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Protecting Group Directed Cyclization: Asymmetric Synthesis of Both *cis* and *trans*-Dihydrexidine from a Common Precursor

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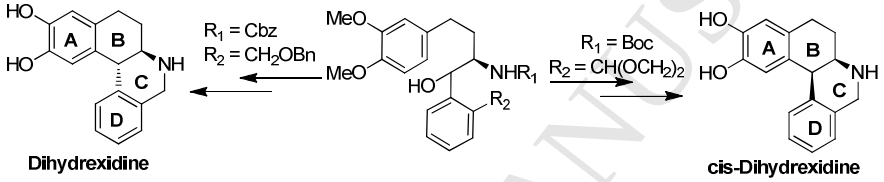

Tetrahedron

Pergamon

TETRAHEDRON

Protecting Group Directed Cyclization: Asymmetric Synthesis of Both *cis*- and *trans*-Dihydrexidine from a Common Precursor

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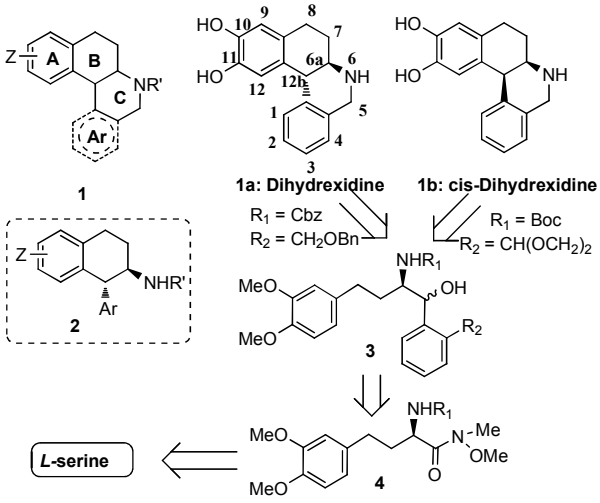
Abstract— Protection group of amino- and tethered *o*-arene functionality of 1,4-aryl-2-amino-1-butanol derived from *L*-serine dictates the cyclization mode under acidic conditions leading to reverse diastereoselectivity. *N*-Boc and acetal protected amino alcohol undergo cascade cyclization providing exclusively *cis*-dihydrexidine *via* reduction, where formation of C-ring (isoquinoline unit) prior to Friedel-Crafts cyclization control the *cis*-stereochemistry of the B-ring. *N*-Cbz and *O*-benzyl protection direct first F-C cyclization yielding the *trans*-1-aryl-2-aminotetralin and subsequent deprotection-cyclization forming the C-ring afforded dihydrexidine.

1. Introduction

Hexahydrobenzophenanthridines **1**, fused tetracyclic skeletons, are often found in various natural products and pharmaceuticals.[1,2] Stereochemistry of the B/C-ring junction of the compounds plays a vital role in biological activity. For example, *trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine **1a**, known as dihydrexidine has been developed as the first high affinity full efficacy agonist for dopamine D1 receptor,[1,2] however, *cis*-isomer **1b** is completely inactive. Dihydrexidine **1a** is presently in clinical trial for the potential treatment of Parkinson's disease and the cognitive deficits of schizophrenia.[3] It also shows a high level of enantiospecificity in its interaction with the D1 receptor. Thus asymmetric synthesis of both *cis*- and *trans*-isomers of hexahydrobenzophenanthridines remains an active field of research in organic synthesis and important to medicinal chemistry too. There are a number of methods for asymmetric synthesis of dihydrexidine[4-8] **1a** and only one report on non-racemic synthesis of *cis*-hexahydrobenzophenanthridines.[9] Major syntheses comprised of construction of the aminotetralin unit **2** followed by creation of C-ring via Pictet-Spengler type cyclization. We have demonstrated elegant asymmetric



Scheme 1. Hexahydrobenzophenanthridines and their retrosynthetic approach

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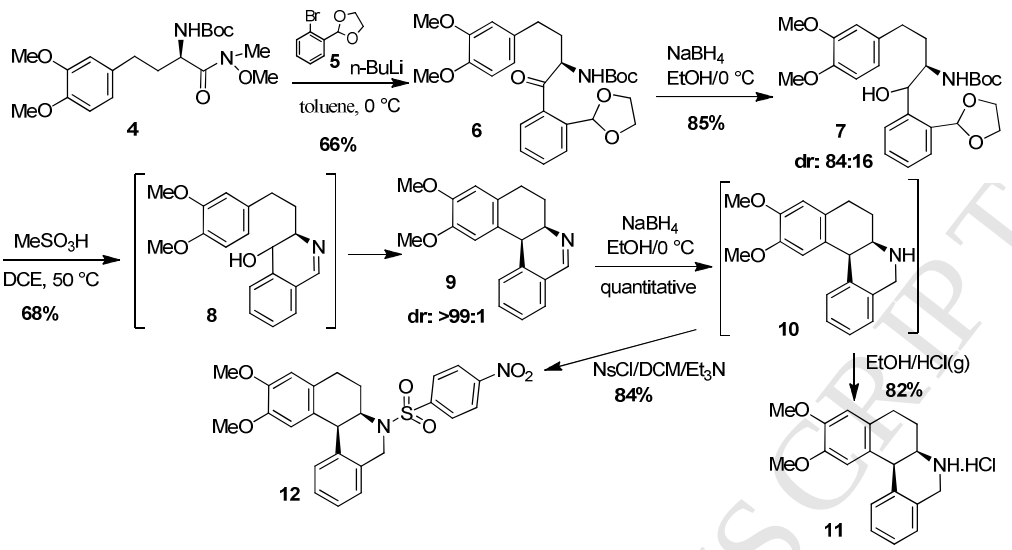
syntheses of dihydrexidine **1**a and other hexahydrobenzophenanthridine dopamine D1 agonists using "chiral pool" as well as catalytic asymmetric approaches.[7,8] Classical Pictet-Spengler reaction of 2-amino-1-phenyltetralin **2a** (Ar = Ph, R′ = H) failed to give tetracyclic unit. A two step protocol was adopted for C-ring construction of dihydrexidine, *via* alkylation of *N*-nosyl aminotetralin **2a** (R = Ns) with MOMCl followed by TMSOTf mediated cyclization.[6a,7a] This reaction was found to be very sensitive to both reagent quality and temperature and provided inconsistent results with 30-46% of yield. To avoid the TMSOTf mediated reaction and to make the synthesis more compact we thought of designing a synthesis in which both B- and C-rings can be constructed concurrently. Thus we report the first divergent synthesis of dihyrexidine **1a** and *cis*-dihydrexidine **1b** from a common intermediate **4** via sequential and cascade cyclization, respectively (Scheme 1).

2. Results and Discussion

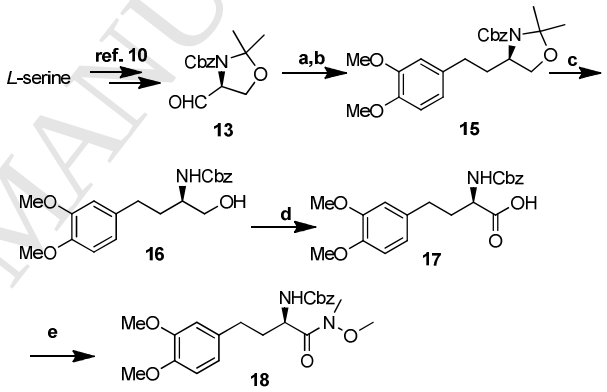
Weinreb amide **4** derived from Garner's aldehyde of *L*-serine is a versatile intermediate for the divergent and scalable synthesis of dihydrexidine **1**a and other hexahydrobenzophenanthridines has been developed in our laboratory.[7b] Thus the study began with the Weinreb amide **4** and it was reacted with protected 2-bromobenzaldehyde **5** using 3.0 equivalents of *n*-BuLi in toluene at 0 ˚C to get ketone **6** in 66% yield (Scheme 2). Ketone **6** was reduced with $NaBH_4$ in MeOH to afford the amino alcohol **7** as a diastereomeric mixture (dr 84:16) in 85% yield. We have chosen the substituent in the phenyl part in such a way that alongside the acid catalyzed Friedel-Crafts cyclization both the protecting groups of the phenyl moiety [-$CH(OCH_2)_2$] as well as the amino protecting group (*N*-Boc) would be cleaved at the same time and the third ring will form concomitantly. The cyclization was carried out on the diastereomeric mixture of **7** using PPA, $MeSO_3H$ and TFA.[7a] We were delighted to observe that all the reagents worked well and the anticipated third ring was also formed in one go. The imine, tetrahydrobenzophenanthridine **9** was isolated in good yield (68%). ^{1}H NMR spectrum of the product showed a doublet at δ 4.02 with coupling constant of 5.7 Hz assigned as the proton at C_{12b} (ArCHAr′), which seems to be designated as having *cis*-stereochemistry. To further corroborate our contention, compound **9** was reduced with $NaBH_4$ to get the free amine **10** in quantitative yield and it was converted to the hydrochloride salt **11**. In 1H NMR spectrum, the proton at C_{12b} (ArCHAr′) of **11** appeared as a doublet at **δ** 4.31 with coupling constant of 3.8 Hz whereas the corresponding proton of the *trans*-isomer showed a doublet at 4.24 with coupling constant of 11.0 Hz.[7a] Again optical rotation of compound **11** {$([\alpha]_D^{25}$ = -63 (c 0.15, EtOH)} did not match with the reported *trans*-isomer {$[\alpha]_D^{25}$ = +123 (c 0.75, EtOH)}.[7a] The compound **10** was also converted to the corresponding nosyl derivative **12.** It showed a doublet of C_{12b}-H at δ 3.89 (d, *J* = 5.1 Hz), but the doublet of the corresponding *trans*-isomer[6a,7a] appeared at δ 4.12 (d, *J* = 11.6 Hz) and optical rotation of compound **12** ($[\alpha]_D^{25}$= -78.2 (c 0.37, $CHCl_3$) also did not match with the reported data for the *trans*-isomer {$[\alpha]_D^{25}$=+38.8 (c 0.37, $CHCl_3$)[7a] and $[\alpha]_D^{25}$=+30.2 (c 1.00, $CHCl_3$)[6a]}. In both the cases the optical rotations and the chemical shifts as well as coupling constants of C_{12b}-H in ^{1}H NMR spectra differ from the *trans*-isomer. In ^{1}H NMR and ^{13}C NMR spectra, the chemical shifts diverge considerably too. These results unambiguously proved *cis*-geometry of compounds **9-12**. Earlier we have unequivocally proved that when the aminotetralin ring was constructed first followed by the C-ring to form hexahydrobenzophenanthridine, *trans*-geometry was obtained.[7] In this case we have started with two very acid labile groups; that might have been deprotected before the Friedel-Crafts cyclization had occurred. Under acidic condition the formation of isoquinoline unit (C-ring) was faster, which in turn guided the geometry of the Friedel-Crafts alkylation to construct the B-ring (Scheme 2). To support the hypothesis, the cascade cyclization was monitored by LC-MS at different intervals. Formation of isoquinoline **8** was detected, which was also identified by ^{1}H NMR. In a nutshell two rings formed in the reverse order than what we have done earlier[7] and this led to *cis*-stereochemistry.



Scheme 2. Cascade cyclization of aminoalcohol 7 to *cis*-*O*-methyldihydrexidine

The above observation led us to look into the protecting groups of the phenyl ring as well as amine more closely so that the C-ring formation can be prevented before the Friedel-Crafts alkylation and protecting groups should not be too labile under acidic condition. Hence, our focus shifted from Boc-protected Weinreb amide to Cbz-protected compound **18** and the acid stable benzyl protected 2-bromobenzyl alcohol. Multi-gram synthesis of Weinreb amide **18** was done from Cbz-protected Garner's aldehyde **13** (Scheme 3).[7b] The Cbz-protected Garner's aldehyde **13** was prepared in five steps following literature procedure[11] starting from *L*-serine as the chiral synthon. The optical purity of the Cbz-protected Garner's aldehyde was verified by comparing the optical rotation. Observed value ($[\alpha]_D^{25}$= -67.6 (c 1.18, $CHCl_3$)) matched excellently with reported values ($[\alpha]_D^{25}$= -70.1 (c 1.01, $CHCl_3$)[10a] and $[\alpha]_D^{22}$= -60.2 (c 1.18, $CHCl_3$)).[10b]

The Garner's aldehyde **13** was reacted with the ylide generated from (3,4-dimethoxybenzyl) triphenyl phosphonium bromide **14** to afford the alkene as a (1:1) mixture E/Z-isomers. The byproduct Ph_3PO was removed



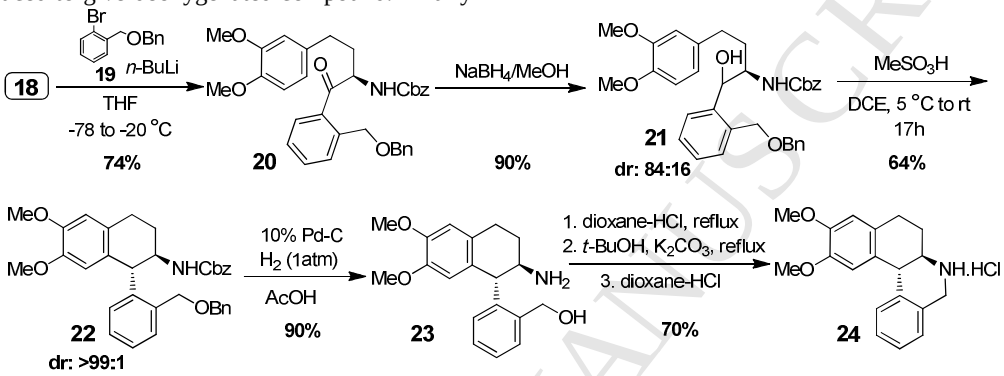
Reagents and conditions: a) (3, 4-$(MeO)_2C_6H_3CH_2PPh_3Br$ **14**, THF ,-70 to -20 °C; b) H_2/Pd-C, MeOH, Ph_2S (cat), 87% (two steps); c) p-TSA/ MeOH/rt/4h, 88%; d) $PhI(OAc)_2$, TEMPO, 1:1ACN: H_2O, 0 °C to rt,17 h (82%); e) *i*-BuOCOCl (1.2 equiv), NMP (2.2 equiv), Me(OMe)NH.HCl (1.6 equiv), CH_2Cl_2, -15 to 0 °C, rt, 1h (76%).

Scheme 3. Synthesis of Weinreb amide 18

by column purification and the product was hydrogenated at atmospheric pressure using Pd-C catalyst poisoned with diphenyl sulfide[11] to prevent removal of Cbz-group to get compound **15** in 87% yield over two steps. Acetonide deprotection using pTSA in MeOH was facile to provide *N*-protected 2-amino-4-arylbutyl alcohol **16** in 88% yield. TEMPO mediated oxidation of **16** using $PhI(OAc)_2$ in aqueous acetonitrile (1:1) gave the corresponding acid **17** in 82% yield. The acid **17** was converted to the Weinreb amide **18** in 76% yield (Scheme 3). All the steps leading to the Weinreb amide from *L*-serine were done in multi-gram scale with high yield.

Lithiated **19** on reaction with Weinreb amide **18** gave ketone **20** (Scheme 4). Use of 3.0 equivalents of lithiated reagent and maintaining the temperature gave best yield of 74%. The reduction using $NaBH_4$ worked very well to

afford **21** as a diastereomeric mixture (dr 84:16) in 90% of yield. The Friedel-Crafts cyclization of diastereomeric mixture of **21** using $MeSO_3H$ that leads exclusively to the aminotetralin **22** (dr >99:1) was optimized under different conditions and gave 64% yield in the presence of 3.0 equivalents of $MeSO_3H$ at rt.[7a] The most unanticipated hurdle faced during the deprotection reaction. The hydrogenation using 10% Pd-C in MeOH and in EtOAc easily removed the Cbz protection at 1atm but the debenzylation did not occur even at 60 psi. The most likely reason could be poisoning of the catalyst by the free $–NH_2$ group. Reduction was tried in MeOH using conc. HCl (3.0 equiv) at 1atm but within half an hour both the benzylic positions reduced to give deoxygenated compound. Finally the reaction worked well in AcOH to afford the desired aminotetralin **23** in 90% of isolated yield. To complete synthesis, the compound **23** was heated with dry HCl in dioxane; this afforded the corresponding chloro-compound. Without any purification it was heated with K_2CO_3 in dioxane followed by treatment with dry HCl in dioxane achieved the synthesis of hydrochloride salt of *O*-methyl dihydrexidine **24·HCl** in 70% of yield over three steps. The optical rotation of the compound **24·HCl** {$[\alpha]_D^{25}$= +126.5 (c 0.6, EtOH)} matched beautifully with the literature data {$[\alpha]_D^{25}$= +123 (c 0.75, EtOH}.[5c,7a] Demethylation of the



Scheme 4. Asymmetric synthesis of dihydrexidine via sequential cyclization approach

compounds **24** and **11**, as was done earlier in our laboratory,[7] accomplished the synthesis of dihydrexidine and its *cis*-isomer from a common intermediate with overall yields of 25.5% (7 steps) and 29.7% (6 steps), respectively, whereas earlier methods[7] provided only 13.1% overall yield over eight steps. The present route is more efficient and scalable, in particular, for the construction of C-ring avoiding costly and sensitive TMSOTf.

3. Conclusion

In summary we have developed the first divergent and scalable asymmetric synthesis of dihydrexidine and its *cis*-isomer from a common advanced intermediate derived from *L*-serine *via* protection group controlled cyclization. *N*-Boc and acetal protected amino alcohol **7** undergo cascade cyclization under acidic condition leading exclusively to *cis*-tetrahydrobenzophenanthridine followed by reduction afforded the *cis*-dihydrexidine (with 29.7% over yield), where formation of C-ring (isoquinoline unit) prior to Friedel-Crafts cyclization detects the *cis*-stereochemistry of the B-ring. *N*-Cbz and *O*-benzyl protection stop the C-ring formation and exclusive F-C cyclization yielded the *trans*-1-aryl-2-aminotetralin and subsequent deprotection-cyclization to form the C-ring afforded dihydrexidine with 25.1% overall yield in seven steps. This protocol is applicable to other hexahydrobenzophenanthridines too.

4. Experimental Section

4.1. General methods

All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar) or nitrogen (N_2). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (100-200 and 230-400 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with F_{254} indicator. The ^1H NMR spectra were recorded with a 400 MHz and ^{13}C NMR spectra were recorded with a 100 MHz using $CDCl_3$ and DMSO-d_6. ^1H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) and DMSO-d_6 (δ =2.49); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0) and DMSO-d_6 (δ = 39.7). High resolution mass spectra (HRMS) were measured with a QTOF I (quadrupole–hexapole TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface.

4.2. [(*R*)-3-(3,4-Dimethoxy-phenyl)-1-(2-[1,3]dioxolan-2-yl-benzoyl)-propyl]-carbamic acid *tert*-butyl ester (6)

To a stirred solution of compound **5** (9.6 g, 41.9 mmol) in anhydrous toluene (95 mL) n-butyl lithium (1.96 M in hexane, 20.0 mL, 39.2 mmol) was added drop wise at 0 °C

and stirred at that temperature for 30 minutes. Compound **4** (5.0 g, 13.07 mmol) in anhydrous toluene (40 mL) was added to the reaction mixture at 0 °C and stirred at ambient temperature for 45 min. Reaction mixture was quenched with saturated NH_4Cl (10 ml) at ice bath temperature and extracted with ethyl acetate (60 mL x 3). Combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulphate and purified by column chromatography (R_f 0.6, 1:1 EtOAc/hexanes) to get compound **6 (**4.1 g, 66%) as colorless oil.^{1}H NMR ($CDCl_3$, 400 MHz) δ : 7.68 (d, *J* = 7.7 Hz, 1H), 7.5- 7.46 (m, 2H), 7.39-7.35 (m, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.65(d, *J* = 8.1 Hz, 1H) 6.63 (s, 1H), 6.19 (s, 1H), 5.35 (d, *J* = 8.7 Hz, 1H), 5.07-5.02 (m, 1H), 4.04-3.93 (m, 4H), 3.83 (s, 3H), 3.8 (s, 3H), 2.66-2.57 (m, 2H), 2.14-2.08 (m, 1H), 1.76-1.72 (m, 1H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.8, 155.6, 148.8, 147.3, 137.1, 136.7, 133.7, 131.1, 128.8, 127.7, 127.0, 120.3, 111.8, 111.2, 100.9, 79.6, 65.1, 65.0, 57.6, 55.8, 55.7, 33.9, 31.2, 28.3(3C). LC–MS (ESI): 472.0 $[M+H]^+$; 489.0 $[M+NH_4]^+$. ν_{max} (neat): 3367 (br), 2969, 2934, 1701, 1591, 1514, 1460, 1366, 1260, 1238, 1162, 1084, 1028, 980, 943, 865, 762, 629 cm^{-1}. HRMS (ESI): Calcd for $C_{26}H_{33}NO_7Na$, 494.2155 m/z $[M+Na]^+$, found 494.2155.

4.3. {(*R*)-3-(3,4-Dimethoxy-phenyl)-1-[(2-[1,3]-di-oxolan-2-yl-phenyl)-hydroxymethyl]-propyl}-carbamic acid *tert*-butyl ester (7)

To a stirred solution of compound **6** (3.4 g, 7.22 mmol) in anhydrous ethanol (30 mL) was added $NaBH_4$ (0.343 g, 9.02 mmol) in portions at 0°C. Reaction mixture was stirred at room temperature for 2h. Excess reagent was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (50 mL x 3). Combined organic layer was washed with brine, dried over anhydrous sodium sulphate and purified by column chromatography (R_f 0.54 in 1:1 EtOAc/hexanes) to get compound **7** (2.9 g, 85%) as diastereomeric mixture (dr 84:16). ^{1}H NMR (400 MHz, $CDCl_3$) δ: Major diastereomer 7.58 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.67 (s, 1H), 5.28 (s, 1H), 5.01 (m, 1H), 4.18-3.88 (m, 5H), 3.82 (s, 6H), 2.66 (m, 1H), 2.53 (m, 1H), 2.01 (m, 1H), 1.70 (m, 1H), 1.3 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8, 148.7, 147.9, 140.6, 134.8, 134.1, 129.3, 127.4, 127.1, 126.5, 120.1, 111.9, 111.3, 102.0, 79.2, 78.8, 72.3, 65.1, 64.9, 55.9, 55.7, 32.3, 31.8, 28.2. LC–MS (ESI): 474.0 $[M+H]^+$, 491.4 $[M+NH_4]^+$. ν_{max} (KBr): 3600-3300 (br), 3066, 2971, 2934, 1706, 1590, 1515, 1454, 1366, 1260, 1239, 1164, 1027, 944, 860, 763 cm^{-1}.HRMS (ESI): Calcd for $C_{26}H_{35}NO_7N$ 496.2311 m/z $[M+Na]^+$, found 496.2311.

4.4. (6a*R*,12b*R*)-10,11-Dimethoxy-6a,7,8,12b-tetra-hydro-benzo[a]phenanthridine (9)

To a stirred solution of compound **7** (0.20 g, 0.423 mmol; dr 84:16) in 1, 2-dichloroethane (2 mL) was added methane sulfonic acid (140 µl, 2.11 mmol) at ambient temperature. Reaction mixture was heated at 50 °C overnight on a preheated oil bath. Reaction mixture was diluted with ethyl acetate (25 mL) and successively washed with saturated aqueous sodium bicarbonate solution (10 mL), brine (25 mL) and organic layer was dried over anhydrous sodium sulphate, concentrated and purified by column chromatography (R_f 0.46 in 1:19 $MeOH/CH_2Cl_2$) to get compound **9** (0.085 g, 68%; dr >99:1) as yellow solid. M.P. 158-160 ˚C. ^{1}H NMR ($CDCl_3$,400 MHz) : δ 8.32 (s, 1H), 7.41-7.37 (m, 1H), 7.33-7.28 (m, 2H), 7.20 (d, *J* = 7.4Hz ,1H), 6.61 (s, 1H), 6.57 (s, 1H), 4.14-4.11(m, 1H), 4.02 (d, *J* = 5.7Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.96-2.90 (m, 1H), 2.85- 2.77 (m, 1H), 2.05-2.0 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 147.9, 147.0, 138.7, 131.1, 128.6, 128.1, 127.4, 127.3, 125.9, 113.1, 111.9, 56.0, 50.9, 55.8, 38.6, 26.9, 24.7. LC–MS (ESI): 294.0 $[M+H]^+$. ν_{max} (KBr): 3001, 2928, 2856, 1629, 1609, 1515, 1450, 1349, 1261, 1214, 1112, 1031, 1013, 963, 821, 534 cm^{-1}. $[\alpha]_D^{25}$ - 22 (c 0.14, CH_2Cl_2). HRMS (ESI): Calcd for $C_{19}H_{20}NO_2$, 294.1494 m/z $[M+H]^+$, found 294.1489.

4.5. (6a*R*,12b*R*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexa-hydro-benzo-[a]-phenanthridine (10)

To compound **9** (0.052 g, 0.177 mmol) in ethanol (0.5 ml) was added $NaBH_4$ (4 mg, 0.10 mmol) in portions at 0 °C. Reaction mixture was stirred at room temperature for 45 minutes. Ethanol was evaporated under reduced pressure and quenched with NH_4Cl solution. Reaction mixture was extracted with ethyl acetate (3x5 mL), washed with brine, dried over anhydrous sodium sulphate, concentrated to get crude compound **10** (quantitative) which was used in the next step without any purification.

4.6. (6a*R*,12b*R*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexa-hydro-benzo[a]phenanthridine hydrochloride (11)

To a solution of compound **10** (0.052 g, 0.176 mmol) in anhydrous ethanol (1 mL) was added ethanolic HCl (1 mL). Reaction mixture was stirred at room temperature for 2h and then solvent was evaporated to dryness under reduced pressure to get a solid which was washed with ether and filtered to get the compound **11** (0.47 g, 82%)**.** M.P. >200 ˚C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.4 (br s, 1H), 9.4 (br s, 1H), 7.29-7.16 (m, 4H), 6.82 (s, 1H), 6.76 (s, 1H), 4.32-4.20 (m, 3H), 3.96 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.82-2.78 (m, 2H), 2.08 (m, 1H), 1.72 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 147.9, 146.8, 135.3, 128.4, 128.3, 127.6, 127.1, 126.75, 126.7, 125.3, 114.1, 112.0, 55.5, 55.3, 50.2, 40.9, 38.1, 25.8, 22.3. LC-MS (ESI): 296.0 $[M+H]^+$. ν_{max} (neat): 3700-3200 (br), 2920, 2767, 2677, 2577, 2420, 1740, 1610, 1518, 1455, 1436, 1406, 1251, 1106, 1022, 870, 797, 754 cm^{-1}. $[\alpha]_D^{25}$ - 63 (c 0.15, EtOH). HRMS (ESI): Calcd for $C_{19}H_{22}NO_2$ 296.1651 m/z $[M+H]^+$, found 296.1647.

(6a*R*,12b*R*)-10,11-Dimethoxy-6-(4-nitro benzene sulfonyl)-5,6,6a,7,8,12b-hexahydrobenzo [*a*] phenanthri -dine (12)

To a stirred solution of crude compound **10** (0.028 g, 0.095 mmol) in anhydrous dichloromethane (0.5 mL) was added

anhydrous triethyl amine (30 µl, 0.237 mmol) and *p*-nitrobenzene sulfonyl chloride (0.022 g, 0.099 mmol) at 0 °C. Reaction mixture was stirred at room temperature for 3h. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (2x10 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulphate, concentrated, purified by column chromatography (R_f~0.68 in 5% MeOH in CH_2Cl_2) to get pure product **12** (0.040 g, 84%) as yellow solid. M.P. >200 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.3 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.7Hz, 2H), 7.19-7.13 (m, 2H), 7.06-7.04 (m, 1H), 6.93-6.91 (m, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 4.47 (d, *J* = 15.0 Hz,1H), 4.38 (d, *J* = 15.0 Hz,1H), 4.32-4.27 (m, 1H), 3.89 (d, *J* = 5.1 Hz,1H), 3.85 (s, 3H), 3.76 (s, 3H), 2.88-2.77 (m, 2H), 2.08-1.99 (m, 1H), 1.86-1.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.9, 148.2, 147.1, 144.7, 137.5, 131.3, 128.4(2C), 128.0, 127.9, 127.7, 126.6, 126.3, 126.2, 124.3(2C), 113.2, 111.5, 55.9, 55.8, 54.0, 45.8, 42,3, 27.0, 26.6. LC-MS (ESI): 481.04 $[M+H]^+$. ν_{max} (KBr): 3105, 2999, 2961, 2938, 2838, 1607, 1538, 1518, 1454, 1347, 1260, 1236, 1160, 1105, 1017, 972, 856, 817, 739, 684, 600 cm^{-1}. $[\alpha]_D^{25}$ - 78.2 (c 0.37, $CHCl_3$). HRMS (ESI): Calcd for $C_{25}H_{24}N_2O_6SNa$, 503.1253 m/z $[M+Na]^+$, found 503.1253.

4.7. (*S*)-4-Formyl-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester (Garner's aldehyde 13)

This was prepared in 83% yield by following the literature procedure.[10]

4.8. (*R*)-4-[2-(3,4-Dimethoxyphenyl)-ethyl]-2,2-dimethyl-oxazolidine-3 carboxylic acid benzyl ester (15)

To a slurry of the 3,4-dimethoxybenzyl phosphonium bromide **14** (77.5 g, 156.6 mmol, 1.25 equiv) in anhydrous tetrahydrofuran (300 mL, 2.4 mL/mmol) at -20 °C was added *n*-BuLi (2 M, 75.2 mL, 150.4 mmol, 1.2 equiv) drop wise over 15 min. After another 20 minutes of stirring at the same temperature, the reaction mixture was cooled to -70 °C and a solution of the aldehyde **13** (33.0 g, 125.3 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (238 mL, 1.9 ml/mmol) over 15 min and stirred for another 45 min. The reaction mixture was then warmed to -15 °C over 45 min. The reaction mass was treated cautiously with saturated aqueous ammonium chloride solution (250 mL). It was then filtered through a celite bed and extracted with ethyl acetate (3x500 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 30% ethyl acetate in hexanes as eluent to provide ~1:1mixture of E/Z isomers as pale-yellow liquid (40.0 g, 80%) which was used as such in the next step. To 20.0 g (50.3 mmol), of the alkene in methanol (120 mL) was added 10% Pd–C catalyst (2.0 g, 10% w/w) poisoned with diphenyl sulphide (0.16 mL, 1.0 mmol, 0.02 equiv) and stirred at room temperature for 17 h under 1 atmosphere hydrogen (balloon) pressure. The reaction mixture was then filtered through a celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and purified by flash column chromatography (R_f 0.57 in 3:7 EtOAc/hexanes) using 30% ethyl acetate in hexanes as eluent to obtain a colorless liquid **15** (19.0 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ major rotamer 7.32 (m, 5H), 6.78-6.68 (m, 2H), 6.58 (s, 1H), 5.15-5.05 (m, 2H), 3.95 (m, 2H), 3.83 (s, 6H), 3.79 (m, 1H), 2.62-2.52 (m, 2H), 1.95 (n, 1H), 1.83 (m, 1H), 1.69 (s, 3H0, 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 152.2, 148.8, 147.2, 136.6, 133.8, 133.6, 128.4 (2C), 127.9, 127.8, 119.9, 111.6, 111.2, 94.0, 66.9, 66.4, 56.8, 55.8, 55.7, 35.1, 32.0, 26.5, 23.1. LC-MS (ESI): 400.0(MH^+), 417.0($M+NH_4^+$). ν_{max} (neat): 2982, 2936, 1701, 1590, 1515, 1459, 1407, 1352, 1306, 1259, 1211, 1145, 1094, 1070, 1029, 843, 763, 698 cm^{-1}. HRMS (ESI): Calcd for $C_{23}H_{29}NO_5Na$, 422.1943 m/z $[M+Na]^+$, found 422.1943. $[\alpha]_D^{25}$ -32.6 (c 1.02, $CHCl_3$).

4.9. [(*R*)-3-(3,4-Dimethoxy-phenyl)-1-hydroxymethyl-propyl]-carbamicacid benzyl ester (16)

A solution of compound **15** (38.0 g, 95.1 mmol) and *p*-toluene sulfonic acid monohydrate (1.0 g, 7.6 mmol, 0.08 equiv) in anhydrous methanol (380 mL) was stirred at room temperature for 4h and then it was concentrated under reduced pressure. The residue was diluted with ethyl acetate (500 mL) and washed successively with a saturated aqueous sodium bicarbonate solution (200 mL), water (200 mL), and brine (500 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography(R_f 0.4 in 7:3 EtOAc/hexanes) using 1:1 ethyl acetate in hexanes as eluent to obtain product as off-white solid **16** (30.0 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.27 (m, 5H), 6.76-6.68 (m, 3H), 5.11-5.06 (m, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.71-3.54 (m, 3H), 2.67-2.54 (m, 2H), 1.86-1.72 (m,2H). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.37-7.3 (m, 5H), 7.07 (d, *J* = 8.4Hz, 1H, exchangeable -NH), 6.82(d, J= 8.1Hz, 1H), 6.75 (s, 1H), 6.67 (d, *J* = 8.1Hz, 1H), 5.06-4.99 (m, 2H), 4.62 (t, *J* = 5.6Hz, 1H, exchangeable -OH), 3.70 (s, 6H), 3.43-3.34 (m, 2H), 3.31-3.22 (m, 1H), 2.60-2.54 (m, 1H), 2.46-2.40 (m, 1H), 1.82-1.73 (m, 1H), 1.6-1.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 148.8, 147.2, 136.3, 133.9, 128.5(2C), 128.1(2C), 128.0, 120.07, 111.7, 111.3, 66.8, 65.3, 55.85, 55.75, 52.75, 33.25, 31.8. LC-MS (ESI): 360.2 $[M+H]^+$, 377.2 $[M+NH_4]^+$. ν_{max} (KBr): 3480 (br), 3308, 3062, 2947, 1688, 1666, 1590, 1547, 1518, 1456, 1341, 1253, 1146, 1065, 1029, 954, 809, 757, 740, 699 cm^{-1}. HRMS (ESI): Calcd for $C_{20}H_{25}NO_5Na$, 382.1630, m/z $[M+Na]^+$, found 382.1631. $[\alpha]_D^{25}$ +13.3˚ (c 0.92, $CHCl_3$).

4.10. (*R*)-2-Benzyloxycarbonylamino-4-(3,4-dimethoxy-phenyl)-butyric acid (17)

To a stirred solution of the alcohol **16** (30.0 g, 83.5 mmol, 1.0 equiv) in aqueous acetonitrile (1:1, 200 mL) were successively added diacetoxyiodobenzene (59.1 g, 183.6 mmol, 2.2 equiv) and 2,2,6,6-tetramethyl-1-piperidinyl free radical (TEMPO) (2.6 g, 16.7 mmol, 0.2 equiv) at 0 °C. The reaction mixture was then stirred 17h at room temperature. The reaction mixture was half-concentrated under reduced pressure and then cooled by ice-bath. To it

was added sodium hydroxide solution (4.0 M, 100 mL). The aqueous part was washed with diethyl ether (2x100 mL). It was then acidified to pH 4 by the drop wise addition of hydrochloric acid solution (4 M) at 5-10 °C. The compound was extracted with ethyl acetate (3x500 mL), combined organic layers was successively washed with water (150 mL), brine (250 mL), dried over anhydrous sodium sulfate and solvents removed under reduced pressure. The crude was purified by column chromatography (R_f 0.46 in 1:9 MeOH/CH_2Cl_2) using 5% methanol in dichloromethane to give **17** (25.5 g, 82%) as a light brown sticky-solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ12.6 (br s, 1H, exchangeable, -CO_2H), 7.6 (br s, 1H, exchangeable -NH), 7.37-7.29 (m, 5H), 6.83(d, *J* = 8.1 Hz, 1H), 6.76 (s, 1H), 6.67 (d, *J* = 7.8 Hz,1H), 5.04 (s, 2H), 3.89-3.84 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.59-2.53 (m, 1H), 1.94-1.82 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 173.9, 156.1, 148.5, 146.9, 137.0, 133.4, 128.2(2C), 127.7, 127.6(2C), 120.0, 112.2, 111.8, 65.3, 55.4, 55.2, 53.2, 32.8, 31.1. LC-MS (ESI): 372.2[M-H]$^-$. ν_{max} (neat): 3700-3200 (br), 2922, 2852, 1718, 1515, 1458, 1418, 1342, 1260, 1237, 1150, 1051, 1026, 807, 763, 738, 697 cm^{-1}. $[\alpha]_D^{25}$ +16.9 (c 1.14, MeOH). HRMS (ESI): Calcd for $C_{20}H_{23}NO_6Na$, 396.1423 m/z $[M+Na]^+$, found 396.1423 .

