Université de Montréal

Synthèse de mimes peptidiques macrocycliques par métathèse d'oléfine et de mimes peptidiques bicycliques par cyclisation électrophilique transannulaire

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Systematic Study of the Synthesis of Macrocyclic Dipeptide β-Turn Mimics Possessing 8-, 9-, and 10- Membered Rings by Ring-Closing Metathesis

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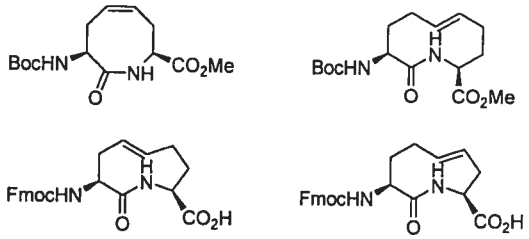

A systematic study was performed to establish general synthesis protocols for forming enantiomerically pure macrocyclic dipeptide lactams. Focusing on macrocycles of 8-, 9-, and 10-membered rings, effective syntheses were achieved by a sequence featuring peptide coupling of allyl- and homoallyl-glycine building blocks followed by ring-closing metathesis. The 8-membered lactam possessing *cis*-amide and *cis*-olefin geometry as well as 9- and 10-membered lactams having *trans*-amide and *trans*-olefin configurations were effectively prepared by a general strategy employing the respective protected dipeptide, the first generation Grubbs' catalyst, and temporary protection of the central amide as a benzyl derivative.

Introduction

β-turns in peptides and proteins are of interest because of their structure and biological activity.[1] Polar in nature, these secondary structures generally occupy the surfaces of protein molecules, where they are involved in recognition and binding.[2] β-turns have also been shown to be important for receptor affinity in biologically active peptides, such as somatostatin,[3] MSH,[4] bradykinin,[5] and LHRH.[6] Mimics of β-turns are thus desirable tools for studying the structure−activity relationships responsible for protein and peptide biology.[7]

Strategies to design β-turn mimics have often constrained the peptide backbone dihedral angles. For example, fused bicyclic systems, such as azabicyclo[X,Y,0]-alkanone amino acids **1**−**4**, of varying ring sizes have been used as rigid dipeptide surrogates[7] that structurally constrain three contiguous dihedral angles, ϕ, ψ, and ω, of a β-turn segment within the body of the heterocycle (Figure 1). Conformational analysis of bicyclic lactams **1**−**4** has demonstrated their propensity to favor type II and II′ β-turns[8,9] contingent on their stereochemistry, as evident from X-ray diffractometry, IR, and NMR spectroscopy as well as theoretical calculations.[10] Because differences in the type II turn dihedral angle have been

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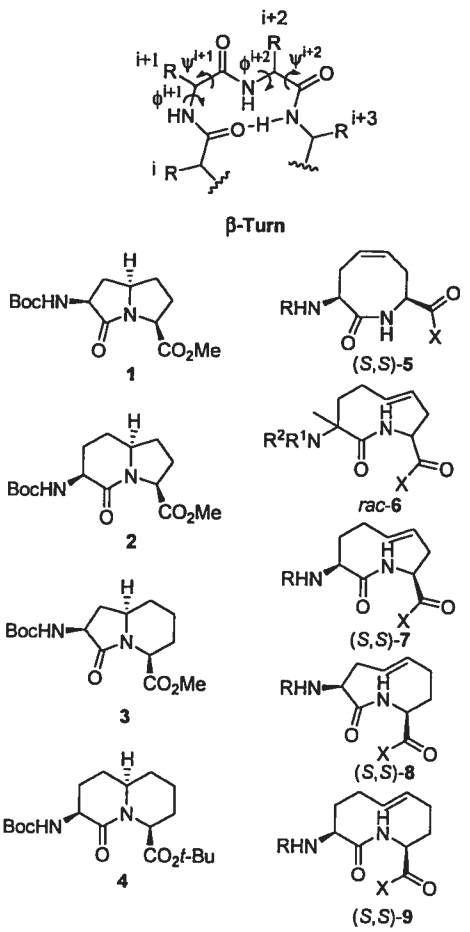

FIGURE 1. Representative β-turn structure as well as bicyclic and macrocyclic constrained dipeptide β-turn mimics.

observed after variation of the ring sizes in these bicyclic mimics, application of sets of related azabicycloalkane amino acids has thus proven effective for studying the effect of turn geometry on the biological activity of native peptides.[11,12]

Alternative scaffolds are needed to cover a wider range of turn geometries in order to better mimic natural diversity and to enhance success in peptide mimicry. Macrocyclic dipeptide lactams of 8-, 9-, and 10-members have been less well investigated relative to their bicyclic cousins, in part due to the difficulties inherent in synthesizing such medium-sized ring systems.[13]

The syntheses of eight-membered macrocycles, such as **5**, have been accomplished by ring-closing metathesis. Constrained dipeptides (*S*,*S*)-**5** and (*R*,*S*)-**5**, (R = Ac, X = NHMe) were shown to adopt conformations similar to an ideal type VIa β-turn, as demonstrated by NMR spectroscopy and the X-ray crystal structure of (*S*,*S*)-**5**.[14] Although the type VI β-turn did not possess proline, the eight-membered macrocycle forced the amide between the $i + 1$ and $i + 2$ residues to adopt the cis-isomer geometry, as illustrated by X-ray structural analysis, which also revealed a *cis*-olefin in a folded twist-boat-boat conformation.[14] The saturated analogue of eight-membered lactam (*R*,*R*)-**5** possessed a *cis*-amide geometry and type VIb β-turn conformation; however, dimerization took place over time in solution and in the solid state, as revealed by NMR dilution experiments and X-ray crystallographic studies.[15,16] Their *cis*-amide geometry and their propensity to favor type VI β-turns makes eight-membered lactams (**5**) structurally comparable to other type VI β-turn mimics, such as 5-*tert*-butylproline-containing peptides.[17]

Among the few syntheses of nine-membered macrocyle dipeptide lactams, an Ugi-multicomponent reaction followed by ring-closing metathesis has been used to prepare unsaturated nine-membered lactam **6** ($R^1 = CH_3CO$, $R^2 = PhCH_2$, X = OEt), albeit as a racemic isomeric mixture.[18] The ring geometry and conformational preferences of nine-membered macrocyclic lactams such as **6**–**8** have, however, yet to be characterized.

The 10-membered macrocycle dipeptide lactam (**9**, R = Boc, X = OMe) has also been synthesized by ring-closing metathesis and shown to possess a *trans*-olefin geometry and ϕ, ψ, and ω torsional angles similar to that of an ideal type I β-turn, as demonstrated by X-ray and NMR analyses.[19]

With the precedent that 8- and 10-membered macrocyclic peptide lactams adopted type VI and type I β-turns, respectively, and with potential for their nine-membered counterparts to serve similarly as turn mimics, we sought to develop a general means for constructing the set of heterocyclic dipeptides (**5** and **7**–**9**, R = Boc or Fmoc, X = OH). We envisioned that this set will serve in studies of biologically active peptides as well as intermediates for trans-annular cyclizations to prepare azabicyclo-[X,Y,0]alkanone amino acids related to **1**–**4**.

Medium-sized macrocyclic lactams of 8-, 9-, and 10-members have been traditionally harder to form than their smaller and larger-sized counterparts;[13] however, ring-closing metathesis has significantly advanced their synthesis. For example, *N*-alkyl lactams of 6–10 members have been prepared by RCM.[20] Transient *N*-alkylation of the central amide with a 2,4-dimethoxy benzyl group (Dmb) was also shown to be essential to favor a *cis*-amide geometry and facilitate metathesis in the synthesis of eight-membered lactams (**5**).[14,15] Moreover,

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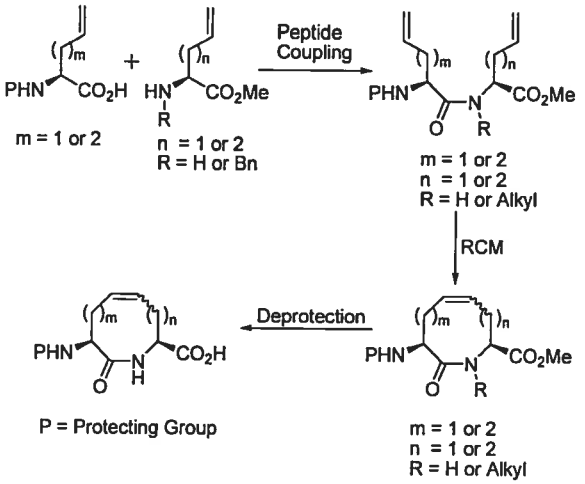
SCHEME 1. General Scheme for the Synthesis of Macrocyclic Dipeptides



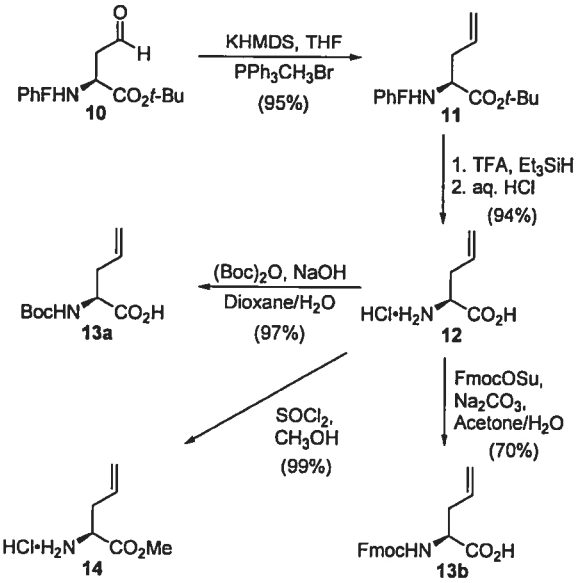
RCM has been used effectively to make larger ring systems that have constrained peptide conformations.[21]

Considering these results and the need for material on a suitable scale and in a protected form for peptide synthesis, we undertook a detailed study to prepare macrocyclic dipeptide lactams of 8−10 members by a general strategy featuring RCM (Scheme 1).

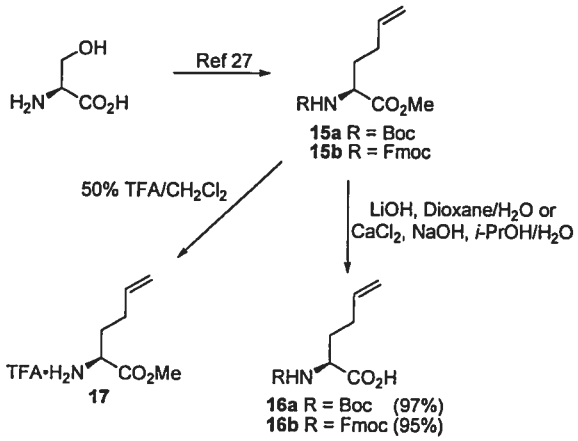
Results and Discussion

Dipeptide Precursor Synthesis. The construction of 8-, 9-, and 10-membered ring sizes necessitated the synthesis and coupling of allylglycine and homoallylglycine units prior to RCM. Allylglycine had been synthesized by a variety of methods;[22] however, our expertise with α-*tert*-butyl *N*-(PhF)aspartate β-aldehyde (**10**, PhF = 9-phenylfluren-9-yl)[23] served as motivation to employ this chiral educt in the synthesis of allylglycine (Scheme 2). Aldehyde **10** was synthesized on a 7-g scale from aspartic acid [23b,24] in five steps and 47% overall yield. *N*-(PhF)Allylglycine *tert*-butyl ester **11** was obtained in 95% yield from the Wittig reaction of aldehyde **10** and the ylide generated from treatment of methyltriphenylphosphonium bromide with KHMDS in THF.[25] Allylglycine hydrochloride **12** was quantitatively prepared from the treatment of **11** with TFA, which cleaved both

SCHEME 2. Synthesis of Allylglycine Components 13 and 14



SCHEME 3. Synthesis of Homoallylglycine Components 16 and 17



the *tert*-butyl ester and PhF groups, followed by conversion of the trifluoroacetate salt to the hydrochloride using aq HCl and lyophilization. *N*-(Boc)- and *N*-(Fmoc)allylglycines **13a** and **13b** were then prepared by the protection of **12** with $(Boc)_2O$[26a] and FmocOSu,[26b] respectively, under basic conditions. Allylglycine methyl ester hydrochloride **14** was quantitatively obtained by the treatment of **12** with methanol and thionyl chloride. The higher *N*-(Boc)- and *N*-(Fmoc)-protected homologues (homoallylglycines **16a** and **16b**) were synthesized respectively in five steps from serine using reported procedures (Scheme 3).[27] Briefly, serine was converted to its methyl ester hydrochloride, which was protected using Boc_2O or FmocOSu and transformed to *N*-(Boc)- or *N*-(Fmoc)iodoalanine methyl ester using iodine, PPh_3, and imidazole.[28] The iodide was then converted to a zincate and coupled to allyl chloride

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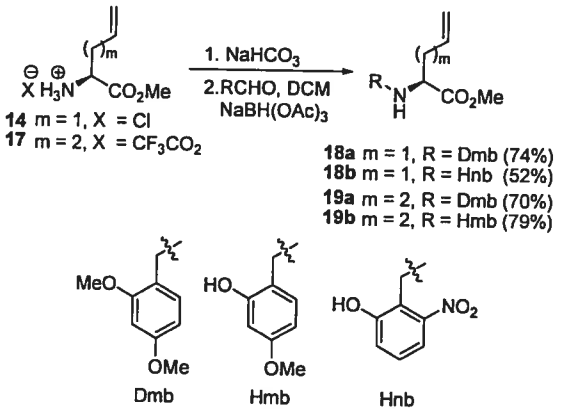
SCHEME 4. Synthesis of *N*-Benzyl Components 18 and 19



using CuBr·DMS. *N*-(Boc)amino ester **15a** was hydrolyzed with LiOH and deprotected with 50% TFA in CH_2Cl_2 to provide *N*-(Boc)homoallylglycine **16a** and homoallylglycine methyl ester trifluoroacetate **17**, respectively, as components for peptide coupling. *N*-(Fmoc)Homoallylglycine **16b** was obtained by hydrolysis of *N*-(Fmoc)-amino ester **15b** using 0.8 M calcium chloride and 0.5 M sodium hydroxide in *i*PrOH/H_2O (7:3).[29]

Considering that rotation around the amide bound would influence the rate of RCM of the dipeptides, we synthesized an array of secondary benzyl amino esters to prepare tertiary amides having a lower barrier for isomerization about the amide bond (Scheme 4). This hypothesis was supported by earlier studies of the synthesis of eight-membered lactams that demonstrated the utility of the acid labile 2,4-dimethoxybenzyl (Dmb) group in the RCM step.[15b] The related 2-hydroxy-4-methoxybenzyl (Hmb) group has been used to surmount difficult couplings in solid-phase peptide synthesis,[30] and we envisioned that secondary amino esters bearing this group could have better reactivity than their Dmb cousins. Similary, the 2-hydroxy-6-nitrobenzyl (Hnb) group was considered as a photocleavable protection reported to favor coupling by O to N acyl transfer in a similar way as the Hmb auxiliary.[31] Reductive aminations of imine prepared with the respective benzaldehyde and allyl and homoallylglycine methyl esters (**14** and **17**) were performed using $NaBH(OAc)_3$ to furnish Dmb-, Hmb-, and Hnb-protected amino esters **18** and **19** in yields varying between 52% and 79%.

Coupling of the Fragments. The set of dipeptides **21a**−**23a** was assembled first by combining allylglycine and homoallylglycine methyl ester salts **14** and **17** as amine components and *N*-(Boc)allyl and *N*-(Boc)homoallylglycines **13a** and **16a** as acid components using TBTU as the coupling agent in 85−87% yields (Table 1). Coupling of the Dmb secondary amino esters proved more difficult, and many coupling conditions were tried;[32] however, only HATU as the coupling agent with *N*-ethylmorpholine as the base was found to be effective for making *N*-Boc-protected dipeptides **20b**−**23b** bearing a 2,4-dimethoxybenzyl tertiary amide bond in yields varying between 71% and 86%. Changing from Boc protection to Fmoc did not affect coupling, and dipeptides **21c** and **22c** were obtained in 85% and 82% yields, respectively. The use of HATU could be avoided by employing *N*-(Hmb)homoallylglycine methyl ester **19b** and the symmetrical anhydride generated from *N*-(Boc)homoallylglycine **16a**, respectively, in situ to furnish **23c** in 86% yields. Attempts to apply the symmetrical anhydride conditions using *N*-(Hnb)allylglycine **18b** gave **22d** in 87% yield; however, this route was not pursued further because of the difficulties in making the requisite 2-hydroxy-6-nitrobenzaldhyde.[33]

Ring-Closing Metathesis. The importance of the rate of amide bond isomerization on the ring-closing metathesis was realized in the synthesis of nine-membered macrocyles, which could not be formed without a tertiary amide. When cyclization by olefin metathesis was examined on dipeptides bearing no benzyl group at the amide nitrogen, secondary amides **21a** and **22a** failed to cyclize using both the first and second generation Grubbs' catalyst in a variety of solvents at reflux and room temperature. Dipeptide **21a** also did not cyclize to a nine-membered ring in the presence of Ti(O-*i*Pr)$_4$, which has been used previously to prevent the formation of a cyclic chelate between the catalyst and an amide.[34] As reported,[19] 10-membered macrocyclic dipeptide **27a** was formed on cyclization of dipeptide **23a** using the first generation of Grubbs' catalyst at high dilution (0.7 mM).

Macrocycles of eight and nine members were synthesized from dipeptides bearing only a benzyl group on the nitrogen of the amide. Dmb-analogues **20b**, **21b** and **c**, **22b** and **c**, and **23b** reacted with the first generation Grubbs' catalyst to provide 8−10 membered macrocycles **24a**, **25b** and **c**, **26b** and **c**, and **27b**, respectively, in 71−81% yields (Table 2). The 10-membered macrocyle (**27b**) was formed in 87% yield from tertiary amide **23b** employing the same conditions used to cyclize secondary amide **23a** at a concentration four and a half times higher. The phenol of the Hmb group was also tolerated by the catalyst, and 10-membered macrocyle **27c** was prepared in 86% yield. The tertiary amide facilitated amide bond rotation and favored conformers in which the ring-closing metathesis was possible. In the smaller-ring cases, without the benzyl group, the *cis*-amide isomer was disfavored energetically, and the barrier for isomerization was higher such that macrocylization was inhibited.

The Dmb and Hmb groups were reported to be easily cleaved under acidic conditions.[30,35] However, *N*-Boc-protected-9- and 10-membered lactams **25b**, **26b**, and

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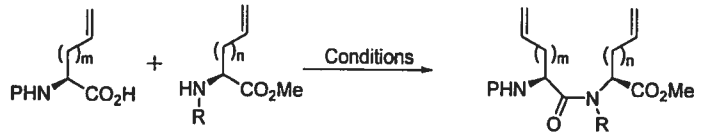
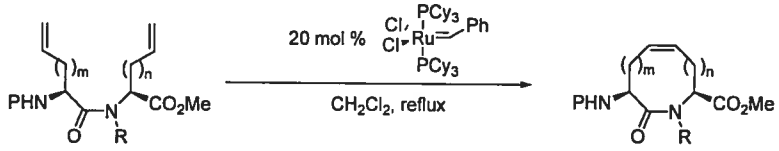
TABLE 1. Dipeptide Assembly



acid	m	P	amine	n	R	conditions[a]	amide	yield (%)
13a	1	Boc	**18a**	1	Dmb	A	**20b**	71
13a	1	Boc	**17**	2	H	B	**21a**	86
13a	1	Boc	**19a**	2	Dmb	A	**21b**	86
13b	1	Fmoc	**19a**	2	Dmb	A	**21c**	85
16a	2	Boc	**14**	1	H	B	**22a**	85
16a	2	Boc	**18a**	1	Dmb	A	**22b**	81
16b	2	Fmoc	**18a**	1	Dmb	A	**22c**	82
16a	2	Boc	**18b**	1	Hnb	C	**22d**	87
16a	2	Boc	**17**	2	H	B	**23a**	87
16a	2	Boc	**19a**	2	Dmb	A	**23b**	74
16a	2	Boc	**19b**	2	Hmb	C	**23c**	86

[a] Condition A: HATU, *N*-ethylmorpholine, CH_2Cl_2, rt; condition B: TBTU, DIEA, CH_2Cl_2, rt; condition C: symmetric anhydride, benzylic amino ester, CH_2Cl_2, rt.

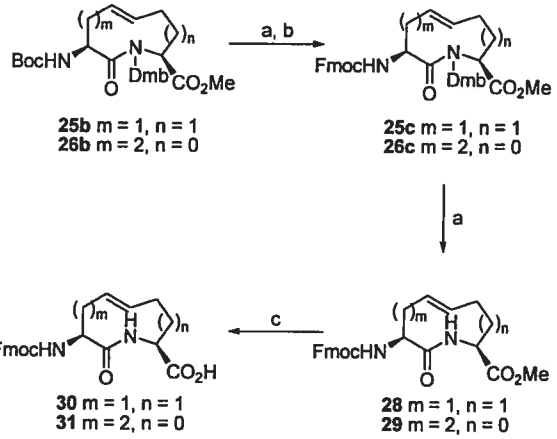
TABLE 2. Macrocycle Formation



amide	P	m	n	R	macrocycle	yield (%)
20b	Boc	1	1	Dmb	**24a**	78
21a	Boc	1	2	H	**25a**	0
21b	Boc	1	2	Dmb	**25b**	80
21c	Fmoc	1	2	Dmb	**25c**	75
22a	Boc	2	1	H	**26a**	0
22b	Boc	2	1	Dmb	**26b**	81
22c	Fmoc	2	1	Dmb	**26c**	71
23a	Boc	2	2	H	**27a**	77
23b	Boc	2	2	Dmb	**27b**	87
23c	Boc	2	2	Hmb	**27c**	86

27b and **c** bearing Dmb and Hmb groups were recovered as deprotected amines without the loss of the benzylic tertiary amide after prolonged treatment with 50% TFA in CH_2Cl_2. Alternatively, both the Boc and Dmb groups were removed upon exposure of eight-membered lactam **24a** to the same TFA in CH_2Cl_2 conditions as reported.[15b] In contrast to the *N*-Boc-protected lactams, *N*-Fmoc-protected lactams **25c** and **26c** were quantitatively converted in 30 min to their secondary amide derivatives **28** and **29** by treatment with 50% TFA in CH_2Cl_2 (Scheme 5). This behavior confirms the hypothesis[36] that difficulties in cleaving Dmb groups are due to the formation of a neighboring positively charged ammonium ion upon deprotection of the Boc moiety, which inhibits protonation of the amide and shuts down the reaction. Conversion of *N*-Boc-protected macrocycles **25b** and **26b** to *N*-Fmoc-derivatives **25c** and **26c** gave average yields of 35−45%, illustrating an advantage in starting with *N*-Fmoc-protected amino acids. Finally, esters **28** and **29** were hydrolyzed using 0.5 M NaOH and 0.8 M $CaCl_2$ in *i*PrOH/water (7:3) to obtain the protected amino acids (**30** and **31**) suitable for incorporation into peptides by solid-phase synthesis.[29]

SCHEME 5. Synthesis of Macrocycle *N*-(Fmoc)-dipeptides 30 and 31



[a] Reagents and conditions: (a) 50% TFA/CH_2Cl_2; (b) FmocOSu, Na_2CO_3, acetone/H_2O; (c) 0.8 M $CaCl_2$/0.5 M NaOH, *i*-PrOH/H_2O.

The olefin geometry was determined based on the vicinal coupling constant of the vinyl protons. In the case of eight-membered lactam (*S*, *S*)-**5**, a coupling-constant value of 10.4 Hz was observed and assigned to *cis*-olefin

(36) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A.; Graham, S. L. *Org. Lett.* **2001**, *3*, 865.

geometry. In the case of 9- and 10-membered lactams **7**–**9**, coupling-constant values ranged from 18.5 to 19.1 Hz and were assigned to *trans*-olefins.

The amide isomer geometry of 8- and 10-membered lactams **5** and **9** were assigned cis and trans, respectively, based on analogy to literature compounds **5**[14] and **9**,[19] for which X-ray structures were obtained. The assignment of the amide isomers of nine-membered lactams **30** and **31** was made based on 2D NMR experiments. Initially, COSY spectra of **30** and **31** were performed in pyridine-d_5 and $CDCl_3$, respectively, to assign the protons for each compound. Subsequently, NOESY spectra were performed to measure long-distance transfers of magnetization. In the NOESY spectrum of both **30** and **31**, no transfer of magnetization between the $C^{\alpha}H$ protons was observed using a variety of mixing times. Because an amide cis isomer would be expected to exhibit strong NOE between the neighboring $C^{\alpha}H$ protons, the lack of such a transfer of magnetization leads us to assign the amide trans isomer geometry for **30** and **31**.

Conclusions

A general methodology has been developed for synthesizing enantiomerically pure 8-, 9-, and 10-membered macrocyclic dipeptides. This methodology has provided the first syntheses of nine-membered lactams **7** and **8**, as well as a more practical route for making 10-membered lactam **9**. The importance of transient *N*-alkylation of the central amide was demonstrated to facilitate ring-closing metathesis, such that higher concentrations (3.15 mM) could be used without evoking dimer or polymer formation. As reported, the *cis*-olefin geometry was found in eight-membered lactam **5**. The 9- and 10-membered lactams (**7**–**9**) possessed *trans*-olefin geometry. The amide bond geometry was shown to be cis in the case of **5** and trans for macrocycles **7**–**9**. A more detailed investigation of the conformation of **7** and **8** in peptide analogues is presently under study. In light of the ability of these constrained dipeptide surrogates to adopt conformations similar to natural β-turns, this practical methodology should be of general utility for research in peptide science and medicinal chemistry.

Experimental Section

***tert*-Butyl (2*S*)-2-[(*N*-(PhF)Amino]pent-4-enoate (11).** A rt solution of methyltriphenylphosphonium bromide (13.2 g, 37 mmol) in THF (103 mL) was treated with a 0.5 M solution of KHMDS in toluene (67 mL, 33 mmol), stirred for 30 min, and treated dropwise with aldehyde **10** (7.64 g, 18.5 mmol, prepared according to ref 23) in THF (103 mL) over 10 min. The reaction mixture was stirred for 1 h, quenched with 200 mL of a saturated solution of NH_4Cl, and the phases were separated. The aqueous layer was extracted twice with 150 mL of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography (7% EtOAc/hexanes) afforded allylglycine **11** (7.22 g, 95% yield) as a clear oil: $[\alpha]^{20}_D$ +163.7° (*c* 1.0, $CHCl_3$), lit.[37] $[\alpha]^{20}_D$ 168.7° (*c* 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectral data were consistent with the literature.[37]

(2*S*)-2-Aminopent-4-enoic Acid Hydrochloride (12). TFA (60 mL) was added dropwise to a solution of allylglycine **11** (7.22 g, 17.5 mmol) in CH_2Cl_2 (60 mL). Once the addition was completed, Et_3SiH (7 mL, 43.8 mmol) was added to the solution, which was stirred for 15 h. The volatiles were evaporated, and the residue was dissolved in 3:1 hexanes/Et_2O (50 mL) and treated with 0.5 N HCl (25 mL). The phases were separated, and the organic layer was extracted twice with 0.5 N HCl. The combined aqueous layers were lyophilized to give amino acid hydrochloride **12** (2.50 g, 94% yield) as a white solid: mp 205–207 °C; ^1H NMR (CD_3OD): δ 5.79 (m, 2H), 5.29 (m, 2H), 4.06 (dd, 1H, *J* = 7.1, 5.1 Hz), 2.68 (m, 2H); ^{13}C NMR (CD_3OD): δ 169.4, 130.1, 119.7, 51.6, 34.0. MS (ESI, *m/z*): 116.0 $(MH)^+$.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]pent-4-enoic Acid (13a). A 1:1 dioxane/H_2O solution (33 mL) containing hydrochloride **12** (750 mg, 4.95 mmol) was treated with NaOH (436 mg, 9.90 mmol). After the NaOH dissolved, Boc_2O (1.30 g, 5.94 mmol) was added to the mixture in three portions over 10 min. The mixture was stirred for 18 h. The dioxane was removed by evaporation. The crude mixture was diluted with H_2O and acidified to pH 3–4 with a 10% $KHSO_4$ solution. This aqueous solution was extracted with Et_2O (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give *N*-(Boc)allylglycine **13a** (1.03 g, 97% yield) as a thick clear oil: $[\alpha]^{20}_D$ +14.5° (*c* 1.28, $CHCl_3$); The ^1H and ^{13}C NMR were consistent with the literature.[22c] HRMS calcd for $C_{10}H_{17}NO_4Na$, 238.10498; found, 238.10538.

(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]pent-4-enoic Acid (13b). A 1:1 acetone/H_2O solution (67 mL) containing hydrochloride **12** (1.5 g, 10 mmol) was treated with Na_2CO_3 (2.1 g, 20 mmol) and FmocOSu (3.3 g, 10 mmol). The mixture was stirred for 18 h at room temperature and concentrated. The crude mixture was diluted with H_2O and acidified to pH 3–4 with a 10% $KHSO_4$ solution. This aqueous solution was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give *N*-(Fmoc)allylglycine **13b** (2.36 g, 70% yield): mp 134–135 °C; $[\alpha]^{20}_D$ +10.6° (*c* 0.93, $CHCl_3$); ^1H NMR (CD_3OD): δ 7.68 (d, 2H, *J* = 9.9), 7.59 (m, 2H), 7.32 (t, 2H, *J* = 9.7), 7.23 (t, 2H, *J* = 9.9), 5.64 (m, 1H), 5.09 (m, 3H), 4.25 (m, 2H), 4.12 (m, 2H), 2.57 (m, 1H), 2.44 (m, 1H); ^{13}C NMR (CD_3OD): δ 175.2, 158.5, 145.3, 145.1, 142.5, 134.7, 128.8, 128.1, 126.3, 120.8, 118.7, 68.0, 55.1, 37.1; HRMS calcd for $C_{20}H_{19}NO_4Na$, 360.12063; found, 360.12080.

Methyl (2*S*)-2-Aminopent-4-enoate Hydrochloride (14). $SOCl_2$ (0.55 mL, 19.8 mmol) was added dropwise to a solution of allylglycine **12** (2.0 g, 13.2 mmol) in MeOH (22 mL) at 0 °C. The mixture was allowed to warm to room temperature, stirred overnight, and evaporated to give methyl ester **14** (2.16 g, 99% yield) as a white solid: mp 91–92 °C; $[\alpha]^{20}_D$ +8.3° (*c* 1.07, CH_3OH); ^1H NMR (CD_3OD): δ 5.76 (m, 1H), 5.28 (m, 2H), 4.15 (dd, 1H, *J* = 6.8, 5.5), 3.83 (s, 3H), 2.69 (m, 2H); ^{13}C NMR (CD_3OD): δ 168.8, 130.1, 120.1, 52.1, 52.0, 34.1; HRMS $(MH)^+$ calcd for $C_6H_{11}NO_2$, 130.08626; found, 130.08636.

(2S)-2-[(*tert*-Butoxycarbonyl)amino]hex-5-enoic Acid (16a). A solution of *N*-(Boc)homoallylglycine methyl ester (**15a**, 400 mg, 1.64 mmol prepared according to ref 27) in 1:1 H_2O/dioxane (16 mL) was treated with $LiOH{\cdot}H_2O$ (103 mg, 2.47 mmol), stirred for 3 h, and evaporated to a residue that was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous phase was acidified with 0.1 M HCl to pH 4 and extracted twice with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford acid **16a** (0.364 g, 97% yield) as a colorless oil: $[\alpha]^{20}_D$ −1.1° (*c* 1.31, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 5.82 (m, 1H), 5.03 (m, 3H), 4.08 (m, 1H), 2.15 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 175.2, 157.1, 137.4, 115.0, 79.4, 53.2, 31.1, 30.0, 27.7; HRMS calcd for $C_{11}H_{19}NO_4Na$, 252.12063; found, 252.12089.

General Procedure A: Reductive Aminations. Allylglycine methyl ester hydrochloride **14** or homoallylglycine methyl ester trifluoroacetate **17** (3 mmol) was treated with 20 mL of a saturated $NaHCO_3$ solution and extracted with 3

(37) Kaul, R.; Broullette, Y.; Sajjadi, Z.; Hansford, K. A.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 6131.

× 25 mL of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine and dried over $MgSO_4$, filtered, and concentrated to a volume of 30 mL. The selected benzaldehyde derivative (3.3 mmol) and $NaBH(OAc)_3$ (4.5 mmol) were added to the mixture, which was stirred for 18 h at room temperature, treated with 20 mL of saturated $NaHCO_3$, and stirred for 30 min. The aqueous layer was separated and washed with 3 × 20 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography.

