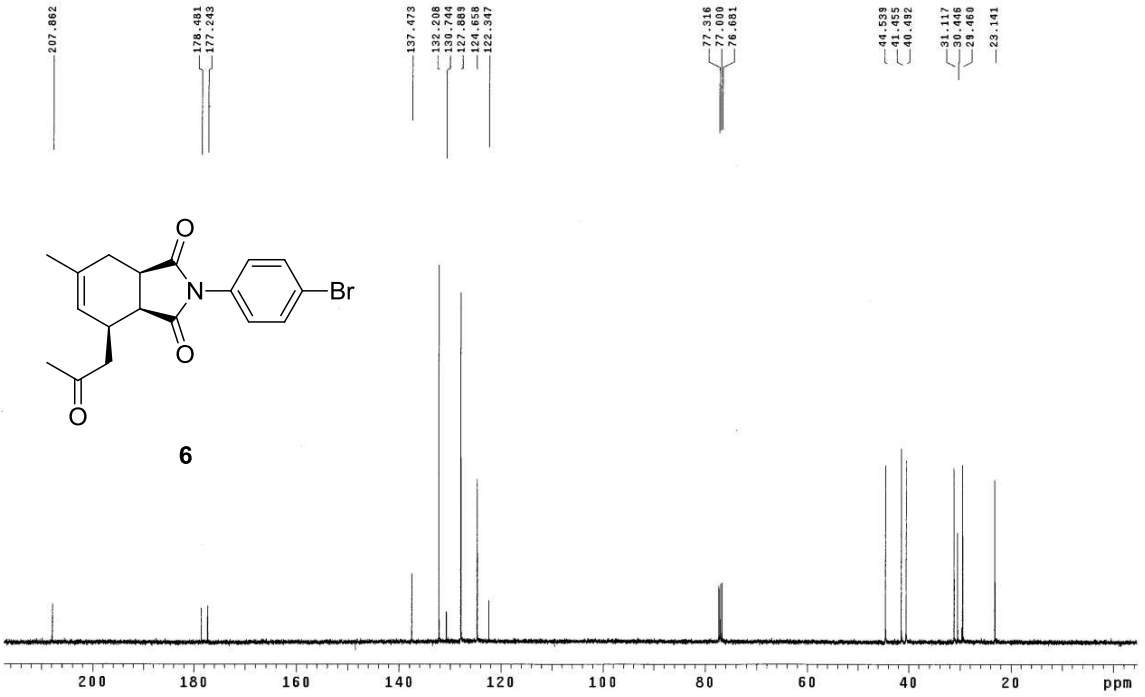


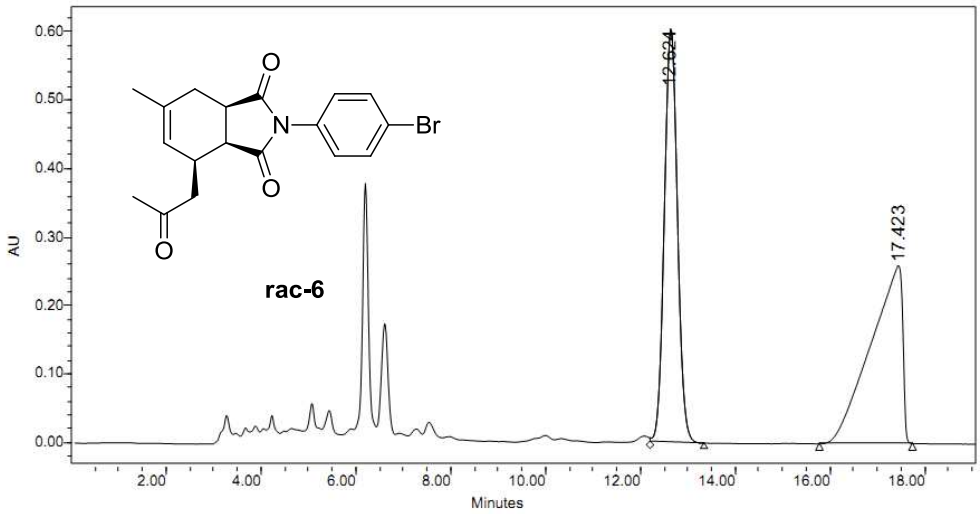

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 6.252 | 7837585 | 50.64 | 689305 | 53.30 |
| 2 | Peak2 | 6.874 | 7638441 | 49.36 | 603996 | 46.70 |



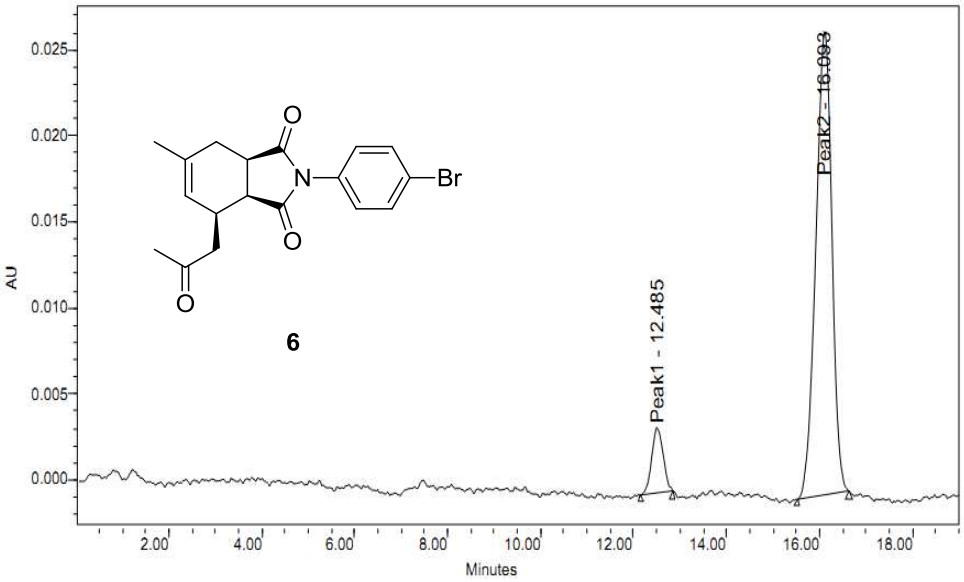

| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 6.319 | 2119693 | 96.61 | 183747 | 96.83 |
| 2 | Peak2 | 6.942 | 74342 | 3.39 | 6023 | 3.17 |






| | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|
| 1 | 12.624 | 11639302 | 48.82 | 605137 | 69.91 |
| 2 | 17.423 | 12201480 | 51.18 | 260480 | 30.09 |




| | Peak Name | RT (min) | Area ( *sec) | % Area | Height ( ) | % Height |
|---|---|---|---|---|---|---|
| 1 | Peak1 | 12.485 | 67227 | 9.39 | 3839 | 12.45 |
| 2 | Peak2 | 16.093 | 648770 | 90.61 | 26987 | 87.55 |