4.11. [(*R*)-3-(3,4-Dimethoxy-phenyl)-1-(methoxymethyl-carbamoyl)-propyl]-carbamic acid benzyl ester (18)

To a solution of the acid **17** (25.0 g, 66.9 mmol) in anhydrous dichloromethane (240 mL) at -15 °C was added *N*-methylmorpholine (16.2 mL, 147.3 mmol, 2.2 equiv). Isobutylchloroformate (10.5 mL, 80.3 mmol, 1.2 equiv) was added in dropwise fashion under vigorous stirring at -15 °C. After 15 min, N,O-dimethylhydroxylamine hydrochloride (10.4 g, 107.1 mmol, 1.6 equiv) was added. The mixture was then stirred at -15 °C for an additional 1h and then allowed to warm to room temperature and stirred for 1h. The reaction mixture was poured into ice cold water (280 ml) and extracted with dichloromethane (2x500 mL). The combined organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. Solvent was removed under vacuum and the crude product was purified by flash column chromatography(R_f 0.5 in 13:7 EtOAc/hexanes) using 40% ethyl acetate in hexanes to obtain **18** (21.3 g, 76%) as a colorless sticky mass. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.31 (m, 5H), 6.78-6.71 (m, 3H), 5.47 (d, *J* = 8.8 Hz,1H), 5.13(d, *J* = 12.3 Hz),1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.74 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.62 (s, 3H), 3.16 (s, 3H), 2.70-2.55 (m, 2H), 2.02 (m, 1H), 1.86-1.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 172.6, 156.1, 148.7, 147.2, 136.3, 133.5, 128.4 (2C), 128.0, 127.9 (2C), 120.3, 111.9, 111.2, 66.8, 61.4, 55.9, 55.8, 50.5, 34.5, 32.0, 31.1. LC-MS (ESI): 417.4 $[M+H]^+$, 434.4 $[M+NH_4]^{1+}$. ν_{max} (KBr): 3277, 2932, 2845, 1715, 1648, 1517, 1459, 1260, 1239, 1153, 1057, 1027, 989, 748, 629 cm^{-1}.HRMS (ESI): Calcd for $C_{22}H_{28}N_2O_6Na$, 439.1845 m/z $[M+Na]^+$, found 439.1845. $[\alpha]_D^{25}$ +51.4 (c 1.01, CH_3OH).

4.12. [(*R*)-1-(2-Benzyloxymethyl-benzoyl)-3-(3,4-di meth -oxyphenyl)-propyl]-carbamic acid benzyl ester (20)

To a solution of the aryl bromide **19** (6.38 g, 23 mmol, 3.0 equiv) in anhydrous THF (60 mL) was added *n*-butyl lithium (2.3 M in hexanes; 9.4 mL, 21.6 mmol) dropwise at -78 °C under nitrogen atmosphere and stirred for 15 min. A pre-cooled (-78 °C) solution of Weinreb amide **18** (3.0 g, 7.2 mmol, 1.0 equiv) in anhydrous THF (60 mL) was then added to it. The reaction mass was stirred at -78°C for 30 min and then brought to -20 °C in another 30 minutes. It was carefully quenched with a saturated aqueous ammonium chloride solution (60 mL) and allowed to come to room temperature. It was extracted with ethyl acetate (2x150 mL). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate and filtered. Solvents removed under vacuum and the crude product was purified by flash column chromatography (R_f 0.56 7:13 EtOAc/hexanes) using 40% ethyl acetate in hexanes to afford the ketone **20** (2.95 g, 74%) as a colorless sticky mass. ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.6(d, *J* = 7.6 Hz, 1H), 7.57(d, *J* = 7.6 Hz, 1H), 7.5 (t, *J* = 7.5 Hz, 1H), 7.36-7.16 (m, 10H), 6.74(d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.59 (s, 1H), 5.70 (d, *J* = 7.3 Hz, 1H), 5.24-5.19 (m, 1H), 5.16-5.09 (m, 2H), 4.78 (s, 2H), 4.57 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 2.58 (quasi t, *J* = 7.7 Hz, 2H), 2.13-2.04 (m, 1H), 1.76-1.67 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.1, 156.1, 148.7, 147.3, 139.5, 137.9, 136.3, 134.3, 133.2, 132.0, 128.5, 128.4(4C), 128.3(2C), 128.0, 127.9, 127.6(2C), 127.5, 127.3, 120.3, 111.7, 111.1, 72.9, 70.1, 66.8, 56.8, 55.8, 55.6, 34.4, 31.1. LC-MS (ESI): 554.4(MH^+), 571.4($M+NH_4^+$).ν_{max}(neat): 3354 (br), 3031, 2933, 2857, 1716, 1695, 1514, 1454, 1353,1260, 1236, 1151, 1072, 1029, 742, 699 cm^{-1}. HRMS (ESI): Calcd for $C_{34}H_{35}NO_6Na$, 576.2362 m/z $[M+Na]^+$, found 576.2362. $[\alpha]_D^{25}$ -5.9˚ (c 1.02, $CHCl_3$).

4.13. [(*R*)-1-[(2-Benzyloxymethyl-phenyl)-hydroxy-methyl]-3-(3,4-dimethoxy-phenyl)-propyl]-carbamic acid benzyl ester (21)

To a solution of the ketone **20** (2.85 g, 5.1 mmol, 1.0 equiv) in absolute ethanol (28 mL) was added sodium borohydride (0.192 g, 5.1 mmol, 1.0 equiv) portion-wise at 0 °C under nitrogen and allowed to stir at ambient temperature for 2 h. The reaction mass was quenched with a chilled saturated aqueous ammonium chloride solution (35 mL). The volatiles were evaporated under reduced pressure followed by extraction into ethyl acetate (2x100 mL); combined organic layer washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude alcohol which was purified by flash column chromatography(R_f 0.5 in 7:13 EtOAc/hexanes) using 40% ethyl acetate in hexanes to obtain **21** (2.6 g, 91%) as a colorless oil . ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.38-7.26 (m, 8H), 7.25-7.18 (m, 5H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.59 (s, 1H), 5.19 (d, *J* = 9.2 Hz, 1H), 5.01 (t_{AB}, *J* = 13.2 Hz, 2H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.55 (q_{AB} *J* = 11.4 Hz, 2H), 3.93 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.70-2.58 (m, 2H), 2.46 (m, 1H), 1.99 (m, 1H), 1.71 (m,

1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 148.6, 146.9, 140.7, 137.5, 136.6, 134.47, 134.43, 130.0, 128.5, 128.37 (2C), 128.35 (2C), 127.9 (2C), 127.8, 127.7 (2C), 127.6, 127.4, 126.8, 120.0, 111.6, 111.1, 72.9, 72.5, 70.4, 66.3, 55.7, 55.6, 31.6, 31.5, 29.6. LC-MS (ESI): 556.2 $[M+H]^+$, 573.2 $[M+NH_4]^+$. ν_{max} (neat): 3600-3300 (br), 3031, 2962, 2856, 1710, 1590, 1515, 1455, 1334, 1237, 1143, 1028, 808, 759, 741, 699 cm^{-1}. HRMS (ESI): Calcd for $C_{34}H_{37}NO_6Na$, 578.2519 m/z $[M+Na]^+$, found 578.2518.

4.14. [(1*S*,2*R*)-1-(2-Benzyloxymethyl-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid benzyl ester (22)

To a solution of the alcohol **21** (0.6 g, 1.07 mmol, 1.0 equiv; dr 84:16) in dichloromethane (12 mL) at 5-10 °C was added methanesulphonic acid (0.21 mL, 3.2 mmol, 3.0 equiv) and the mixture was allowed to stir at room temperature for 17 h. It was cooled to 5-10 °C; aqueous saturated sodium bicarbonate (20 mL) was added to it followed by extraction with dichloromethane (3x 50 mL). The combined organic part was washed with brine, shaken with anhydrous sodium sulphate, filtered and evaporated under reduced pressure. It was purified by flash column chromatography(R_f 0.4 in 7:13 EtOAc/hexanes) using 30% ethyl acetate in hexanes to obtain **22** (0.37 g, 64%; dr >99:1) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.19 (m, 13H), 6.98 (d, *J* = 6.8 Hz, 1H), 6.62 (s, 1H), 6.03 (s, 1H), 5.9 (d, *J* = 6.4 Hz, 1H), 4.99 (d, *J* = 12.4 Hz,1H), 4.91 (d, *J* = 12.4 Hz,1H), 4.76 (d, *J* = 10.8 Hz,1H), 4.67-4.58 (m, 3H), 4.27 (d, *J* = 8.4 Hz, 1H), 3.99-3.93 (m, 1H), 3.85 (s, 3H), 3.50 (s, 3H), 3.07-3.02 (m, 1H), 2.87-2.79 (m, 1H), 2.36 (m, 1H), 1.74-1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.6, 147.3, 143.6, 137.5, 136.9, 136.0, 130.1, 130.0, 129.4, 129.1, 128.4(4C), 128.3, 128.1(2C), 127.8, 127.7, 127.6(2C), 126.5, 113.0, 110.9, 72.6, 71.0, 65.9, 55.8 (2C), 54.1, 45.7, 28.1, 27.2. LC-MS (ESI): 538.4 $[M+H]^+$, 555.4 $[M+NH_4]^+$. ν_{max} (neat): 3339, 3030, 2934, 2855, 1715, 1609, 1513, 1453, 1404, 1357, 1253, 1229, 1115, 1045, 752, 699 cm^{-1}. HRMS (ESI): Calcd for $C_{34}H_{35}NO_5Na$, 560.2413 m/z $[M+Na]^+$, found 560.2413. $[\alpha]_D^{25}$ -51.6 (c 1.0, $CHCl_3$).

4.15. [2-((1*S*,2*R*)-2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-phenyl]-methanol (23)

To a solution of protected amine **22** (0.4 g, 1.27 mmol) in acetic acid (2.5 mL) was added 10% Pd-C (0.040 g, 10% w/w) and stirred under 1atm (H_2 balloon) for 7h. The reaction mixture was filtered over a celite bed using 150 mL of ethyl acetate and the volatiles were concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with aqueous saturated sodium bicarbonate (30 mL). The organic part was separated and washed with brine, dried over anhydrous sodium sulphate and evaporated under vacuum. It was purified by flash column chromatography (R_f 0.4 in 1:9 $MeOH/CH_2Cl_2$) using 10% methanol in DCM to obtain yellow oil **23** (0.210 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.3 6 (m, 1H), 7.23-7.19 (m, 2H), 6.97-6.95 (m, 1H), 6.60 (s, 1H), 6.03 (s, 1H), 4.97 (d, *J* =11.4 Hz,1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.20 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H), 3.53 (s, 3H), 3.17 (t, *J* = 11.0 Hz, 1H), 3.08-3.01 (m, 1H), 2.88 (m, 1H), 2.09-2.0 (m, 1H), 1.95 (m,1H), 1.91 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 147.5, 142.9, 140.5, 130.4, 130.1, 129.3, 128.8, 128.0, 126.9, 112.8, 110.8, 63.1, 55.83, 55.8, 54.8, 48.1, 30.6, 28.2. LC-MS (ESI): 314.2 $[M+H]^+$. ν_{max} (neat): 3700-3200 (br), 3064, 2932, 1609, 1561, 1514, 1450, 1405, 1255, 1219, 1117, 1014, 870, 755 cm^{-1}. HRMS (ESI): Calcd for $C_{19}H_{24}NO_3$, 314.1756 m/z $[M+H]^+$, found 314.1751. $[\alpha]_D^{25}$ -40.3 (c 0.69, EtOH)

4.16. (6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydro-benzo[a]phenanthridine hydrochloride (24)

A solution of amino alcohol **23** (0.085 g, 0.27 mmol, 1.0 equiv) in 1,4-dioxane (3.6 mL) and 12 N aqueous HCl (3.2 mL) was heated under reflux for 2h. The reaction mixture was concentrated under reduced pressure to afford the intermediate chloride. It was immediately dissolved in anhydrous *t*-BuOH (6.5 mL); anhydrous potassium carbonate (1.49 g, 10.8 mmol, 40.0 equiv) was added and the mixture was heated under reflux for 1h. The mixture was cooled to room temperature, poured into water and extracted with chloroform (3x10 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (10% MeOH in EtOAc, R_f~0.4) to give the desired amine (0.60 g, 75%) which was converted to its hydrochloride salt by stirring with 4 mL of 2N HCl in dioxane for 30 min. It was then evaporated and the solid obtained was recrystallised from methanol/diethyl ether to get pure compound **24** (0.063 g, 70%) as a light brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.82 (br s, 1H), 9.61 (br s, 1H), 7.45-7.33 (m, 4H), 6.87 (s, 2H), 4.38 (m, 2H), 4.24 (d, *J* = 11.0 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.98 (m,1H), 2.83(m, 2H), 2.20 (m, 1H), 1.95 (m, 1H). ^{13}C NMR (DMSO-d_6, 400MHz): δ 147.5, 146.5, 137.3, 129.4, 127.7, 127.5, 126.7, 125.0, 124.7, 112.5, 112.0, 56.5, 55.5, 55.4, 43.3, 40.1, 26.9, 25.1. LC-MS (ESI): 296.2 $[M+H]^+$. $[\alpha]_D^{25}$= +126.5 (c 0.6, EtOH); {Lit [5b,c] $[\alpha]_D^{25}$ = +123.0 (c 0.3, EtOH); Lit[2a] $[\alpha]_D^{25}$ +106.0 (c 0.75, EtOH)}.

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Supplementary data

^{1}H NMR-, ^{13}C NMR spectra and LC-mass spectra for compounds **6, 7, 9, 11, 12, 15, 16, 17, 18, 20, 21, 22, 23** and **24**. This material is available free of charge via the Internet at http://dx.doi.org/.

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Supporting Information

Protecting Group Directed Cyclization: Asymmetric Synthesis of Both *cis*-and *trans*-Dihydrexidine from a Common Precursor

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Content

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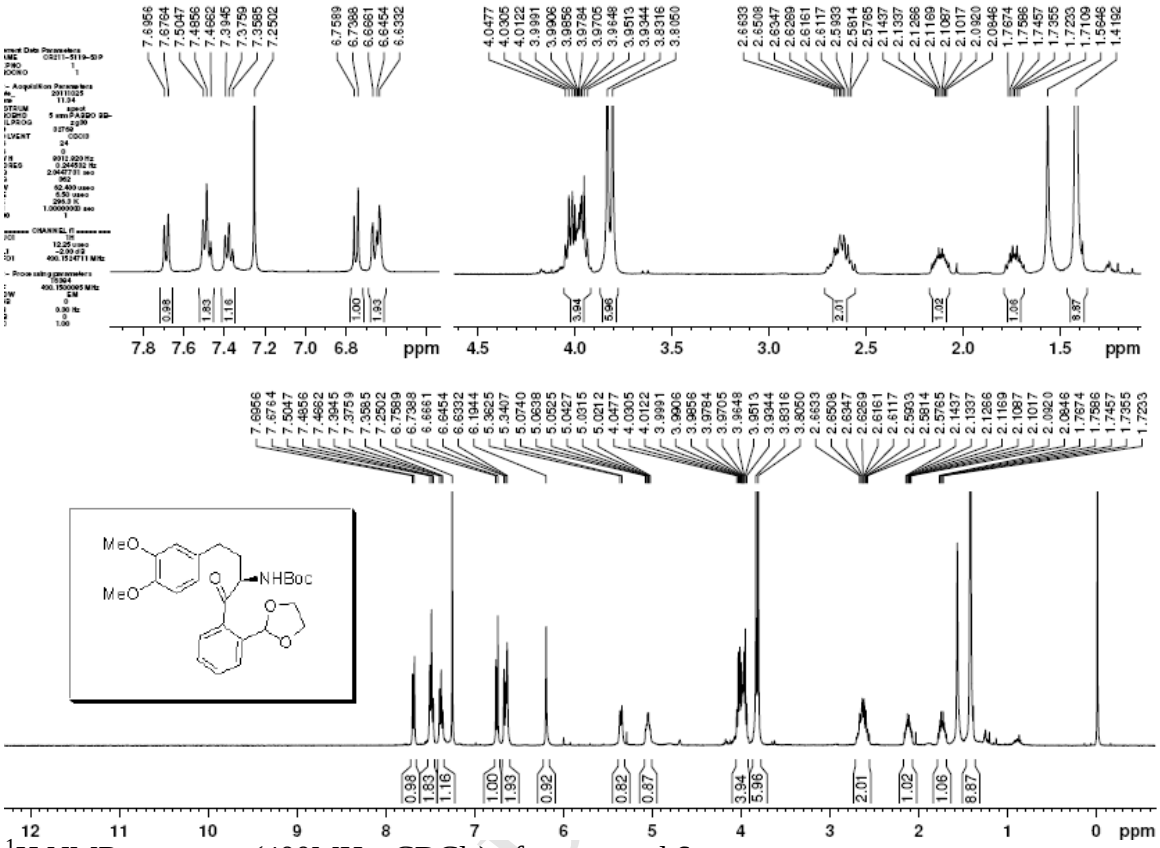
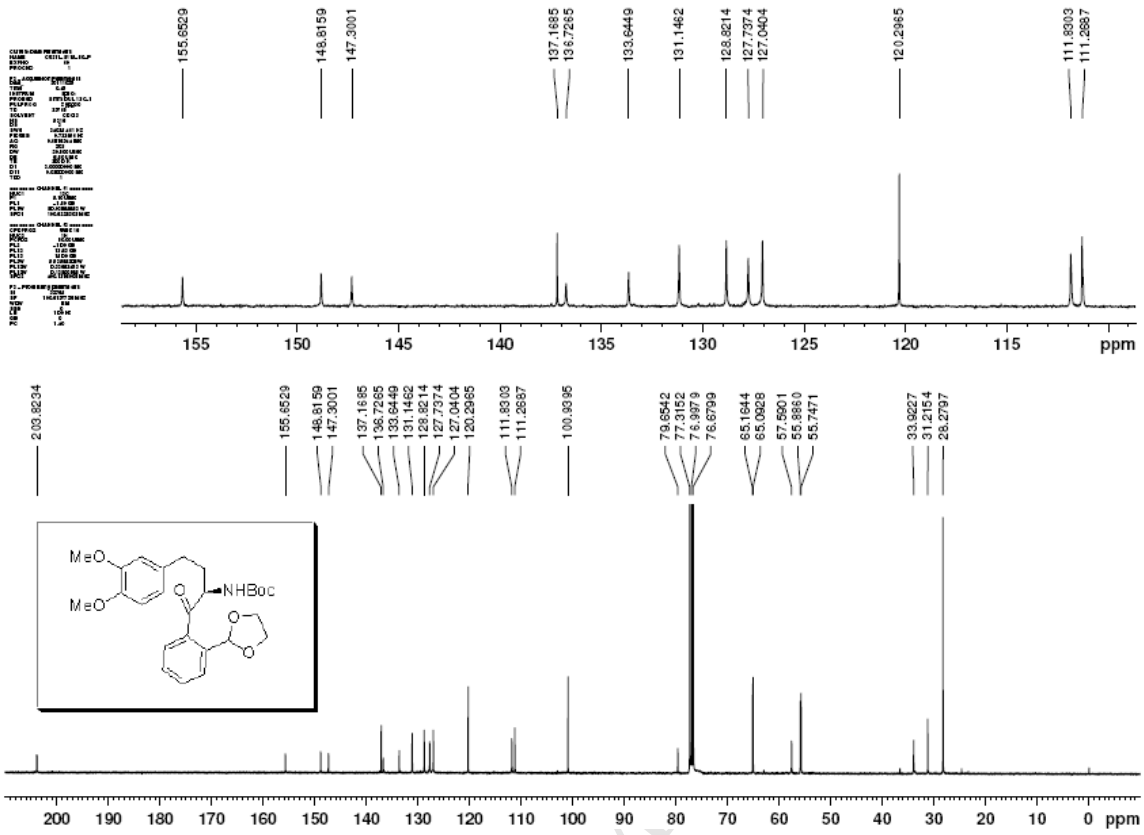
[(*R*)-3-(3,4-Dimethoxy-phenyl)-1-(2-[1,3]dioxolan-2-yl-benzoyl)-propyl]-carbamic acid tert-butyl ester 6:



^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **6**.



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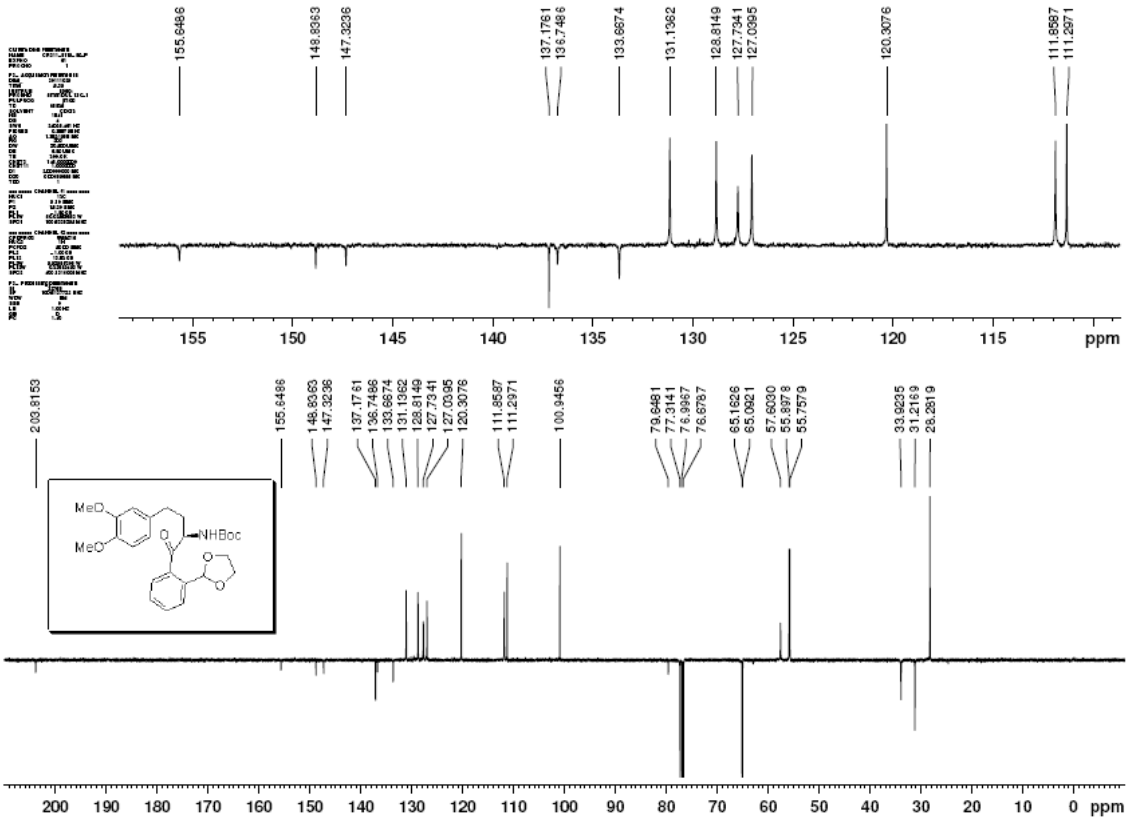
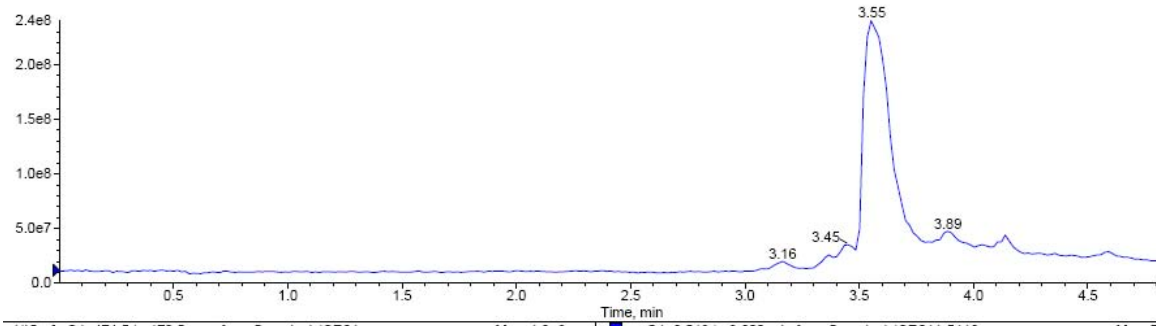
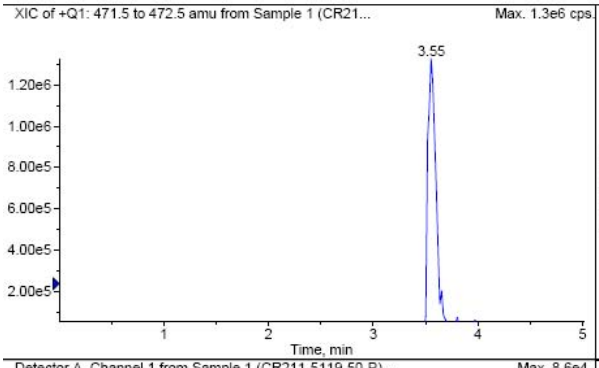
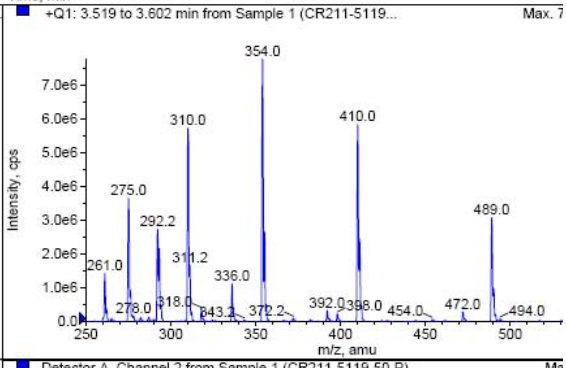
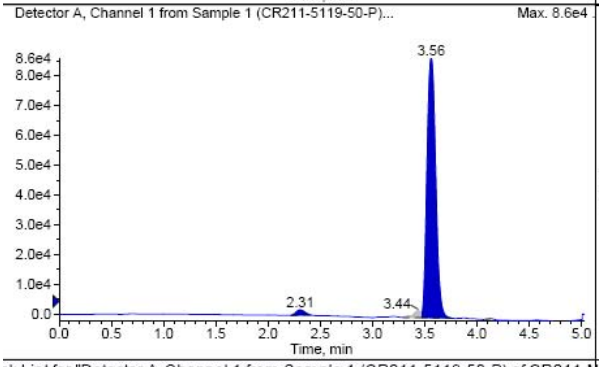


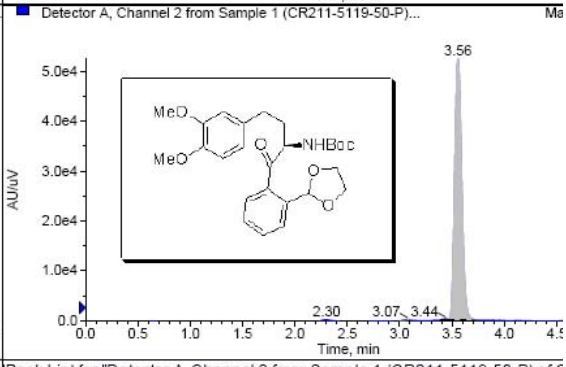
APT spectrum (100MHz, $CDCl_3$) of compound **6**.











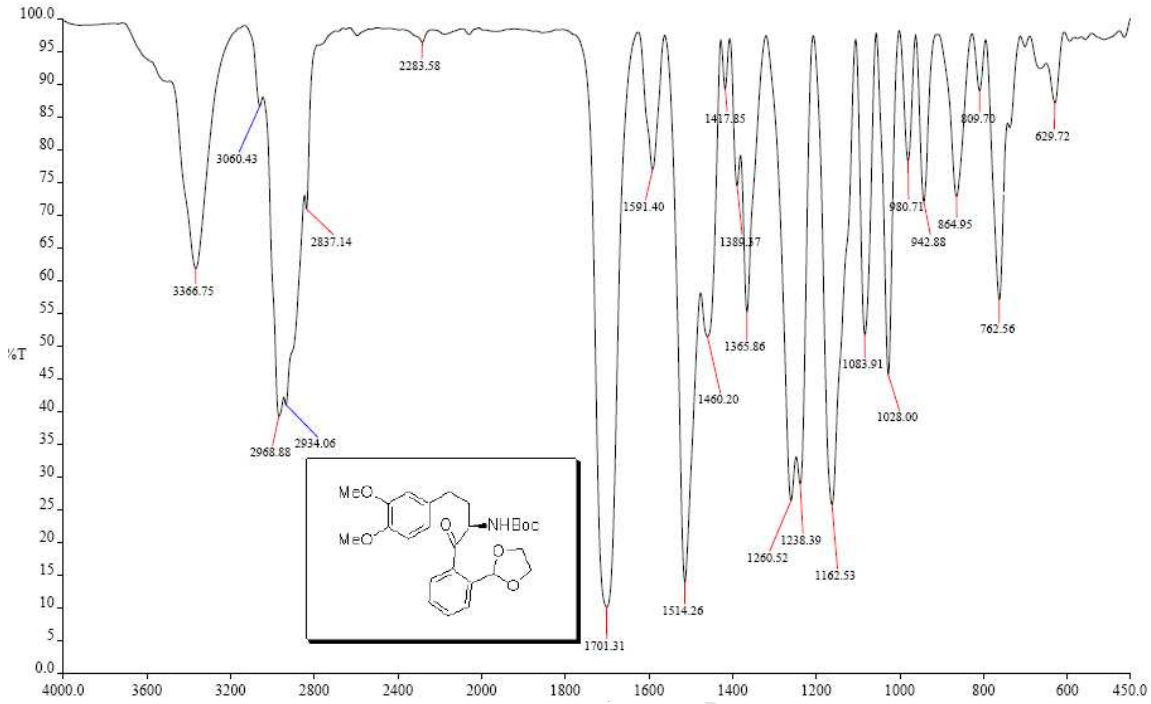
ak List for "Detector A, Channel 1 from Sample 1 (CR211-5119-50-P) of CR211-M

	Time (min)	Area (counts)	% Area	Height	% Height
	2.3075	1.0091e4	1.9568	1759.2871	1.9283
	3.4362	1.0502e4	2.0365	2181.1033	2.3906
	3.5618	4.9486e5	95.9635	8.7199e4	95.5750
	4.1258	222.6825	0.0432	96.7770	0.1061

Peak List for "Detector A, Channel 2 from Sample 1 (CR211-5119-50-P) of C

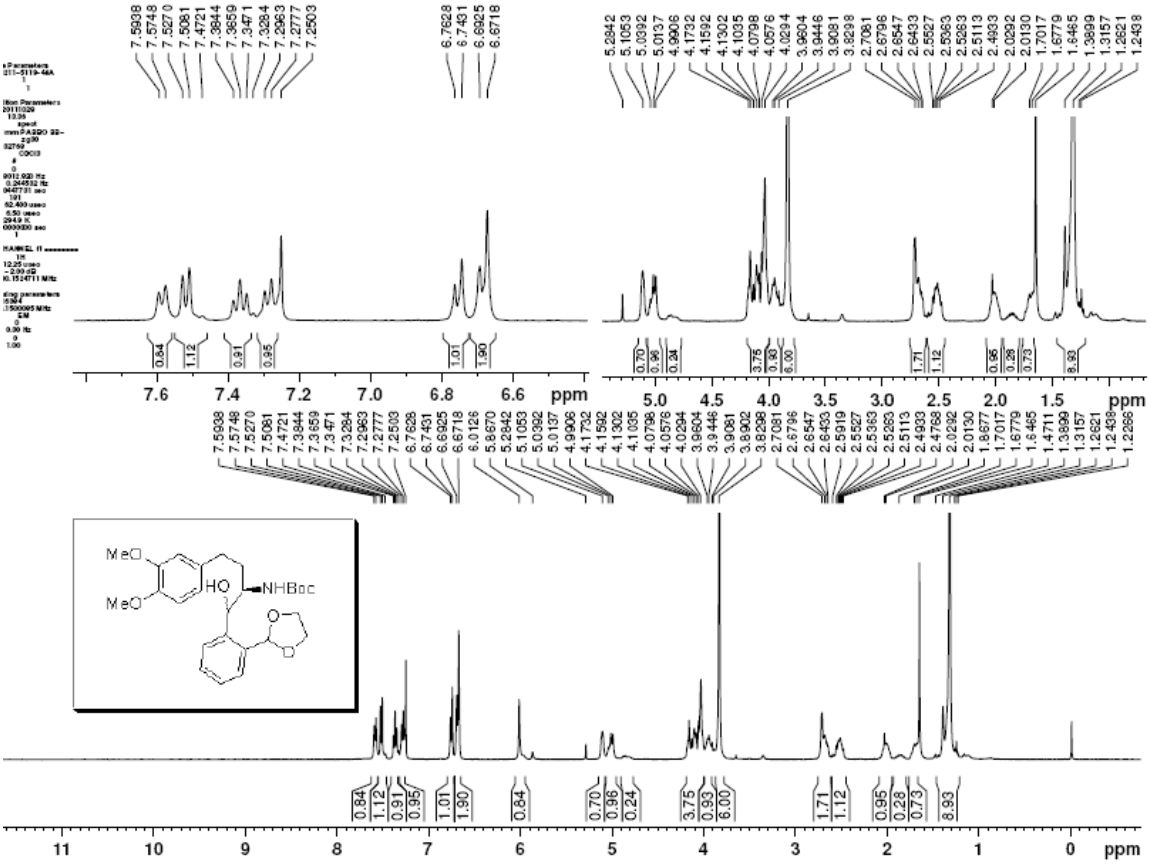
	Time (min)	Area (counts)	% Area	Height	% Height
1	2.3025	150.8907	0.0618	50.8164	0.0966
2	3.0708	236.0108	0.0967	68.0288	0.1294
3	3.4375	427.2087	0.1750	139.9882	0.2662
4	3.5569	2.4325e5	99.6664	5.2328e4	99.5078

LCMS spectrum of compound **6**.