Methyl (2*S*)-2-[(2,4-Dimethoxybenzyl)amino]pent-4-enoate (18a). Chromatography of the product from **14** (20 mmol) using 30:70 EtOAc/hexanes as the eluant gave **18a** as a yellow oil (74% yield): ^{1}H NMR: δ 7.10 (d, 1H, J = 7.8), 6.39 (m, 2H), 5.69 (m, 1H), 5.08 (m, 2H), 3.81−3.64 (m, 11H), 3.11 (t, 1H, J = 6.6), 2.39 (t, 2H, J = 6.5), 2.22 (bs, 1H); ^{13}C NMR: δ 174.8, 160.0, 158.4, 133.6, 130.2, 120.0, 117.6, 103.5, 98.2, 60.0, 55.1, 55.0, 51.4, 46.8, 37.5. MS (ESI, *m/z*): 280.1 $(MH)^+$.

General Procedure B: Peptide Coupling using HATU. The selected *N*-protected amino acid (1.5 equiv) and *N*-benzyl amino ester (1.0 equiv) were dissolved in CH_2Cl_2 (0.07 M), treated with *N*-ethylmorpholine (1.5 equiv) and HATU (1.5 equiv), stirred for 24h, and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography.

***N*-(Fmoc)-L-Allylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-homoallylglycine Methyl Ester (21c).** Chromatography of the product from **13b** (1.5 mmol) and **19a** (1.0 mmol) using 30:70 EtOAc/hexanes as the eluant gave **21c** (85% yield):^{1}H NMR: δ 7.76 (d, 2H, J = 7.5), 7.62 (dd, 2H, J = 3.3, 3.4), 7.39 (t, 2H, J = 7.5), 7.30 (t, 2H, J = 7.4), 7.07 (d, 1H, J = 8.0), 6.40 (dd, 2H, J = 2.1, 2.3), 5.81−5.65 (m, 3H), 5.14 (m, 2H), 5.05 (m, 1H), 4.98 (m, 2H), 4.67 (d, 1H, J = 15.8), 4.46−4.29 (m, 3H), 4.24−4.22 (t, 1H, J = 7.1), 4.13 (m, 1H), 3.76 (s, 6H), 3.57 (s, 3H), 2.59 (m, 1H), 2.45 (m, 1H), 2.11 (m, 1H), 2.03 (m, 2H), 1.80 (m, 1H); ^{13}C NMR: δ 171.6, 171.0, 160.9, 158.6, 155.3, 143.7, 141.1, 137.3, 132.3, 130.2, 127.5, 126.8, 125.0, 124.9, 119.8, 118.7, 115.8, 115.4, 103.5, 98.3, 66.7, 57.7, 55.2, 55.0, 51.8, 50.7, 47.0, 37.8, 30.4, 28.1. MS (ESI, *m/z*): 635.2 $(MNa)^+$.

General Procedure C: Ring-Closing Metathesis. In a flame dried flask, dipeptide (1.0 equiv) was dissolved in dry CH_2Cl_2 (3 mM). The mixture was heated for 10 min at 35 °C, treated with bis(tricyclohexylphosphonium)benzylidine ruthenium (IV) dichloride ($RuCl_2$(=CHPh)$(PCy_3)_2$, 20 mol %), heated at reflux for 72h, and concentrated. The crude residue was purified by chromatography to afford the unsaturated lactam.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-Azonine-9-carboxylate (25c). Chromatography of the product from **21c** (0.4 mmol) using 20:80 EtOAc/hexanes as the eluant gave **25c** (75% yield) as a brown solid: mp 96−101 °C; $[\alpha]^{20}_D$ −37.8° (*c* 0.93, $CHCl_3$); ^{1}H NMR: δ 7.76 (d, 2H, J = 7.5), 7.62 (d, 2H, J = 7.4), 7.40 (t, 2H, J = 7.4), 7.30 (t, 2H, J = 7.3), 7.23(d, 1H, J = 8.3), 6.49 (d, 1H, J = 6.6), 6.45−6.36 (m, 2H), 6.09 (dd, 1H, J = 9.1, 18.0), 5.61 (dd, 1H, J = 9.1, 18.0), 4.66−4.35 (m, 5H), 4.23 (t, 1H, J = 7.1), 3.79 (s, 3H), 3.77 (s, 3H), 3.46 (s, 3H), 2.67 (m, 1H), 2.30−2.15 (m, 2H), 1.90 (m, 2H), 1.75−1.65 (m, 2H); ^{13}C NMR: δ 173.3, 170.4, 159.8, 157.4, 155.2, 143.8, 141.1, 130.9, 129.9, 129.0, 127.5, 126.9, 125.0, 125.0 119.8, 117.5, 104.0, 97.9, 66.8, 56.9, 55.1, 52.0, 51.7, 47.0, 39.9, 35.0, 27.8, 22.0; HRMS $(MH)^+$ calcd for $C_{34}H_{37}N_2O_7$, 585.25953; found, 585.25918.

General Procedure D: Removal of Dmb. A stirred solution of Fmoc-protected dipeptide lactam (0.2 mmol) in CH_2Cl_2 (8 mL) was treated dropwise with TFA (2 mL), stirred for 18 h, and evaporated to a residue that was purified by chromatography.

Methyl (3*S*,9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylate (28). Chromatography of the product from **25c** (0.5 mmol) using EtOAc as the eluant gave **28** (95% yield) as a brown gum: ^{1}H NMR: δ 7.76 (d, 2H, J = 7.4), 7.60 (d, 2H, J = 7.3), 7.39 (t, 2H, J = 7.4), 7.30 (t, 2H, J = 7.4), 6.35 (d, 1H, J = 7.0), 6.25 (d, 1H, J = 11.6), 6.08 (dd, 1H, J = 8.8, 18.9), 5.65 (ddd, 1H, J = 6.04, 10.95, 10.84), 4.39−4.38 (m, 2H), 4.25 (m, 3H), 3.73 (s, 3H), 2.70 (m, 1H), 2.30 (dd, 2H, J = 8.5, 8.7), 2.12 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H); ^{13}C NMR: δ 172.7, 172.0, 155.2, 143.7, 143.6, 141.1, 130.1, 128.7, 127.5, 126.9, 124.9, 119.8, 66.8, 52.5, 52.1, 47.0, 34.1, 33.8, 22.5; HRMS $(MH)^+$ calcd for $C_{25}H_{27}N_2O_5$, 435.19145; found, 435.19184.

General Procedure E: Methyl Ester Hydrolysis. A stirred solution of methyl ester (0.5 mmol) in 0.8 M $CaCl_2$ in a 7:3 *i*-PrOH/H_2O solution (10 mL) was treated with 0.5 M NaOH solution (2 mL). After 2 h, ether was added, and the phases were separated. The aqueous layer was acidified with 1.0 N HCl and extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the acid.

(*E*,3*S*,9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylic Acid (30). Hydrolysis of **28** (0.4 mmol) gave **30** (99% yield) as a white solid: mp 190−193 °C; ^{1}H NMR (400 MHz, pyridine-d_5): δ 8.90 (d, 1H, J = 11.0), 8.38 (d, 1H, J = 7.1), 7.8 (m, 3H), 7.7 (t, 1H, J = 7.5), 7.35 (m, 3H), 7.25 (t, 1H, J = 9.0), 6.04 (dd, 1H, J = 8.6, 18.5), 5.75 (bs, 1H), 5.56 (dd, 1H, J = 8.7, 18.5), 4.84 (t, 1H, J = 7.8), 4.69 (m, 1H), 4.55 (d, 2H, J = 7.16), 4.33 (t, 1H, J = 6.8), 2.95−2.88 (m, 1H), 2.5 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.9 (m, 2H); ^{13}C NMR: δ 175.3, 174.1, 156.7, 145.2, 144.9, 142.1, 131.5, 129.3, 128.5, 127.9, 126.1, 120.8, 67.3, 52.9, 48.2, 41.4, 34.8, 31.0; HRMS $(MH)^+$ calcd for $C_{24}H_{25}N_2O_5$, 421.17580; found, 421.17599.

Acknowledgment. This work was supported by grants from Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT), Valorisation-Recherche Québec (VRQ), the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Society for Chemistry (CSC), Merck Frosst Canada, Boehringer Ingelheim Recherche Inc., Shire Biochem., and AstraZeneca Canada for financial support. We thank Hassan Iden for assistance in making starting materials, Dr. Alexandra Frutos and Mr. Dalbir Sekhon for mass spectral analysis, and Sylvie Bilodeau and Dr. M. T. Pham Viet of the Regional High-field NMR Laboratory for their assistance in running 2D NOESY/COSY experiments.

Supporting Information Available: General experimental section, general procedures for TBTU and symmetric anyhydride couplings, ^{1}H and ^{13}C NMR data for **18b**, **19a** and **b**, **21a** and **b**, **22a−d**, **23b** and **c**, **25b**, **26b** and **c**, **27b** and **c**, **29**, and **31**, ^{1}H and ^{13}C NMR spectra of **12**, **13b**, **14**, **16a**, **18a** and **b**, **19a** and **b**, **21a−c**, **22a−d**, **23b** and **c**, **25b** and **c** **26b** and **c**, **27b** and **c**, and **28−31**, 2D COSY and NOESY spectra of **30** and **31**, and HPLC profiles of **30** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

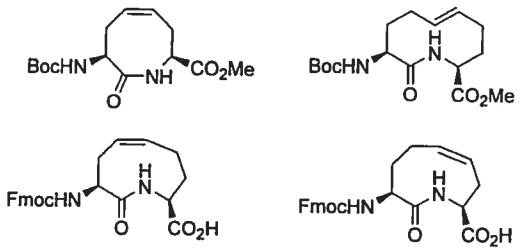
JO0477648

JOC Additions and Corrections

Vol. 70, 2005

Ramesh Kaul, Simon Surprenant, and William D. Lubell.* Systematic Study of the Synthesis of Macrocyclic Dipeptide β-Turn Mimics Possessing 8-, 9-, and 10-Membered Rings by Ring-Closing Metathesis.

Page 3838, Abstract and Table of Contents. The Abstract and Table of Contents graphic should be replaced with the revised graphic shown below:



Page 3838, Abstract, third sentence. The sentence should read as follows: "The 8-membered lactam possessing *cis*-amide and *cis*-olefin geometry as well as 9-membered lactams having *trans*-amide and *cis*-olefin configurations were effectively prepared by a general strategy employing the respective protected dipeptide, the first generation of Grubbs' catalyst, and temporary protection of the central amide as a benzyl derivative. The 10-membered macrocycle was synthesized possessing *cis*- or *trans*-olefin geometry by employing similar metathesis conditions in the presence or absence of temporary benzyl amide protection, respectively."

Page 3839. Figure 1 should be replaced with the revised Figure 1 shown.

Page 3839, column 1, third paragraph, second sentence. The sentence should read as follows: "Constrained dipeptide (*S,R*)-**5** (R = Ac, X = NHMe) was shown to adopt a conformation similar to that of an ideal type VIa β-turn, as demonstrated by NMR spectroscopy and X-ray analysis.[14]"

Page 3839, column 2, first paragraph. Line 6 reads "twist-boat-boat" and should read "boat-boat".

Page 3839, column 2, first paragraph, line 7. The sentence should read as follows: "The saturated analogue of 8-membered lactam (*S,R*)-**5** was also shown to adopt a *cis*-amide type VIb β-turn conformation by NMR, computational, and X-ray analyses.[16]"

Page 3839, column 2, second paragraph, second sentence. The sentence should read as follows: "These nine-membered macrocycles were shown to possess *cis*-olefin and *trans*-amide geometry by NMR analysis. The (*S,S*)-isomer of **6** (R^1 = Bn, R^2 = $COCH_2NHBoc$, X = OEt) was shown to adopt a type II′ β-turn by computational analysis and NMR spectroscopy."

Page 3839, column 2, fourth paragraph, first sentence. The sentence should read as follows: "With the precedent that 8-, 9-, and 10-membered macrocyclic peptide lactams adopted respectively type VI, II′, and I β-turns, respectively, we sought to develop a general means for constructing the set of heterocyclic dipeptides **5** and **7**–**9** (R = Boc or Fmoc, X = OH)."

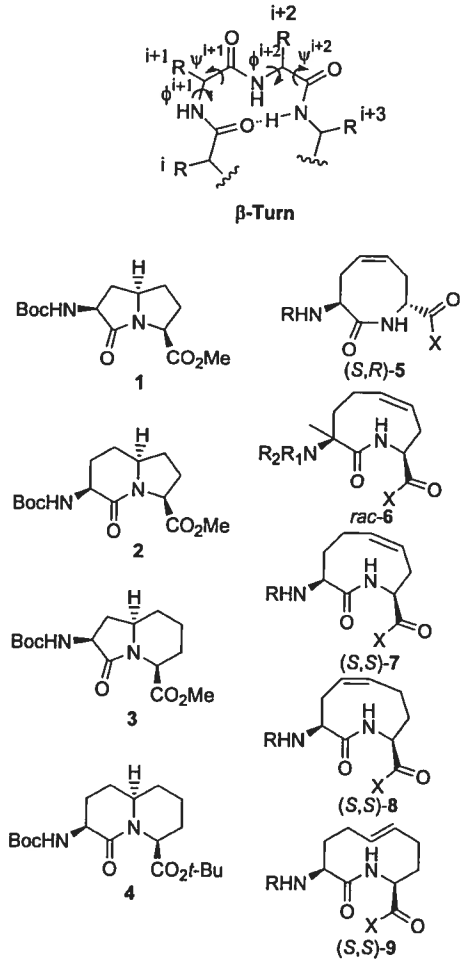


FIGURE 1. Representative β-turn structures as well as bicyclic and macrocyclic constrained dipeptide β-turn mimics.

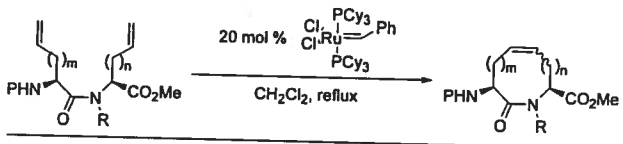
Page 3839. Reference 15a should be changed to ref 16b. Reference 18 should have the following reference added: (b) Dietrich, S. A.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97.

Page 3841, column 2, third paragraph, third sentence. The sentence should read as follows: "The 10-membered macrocycle (**27b**) was formed in 87% yield from tertiary amide **23b** employing the same conditions used to cyclize secondary amide **23a** at a concentration four and a half times higher; however, the olefin geometry was shown to be *cis* as discussed below."

Page 3842. Table 2 and Scheme 5 should be replaced as shown.

Page 3843, column 1, first sentence. The sentence should read as follows: "The vinyl protons of the olefin in 9-membered lactams **25c** and **31** were observed as quadruplets; however, decoupling experiments by irradiation of the allylic signals at 2.70 and 2.30 ppm for **25c** and at 2.69 ppm for **31** demonstrated that the vinylic coupling constant for both compounds was 10.5 Hz consistent with a *cis*-olefin. Similarly, the vinyl coupling constant of the olefin of 10-membered tertiary lactam

TABLE 2. Macrocycle Formation



amide	P	*m*	*n*	R	macrocycle	*E*/*Z*	yield (%)
20b	Boc	1	1	Dmb	**24a**	*Z*	78
21a	Boc	1	2	H	**25a**		0
21b	Boc	1	2	Dmb	**25b**	*Z*	80
21c	Fmoc	1	2	Dmb	**25c**	*Z*	75
22a	Boc	2	1	H	**26a**		0
22b	Boc	2	1	Dmb	**26b**	*Z*	81
22c	Fmoc	2	1	Dmb	**26c**	*Z*	71
23a	Boc	2	2	H	**27a**	*E*	77
23b	Boc	2	2	Dmb	**27b**	*Z*	87
23c	Boc	2	2	Hmb	**27c**	*Z*	86

27b was 11.0 Hz, indicative of a *cis* double bond. The X-ray structure of macrocycle **27a** which was prepared from linear precursor **23a** bearing a secondary amide had previously demonstrated the presence of a *trans*-olefin.[19]"

Page 3843, Conclusions, fifth sentence. The sentence should read as follows: "The 9-membered lactams **7** and **8** also possessed *cis*-olefin geometry. On the other hand, olefin geometry was contingent on the manner that 10-membered lactams **27b** and **27a** were synthesized; tertiary amide **23b** gave the *cis*-olefin and secondary amide **23a** provided *trans*-olefin."

Page 3844, column 1, sixth paragraph, line 8. Replace "6.09 (dd, 1H, J = 9.1, 18.0), 5.61 (dd, 1H, J = 9.1, 18.0)" with "6.09 (q, 1H, J = 9.3), 5.61 (q, 1H, J = 9.1)".

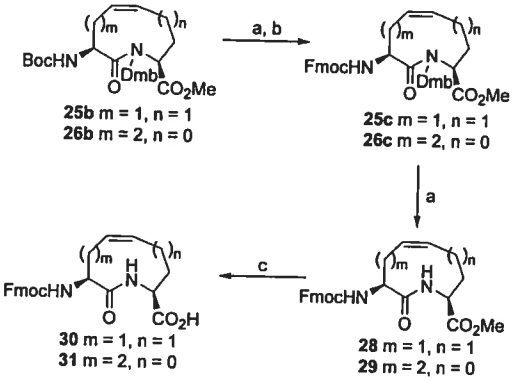
Page 3844, column 2, second paragraph, line 7. Replace "6.08 (dd, 1H, J = 8.8, 18.9), 5.65 (ddd, 1H, J = 6.04, 10.95, 10.84)" with "6.08 (q, 1H, J = 9.3), 5.65 (ddd, 1H, J = 6.0, 11.0, 10.8)".

Page 3844, column 2, fourth paragraph, line 6. Replace "6.04 (dd, 1H, J = 8.6, 18.5), 5.75 (bs, 1H), 5.56 (dd, 1H, J = 8.7, 18.5)" with "6.04 (q, 1H, J = 9.1), 5.75 (bs, 1H), 5.56 (m, 1H)".

Page 3844. The following sentence should be added to the Acknowledgment. "We acknowledge Professor Luca Banfi for advice concerning olefin stereochemistry."

Page 3844. The following text should be added to the Supporting Information paragraph: "decoupling experiments on compounds **25c** and **31**".

SCHEME 5. Synthesis of Macrocycle *N*-(Fmoc)-dipeptides 30 and 31



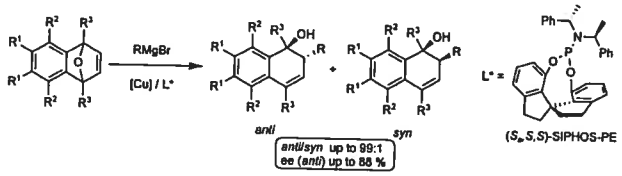
JO056027O

10.1021/jo056027o
Published on Web 05/11/2005

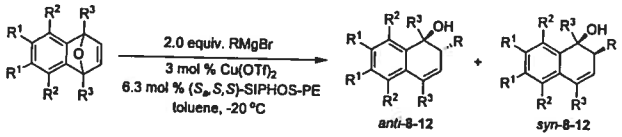
Wei Zhang, Li-Xin Wang, Wen-Jian Shi, and Qi-Lin Zhou*. Copper-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Grignard Reagents.

Pages 3734−3736. The structures of the *syn* products in the TOC, abstract, and Table 3 are incorrect. The correct structures of syn products are shown below.

Equation in TOC and abstract:



Equation in Table 3:



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JOC*Note*

9-(4-Bromophenyl)-9-fluorenyl as a Safety-Catch Nitrogen Protecting Group

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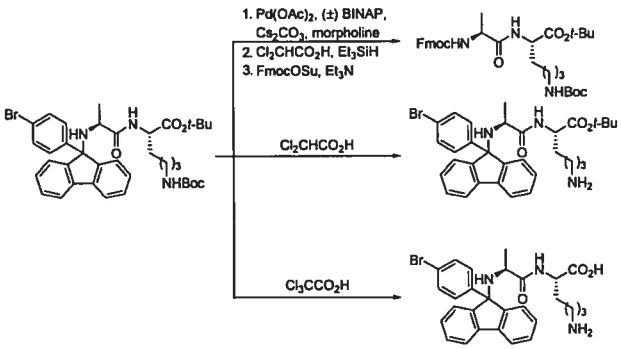
Received October 20, 2005



The 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group has been developed as a novel safety-catch amine protection. This relatively acid-stable protecting group can be successfully activated by palladium-catalyzed cross-coupling reaction of the aryl bromide with morpholine and then cleaved effectively under mild conditions using dichloroacetic acid and triethylsilane. Complementary conditions are reported for selective removal of the BrPhF group in the presence of *tert*-butyl esters and carbamates as well as deprotection of *tert*-butyl esters and carbamates in the presence of BrPhF amines.

Protecting groups have been essential for controlling the reactivity of amines in organic synthesis, peptide science, and medicinal chemistry.[1,2] In the context of our research on the synthesis of peptide mimics,[3] the 9-phenyl-9-fluorenyl (PhF) group has been used to prevent the loss of enantiomeric purity during the employment of various amino carbonyl compounds.[4] The PhF group offers several advantages as amine protection. The steric bulk created by the PhF group acts as a barrier that prevents deprotonation of α-amino carbonyl compounds at the α-carbon. The PhF group is significantly more stable under acid conditions relative to the trityl group because of the anti-aromatic character of the 9-phenyl-9-fluorenyl carbocation.[5] Furthermore, if deprotonation of the α-carbon occurs under severe conditions, the PhF anion can act as a leaving group and eliminate to furnish an imine intermediate prior to reprotonation and epimerization.[6] The PhF group is usually removed by hydrogenolysis[7] and by solvolysis with treatment under strongly acidic conditions.[8] Alternatively, the PhF group has been removed using sodium or lithium in liquid ammonia,[9] TMSOTf in the presence of triethylsilane,[10] and iodine in MeOH.[11]

Perceiving the advantages of having a chemical means for rendering the PhF group cleavable under mildly acidic conditions, we considered that *p*-aminophenylfluorenyl cations would be significantly more stable than the parent PhF cation. Strategies have been conceived for generating *p*-aminobenzylic intermediates from suitable para-substituted benzyl derivatives. For example, the *p*-nitrobenzyl ester has been used in the synthesis of carbapenems and removed by nitro group reduction and solvolysis.[12] More recently, *p*-halobenzyl ethers were reported to be as stable as normal benzyl ethers yet cleavable using a two-step process featuring catalytic amination of the aryl halide and solvolysis with acid.[13]

In our previous work, we used the 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group in a linking-protecting group strategy for the synthesis of enantiopure norephedrines on solid support.[14] The BrPhF group proved tolerant to similar chemistry previously developed with PhF-protected amino acids before it reacted in a palladium-catalyzed cross-coupling with bis(pinacolato)-diboron ester to give a suitable boronate for attaching the PhF-protected substrate to aryl halide resins. Pursuing the development of this protecting group, we demonstrate now that the BrPhF group can be employed as a safety-catch[15] amine protecting group which can be released by catalytic amination followed by treatment with mild acid.

The relative acid stability of the PhF group and an analogue bearing a *p*-aminophenyl substituent was studied by the synthesis of *N*-(9-(4-morpholinophenyl)-9-fluorenyl)alanine methyl ester **2** and comparison of its reactivity under acid conditions with *N*-(PhF)alanine methyl ester (Scheme 1, MPF = 9-(4-morpholinophenyl)-9-fluorenyl).

Both *N*-(PhF)- and *N*-(BrPhF)alanine methyl esters were synthesized as previously described.[14,16] Amination of BrPhF-Ala-OMe (**1**) with morpholine using 5 mol % of $Pd(OAc)_2$, (±)-BINAP, and excess Cs_2CO_3 provided *N*-(MPF)alanine methyl ester (**2**) in 81% yield. Competitive cleavage of *N*-(PhF)alanine

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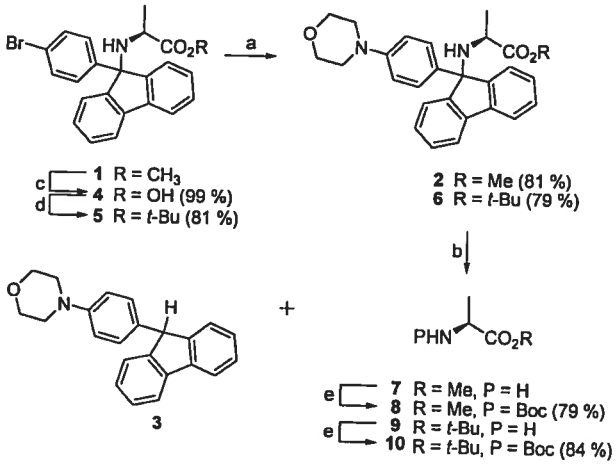
10.1021/jo0521910 CCC: $33.50
Published on Web 12/15/2005

SCHEME 1. Synthesis and Solvolysis of *N*-(MPF)alanine Esters[a]



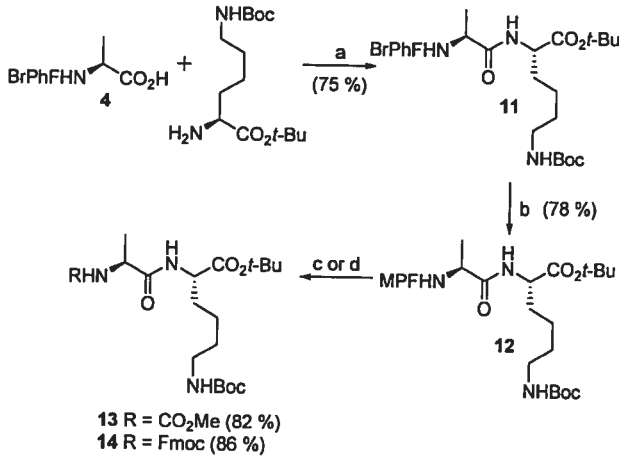
[a] Key: (a) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (b) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2; (c) LiOH, H_2O/dioxane; (d) *O-tert*-butyl trichloroacetamidate, CH_2Cl_2; (e) Boc_2O, Et_3N, CH_2Cl_2.

methyl ester and *N*-(MPF)alanine methyl ester (**2**) was performed by treating an equimolar mixture of the protected amino acids in CH_2Cl_2 with trichloroacetic acid and triethylsilane. Under these conditions, the 9-(4-morpholinophenyl)-9-fluorenyl group was cleaved within 5 min as monitored by HPLC, which detected 9-(4-morpholinophenyl)-9-fluorene (**3**). The PhF-protected methyl ester remained stable and no trace corresponding to PhFH was observed by HPLC. Employing the milder dichloroacetic acid under the same conditions, complete solvolysis of *N*-(MPF)alanine methyl ester (**2**) occurred within 30 min.

The selective removal of the BrPhF group from an amino *tert*-butyl ester was next studied to establish cleaving conditions tolerant to a more acid-labile group. *N*-(BrPhF)Alanine **4** was synthesized as previously described by hydrolysis of methyl ester **1** using LiOH.[14] *N*-(BrPhF)alanine *tert*-butyl ester (**5**) was then prepared in 81% yield by treating the amino acid with *O-tert*-butyl trichloroacetimidate[17] in dichloromethane followed by chromatography. The conversion of *N*-(BrPhF)alanine *tert*-butyl ester (**5**) to *N*-(MPF)alanine *tert*-butyl ester (**6**) was achieved in 79% yield using the palladium-catalyzed reaction conditions mentioned above. Exposure of a 1:1 mixture of *N*-(PhF)alanine *tert*-butyl ester[18] and *N*-(MPF)alanine *tert*-butyl ester (**6**) to dichloroacetic acid and triethylsilane in CH_2Cl_2 caused selective deprotection in 30 min as monitored by HPLC which indicated the appearance of morpholine **3** and no traces of 9-phenylfluorene nor any corresponding acids after 30 min. Treatment of *N*-(MPF)alanine *tert*-butyl ester (**6**) with 20 equiv of dichloroacetic acid and 2 equiv of triethylsilane in CH_2Cl_2 for 30 min followed by addition of 22 equiv of triethylamine and Boc_2O provided *N*-(Boc)alanine *tert*-butyl ester in 84% yield. Alternatively, alanine *tert*-butyl ester could be isolated as its hydrochloride salt in 89% yield after MPF deprotection, extraction with dilute aqueous HCl, and lyophilization.

To explore more deeply the strengths and limitations of this protection group *N*-(BrPhF)alaninyl(ω-Boc)lysine *tert*-butyl ester (**11**) was synthesized by coupling acid **4** with (ω-Boc)-lysine *tert*-butyl ester using DCC and HOBt in 75% yield (Scheme 2).

SCHEME 2. Synthesis and Solvolysis of *N*-(MPF)-Protected Dipeptides[a]



[a] Key: (a) DCC, HOBt, DIEA, CH_2Cl_2; (b) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (c) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, $ClCO_2Me$; (d) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, FmocOSu.

Conversion to the *N*-(MPF) dipeptide **12** was effected as previously described in 78% yield. The MPF-protected amine was selectively deblocked using $CHCl_2CO_2H$ and Et_3SiH and the free amine was subsequently converted in situ to a methyl carbamate using methylchloroformate and Et_3N in 82% yield. The ^1H NMR spectrum of the crude mixture showed a one-to-three ratio of singlets corresponding to the methyl and *tert*-butyl protons for the carbamates indicating that no deprotection of the Boc-protected amine had occurred. The LC−MS analysis of the crude mixture also confirmed that Boc-deprotection did not occur during the sequence. Using a similar protocol, *N*-(Fmoc)alaninyl(ω-Boc)lysine *tert*-butyl ester (**14**) was synthesized by deprotecting the MPF-amine and reprotecting using FmocOSu and Et_3N in 86% yield.

Selective removal of *tert*-butyl esters in the presence of PhF amines has been recently reported to be effectively accomplished using $ZnBr_2$ in CH_2Cl_2.[18] When BrPhF-Ala-O*t*Bu (**5**) was submitted to these conditions, *N*-(BrPhF)alanine was obtained in 82% yield (Scheme 3). The acid stability of the BrPhF group was demonstrated by the selective removal of the Boc group using Cl_2CHCO_2H which afforded dipeptide **15** in 72% yield, as well as by removal of both the *tert*-butyl ester and carbamate groups using the stronger acid Cl_3CCO_2H to give dipeptide **16** in 73% yield. These results demonstrated that the orthogonal nature of the BrPhF/*tert*-Bu combination of protecting groups can be utilized in both directions.

In sum, we have demonstrated the utility of the 9-(4-bromophenyl)-9-fluorenyl group as safety-catch amine protection. Similar to the PhF group, the BrPhF group may be used to ensure the configurational stability of amino carbonyl compounds. This relatively acid stable group can then be rendered susceptible to mild acid solvolysis by palladium-catalyzed amination. The potential of this strategy has been illustrated by the palladium-mediated selective cleavage of the BrPhF-amine in the presence of the acid labile *tert*-butyl ester and carbamate groups and complementary removal of either Boc

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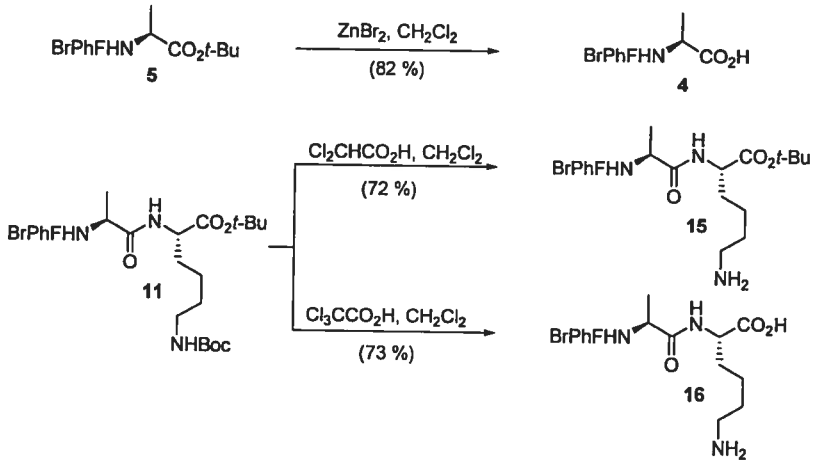
SCHEME 3. Selective *tert*-Butyl Ester and Carbamate Cleavage



group or both Boc and *tert*-butyl ester groups in the presence of the BrPhF-amine. Considering the need for selective methods for removing acid labile protecting groups, the BrPhF group should find general utility in the synthesis of amines.

Experimental Section

(2*S*)-*N*-(BrPhF)alanine *tert*-Butyl Ester (5). To a stirred suspension of (2*S*)-*N*-(BrPhF)alanine (540 mg, 1.32 mmol, prepared according to ref 14) in CH_2Cl_2 (4 mL) was added *O*-*tert*-butyl trichloroacetimidate (578 mg, 2.64 mmol). The mixture was stirred for 1 day, filtered, evaporated, and resubmitted to the same conditions as above for 2 days. Filtration and evaporation, followed by chromatography (5% EtOAc in hexanes) gave ester **5** (495 mg, 81%) as a clear oil: $[\alpha]^{20}_D$ −51.3 (*c* 1.5, CH_3OH); ^1H NMR δ 7.72 (d, J = 7.8 Hz, 2H) 7.40−7.26 (m, 10H), 3.09 (s, 1H), 2.69 (q, J = 7.1 Hz, 1H), 1.23 (s, 9H), 1.13 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 175.4, 148.9, 148.6, 143.7, 140.3, 139.7, 130.9, 127.99, 127.96, 127.7, 127.6, 127.5, 125.4, 124.8, 120.7, 119.7, 119.5, 80.1, 72.3, 51.6, 27.5, 21.8; HRMS calcd for $C_{26}H_{27}BrNO_2$ $[M + H]^+$ 464,1227, found 464.1219.