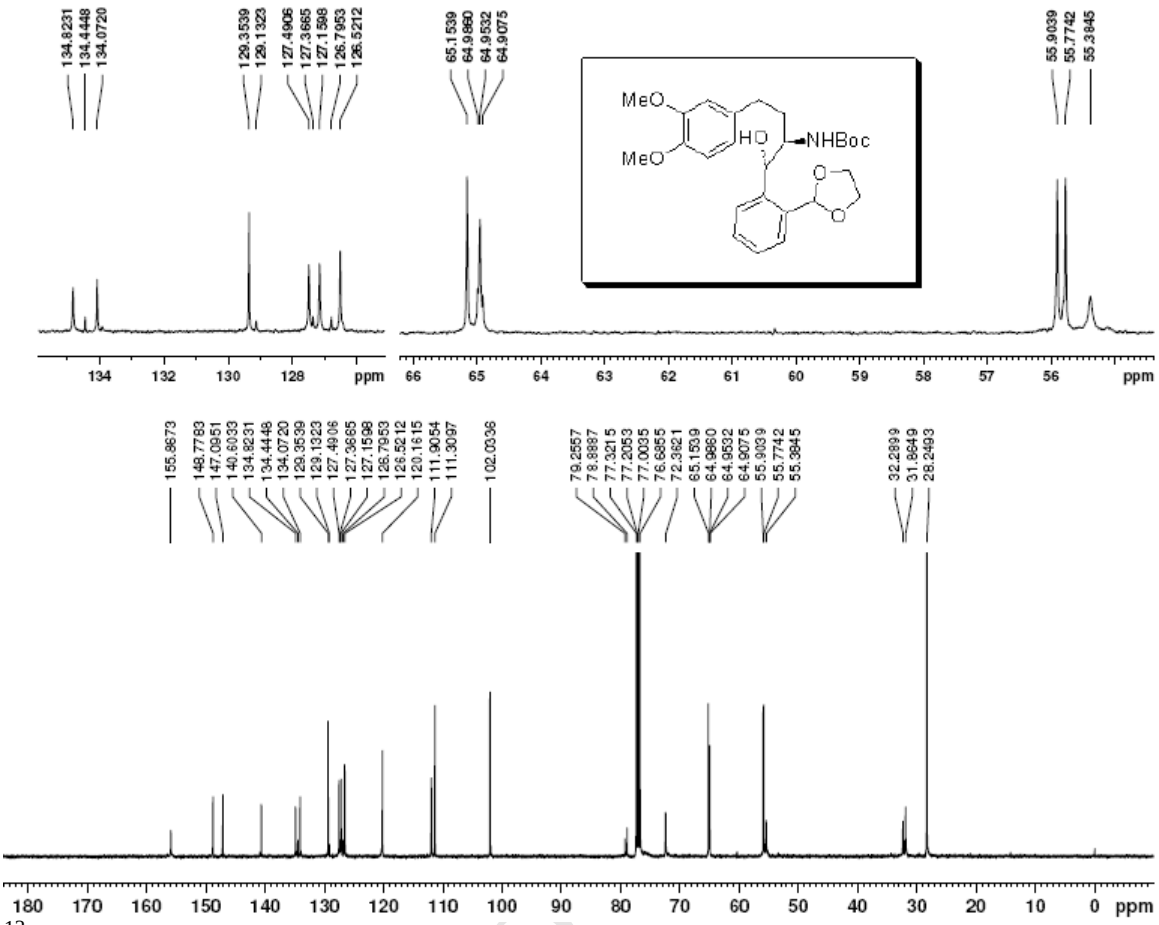


IR spectrum (neat) of compound **6**

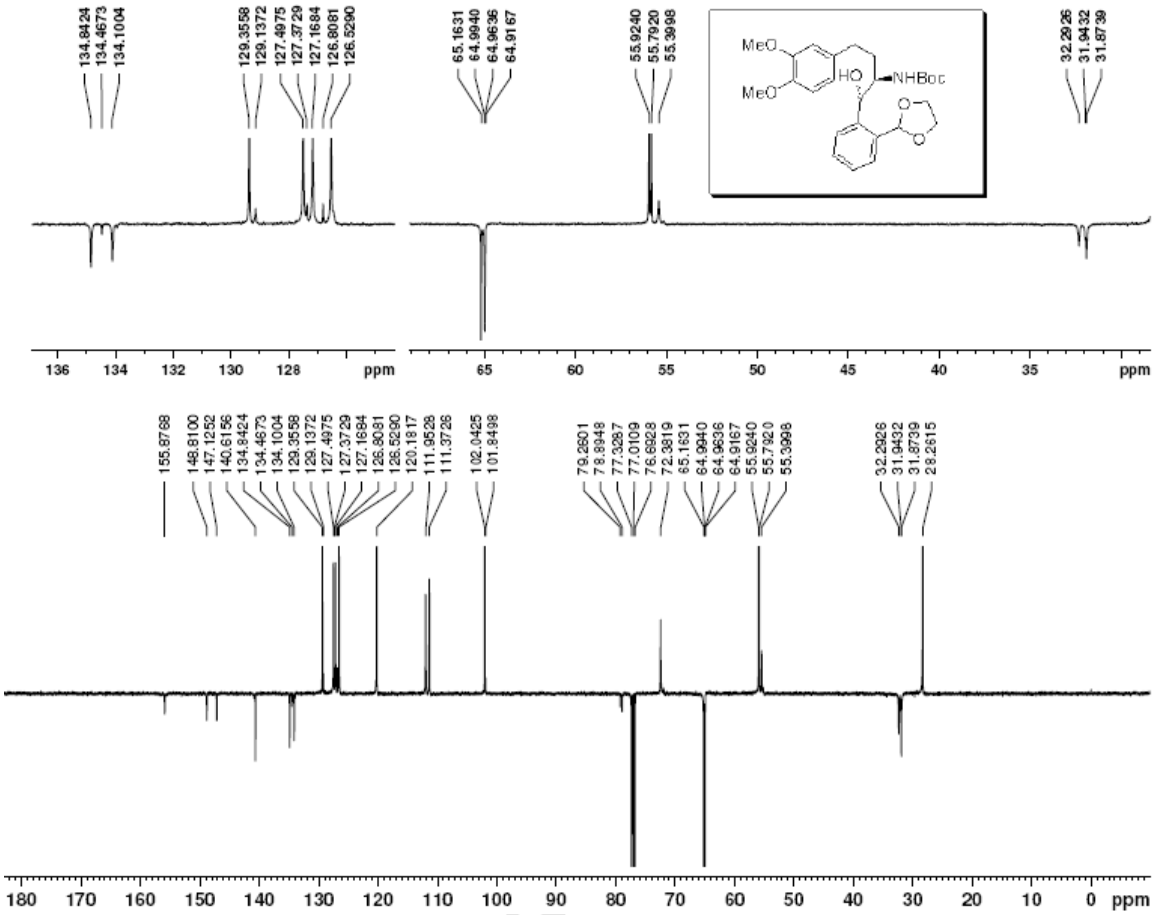
{(*R*)-3-(3,4-Dimethoxy-phenyl)-1-[(2-[1,3]dioxolan-2-yl-phenyl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester 7:



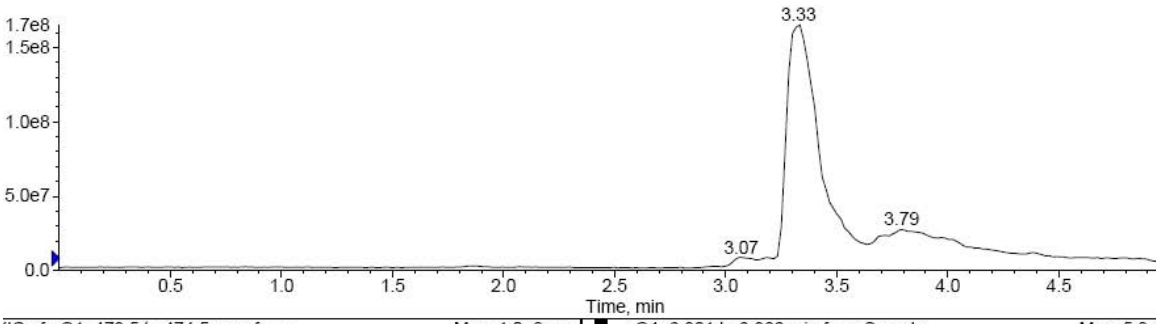
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **7**

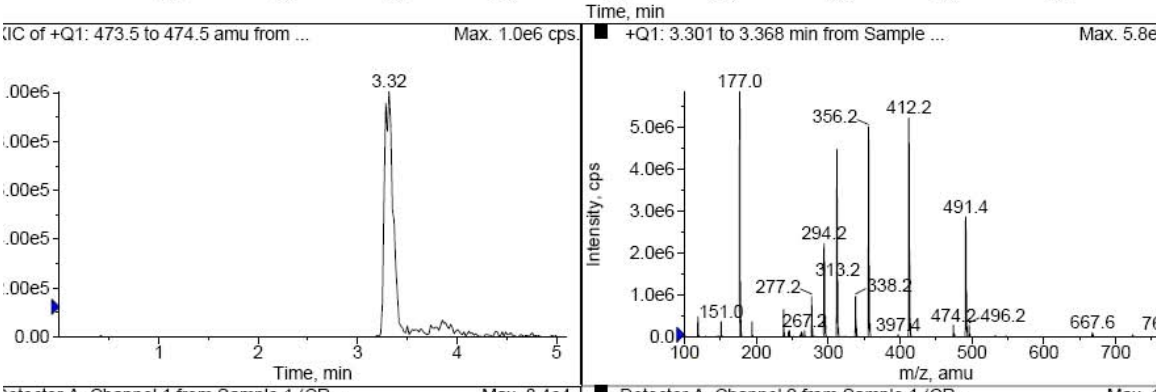


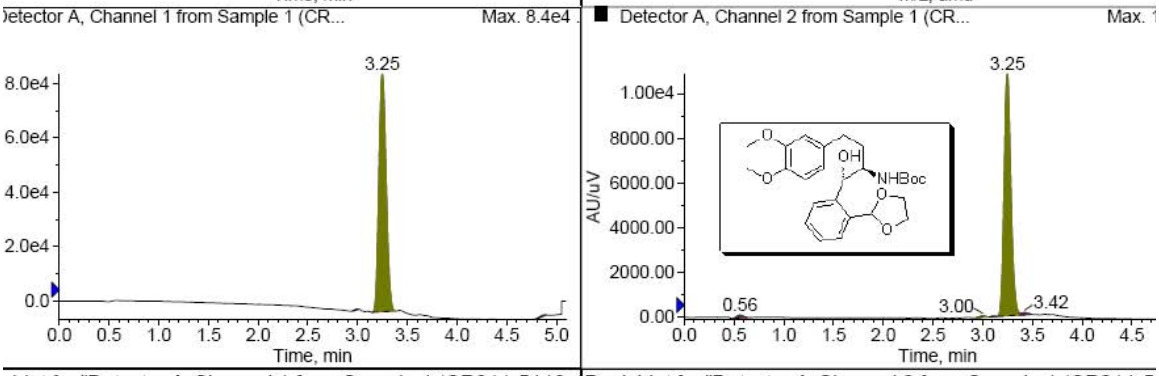
^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **7**



APT spectrum (100MHz, $CDCl_3$) of compound **7**







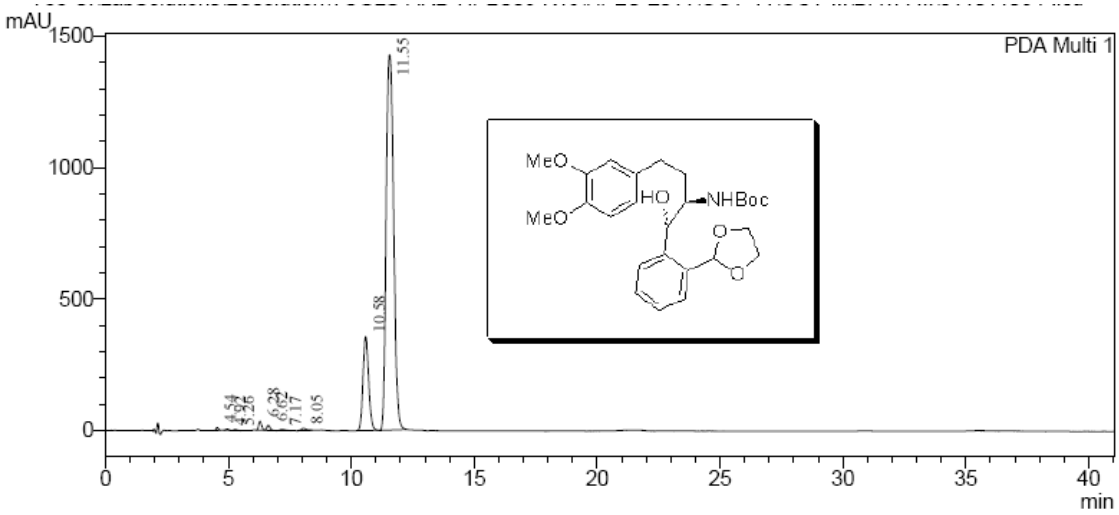
List for "Detector A, Channel 1 from Sample 1 (CR211-5119-4

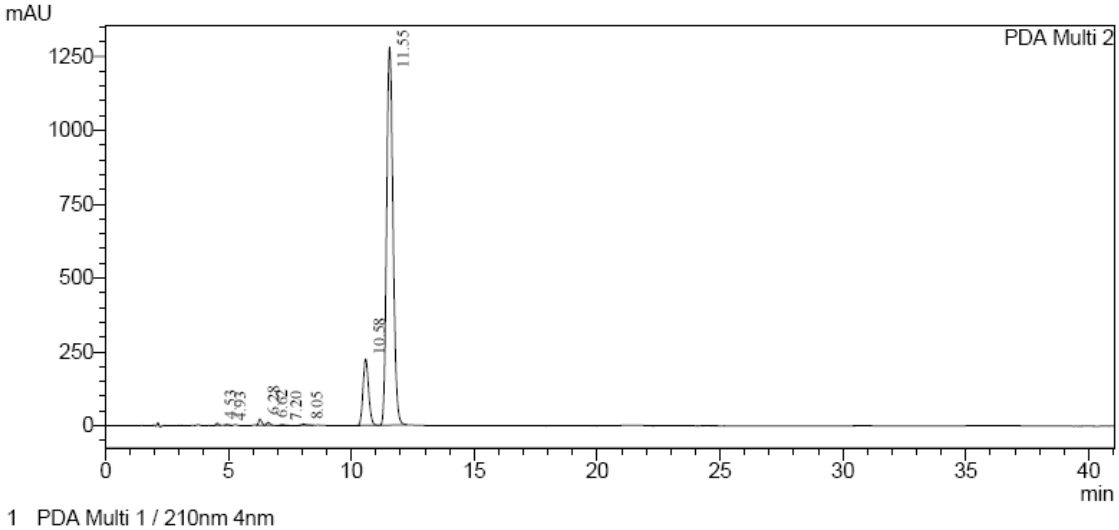
	Time (min)	Area (counts)	%Area	Height
	3.0012	515.6553	0.1171	188.6554
	3.2470	4.3852e5	99.5502	8.7477e4
	4.8842	1465.8704	0.3328	244.8074

Peak List for "Detector A, Channel 2 from Sample 1 (CR211-5

	Time (min)	Area (counts)	%Area	Height
1	0.5592	605.1068	1.1590	131.6248
2	2.9992	260.9460	0.4998	70.9174
3	3.1108	62.8974	0.1205	24.1433
4	3.2486	5.0927e4	97.5412	1.0811e4
5	3.4225	354.7837	0.6795	85.8301

LCMS spectrum of compound **7**





1 PDA Multi 1 / 210nm 4nm
2 PDA Multi 2 / 220nm 4nm

PeakTable

PDA Ch1 210nm 4nm

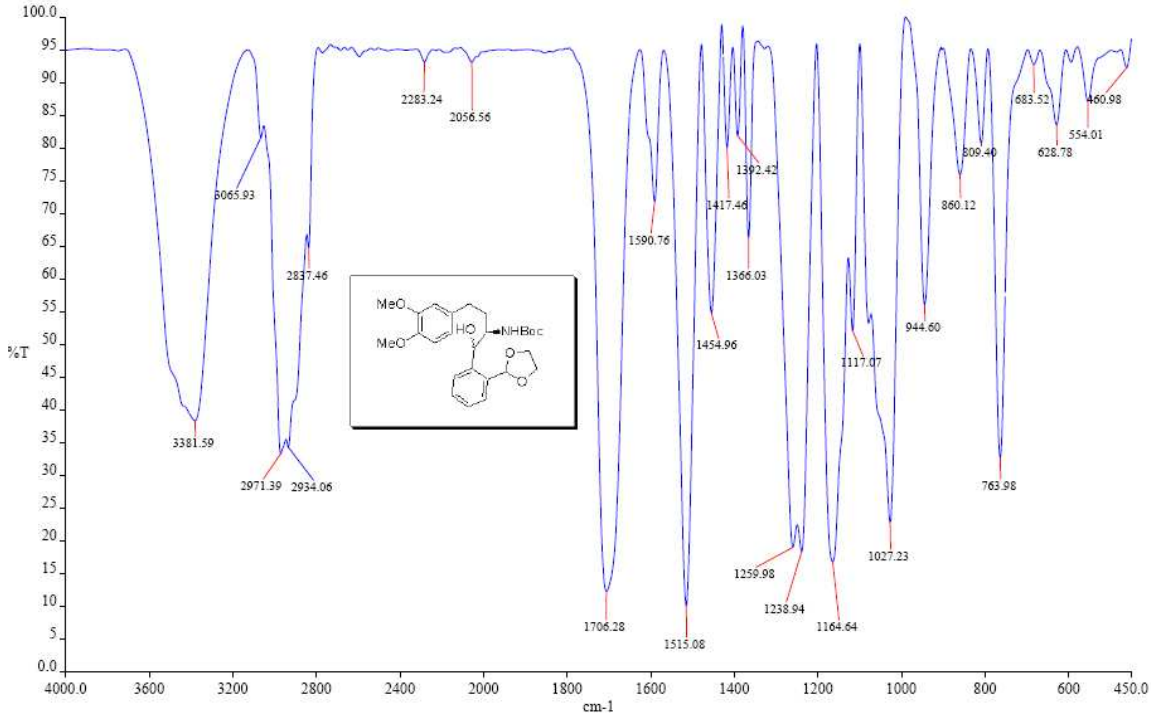
Peak#	Ret. Time	Area	Area %
1	4.54	70233	0.19
2	4.92	38664	0.11
3	5.26	40020	0.11
4	6.28	282835	0.77
5	6.62	179939	0.49
6	7.17	68887	0.19
7	8.05	122199	0.33
8	10.58	5701627	15.61
9	11.55	30022189	82.19
Total		36526592	100.00

PeakTable

PDA Ch2 220nm 4nm

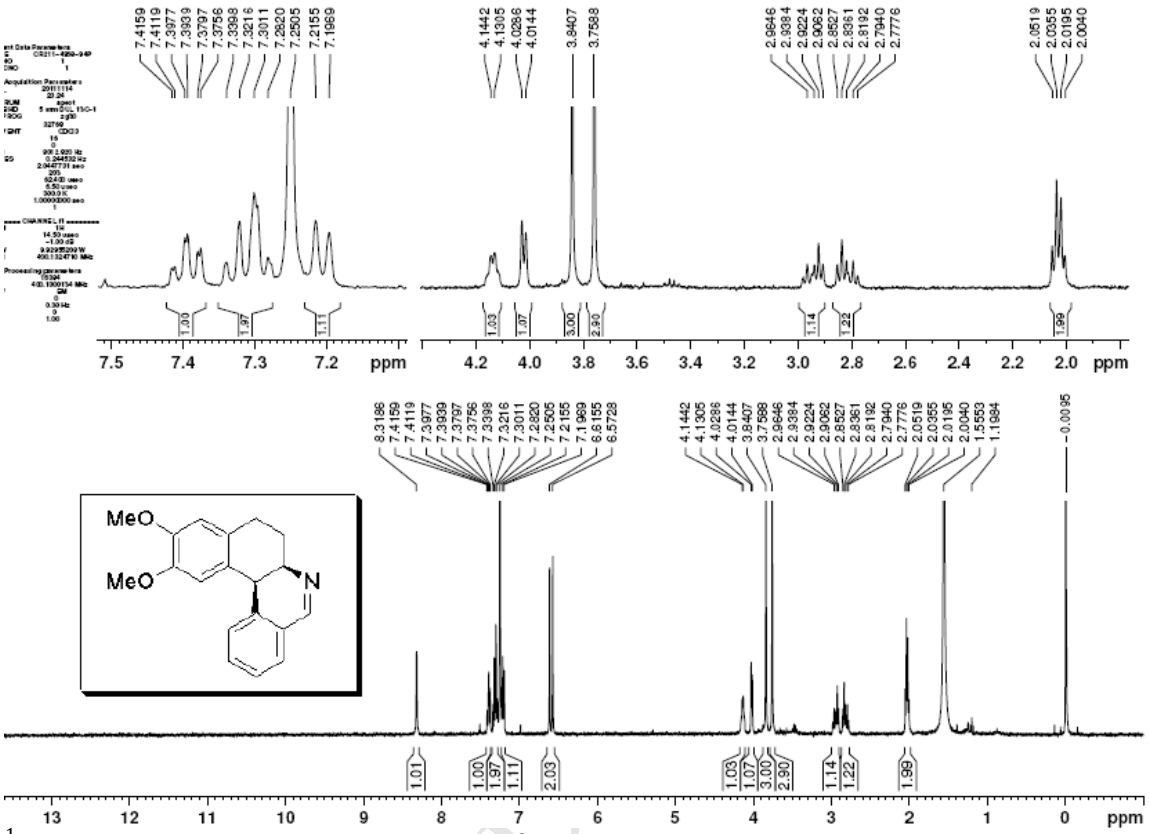
Peak#	Ret. Time	Area	Area %
1	4.53	47987	0.18
2	4.93	26842	0.10
3	6.28	176100	0.65
4	6.62	94530	0.35
5	7.20	43159	0.16
6	8.05	73027	0.27
7	10.58	3545113	13.05
8	11.55	23167554	85.26
Total		27174311	100.00

HPLC spectrum [(Zorbax-SB C8column (250x4.6mm)5µ; Mobile phase: ACN containing 10mM NH_4OAc in H_2O; Diluent :MeOH)] of compound 7

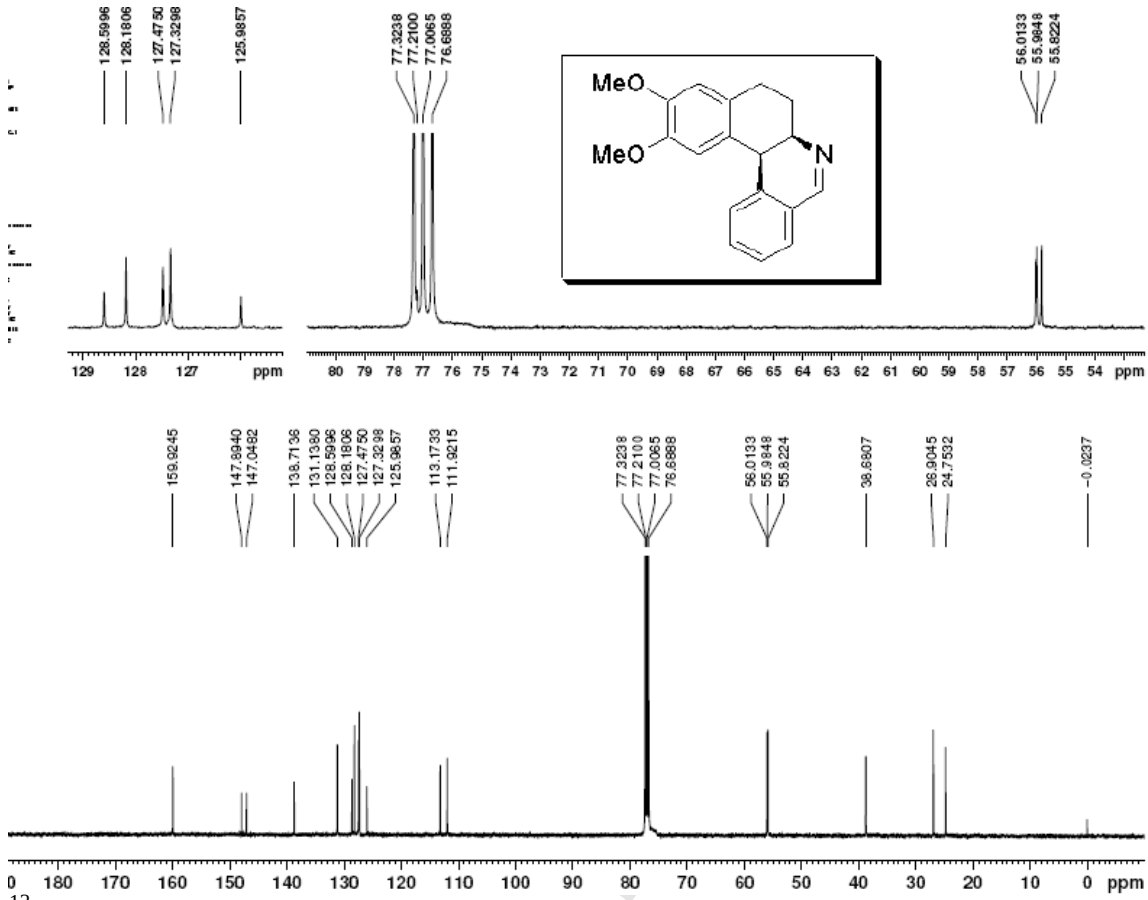


IR spectrum (KBr) of compound **7**.

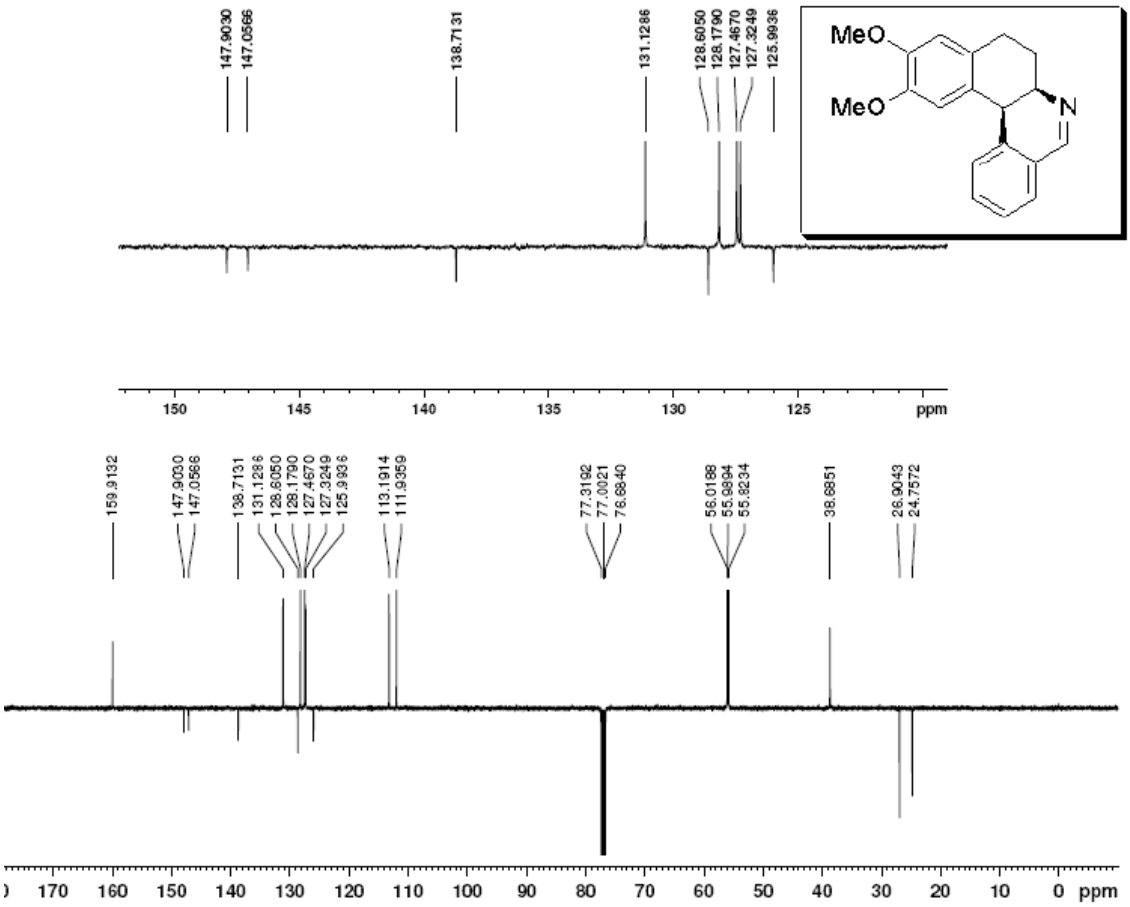
(6a*R*,12b*R*)-10,11-Dimethoxy-6a,7,8,12b-tetrahydro-benzo[a]phenanthridine 9:



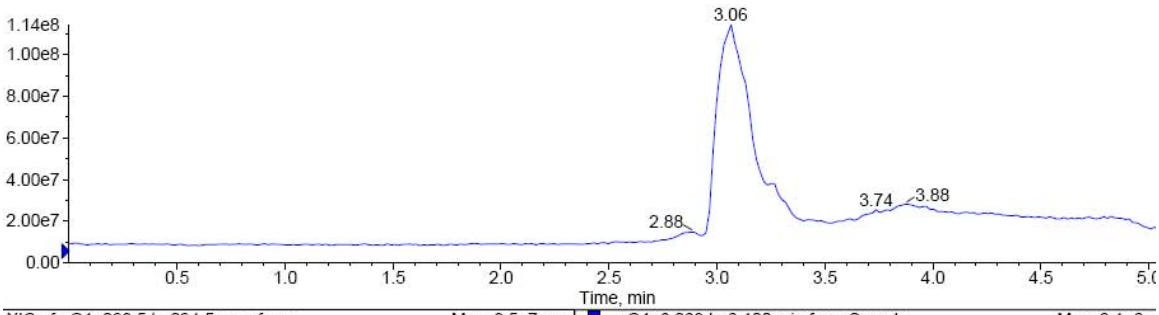
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **9**

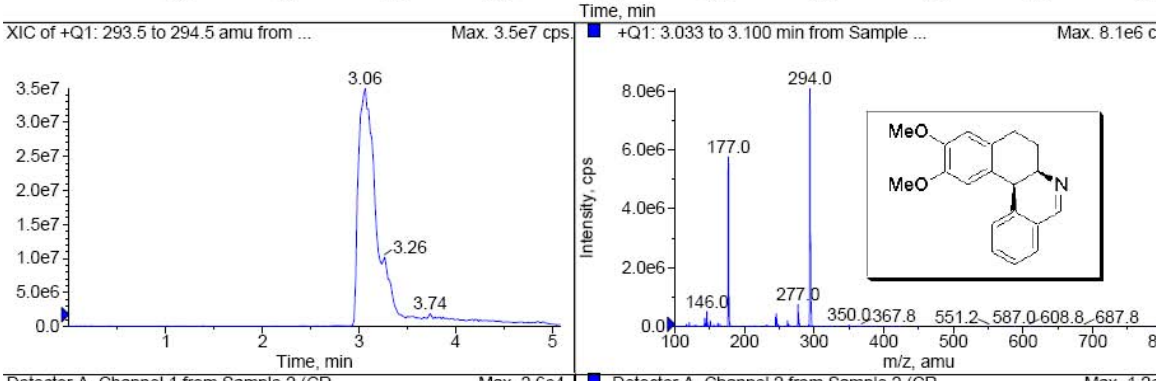


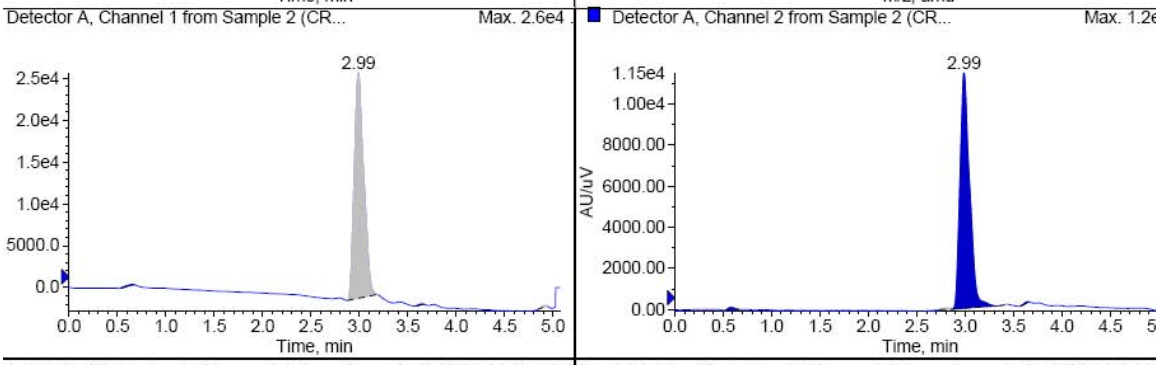
^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **9**



APT spectrum (100MHz, $CDCl_3$) of compound **9**







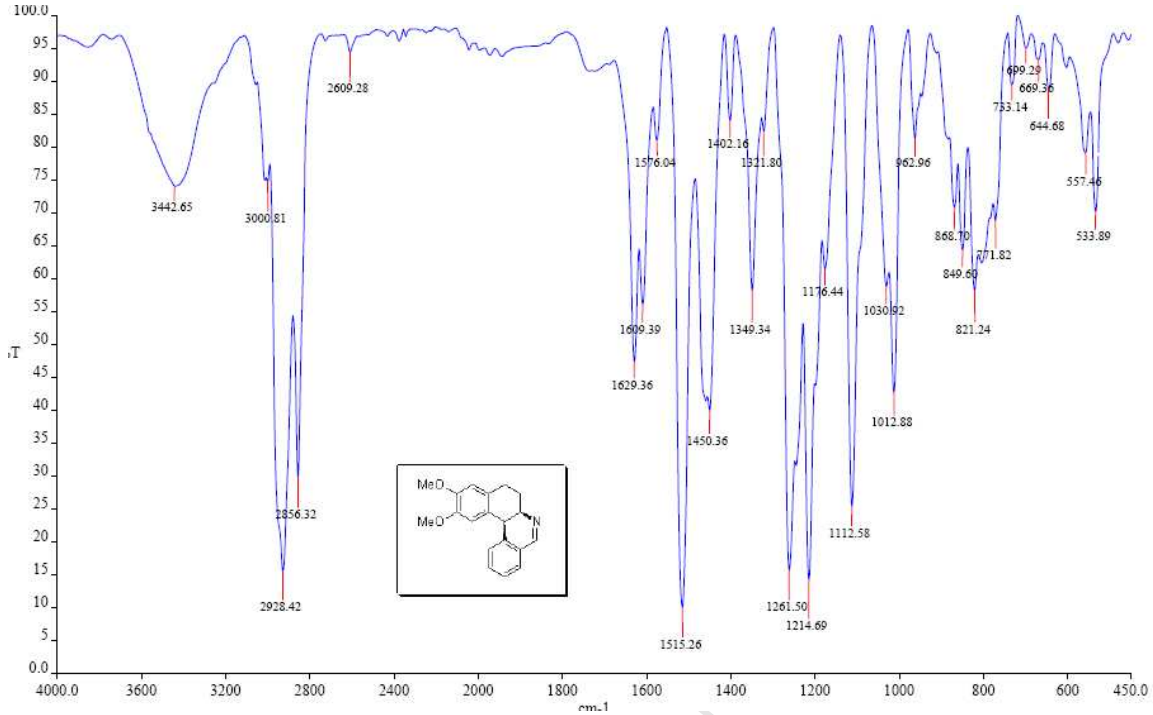
ak List for "Detector A, Channel 1 from Sample 2 (CR211-5119-5

	Time (min)	Area (counts)	%Area	Height
	0.6567	498.6226	0.2764	67.3020
	2.9896	1.7939e5	99.4371	2.6937e4
	3.6458	212.0433	0.1175	64.6761
	4.9158	304.7575	0.1689	93.8309

Peak List for "Detector A, Channel 2 from Sample 2 (CR211-511

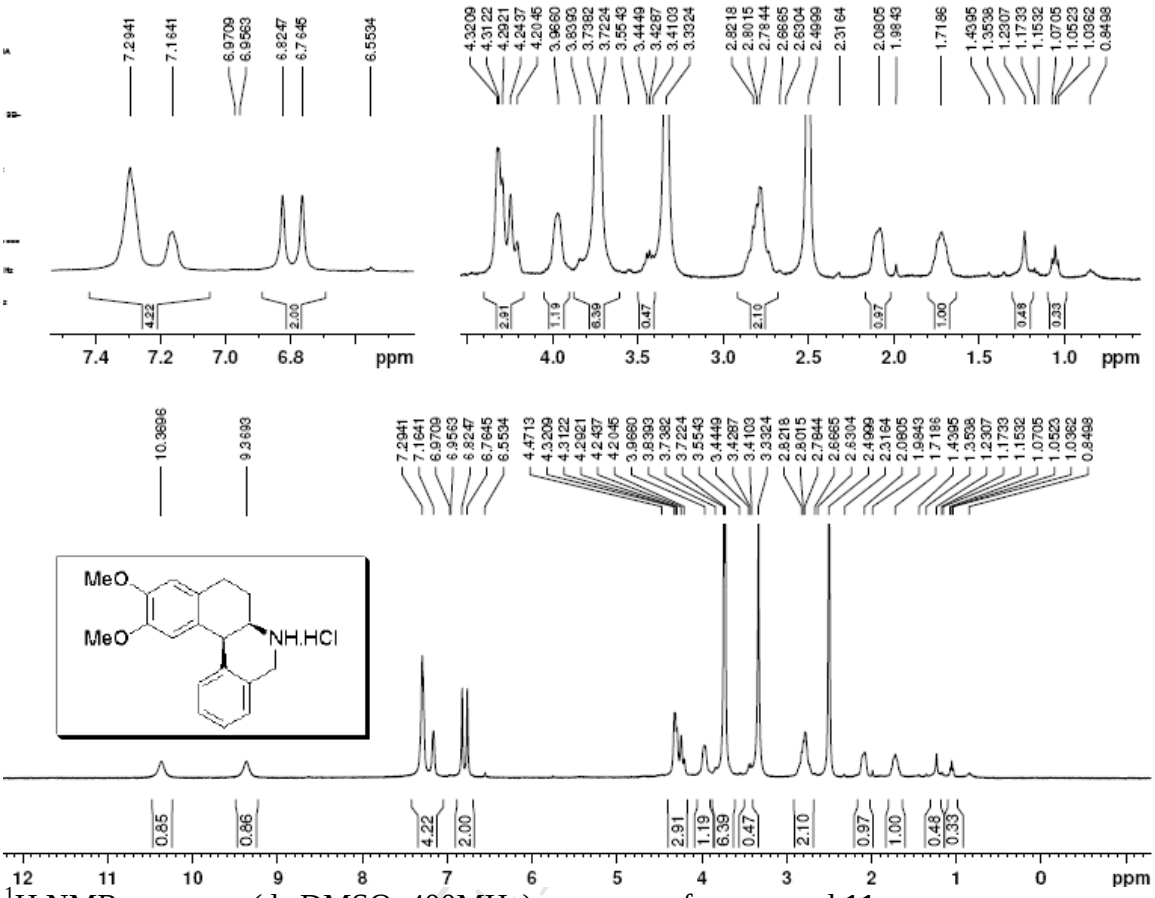
	Time (min)	Area (counts)	%Area	Height
1	0.5792	565.4149	0.7156	125.1024
2	2.8058	248.2127	0.3142	60.6682
3	2.9877	7.7993e4	98.7149	1.1441e4
4	3.4208	64.8984	0.0821	19.6082
5	3.6458	136.8178	0.1732	37.9141

LCMS spectrum of compound **9**.

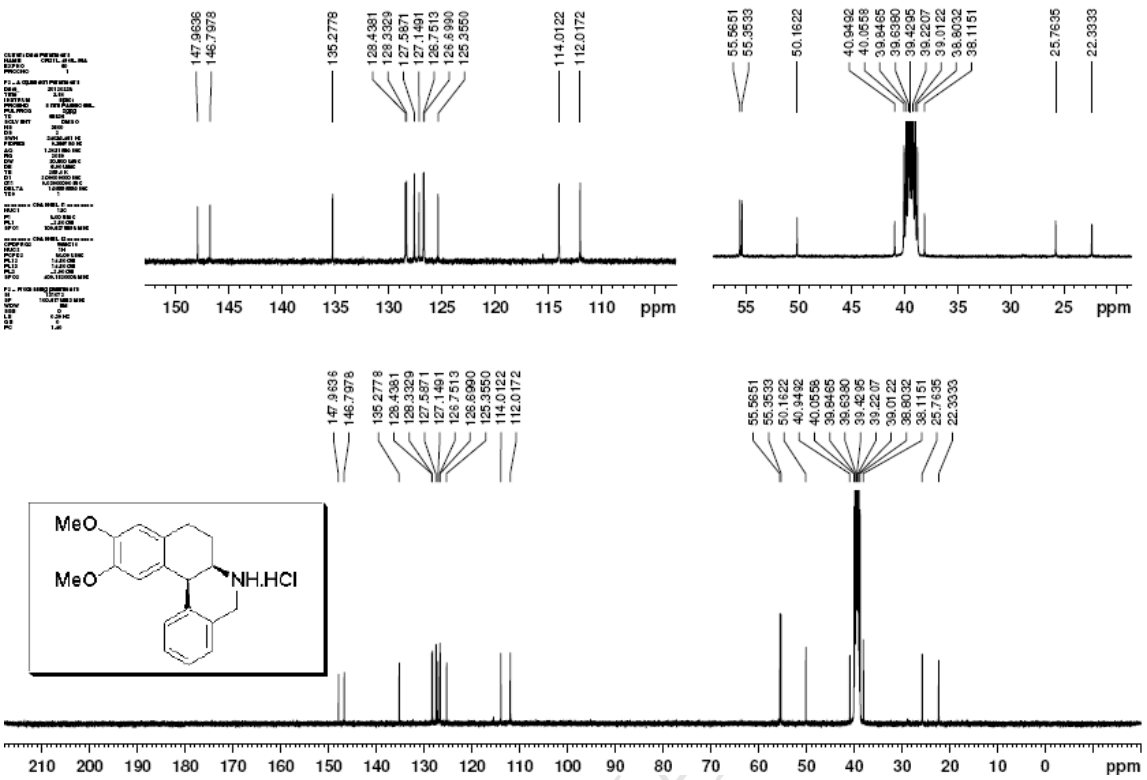


IR spectrum (KBr) of compound **9**

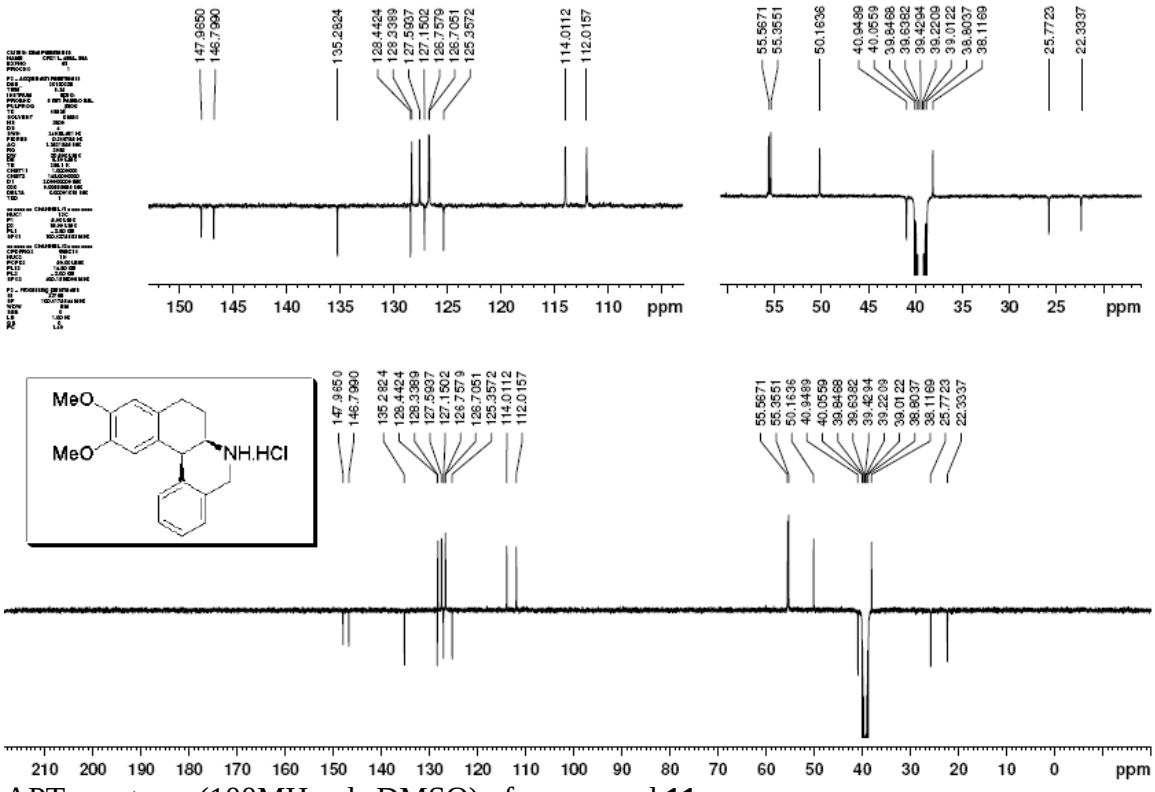
(6a*R*, 12b*R*)-10, 11-Dimethoxy-5, 6, 6a, 7, 8,12b-hexahydro-benzo [a] phenanthridine hydrochloride 11:



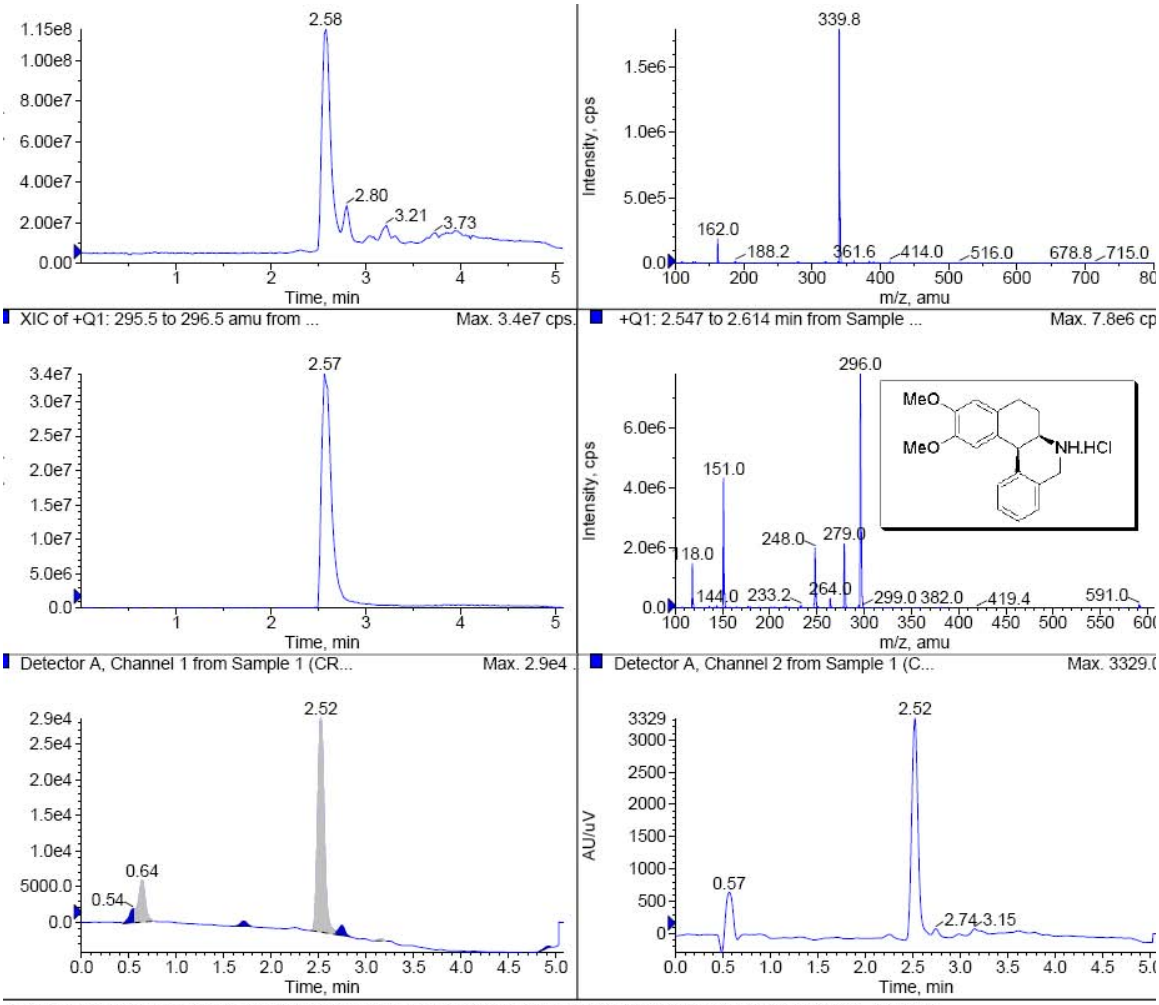
^{1}H NMR spectrum (d_6-DMSO, 400MHz) spectrum of compound **11**



^{13}C NMR spectrum (d_6-DMSO, 100MHz) spectrum of compound **11**



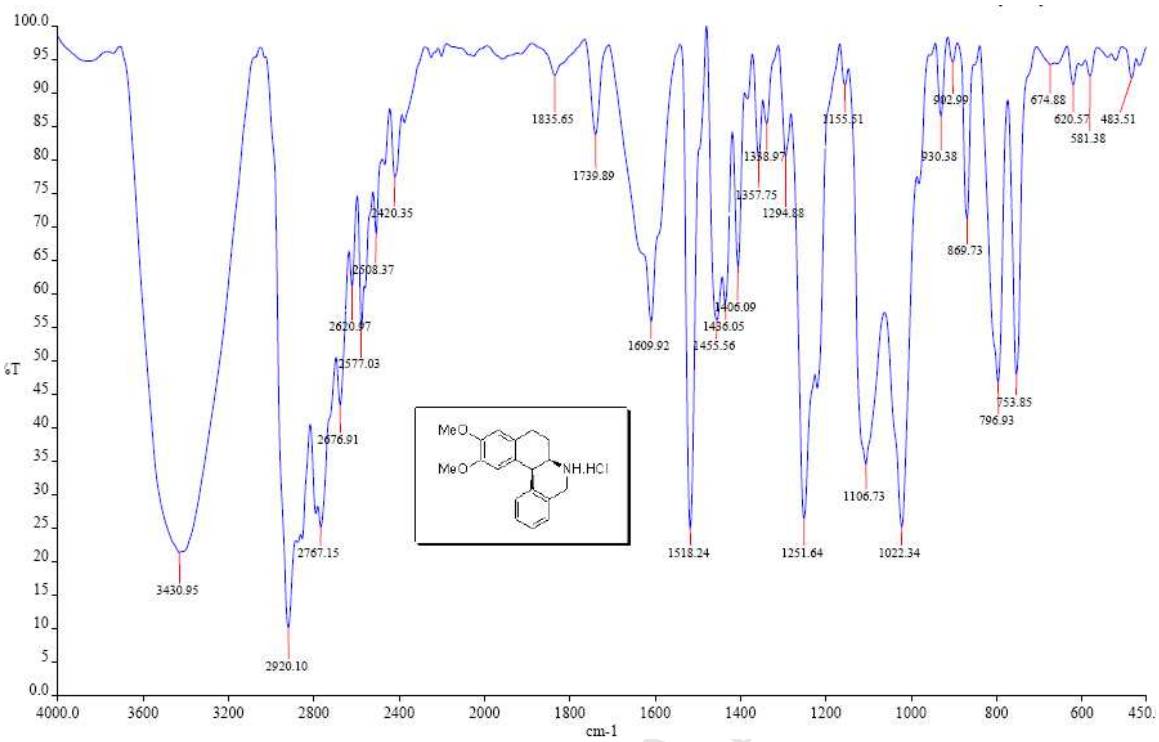
APT spectrum (100MHz, d_6-DMSO) of compound **11**.



eak List for "Detector A, Channel 1 from Sample 1 (CR211-4968-96A) of CR211-MONI-09-NOV-B3-AA.wiff"

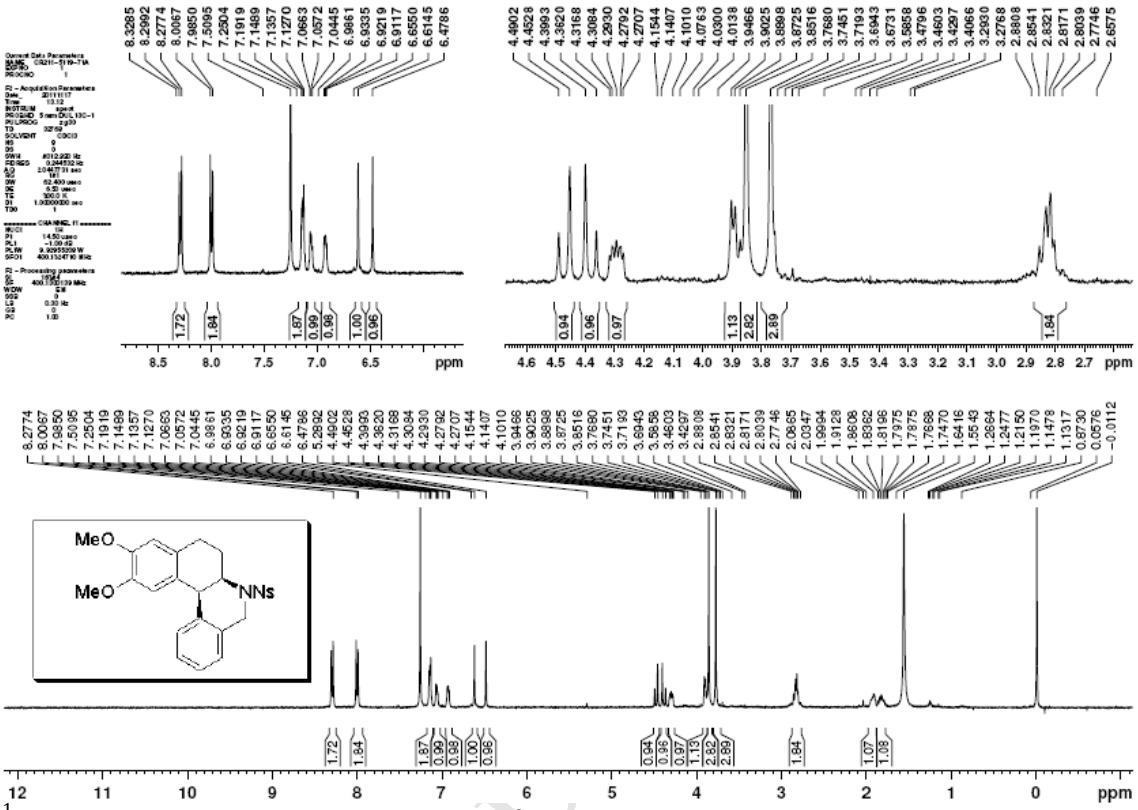
	Time (min)	Area (counts)	%Area	Height	%Height	Width (min)	Baseline Type
	0.5425	7294.5153	3.8704	1934.0530	4.7759	0.1217	Valley
	0.6390	2.9019e4	15.3970	5901.0205	14.5719	0.2000	Valley
	1.7108	3288.7383	1.7450	720.1566	1.7783	0.1567	Base to Base
	2.5215	1.4071e5	74.6611	3.0030e4	74.1553	0.2633	Valley
	2.7412	6275.4472	3.3297	1403.3867	3.4655	0.1467	Valley
	3.1550	1053.4281	0.5589	316.1936	0.7808	0.1033	Base to Base
	4.9183	825.4544	0.4380	191.2404	0.4722	0.1150	Base to Base

LCMS spectrum of compound **11**.

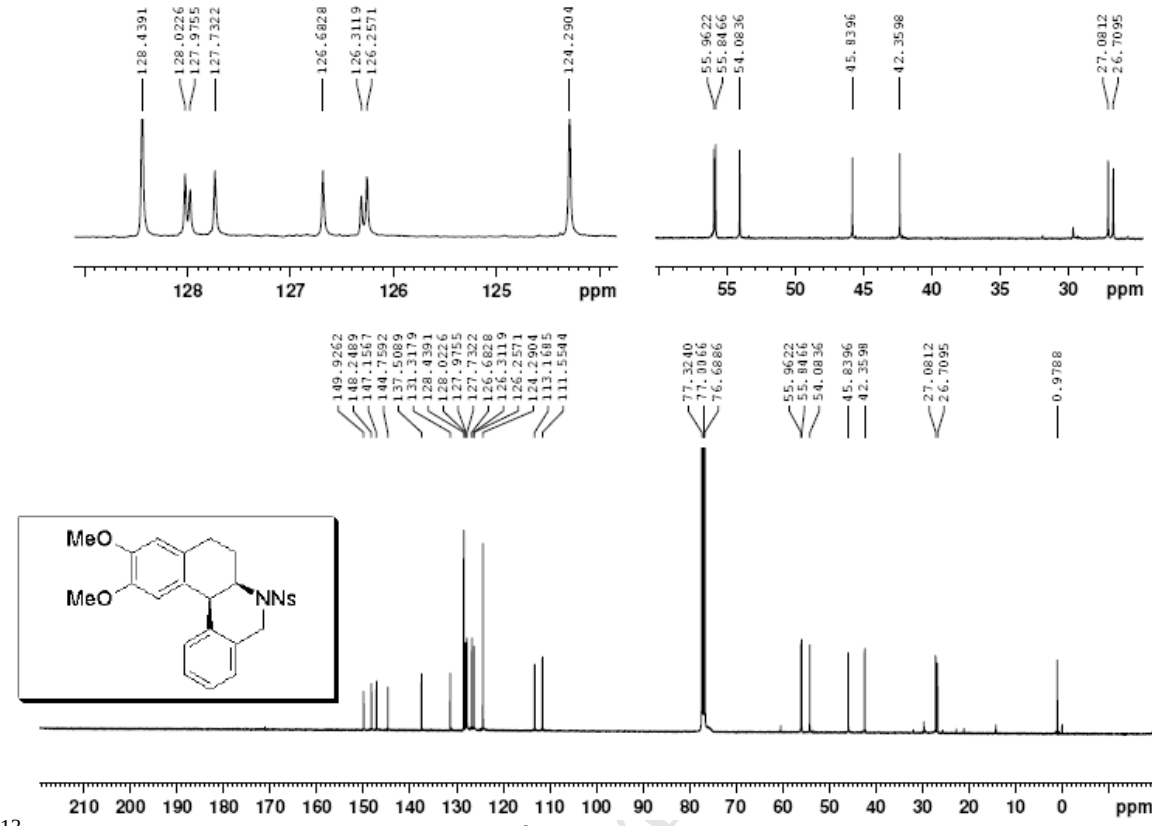


IR spectrum (neat) of compound **11**.

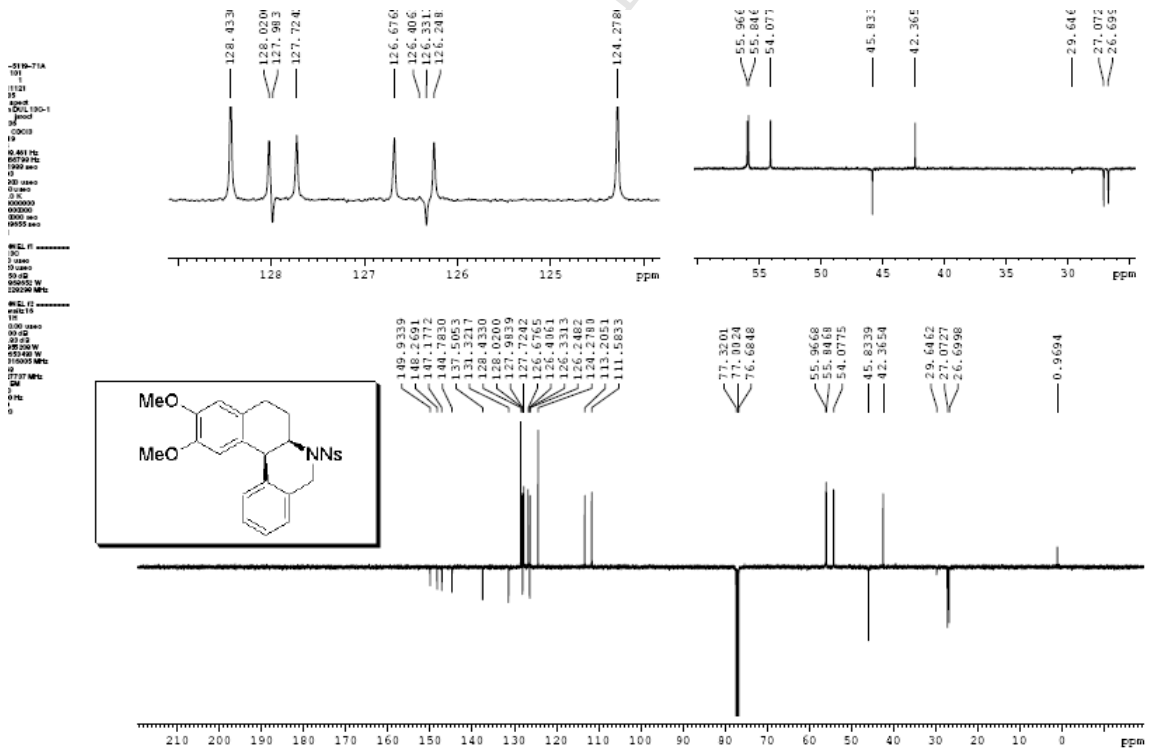
(6a*R*,12b*R*)-10,11-Dimethoxy-6-(4-nitro-benzenesul-fonyl)-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (12):



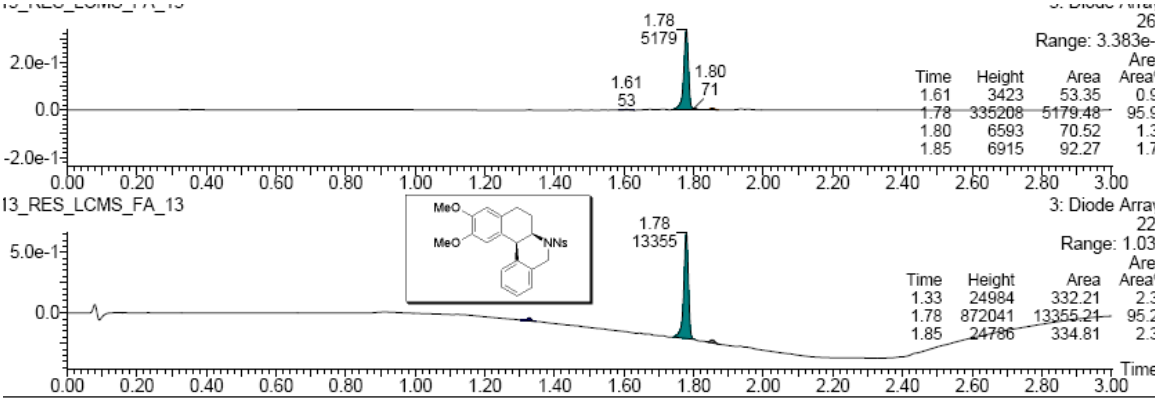
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **12**

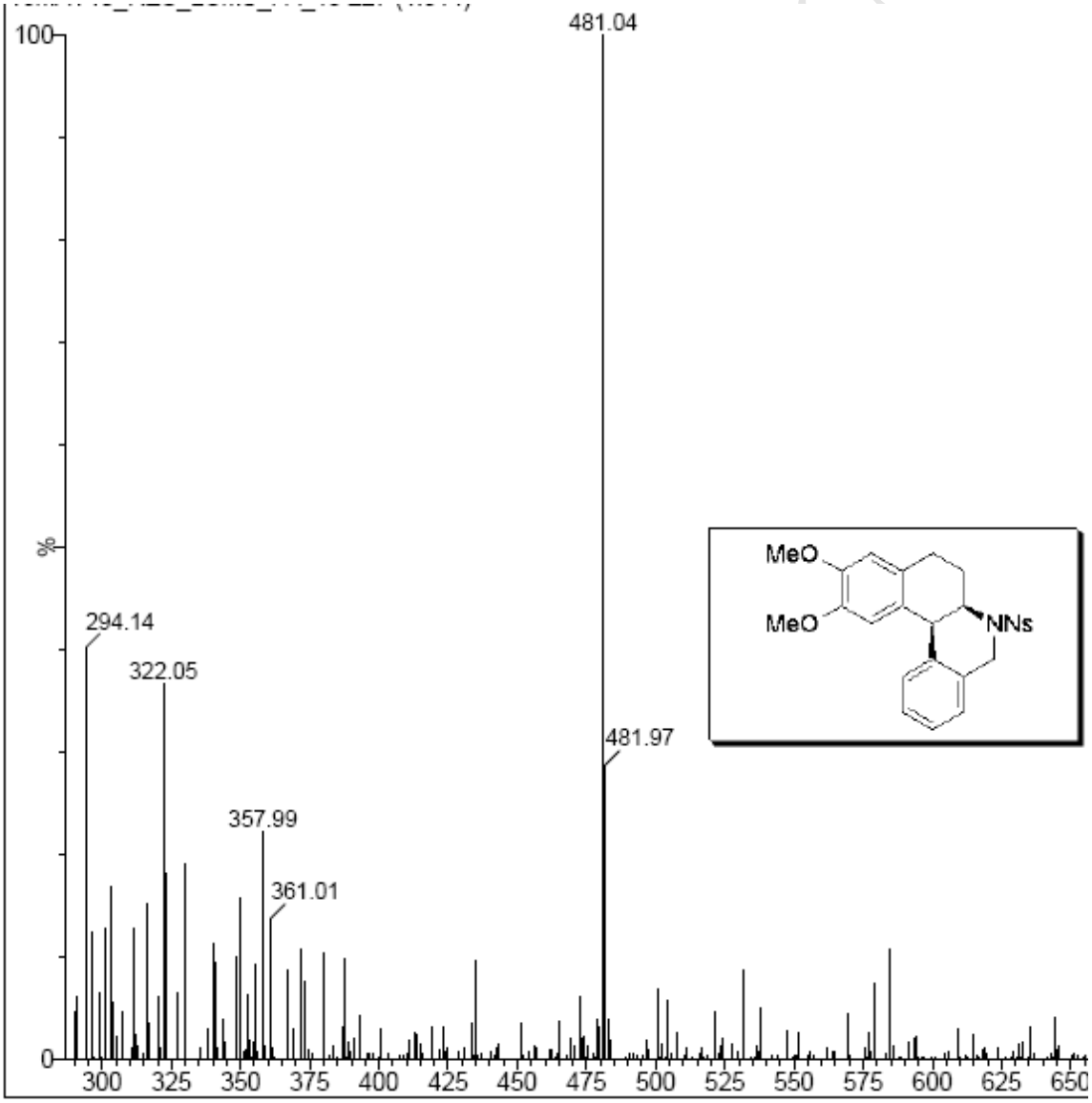


^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **12**

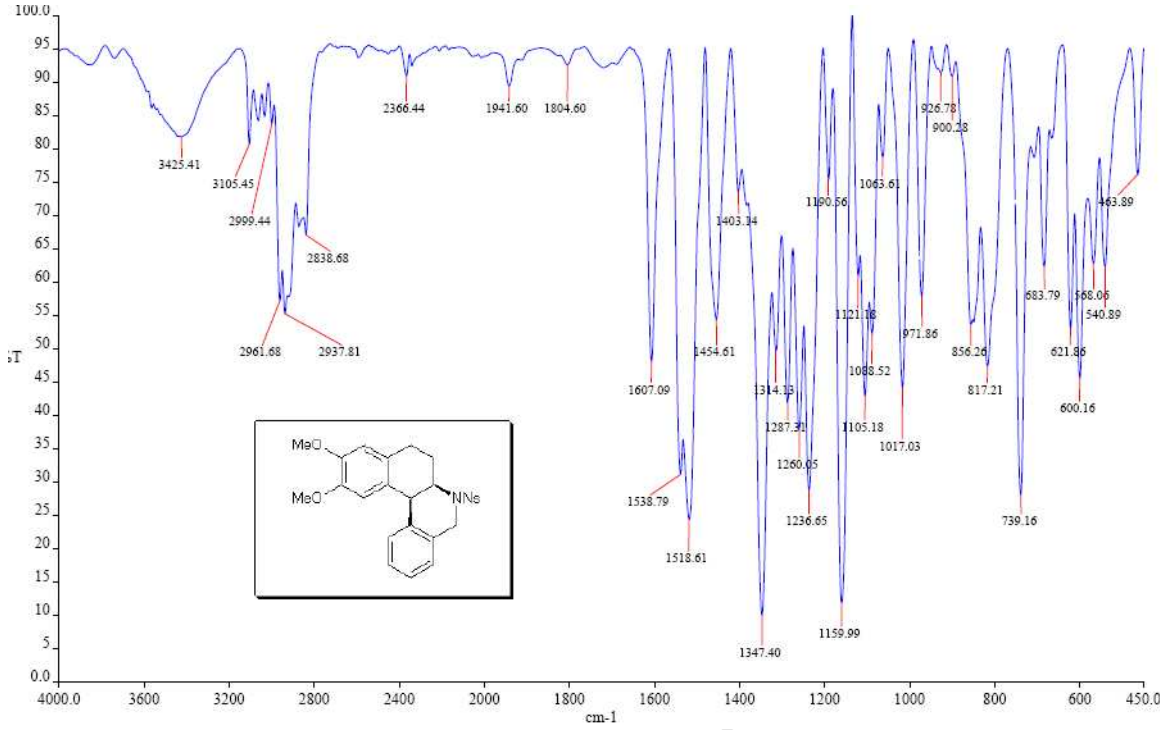


APT spectrum (400MHz, $CDCl_3$) of compound **12**



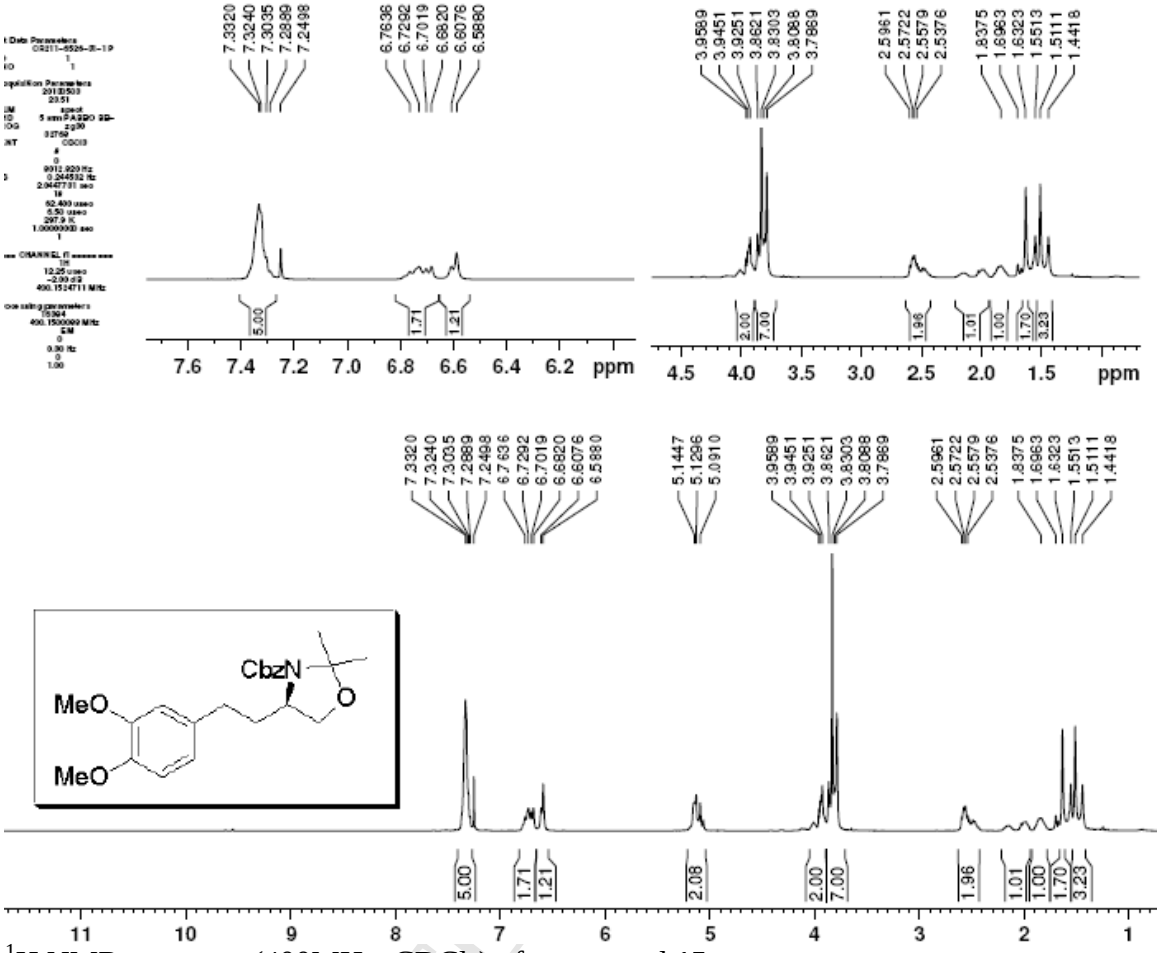


LCMS spectrum of compound **12**.

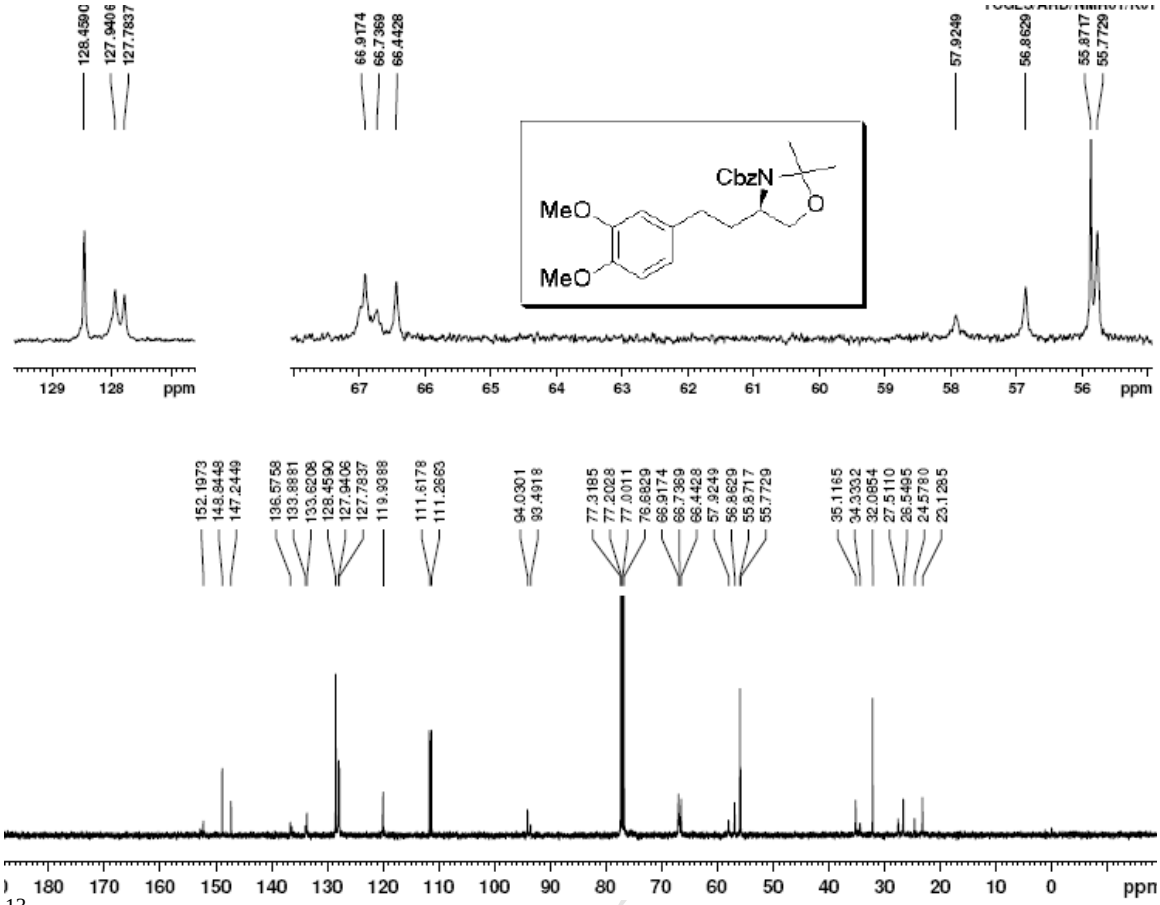


IR spectrum (KBr) of compound **12**.