General Procedure for *N*-(MPF)amine Synthesis. The BrPhF-protected amine (2.5 mmol) was dissolved in 5 mL of dry and degassed toluene and treated with $Pd(OAc)_2$ (28 mg, 0.13 mmol), BINAP (79 mg, 0.13 mmol), and dry Cs_2CO_3 (4.07 g, 12.5 mmol), followed by morpholine (257 μL, 3.0 mmol). The mixture was heated at reflux and stirred for 24 h, filtered on Celite, washed with CH_2Cl_2, and the combined filtrate and washings were evaporated. The residue was chromatographed to afford the MPF-protected amine.

(2*S*)-*N*-(MPF)alanine Methyl Ester (2). Chromatography of the product from **1** (1.00 g, 2.4 mmol) using 20% EtOAc in hexanes as eluant gave **2** (820 mg, 81% yield) as a yellowish solid: mp 62−64 °C; $[\alpha]^{20}_D$ −121.1 (*c* 2.2, CH_3OH); ^1H NMR δ 7.68 (dd, J = 7.5 Hz, 2.5 Hz, 2H), 7.33 (m, 5H), 7.23 (m, 3H), 6.77 (d, J = 8.9 Hz, 2H), 3.82 (t, J = 4.8 Hz, 4H), 3.30 (s, 3H), 3.10 (t, J = 4.8 Hz, 4H), 2.77 (q, J = 7.0 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.1, 150.1, 149.4, 148.8, 140.6, 139.9, 135.6, 128.0, 127.6, 127.2, 126.9, 125.8, 124.8, 119.8, 119.7, 115.1, 72.4, 66.7, 51.4, 51.2, 49.0, 21.4; HRMS calcd for $C_{27}H_{28}N_2O_3Na$ $[M + Na]^+$ 451.1989, found 451.1992.

General Procedure for MPF-Solvolysis. The MPF-protected amine (0.4 mmol) was dissolved in 4 mL of CH_2Cl_2, treated with dichloroacetic acid (660 μL, 8 mmol) and triethylsilane (128 μL, 0.8 mmol), stirred at rt for 30 min, and evaporated on a rotary evaporator. The residue was dissolved in 10 mL of Et_2O and treated with 10 mL of 0.5 M HCl solution. The aqueous phase was separated, washed twice with 5 mL of Et_2O, and lyophilized to give the unprotected amine as a hydrochloride salt. Alternatively, after complete solvolysis of MPF-amine was observed by TLC, the reaction mixture was treated with 22 equiv of Et_3N followed by 200 mol % of either Boc_2O, methyl chloroformate or FmocOSu, stirred overnight, diluted with CH_2Cl_2, washed with H_2O, 0.5 N HCl, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography[20] to give, respectively, the Boc-, methyl carbamoyl- or Fmoc-protected amino ester.

(2*S*)-Alanine *tert*-Butyl Ester Hydrochloride (9). Lyophilization of aqueous layer after solvolysis of **6** (190 mg, 0.4 mmol) gave **9** (65 mg, 89% yield) as a white solid: mp 170 °C dec (lit.[19] mp 168 °C dec); $[\alpha]^{20}_D$ 6.1 (*c* = 1.0, EtOH) [lit.[19] $[\alpha]^{20}_D$ 3.0 (*c* = 2.0, EtOH)]; HRMS calcd for $C_7H_{15}NO_2Na$ $[M + Na]^+$ 168.0995, found 168.0987.

***N*-(Fmoc)alaninyl-ω-(Boc)lysine *tert*-Butyl Ester (14).** Chromatography of the product from **12** (30 mg, 0.11 mmol) using 30% EtOAc/hexanes as eluant gave **14** as a white powder (22.0 mg, 86% yield): mp 67−69 °C; $[\alpha]^{20}_D$ −16.5 (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.76 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.31 (tt, J = 7.5, 1.2 Hz, 2H), 6.59 (d, J = 6.7 Hz, 1H), 5.59 (s, 1H), 4.69 (s, 1H), 4.45 (m, 1H), 4.38 (d, J = 7.0 Hz, 2H), 4.29 (m, 1H), 4.22 (t, J = 7.0 Hz, 1H), 3.06 (d, J = 5.5 Hz, 1H), 1.84 (m, 2H), 1.65 (m, 1H), 1.52−1.27 (m, 6H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR δ 171.8, 171.0, 156.0, 155.8, 143.6, 141.1, 127.6, 126.9, 125.0, 119.8, 82.1, 79.0, 67.0, 52.4, 50.3, 47.0, 39.9, 33.5, 29.2, 28.3, 27.8, 21.9, 18.6; HRMS calcd for $C_{33}H_{45}N_3O_7$ $[M + Na]^+$ 618.31389, found 618.31389.

4-[4-(9*H*-Fluoren-9-yl)phenyl]morpholine (3). The *N*-arylamine **3** was isolated by flash chromatography as the second eluting compound of the crude residue in the solvolysis of the MPF-protected amine **5**: ^1H NMR δ 7.82 (d, J = 7.5 Hz, 2H), 7.42−7.26 (m, 6H), 7.03 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 5.02 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H); ^{13}C NMR δ 149.7, 147.9, 140.5, 128.7, 126.9, 126.8, 124.9, 119.4, 115.5, 66.6, 53.3, 49.0; MS (ESI, *m/z*) 328.3 $(MH)^+$.

(2*S*)-*N*-(BrPhF)alanine (4). A stirred solution of *N*-(BrPhF)-alanine *tert*-butyl ester (**6**) (45 mg, 0.1 mmol) in 0.5 mL of dichloromethane was treated with $ZnBr_2$ (110 mg, 0.5 mmol) at rt,

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stirred for 24 h, treated with water (2 mL), stirred for 2 h, and treated with CH_2Cl_2 (5 mL). The organic phase was separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 mL). The organic portions were combined, dried, filtered, and evaporated. The residue was chromatographed (50% EtOAc:hexanes containing 1% AcOH) to afford 32.5 mg (82% yield) of *N*-(BrPhF)alanine as a white solid: mp 116−118 °C; $[\alpha]^{20}_D$ −16.5 (*c* 1.1, CH_3OH). The spectroscopic data were identical to those reported.[14]

***N*-(BrPhF)alaninyl-ω-(Boc)lysine *tert*-Butyl Ester (11).** *N*-(BrPhF)alanine (**4**), (514 mg, 1.26 mmol), DCC (311 mg, 1.51 mmol), and HOBt (204 mg, 1.51 mmol) were dissolved in 13 mL of CH_2Cl_2, treated with ω-(Boc)lysine *tert*-butyl ester (380 mg, 1.26 mmol), stirred for 24 h, filtered, washed with a 10% HCl solution, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography (50% EtOAc/hexanes) to afford 651 mg (75% yield) of **11** as a white powder: mp 83−85 °C; $[\alpha]^{20}_D$ −20.8 (*c* 1.0, CH_3OH); ^1H NMR δ 7.96 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.44−7.25 (m, 9H), 7.05 (t, J = 7.5 Hz, 1H), 4.68 (m, 1H), 4.27 (q, J = 7.2 Hz, 1H), 3.10 (m, 2H), 2.47 (q, J = 7.1 Hz, 1H), 2.25−1.80 (bs, 1H), 1.75 (m, 1H), 1.62 (m, 1H), 1.54 (s, 9H), 1.43 (s, 9H), 1.54−1.43 (m, 2H), 1.29 (m, 2H), 1.09 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 175.1, 171.8, 156.1, 148.9, 147.3, 143.5, 141.4 140.0, 131.6, 128.9, 128.8, 128.2, 128.1, 127.7, 126.1, 124.3, 121.4, 120.4, 120.2, 82.2, 79.1, 73.0, 52.8, 51.9, 40.4, 33.0, 29.5, 28.5, 28.1, 22.2, 21.8; HRMS calcd for $C_{37}H_{46}BrN_3O_5Na$ [M + Na]$^+$ 714.25131, found 714.25002.

***N*-(BrPhF)alaninyllysine *tert*-Butyl Ester (15).** *N*-(BrPhF)-alaninyl(ω-Boc)lysine *tert*-butyl ester **11** (50 mg, 0.072 mmol) was dissolved in 150 μL of CH_2Cl_2, treated with 150 μL of Cl_2CHCO_2H, and stirred for 21 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, concentrated, and purified by chromatography (5% MeOH/$CHCl_3$ + 1% Et_3N) to give amine **15** (30.7 mg, 72% yield) as a brownish oil: $[\alpha]^{20}_D$ 39.7 (*c* 2.6, $CHCl_3$); ^1H NMR (CD_3OD) δ7.80 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.46−7.26 (m, 9H), 7.08 (dt, J = 1.0, 7.6 Hz, 1H), 4.06 (m, 1H), 2.90 (m, 2H), 2.44 (q, J = 7.1 Hz, 1H), 1.73 (m, 1H), 1.64 (m, 3H), 1.53 (s, 9H), 1.29 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 178.6, 172.5, 150.5, 149.3, 145.3, 142.4, 141.6, 132.3, 129.9, 129.7, 129.3, 128.4, 127.2, 125.8, 122.0, 121.1, 83.5, 74.2, 53.8, 53.3, 40.5, 33.1, 28.3, 28.0, 23.5, 21.5; HRMS calcd for $C_{32}H_{39}BrN_3O_3Na$ [M + H]$^+$ 592.21693, found 592.21666.

***N*-(BrPhF)alaninyllysine (16).** The BrPhF-protected dipeptide **11** (40 mg, 0.058 mmol) was dissolved in 300 μL of CH_2Cl_2, treated with Cl_3CCO_2H (236 mg, 1.44 mmol), and stirred for 72 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with 0.1 N HCl (2 × 3 mL), lyophilized, triturated with Et_2O, and purified on reversed-phase preparative HPLC to afford **16** (22.6 mg, 73% yield) as a white gum: $[\alpha]^{20}_D$ −3.1 (*c* 1.1, CH_3OH); ^1H NMR (D_2O) δ 7.78 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.32 (m, 3H) 7.21 (d, J = 8.5 Hz, 2H), 7.12 (m, 2H), 6.98 (d, J = 8.6 Hz, 2H), 3.47 (t, J = 6.6 Hz, 1H), 3.12 (q, J = 6.6 Hz, 1H), 2.87 (m, 2H), 1.51 (m, 2H), 1.33 (m, 2H), 1.19 (d, J = 7.1 Hz, 3H), 1.01 (m, 2H);^{13}C NMR (D_2O) δ 175.5, 170.1, 140.8, 140.3, 140.1, 131.6, 130.8, 130.6, 129.0, 127.9, 126.9, 126.8, 124.9, 122.0, 120.9, 120.4, 73.3, 53.2, 52.7, 38.6, 29.5, 26.0, 21.6, 16.9; HRMS calcd for $C_{28}H_{31}BrN_3O_3$ [M + H]$^+$ 536.15433, found 536.15304.

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Supporting Information Available: General Experimental Section, ^1H and ^{13}C NMR data for compounds **6**, **8**, **10**, **12**, and **13**, copies of ^1H and ^{13}C NMR spectra of compounds **2**, **3**, **5**, **6**, and **11**−**16**, and HPLC traces of competitive cleavage experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Université de Montréal

Faculté des Études Supérieures

Ce mémoire intitulé :

Synthèse de mimes peptidiques macrocycliques par métathèse d'oléfine et de mimes peptidiques bicycliques par cyclisation électrophilique transannulaire

Présenté par :

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a été évalué par un jury composé des personnes suivantes :

Président Rapporteur : Professeur Stephen Hanessian

Membre du Jury : Professeur Andreea R. Schmitzer

Directeur de recherche : Professeur William D. Lubell

Accepté le :

En mémoire d'Arthur, une profonde source d'inspiration.

RÉSUMÉ

Des stratégies de synthèse de mimes peptidiques de tour β ont été développées dans le but d'obtenir des dipeptides macrocycliques et bicycliques. Les dipeptides macrocycliques ont été synthétisés à partir de dipeptide comportant des chaînes latérales oléfiniques qui ont servies dans une réaction de fermeture de cycle par métathèse. Ainsi, des dipeptides macrocycliques de 8, 9, et 10 membres ont pu être obtenus.

Ces derniers mimes macrocyclciques ont par la suite servi de précurseurs pour obtenir de mimes dipeptidiques bicycliques. En effet ces macrocycliques ont pu être traités dans une réaction de cyclisation transannulaire électrophilique. L'iode ainsi que le bromure de phénylselenium ont pu être utilisés comme source d'électrophile pour donner des acides aminés bicycliques de type [6.5.0] et [7.5.0].

Aussi, un nouveau groupement protecteur d'amines de type «safety-catch» a été développé. Le groupement 9-(4-bromophényl)-9-fluorényl possède les mêmes caractéristiques que son cousin, le 9-phényl-fluorényl, et en plus de pouvoir être clivé en conditions douces avec une séquence impliquant un couplage d'amine catalysé par le palladium et une hydrolyse en condition faiblement acidique.

Finalment des résultats préliminaires concernant l'application de la synthèse de mimes peptidiques macrocycliques et bicycliques sur support solide sont rapportés. Ces résultats pourront former la base d'un futur projet permettant de d'introduire des mimes peptidiques directement lors de la synthèse d'un peptide sur support solide sans avoir à synthètiser au préalable en solution le mime à être inséré.

MOTS CLÉS

Mimes de tours ß macrocycliques, fermeture de cycle par métathèse d'oléfine, mimes de tours ß bicycliques, cyclisation électrophilique transannulaire, iodolactamisation, synthèse peptidique sur support solide, résine de Wang, balyage conformationnel de peptides, groupes protecteurs, 9-(4-bromophényl)-9-fluorényl, orthogonalité.

ABSTRACT

Strategies for the synthesis of β turn peptide mimetics have been developed to obtain macrocyclic and bicyclic dipeptides. The macrocyclic dipeptides were synthesized from dipeptides bearing olefinic side chains which were used in a ring-closing metathesis. This strategy has led to the synthesis of macrocyclic dipeptides of 8-, 9-, and 10-membered rings.

Those macrocyclic mimetics where also used as precursors for the synthesis of bicyclic dipeptides. Effectively, these macrocycles were treated in an electrophilic transannular cyclization. Iodine and phenylselenium bromide were used as electrophiles to yield the [6.5.0]- and [7.5.0]-bicyclic amino acids.

Also, a new amine safety-catch protecting group was developed. The protecting group, the 9-(4-bromophenyl)-9-fluorényl, possesses the same characteristics as its close cousin, the 9-phenyl-9-fluorenyl group, and can be cleaved under mild conditions after a two-steps process involving a palladium-catalyzed cross-coupling of an amine followed by a mild acid hydrolysis.

Finally, preliminary results were disclosed for the future synthesis of macrocyclic and bicyclic peptidomimetics on solid phase. These results can be the basis of a future project allowing the synthesis of peptidomimetics directly on the growing peptide chain in a synthesis on solid support without having to synthesize the peptidomimetics in solution prior to inserting it in the peptide.

KEY WORDS

Macrocyclic ß-turn mimics, olefin ring closing metathesis, bicyclic ß-turn mimics, electrophilic transannular cyclization, iodolactamization, solid support peptide synthesis, Wang resin, conformational peptide scan, protecting groups, 9-(4-bromophenyl)-9-fluorenyl, orthogonality.

TABLE DES MATIÈRES

LISTE DES FIGURES

CHAPITRE 1

CHAPITRE 2

CHAPITRE 3

CHAPITRE 5

LISTE DES SCHÉMAS

CHAPITRE 1

CHAPITRE 2

CHAPITRE 3

CHAPITRE 4

CHAPITRE 5

LISTE DES TABLEAUX

CHAPITRE 2

LISTE DES ABRÉVIATIONS ET SYMBOLES

[α]	: Rotation spécifique [en (deg mL) / (g dm)]
Å	: Ångström
aa	: Acide aminé
Ac	: Acétyl
Agly	: Allylglycine
alloc	: Allyloxycarbonyle
Anal. Cald.	: Analyse élémentaire
Ar	: Aryle
Arg	: Arginie
Asp	: Asparagine
atm	: Atmosphère
Bn	: Benzyl
Boc	: *tert*-Butyloxycarbonyl
bp	: *Boiling point* (point d'ébullition)
br	: *Broad* (large)
Bz	: Benzoyl
c	: Concentration
°C	: Degré Celcius
calcd	: *Calculated* (calculé)
COSY	: *Correlated spectroscopy*
Cys	: Cystéine
δ	: Déplacement chimique en partie par million
d	: Doublet
dd	: Doublet de doublet
DBU	: 1,8-Diazabicyclo[4.5.0]undec-7-ène
DCC	: *N,N'*-dicyclohexylcarbodiimide
DIEA	: *N,N*-diisopropyléthylamine

DMAP	: 4-Diméthylaminopyridine
Dmb	: 2,4-diméthoxybenzyl
DMF	: *N,N*-diméthylformamide
DMSO	: Diméthylsulfoxyde
DVB	: Divinylbenzène
ee	: Excès énantiomérique
Et	: Éthyl
EtOH	: Éthanol
Fm	: 9-fluorénylmethyl
Fmoc	: 9-Fluorénylmethylcarbamate
FTIR	: Infrarouge à transformé de Fourier
g	: Gramme
Gln	: Glutamine
Gly	: Glycine
h	: Heure
HAgly	: Homoallylglycine
HATU	:*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	: *O*-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Hmb	: 2-hydroxy-4-méthoxybenzyl
HMBC	: *Heteronuclear multiple bond correlation*
HMPA	: Acide 4-hydroxymethylbenzoïque
HMQC	: *Heteronuclear multiple quantum coherence*
Hnb	: 2-hydroxy-6-nitrobenzyl
HOBt	: Hydroxybenzotriazole
HPLC	: *High performance liquid chromatography* (chromatographie liquide à haute performance)
HRMS	: *High resolution mass spectrometry* (spectrométrie de masse haute resolution)

Hz	: Hertz
IC_{50}	: 50% *Inhibitory concentration* (concentration inhibitrice à 50%)
Ile	: Isoleucine
IR	: Infra-rouge
J	: Constante de couplage (hertz)
LCMS	: *Liquid chromatography mass spectrometry* (chromatographie liquide spectrométrie de masse)
Leu	: Leucine
LDA	: Lithium diisopropylamide (diisopropylamidure de lithium)
LRMS	: *Low resolution mass spectrometry* (spectrométrie de masse basse resolution)
μ	: Micro (10^{-6})
m	: Multiplet
M	: Mole par litre
Me	: Méthyl
MeOH	: Méthanol
mg	: Milligramme
MHz	: Mégahertz
min	: Minute
mL	: Millilitre
mmol	: Millimole
Mol	: Mole
mol %	: Pourcentage par mole
mp	: *Melting point* (point de fusion)
MS	: *Mass spectrometry* (spectrométrie de masse)
NBS	: *N*-bromosuccinimide
NEM	: *N*-éthylmorpholine
NMR	: *Nuclear magnetic resonance* (resonance magnétique nucléaire)
NOE	: *Nuclear Overhauser effect* (effet nucléaire Overhauser)

NOESY	: *Nuclear Overhause enhancementt spectroscopy*
pf	: Point de fusion
PEGA	: Polyéthylène glycol diméthyl acrylamide
Ph	: Phényl
Phe	: Phénylalanine
PhF	: 9-Phényl-9-fluorényl
Pip	: Pipéridine
ppm	: Partie par million
Pro	: Proline
q	: Quadruplet
RCM	: *Ring Closing Metathesis* (métathèse par fermeture de cycle)
R_f	: *Rentention factor* (facteur de retention)
RMN	: Résonance magnétique nucléaire
rt	: *Room temperature* (temperature pièce)
R_t	: *Retention time* (temps de rétention)
s	: Singulet
SS	: Support solide
SPPS	: Synthèse de peptide sur phase solide
t	: Triplet
TIPS	: Triisopropylsilane
TBTU	: *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate
TFA	: Acide trifluoroacétique
THF	: Tétrahydrofurane
TLC	: *Thin layer chromatography* (chromatographie sur couche mince)
TMS	: Triméthylsilyl
tp	: Température de la pièce
Tyr	: Tyrosine
UV	: Ultraviolet
Z	: Benzyloxycarbonyl

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CHAPITRE 1

Introduction

1.1 Peptidomimétisme

Les peptides endogènes sont reconnus pour être des molécules très importantes pour la communication intercellulaire dans plusieurs systèmes biologiques.[1] Parmi les peptides les plus connus, on retrouve bien sûr l'insuline (un peptide de 51 aa) qui, entre autres, stimule la consommation de glucose et la synthèse de glycogène, l'oxytocine (un peptide de 9 aa, Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2) qui induit les contractions utérines lors de l'accouchement et la vasopressine (un peptide de 9 aa, Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2) qui sert de diurétique. Toutefois, les peptides endogènes souffrent de plusieurs limitations, ce qui a restreint leur utilisation en tant que médicaments[2] : ils sont rapidement métabolisés lors de la protéolyse dans le tractus gastro-intestinal, dans le sang et dans différents tissus; ils sont difficilement transportés du tractus gastro-intestinal vers le sang et du sang vers le cerveau; ils sont rapidement excrétés par le foie et les reins.

Au cours des trente dernières années, beaucoup de recherche a été effectuée dans le but d'améliorer la biodisponibilité des peptides afin d'obtenir des composés qui pourraient devenir des médicaments. Ceci a amené le concept de peptidomimétisme[3] où un composé possède une structure différente d'un peptide endogène, mais possède toujours la possibilité d'interagir avec un récepteur spécifique. Le design d'un mime peptidique dans le but d'en obtenir un composé biologiquement actif se doit de prendre compte de deux facteurs structurels:[4] l'ajustement optimal de la conformation du mime avec le site actif et

l'emplacement d'éléments structuraux (groupes fonctionnels, régions polaires et hydrophobes) à des positions définies afin que des interactions se produisent. De plus, le mime peptidique devrait contenir des éléments qui pourraient contribuer à ralentir le métabolisme du composé.

Le design d'un mime peptidique peut donc se faire en modifiant quatre domaines différents d'un peptide. Tout d'abord, les chaînes latérales des peptides peuvent être modifiées. Le remplacement d'acides aminés naturels par des acides aminés synthétiques peut permettre d'améliorer la vitesse à laquelle le peptide est métabolisé dans le corps et peut aussi donner une meilleure activité biologique. Une autre pratique courante consiste à modifier les chaînes latérales des peptides en remplaçant les acides aminés de configuration L formant le peptide par des acides aminés de configuration D afin de modifier la stéréochimie du squelette peptidique. Une deuxième possibilité implique la modification du squelette du peptide par des groupements isostériques (Figure 1). Chaque acide aminé constituant le peptide peut être divisé en trois portions pouvant être subtituées par des groupements isostériques : la portion NH, la portion CH et la portion CO. La portion NH peut être remplacée par un atome d'oxygène ce qui a pour effet de transformer une fonction amide en ester pour former un depsi peptide. La portion NH peut aussi être remplacée par un atome de souffre pour former un thioester ou par une unité cétométhylène. Quant à la portion CH, elle peut être remplacée par un atome d'azote pour former un azapeptide. On peut aussi utiliser des acides aminés comportant deux chaînes latérales ou remplacer le groupe CH par BH pour former un borapeptide. Le groupement carbonyle peut être substitué par un

thiocarbonyl, un sulfoxide, une sulfone, un acide phosphorique ou un acide

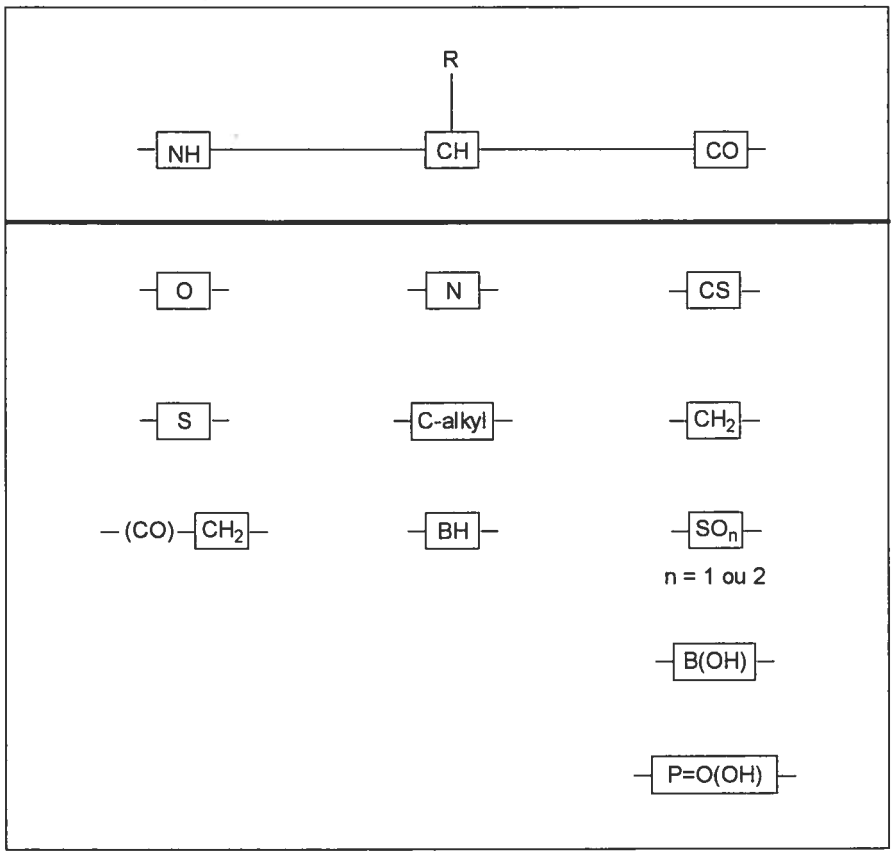


Figure 1. Modifications fréquentes du squelette peptidique.[4]

boronique. Il peut aussi être réduit en méthylène pour donner plus de stabilité métabolique.

En plus de faire des modifications sur les portions NH, CH et CO d'un peptide, des extensions de la chaîne peptidique comme l'utilisation d'acides aminés de type β ont été employée pour faire des mimes peptidiques. Aussi la fonction amide a été modifié de plusieurs manières comme dans le cas d'un peptide retro-inverso où la position d'un carbonyle est inversée avec celle de l'azote.

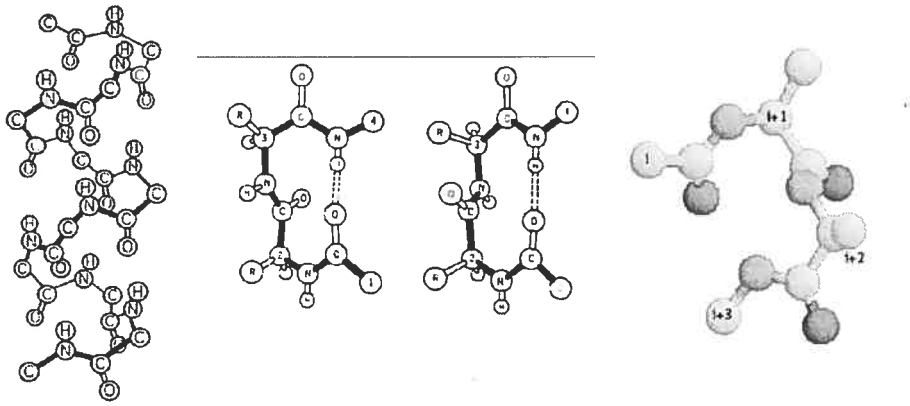
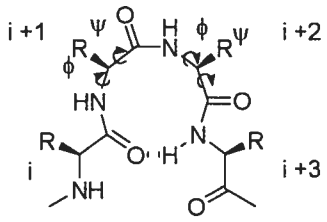


Figure 2. Représentation d'une hélice α, de tours β de type I et de type II ainsi que d'un tour γ de type I.

Bien entendu, la modification du squelette peptidique peut aider à combattre la dégradation du mime peptidique contre le métabolisme physiologique, mais un mime dont le squelette a été modifiée en utilisant les fonctions citées précédemment ne génère pas nécessairement la conformation nécessaire pour qu'il y ait un bon contact entre le mime peptidique et le récepteur. C'est pourquoi beaucoup d'efforts ont été consacrés à la synthèse de mimes comportant des éléments induisant des conformations étant reconnues comme étant importantes pour la reconnaissance entre un peptide et son récepteur, par exemple, les hélices α, les tours β et les tours γ (Figure 2). Dans le cas spécifique des tours β, les différents types de tour sont caractérisés par les angles dièdres ϕ et ψ du second (i + 1) et troisième (i + 2) acide aminé formant le tour (Figure 3). Une méthode qui a couramment utilisée pour induire des conformations est la formation de pont entre différentes parties du peptide. Plus spécifiquement dans le cas des tours β, des modèles de lactames dipeptidiques et les dipeptides



Type de tour β	Angle dihèdre ϕ (i + 1)	Angle dihèdre ψ (i + 1)	Angle dihèdre ϕ (i + 1)	Angle dihèdre ψ (i + 1)	Abondance (%)
I	-60	-30	-90	0	34
I'	60	30	90	0	4
II	-60	120	80	0	13
II'	60	120	-80	0	4
IV	-60	10	-50	20	35
VIa	-60	120	-90	0	<1
VIb	-120	120	-60	0	1
VIII	-60	-30	-120	120	9

Figure 3. Angles de torsion caractéristiques d'un tour β

bicycliques ont été utilisés pour mimer les différents types de cette structure secondaire.

1.2 Les lactames dipeptidiques

Depuis presque trois décennies, les lactames dipeptidiques ont été utilisées afin de contraindre les conformations des peptides. Bien entendu, le modèle le plus connu est celui développé par Freidinger, mieux connu sous le nom de lactames de Friedinger (Figure 4).[5] Ces lactames dipeptidiques, une fois insérées dans des peptides, permettent de mimer des tours β de type II'. Par exemple, la lactame **1** a été utilisée lors de la synthèse d'un mime peptidique de la « luteinizing hormone–releasing hormone » (LH–RH), une hormone importante pour la fertilité chez les mammifères.[6] Certaines observations semblaient montrer

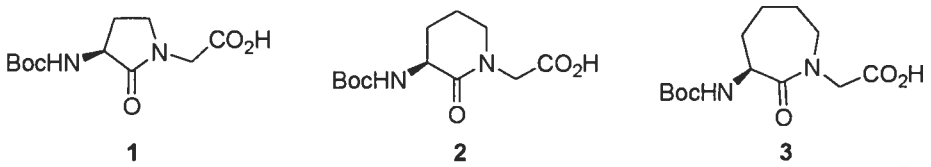


Figure 4. Représentations des différentes lactames de Freidinger sous formes protégées.

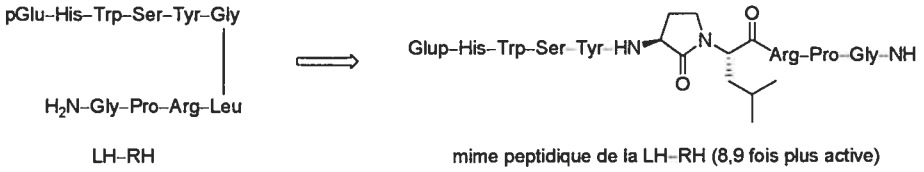


Figure 5. Transformation de la LH–RH en mime peptidique en insérant une γ-lactame de Freidinger.

que les acides aminés tyrosine, glycine, leucine et arginine en position 5,6,7 et 8 formaient un tour β de type II' lorsque l'hormone se liait à son récepteur (Figure 5). En effet le remplacement de la glycine en position six par la D-alanine augmentait l'activité thérapeutique tandis qu'un remplacement par la L-alanine diminuait l'activité thérapeutique. De plus le remplacement de la leucine par la *N*-(methyl)leucine a permis de conserver la même activité thérapeutique que le peptide parent suggérant la présence d'un tour de type β. Lorsque la glycine à la position six et la leucine en position 7 ont été remplacées par une γ-lactame, il a été possible de confirmer que la LH–RH adopte un tour β de type II' lorsqu'elle se lie à son récepteur puisque ce mime peptidique a permis d'augmenter l'activité thérapeutique du peptide de 8,9 fois par rapport au peptide original en culture cellulaire.

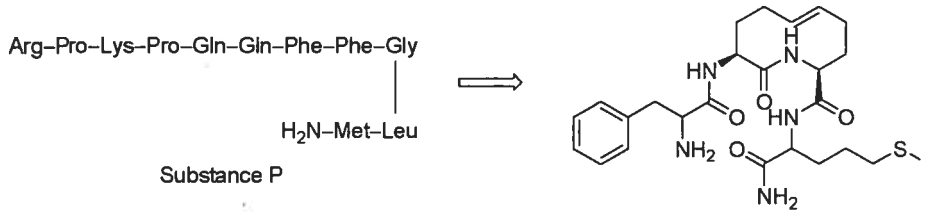


Figure 6. Substance P représentant un tour β proposé ainsi qu'un mime de la substance P incorporant une lactame dipeptidique de 10 membres.

Plus récemment, des lactames dipeptidiques macrocycliques ont été synthétisées aussi dans le but de mimer des tours β (Figure 6). En 1998, un dipeptide macrocyclique insaturé de 10 membres a été synthétisé afin de produire un mime de subtance P (Arg–Pro–Lys–Pro–Gln–Gln–Phe–Phe–Gly–Leu-Met–NH_2), un undecapeptide qui est impliqué dans la transmission de la douleur, dans les constrictions brachiales et dans la vasodilatation.[7] Des études cristallographiques ainsi que des études par RMN ont permis de démontrer que le dipeptide permettait de mimer le tour β de type I. Toutefois, lorsque ce modèle fut inséré pour remplacer la glycine en position 9 et la leucine en position 10, aucune activité thérapeutique n'a été observée, ce qui pourrait indiquer que la substance P n'adopte pas de tour β de type I à cette position lorsqu'elle se lie à son récepteur.

Plus dernièrement, des dipeptides macrocycliques de 8 membres ont été utilisés dans l'élaboration de mimes peptidiques (Figure 7). Deux différents groupes ont entrepris de synthétiser les composés **4-8** qui pourraient mimer le modèle Cys–Cys oxidé retrouvé entre autres dans le domaine extracellulaire *N*-

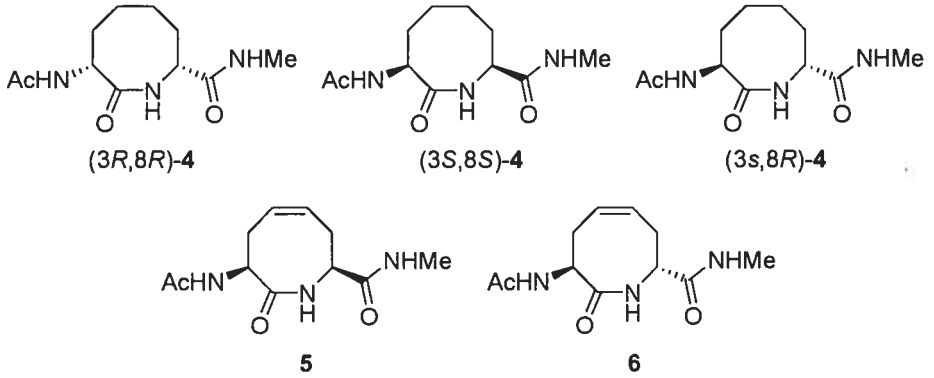


Figure 7. Structures des différentes lactames dipeptidiques de 8 membres synthétisées.

terminal de la plupart des récepteurs acétylcholine nicotinique.[8] Des études computationnelles préliminaires avaient relevé des différences importantes reliées à la stéréochimie des deux composés.[9] En effet des calculs de mécanique moléculaire effectués dans les différents champs de force MM3 et AMBER ont montré le composé (3*R*,8*R*)-**4** dans une conformation étendue. Toutefois, les champs de force MM2, MM3 et AMBER ont tous montré une distance inférieure à 7Å entre les carbones α en position 1 et 4 du composé (3*S*,8*R*)-**4**, ce qui semblait montrer la présence d'un tour β. Lorsque synthétisé, les analyses cristallographiques ont montré une dimérisation du composé (3*R*,8*R*)-**4** où deux conformations étendues ont pu être observées.[10] Son énantiomère, le composé (3*S*,8*S*)-**4**, a aussi montré une conformation étendue qui mimait avec beaucoup de précision le dipeptide Cys–Cys oxydé.[11] Une fois synthétisé, le dipeptide (3*R*,8*S*)-**4** a aussi montré l'exactitude des calculs effectués.[9,11] En effet, la structure obtenue par diffractions de rayons X ainsi que les différentes expériences RMN ont montré que le composé (3*S*,8*R*)-**4** adoptait une conformation typique d'un tour β de type VIb. L'introduction d'une insaturation à l'intérieur de la lactame peut aussi apporter quelques changements. Bien que le composé insaturé

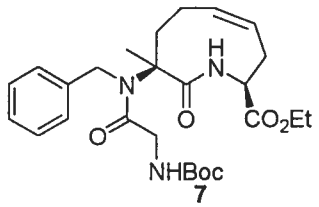


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Figure 8. Représentation d'une lactame dipeptidique de 9 membres.

5 adopte toujours une conformation étendue, le composé **6** est quelque peu différent du composé (3*S*,8*R*)-**4** et mime un tour β de type VIa plutôt qu'un tour β de type VIb.

Quelques travaux ont aussi été effectués sur des lactames macrocycliques de 9 membres (Figure 8).[12] La synthèse du composé **7** a permis d'entreprendre des études RMN qui ont montré que le dipeptide adoptait une conformation qui mimait un tour β de type II'.

En plus de pouvoir servir comme mimes de tour β, les peptides comprenant des cycles de plus grande taille ont montré leur utilité comme mimes de brins β.[13] En effet, la condensation de deux chaînes latérales pour former des chaînons de 14 à 18 membres semblerait empêcher la formation intramoléculaire de pont hydrogène. Ainsi cette cyclisation permet de garder le mime peptidique dans sa forme étendue pour se fixer au récepteur de diverses protéases. En utilisant cette stratégie, plusieurs puissants inhibiteurs de la protéase du VIH ont pu être synthétisés.[14]

1.3 Les dipeptides bicycliques

Autres l'utilisation de lactames dipeptidiques, l'incorporation d'un peptide à l'intérieur d'une structure bicyclique a permis de restreindre la rotation des liens qui forment les angles dièdres φ et ψ. Il y a plus de vingt ans, le dipeptide **8**, connu sous l'acronyme BTD (Bicyclic Turned Dipeptide), a été indroduit comme mime de tour β de type II' (Figure 9).[13] Ce dipeptide a été introduit dans plusieurs peptides[14] dans le but de forcer ces derniers à adopter un tour de type β. Par exemple, la séquence Arg–Gly–Asp (RGD) est contenue dans plusieurs peptides comme la fibronectine, la vitronectine, l'osteopontine, les collagènes, la thrombospondine et la fibrinogène. L'introduction du BTD dans un decapeptide cyclique contenant cette séquence RGD a permis de mettre au point un mime peptidique se liant sélectivement au récepteur $\alpha_v\beta_3$.[15]

Le succès de l'incorporation du BTD dans les peptides a mené vers de nouveaux types d'acides aminés azabicylciques dépourvus d'hétéroatomes dans le squelette régidifiant le dipeptide. Ces acides aminés azabicyliques sont reconnus pour être plus stables face au métabolisme du corps humain que le BTD. La synthèse d'acides aminés azabicycliques a d'ailleurs fait l'objet de plusieurs revues[16] et constitue un sujet de pointe de chimie organique. De plus en plus

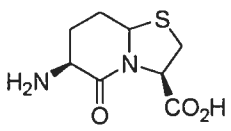

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Figure 9. Structure du « Bicyclic Turned Dipeptide » (BTD).

d'efforts sont maintenant consacrés à l'obtention des acides aminés azabicycliques portant des chaînes latérales qui permettraient de mimer avec plus de précision la chaîne latérale des acides aminés endogènes. Ces mimes peptidiques ont fait leur preuve en améliorant l'activité thérapeutique de certains peptides lorsqu'ils ont été insérés dans divers peptides.

Par exemple, une librairie de pseudopentapeptides cycliques contenant les acides aminés Arg-Gly-Asp (RGD) et différents azabicycles a été synthétisée dans le but d'obtenir des inhibiteurs du récepteur $\alpha_v\beta_3$.[17] Le récepteur $\alpha_v\beta_3$ est connu pour être exprimé à la surface d'une variété de cellules et pour être impliqué dans plusieurs processus pathologiques comme l'angiogenèse, l'ostéoporose et la métastase tumorale. Ainsi les dipeptides azabicycliques **9-16** ont été synthétisés[18] et utilisés dans une synthèse peptidique sur support solide pour obtenir les pseudopentapeptides qui ont été examinés lors de tests in vitro pour leurs habilités à se lier au récepteur $\alpha_v\beta_3$ purifié par rapport à la ^{125}I-echistatine (Figure 10). Ainsi, l'incorporation des dipeptides **12** et **16** a permis d'obtenir des inhibiteurs donnant une valeur d'IC_{50} de 14.3 et 3.7 nM respectivement.

Plus nouvellement, une petite chimiothèque de tripeptides a été mise au point dans le but d'obtenir des mimes du second activateur de la caspase dérivé de la mitochondrie (*s*econd *m*itochondria-drived *a*ctivator of *c*aspas, Smac).[19] Cette protéine est associée à l'apoptose dans les cellules. Certains petits peptides mimant son activité ont montré une hausse de l'activité anti-cancéreuse de certaines drogues sans montrer de toxicité chez les cellules normales. Les trois

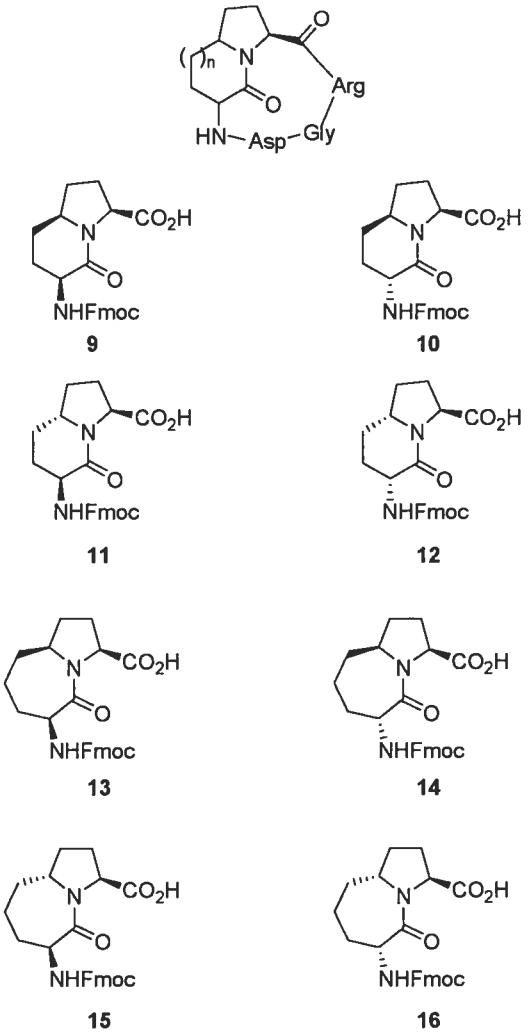


Figure 10. Incorporation de différents dipeptides azabicycliques dans la synthèse d'inhibiteurs du récepteur $\alpha_v\beta_3$.

différents azabicycles **17-19** ont été examinés comme peptide mimant la protéine Smac. Le bicycle 7-5 **19** a été identifié comme ligand avec un K_i de 150 μM avec le XIAP BIR3 (XIAP = X-linked inhibitors of apoptosis protein, BIR3 = third baculovirus inhibitors of apoptosis reapeat) (Figure 11). L'optimisation du composé **19** a mené vers le tripeptide **20** et finalement au peptide **21** avec un K_i

de 0.025 μM. De plus, la stéréospécificité du composé **21** a pu être confirmé par le K_i de 16.9 μM obtenu lorsque le composé **22** a été soumis au dosage.

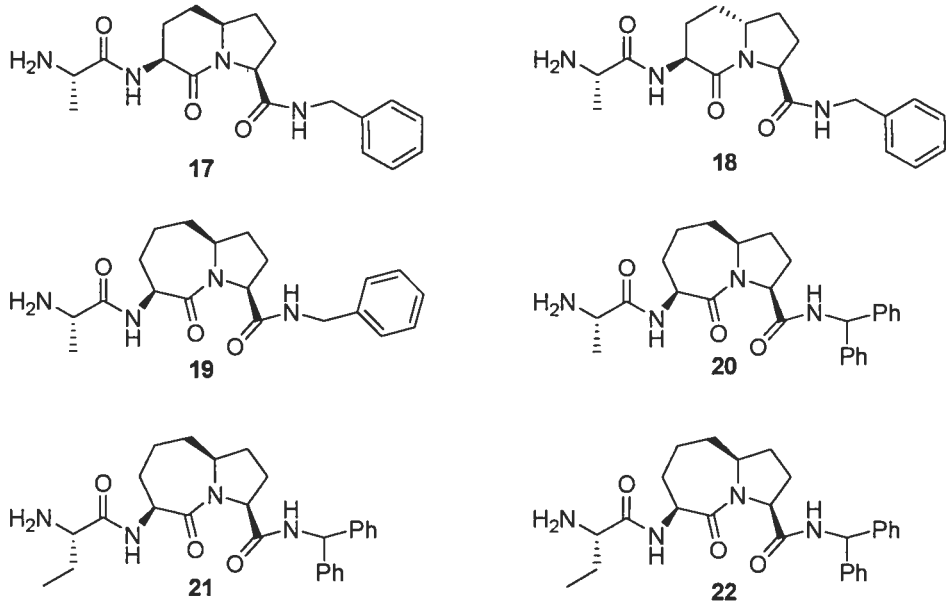


Figure 11. Tripeptides synthétisés comme mimes du Smac.

1.4 Notre approche

Les deux sections précédentes ont fait mention de l'importance et de l'utilité de l'emploi des dipeptides macrocycliques et bicycliques en peptidomimétisme. Une méthode rapide et efficace permettant la synthèse de ces deux types de mimes peptidiques serait donc d'une grande utilité. Nous avons donc pensé à développer une stratégie qui permettrait d'obtenir rapidement et efficacement soit un lactame dipeptidique, soit un dipeptide azabicyclique. Notre stratégie implique donc le couplage de deux acides aminés comportant des chaînes latérales avec des oléfines terminales (Schéma 1). Ces deux oléfines

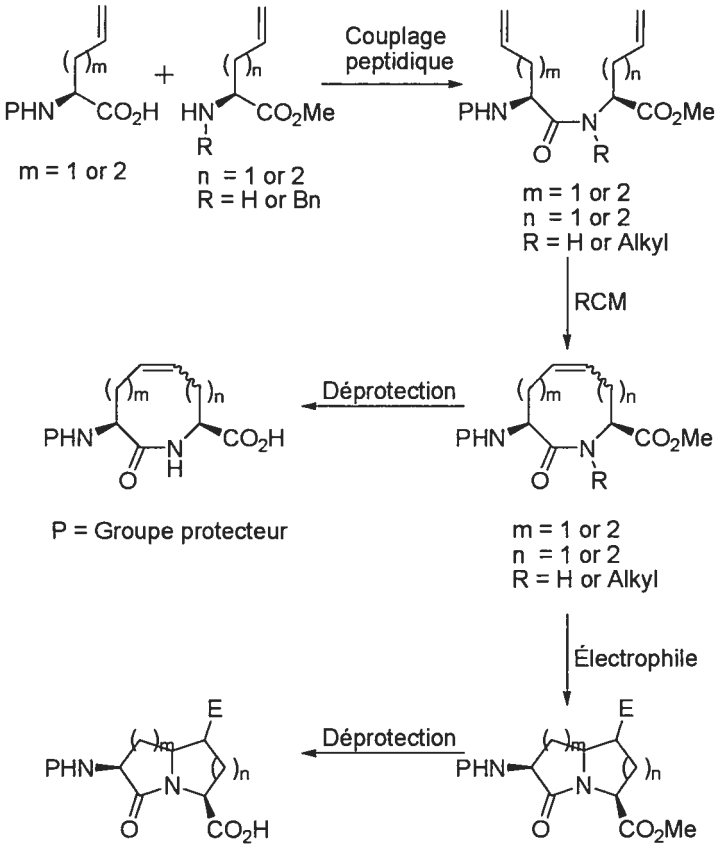


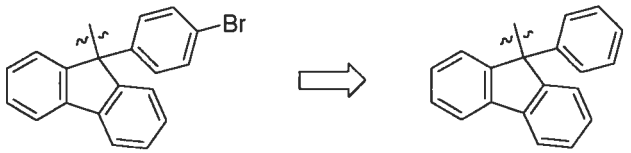
Schéma 1. Stratégie générale de synthèse de mimes dipeptidiques macrocycliques et bicycliques.

pourront par la suite réagir dans une réaction de fermeture de cycle par métathèse d'oléfines (RCM)[20] pour former une lactame de 8, 9 ou 10 membres tout dépendant de la longueur des deux chaînes latérales des acides aminés utilisés lors du couplage. Le mime peptidique obtenu pourrait par la suite être transformé en mime bicyclique via une réaction de cyclisation transannulaire qui serait induite par la présence d'un électrophile. Ce dernier aurait pour rôle d'activer la liaision double du macrocycle obtenu. De plus, l'utilisation d'électrophile comme l'iode, les dérivés du sélénium ainsi que du mercure permettrait par la suite de fonctionnaliser l'acide aminé azabicyclique obtenu afin de mieux mimer les chaînes latérales des peptides.

Cette stratégie s'illustre par sa simplicité. En effet, autre que l'étape du couplage peptidique requis lors de toute synthèse de peptide, une seule réaction de RCM nous sépare du mime macrocyclique tandis qu'une réaction de RCM et une cyclisation transannulaire nous sépare du mime bicyclique. Il est donc réaliste de penser que cette stratégie de synthèse pourrait être adaptée à une synthèse sur support solide qui est généralement utilisée pour la synthèse de peptides. Le passage de la synthèse en solution vers la synthèse sur support solide permettrait entre autres de faire un balayage complet d'un peptide en remplaçant chaque duo d'acides aminés possible par soit un mime dipeptidique macrocyclique ou par un mime dipeptidique azabicyclique afin d'obtenir plus d'informations sur la conformation qu'adopte le peptide lors qu'il se lie à son récepteur.

1.5 Les groupes protecteurs

Bien entendu, toute synthèse multi-étapes effectuée doit tenir compte de la réactivité de tous les groupements fonctionnels présents sur la molécule à être transformée. Afin d'éviter certaines réactions secondaires, les groupements protecteurs ont été utilisés afin de transformer certaines fonctions réactives en fonctions moins réactives, donc moins susceptibles de réagir. L'utilisation d'un groupe protecteur, même si elle nécessite généralement l'ajout de deux étapes (soit la protection et la déprotection), est donc essentielle lors de la synthèse de dipeptides macrocycliques et bicycliques comportant plusieurs groupements fonctionnels possédant divers degrés de réactivité.



Groupement 9-(4-bromophényl)-9-fluorényl — Groupement 9-phényl-9-fluorényl

Figure 12. Élaboration du groupement 9-(4-bromophényl)-9-fluorényl comme groupement protecteur « safety-catch ».

Tout au long du développement de notre approche sur la synthèse de mimes peptidiques macrocycliques et bicycliques, un nouveau type de groupe protecteur a été mis au point. Cette dernière stratégie de protection a été inspirée par le groupement 9-phényl-9-fluorényl, largement utilisé pour la protection d'amines (figure 12). Ce groupement à, entre autres, la propriété d'être stable en condition modérément acides, mais surtout de protéger la configuration stéréochimique du centre α d'un acide aminé.[21] Le groupement 9-(4-bromophényl)-9-fluorényl a donc été mis au point comme groupement protecteur « safety-catch » pouvant être clivé dans des conditions acides plus douces lors d'un couplage croisé d'une amine catalysé par le palladium, suivi d'une solvolyse. Les groupements protecteurs « safety-catch » sont des groupements reconnus pour être stables par rapport à une panoplie de conditions réactionnelles, mais facilement clivables lorsqu'on décide de les activer. Un bon exemple de groupement protecteur « safety-catch » est l'utilisation d'une phénylsulfonamide pour prévenir toute réaction sur un groupement carbonyle (Schéma 2).[22] Le groupement *N*-acyl sulfonamide est stable sous des conditions acides et basiques permettant de modifier le reste de la molécule sans avoir à ce soucier du groupement acyle. Lorsque désiré, le groupement sulfonamide peut être clivé en

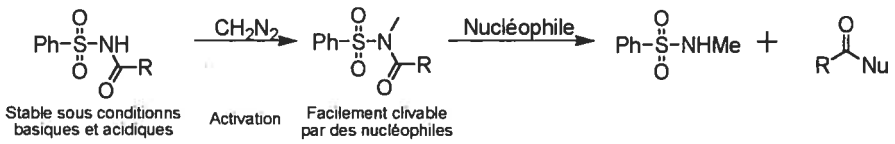


Schéma 2. Utilisation du groupement phénylsulfonamide comme groupement protecteur « safety-catch ».

l'activant avec le diazométhane et en le déplaçant avec un nucléophile comme une amine ou un ion hydroxyde.

En conclusion, le present mémoire élaborera sur des nouvelles méthodes de synthèse de mimes peptidiques, plus spécialement dans le cadre de synthèse de dipeptides macrocycliques et dipeptides bicycliques. Le point fort de cette méthodologie est la conversion directe d'un mime macrocyclique en mime bicyclique. De plus, la conception d'un nouveau groupe protecteur de type «safety-catch» pouvant être clivé dans des conditions douces, lorsque désiré.

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CHAPITRE 2

Article 1 :

Kaul, R., Surprenant, S.; Lubell, W. D. Systematic Study of the Synthesis of Macrocyclic Dipeptide ß-Turn Mimics Possessing 8-, 9-, and 10-Membered Rings by Ring-Closing Metathesis *J. Org. Chem.* **2005** *70*, 3838.

Addition/Correction : Kaul, R., Surprenant, S.; Lubell, W. D. Systematic Study of the Synthesis of Macrocyclic Dipeptide ß-Turn Mimics Possessing 8-, 9-, and 10-Membered Rings by Ring-Closing Metathesis *J. Org. Chem.* **2005** *70*, 4901.

2.1 Note

Ce chapitre provient de la fusion entre un article publié dans le *Journal of Organic Chemistry* ainsi que les corrections et additions qui ont été publiées dans le même journal. L'article présenté s'avère donc à être une version modifiée de l'article original.

2.2 Abstract

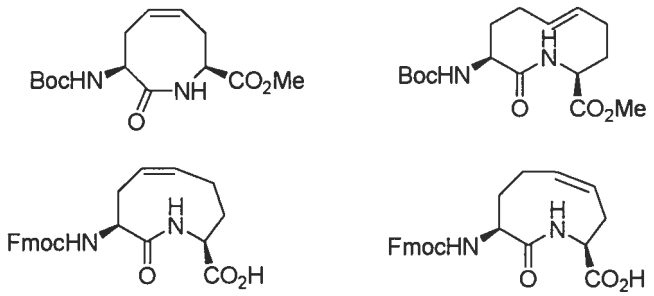


Figure 13 Graphical Abstract

A systematic study was performed to establish general synthesis protocols for forming enantiomerically pure macrocyclic dipeptide lactams. Focusing on macrocycles of 8-, 9-, and 10-membered rings, effective syntheses were achieved by a sequence featuring peptide coupling of allyl- and homoallyl-glycine building blocks followed by ring-closing metathesis. The 8-membered lactam possessing *cis*-amide and *cis*-olefin geometry as well as 9-membered lactams having *trans*-amide and *cis*-olefin configurations were effectively prepared by a general strategy employing the

respective protected dipeptide, the first generation of Grubbs' catalyst, and temporary protection of the central amide as a benzyl derivative. The 10-membered macrocycle was synthesized possessing *cis*- or *trans*-olefin geometry by employing similar metathesis conditions in the presence or absence of temporary benzyl amide protection, respectively.

2.3 Introduction

ß-Turns in peptides and proteins are of interest because of their structure and biological activity.[1] Polar in nature, these secondary structures generally occupy the surfaces of protein molecules, where they are involved in recognition and binding.[2] ß-turns have also been shown to be important for receptor affinity in biologically active peptides, such as somatostatin,[3] MSH,[4] bradykinin,[5] and LHRH.[6] Mimics of ß-turns are thus desirable tools for studying the structure-activity relationships responsible for protein and peptide biology.[7]

Strategies to design ß-turn mimics have often constrained the peptide backbone dihedral angles. For example, fused bicyclic systems, such as azabicyclo[X,Y,0]alkanone amino acids **23-26**, of varying ring sizes have been used as rigid dipeptide surrogates[7] that structurally constrain three contiguous dihedral angles, φ, ψ, and ω, of a ß-turn segment within the body of the heterocycle (Figure 14). Conformational analysis of bicyclic lactams **23-26** has demonstrated their propensity to

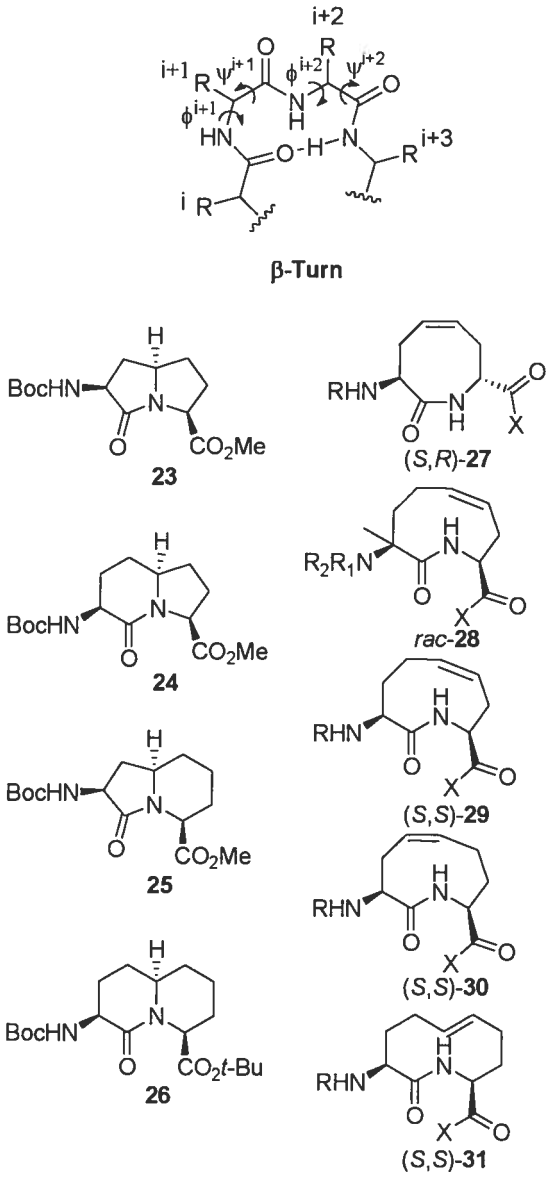


Figure 14 Representative ß-turn structures as well as bicyclic and macrocyclic constrained dipeptide ß-turn mimics.

favor type II and II' ß-turns[8,9] contingent on their stereochemistry, as evident from X-ray diffractometry, IR, and NMR spectroscopy as well as theoretical calculations.[10] Because differences in the type II turn dihedral angle have been observed after variation of the ring sizes in these bicyclic mimics, application of sets of related azabicycloalkane amino acids has thus proven effective for studying the effect of turn geometry on the biological activity of native peptides.[11,12]

Alternative scaffolds are needed to cover a wider range of turn geometries in order to better mimic natural diversity and to enhance success in peptide mimicry. Macrocyclic dipeptide lactams of 8-, 9-, and 10-members have been less well investigated relative to their bicyclic cousins, in part due to the difficulties inherent in synthesizing such medium-sized ring systems.[13]

The syntheses of eight-membered macrocycles, such as **27**, have been accomplished by ring-closing metathesis. Constrained dipeptide (*S,R*)-**27** (R = Ac, X = NHMe) was shown to adopt a conformation similar to that of an ideal type VIa ß-turn, as demonstrated by NMR spectroscopy and X-ray analysis.[14] Although the type VI -turn did not possess proline, the eight-membered macrocycle forced the amide between the i + 1 and i + 2 residues to adopt the cis-isomer geometry, as illustrated by X-ray structural analysis, which also revealed a cis-olefin in a folded boat-boat conformation.[14] The saturated analogue of 8-membered lactam (*S,R*)-**27** was also shown to adopt a *cis*-amide type VIb ß-turn conformation by NMR, computational, and X-ray analyses.[14] Their cis-amide geometry and their propensity to favor type VI

ß-turns makes eight-membered lactams (**27**) structurally comparable to other type VI ß-turn mimics, such as 5-tert-butylproline-containing peptides.[17]

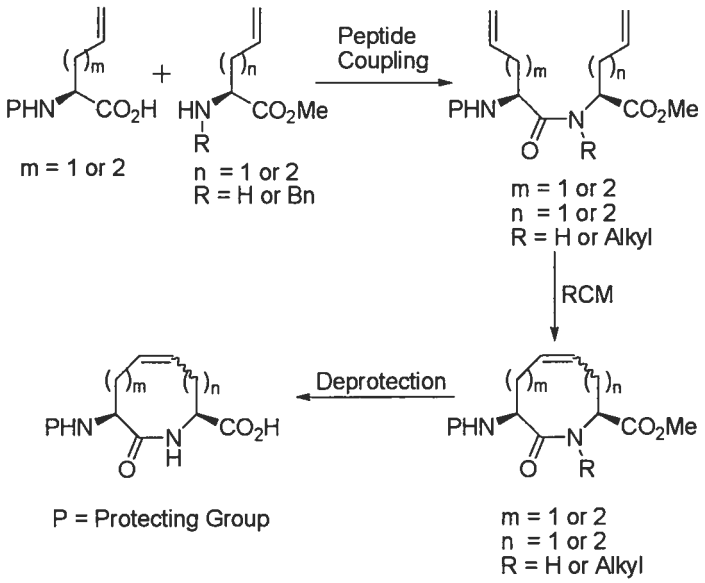
Among the few syntheses of nine-membered macrocyle dipeptide lactams, an Ugi-multicomponent reaction followed by ring-closing metathesis has been used to prepare unsaturated nine-membered lactam **28** (R1 = CH3CO, R2 = PhCH2, X = OEt), albeit as a racemic isomeric mixture.[18] These nine-membered macrocycles were shown to possess *cis*-olefin and *trans*-amide geometry by NMR analysis. The (*S*,*S*)-isomer of **28** (R^1 = Bn, R^2 = $COCH_2NHBoc$, X = OEt) was shown to adopt a type II' ß-turn by computational analysis and NMR spectroscopy.

The 10-membered macrocycle dipeptide lactam (**31**, R = Boc, X = OMe) has also been synthesized by ring-closing metathesis and shown to possess a trans-olefin geometry and φ, ψ, and ω torsional angles similar to that of an ideal type I ß-turn, as demonstrated by X-ray and NMR analyses.[19]

With the precedent that 8-, 9-, and 10-membered macrocyclic peptide lactams adopted respectively type VI, II', and I ß-turns, respectively, we sought to develop a general means for constructing the set of heterocyclic dipeptides **27** and **29-31** (R = Boc or Fmoc, X = OH). We envisioned that this set will serve in studies of biologically active peptides as well as intermediates for trans-annular cyclizations to prepare azabicyclo[X,Y,0]alkanone amino acids related to **23-26**.

Medium-sized macrocyclic lactams of 8-, 9-, and 10- members have been traditionally harder to form than their smaller and larger-sized counterparts;[13] however, ring-closing metathesis has significantly advanced their synthesis. For example, *N*-alkyl lactams of 6-10 members have been prepared by RCM.[20] Transient *N*-alkylation of the central amide with a 2,4-dimethoxy benzyl group (Dmb) was also shown to be essential to favor a *cis*-amide geometry and facilitate metathesis in the synthesis of eight-membered lactams (**5**).[14,15] Moreover, RCM has been used effectively to make larger ring systems that have constrained peptide conformations.[21]

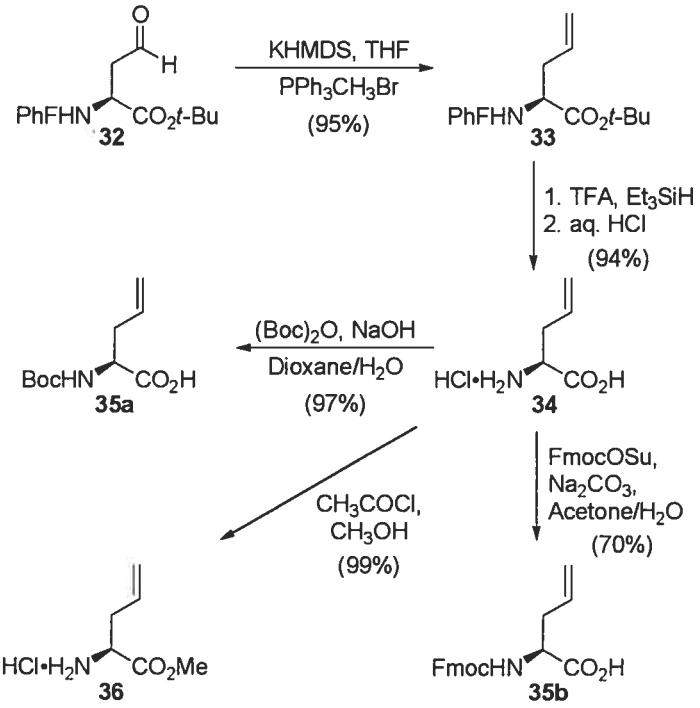
Considering these results and the need for material on a suitable scale and in a protected form for peptide synthesis, we undertook a detailed study to prepare macrocyclic dipeptide lactams of 8-10 members by a general strategy featuring RCM (Scheme 3).