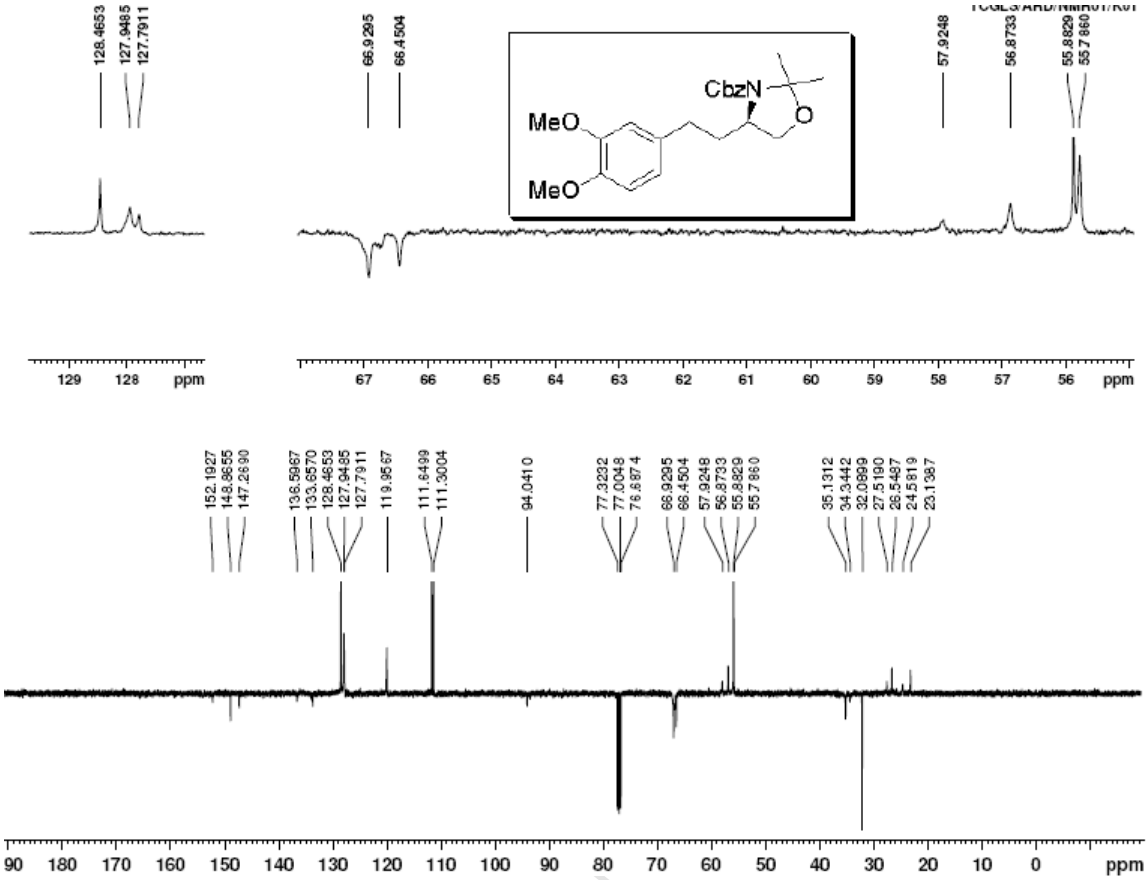
(*R*)-4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,2-dimethyl-oxazolidine-3 carboxylic acid benzyl ester 15:



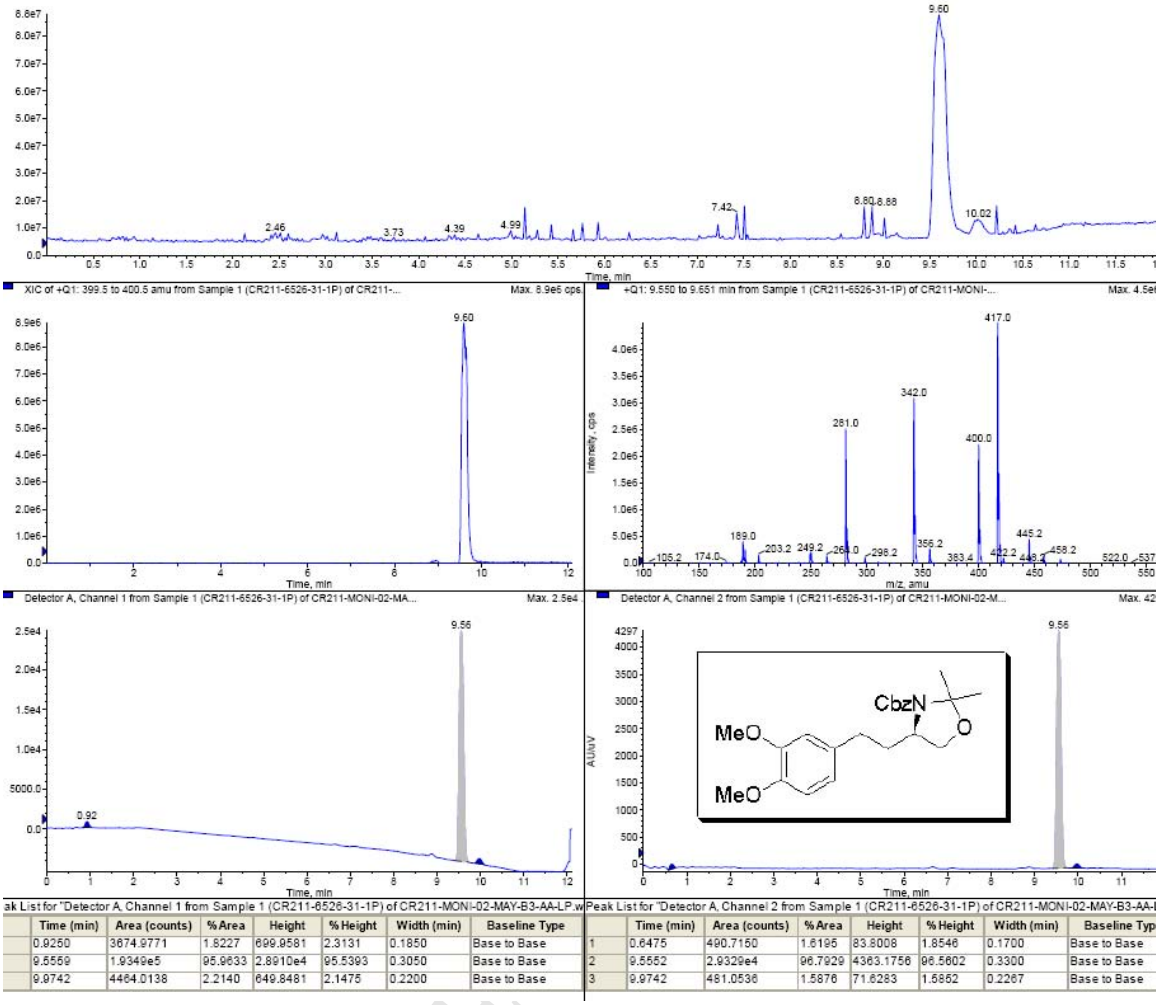
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **15**.



^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **15**.



APT spectrum (400MHz, $CDCl_3$) of compound **15**.



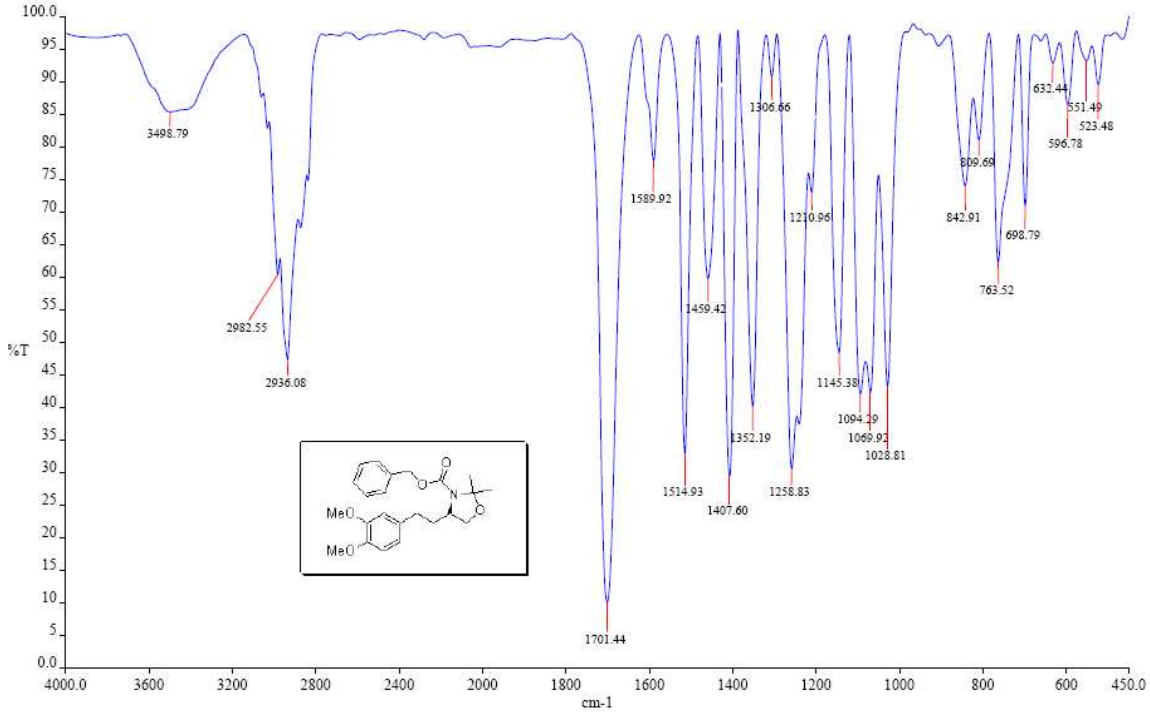
Peak List for "Detector A, Channel 1 from Sample 1 (CR211-6526-31-1P) of CR211-MONI-02-MAY-B3-AA-LP.w

	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
	0.9250	3674.9771	1.8227	699.9581	2.3131	0.1850	Base to Base
	9.5559	1.9349e5	95.9633	2.8910e4	95.5393	0.3050	Base to Base
	9.9742	4464.0138	2.2140	649.8481	2.1475	0.2200	Base to Base

Peak List for "Detector A, Channel 2 from Sample 1 (CR211-6526-31-1P) of CR211-MONI-02-MAY-B3-AA-I

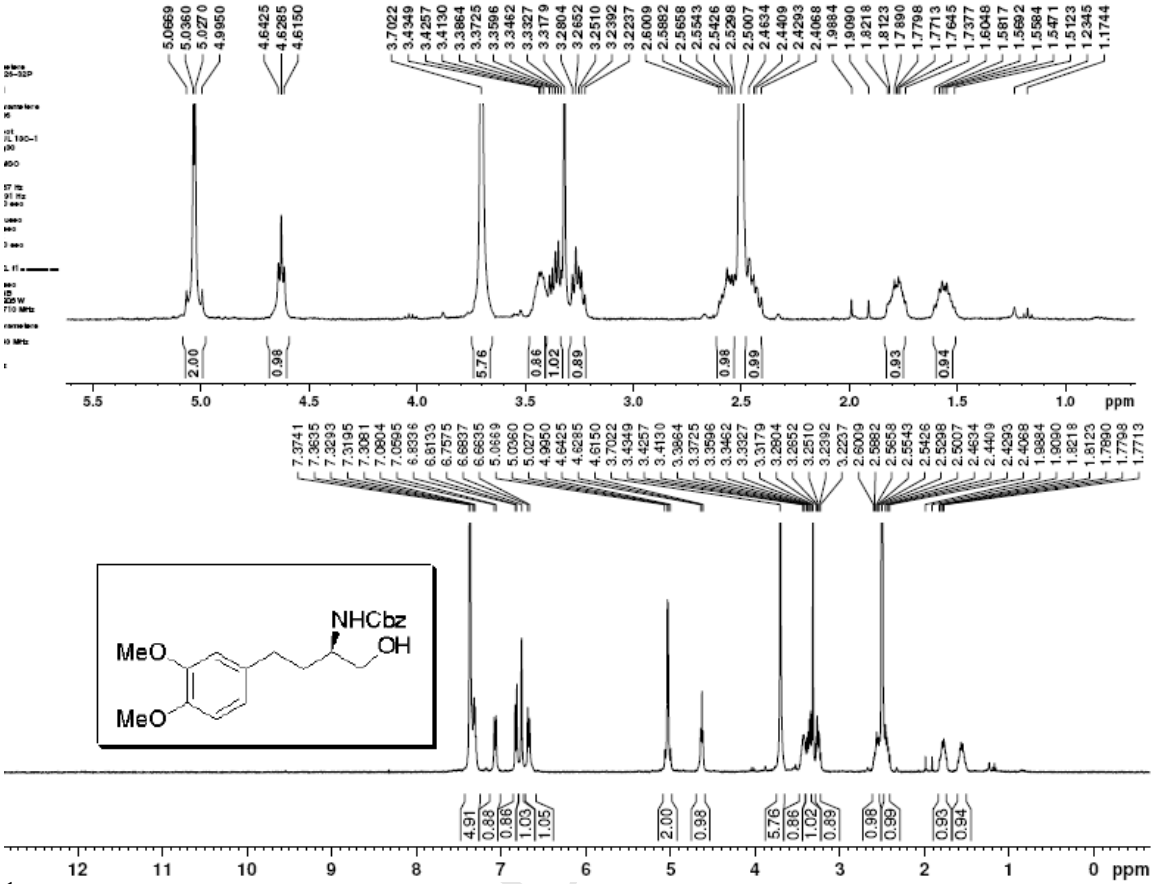
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Typ
1	0.6475	490.7150	1.6195	83.8008	1.8546	0.1700	Base to Base
2	9.5552	2.9329e4	96.7929	4363.1756	96.5602	0.3300	Base to Base
3	9.9742	481.0536	1.5876	71.6283	1.5852	0.2267	Base to Base

LCMS spectrum of compound **15**.

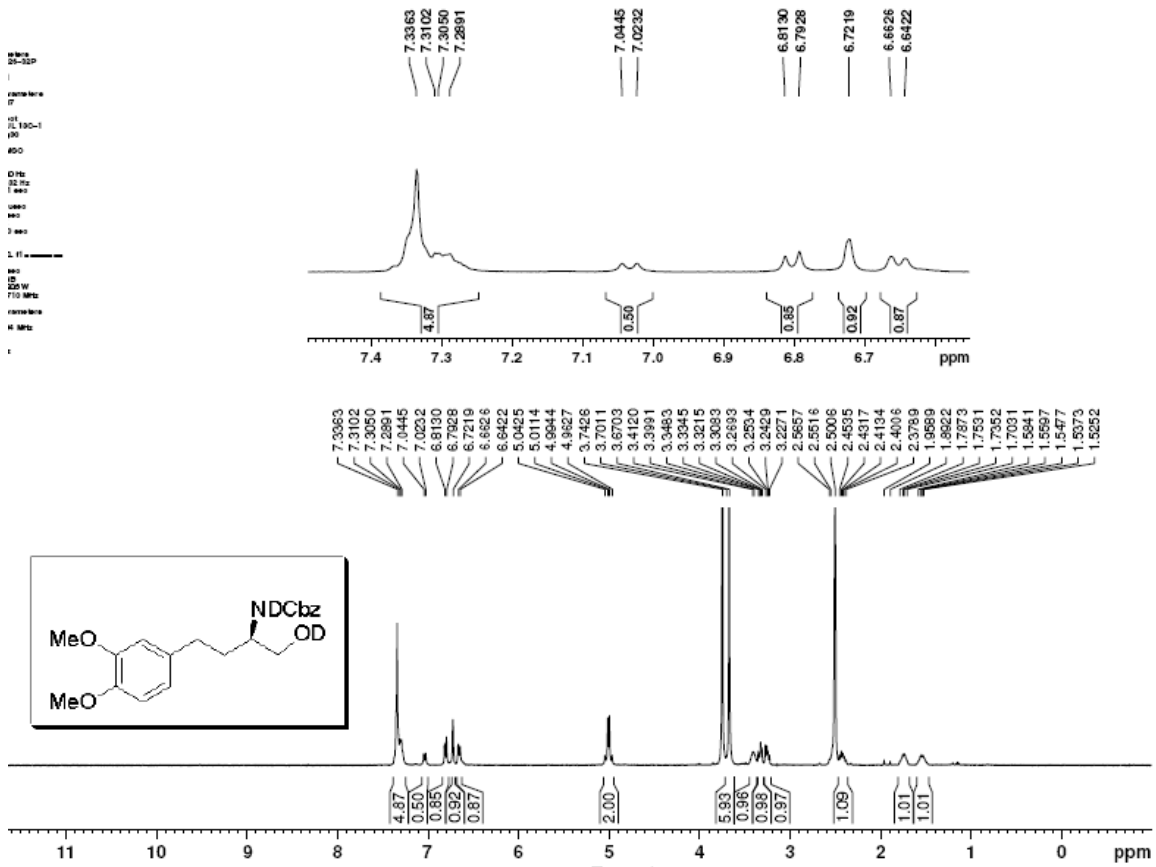


IR spectrum (neat) of compound **15**

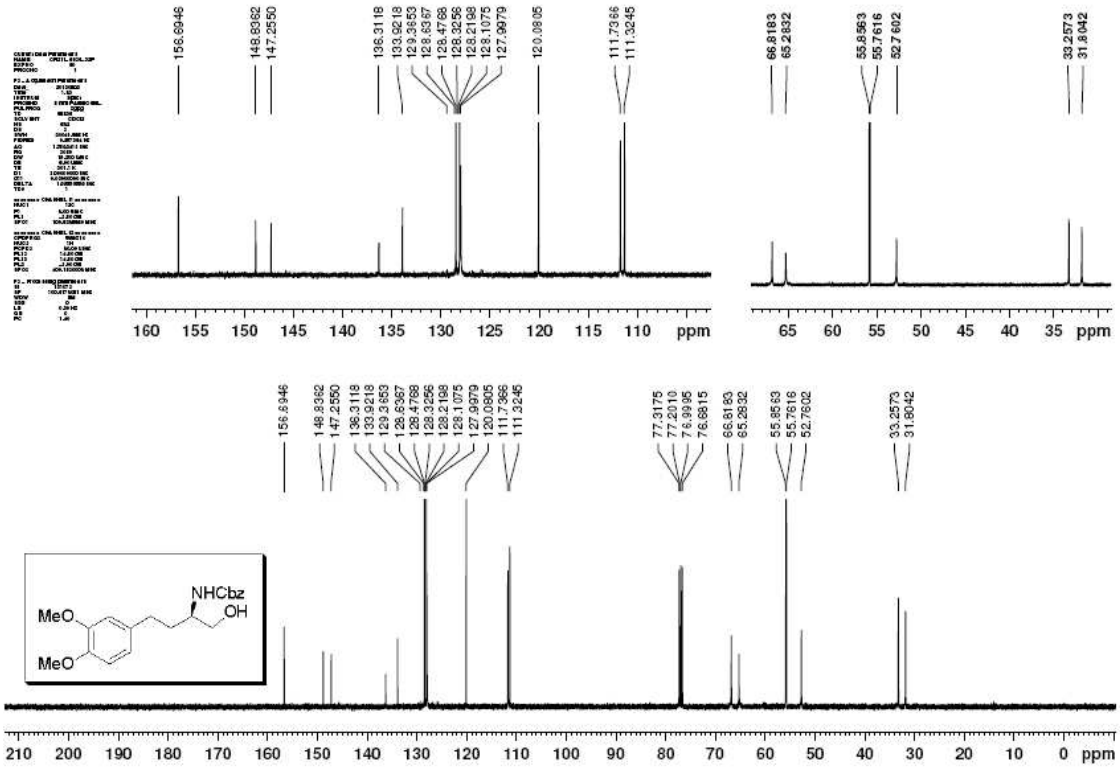
[(*R*)-3-(3,4-Dimethoxy-phenyl)-1-hydroxymethyl-propyl]-carbamicacid benzyl ester 16:



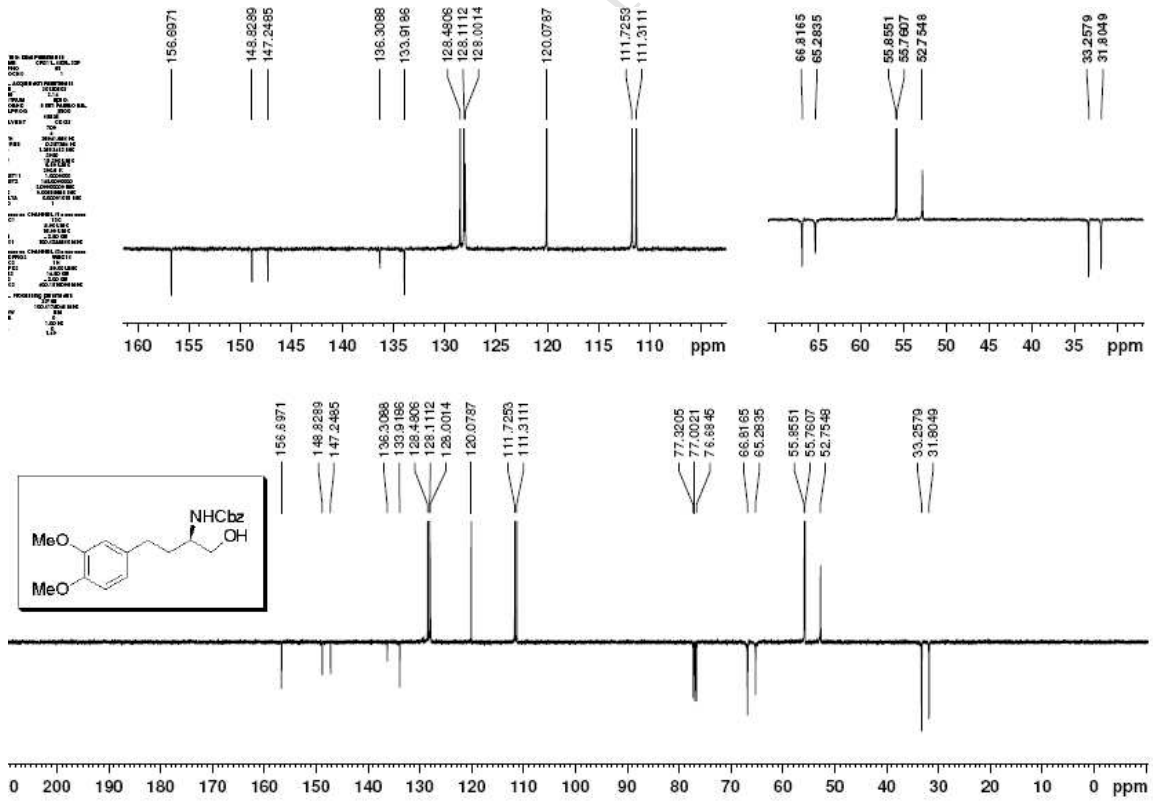
^{1}HNMR spectrum (400MHz, $CDCl_3$) of compound **16**



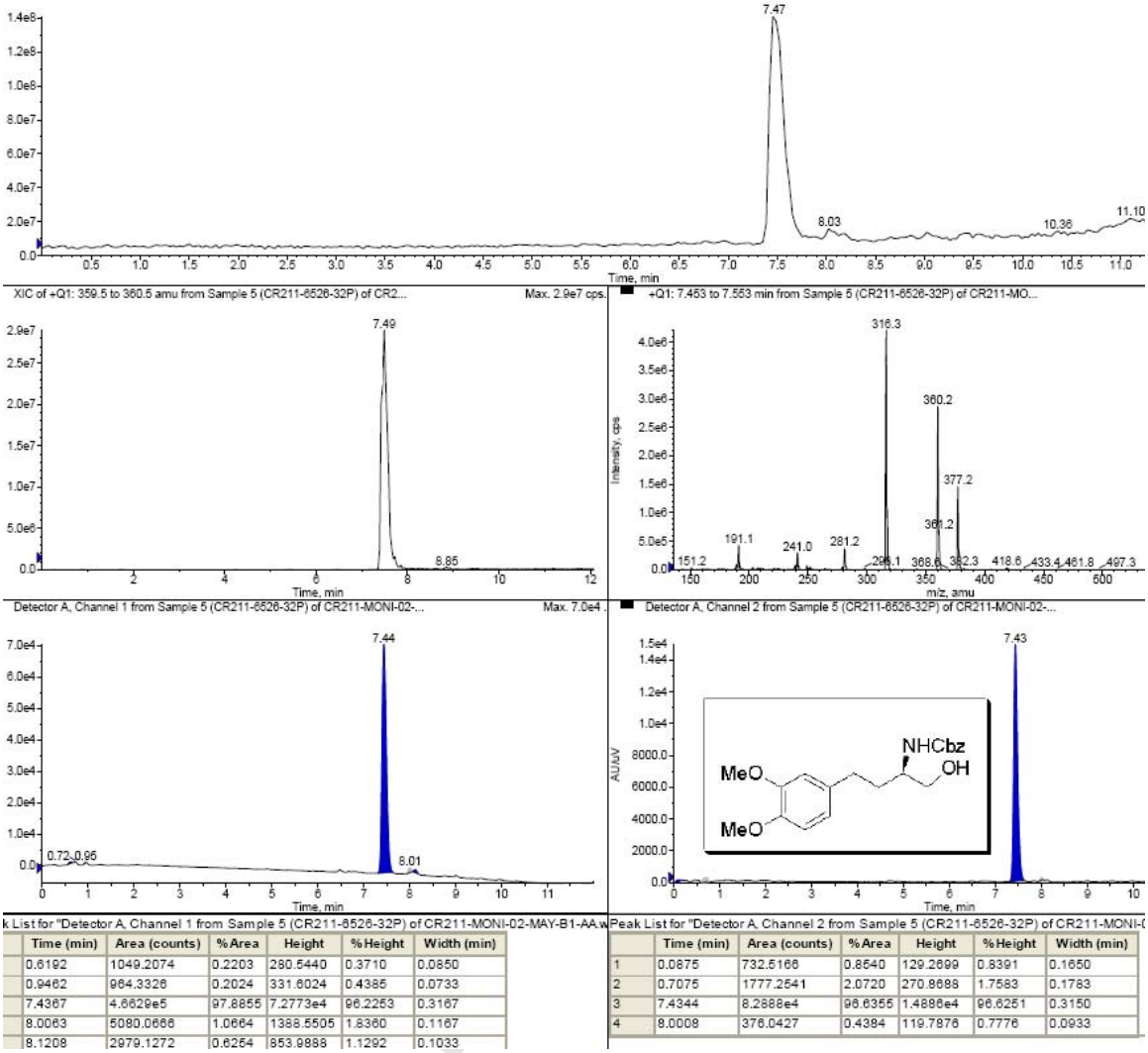
D_2O spectrum (400MHz, $CDCl_3$) of compound **16**



^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **16**.



APT spectrum (100MHz, $CDCl_3$) of compound **16**



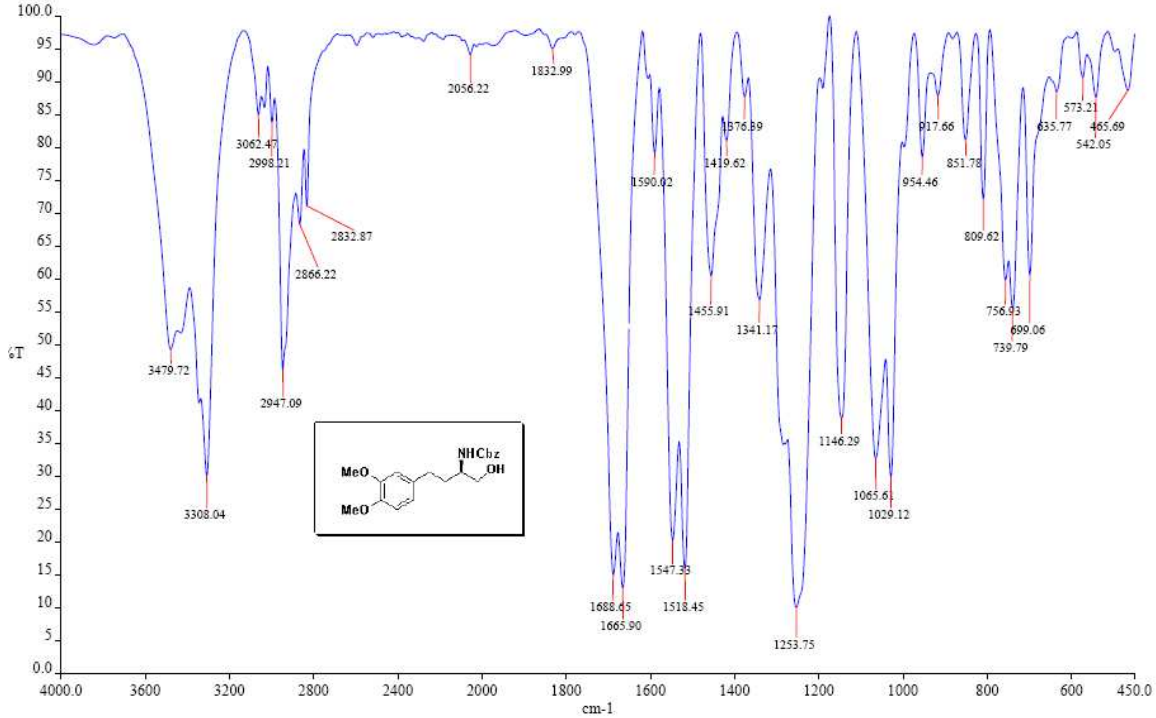
k List for "Detector A, Channel 1 from Sample 5 (CR211-6526-32P) of CR211-MONI-02-MAY-B1-AA.w

	Time (min)	Area (counts)	%Area	Height	%Height	Width (min)
	0.6192	1049.2074	0.2203	280.5440	0.3710	0.0850
	0.9462	984.3326	0.2024	331.6024	0.4385	0.0733
	7.4367	4.6629e5	97.8855	7.2773e4	96.2253	0.3167
	8.0063	5080.0666	1.0664	1388.5505	1.8360	0.1167
	8.1208	2979.1272	0.6254	853.9888	1.1292	0.1033

Peak List for "Detector A, Channel 2 from Sample 5 (CR211-6526-32P) of CR211-MONI-

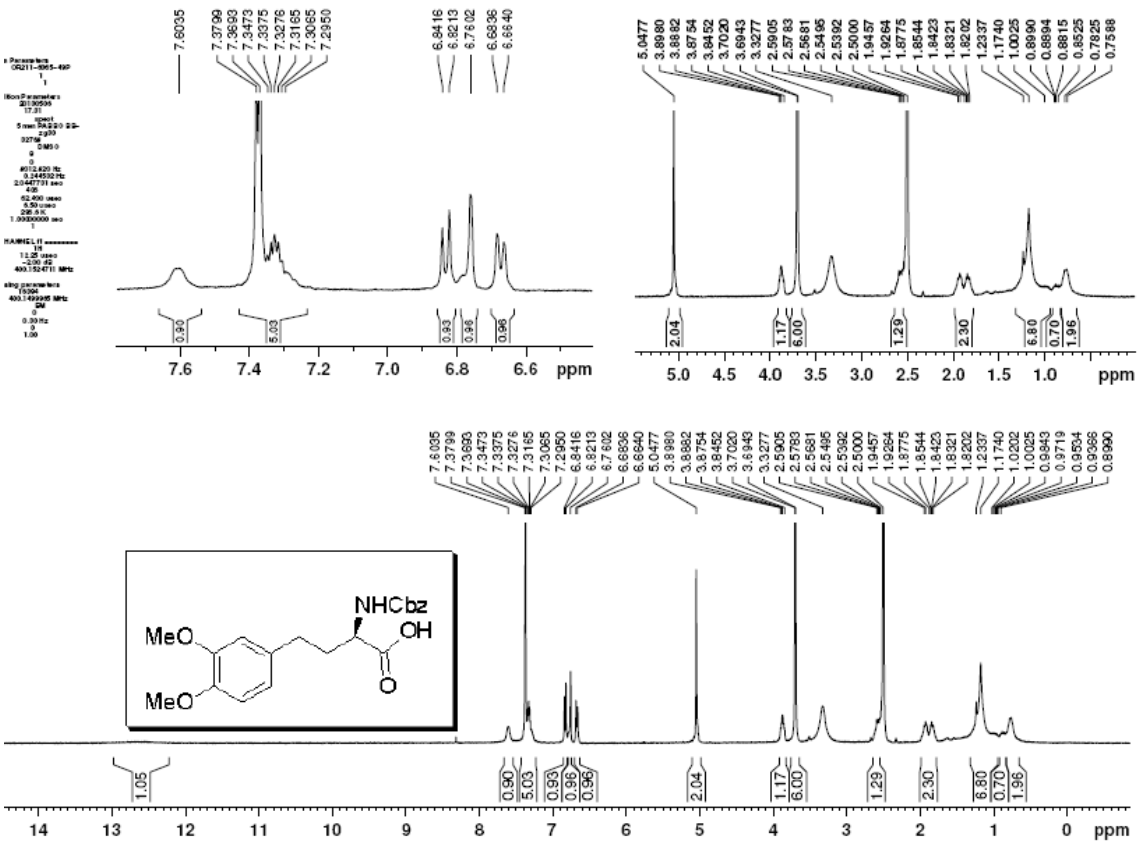
	Time (min)	Area (counts)	%Area	Height	%Height	Width (min)
1	0.0875	732.5166	0.8540	129.2699	0.8391	0.1650
2	0.7075	1777.2541	2.0720	270.8688	1.7583	0.1783
3	7.4344	8.2888e4	96.6355	1.4886e4	96.6251	0.3150
4	8.0008	376.0427	0.4384	119.7876	0.7776	0.0933