Scheme 3. General Scheme for the Synthesis of Macrocyclic Dipeptides

2.4 Results and Discussion

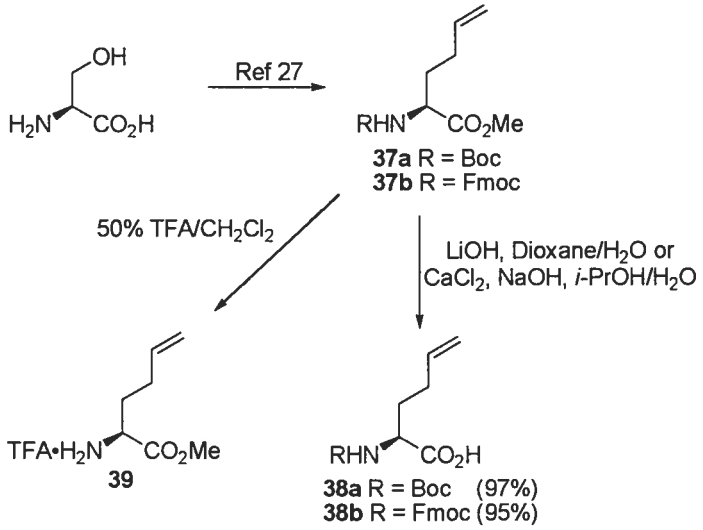
2.4.1 Dipeptide Precursor Synthesis. The construction of 8-, 9-, and 10-membered ring sizes necessitated the synthesis and coupling of allylglycine and homoallylglycine units prior to RCM. Allylglycine had been synthesized by a variety of methods;[22] however, our expertise with α-*tert*-butyl *N*-(PhF)aspartate β-aldehyde (**32**, PhF = 9-phenylfluren-9-yl)[23] served as motivation to employ this chiral educt in the synthesis of allylglycine (Scheme 4). Aldehyde **32** was synthesized on a 7-g scale from aspartic acid[23b,24] in five steps and 47% overall yield. *N*-(PhF)Allylglycine *tert*-butyl ester **33** was obtained in 95% yield from the Wittig reaction of aldehyde **32** and the ylide generated from treatment of methyltriphenylphosphonium bromide with



Scheme 4 Synthesis of Allylglycine Components **35** and **36**

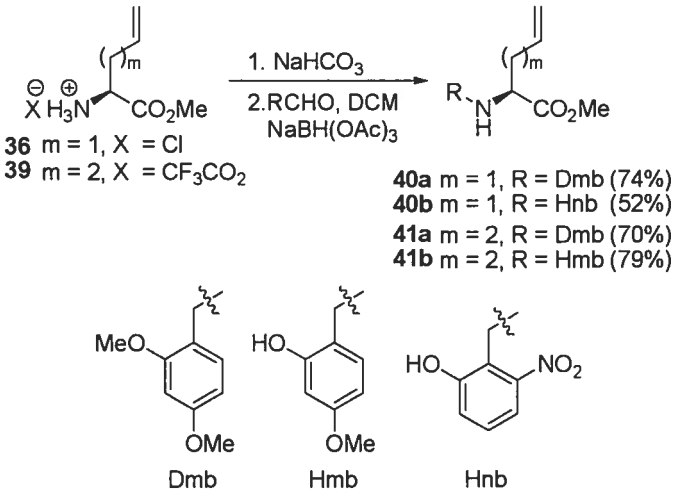
KHMDS in THF.[25] Allylglycine hydrochloride **34** was quantitatively prepared from the treatment of **33** with TFA, which cleaved both the *tert*-butyl ester and PhF groups, followed by conversion of the trifluoroacetate salt to the hydrochloride using aq HCl and lyophilization. *N*-(Boc)- and *N*-(Fmoc)allylglycines **35a** and **35b** were then prepared by the protection of **34** with $(Boc)_2O$[26a] and FmocOSu,[26b] respectively, under basic conditions. Allylglycine methyl ester hydrochloride **36** was quantitatively obtained by the treatment of **34** with methanol and thionyl chloride. The higher *N*-(Boc)- and N-(Fmoc)-protected homologues (homoallylglycines **38a** and **38b**) were synthesized respectively in five steps from serine using reported procedures (Scheme

5).[27] Briefly, serine was converted to its methyl ester hydrochloride, which was protected using Boc_2O or FmocOSu and transformed to *N*-(Boc)- or *N*-(Fmoc)iodoalanine methyl ester using iodine, PPh_3, and imidazole.[28] The iodide was then converted to a zincate and coupled to allyl chloride using CuBr·DMS. *N*-(Boc)amino ester **37a** was hydrolyzed with LiOH and deprotected with 50% TFA in CH_2Cl_2 to provide *N*-(Boc)homoallylglycine **38a** and homoallylglycine methyl ester trifluoroacetate **39**, respectively, as components for peptide coupling. *N*-(Fmoc)Homoallylglycine **38b** was obtained by hydrolysis of *N*-(Fmoc)amino ester **37b** using 0.8 M calcium chloride and 0.5 M sodium hydroxide in *i*PrOH/H_2O (7:3).[29]



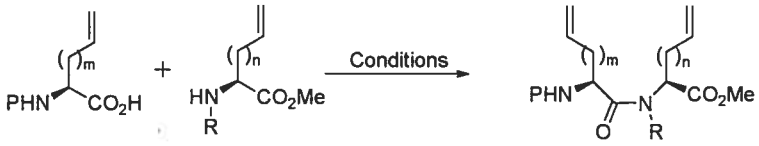
Scheme 5. Synthesis of Homoallylglycine Components **38** and **39**

Considering that rotation around the amide bound would influence the rate of RCM of the dipeptides, we synthesized an array of secondary benzyl amino esters to prepare tertiary amides having a lower barrier for isomerization about the amide bond (Scheme 6). This hypothesis was supported by earlier studies of the synthesis of eight-membered lactams that demonstrated the utility of the acid labile 2,4-dimethoxybenzyl (Dmb) group in the RCM step.[15] The related 2-hydroxy-4-methoxybenzyl (Hmb) group has been used to surmount difficult couplings in solid-phase peptide synthesis,[30] and we envisioned that secondary amino esters bearing this group could have better reactivity than their Dmb cousins. Similary, the 2-hydroxy-6-nitrobenzyl (Hnb) group was considered as a photocleavable protection reported to favor coupling by O to N acyl transfer in a similar way as the Hmb auxiliary.[31] Reductive aminations of imine prepared with the respective benzaldehyde and allyl and homoallylglycine methyl esters (**36** and **39**) were performed using $NaBH(OAc)_3$ to furnish Dmb-, Hmb-, and Hnb-protected amino esters **40** and **41** in yields varying between 52% and 79%.



Scheme 6. Synthesis of N-Benzyl Components **40** and **41**

2.4.2 Coupling of the Fragments. The set of dipeptides **43a-45a** was assembled first by combining allylglycine and homoallylglycine methyl ester salts **36** and **39** as amine components and *N*-(Boc)allyl- and *N*-(Boc)homoallylglycines **35a** and **38a** as acid components using TBTU as the coupling agent in 85-87% yields (Table 1). Coupling of the Dmb secondary amino esters proved more difficult, and many coupling conditions were tried;[32] however, only HATU as the coupling agent with N-ethylmorpholine as the base was found to be effective for making N-Boc-protected dipeptides **42b-45b** bearing a 2,4-dimethoxybenzyl tertiary amide bond in yields varying between 71% and 86%. Changing from Boc protection to Fmoc did not affect coupling, and dipeptides **43c** and **44c** were obtained in 85% and 82% yields, respectively. The use of HATU could be avoided by employing *N*-(Hmb)homoallylglycine methyl ester **41b** and the symmetrical anhydride generated



Acid	m	P	Amine	n	R	Conditions[a]	Amide	Yield (%)
35a	1	Boc	**40a**	1	Dmb	A	**42b**	71
35a	1	Boc	**39**	2	H	B	**43a**	86
35a	1	Boc	**41a**	2	Dmb	A	**43b**	86
35b	1	Fmoc	**41a**	2	Dmb	A	**43c**	85
38a	2	Boc	**36**	1	H	B	**44a**	85
38a	2	Boc	**40a**	1	Dmb	A	**44b**	81
38b	2	Fmoc	**40a**	1	Dmb	A	**44c**	82
38a	2	Boc	**40b**	1	Hnb	C	**44d**	87
38a	2	Boc	**39**	2	H	B	**45a**	87
38a	2	Boc	**41a**	2	Dmb	A	**45b**	74
38a	2	Boc	**41b**	2	Hmb	C	**45c**	86

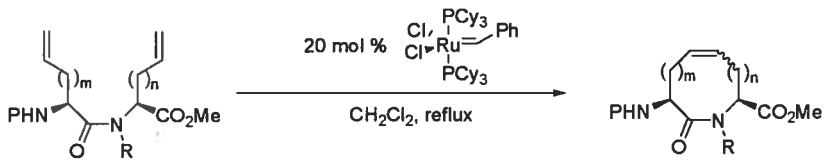
Table 1. Dipeptide Assembly [a] Condition A: HATU, *N*-Ethylmorpholine, CH_2Cl_2, rt; condition B: TBTU, DIEA, CH_2Cl_2, rt; condition C: symmetric anhydride, benzylic amino ester, CH_2Cl_2, rt.

from *N*-(Boc)homoallylglycine **38a**, respectively, in situ to furnish **45c** in 86% yields. Attempts to apply the symmetrical anhydride conditions using *N*-(Hnb)allylglycine **40b** gave **44d** in 87% yield; however, this route was not pursued further because of the difficulties in making the requisite 2-hydroxy-6-nitrobenzaldhyde.[33]

2.4.3 Ring-Closing Metathesis. The importance of the rate of amide bond isomerization on the ring-closing metathesis was realized in the synthesis of nine-membered macrocyles, which could not be formed without a tertiary amide. When cyclization by olefin metathesis was examined on dipeptides bearing no benzyl group

at the amide nitrogen, secondary amides **43a** and **44a** failed to cyclize using both the first and second generation Grubbs' catalyst in a variety of solvents at reflux and room temperature. Dipeptide **43a** also did not cyclize to a nine-membered ring in the presence of $Ti(O\text{-}iPr)_4$, which has been used previously to prevent the formation of a cyclic chelate between the catalyst and an amide.[34] As reported,[19] 10-membered macrocyclic dipeptide **49a** was formed on cyclization of dipeptide **45a** using the first generation of Grubbs' catalyst at high dilution (0.7 mM).

Macrocycles of eight and nine members were synthesized from dipeptides bearing only a benzyl group on the nitrogen of the amide. Dmb-analogues **42b**, **43b** and **c**, **44b** and **c**, and **45b** reacted with the first generation Grubbs' catalyst to provide 8-10 membered macrocycles **46a**, **47b** and **c**, **48b** and **c**, and **49b**, respectively, in 71-81% yields (Table 2). The 10-membered macrocycle (**49b**) was formed in 87% yield from tertiary amide **45b** employing the same conditions used to cyclize secondary amide **45a** at a concentration four and a half times higher; however, the olefin geometry was shown to be *cis* as discussed below. The phenol of the Hmb group was also tolerated by the catalyst, and 10-membered macrocyle **49c** was prepared in 86% yield. The tertiary amide facilitated amide bond rotation and favored conformers in which the ring-closing metathesis was possible. In the smaller-ring cases, without the benzyl group, the *cis*-amide isomer was disfavored energetically, and the barrier for isomerization was higher such that macrocylization was inhibited.

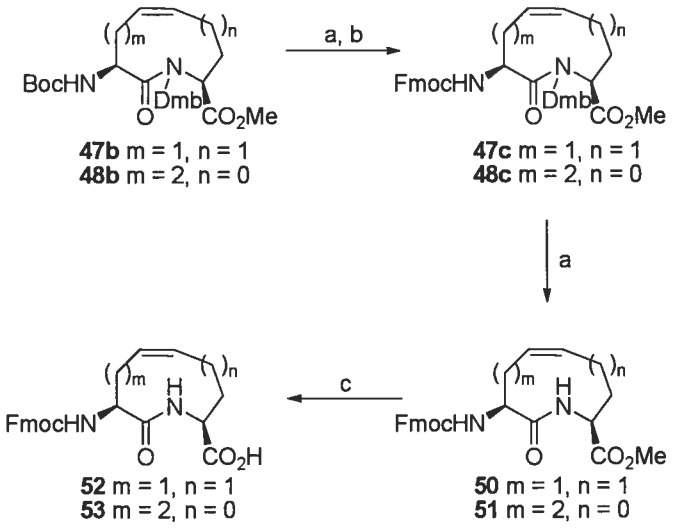


Amide	P	m	n	R	Macrocycle	*E*/*Z*	Yield (%)
42b	Boc	1	1	Dmb	**46a**	*Z*	78
43a	Boc	1	2	H	**47a**	-	0
43b	Boc	1	2	Dmb	**47b**	*Z*	80
43c	Fmoc	1	2	Dmb	**47c**	*Z*	75
44a	Boc	2	1	H	**48a**	-	0
44b	Boc	2	1	Dmb	**48b**	*Z*	81
44c	Fmoc	2	1	Dmb	**48c**	*Z*	71
45a	Boc	2	2	H	**49a**	*E*	77
45b	Boc	2	2	Dmb	**49b**	*Z*	87
45c	Boc	2	2	Hmb	**49c**	*Z*	86

Table 2. Macrocycle Formation

The Dmb and Hmb groups were reported to be easily cleaved under acidic conditions.[30,35] However, *N*-Boc-protected-9- and 10-membered lactams **47b**, **48b**, and **49b** and **c** bearing Dmb and Hmb groups were recovered as deprotected amines without the loss of the benzylic tertiary amide after prolonged treatment with 50% TFA in CH_2Cl_2. Alternatively, both the Boc and Dmb groups were removed upon exposure of eight-membered lactam **46a** to the same TFA in CH_2Cl_2 conditions as reported.[15] In contrast to the *N*-Boc-protected lactams, *N*-Fmoc-protected lactams **47c** and **48c** were quantitatively converted in 30 min to their secondary amide derivatives **50** and **51** by treatment with 50% TFA in CH_2Cl_2 (Scheme 7). This behavior confirms the hypothesis[36] that difficulties in cleaving Dmb groups are due to the formation of a neighboring positively charged ammonium ion upon deprotection of the Boc moiety,

which inhibits protonation of the amide and shuts down the reaction. Conversion of *N*-Boc-protected macrocycles **47b** and **48b** to *N*-Fmoc-derivatives **47c** and **48c** gave average yields of 35-45%, illustrating an advantage in starting with *N*-Fmoc-protected amino acids. Finally, esters **50** and **51** were hydrolyzed using 0.5 M NaOH and 0.8 M $CaCl_2$ in *i*PrOH/water (7:3) to obtain the protected amino acids (**52** and **53**) suitable for incorporation into peptides by solid-phase synthesis.[29]



Scheme 7. Synthesis of Macrocycle *N*-(Fmoc)-dipeptides **52** and **53** [a] Reagents and conditions: (a) 50% TFA/CH_2Cl_2; (b) FmocOSu, Na_2CO_3, acetone/H_2O; (c) 0.8 M $CaCl_2$/ 0.5 M NaOH, *i*-PrOH/H_2O.

The olefin geometry was determined based on the vicinal coupling constant of the vinyl protons. In the case of eight-membered lactam (*S*, *S*)-**27**, a coupling-constant value of 10.4 Hz was observed and assigned to *cis*-olefin geometry. The vinyl protons of the olefin in 9-membered lactams **47c** and **53** were observed as quadruplets; however, decoupling experiments by irradiation of the allylic signals at 2.70 and 2.30 ppm for **47c** and at 2.69 ppm for **53** demonstrated that the vinylic coupling constant for both compounds was 10.5 Hz consistent with a *cis*-olefin. Similarly, the vinyl coupling constant of the olefin of 10-membered tertiary lactam **49b** was 11.0 Hz, indicative of a *cis* double bond. The X-ray structure of macrocycle **49a** which was prepared from linear precursor **45a** bearing a secondary amide had previously demonstrated the presence of a *trans*-olefin.[19]

The amide isomer geometry of 8- and 10-membered lactams **27** and **31** were assigned cis and trans, respectively, based on analogy to literature compounds **27**[14] and **31**,[19] for which X-ray structures were obtained. The assignment of the amide isomers of nine-membered lactams **52** and **53** was made based on 2D NMR experiments. Initially, COSY spectra of **52** and **53** were performed in pyridine-d_5 and $CDCl_3$, respectively, to assign the protons for each compound. Subsequently, NOESY spectra were performed to measure long-distance transfers of magnetization. In the NOESY spectrum of both **52** and **53**, no transfer of magnetization between the $C^{\alpha}H$ protons was observed using a variety of mixing times. Because an amide cis isomer would be expected to exhibit strong NOE between the neighboring $C^{\alpha}H$ protons, the

lack of such a transfer of magnetization leads us to assign the amide trans isomer geometry for **52** and **53**.

2.5 Conclusion

A general methodology has been developed for synthesizing enantiomerically pure 8-, 9-, and 10-membered macrocyclic dipeptides. This methodology has provided the first syntheses of nine-membered lactams **29** and **30**, as well as a more practical route for making 10-membered lactam **31**. The importance of transient *N*-alkylation of the central amide was demonstrated to facilitate ring-closing metathesis, such that higher concentrations (3.15 mM) could be used without evoking dimer or polymer formation. As reported, the *cis*-olefin geometry was found in eight-membered lactam **27**. The 9-membered lactams **29** and **30** also possessed *cis*-olefin geometry. On the other hand, olefin geometry was contingent on the manner that 10-membered lactams **49b** and **49a** were synthesized; tertiary amide **45b** gave the *cis*-olefin and secondary amide **45a** provided *trans*-olefin. The amide bond geometry was shown to be *cis* in the case of **27** and trans for macrocycles **29-31**. A more detailed investigation of the conformation of **29** and **30** in peptide analogues is presently under study. In light of the ability of these constrained dipeptide surrogates to adopt conformations similar to natural β-turns, this practical methodology should be of general utility for research in peptide science and medicinal chemistry.

2.6 Experimental Section

***tert*-Butyl (2*S*)-2-[(*N*-(PhF)amino]pent-4-enoate (33).** A rt solution of methyltriphenylphosphonium bromide (13.2 g, 37 mmol) in THF (103 mL) was treated with a 0.5 M solution of KHMDS in toluene (67 mL, 33 mmol), stirred for 30 min, and treated dropwise with aldehyde **32** (7.64 g, 18.5 mmol, prepared according to ref 23) in THF (103 mL) over 10 min. The reaction mixture was stirred for 1 h, quenched with 200 mL of a saturated solution of NH_4Cl, and the phases were separated. The aqueous layer was extracted twice with 150 mL of Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography (7% EtOAc/hexanes) afforded allylglycine **33** (7.22 g, 95% yield) as a clear oil: $[\alpha]^{20}_D$ +163.7° (*c* 1.0, $CHCl_3$), lit.[37] $[\alpha]^{20}_D$ 168.7° (*c* 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectral data were consistent with the literature.[37]

(2*S*)-2-Aminopent-4-enoic acid hydrochloride (34). TFA (60 mL) was added dropwise to a solution of allylglycine **33** (7.22 g, 17.5 mmol) in CH_2Cl_2 (60 mL). Once the addition was completed, Et_3SiH (7 mL, 43.8 mmol) was added to the solution, which was stirred for 15 h. The volatiles were evaporated, and the residue was dissolved in 3:1 hexanes/Et_2O (50 mL) and treated with 0.5 N HCl (25 mL). The phases were separated, and the organic layer was extracted twice with 0.5 N HCl. The combined aqueous layers were lyophilized to give amino acid hydrochloride **34** (2.50 g, 94% yield) as a white solid: mp 205-207°C; ^1H NMR (CD_3OD): δ5.79 (m, 2H),

5.29 (m, 2H), 4.06 (dd, 1H, J = 7.1, 5.1 Hz), 2.68 (m, 2H); ^{13}C NMR (CD_3OD): δ169.4, 130.1, 119.7, 51.6, 34.0. MS (ESI, *m/z*): 116.0 $(MH)^+$.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]pent-4-enoic acid (35a). A 1:1 dioxane/H_2O solution (33 mL) containing hydrochloride **34** (750 mg, 4.95 mmol) was treated with NaOH (436 mg, 9.90 mmol). After the NaOH dissolved, Boc_2O (1.30 g, 5.94 mmol) was added to the mixture in three portions over 10 min. The mixture was stirred for 18h. The dioxane was removed by evaporation. The crude mixture was diluted with H_2O and acidified to pH 3-4 with a 10% $KHSO_4$ solution. This aqueous solution was extracted with Et_2O (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give *N*-(Boc)allylglycine **35a** (1.03 g, 97% yield) as a thick clear oil: $[\alpha]^{20}_D$ +14.5° (*c* 1.28, $CHCl_3$); The ^{1}H and ^{13}C NMR were consistent with the literature.[22c] HRMS calcd for $C_{10}H_{17}NO_4Na$, 238.10498; found, 238.10538.

(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]pent-4-enoic acid (35b). A 1:1 acetone/H_2O solution (67 mL) containing hydrochloride **34** (1.5 g, 10 mmol) was treated with Na_2CO_3 (2.1 g, 20 mmol) and FmocOSu (3.3 g, 10 mmol). The mixture was stirred for 18 h at room temperature and concentrated. The crude mixture was diluted with H_2O and acidified to pH 3-4 with a 10% $KHSO_4$ solution. This aqueous solution was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give *N*-(Fmoc)allylglycine **35b** (2.36 g, 70% yield): mp 134-135°C; $[\alpha]^{20}_D$ +10.6° (*c* 0.93, $CHCl_3$); ^{1}H NMR (CD_3OD): δ7.68 (d, 2H, J = 9.9), 7.59 (m, 2H), 7.32 (t, 2H, J =

9.7), 7.23 (t, 2H, J = 9.9), 5.64 (m, 1H), 5.09 (m, 3H), 4.25 (m, 2H), 4.12 (m, 2H), 2.57 (m, 1H), 2.44 (m, 1H); ^{13}C NMR (CD_3OD): δ175.2, 158.5, 145.3, 145.1, 142.5, 134.7, 128.8, 128.1, 126.3, 120.8, 118.7, 68.0, 55.1, 37.1; HRMS calcd for $C_{20}H_{19}NO_4Na$, 360.12063; found, 360.12080.

Methyl (2*S*)-2-aminopent-4-enoate hydrochloride (36). $SOCl_2$ (0.55 mL, 19.8 mmol) was added dropwise to a solution of allylglycine **34** (2.0g, 13.2 mmol) in MeOH (22 mL) at 0°C. The mixture was allowed to warm to room temperature, stirred overnight, and evaporated to give methyl ester **36** (2.16g, 99% yield) as a white solid: mp 91-92°C; $[\alpha]^{20}_D$ +8.3° (c 1.07, CH_3OH); ^{1}H NMR (CD_3OD): δ5.76 (m, 1H), 5.28 (m, 2H), 4.15 (dd, 1H, J = 6.8, 5.5), 3.83 (s, 3H), 2.69 (m, 2H); ^{13}C NMR (CD_3OD): δ168.8, 130.1, 120.1, 52.1, 52.0, 34.1; HRMS $(MH)^+$ calcd for $C_6H_{11}NO_2$, 130.08626; found, 130.08636.

(2S)-2-[(*tert*-Butoxycarbonyl)amino]hex-5-enoic acid (38a). A solution of *N*-(Boc)homoallylglycine methyl ester (**37a**, 400 mg, 1.64 mmol prepared according to ref 27) in 1:1 H_2O/dioxane (16 mL) was treated with $LiOH{\cdot}H_2O$ (103 mg, 2.47 mmol), stirred for 3 h, and evaporated to a residue that was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous phase was acidified with 0.1 M HCl to pH 4 and extracted twice with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford acid **38a** (0.364 g, 97% yield) as a colorless oil: $[\alpha]^{20}_D$ -1.1° (c 1.31, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ5.82 (m, 1H), 5.03 (m, 3H), 4.08 (m, 1H), 2.15 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ175.2, 157.1, 137.4,

115.0, 79.4, 53.2, 31.1, 30.0, 27.7; HRMS calcd for $C_{11}H_{19}NO_4Na$, 252.12063; found, 252.12089.

General Procedure A: Reductive Aminations. Allylglycine methyl ester hydrochloride **36** or homoallylglycine methyl ester trifluoroacetate **39** (3 mmol) was treated with 20 mL of a saturated $NaHCO_3$ solution and extracted with 3 × 25 mL of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine and dried over $MgSO_4$, filtered, and concentrated to a volume of 30 mL. The selected benzaldehyde derivative (3.3 mmol) and $NaBH(OAc)_3$ (4.5 mmol) were added to the mixture, which was stirred for 18 h at room temperature, treated with 20 mL of saturated $NaHCO_3$, and stirred for 30 min. The aqueous layer was separated and washed with 3 × 20 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography.

Methyl (2*S*)-2-[(2,4-Dimethoxybenzyl)amino]pent-4-enoate (40a). Chromatography of the product from **36** (20 mmol) using 30:70 EtOAc/hexanes as the eluant gave **40a** as a yellow oil (74% yield): ^{1}H NMR: δ7.10 (d, 1H, J = 7.8), 6.39 (m, 2H), 5.69 (m, 1H), 5.08 (m, 2H), 3.81-3.64 (m, 11H), 3.11 (t, 1H, J = 6.6), 2.39 (t, 2H, J = 6.5), 2.22 (bs, 1H); ^{13}C NMR: δ174.8, 160.0, 158.4, 133.6, 130.2, 120.0, 117.6, 103.5, 98.2, 60.0, 55.1, 55.0, 51.4, 46.8, 37.5. MS (ESI, *m/z*): 280.1 $(MH)^+$.

General Procedure B: Peptide Coupling using HATU. The selected *N*-protected amino acid (1.5 equiv) and *N*-benzyl amino ester (1.0 equiv) were dissolved in

CH_2Cl_2 (0.07 M), treated with *N*-ethylmorpholine (1.5 equiv) and HATU (1.5 equiv), stirred for 24h, and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography.

***N*-(Fmoc)-L-Allylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-homoallylglycine methyl ester (43c).** Chromatography of the product from **35b** (1.5 mmol) and **41a** (1.0 mmol) using 30:70 EtOAc/hexanes as the eluant gave **43c** (85% yield):^{1}H NMR: δ7.76 (d, 2H, J = 7.5), 7.62 (dd, 2H, J = 3.3, 3.4), 7.39 (t, 2H, J = 7.5), 7.30 (t, 2H, J = 7.4), 7.07 (d, 1H, J = 8.0), 6.40 (dd, 2H, J = 2.1, 2.3), 5.81-5.65 (m, 3H), 5.14 (m, 2H), 5.05 (m, 1H), 4.98 (m, 2H), 4.67 (d, 1H, J = 15.8), 4.46-4.29 (m, 3H), 4.24-4.22 (t, 1H, J = 7.1), 4.13 (m, 1H), 3.76 (s, 6H), 3.57 (s, 3H), 2.59 (m, 1H), 2.45 (m, 1H), 2.11 (m, 1H), 2.03 (m, 2H), 1.80 (m, 1H); ^{13}C NMR: δ171.6, 171.0, 160.9, 158.6, 155.3, 143.7, 141.1, 137.3, 132.3, 130.2, 127.5, 126.8, 125.0, 124.9, 119.8, 118.7, 115.8, 115.4, 103.5, 98.3, 66.7, 57.7, 55.2, 55.0, 51.8, 50.7, 47.0, 37.8, 30.4, 28.1. MS (ESI, *m/z*): 635.2 $(MNa)^+$.

General Procedure C: Ring-Closing Metathesis. In a flame dried flask, dipeptide (1.0 equiv) was dissolved in dry CH_2Cl_2 (3 mM). The mixture was heated for 10 min at 35 °C, treated with bis(tricyclohexylphosphonium)benzylidine ruthenium (IV) dichloride ($RuCl_2(=CHPh)(PCy_3)_2$, 20 mol %), heated at reflux for 72h, and concentrated. The crude residue was purified by chromatography to afford the unsaturated lactam.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-Azonine-9-carboxylate (47c). Chromatography of the product from **43c** (0.4 mmol) using 20:80 EtOAc/hexanes as the eluant gave **47c** (75% yield) as a brown solid: mp 96-101°C; $[\alpha]^{20}_{D}$ -37.8° (*c* 0.93, $CHCl_3$); ^{1}H NMR: δ7.76 (d, 2H, *J* = 7.5), 7.62 (d, 2H, *J* = 7.4), 7.40 (t, 2H, *J* = 7.4), 7.30 (t, 2H, *J* = 7.3), 7.23(d, 1H, *J* = 8.3), 6.49 (d, 1H, *J* = 6.6), 6.45-6.36 (m, 2H), 6.09 (q, 1H, *J* = 9.3), 5.61 (q, 1H, *J* = 9.1), 4.66-4.35 (m, 5H), 4.23 (t, 1H, *J* = 7.1), 3.79 (s, 3H), 3.77 (s, 3H), 3.46 (s, 3H), 2.67 (m, 1H), 2.30-2.15 (m, 2H), 1.90 (m, 2H), 1.75-1.65 (m, 2H); ^{13}C NMR: δ173.3, 170.4, 159.8, 157.4, 155.2, 143.8, 141.1, 130.9, 129.9, 129.0, 127.5, 126.9, 125.0, 125.0 119.8, 117.5, 104.0, 97.9, 66.8, 56.9, 55.1, 52.0, 51.7, 47.0, 39.9, 35.0, 27.8, 22.0; HRMS $(MH)^+$ calcd for $C_{34}H_{37}N_2O_7$, 585.25953; found, 585.25918.

General Procedure D: Removal of Dmb. A stirred solution of Fmoc-protected dipeptide lactam (0.2 mmol) in CH_2Cl_2 (8 mL) was treated dropwise with TFA (2 mL), stirred for 18 h, and evaporated to a residue that was purified by chromatography.

Methyl (3*S*,9*S*)-3-*N*-(Fmoc)amino-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylate (50). Chromatography of the product from **47c** (0.5 mmol) using EtOAc as the eluant gave **50** (95% yield) as a brown gum: ^{1}H NMR: δ7.76 (d, 2H, *J* = 7.4), 7.60 (d, 2H, *J* = 7.3), 7.39 (t, 2H, *J* = 7.4), 7.30 (t, 2H, *J* = 7.4), 6.35 (d, 1H, *J* = 7.0), 6.25 (d, 1H, *J* = 11.6), 6.08 (q, 1H, *J* = 9.3), 5.65 (ddd, 1H, *J* = 6.0, 11.0, 10.8), 4.39-4.38 (m, 2H), 4.25 (m, 3H), 3.73 (s, 3H), 2.70 (m, 1H), 2.30 (dd, 2H, *J* = 8.5, 8.7), 2.12 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H); ^{13}C NMR: δ172.7, 172.0, 155.2, 143.7,

143.6, 141.1, 130.1, 128.7, 127.5, 126.9, 124.9, 119.8, 66.8, 52.5, 52.1, 47.0, 34.1, 33.8, 22.5; HRMS $(MH)^+$ calcd for $C_{25}H_{27}N_2O_5$, 435.19145; found, 435.19184.

General Procedure E: Methyl Ester Hydrolysis. A stirred solution of methyl ester (0.5 mmol) in 0.8 M $CaCl_2$ in a 7:3 *i*-PrOH/H_2O solution (10 mL) was treated with 0.5 M NaOH solution (2 mL). After 2 h, ether was added, and the phases were separated. The aqueous layer was acidified with 1.0 N HCl and extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the acid.

(*E*,3*S*,9*S*)-3-*N*-(Fmoc)amino-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylic acid (52). Hydrolysis of **50** (0.4 mmol) gave **52** (99% yield) as a white solid: mp 190-193°C; ^{1}H NMR (400 MHz, pyridine-d_5): δ8.90 (d, 1H, J = 11.0), 8.38 (d, 1H, J = 7.1), 7.8 (m, 3H), 7.7 (t, 1H, J = 7.5), 7.35 (m, 3H), 7.25 (t, 1H, J = 9.0), 6.04 (q, 1H, J = 9.1), 5.75 (bs, 1H), 5.56 (m, 1H), 4.84 (t, 1H, J = 7.8), 4.69 (m, 1H), 4.55 (d, 2H, J = 7.16), 4.33 (t, 1H, J = 6.8), 2.95-2.88 (m, 1H), 2.5 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.9 (m, 2H); ^{13}C NMR: δ175.3, 174.1, 156.7, 145.2, 144.9, 142.1, 131.5, 129.3, 128.5, 127.9, 126.1, 120.8, 67.3, 52.9, 48.2, 41.4, 34.8, 31.0; HRMS $(MH)^+$ calcd for $C_{24}H_{25}N_2O_5$, 421.17580; found, 421.17599.

2.7 Acknowledgment

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2.8 Supporting Information Available

General experimental section, general procedures for TBTU and symmetric anyhydride couplings, ^{1}H and ^{13}C NMR data for **40b**, **41a** and **b**, **43a** and **b**, **44a-d**, **45b** and **c**, **47b**, **48b** and **c**, **49b** and **c**, **51**, and **53**, ^{1}H and ^{13}C NMR spectra of **34**, **35b**, **36**, **38a**, **40a** and **b**, **41a** and **b**, **43a-c**, **44a-d**, **45b** and **c**, **47b** and **c** **48b** and **c**, **49b** and **c**, and **50-53**, 2D COSY and NOESY spectra of **52** and **53**, decoupling

experiments on compounds **47c** and **53** and HPLC profiles of **52** and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CHAPITRE 3

Article 2 :

Surprenant, S.; Lubell, W. D. From Macrocycle Dipeptide Lactams To Azabicyclo[X.Y.0]alkanone Amino Acids, A Transannular Cyclization Route For Peptide Mimic Synthesis *Org. Lett.* **2006**, *8*, 2851.

3.1 Abstract

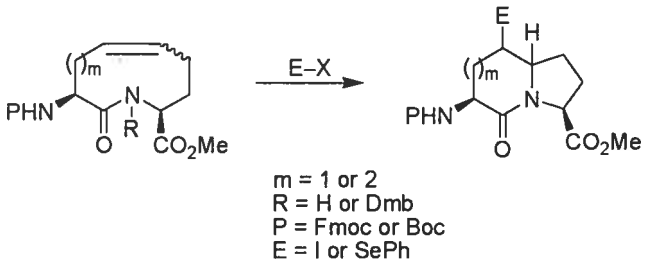


Figure 15. Graphical Abstract

Macrocyclic and fused bicyclic dipeptides are complementary motifs for mimicry of different types of β-turn geometry. Macrocyclic dipeptide mimics have served as precursors for the synthesis of their bicyclic counterparts using electrophilic transannular cyclizations of 9- and 10-membered ring lactams **62-65** to form azabicyclo[4.3.0]- and [5.3.0]alkanone amino esters **66-69**

3.2 Introduction

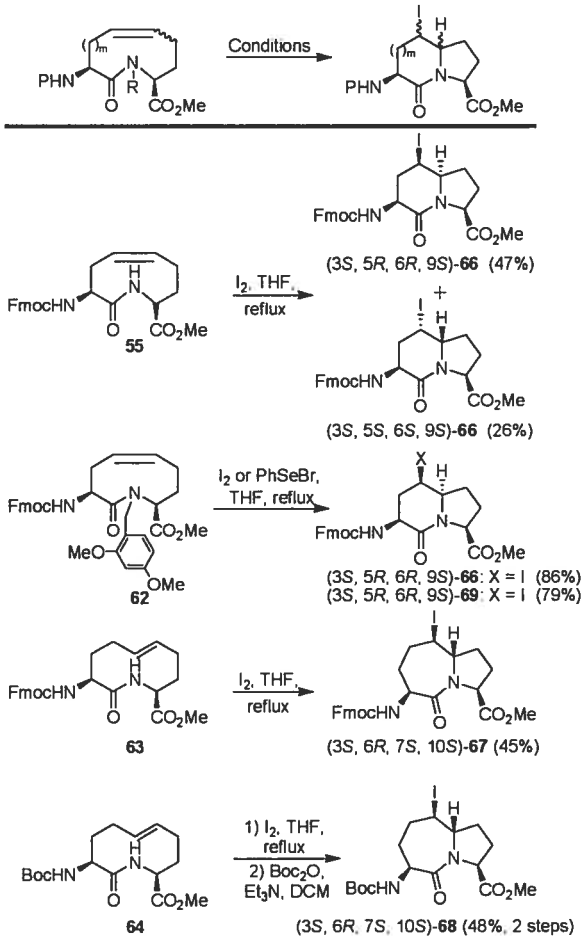
Peptides are important endogenous molecules responsible for a multitude of roles in human physiology; however, their therapeutic potential is often limited due to their poor bioavailability, rapid metabolism and short duration of action. Peptide mimics have thus been developed to retain the desired biological effects of the parent peptide and to remove such undesirable characteristics.[1] In this respect, azabicyclo[X.Y.0]-alkanone amino acids have proven to be effective dipeptide mimics, because their fused bicyclic ring system can constrain the backbone dihedral

angle geometry to induce secondary structures such as β-turns. Although many approaches have been conceived for making azabicycloalkanone amino acids[2], few examples have made practical use of common precursors for making a set of ring systems.

The introduction of a set of dipeptide mimics is often desired to provide detailed information about the conformation specifically required by the peptide to effectively bind and activate the receptor. The acquisition of a set of azabicycloalkanone amino acids requires, however, performing a series of multistep syntheses because few dipeptide mimics are commercially available. For example, to study opioid receptor like 1 (ORL1) receptor antagonists,[3] replacement of the commercially available fused-6,5 thiaindolizidinone amino acid with fused-6,5, -5,6 and -6,6 azabicycloalkanone amino acids , required syntheses of 7, 7, and 5 steps respectively from suitably protected amino dicarboxylic acids in overall yields ranging from 45% to 61%.[4] The use of such a tour de force of peptide scaffolds did deliver analogs with remarkable potency and selectivity for the ORL1-receptor over the other opioid receptor sub-types. For such structure-activity studies to become more practical, however, more efficient methodology is needed for making such mimics.

Considering that electrophilic transannular cyclization of unsaturated macrocyclic lactams of 9- and 10-membered rings has been previously used to prepare indolizidinone and quinolizidinone ring systems[5], we have pursued this

approach for converting macrocyclic dipeptide surrogates into their azabicycloalkanone amino acid counterparts (Scheme 8).

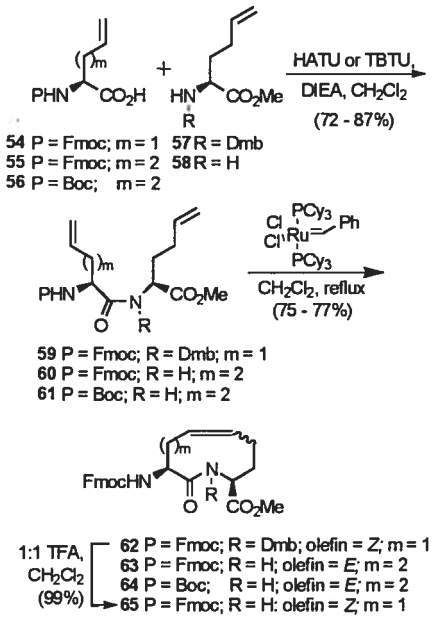


Scheme 8. Conversion of macrocyclic dipeptides into bicyclic dipeptides by electrophilic transannular cyclization

3.3 Results and Discussion

The set of 9- and 10-membered unsaturated macrocyclic dipeptides **56-65** was synthesized using our recently described protocol[6] (Scheme 9). Briefly, suitably Fmoc- and Boc-protected allyl- and homoallylglycine **54-56** were coupled to homoallylglycine methyl ester **58** using TBTU and DIEA, and to *N*-(Dmb)homoallylglycine methyl ester **57** using HATU and DIEA in yields varying between 75% and 87% (Dmb = 2,4-dimethoxybenzyl). Annulation of the dipeptides **59-61** bearing two olefinic side chains was achieved using the first generation of Grubbs catalyst to afford the macrocyclic unsaturated lactams **62-64** in yields between 71% and 77%. Finally, the Dmb group, which was essential for the annulation of the 9-membered lactams, was removed by treatment with 50% TFA in CH_2Cl_2 to afford quantitatively secondary amide **65**.

The electrophilic transannular cyclization was initially performed on 9- and 10-membered lactams **62-65** using iodine as the source of electrophile (Scheme 8). Treatment of the Fmoc-protected, 9-membered lactam **65** with four equivalents of I_2 in THF at reflux gave two isomeric bicyclic products (3*S*, 5*R*, 6*R*, 9*S*)- and (3*S*, 5*S*, 6*S*, 9*S*)-**66** in 46% and 27% respective yields (see below for stereochemical assignments). On the other hand, treatment of the corresponding tertiary Dmb-amide **62** under similar conditions afforded bicycle (3*S*, 5*R*, 6*R*, 9*S*)-**66** as a single product in 86% yield.



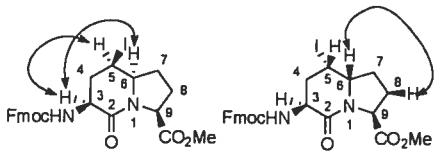
Scheme 9. Unsaturated macrocyclic dipeptide lactam synthesis[a] DMB = 2,4-dimethoxybenzyl

(3S, 6*R*, 7*S*, 10*S*)-Azabicyclo[5.3.0]alkanone **67** was similarly prepared in 45% yield by treating Fmoc-protected secondary lactam **63**, bearing the *trans* double bond, with iodine in THF at reflux. Loss of the Boc group was observed in the reaction of the corresponding Boc-protected 10-membered macrocycle **64** with iodine in THF; however, pyrroloazepinone **67** with the same stereochemistry as its Fmoc counterpart could be isolated in 48% overall yield after reprotection using Boc_2O and triethylamine in CH_2Cl_2.

In light of the effective transannular cyclizations using iodine, a cursory investigation of alternative electrophiles was performed using macrocycle **62** in order to examine effects on reaction stereochemistry and product structure. Treatment of **62**

with bromine or *N*-bromosuccinimide did not afford bicycle; instead, bromination of the aromatic ring was observed by LC/MS. Also treatement of **62** with mercuric acetate did not lead to bicyclic products. Alternatively, exposure of dipeptide **62** to 4 eq of phenylselenium bromide in THF at reflux provided bicyclic amino ester **69** in 79% yield (Scheme 8).

The assignment of the structures and stereochemistry of the different azabicyclo[X.Y.0]alkanone amino acids was performed using NMR spectroscopy and X-ray crystallography (Supporting Information). For bicycle **66,** the ring protons came at distinct chemical shifts and their sequential order was assigned using a COSY experiment. Coupling between the downfield carbamate proton and the proton of the adjacent backbone carbon was used as the starting point for tracing the through bond connectivities of the various protons around the bicycle. With the through bond connectivities ascertained, the through space connectivities observed in the NOESY spectra were used to assign relative stereochemistry. In the NOESY spectrum of indolizidinone (5*R*, 6*R*)-**66**, long distance transfer of magnetization between the C3 proton and the iodinated C5 and ring-fusion C6 protons, respectively, confirmed the concave bicycle structure and the *trans* relation between the ring-fusion proton and the iodide (Figure 16). In (5*S*,6*S*)-**66**, the bridgehead stereochemistry was assigned based on NOE with the C8 beta-proton which came downfield relative to its alpha-proton counterpart due to the anisotropic effect of the C9 carboxylate (beta is on the same face as the C3-amine).[7] In the cases of fused-7,5 systems **67** and **68**, the relative stereochemistry of the newly formed centres was confirmed by X-ray



(3*S*, 5*R*, 6*R*, 9*S*)-**66** (3*S*, 5*S*, 6*S*, 9*S*)-**66**

Figure 16. NOESY correlations observed for compounds (3*S*, 5*R*, 6*R*, 9*S*)-**66** and (3*S*, 5*S*, 6*S*, 9*S*)-**66**

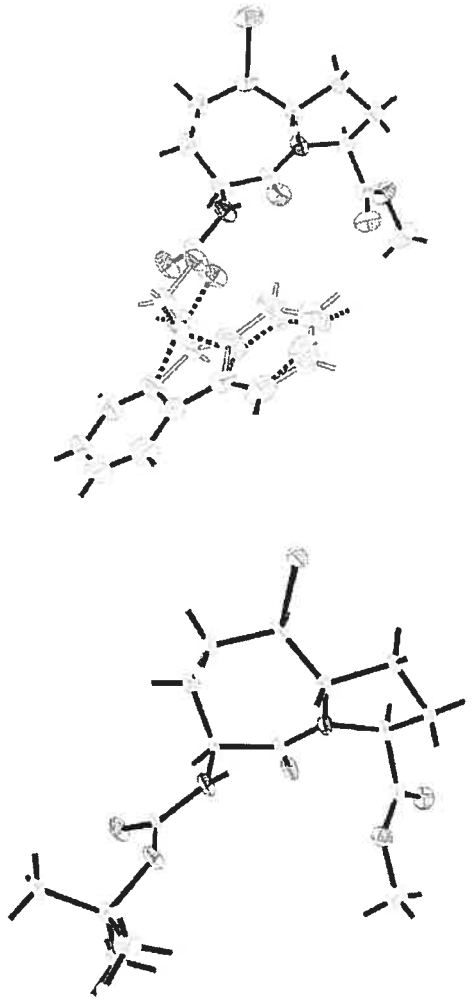
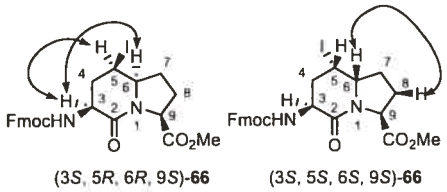


Figure 17. X-ray crystal structures of **67** (top) and **68** (bottom).



(3*S*, 5*R*, 6*R*, 9*S*)-**66** (3*S*, 5*S*, 6*S*, 9*S*)-**66**

Figure 16. NOESY correlations observed for compounds (3*S*, 5*R*, 6*R*, 9*S*)-**66** and (3*S*, 5*S*, 6*S*, 9*S*)-**66**

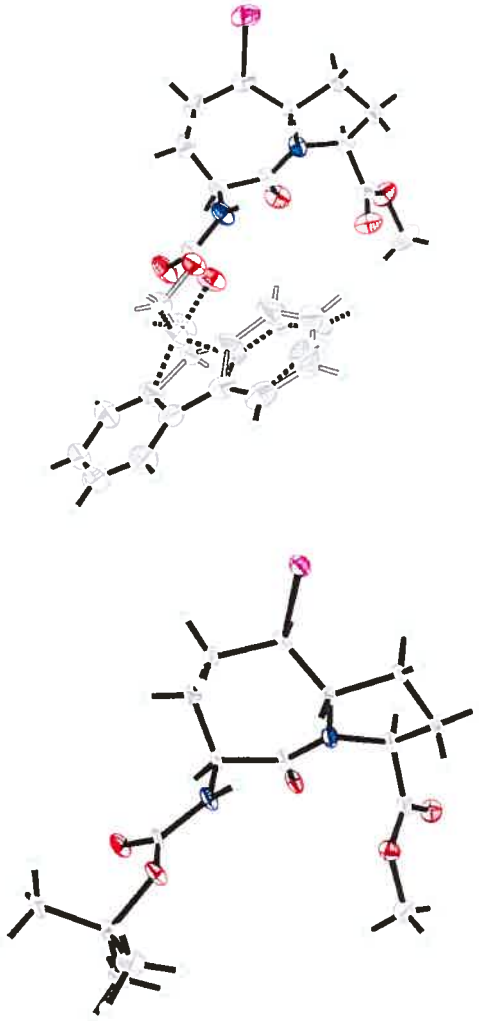


Figure 17. X-ray crystal structures of **67** (top) and **68** (bottom).

crystallographic analysis of crystals from acetone/hexanes and ethyl acetate/hexanes, respectively (Figure 17).[8] The *cis* relationship between the iodide and the bridgehead proton and the convex bicycle was observed in both structures.

In concurance with an earlier computational study of the parent pyrroloazepinone,[9] in their respective X-ray structures, the psi and phi dihedral angles within bicycles **67** (-64.1°; -49.4°) and **68** (-63.5°; -46.6°) were similar to ideal values for the central residues in a type I β-turn (-30°; -90°);[10] however, less similar than the dihedral angles of the parent macrocyclic dipeptide, which exhibited psi = -20° and phi = -107° in the X-ray structure of a model peptide.[11] Moreover, the phi dihedral angle was consistent with an inverse γ-turn (phi = -70 to -85°).[12] Power to pass from macrocycle to bicycle constrained dipeptide surrogates provides thus opportunity to explore different turn geometry with mimics derived from a common reaction sequence.

3.4 Conclusion

A novel effective approach for the synthesis of azabicyclo[4.3.0] and [5.3.0]alkanone amino esters has been developed featuring the electrophilic transannular cyclization of 9- and 10-membered macrocyclic dipeptides. This approach offers potential for converting one turn mimic into another. Furthermore,

the resulting iodide provides opportunity for the introduction of side-chains onto the heterocycle ring. We are now developing these avenues for peptide mimicry.

3.5 Acknowledgment

This work was supported by grants from Fonds Québecois de la Recherche sur la Nature et les Technologies (FQRNT) and the Natural Sciences and Engineering Research Council of Canada (NSERC). We are grateful for a Collaborative Research Development Grant from NSERC, the Canadian Society for Chemistry, AstraZeneca, Boehringer Ingelheim, Merck Frosst and Shire Biochem. We thank Mr. Dalbir Sekhon and Dr Alexandra Furtos from the Regional Laboratory for Mass Spectrometry, Sylvie Bilodeau from the Regional Laboratory for NMR Spectroscopy and Francine Bélanger-Gariépy from the Regional Laboratory for X-ray Analysis, at the Université de Montréal, for their assistance in compound analysis.

3.6 Supporting Information Available

Experimental procedures and spectral data for compounds **66-69**. Copies of ^{1}H and ^{13}C NMR, DEPT 135, COSY and HMQC experiments for coumpounds **66-69** and X-ray data for compounds **67** and **68** This material is available free of charge via the Internet at http://pubs.acs.org.

3.7 Considérations mécanistiques

Bien entendu, les résultats présentés dans le Schéma 8 peuvent mener vers divers points d'interrogation concernant la régiosélectivité et la stéréosélectivité obtenues lors de la réaction de cyclisation transannulaire. Malgré l'utilisation de cette stratégie dans plusieurs cas, seulement quelques travaux ont été publiés avec des considérations mécanistiques. Au début des années 1980, cette méthodologie a été utilisée pour la synthèse de d'indolizidine.[5a] En effet, des lactames de neuf membres comportant une double liaison *cis* entre les carbones 5 et 6 ont été traités avec de l'acétate de mercure suivi d'une réduction au $NaBH_4$ pour obtenir les azabicyclo[4.3.0.]alcanes. Malheureusement, puisque l'intermédiaire alkylé de mercrure n'a pu être isolé, aucune discussion sur la stéréochimie n'a été faite. D'autre part, des lactames de 10 membres pourtant une double liasion *trans* entre les carbones 5 et 6 ont été utilisés pour synthétiser des azabicyclo[4.4.0]alkanone.[13] Les auteurs ont utilisé le brome comme électrophile et obtenu une stéréochimie *anti* entre l'atome d'hydrogène en tête de pont et l'atome de brome. Cette stéréochimie a été expliquée par une addition du brome sur la liasion double pour former un intermédiaire dibromé suivi d'une attaque par l'atome d'azote de l'amide pour former le bicycle. Dans un autre cas un peu plus différent des cas discutés dans le présent chapitre, des lactames de neuf membres comportant une liaison double *trans* entre les carbones 5 et 6 ont été transformés soit en azabicyclo[4.3.0]alcanone ou en azabicyclo[3.4.0]alkanone.[5g] Les auteurs ont pu établir qu'à température pièce le macrocycle formé par une réaction diastéréosélective Aza-Claisen subissait une

relaxation conformationelle et que chaque conformère différent était responsable de la formation d'un bicycle différent.

Dans notre cas, on observe tout d'abord deux produits de cyclisation transannulaire lorsque le produit de départ est l'amide secondaire **55**. Dans les deux cas, on observe une stéréochimie relative *anti* par rapport à l'atome d'iode et l'hydrogène en tête de pont. Cette stéréochimie relative peut être expliquée par l'attaque de la liasion double *cis* sur l'iode pour former un ion iodonium cyclique (Figure 18). Vu la petite taille du cycle, seul la face extérieure de l'oléfine pourra attaquer la molécule d'iode pour former l'iodonium cyclique. Ce cycle tendu est par la suite ouvert avec inversion de configuration lorsque l'atome d'azote de la fonction amide attaque l'atome de carbone le plus près spatialement du nucléophile pour donner les produits (3*S*, 5*R*, 6*R*, 9*S*)-**66** et (3*S*, 5*S*, 6*S*, 9*S*)-**66**. Malheureusement, les règles de Baldwin[14] ne peuvent être utilisées ici pour prédire lequel des deux régioisomères possible est le plus apte à être produit. En effet, dans les deux cas de régioisomère possible, on observerait soit une cyclisation 5-*exo-tet* ou 6-*endo-tet*. L'obtention des deux différents stéréoisomères pourrait être expliquée par un équilibre entre deux conformations permettant ainsi aux deux faces de l'oléfine d'attaquer l'iode. Toutefois, lorsque l'amide tertiaire réagit, seulement le produit (3*S*, 5*R*, 6*R*, 9*S*)-**66** est formé. Ceci pourrait être expliqué par le fait que le conformère de type B est fortement énergétiquement désavantagé par rapport au conformère de type A par une interaction de type tension allylique A1,3 entre le groupement benzylique en position 1 et le groupement carbamate en position 3.

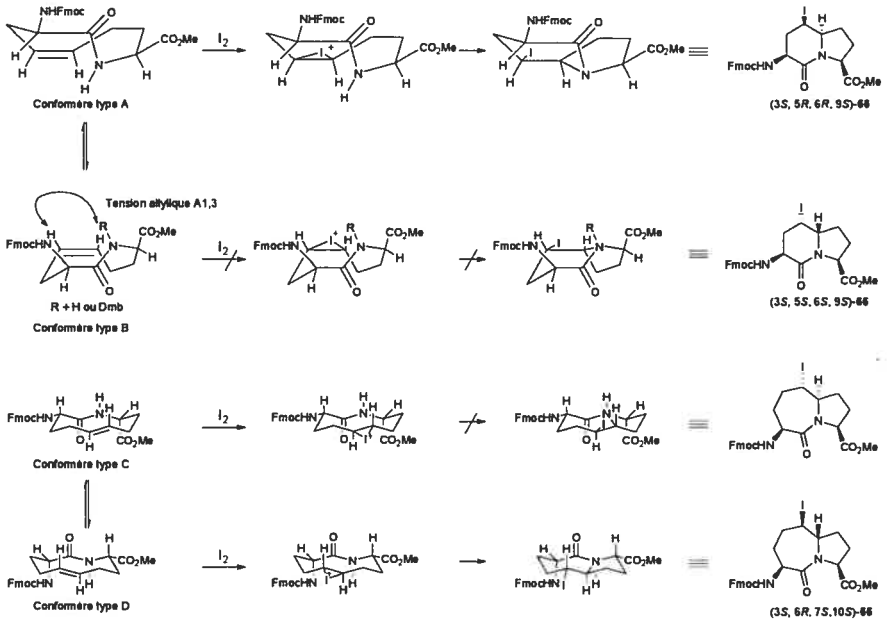


Figure 18. Considérations mécanistiques

Dans le cas de la cyclisation de l'amide cycle de 10 membres, la stéréochimie relative *syn* peut encore une fois être expliquée par la formation d'un intermédiaire iodonium cyclique. Cette fois-ci, la liaison double *trans* située entre les carbones 6 et 7 mène à une stéréochimie relative *syn* inversement à la stéréochimie relative *anti* obtenue avec le lactame de 9 membres comportant une double liaison *cis*. Cette fois, la régiosélectivité peut être rationalisée avec les règles de Baldwin. En effet, le produit obtenu provient d'une cyclisation 5-*exo-tet* ou 7-*endo-tet* alors que l'autre régioisomère serait issu d'une cyclisation 6-*exo-tet* ou 6-*endo-tet* et, selon les règles de Baldwin, la formation d'un cycle par une cyclisation 6-*endo-tet* n'est pas favorisée.

L'obtention d'un seul produit est toutefois plus complexe à rationaliser. Encore une fois, deux conformères sont possiblement en équilibre et le conformère de type D semble être l'unique conformère réactif. Cette différence de réactivité entre les deux conformères pourrait possiblement être expliquée par l'orientation du carbonyle de l'amide et celui de l'ester du conformère de type C qui forme un fort moment dipolaire défavorable.

3.8 References

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8. (a) Crystallographic data for **67**: $C_{26}H_{27}IN_2O_5$; M = 574.40; orthorhombic crystals; space group P212121; unit cell dimensions: a = 5.7630(2) Å, b = 17.0035(8) Å, c = 25.3668(11) Å; volume of unit cell: 2485.72(18) Å^3; Z = 4; d = 1.535 g/cm^3; R_f = 0.0354 R_w = 0.0565 for all data; GOF = 1.005. (b) Crystallographic data for **68**: $C_{16}H_{25}IN_2O_5$; M = 452.28; monoclinic crystals; space group P21; unit cell dimensions: a = 11.6497(11) Å, b = 5.8377(6) Å, c = 13.4469(14) Å, β = 100.394(5) Å; volume of unit cell: 899.48(16) Å^3; Z = 2; d = 1.670 g/cm^3; R_f = 0.0998 R_w = 0.2443 for all data; GOF = 1.005. The author has deposited the atomic coordinates for the structures of **67** and **68** with the Cambridge Crystallographic Data Centre. The

coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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CHAPITRE 4

Article 3 :

Surprenant, S.; Lubell, W. D. 9-(4-Bromophenyl)-9-fluorenyl as a Safety-Catch Nitrogen Protecting Group *J. Org. Chem.* **2006**, *71*, 848.

4.1 Abstract

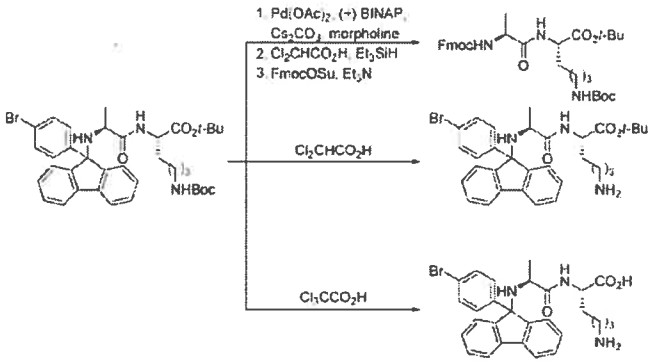


Figure 1 Graphical Abstract

The 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group has been developed as a novel safety-catch amine protection. This relatively acid-stable protecting group can be successfully activated by palladium-catalyzed cross-coupling reaction of the aryl bromide with morpholine and then cleaved effectively under mild conditions using dichloroacetic acid and triethylsilane. Complementary conditions are reported for selective removal of the BrPhF group in the presence of *tert*-butyl esters and carbamates as well as deprotection of *tert*-butyl esters and carbamates in the presence of BrPhF amines.

4.2 Introduction

Protecting groups have been essential for controlling the reactivity of amines in organic synthesis, peptide science, and medicinal chemistry.[1,2] In the context of our

research on the synthesis of peptide mimics,[3] the 9-phenyl-9-fluorenyl (PhF) group has been used to prevent the loss of enantiomeric purity during the employment of various amino carbonyl compounds.[4] The PhF group offers several advantages as amine protection. The steric bulk created by the PhF group acts as a barrier that prevents deprotonation of α-amino carbonyl compounds at the α-carbon. The PhF group is significantly more stable under acid conditions relative to the trityl group because of the anti-aromatic character of the 9-phenyl-9-fluorenyl carbocation.[5] Furthermore, if deprotonation of the α-carbon occurs under severe conditions, the PhF anion can act as a leaving group and eliminate to furnish an imine intermediate prior to reprotonation and epimerization.[6] The PhF group is usually removed by hydrogenolysis[7] and by solvolysis with treatment under strongly acidic conditions.[8] Alternatively, the PhF group has been removed using sodium or lithium in liquid ammonia,[9] TMSOTf in the presence of triethylsilane,[10] and iodine in MeOH.[11]

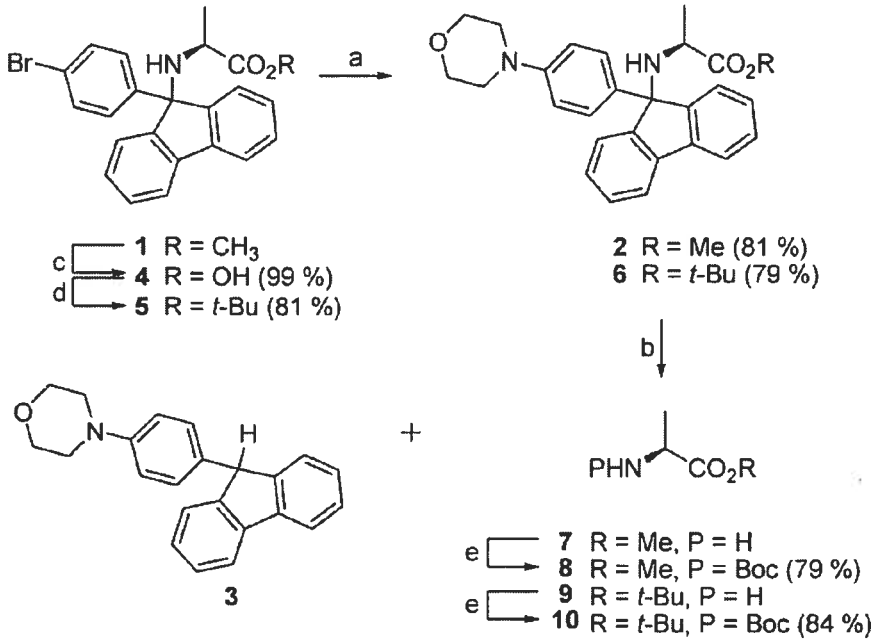
Perceiving the advantages of having a chemical means for rendering the PhF group cleavable under mildly acidic conditions, we considered that *p*-aminophenylfluorenyl cations would be significantly more stable than the parent PhF cation. Strategies have been conceived for generating *p*-aminobenzylic intermediates from suitable *para*-substituted benzyl derivatives. For example, the *p*-nitrobenzyl ester has been used in the synthesis of carbapenems and removed by nitro group reduction and solvolysis.[12] More recently, *p*-halobenzyl ethers were reported to be as stable as normal benzyl ethers yet cleavable using a two-step process featuring catalytic amination of the aryl halide and solvolysis with acid.[13]

In our previous work, we used the 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group in a linking-protecting group strategy for the synthesis of enantiopure norephedrines on solid support.[14] The BrPhF group proved tolerant to similar chemistry previously developed with PhF-protected amino acids before it reacted in a palladium-catalyzed cross-coupling with bis(pinacolato)diboron ester to give a suitable boronate for attaching the PhF-protected substrate to aryl halide resins. Pursuing the development of this protecting group, we demonstrate now that the BrPhF group can be employed as a safety-catch[15] amine protecting group which can be released by catalytic amination followed by treatment with mild acid.

4.3 Results and Discussion

The relative acid stability of the PhF group and an analogue bearing a *p*-aminophenyl substituent was studied by the synthesis of *N*-(9-(4-morpholinophenyl)-9-fluorenyl)alanine methyl ester **71** and comparison of its reactivity under acid conditions with *N*-(PhF)alanine methyl ester (Scheme 10, MPF = 9-(4-morpholinophenyl)-9-fluorenyl).