LCMS spectrum of compound **16**

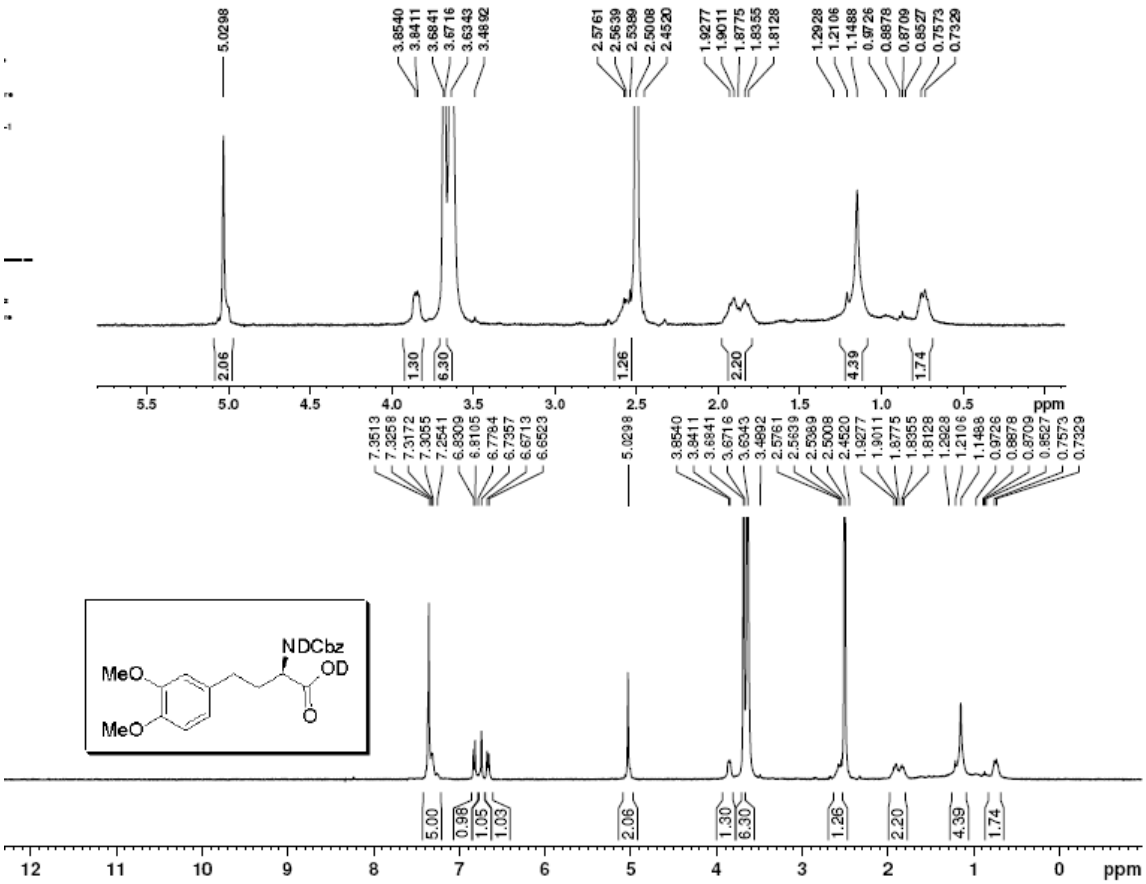


IR spectrum (KBr) of compound **16**

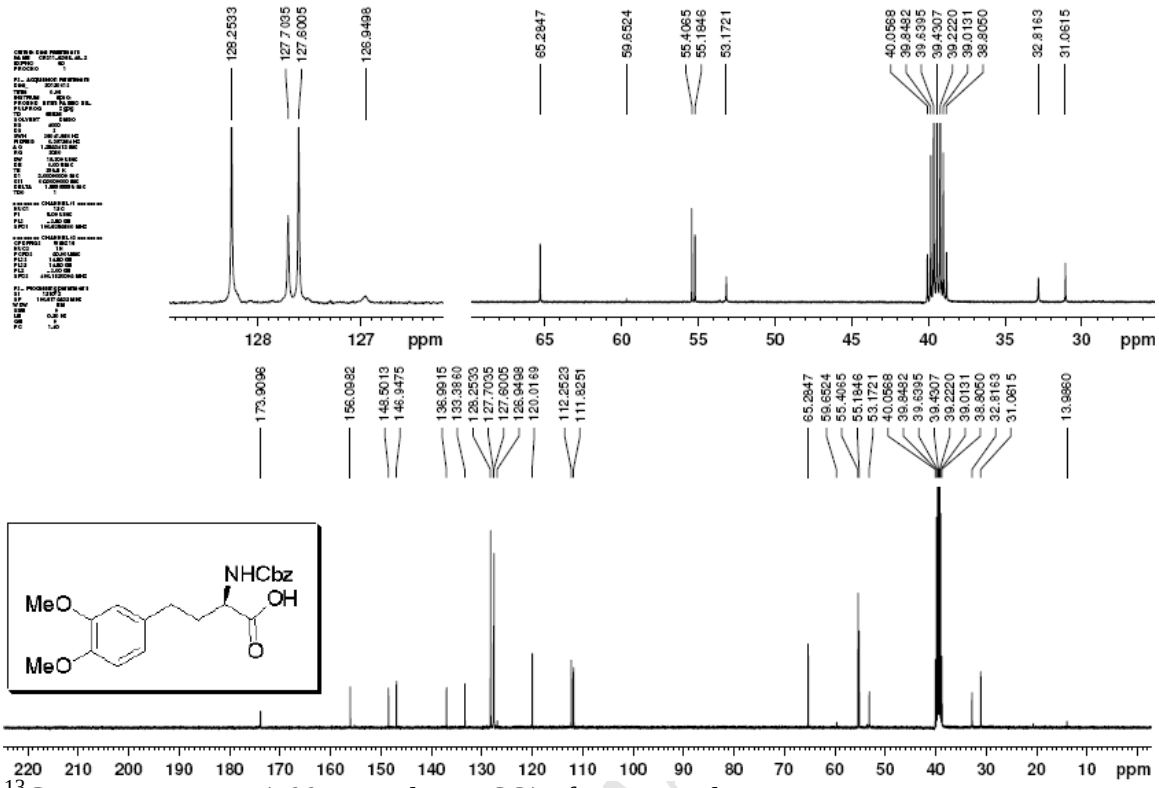
(*R*)-2-Benzyloxycarbonylamino-4-(3,4-dimethoxy-phenyl)-butyric acid 17:



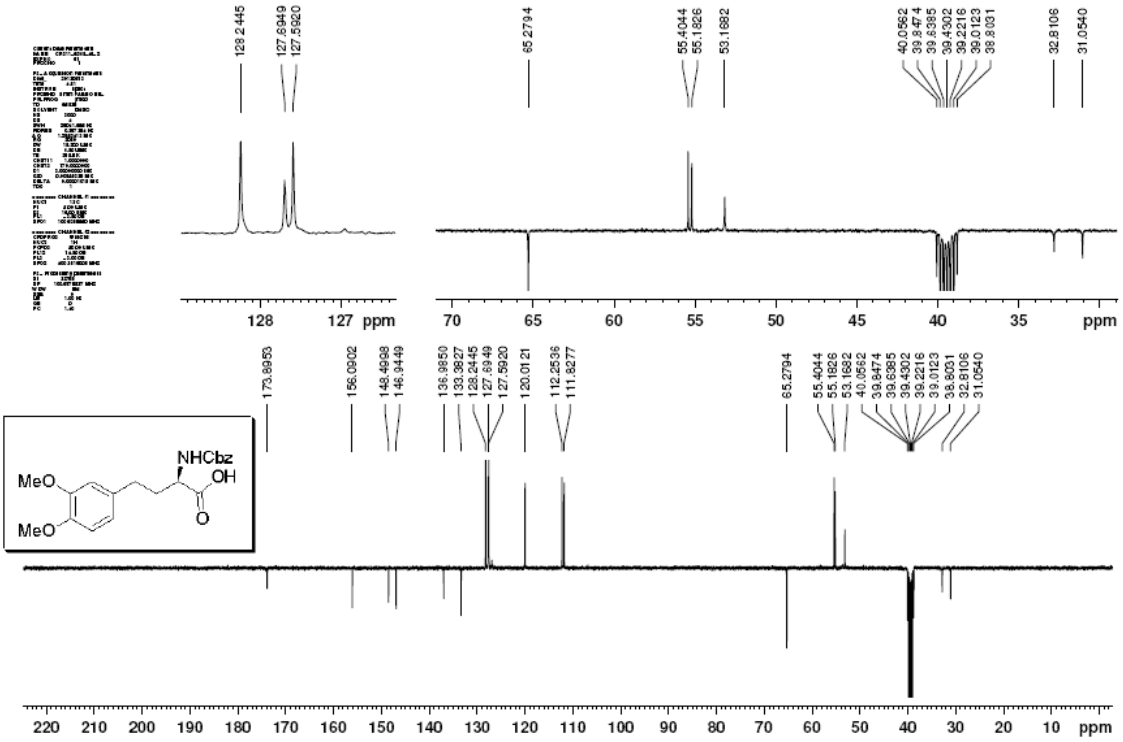
^{1}H NMR spectrum (400MHz, d_6-DMSO) of compound **17**.



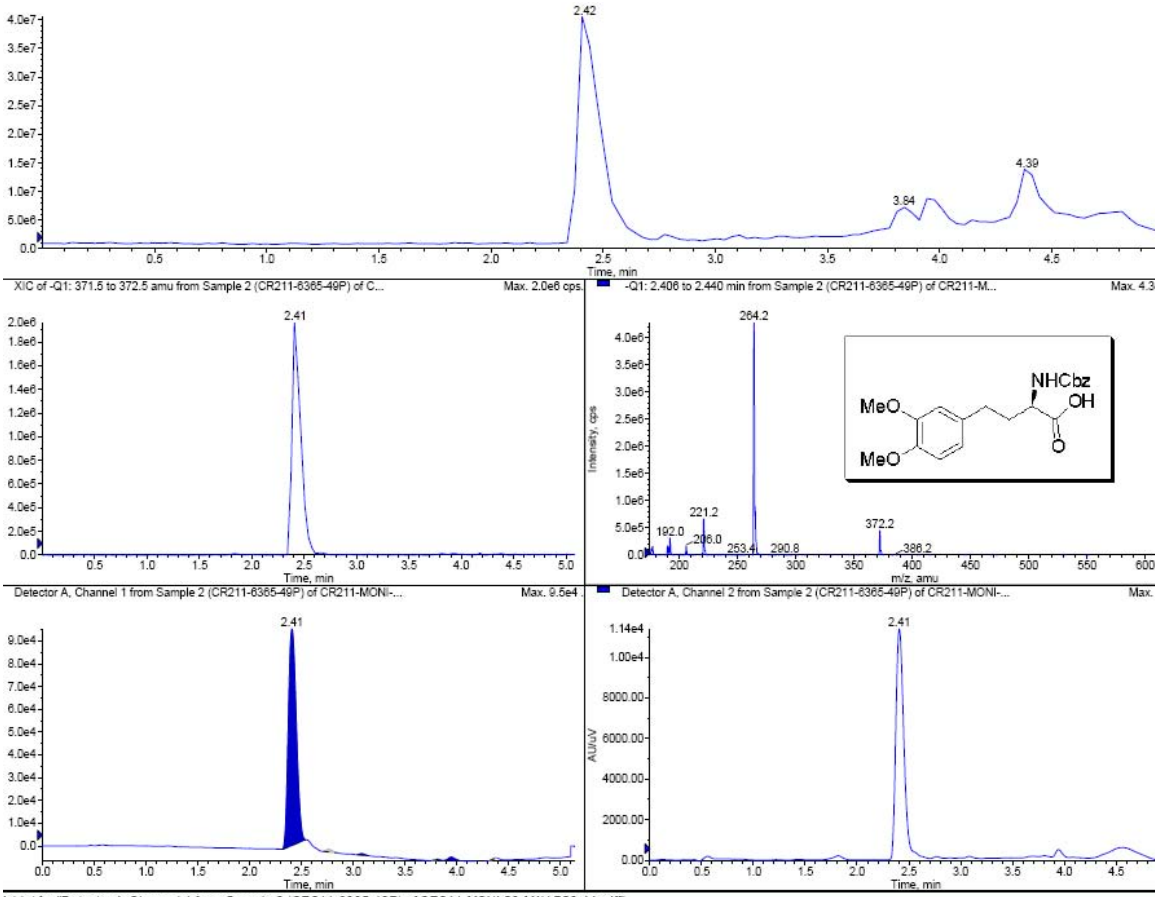
D_2O spectrum (400MHz, d_6-DMSO) of compound **17**



^{13}C NMR spectrum (100MHz, d_6-DMSO) of compound **17**.



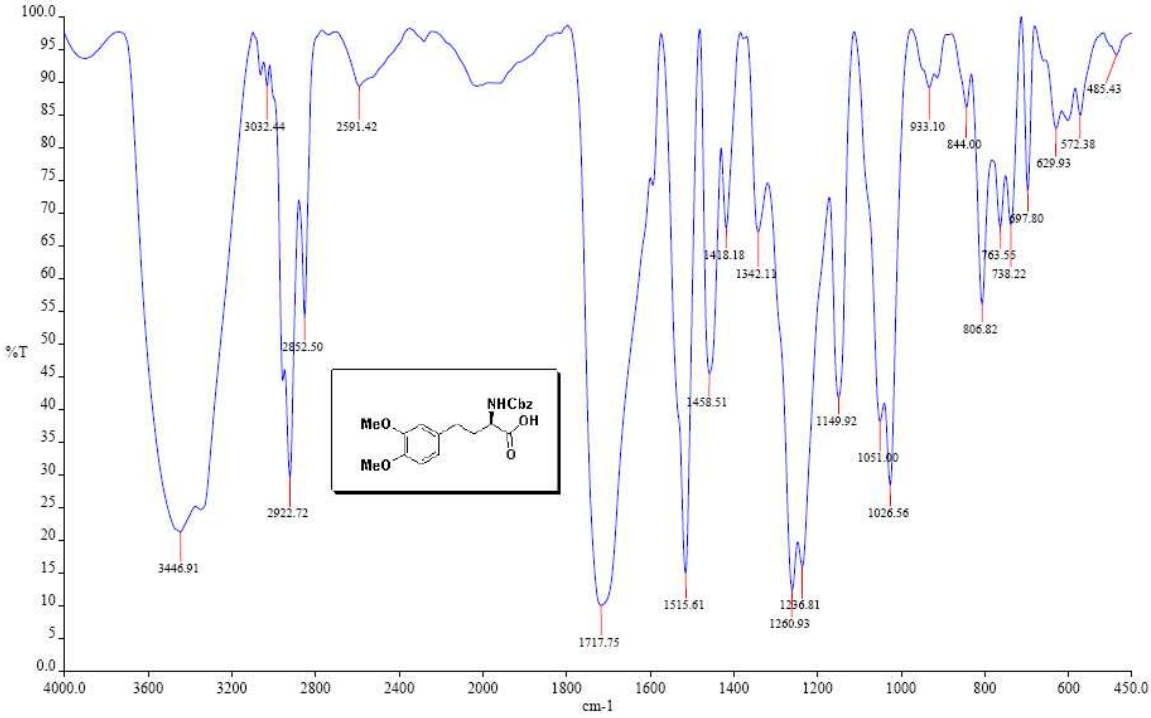
APT spectrum (100MHz, d_6-DMSO) of compound **17**.



k List for "Detector A, Channel 1 from Sample 2 (CR211-6365-49P) of CR211-MONI-03-MAY-B03-AA.wiff"

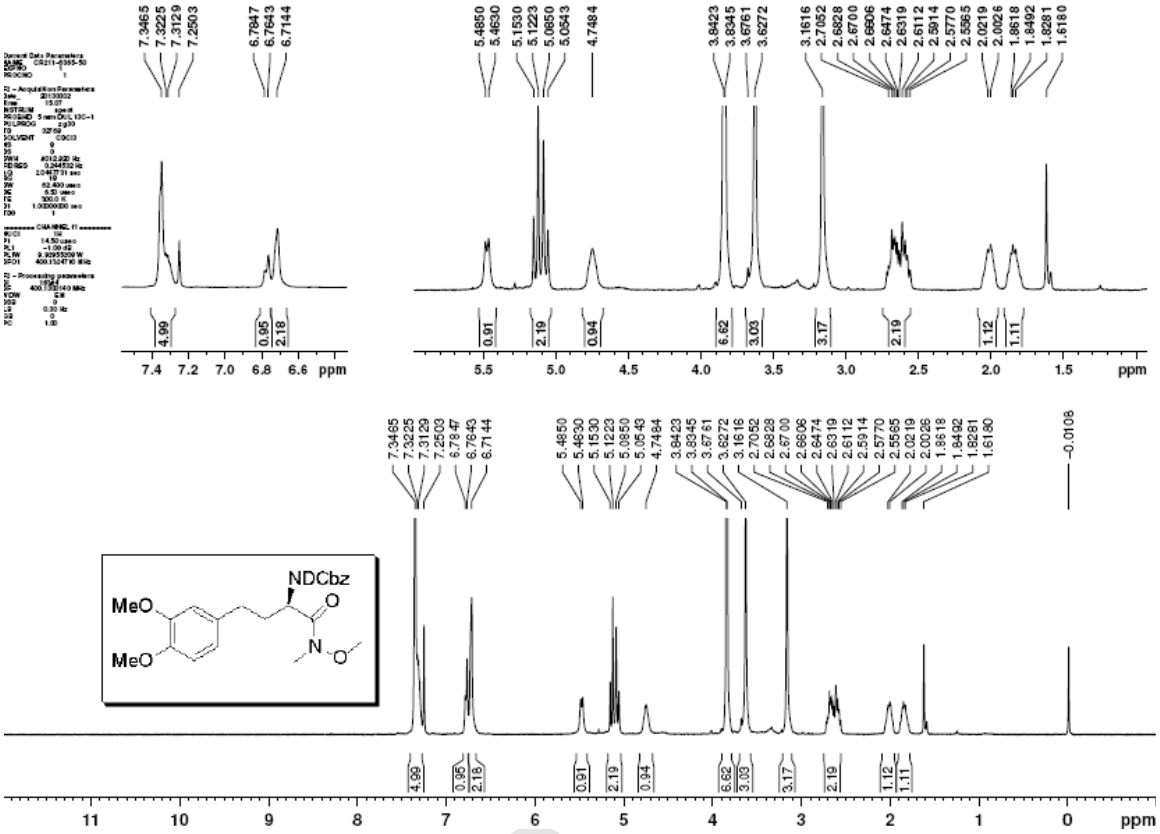
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
	2.4087	4.9893e5	97.4703	9.4975e4	96.4310	0.2217	Base to Base
	2.7642	3925.0161	0.7668	1010.7327	1.0262	0.1317	Base to Base
	3.0814	2004.8984	0.3917	596.6935	0.6058	0.1033	Base to Base
	3.8125	368.6782	0.0720	154.2871	0.1567	0.0583	Base to Base
	3.9451	5791.8093	1.1315	1479.8346	1.5023	0.1383	Base to Base
	4.3725	858.4412	0.1677	273.7156	0.2779	0.0717	Base to Base

LCMS spectrum of compound **17**.

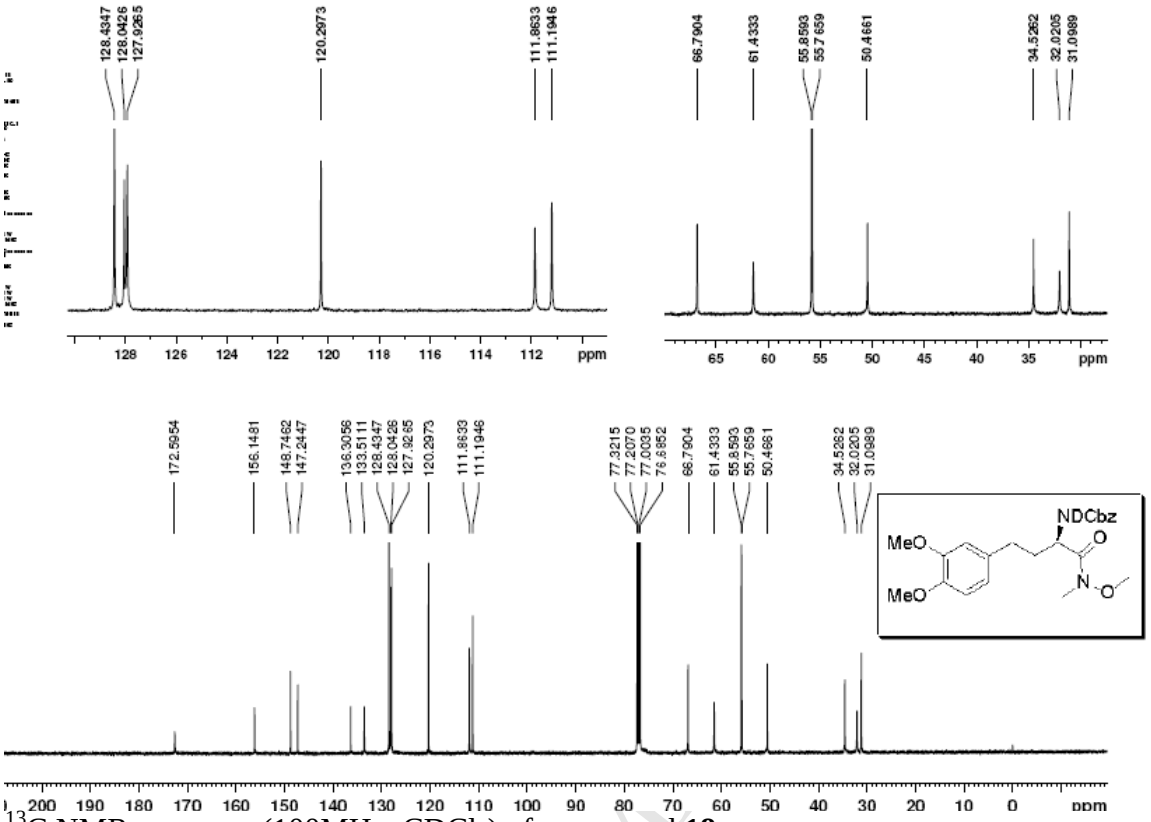


IR spectrum (neat) of compound **17**

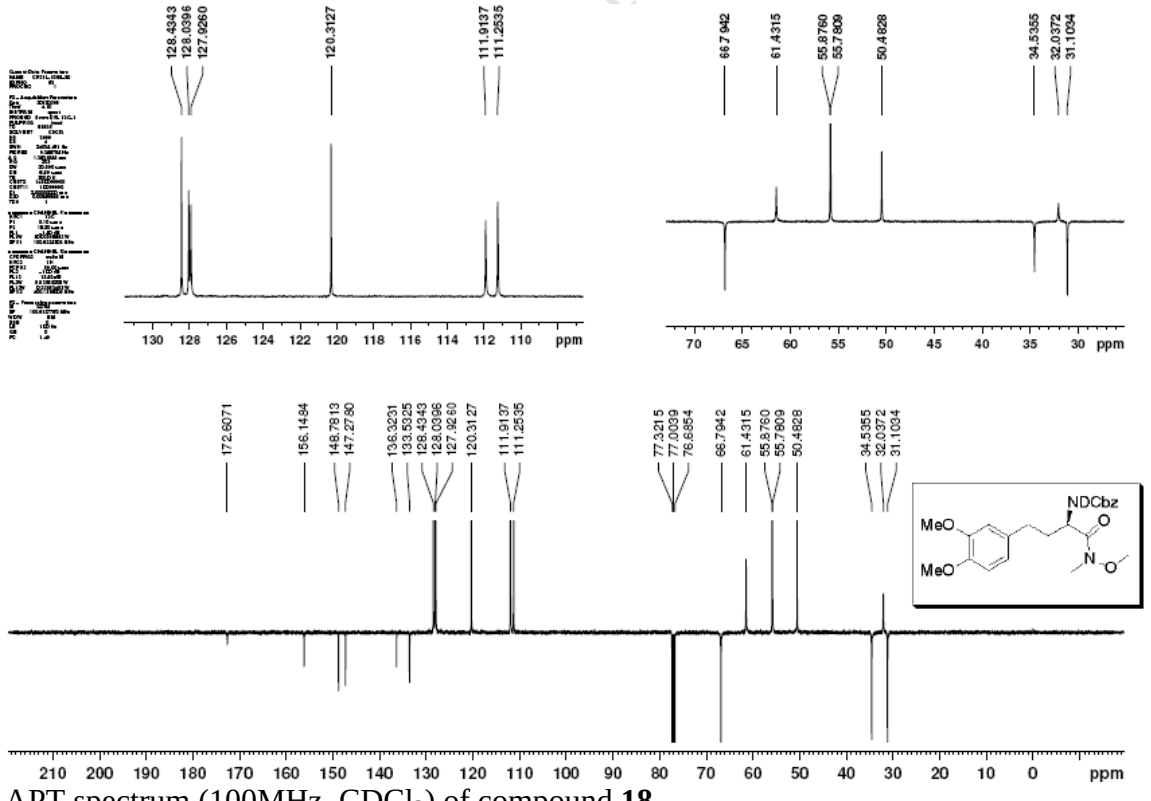
[(*R*)-3-(3,4-Dimethoxy-phenyl)-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid benzyl ester 18:



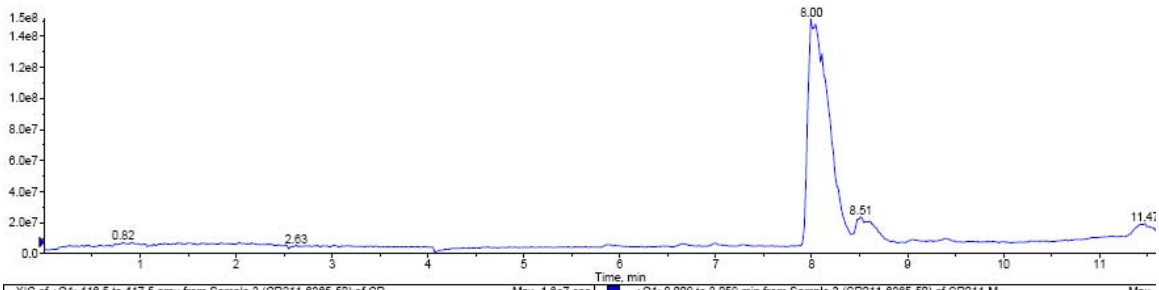
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **18**

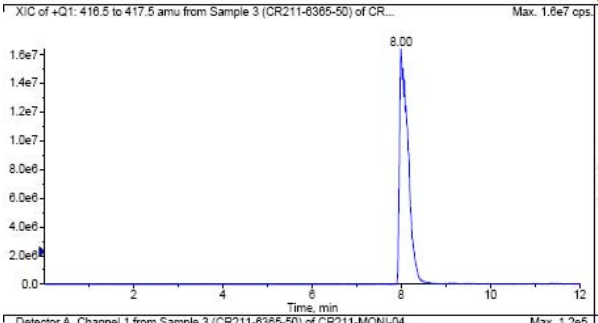


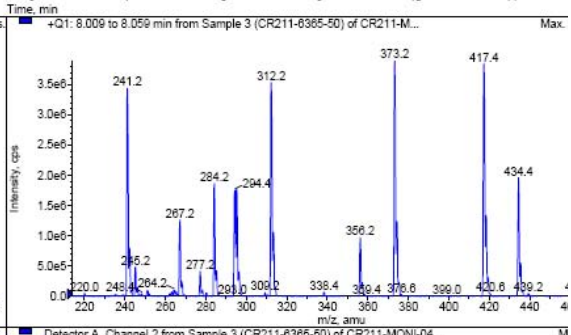
^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **18**

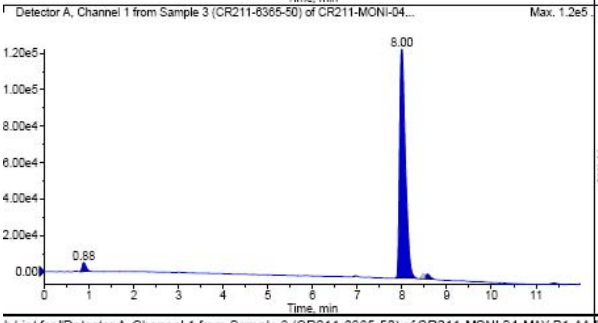


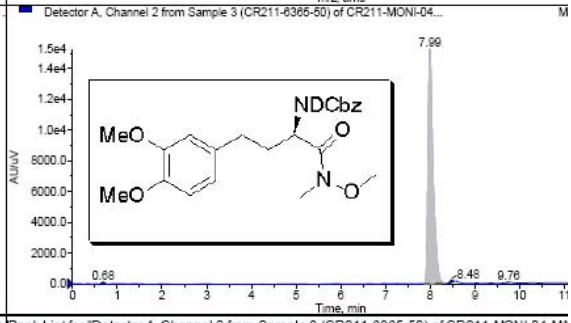
APT spectrum (100MHz, $CDCl_3$) of compound **18**











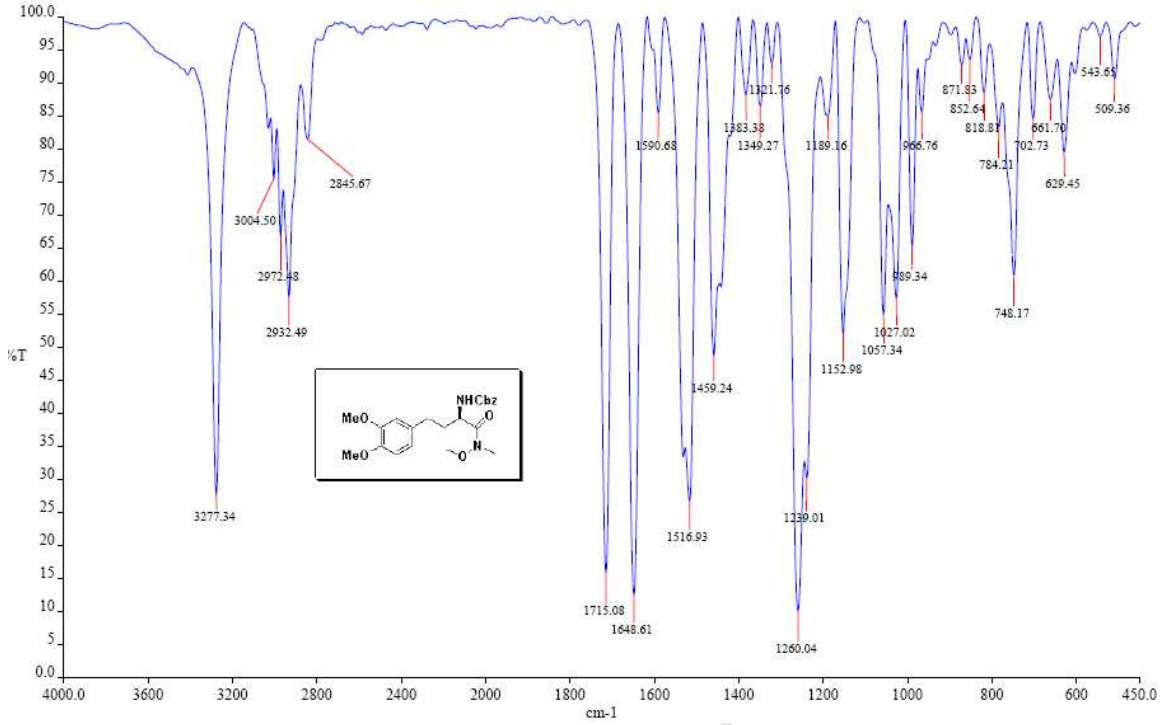
k List for "Detector A, Channel 1 from Sample 3 (CR211-6365-50) of CR211-MONI-04-MAY-B1-AA

	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)
	0.8832	2.5929e4	2.2600	4731.9022	3.4880	0.2117
	6.9617	415.7166	0.0362	127.2102	0.0938	0.0717
	7.9969	1.0930e6	95.2627	1.2564e5	92.6092	0.4633
	8.4787	1.3166e4	1.1476	2666.0363	1.9652	0.1367
	8.5762	1.4841e4	1.2936	2501.4626	1.8439	0.1783

Peak List for "Detector A, Channel 2 from Sample 3 (CR211-6365-50) of CR211-MONI-04-MA

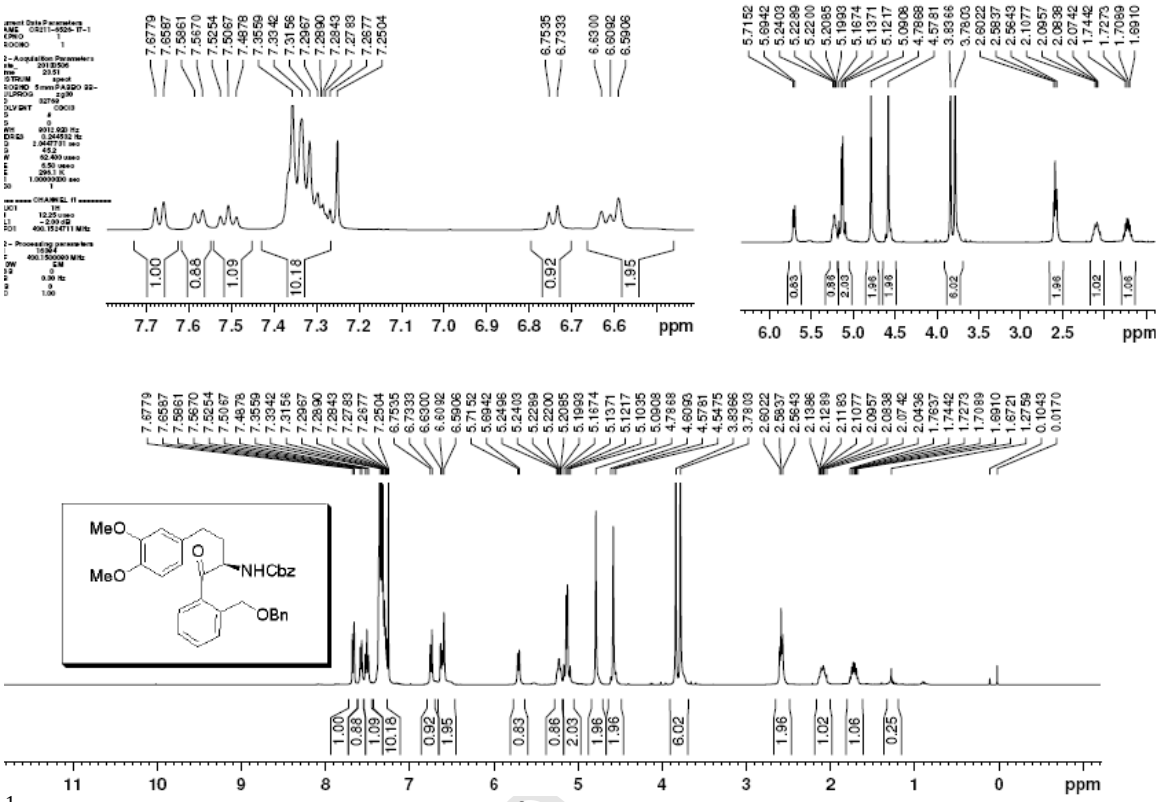
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)
1	0.6842	804.6176	0.6608	145.9473	0.9037	0.1767
2	7.9924	1.1390e5	93.5475	1.5258e4	94.4770	0.4617
3	8.4758	445.2673	0.3657	114.1682	0.7069	0.1233
4	9.7558	45.7077	0.0375	14.7294	0.0912	0.0717
5	11.4058	6560.7132	5.3884	617.0986	3.8212	0.4033