Both *N*-(PhF)- and *N*-(BrPhF)alanine methyl esters were synthesized as previously described.[14,16] Amination of BrPhF-Ala-OMe (**70**) with morpholine using 5 mol% of $Pd(OAc)_2$, (±)-BINAP, and excess Cs_2CO_3 provided *N*-(MPF)alanine methyl ester (**71**) in 81% yield. Competitive cleavage of *N*-(PhF)alanine methyl ester

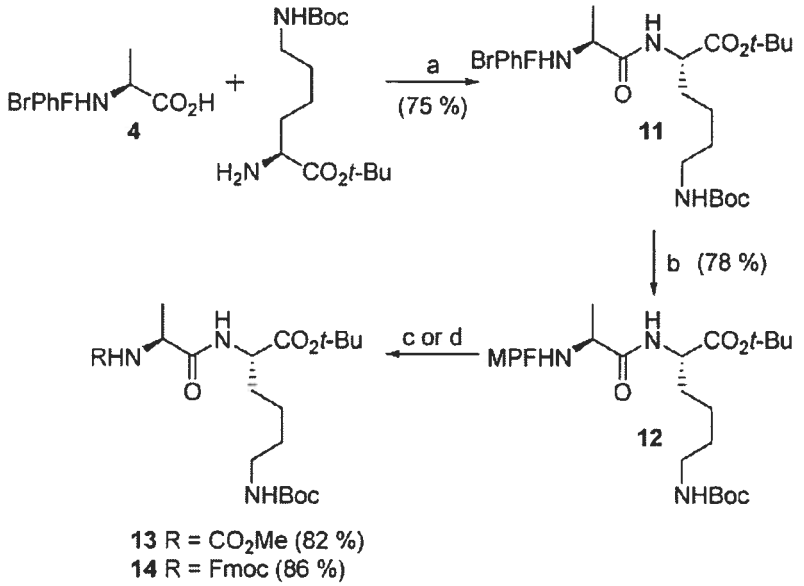


Scheme 10. Synthesis and Solvolysis of *N*-(MPF)alanine Esters[a] [a] Key: (a) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (b) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2; (c) LiOH, H_2O/dioxane; (d) *O-tert*-butyl trichloroacetamidate, CH_2Cl_2; (e) Boc_2O, Et_3N, CH_2Cl_2.

and *N*-(MPF)alanine methyl ester (**71**) was performed by treating an equimolar mixture of the protected amino acids in CH_2Cl_2 with trichloroacetic acid and triethylsilane. Under these conditions, the 9-(4-morpholinophenyl)-9-fluorenyl group was cleaved within 5 min as monitored by HPLC, which detected 9-(4-morpholinophenyl)-9-fluorene (**72**). The PhF-protected methyl ester remained stable and no trace corresponding to PhFH was observed by HPLC. Employing the milder dichloroacetic acid under the same conditions, complete solvolysis of *N*-(MPF)alanine methyl ester (**71**) occurred within 30 min.

The selective removal of the BrPhF group from an amino *tert*-butyl ester was next studied to establish cleaving conditions tolerant to a more acid-labile group. *N*-(BrPhF)Alanine **73** was synthesized as previously described by hydrolysis of methyl ester **70** using LiOH.[14] *N*-(BrPhF)alanine *tert*-butyl ester (**74**) was then prepared in 81% yield by treating the amino acid with *O-tert*-butyl trichloroacetimidate[17] in dichloromethane followed by chromatography. The conversion of *N*-(BrPhF)alanine *tert*-butyl ester (**74**) to *N*-(MPF)alanine *tert*-butyl ester (**75**) was achieved in 79% yield using the palladium-catalyzed reaction conditions mentioned above. Exposure of a 1:1 mixture of *N*-(PhF)alanine *tert*-butyl ester[18] and *N*-(MPF)alanine *tert*-butyl ester (**75**) to dichloroacetic acid and triethylsilane in CH_2Cl_2 caused selective deprotection in 30 min as monitored by HPLC which indicated the appearance of morpholine **72** and no traces of 9-phenylfluorene nor any corresponding acids after 30 min. Treatment of *N*-(MPF)alanine *tert*-butyl ester (**75**) with 20 equiv of dichloroacetic acid and 2 equiv of triethylsilane in CH_2Cl_2 for 30 min followed by addition of 22 equiv of triethylamine and Boc_2O provided *N*-(Boc)alanine *tert*-butyl ester in 84% yield. Alternatively, alanine *tert*-butyl ester could be isolated as its hydrochloride salt in 89% yield after MPF deprotection, extraction with dilute aqueous HCl, and lyophilization.

To explore more deeply the strengths and limitations of this protection group *N*-(BrPhF)alaninyl(ω-Boc)lysine *tert*-butyl ester (**80**) was synthesized by coupling



Scheme 11. Synthesis and Solvolysis of *N*-(MPF)-Protected Dipeptides[a] [a] Key: (a) DCC, HOBt, DIEA, CH_2Cl_2; (b) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (c) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, $ClCO_2Me$; (d) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, FmocOSu.

acid **73** with (ω-Boc)lysine *tert*-butyl ester using DCC and HOBt in 75% yield (Scheme 11).

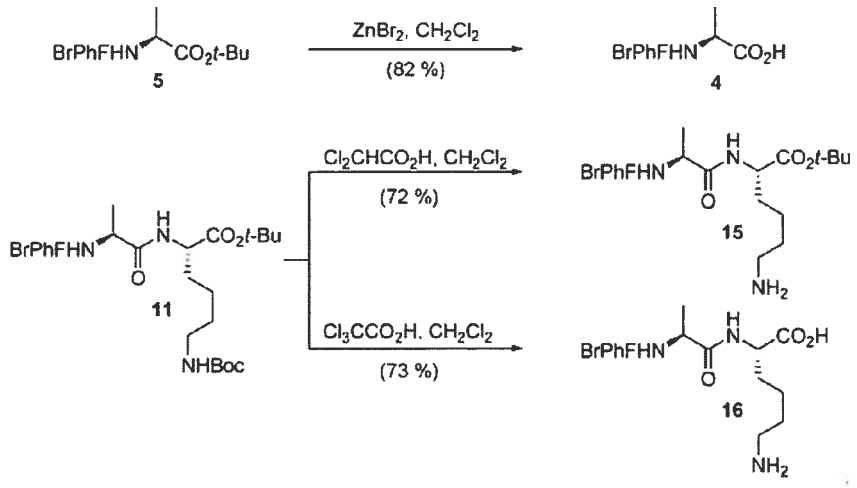
Conversion to the *N*-(MPF) dipeptide **81** was effected as previously described in 78% yield. The MPF-protected amine was selectively deblocked using $CHCl_2CO_2H$ and Et_3SiH and the free amine was subsequently converted in situ to a methyl carbamate using methylchloroformate and Et_3N in 82% yield. The ^1H NMR spectrum of the crude mixture showed a one-to-three ratio of singlets corresponding to the methyl and *tert*-butyl protons for the carbamates indicating that no deprotection

of the Boc-protected amine had occurred. The LC-MS analysis of the crude mixture also confirmed that Boc-deprotection did not occur during the sequence. Using a similar protocol, *N*-(Fmoc)alaninyl(ω-Boc)lysine *tert*-butyl ester (**83**) was synthesized by deprotecting the MPF-amine and reprotecting using FmocOSu and Et_3N in 86% yield.

Selective removal of *tert*-butyl esters in the presence of PhF amines has been recently reported to be effectively accomplished using $ZnBr_2$ in CH_2Cl_2.[18] When BrPhF-Ala-O*t*Bu (**74**) was submitted to these conditions, *N*-(BrPhF)alanine was obtained in 82% yield (Scheme 12). The acid stability of the BrPhF group was demonstrated by the selective removal of the Boc group using Cl_2CHCO_2H which afforded dipeptide **84** in 72% yield, as well as by removal of both the *tert*-butyl ester and carbamate groups using the stronger acid Cl_3CCO_2H to give dipeptide **85** in 73% yield. These results demonstrated that the orthogonal nature of the BrPhF/*tert*-Bu combination of protecting groups can be utilized in both directions.

4.4 Conclusion

In sum, we have demonstrated the utility of the 9-(4-bromophenyl)-9-fluorenyl group as safety-catch amine protection. Similar to the PhF group, the BrPhF group may be used to ensure the configurational stability of amino carbonyl compounds. This relatively acid stable group can then be rendered susceptible to mild acid solvolysis by palladium-catalyzed amination. The potential of this strategy has



Scheme 12. Selective *tert*-Butyl Ester and Carbamate Cleavage

been illustrated by the palladium-mediated selective cleavage of the BrPhF-amine in the presence of the acid labile *tert*-butyl ester and carbamate groups and complementary removal of either Boc group or both Boc and *tert*-butyl ester groups in the presence of the BrPhF-amine. Considering the need for selective methods for removing acid labile protecting groups, the BrPhF group should find general utility in the synthesis of amines.

5.5 Experimental Section

(2*S*)-*N*-(BrPhF)Alanine *tert*-butyl ester (74). To a stirred suspension of (2*S*)-*N*-(BrPhF)alanine (540 mg, 1.32 mmol, prepared according to ref 14) in CH_2Cl_2 (4 mL) was added *O*-*tert*-butyl trichloroacetimidate (578 mg, 2.64 mmol). The mixture was stirred for 1 day, filtered, evaporated, and resubmitted to the same conditions as

above for 2 days. Filtration and evaporation, followed by chromatography (5% EtOAc in hexanes) gave ester **74** (495 mg, 81%) as a clear oil: $[\alpha]^{20}_{D}$ -51.3 (*c* 1.5, CH_3OH); ^1H NMR δ7.72 (d, *J* = 7.8 Hz, 2H) 7.40-7.26 (m, 10H), 3.09 (s, 1H), 2.69 (q, *J* = 7.1 Hz, 1H), 1.23 (s, 9H), 1.13 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ175.4, 148.9, 148.6, 143.7, 140.3, 139.7, 130.9, 127.99, 127.96, 127.7, 127.6, 127.5, 125.4, 124.8, 120.7, 119.7, 119.5, 80.1, 72.3, 51.6, 27.5, 21.8; HRMS calcd for $C_{26}H_{27}BrNO_2$ [M + H]$^+$ 464,1227, found 464.1219.

General Procedure for *N*-(MPF)amine Synthesis. The BrPhF-protected amine (2.5 mmol) was dissolved in 5 mL of dry and degassed toluene and treated with $Pd(OAc)_2$ (28 mg, 0.13 mmol), BINAP (79 mg, 0.13 mmol), and dry Cs_2CO_3 (4.07 g, 12.5 mmol), followed by morpholine (257 μL, 3.0 mmol). The mixture was heated at reflux and stirred for 24 h, filtered on Celite, washed with CH_2Cl_2, and the combined filtrate and washings were evaporated. The residue was chromatographed to afford the MPF-protected amine.

(2*S*)-*N*-(MPF)Alanine methyl ester (71). Chromatography of the product from **70** (1.00 g, 2.4 mmol) using 20% EtOAc in hexanes as eluant gave **71** (820 mg, 81% yield) as a yellowish solid: mp 62-64 °C; $[\alpha]^{20}_{D}$ -121.1° (*c* 2.2, CH_3OH); ^1H NMR δ.68 (dd, *J* = 7.5 Hz, 2.5 Hz, 2H), 7.33 (m, 5H), 7.23 (m, 3H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.82 (t, *J* = 4.8 Hz, 4H), 3.30 (s, 3H), 3.10 (t, *J* = 4.8 Hz, 4H), 2.77 (q, *J* = 7.0 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ177.1, 150.1, 149.4, 148.8, 140.6, 139.9, 135.6, 128.0, 127.6, 127.2, 126.9, 125.8, 124.8, 119.8, 119.7, 115.1, 72.4,

66.7, 51.4, 51.2, 49.0, 21.4; HRMS calcd for $C_{27}H_{28}N_2O_3Na$ $[M + Na]^+$ 451.1989, found 451.1992.

General Procedure for MPF-Solvolysis. The MPF-protected amine (0.4 mmol) was dissolved in 4 mL of CH_2Cl_2, treated with dichloroacetic acid (660 μL, 8 mmol) and triethylsilane (128 μL, 0.8 mmol), stirred at rt for 30 min, and evaporated on a rotary evaporator. The residue was dissolved in 10 mL of Et_2O and treated with 10 mL of 0.5 M HCl solution. The aqueous phase was separated, washed twice with 5 mL of Et_2O, and lyophilized to give the unprotected amine as a hydrochloride salt. Alternatively, after complete solvolysis of MPF-amine was observed by TLC, the reaction mixture was treated with 22 equiv of Et_3N followed by 200 mol % of either Boc_2O, methyl chloroformate or FmocOSu, stirred overnight, diluted with CH_2Cl_2, washed with H_2O, 0.5 N HCl, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography[20] to give, respectively, the Boc-, methyl carbamoyl- or Fmoc-protected amino ester.

(2*S*)-Alanine *tert*-butyl ester hydrochloride (68). Lyophilization of aqueous layer after solvolysis of **6** (190 mg, 0.4 mmol) gave **68** (65 mg, 89% yield) as a white solid: mp 170°C dec (lit.[19] mp 168°C dec); $[\alpha]^{20}_D$ 6.1° (*c* = 1.0, EtOH) [lit.[19] $[\alpha]^{20}_D$ 3.0° (*c* = 2.0, EtOH)]; HRMS calcd for $C_7H_{15}NO_2Na$ $[M + Na]^+$ 168.0995, found 168.0987.

***N*-(Fmoc)alaninyl-ω-(Boc)lysine *tert*-butyl ester (83).** Chromatography of the product from **81** (30 mg, 0.11 mmol) using 30% EtOAc/hexanes as eluant gave **83** as a white powder (22.0 mg, 86% yield): mp 67-69°C; $[\alpha]^{20}_D$ -16.5° (*c* 1.0, $CHCl_3$); ^1H

NMR δ7.76 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.31 (tt, J = 7.5, 1.2 Hz, 2H), 6.59 (d, J = 6.7 Hz, 1H), 5.59 (s, 1H), 4.69 (s, 1H), 4.45 (m, 1H), 4.38 (d, J = 7.0 Hz, 2H), 4.29 (m, 1H), 4.22 (t, J = 7.0 Hz, 1H), 3.06 (d, J = 5.5 Hz, 1H), 1.84 (m, 2H), 1.65 (m, 1H), 1.52-1.27 (m, 6H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR δ171.8, 171.0, 156.0, 155.8, 143.6, 141.1, 127.6, 126.9, 125.0, 119.8, 82.1, 79.0, 67.0, 52.4, 50.3, 47.0, 39.9, 33.5, 29.2, 28.3, 27.8, 21.9, 18.6; HRMS calcd for $C_{33}H_{45}N_3O_7$ $[M + Na]^+$ 618.31389, found 618.31389.

4-[4-(9*H*-Fluoren-9-yl)phenyl]morpholine (72). The *N*-arylamine **72** was isolated by flash chromatography as the second eluting compound of the crude residue in the solvolysis of the MPF-protected amine **5**: ^{1}H NMR δ7.82 (d, J = 7.5 Hz, 2H), 7.42-7.26 (m, 6H), 7.03 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 5.02 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H); ^{13}C NMR δ149.7, 147.9, 140.5, 128.7, 126.9, 126.8, 124.9, 119.4, 115.5, 66.6, 53.3, 49.0; MS (ESI, *m/z*) 328.3 $(MH)^+$.

(2*S*)-*N*-(BrPhF)Alanine (73). A stirred solution of *N*-(BrPhF)alanine *tert*-butyl ester (**75**) (45 mg, 0.1 mmol) in 0.5 mL of dichloromethane was treated with $ZnBr_2$ (110 mg, 0.5 mmol) at rt, stirred for 24 h, treated with water (2 mL), stirred for 2 h, and treated with CH_2Cl_2 (5 mL). The organic phase was separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 mL). The organic portions were combined, dried, filtered, and evaporated. The residue was chromatographed (50% EtOAc:hexanes containing 1% AcOH) to afford 32.5 mg (82% yield) of *N*-(BrPhF)alanine as a white solid: mp 116-118°C; $[\alpha]^{20}_D$ -16.5° (*c* 1.1, CH_3OH). The spectroscopic data were identical to those reported.[14]

***N*-(BrPhF)-L-Alanyl-ω-(Boc)-L-lysine *tert*-butyl ester (80).** *N*-(BrPhF)alanine (**73**), (514 mg, 1.26 mmol), DCC (311 mg, 1.51 mmol), and HOBt (204 mg, 1.51 mmol) were dissolved in 13 mL of CH_2Cl_2, treated with ω-(Boc)lysine *tert*-butyl ester (380 mg, 1.26 mmol), stirred for 24 h, filtered, washed with a 10% HCl solution, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography (50% EtOAc/hexanes) to afford 651 mg (75% yield) of **80** as a white powder: mp 83-85°C; $[\alpha]^{20}_D$ -20.8° (*c* 1.0, CH_3OH); ^1H NMR δ7.96 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.44-7.25 (m, 9H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.68 (m, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 3.10 (m, 2H), 2.47 (q, *J* = 7.1 Hz, 1H), 2.25-1.80 (bs, 1H), 1.75 (m, 1H), 1.62 (m, 1H), 1.54 (s, 9H), 1.43 (s, 9H), 1.54-1.43 (m, 2H), 1.29 (m, 2H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ175.1, 171.8, 156.1, 148.9, 147.3, 143.5, 141.4 140.0, 131.6, 128.9, 128.8, 128.2, 128.1, 127.7, 126.1, 124.3, 121.4, 120.4, 120.2, 82.2, 79.1, 73.0, 52.8, 51.9, 40.4, 33.0, 29.5, 28.5, 28.1, 22.2, 21.8; HRMS calcd for $C_{37}H_{46}BrN_3O_5Na$ $[M + Na]^+$ 714.25131, found 714.25002.

***N*-(BrPhF)-L-Alanyl-L-lysine *tert*-butyl ester (84).** *N*-(BrPhF)alaninyl(ω -Boc)lysine *tert*-butyl ester **80** (50 mg, 0.072 mmol) was dissolved in 150 μL of CH_2Cl_2, treated with 150 μL of Cl_2CHCO_2H, and stirred for 21 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, concentrated, and purified by chromatography (5% MeOH/$CHCl_3$ + 1% Et_3N) to give amine **84** (30.7 mg, 72% yield) as a brownish oil: $[\alpha]^{20}_D$ 39.7° (*c* 2.6, $CHCl_3$); ^1H NMR (CD_3OD) δ7.80 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.46-

7.26 (m, 9H), 7.08 (dt, J = 1.0, 7.6 Hz, 1H), 4.06 (m, 1H), 2.90 (m, 2H), 2.44 (q, J = 7.1 Hz, 1H), 1.73 (m, 1H), 1.64 (m, 3H), 1.53 (s, 9H), 1.29 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ178.6, 172.5, 150.5, 149.3, 145.3, 142.4, 141.6, 132.3, 129.9, 129.7, 129.3, 128.4, 127.2, 125.8, 122.0, 121.1, 83.5, 74.2, 53.8, 53.3, 40.5, 33.1, 28.3, 28.0, 23.5, 21.5; HRMS calcd for $C_{32}H_{39}BrN_3O_3Na$ $[M + H]^+$ 592.21693, found 592.21666.

***N*-(BrPhF)-L-Alanyl-L-lysine (85).** The BrPhF-protected dipeptide **80** (40 mg, 0.058 mmol) was dissolved in 300 μL of CH_2Cl_2, treated with Cl_3CCO_2H (236 mg, 1.44 mmol), and stirred for 72 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with 0.1 N HCl (2 × 3 mL), lyophilized, triturated with Et_2O, and purified on reversed-phase preparative HPLC to afford **85** (22.6 mg, 73% yield) as a white gum: $[\alpha]^{20}_D$ -3.1° (*c* 1.1, CH_3OH); ^{1}H NMR (D_2O) δ7.78 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.32 (m, 3H) 7.21 (d, J = 8.5 Hz, 2H), 7.12 (m, 2H), 6.98 (d, J = 8.6 Hz, 2H), 3.47 (t, J = 6.6 Hz, 1H), 3.12 (q, J = 6.6 Hz, 1H), 2.87 (m, 2H), 1.51 (m, 2H), 1.33 (m, 2H), 1.19 (d, J = 7.1 Hz, 3H), 1.01 (m, 2H);^{13}C NMR (D_2O) δ175.5, 170.1, 140.8, 140.3, 140.1, 131.6, 130.8, 130.6, 129.0, 127.9, 126.9, 126.8, 124.9, 122.0, 120.9, 120.4, 73.3, 53.2, 52.7, 38.6, 29.5, 26.0, 21.6, 16.9; HRMS calcd for $C_{28}H_{31}BrN_3O_3$ $[M + H]^+$ 536.15433, found 536.15304.

4.6 Acknowledgment

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4.7 Supporting Information Available

General Experimental Section, ^{1}H and ^{13}C NMR data for compounds **75**, **77**, **79**, **81**, and **82**, copies of ^{1}H and ^{13}C NMR spectra of compounds **71**, **72**, **74**, **75**, and **80-85**, and HPLC traces of competitive cleavage experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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CHAPITRE 5

Perspective et conclusion

5.1 Perspective

Les deuxième et troisième chapitres ont montré le développement de deux méthodologies de synthèse permettant d'obtenir deux différents types de mimes de tours β. En effet, le chapitre 2 traite d'une stratégie de synthèse permettant d'obtenir des dipeptides macrocyliques tandis que le chapitre 3 en discute une autre permettant d'obtenir des dipeptides bicycliques. Tel que mentionné dans le chapitre 1, l'insertion de ces différents mimes dans des peptides permet d'obtenir plus d'information sur la conformation du peptide requise pour se lier avec le récepteur et ainsi induire un effet biologique.

Toutefois, malgré que le développement de la synthèse peptidique sur support solide[1] ait permis de produire rapidement et efficacement des quantités appréciables de différents peptides, l'incorporation de mimes peptidiques dans des peptides est souvent limitée par la synthèse multi-étapes en solution requise pour la mise au point de ces différents mimes. De plus, puisque la synthèse d'une quantité appréciable d'une combinaison de différents mimes demande beaucoup d'efforts synthétiques, l'emplacement de l'incorporation de ces derniers mimes doit être planifié et ne permet pas de sonder toutes les possibilités conformationnelles d'un peptide. Évidement une des solutions à ce problème consisterait à faire la synthèse du mime peptidique sur phase solide au fur et à mesure que la chaîne peptidique est construite sur le support solide, ce qui éviterait la tâche fastidieuse des multiples purification et

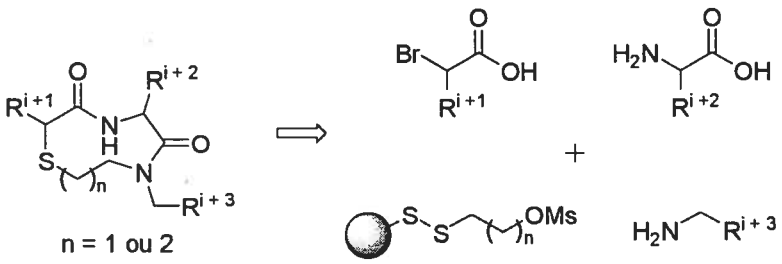

Figure 19. Synthèse de mimes de tours β cycliques sur support solide

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ermettrait de faire un balayage conformationnel en remplaçant chaque duo d'acides aminés formant le peptide par un mime peptidique.

Quelques groupes de recherches ont tenté de mettre au point des méthodologies de synthèse sur support solide qui permettraient d'obtenir rapidement des mimes peptidiques qui pourront être testés pour connaître leur activité biologique. Par exemple, une stratégie permettant de synthétiser des mimes de tours β cycliques a été mise au point en utilisant quatre blocs de construction simples (Figure 18).[2] En effet, un acide aminé est utilisé en position i + 2, une amine primaire permet de mimer l'interaction de la chaîne latérale de l'acide aminé en position i + 3, tandis que celle de la position i + 1 est introduite par l'utilisation d'un α-bromo acide. Finalement la synthèse du mime peptidique peut être effectué sur support solide en utilisant une résine de polystyrène aminométhylée comportant un espaceur formé d'un lien disulfure et terminé d'un mesylate. En utilisant cette stratégie, une chimiothèque de 172 membres a pu être synthétisée ce qui a permis la découverte

d'un ligand se liant au récepteur de la somostatine hSST5 avec une valeur d'IC_{50} de 87 nm.

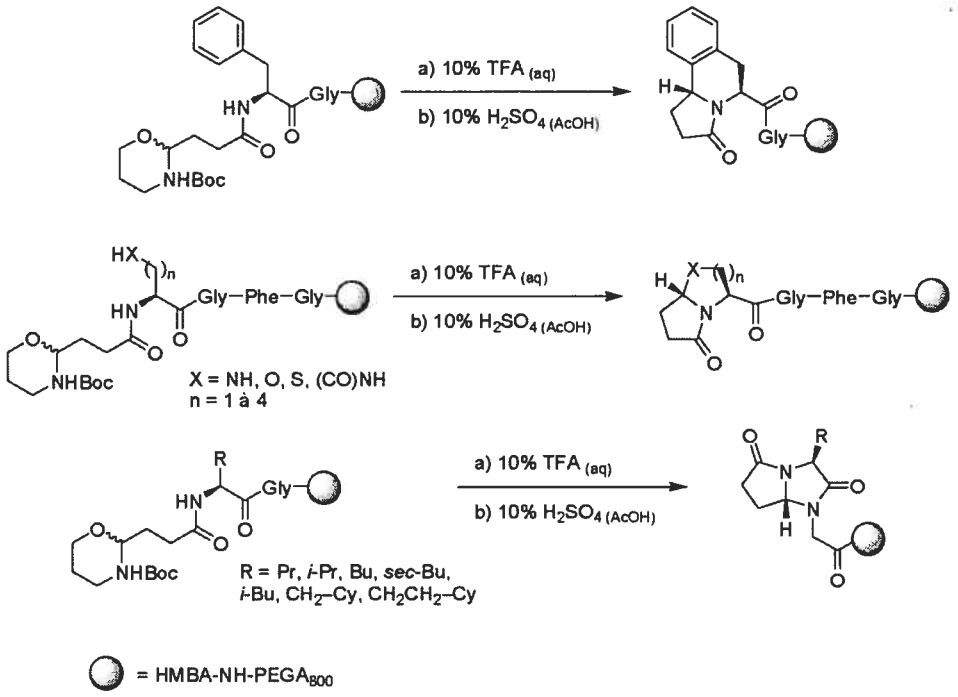

Schéma 13. Synthèse de différents mimes peptidiques bicycliques sur support solide.

Plus récemment, une stratégie générale de synthèse de mimes peptidiques sur support solide a été développée afin d'obtenir différents dipeptides bicycliques. Cette méthodologie tire profit d'un aldéhyde masqué installé en fin de chaîne peptidique qui réagit pour former un ion *N*-acyliminium qui est à son tour trappé par différents nucléophiles (Schéma 13).[3] En effet, tout dépendamment de la chaîne latérale présente sur le dernier acide aminé du peptide en construction, trois différents types de mimes peptidiques bicycliques peuvent être synthétisés avec d'excellentes puretés.

L'utilisation d'un acide aminé comportant un groupement aryle sur la chaîne latérale permettra une réaction de type Pictet–Spengler. D'un autre côté, si un nucléophile est

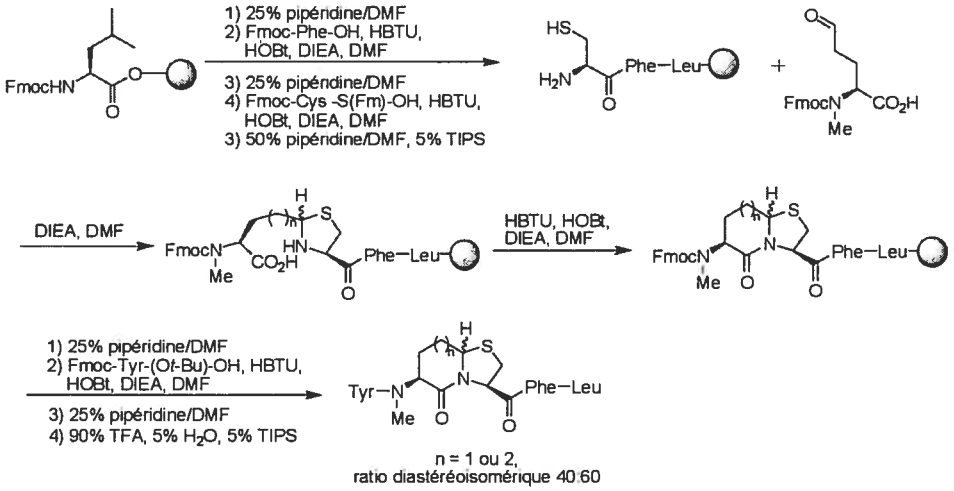

Schéma 14. Synthèse d'une chimiothèque d'analogues de Leu-Enképhaline incorporant un mime de type BTD.

pré

sent sur la chaîne latérale, ce dernier attrappera l'ion *N*-acyliminium alors que, dans le cas contraire, l'ion sera attrappé par l'azote de l'amide de l'avant dernier résidu du peptide.

De plus, une stratégie de synthèse permettant d'incorporer le mime BTD directement au peptide en construction sur support solide a été mise au point dernièrement (Schéma 14).[4] Un des concepts clés de cette méthodologie réside en l'utilisation des acides aminés ω-carboxaldehyde *N*-méthylés, pour contrer la formation d'hémiaminales lors de la formation de la thiazolidine. Ainsi, onze

analogues bicycliques de la Leu-Enképhaline *N*-méthylés ont pu être synthétisés et examinés pour leurs affinités liantes à différents récepteurs opioïdes. L'avantage d'utiliser une méthodologie sur support solide a été démontré en indiquant que chaque analogue de la Leu-Enképhaline avait été synthétisé en douze étapes et ce, en seulement deux jours.

Notre méthodologie de synthèse de mime peptidique macrocyclique ainsi que d'acides aminés azabicycloalkanone possède l'avantage d'utiliser des blocs de construction semblables. Il est donc facile d'imaginer que la méthodologie pourrait être adaptée à une méthodologie de synthèse sur support solide (Schéma 15). À première vue la synthèse de mimes macrocycliques sur support solide semble possible, mais réside surtout dans la réalisation de la fermeture de cycle par métathèse d'oléfines dans des conditions hétérogènes. Bien que les rapports de RCM sur des substrats immobilisés sur un support solide sont beaucoup moins nombreux cette dernière méthodologie est maintenant utilisé avec un certain succès. Notablement, des mimes du peptide oxytocine ont été mis au point en utilisant la méthodologie de RCM sur support solide.[5] L'oxytocine est un peptide cyclique constitué de 9 acides aminés et possède un pont disulfure entre les cystéines en positions 1 et 6 formant un macrocycle de 20 membres. Puisque le temps de demi-vie de l'oxcytocine varie entre 2 et 5 minutes, les chercheurs ont tenté de ralentir le métabolisme du peptide en remplaçant chaque atome de souffre formant le macrocycle par une unité méthylène ou méthine. Ainsi des peptides comportant des macrocyles de 20 à 22 membres ont été synthétisés sur support solide en remplaçant l'acide aminé cystéine par des unités

allylglycines ou homoallylglycine lors de la synthèse du peptide et en effectuant ensuite la fermeture de cycle par métathèse d'oléfines toujours sur support solide. Bien que thérapeutiquement moins actifs, ces analogues d'oxytocin ont montré leur utilité en ayant un temps de demie-vie de 24 minutes dans des tissus de placenta comparativement à 4 minutes pour l'oxytocine.

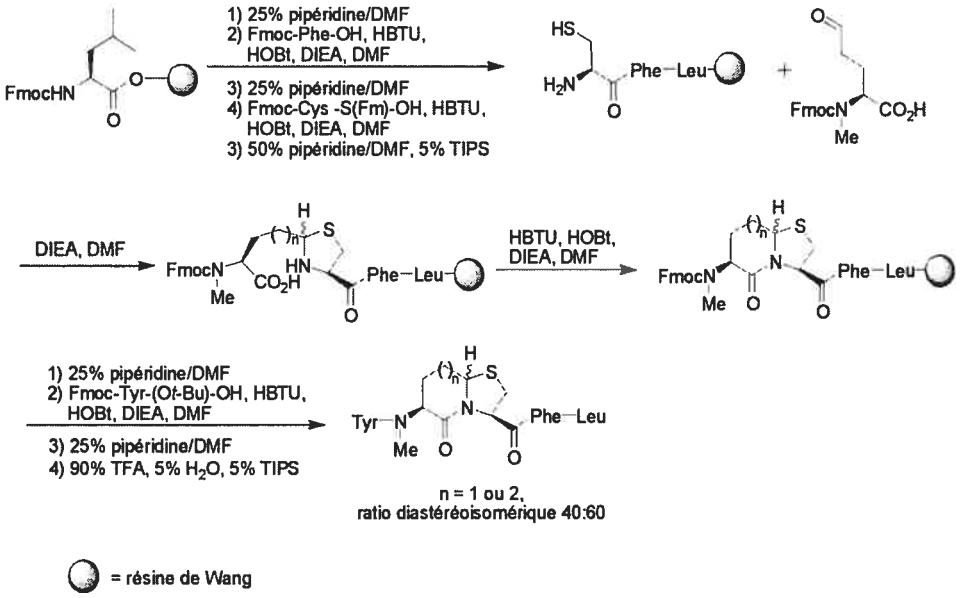

Schéma 15. Synthèse sur phase solide de peptides comportant soit un mime macrocyclique soit un mime bicyclique.