LCMS spectrum of compound **18**

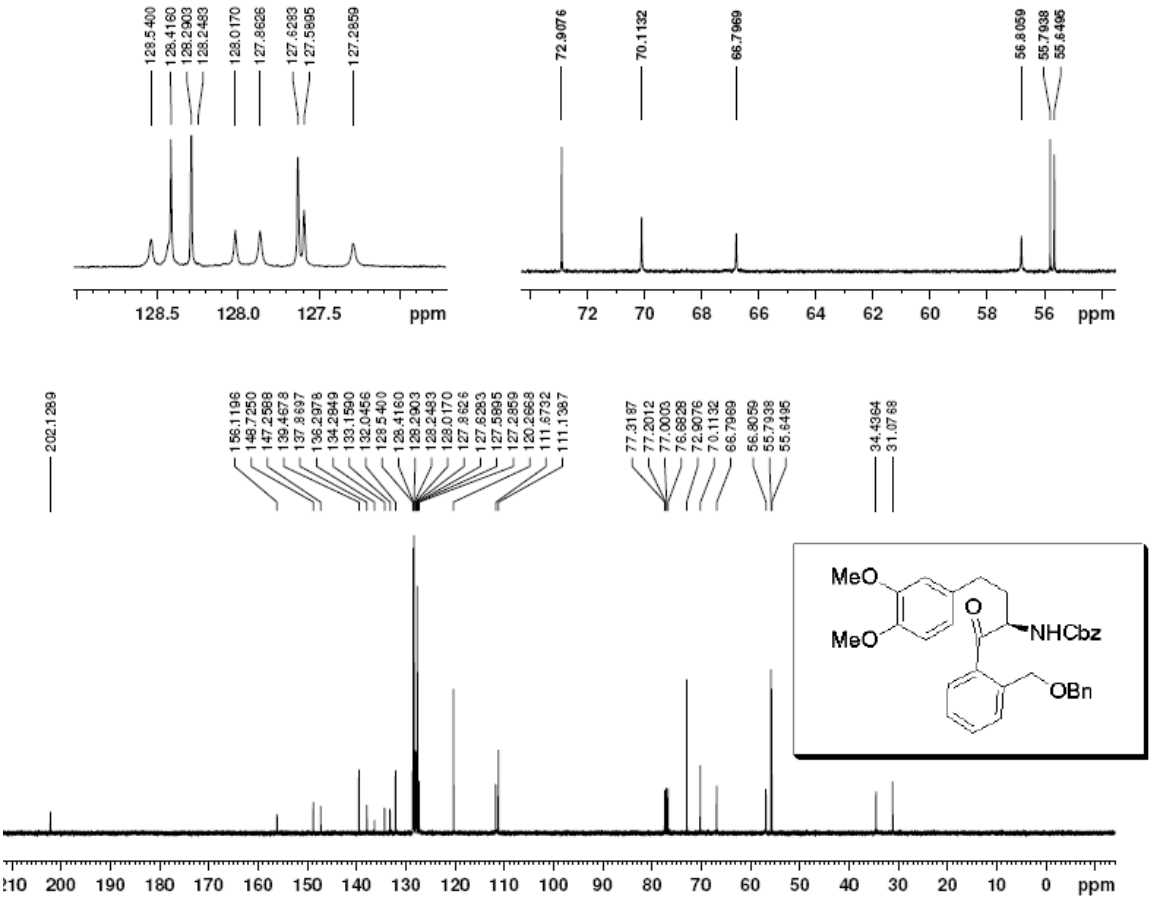


IR spectrum (KBr) of compound **18**

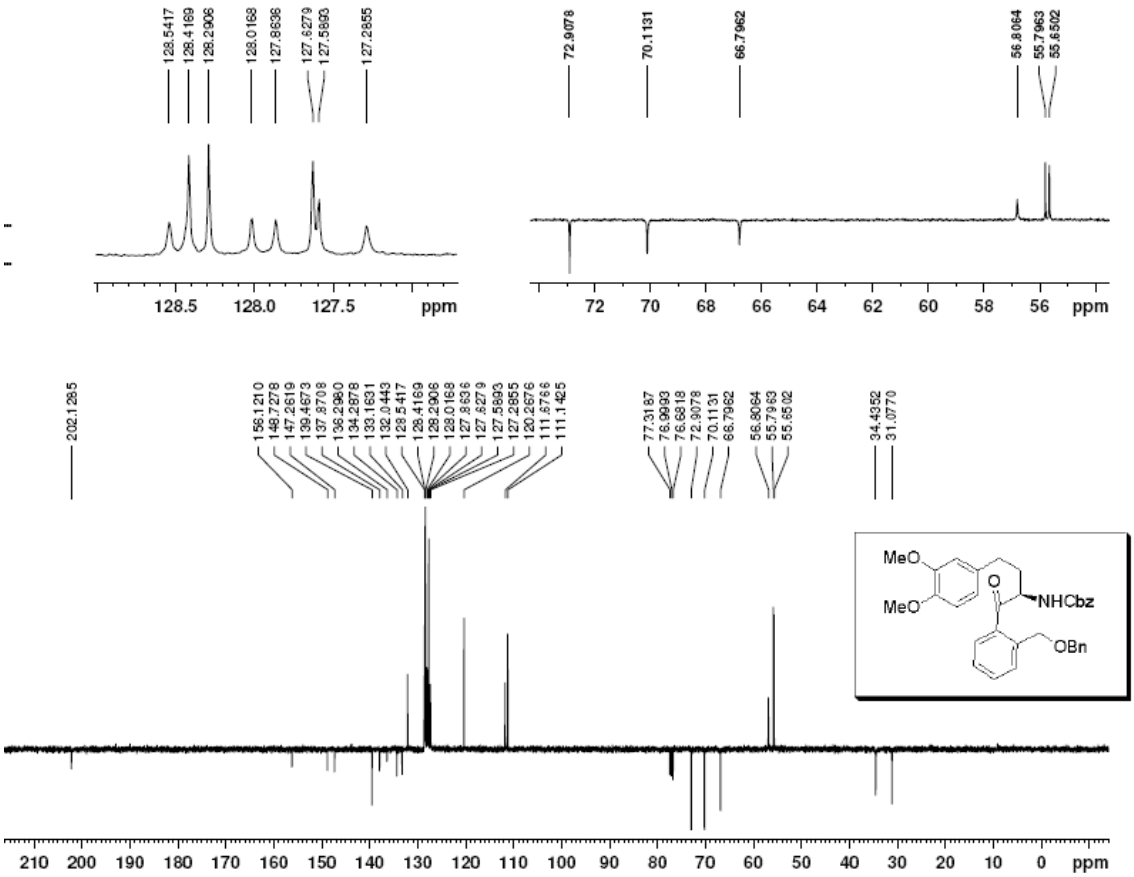
[(*R*)-1-(2-Benzyloxymethyl-benzoyl)-3-(3,4-dimethoxy-phenyl)-propyl]-carbamic acid benzyl ester 20:



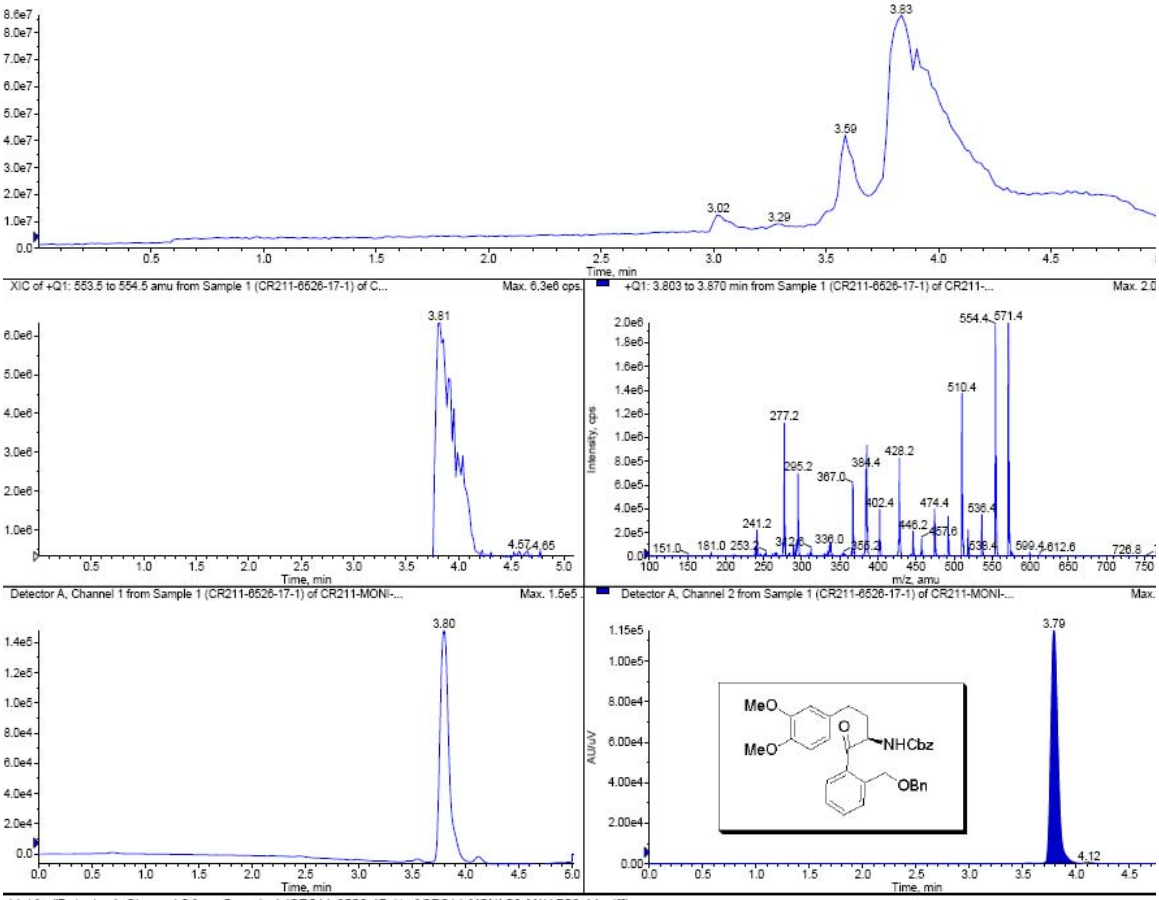
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **20**



^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **20**



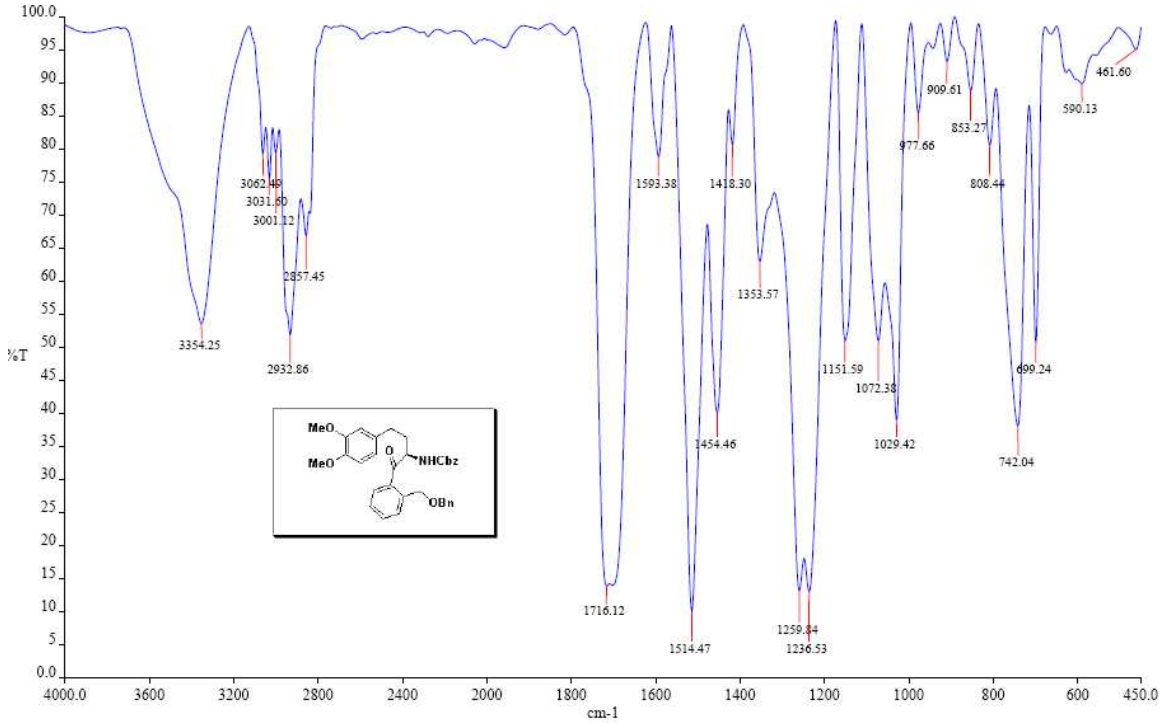
APT spectrum (100MHz, $CDCl_3$) of compound **20**



List for "Detector A, Channel 2 from Sample 1 (CR211-6526-17-1) of CR211-MONI-03-MAY-B03-AA.wiff"

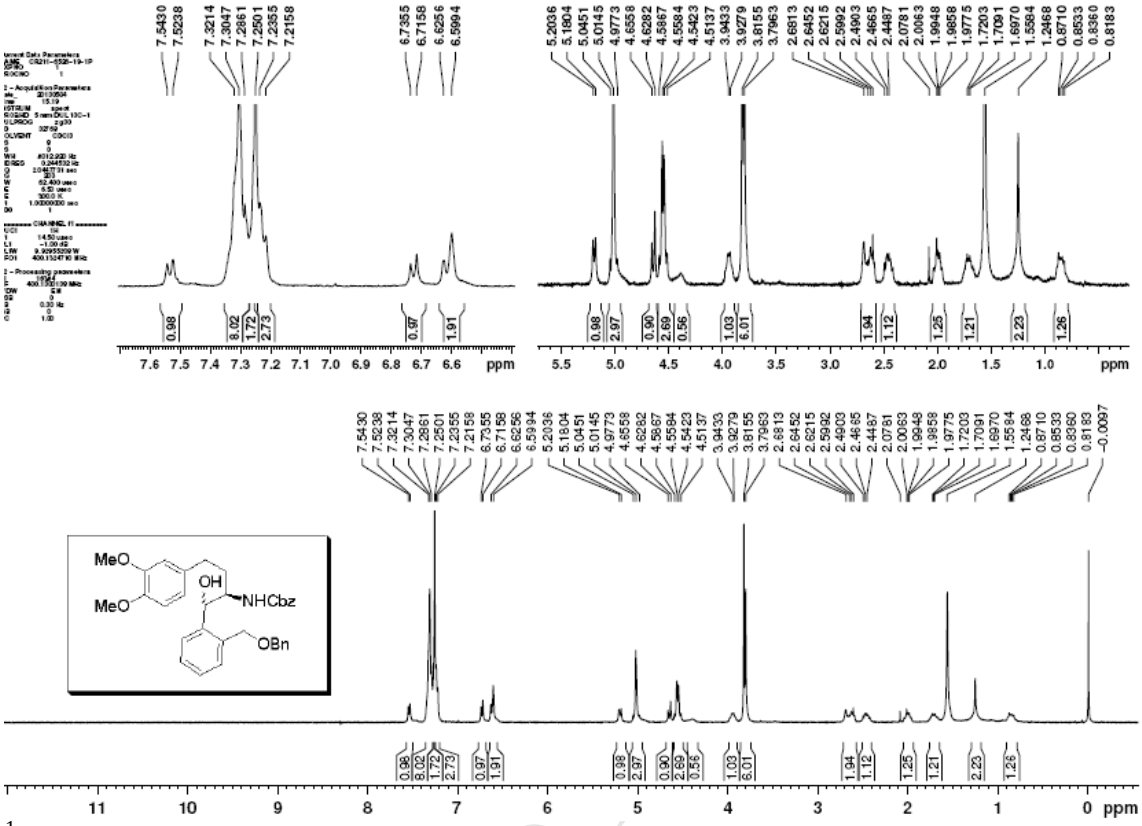
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
	3.7906	5.1005e5	99.9283	1.1459e5	99.8843	0.3017	Base to Base
	4.1208	366.1806	0.0717	132.6870	0.1157	0.0667	Base to Base

LCMS spectrum of compound **20**

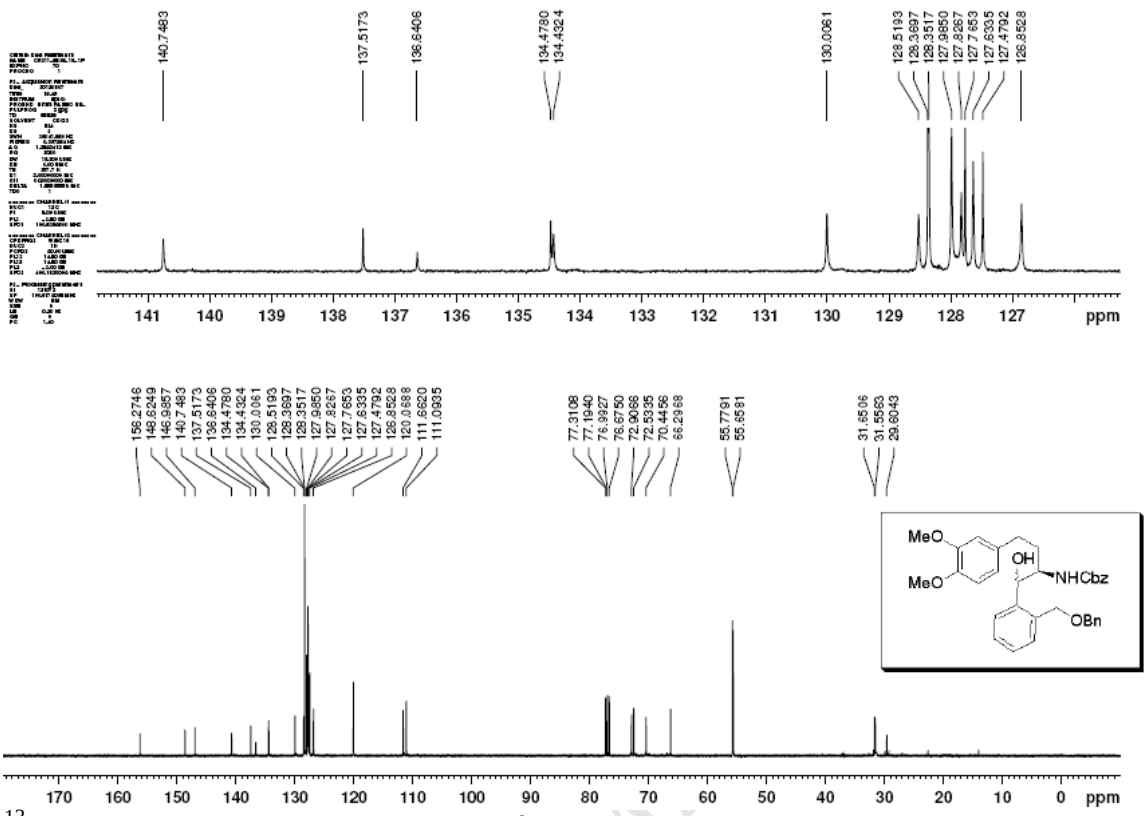


IR spectrum (neat) of compound **20**

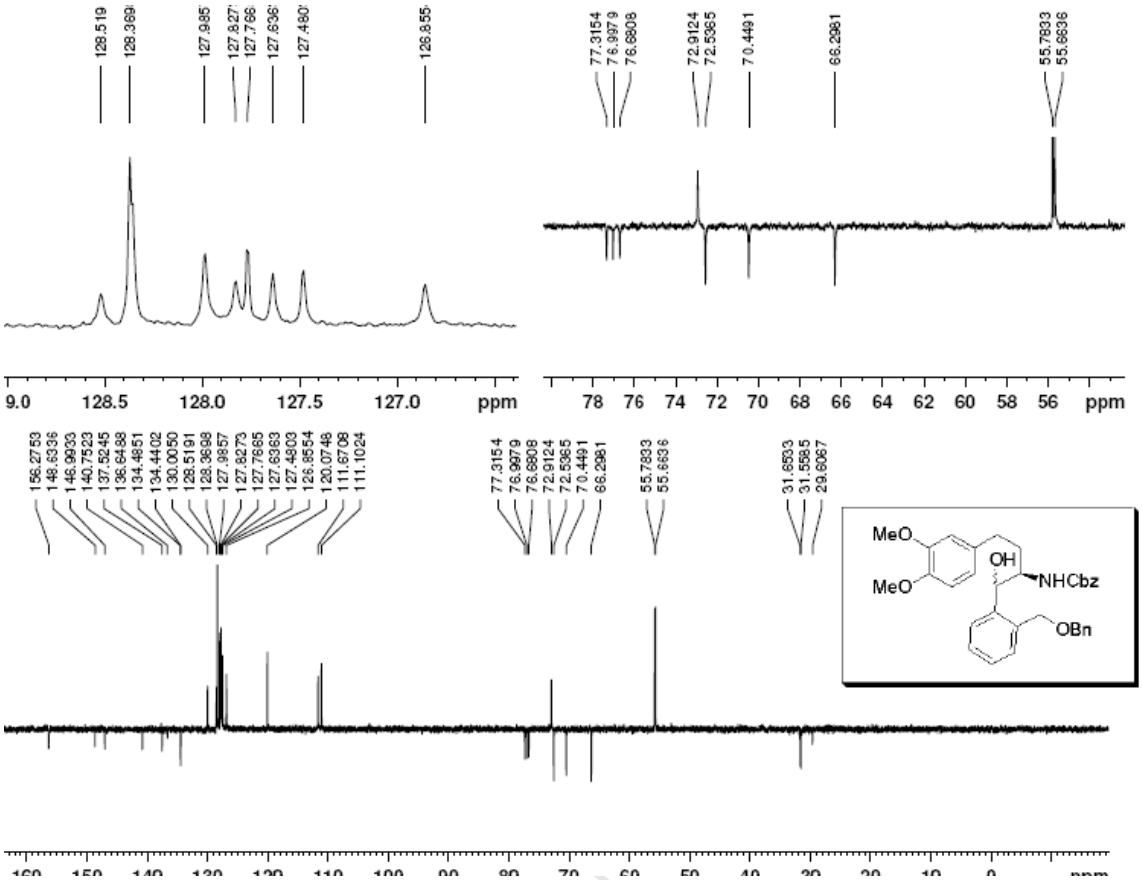
[(*R*)-1-[(2-Benzyloxymethyl-phenyl)-hydroxy-methyl]-3-(3,4-dimethoxy-phenyl)-propyl]-carbamic acid benzyl ester 21:



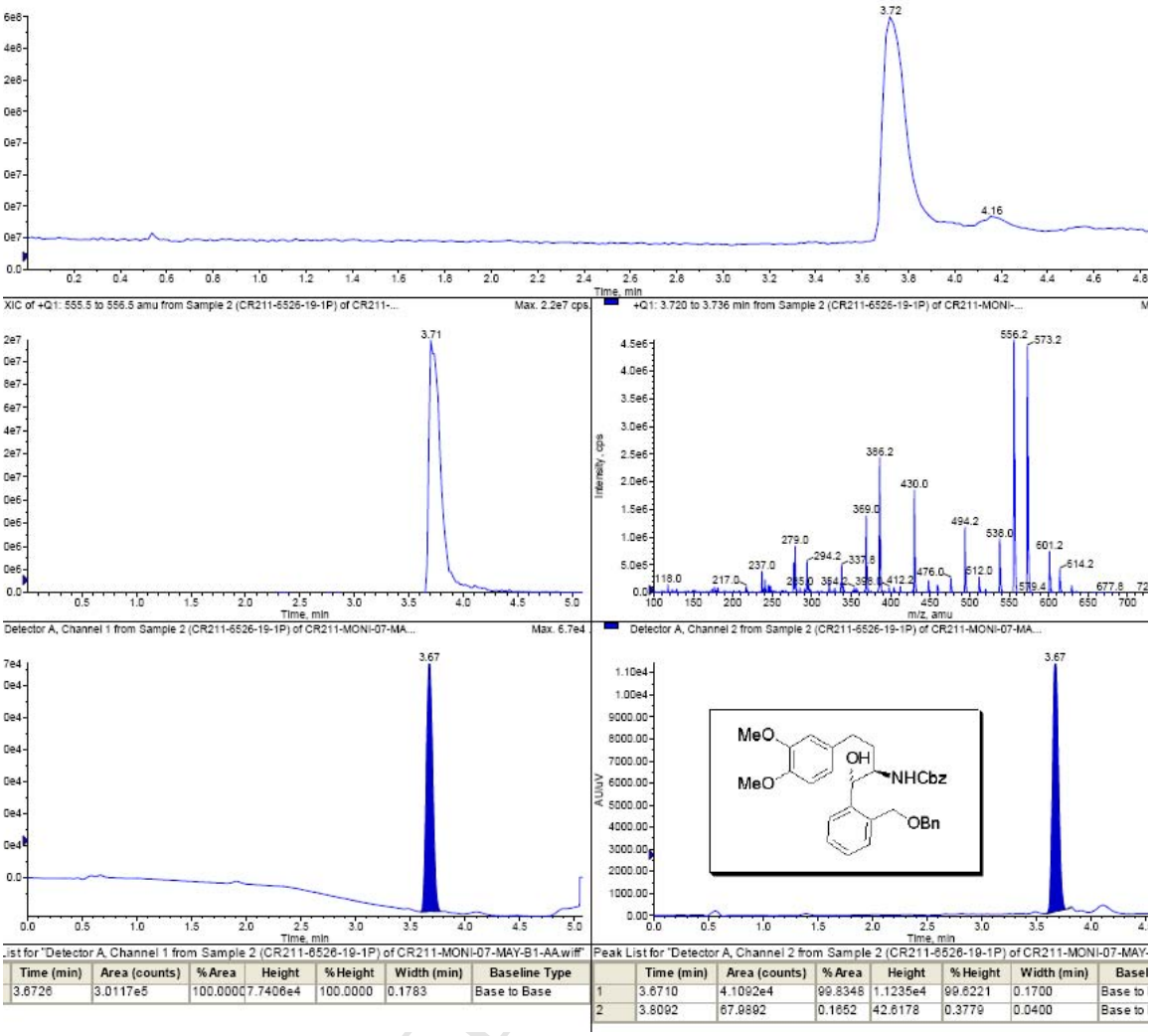
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **21**



^{13}CNMR spectrum (100MHz, $CDCl_3$) of compound **21**



APT spectrum (400MHz, $CDCl_3$) of compound **21**



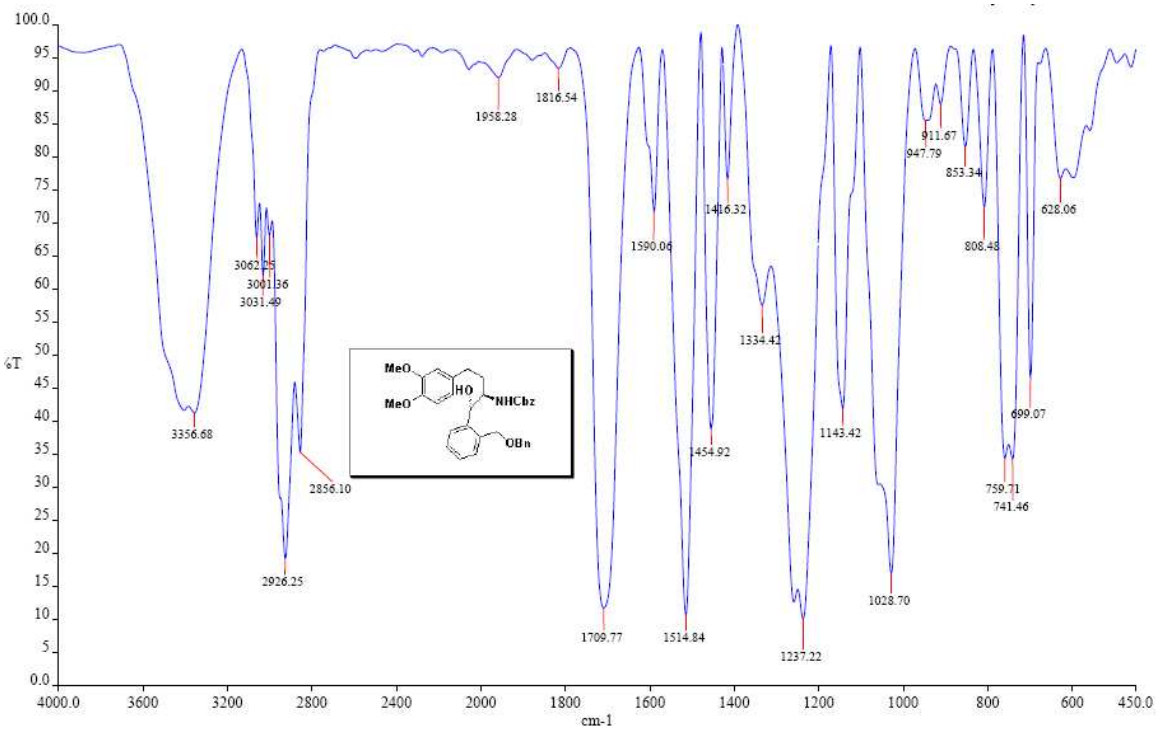
ist for "Detector A, Channel 1 from Sample 2 (CR211-6526-19-1P) of CR211-MONI-07-MAY-B1-AA.wiff"

Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
3.6726	3.0117e5	100.0000	7.7406e4	100.0000	0.1783	Base to Base

Peak List for "Detector A, Channel 2 from Sample 2 (CR211-6526-19-1P) of CR211-MONI-07-MAY-

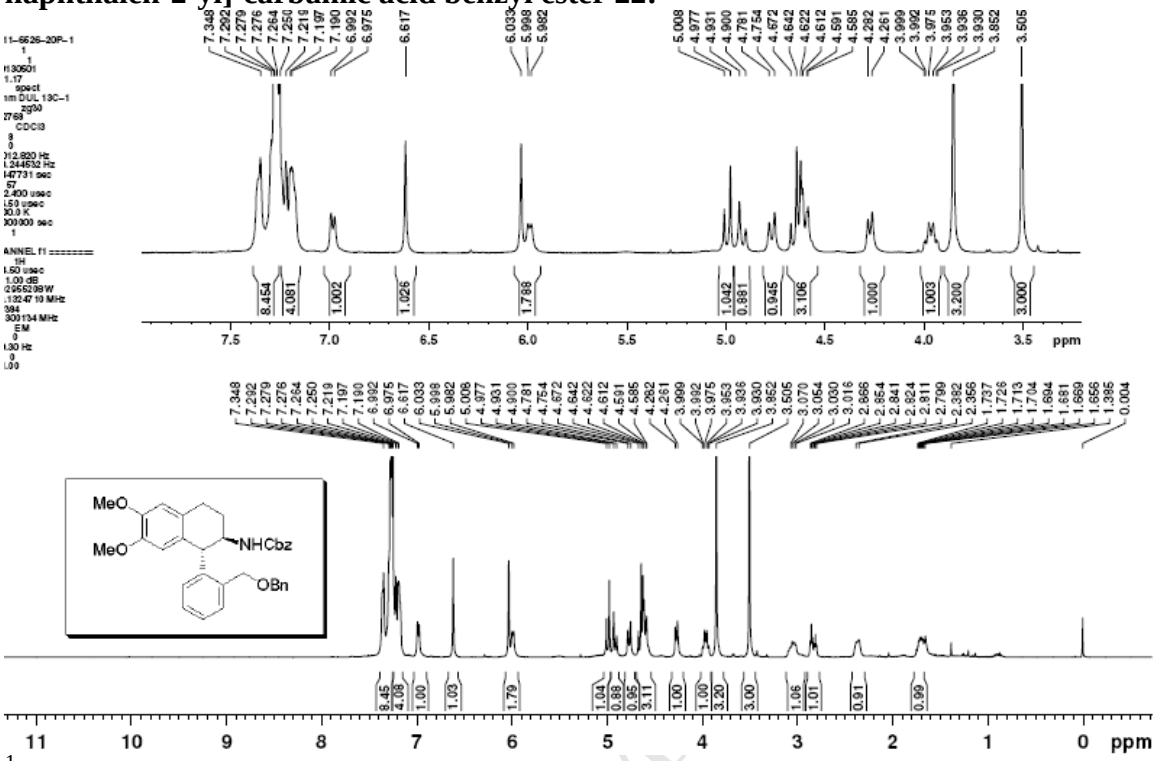
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Basel
1	3.6710	4.1092e4	99.8348	1.1235e4	99.6221	0.1700	Base to
2	3.8092	67.9892	0.1652	42.6178	0.3779	0.0400	Base to

LCMS spectrum of compound **21**

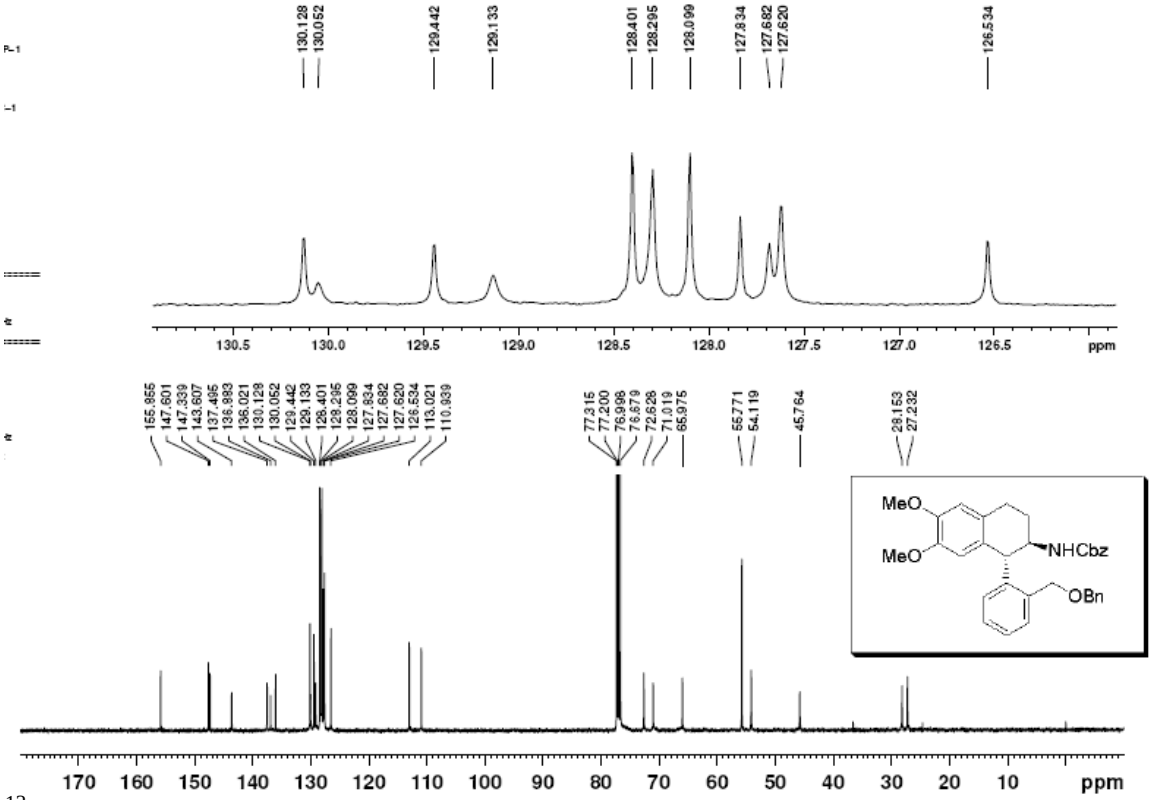


IR spectrum (neat) of compound **21**

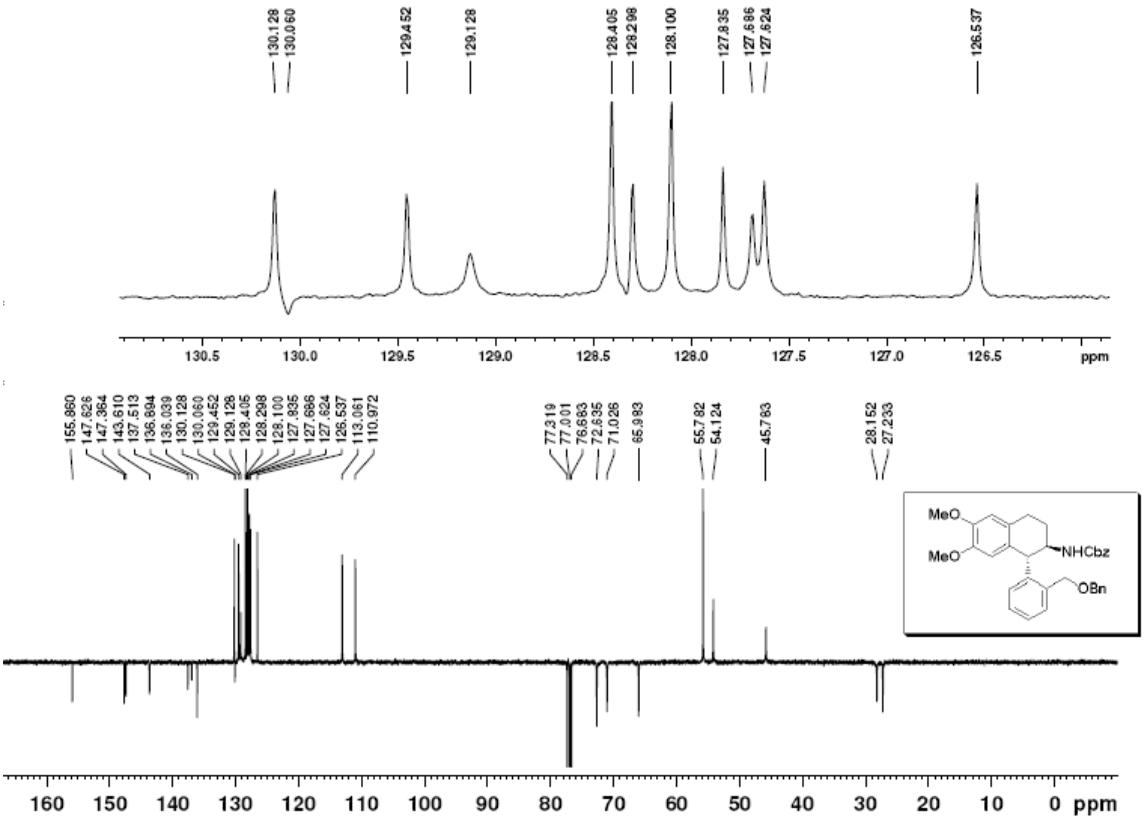
[(1*S*,2*R*)-1-(2-Benzyloxymethyl-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid benzyl ester 22:



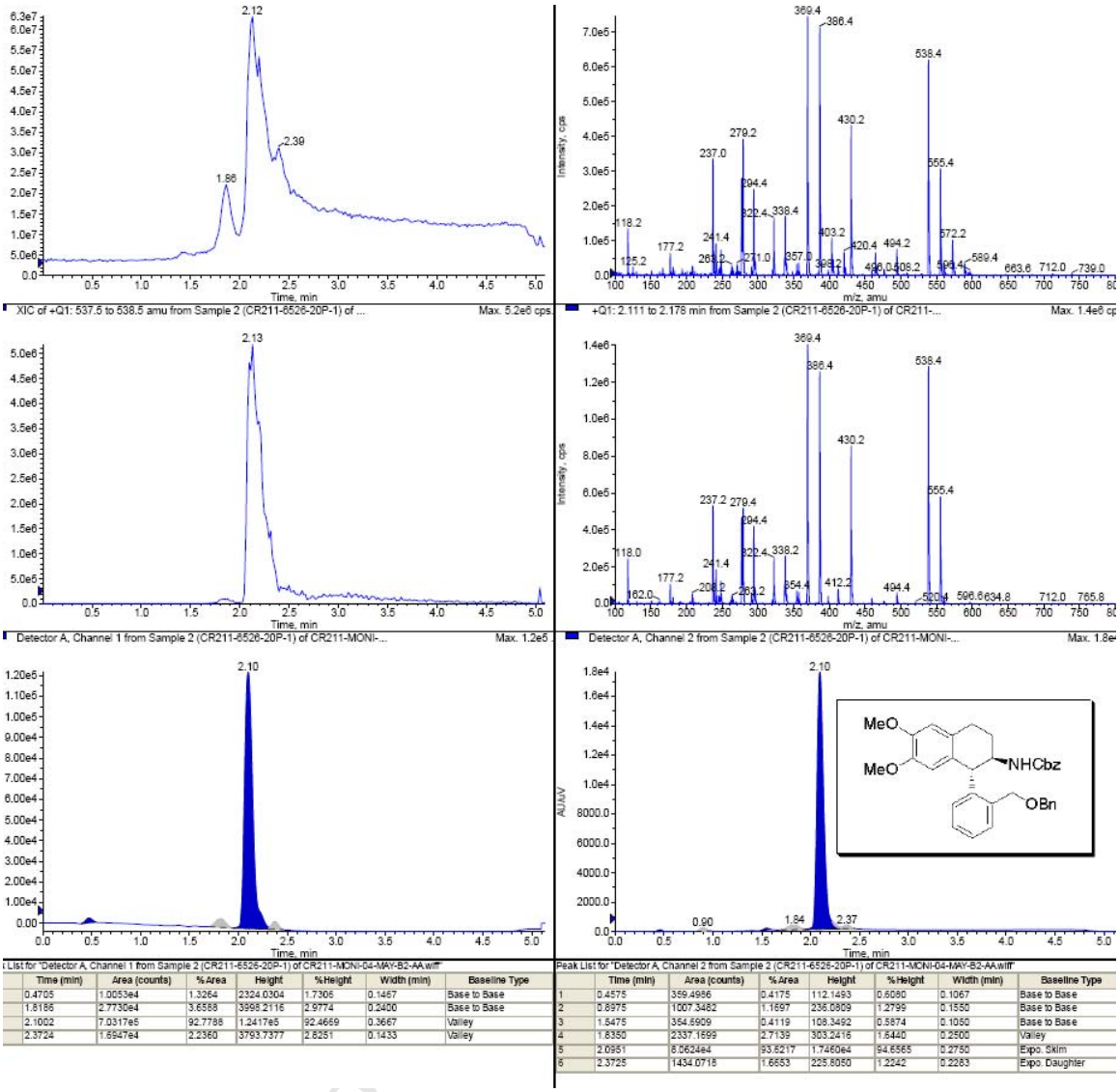
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **22**



^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **22**



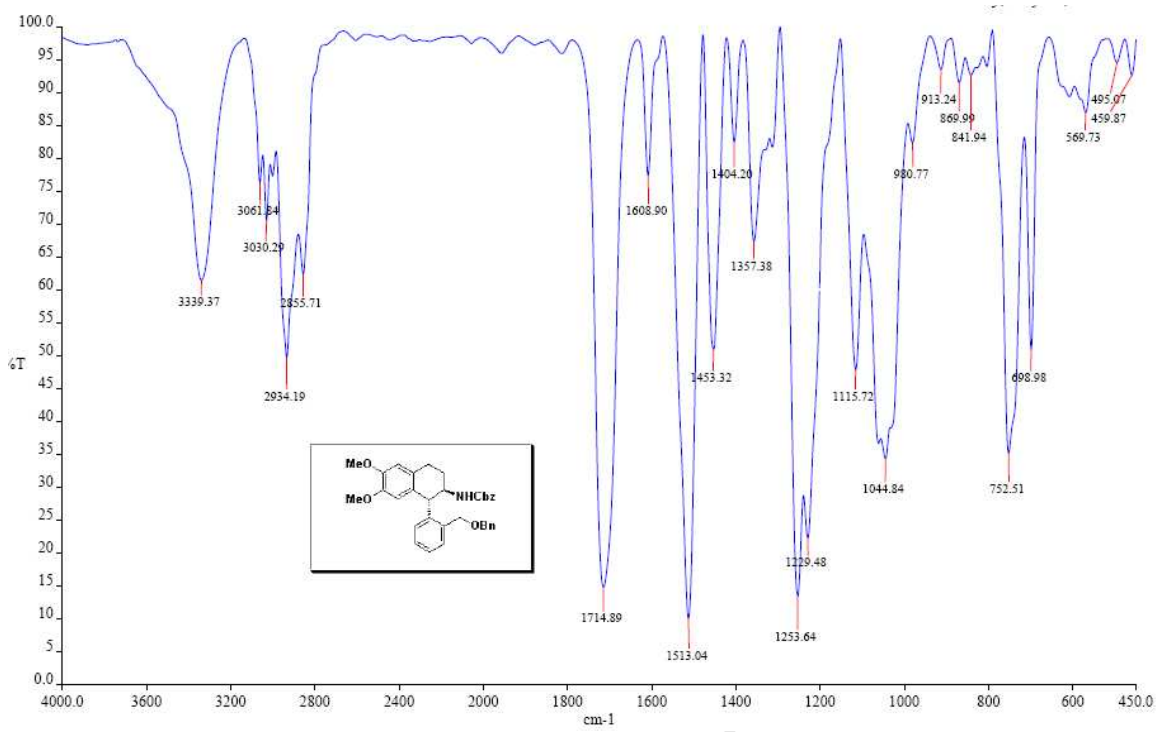
APT spectrum (100MHz, $CDCl_3$) of compound **22**



	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
	0.4705	1.0053e4	1.3264	2324.0304	1.7306	0.1467	Base to Base
	1.8186	2.7730e4	3.6588	3998.2116	2.9774	0.2450	Base to Base
	2.1002	7.0317e5	92.7788	1.2417e5	92.4659	0.3667	Valley
	2.3724	1.6947e4	2.2360	3793.7377	2.8251	0.1433	Valley

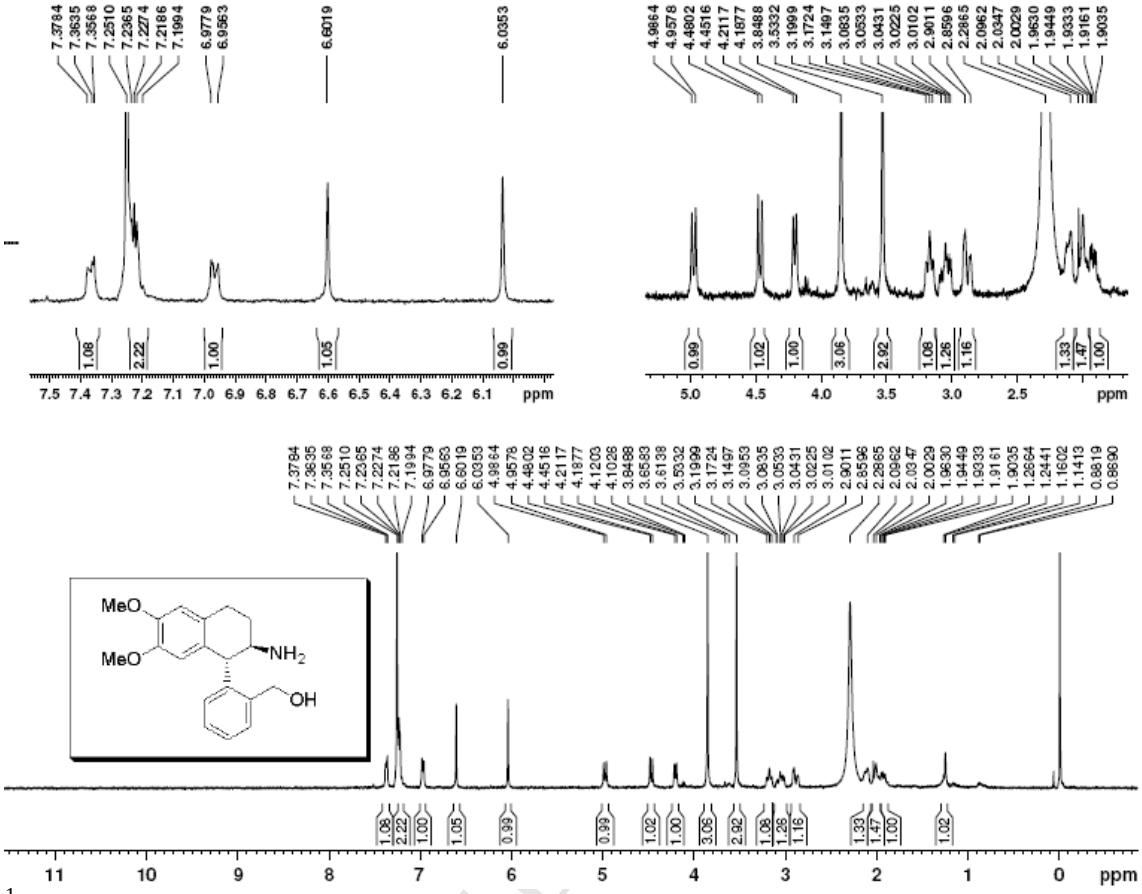
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
1	0.4575	359.4986	0.4175	112.1493	0.6080	0.1067	Base to Base
2	0.8975	1007.3482	1.1697	236.0809	1.2795	0.1550	Base to Base
3	1.5475	354.6909	0.4119	108.3492	0.5874	0.1050	Base to Base
4	1.8350	2337.1699	2.7139	303.2416	1.6440	0.2500	Valley
5	2.0951	8.062e4	93.6217	1.746e4	94.6565	0.2750	Expo. Skim
6	2.3725	1434.0718	1.6653	225.8080	1.2242	0.2283	Expo. Daughter

LCMS spectrum of compound **22**

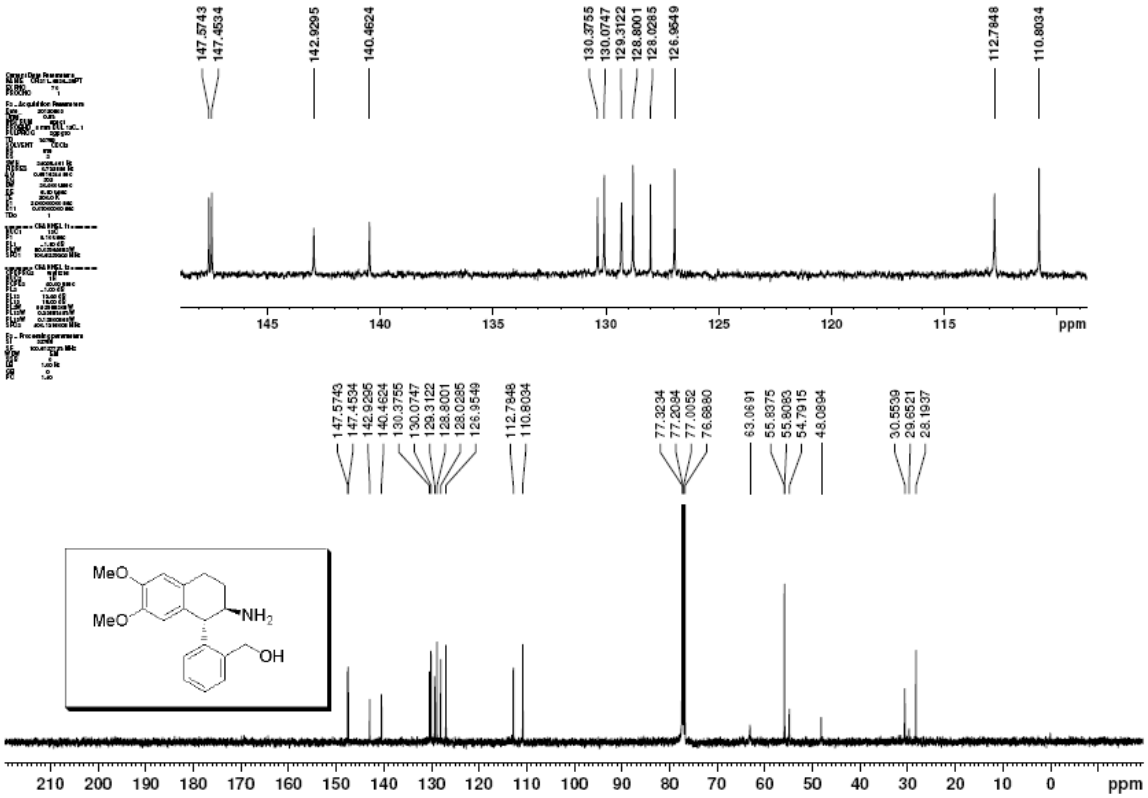


IR spectrum (neat) of compound **22**

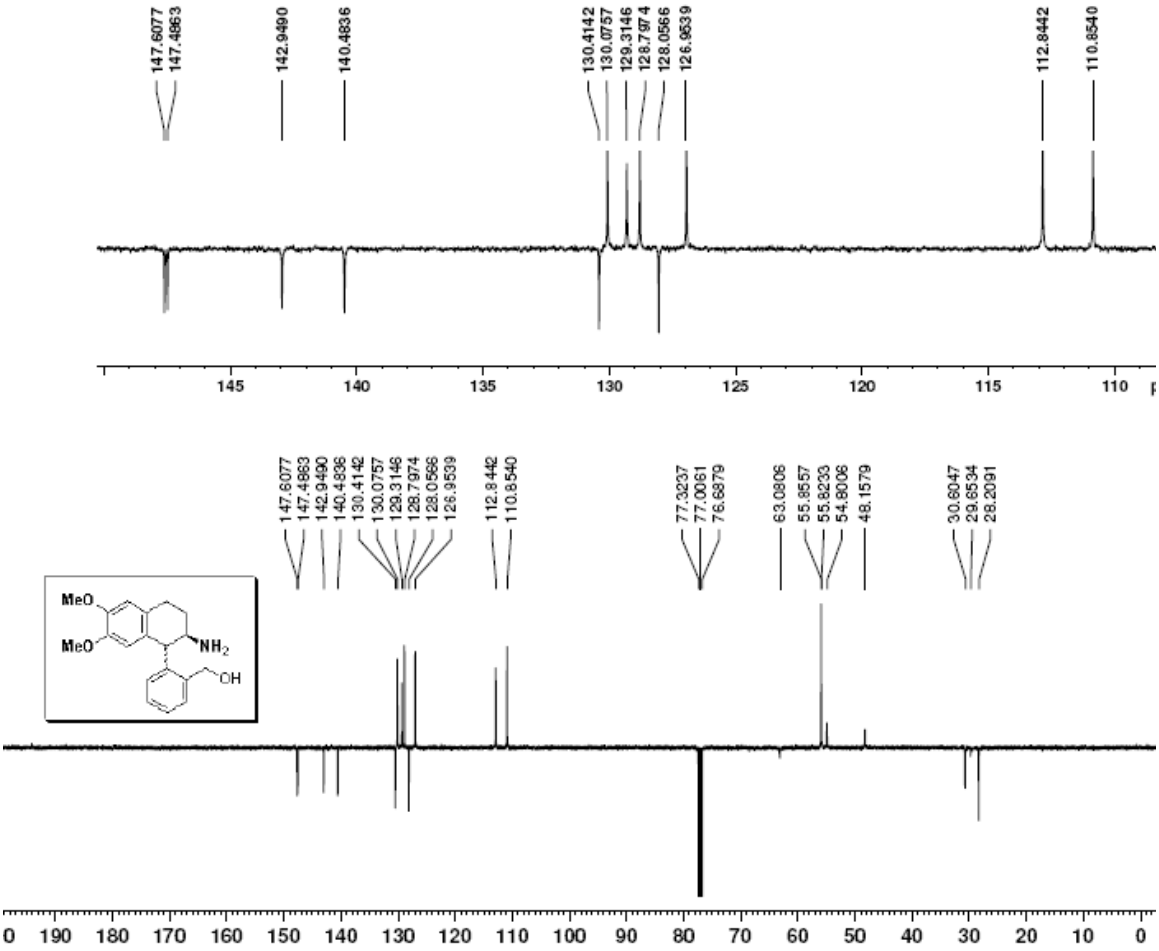
2-((1*S*,2*R*)-2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-phenyl]-methanol 23:



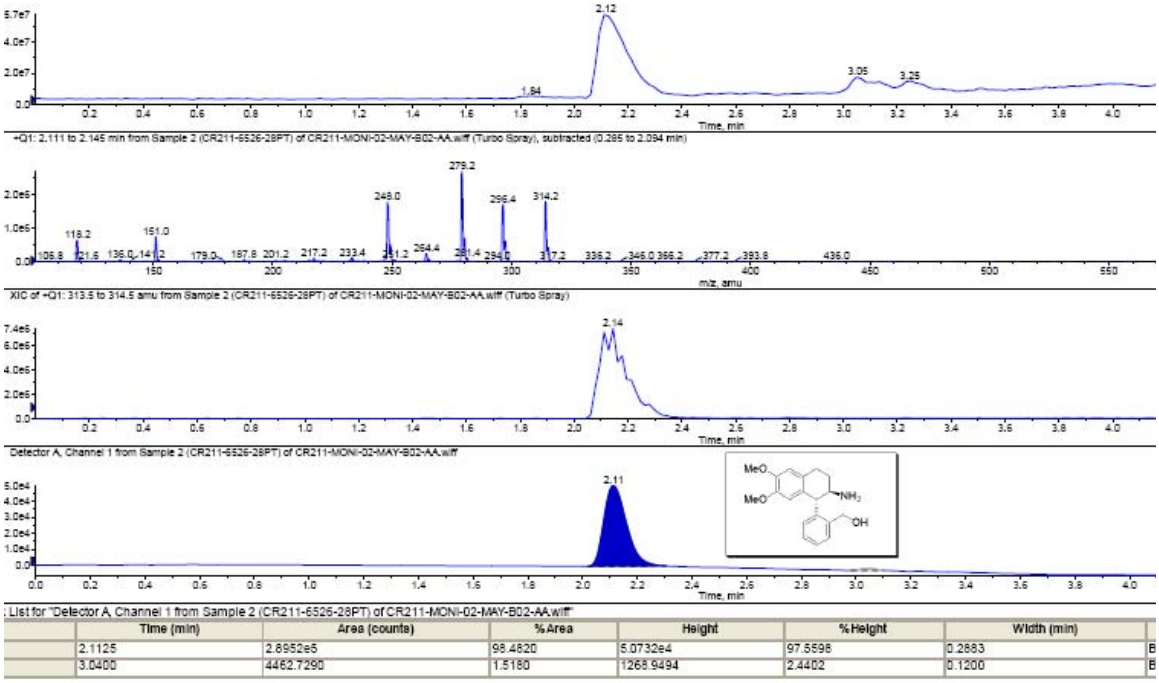
^{1}H NMR spectrum (400MHz, $CDCl_3$) of compound **23**



^{13}C NMR spectrum (100MHz, $CDCl_3$) of compound **23.**

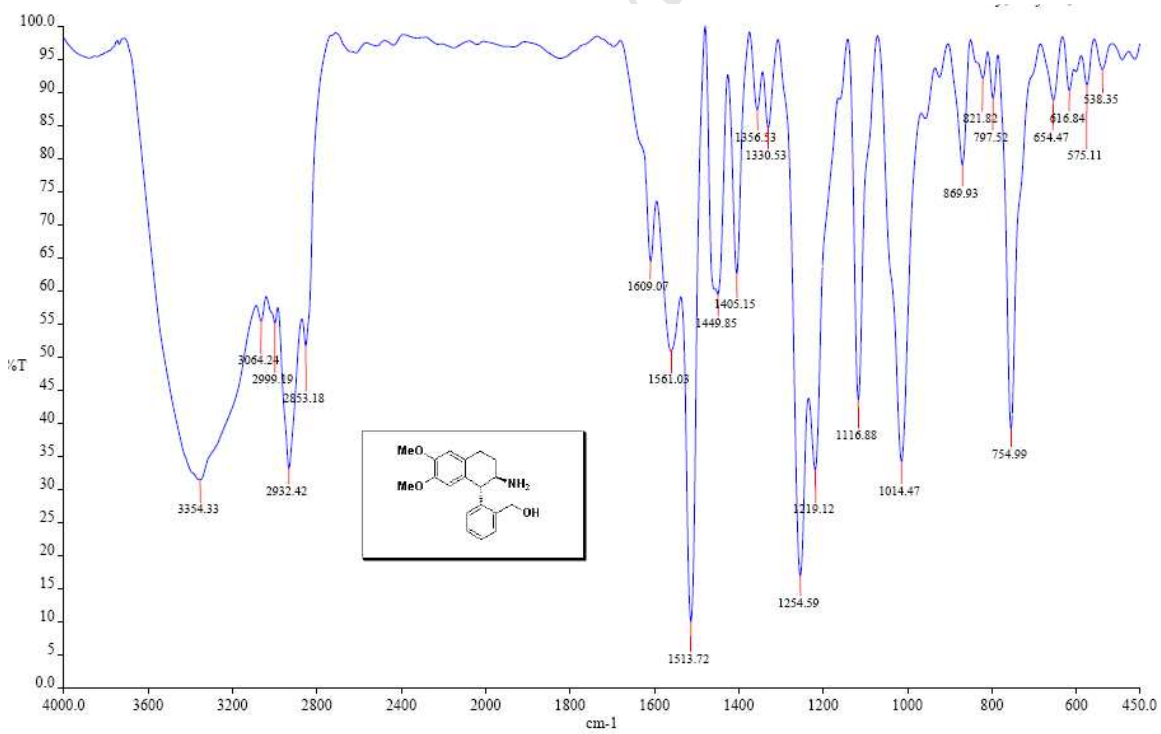


APT spectrum (100MHz, $CDCl_3$) of compound **23**



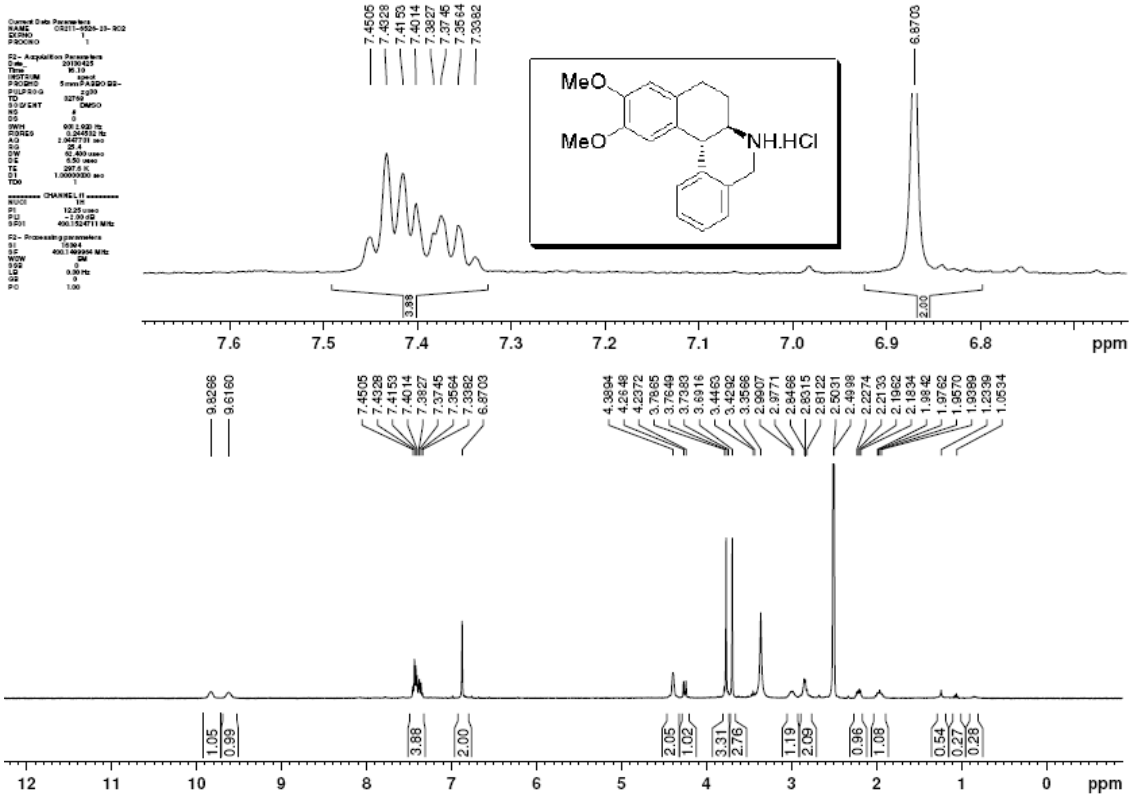
	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	
	2.1125	2.8952e5	98.4820	5.0732e4	97.5598	0.2883	B
	3.0400	4462.7290	1.5180	1268.9494	2.4402	0.1200	B

LCMS spectrum of compound **23**

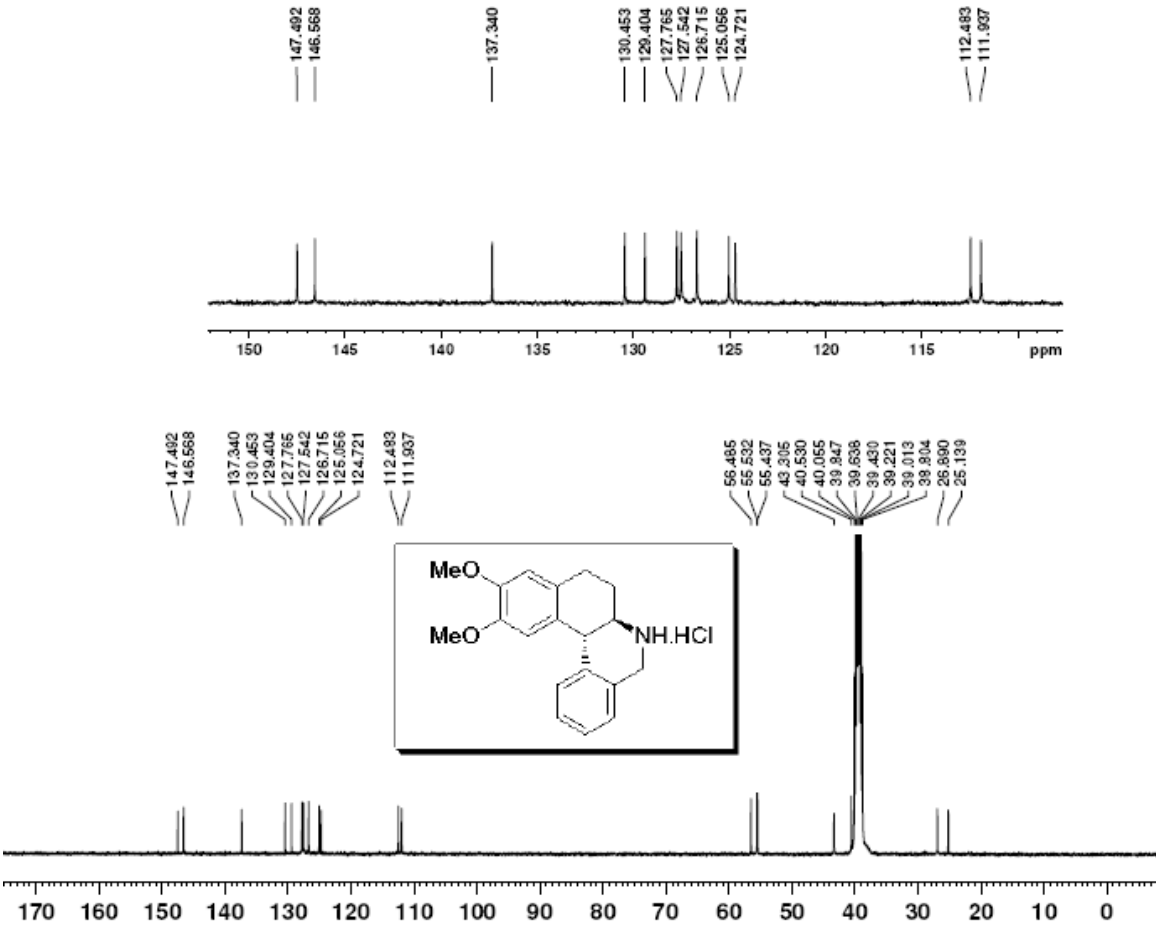


IR spectrum (neat) of compound **23**

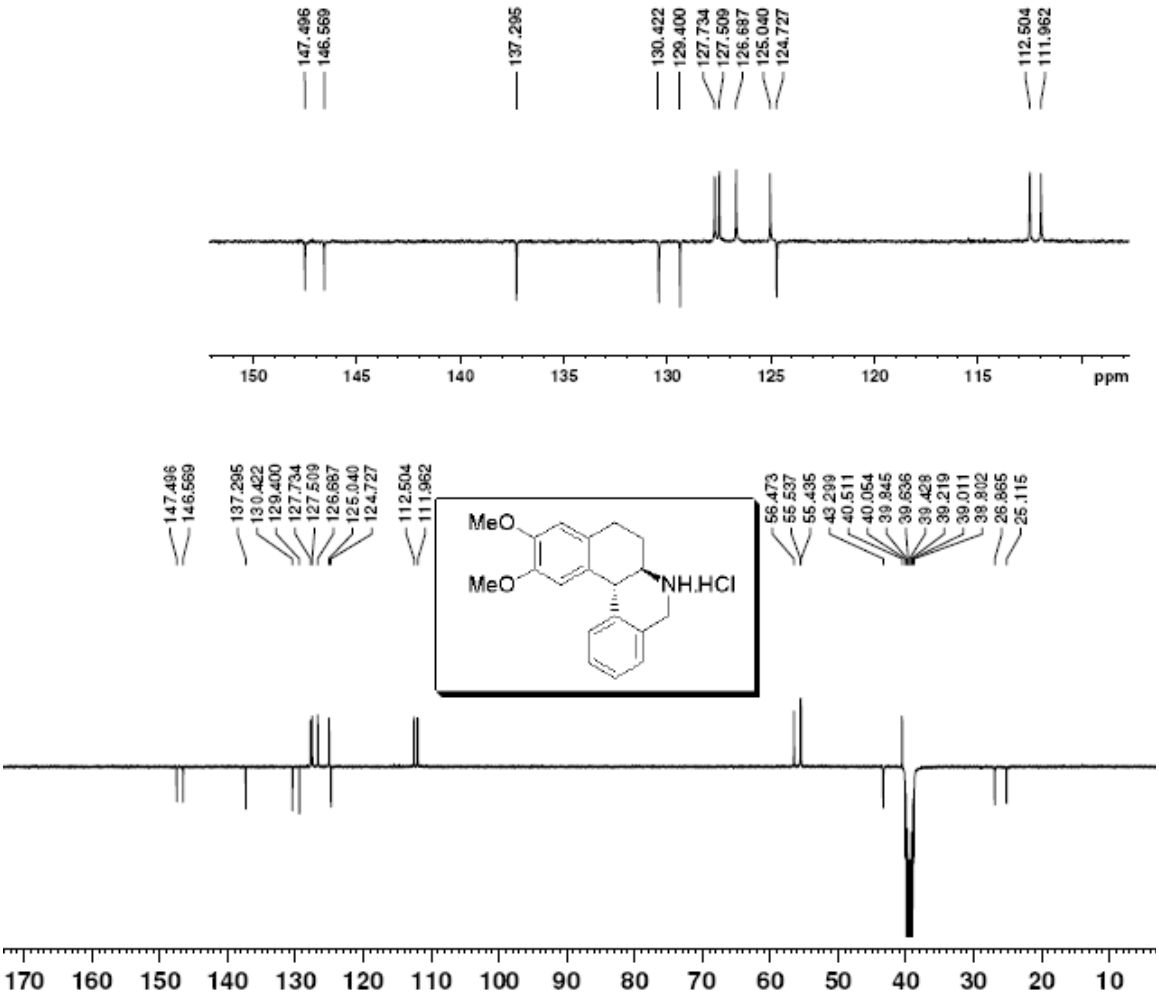
(6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydro-benzo[a]phenanthridine hydrochloride 24:



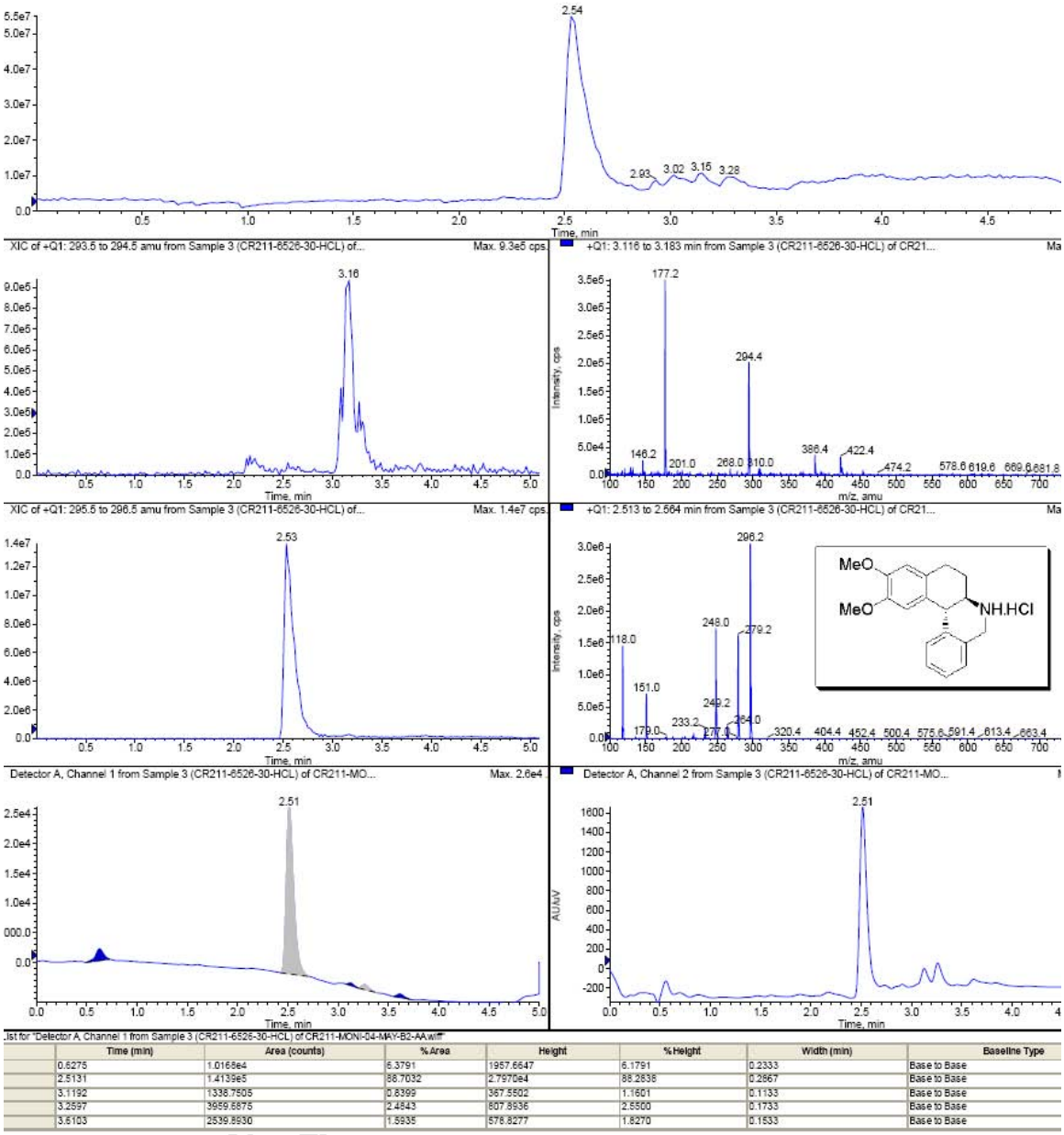
^{1}H NMR spectrum (400MHz, d_6-DMSO) of compound **24**.



^{13}C NMR spectrum (100MHz, d_6-DMSO) of compound **24**.



APT spectrum (400MHz, d_6-MSO) of compound **24**.



List for "Detector A, Channel 1 from Sample 3 (CR211-6526-30-HCL) of CR211-MONI-04-MAY-B2-AA.wiff"

	Time (min)	Area (counts)	% Area	Height	% Height	Width (min)	Baseline Type
	0.6275	1.0166e4	6.3791	1957.6647	6.1791	0.2333	Base to Base
	2.5131	1.4139e5	88.7032	2.7970e4	88.2838	0.2867	Base to Base
	3.1192	1338.7505	0.8399	367.5502	1.1601	0.1133	Base to Base
	3.2597	3959.6875	2.4843	607.8936	2.5500	0.1733	Base to Base
	3.5103	2539.8930	1.5935	576.8277	1.8270	0.1533	Base to Base

LCMS spectrum of compound **24**