5.2 Synthèse de mimes peptidiques sur support solide

Afin de prouver que la méthodologie pouvait être adaptée à une synthèse sur support solide, nous avons donc choisi de synthétiser un hexapeptide constitué d'acides aminés possédant des chaînes latérales non-fonctionnalisées comme la leucine et la valine et où les acides aminés en position 3 et 4 seraient substitués par un

dipeptide macrocyclique. La synthèse a donc débuté en couplant la Fmoc-Val-OH à la résine de Wang[6] en utilisant le TBTU[7] comme agent de couplage et le HOBt[8] comme agent suppresseur de racémisation (Schéma 16). Le groupe protecteur Fmoc

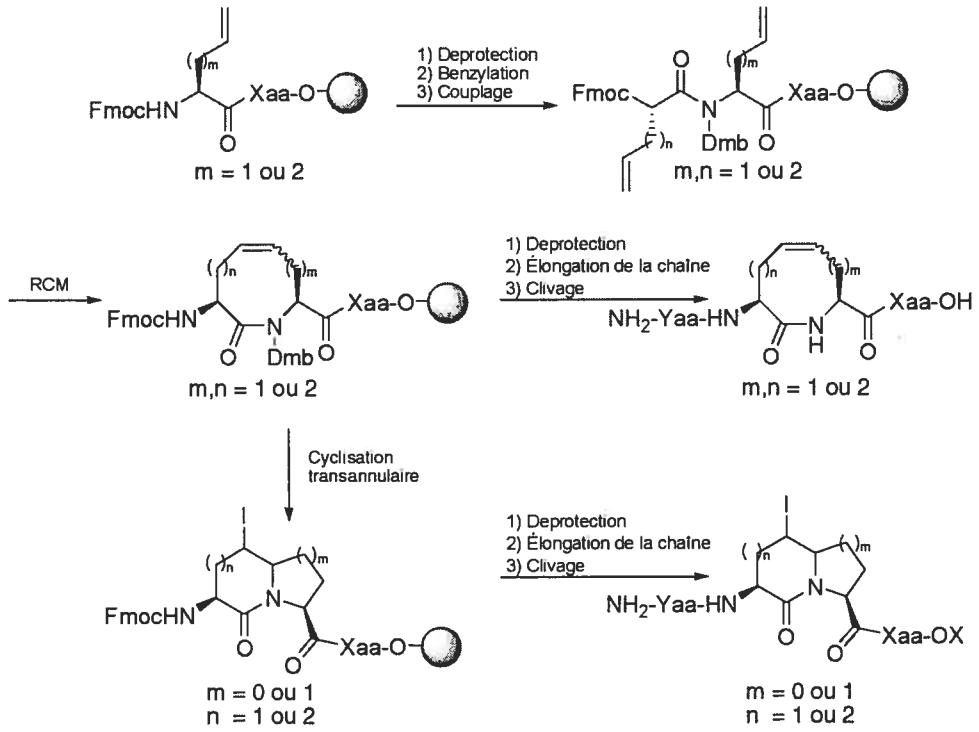

Schéma 16. Synthèse d'un tétrapeptide dioléfinique.

a ensuite été enlevé en utilisant un mélange constitué de 20% pipéridine dans le DMF et la Fmoc-Leu-OH a ensuite été couplée en utilisant les conditions citées précédemment pour obtenir le dipeptide **88** sur support solide. La même séquence a été utilisée pour coupler la *N*-(Fmoc)homoallylglycine pour obtenir le tripeptide sur résine **89**. Contrairement à la méthode utilisée en solution, l'installation d'un groupe 2,4-diméthoxybenzyl sur l'amine terminal a dû se faire en deux étapes afin de minimiser les doubles alkylations et pour obtenir un rendement quantitatif. Le groupe

Fmoc du tripeptide **89** sur résine a donc été clivé, puis l'amine libre a été traitée avec 2 équivalents d'acide acétique et un excès de 2,4-diméthoxybenzaldéhyde dans un mélange 1:1 de dichlorométhane et de triméthylorthoformate.[9] Après 3h d'agitation le mélange a été filtré et lavé, puis traité avec une solution de $NaBH_3CN$ et agiter durant une journée pour obtenir le tripeptide sur résine protégé **90**. Le deuxième acide aminé oléfinique, la Fmoc-HAgly-OH, a ensuite été couplée en utilisant le HATU[10] comme agent de couplage et la *N*-éthylmorpholine comme base pour obtenir le tétrapeptide **91** sur support solide.

Avec le peptide dioléfinique **91** entre nos mains, la cyclisation par métathèse d'oléfine a été tentée (Schéma 17). Lorsque ce dernier peptide a été traité avec une quantité supérieure à celle utilisée précédemment[11] de catalyseur de Grubbs de première génération, soit avec 50 mol %, le tétrapeptide macrocyclique correspondant au produit clivé du macrocycle sur résine **92** a pu être observé par spectre de masse.

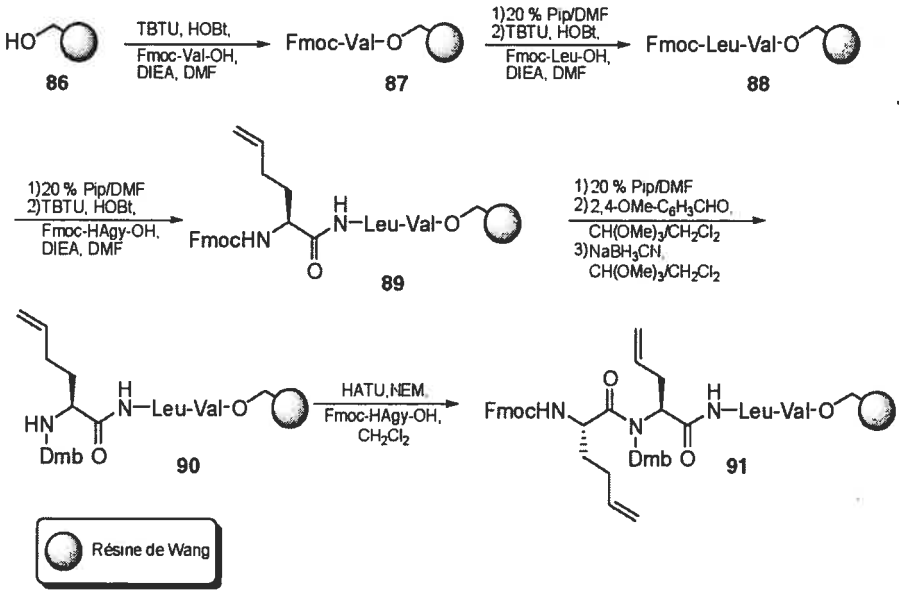

Schéma 17. Synthèse d'hexapeptide macrocyclique à 10 membres par RCM.

Nous avons réalisé qu'une bonne agitation est essentielle au bon fonctionnement de la réaction. Par la suite la chaîne peptidique a été allongée, premièrement en déprotégeant la fonction amine terminale puis en couplant la Fmoc-Val-OH en utilisant le TBTU et le HOBt comme décrit précédemment. Cette séquence déprotection-couplage a été effectuée une fois de plus pour coupler la Fmoc-Leu-OH pour obtenir l'hexapeptide sur support solide **93**. Le peptide a été clivé de son support par traitement avec de l'acide trifluoroacétique 95% dans le DCM. Toutefois, lors de l'analyse par spectre de masse, on a pu constater que le groupe 2,4-diméthoxybenzyl connu pour être labile en conditions acides n'était pas clivé avec ces conditions de clivage. Une prolongation du temps de réaction, ni l'ajout d'anisole[12] n'ont pas aidé le clivage du groupe Dmb.

Puisque l'étape redoutée, la cyclisation par métathèse d'oléfines, a pu être accomplie, la synthèse de macrocycles à neuf membres sur support solide a été tentée (schéma 18). Les mêmes conditions citées précédemment ont été utilisées pour synthétiser les hexapeptides sur support solide **95** et **96**. Malheureusement, lorsque les peptides ont été clivés de leur support en utilisant du TFA à 95% dans le DCM, un mélange d'hexapeptides comportant une fonction amide protégé par un 2,4-diméthoxybenzyl (**97** et **99**) et d'hexapeptides non protégés (**98** et **100**) ont été observés par LC/MS dans un ratio de 9 : 1 respectivement.

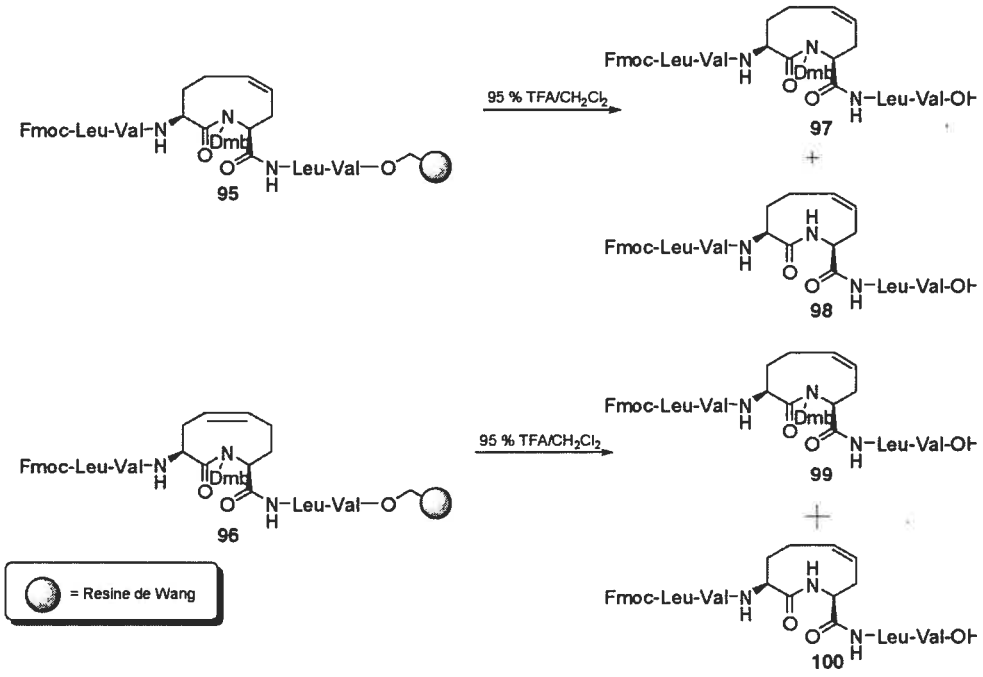

Schéma 18. Synthèse d'hexapeptides macrocycliques à 9 membres par RCM.

5.3 Travaux futurs

Bien entendu, les travaux présentés jusqu'à maintenant ne représente que le début de ce projet. Afin de mener à bien ce projet, deux facettes du projet devront être optimisée. Tout d'abord, il faudra trouver des conditions permettant le clivage simultané du peptide de son support et du groupe protecteur Dmb. Dans le cas où le clivage du groupe Dmb s'avèrerait trop difficile, il pourrait être intéressant de substituer ce groupe par un groupement plus labile en conditions acides comme le methyl-3-indoyl qui est beaucoup plus riches en électron que le groupement 2,4-

diméthoxybenzyl. En effet, il a été démontré que le groupe methyl-indoyl pouvait être clivé d'un amide en utilisant seulement 1% de TFA.[13]

Toutefois, comme présenté dans le chapitre précédent, le clivage du groupe DMB n'est pas nécessaire pour effectuer la cyclisation électrophilique transannulaire. La deuxième étape d'optimisation consisterait donc à transformer les macrocycles sur support solide en azabicycles sur support solide en utilisant l'iode comme électrophile. Bien entendu, la fonctionnalisation des azabicycles obtenus présenterait un autre projet intéressant. En effet, la présence d'un lien carbone-iode peut amener plusieurs idées pour fonctionnaliser les azabicycles. Bien que infructeux à ce jour, le groupement iodure pourrait être déplacé par un azidure qui serait ensuite réduit pour donner une poignée supplémentaire pour la fonctionnalisation. Aussi, l'iodure pourrait être déplacé par un ion cyanure pour donner un nitrile qui pourrait être réduit ou hydrolysé pour obtenir un groupement aminomethyl qui pourrait servir à mimer l'ornitine ou la lysine. D'autres groupes pourraient aussi être introduit en utilisant les récentes procédures développées afin de faire un couplage croisé impliquant des centres secondaires halogénés.[14] De plus, l'iodure pourrait être éliminé donnant ainsi un azabicycle plus rigide et pourrait permettre le marquage radioactif d'un peptide biologiquement actif contenant un azabicycle par tritiation.

5.4 Conclusion

Une méthodologie de synthèse de mimes peptidiques macrocycliques a été mise au point. Les mimes peptidiques macrocycliques de 8, 9 et 10 membres ont été synthétisés en utilisant des dipeptides constitués d'allylglycine et d'homoallylglycine. Les deux oléfines terminales présentent ont servi à cycliser le dipeptide en utilisant la méthodologie de fermeture de cycles par métathèse d'oléfines. Lors de la synthèse, il a été observé que l'utilisation du dipeptide possédant une fonction amide tertiaire était essentiel pour que l'étape de RCM soit réussie avec succès.

Les mimes dipeptidiques macrocycliques ont par la suite servi lors d'une cyclisation électrophile transannulaire à former des mimes dipeptidiques azabicycliques. En effet lorsque les mimes macrocycliques ont été soumis a différents électrophiles comme de l'iode ou du bromure de phénylsélénium, des amino esters azabicyclo[6.5]- ou azabicyclo[7.5.0]alcanone ont été obtenus. L'utilisation ou pas d'un groupement Dmb sur l'azote formant la fonction amide du dipeptide a permis de donner différente stéréochimie sur les atomes de carbones situés en tête de pont et portant l'iodure.

Des résultats préliminaires concernant la synthèse de mimes peptidiques macrocyliques ont été dévoilés. La stratégie, utilisant la résine de Wang comme support polymérique, permet d'élaborer une chaîne peptidique comme on le fait en synthèse peptidique sur support solide et d'insérer les différents acides aminés oléfiniques nécessaires pour former les lactames de 9 et de 10 membres. Une fois que les deux acides aminés oléfiniques ont été introduits, la fermeture de cyclique par métathèse a permis de former la lactame et la synthèse de la chaîne peptidique a pu être continuée par la suite. Toutefois, lors du clivage du peptide, le groupe protecteur 2,4-diméthoxybenzyl n'a pu être entièrement clivé par les conditions acides utilisées.

En plus d'avoir mis au point deux strategies de synthèse pour obtenir de mimes peptidiques macrocycliques et bicycliques, un nouveau groupe protecteur d'amines a été synthétisé. Ce groupement protecteur de type « safety-catch », le 9-(4-bromophényl)-9-fluorényl, possède la stabilité de son cousin, le 9-phényl-9-fluorényl, ainsi que la possibilité d'être clivé dans des conditions acides plus douces lorsque requis. En effet, après avoir été activé par un couplage croisé avec la morpholine catalysé par le palladium, le groupe protecteur peut être clivé en employant de l'acide dichloroacétique. Les conditions douces utilisées ont aussi montré que les groupes labiles en conditions acides comme l'ester et le carbamate *tert*-butylique pouvait être maintenu en place lors de la déprotection de l'amine portant le 9-(4-bromophényl)-9-fluorényl.

5.5 Section expérimentale

Procédure générale d'ancrage sur la résine Wang La résine de Wang (3.00 g, 2.4 mmol), dans le DMF (15 mL), a été successivement traitée avec la Fmoc-Val-OH (3.26 g, 9.6 mmol), le TBTU (3.08 g, 9.6 mmol), le HOBt (1.30 g, 9.6 mmol) et avec la DIEA (2.5 mL, 14.4 mmol). La résine a ensuite été agitée pendant 24 h, puis filtrée, lavée (3 × DMF, 3 × MeOH, 3 × DCM) et séchée sous vide pour obtenir la résine Fmoc-Val-Wang. Le chargement de la résine a par la suite été déterminé par absoption UV du dibenzofulvene lors du clivage du groupement Fmoc comme étant de 0.43 mmol/g.[15]

Procédure générale de clivage du groupement Fmoc La résine Fmoc-Val-Wang (3.00 g, 1.29 mmol) a été traitée avec une solution 20% vol. de pipéridine (15 mL) dans le DMF et agitée pendant 30 min, filtrée, traitée une seconde fois avec la solution de pipéridine 20%, filtrée, lavée (3 × DMF, 3 × MeOH, 3 × DCM) et séchée sous vide pour obtenir la résine H-Val-Wang.

Procédure générale de couplage sur la résine, méthode A La résine H-Val-Wang (3.00 g, 1.29 mmol), dans le DMF (15 mL), a été succesivement traitée avec la Fmoc-Leu-OH (1.82 g, 5.16 mmol), le TBTU (1.66 g, 5.16 mmol), le HOBt (697 mg, 5.16 mmol) et avec la DIEA (1.35 mL, 7.74 mmol). La résine a ensuite été agitée pendant 24 h, puis filtrée, lavée (3 × DMF, 3 × MeOH, 3 × DCM) et séchée pour obtenir la

résine Fmoc-Leu-Val-Wang. Un test de Kaiser négatif a indiqué un couplage complet.[16]

Procédure générale de couplage sur la résine, méthode B La résine Dmb-HAgly-Leu-Val-Wang (100 mg, 0.08 mmol), dans le DCM (1.5 mL), a été succesivement traitée avec la Fmoc-HAgly-OH (112 mg, 0.32 mmol), le HATU (122 mg, 0.32 mmol) et avec la la *N*-ethylmorpholine (61 µL, 0.48 mmol). La résine a ensuite été agitée pendant 24 h, puis filtrée, lavée (3 × DCM, 3 × MeOH, 3 × DCM) et séchée sous vide pour obtenir la résine Fmoc-HAgly-(Dmb)HAgly-Leu-Val-Wang.

Procédure générale d'amination réductrice La résine H-HAgly-Leu-Val-Wang (100 mg, 0.08 mmol), dans une solution 1:1 DCM/triméthylorthoformate (1.5 mL) a été traitée avec le 2,4-diméthoxybenzaldéhyde (292 mg, 1.76 mmol) puis avec l'acide acétique (9.0 µL, 0.16 mmol). La résine a été agitée pendant 3 h, filtrée, lavée (3 × DCM), traitée avec une solution de $NaBH_3CN$ (111 mg, 1.76 mmol) dans une solution 1:1 DCM/triméthylorthoformate (1.5 mL) et agitée pendant une nuit. La résine a ensuite été filtrée, lavée (3 × DCM, 3 × MeOH, 3 × DCM) et séchée sous vide pour donner la résine Dmb-Agly-Leu-Val-Wang

Procédure générale de cyclisation par métathèse d'oléfine La résine Fmoc-HAgly-(Dmb)HAgly-Leu-Val-Wang (50 mg, 0.040 mmol) a été chargée dans un tube de verre 18mm×150mm muni d'un capuchon de teflon, traitée avec une solution de DCM (5 mL), agitée orbitalement , chaufée à reflux, et traitée avec le benzylidène bis(tricyclohexylphosphine)dichlororuthenium (catalyseur de Grubbs de première

génération) (16 mg, 0.020 mmol). La résine a été agitée et chauffée à reflux pendant trois jours, traitée avec du DMSO (71 µL, 1.0 mmol), agitée pendant 12 heures à température pièce, filtrée, lavée (3 × DCM, 3 × DMSO, 3 × MeOH, 3 × DCM) et séchée sous vide pour donner la résine macrocyclique.

Procédure générale de clivage de la résine Wang La résine Fmoc-Leu-Val-Wang (5 mg, 0.004 mmol) a été traitée avec une solution 95:5 TFA/DCM (0.3 mL), agitée pendant 30 min et filtrée. Le filtrat a été concentr. pour donner la Fmoc-Leu-Val-OH.

Résine Fmoc-Val-Wang (87) La résine titre a été synthétisée à partir de la résine de Wang en utilisant la procédure générale d'ancrage sur la résine Wang. Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné la Fmoc-Val-OH : MS calculé pour $C_{20}H_{22}NO_4$: 340.2 $(MH)^+$, MS obtenu : 340.3.

Résine Fmoc-Leu-Val-Wang (88) La résine titre a été synthétisée à partir de la résine **87** en utilisant la procédure générale de clivage du groupe Fmoc suivi de la procédure générale de couplage (méthode A) sur la résine Wang._ Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné la Fmoc-Leu-Val-OH : MS calculé pour $C_{26}H_{33}N_2O_5$: 453.2 $(MH)^+$, MS obtenu : 453.3.

Résine Fmoc-HAgly-Leu-Val-Wang (89) La résine titre a été synthétisée à partir de la résine **88** en utilisant la procédure générale de clivage du groupe Fmoc suivi de la procédure générale de couplage (méthode A) sur la résine Wang. Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné la

Fmoc-HAgly-Leu-Val-OH : MS calculé pour $C_{32}H_{42}N_3O_6$: 564.3 $(MH)^+$, MS obtenu : 564.4.

Résine Dmb-HAgly-Leu-Val-Wang (90) La résine titre a été synthétisée à partir de la résine **89** en utilisant la procédure générale de clivage du groupe Fmoc suivi de la procédure générale d'amination réductrice. Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné la Dmb-HAgly-Leu-Val-OH : MS calculé pour $C_{26}H_{42}N_3O_6$: 492.3 $(MH)^+$, MS obtenu : 492.3.

Résine Fmoc-HAgly-(Dmb)-HAgly-Leu-Val-Wang (91) La résine titre a été synthétisée à partir de la résine **90** en utilisant la procédure générale de couplage (méthode B) sur la résine Wang. Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné la Fmoc-HAgly-(Dmb)-HAgly-Leu-Val-OH : MS calculé pour $C_{38}H_{51}N_4O_7$: 675.2 $(MH\text{-}Dmb)^+$, MS obtenu : 675.4.

Résine [(*E*, 3*S*, 10*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxyl]-Leu-Val-Wang 92 La résine titre a été synthétisée à partir de la résine **91** en utilisant la procédure générale en utilisant la procédure générale de cyclisation par métathèse d'oléfines. Le clivage de la résine en utilisant la procédure générale de clivage de la résine Wang a donné le tétrapeptide comprenant la lactame de 10 membres correspondant : MS calculé pour $C_{45}H_{56}N_4O_9$: 797.4 $(MH)^+$, MS obtenu : 797.2.

Résine Fmoc-Leu-Val-[(*E*, 3*S*, 10*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxyl]-Leu-Val-Wang 93 La

résine titre a été synthétisée à partir de la résine **92** en utilisant la procédure générale de clivage du groupe Fmoc suivi de la procédure générale de couplage (méthode A) pour coupler la Fmoc-Val-OH. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale de couplage (méthode A) a été utilisée pour coupler la Fmoc-Leu-OH pour donner la résine **93**.

Fmoc-Leu-Val-[(*E*, 3*S*, 10*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxyl]-Leu-Val-OH 94 Le clivage de la résine **93** en utilisant la procédure générale de clivage de la résine Wang a donné l'hexapeptide **94** : MS calculé pour $C_{56}H_{77}N_6O_{11}$: 1009.6 $(MH)^+$, MS obtenu : 1009.4.

Résine Fmoc-Leu-Val-[(*E*, 3*S*, 9*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxyl]-Leu-Val-Wang 95 La résine titre a été synthétisée à partir de la résine **88** en utilisant la procédure générale de clivage du groupe Fmoc, suivi de la procédure générale de couplage (méthode A) pour coupler la Fmoc-Agly-OH. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale d'amination réductrice et de couplage (méthode B) ont été utilisées pour coupler la Fmoc-HAgly-OH. La procédure générale de cyclisation par métathèse d'oléfines a été utilisée pour obtenir le macrocycle sur support solide. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale de couplage (méthode A) a été utilisée pour coupler la Fmoc-Val-OH. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale de couplage (méthode

A) a été utilisée pour coupler la Fmoc-Leu-OH sur la résine Wang pour donner la résine **95**.

Résine Fmoc-Leu-Val-[(3*S*,9*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxyl]-Leu-Val-Wang 96 La résine titre a été synthétisée à partir de la résine **88** en utilisant la procédure générale de clivage du groupe Fmoc, suivi de la procédure générale de couplage (méthode A) pour coupler la Fmoc-HAgly-OH. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale d'amination réductrice et de couplage (méthode B) ont été utilisées pour coupler la Fmoc-Agly-OH. La procédure générale de cyclisation par métathèse d'oléfines a été utilisée pour obtenir le macrocycle sur support solide. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale de couplage (méthode A) a été utilisée pour coupler la Fmoc-Val-OH. Le groupement protecteur Fmoc a ensuite été clivé puis la procédure générale de couplage (méthode A) a été utilisée pour coupler la Fmoc-Leu-OH sur la résine Wang pour donner la résine **96**.

Hexapeptides 97 et 98 Le clivage de la résine **95** en utilisant la procédure générale de clivage de la résine Wang a donné les hexapeptides **97** et **98** dans un ration 9:1 par LC/MS : MS calculé pour $C_{55}H_{76}N_6O_{11}$ (**97**): 995.5 $(MH)^+$, MS obtenu : 995.3, MS calculé pour $C_{46}H_{65}N_6O_9$ (**98**): 846.5 $(MH)^+$, MS obtenu : 846.3.

Hexapeptides 99 et 100 Le clivage de la résine **96** en utilisant la procédure générale de clivage de la résine Wang a donné les hexapeptides **99** et **100** dans un ration 9:1

par LC/MS : MS calculé pour $C_{55}H_{76}N_6O_{11}$ (**99**): 995.5 $(MH)^+$, MS obtenu : 995.3, MS calculé pour $C_{46}H_{65}N_6O_9$ (**100**): 846.5 $(MH)^+$, MS obtenu : 846.3

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Systematic Study of the Synthesis of Macrocyclic Dipeptide β-Turn Mimics Possessing 8-, 9- and 10- Membered Rings by Ring Closing Metathesis

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Supporting Information

Table of contents

General Experimental Section. Unless otherwise noted, all reactions were performed under argon atmosphere and distilled solvents were transferred by syringe. Anhydrous CH_2Cl_2 (DCM), THF and diethyl ether were obtained from a solvent filtration system. Final reaction mixture solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered and rotary-evaporated under reduced pressure. Melting points are uncorrected. Mass spectral data, HRMS/LRMS (EI and FAB), were obtained by the Université de Montréal Mass Spectrometry facility. Unless otherwise noted, ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane ($(CH_3)_4Si$), residual $CHCl_3$ (δ 7.27 and 77.2), residual MeOH (δ 3.31 and 49.0) or residual DMSO (δ 2.50 and 39.5); coupling constant *J*-values are reported in hertz (Hz). Two dimensional NMR experiments COSY and NOESY for **30** and **31** were performed at 500 MHz with mixing times of 400 ms and 800 ms. Analytical thin-layer chromatography (TLC) was performed by using aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Compounds were purified by column chromatography using 230-400 mesh silica gel.

Methyl (2S)-2-[(2-Hydroxy-6-nitrobenzyl)amino]pent-4-enoate (40b). Using General Procedure **A**, followed by chromatography of the product from **36** (1 mmol) using 50:50 EtOAc/hexanes as eluant gave **40b** as a brown gum (52% yield): ^{1}H NMR δ7.28 (m, 2H), 7.03 (m, 1H), 5.65 (m, 1H), 5.15 (m, 2H), 4.22-4.0 (q, 2H, J = 15.0), 3.77 (s, 3H), 3.45 (m, 1H), 2.5-2.41 (m, 2H); ^{13}C NMR δ 173.0 159.5, 150.2, 131.9, 128.6, 121.2, 119.5, 115.8, 114.8, 59.0, 52.2, 45.5, 36.9. MS (ESI, *m/z*) 281.1 $(MH)^+$.

Methyl (2*S*)-2-[(2,4-Dimethoxybenzyl)amino]hex-5-enoate (41a). Using General Procedure **A**, followed by chromatography of the product from **39** (20 mmol) using 30:70 EtOAc/hexanes as eluant gave **41a** as a yellow oil (70% yield); ^{1}H NMR δ7.14 (d, 1H, J = 8.6), 6.43 (m, 2H), 5.77 (m,

1H), 5.00 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73-3.64 (m, 5H), 3.28 (t, 1H, J = 6.9), 2.11 (m, 3H), 1.73 (m, 2H); ^{13}C NMR δ 175.6, 159.9, 158.4, 137.5, 130.1, 120.3, 114.9, 103.5, 98.2, 60.0, 55.1, 55.0, 51.3, 46.9, 32.5, 29.7. MS (ESI, *m/z*) 293.9 $(MH)^+$.

Methyl (2*S*)-2-[(2-Hydroxy-4-methoxybenzyl)amino]hex-5-enoate (41b). Using General Procedure **A**, followed by chromatography of the product from **39** (3.0 mmol) using 20:80 EtOAc/hexanes as eluant gave **41b** (79% yield) as a yellow oil: ^{1}H NMR δ 8.23 (s, 1H), 6.85 (d, 1H, J = 8.2), 6.45 (m, 1H), 6.36 (m, 1H), 5.76 (m, 1H), 5.30-4.99 (m, 2H), 4.00 (d, 1H, J = 13.6), 3.82 (m, 1H), 3.78-3.76 (m, 6H), 3.69 (d, 1H, J = 13.6), 3.38 (t, 1H, J = 6.6), 2.12 (m, 2H), 1.80 (m, 2H). MS (ESI, *m/z*) 279.2 $(MH)^+$.

General Procedure F: Peptide Coupling using TBTU. The selected *N*-protected amino acid (1.0 eq) and amino ester (1.0 eq) were dissolved in CH_2Cl_2 (0.1 M), treated with DIEA (1.5 eq), stirred for 10 min, treated with TBTU (1.5 eq), stirred for 24h and diluted with water. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to a residue that was purified by chromatography.

***N*-(Boc)-L-Allylglycinyl-L-homoallylglycine Methyl Ester (43a).** Using General Procedure **F**, followed by chromatography of the product from **35a** (1.15 mmol) and **39** (1.15 mmol) using 20:80 EtOAc/hexanes as eluant gave **43a** (86% yield) as a white solid: mp 105.3-106.7 °C; $[\alpha]^{20}_D$ −6.8° (*c* 1.34, $CHCl_3$); ^{1}H NMR δ 6.68 (d, 1H, J = 7.8), 5.74 (m, 2H), 5.05 (m, 5H), 4.60 (m, 1H), 4.17 (m, 1H), 3.73 (s, 3H), 2.50 (m, 2H), 2.06 (m, 2H), 1.95 (m, 1H), 1.78 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ 172.2, 171.0, 155.3, 136.6, 132.8, 118.8, 115.6, 80.0, 53.5, 52.1, 51.5, 36.3, 31.6, 29.1, 28.0. HRMS calcd for $C_{17}H_{28}N_2O_5Na$ 363.18904, found 363.18950.

***N*-(Boc)-L-Homoallylglycinyl-L-allylglycine Methyl Ester (44a).** Using General Procedure **F**, followed by chromatography of the product from **38a** (1.15 mmol) and **36** (1.15 mmol) using 20:80 EtOAc/hexanes as eluant gave **44a** (85% yield) as an oil: $[\alpha]^{20}_D$ –6.8° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 6.48 (d, 1H, *J* = 7.57), 5.85 (m, 1H), 5.65 (m, 1H), 5.05 (m, 5H), 4.66 (m, 1H), 4.10 (m, 1H), 3.75 (s, 3H), 2.55 (m, 2H), 2.15 (q, 2H, *J* = 7.1), 1.95 (m, 1H), 1.70 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 172.2, 172.1, 155.8, 137.6, 132.4, 119.6, 116.0, 80.3, 54.2, 52.7, 52.0, 36.7, 31.9, 30.0, 28.7. HRMS calcd for $C_{17}H_{28}N_2O_5$ Na: 363.18904, found 363.18886.

***N*-(Boc)-Allylglycinyl-*N*-(2,4-dimethoxybenzyl)homoallylglycine Methyl Ester (43b).** Using General Procedure **B**, followed by chromatography of the product from **25a** (1.5 mmol) and **41a** (1.0 mmol) using 30:70 EtOAc/hexanes as eluant gave **43b** (86% yield) as an oil; $[\alpha]^{20}_D$ –42.6° (*c* 1.12, $CHCl_3$); : ^{1}H NMR δ 7.10 (d, 1H, *J* = 7.4), 6.42 (m, 2H,), 5.87- 5.60 (m, 2H), 5.40 (d, 1H, *J* = 8.5), 5.08-5.16 (m, 2H), 4.99 (m, 2H), 4.64 (d, 1H, *J* = 15.7), 4.36 (d, 1H, *J* = 15.7), 4.11 (dd, 1H, *J* = 6.0, 9.0), 3.80 (s, 6H), 3.57 (s, 3H), 2.55 (m, 1H), 2.45 (m, 1H), 2.15-1.95 (m, 3H), 1.85-1.75 (m, 2H), 1.4(s, 9H); ^{13}C NMR δ 172.2, 171.0, 160.8, 158.7, 154.9, 137.4, 132.7, 130.3, 118.2, 115.9, 115.2, 103.5, 98.3, 79.1, 57.5, 55.1, 54.9, 51.7, 50.2, 47.1, 37.8, 30.4, 29.4, 28.1. HRMS calcd for $C_{26}H_{39}N_2O_7$ $(MH)^+$ 491.27518, found 491.27280.

***N*-(Boc)-L-Homoallylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-allylglycine Methyl Ester (44b).** Using General Procedure **B**, followed by chromatography of the product from **38b** (1.0 mmol) and **40a** (0.5 mmol) using 30:70 EtOAc/hexanes as eluant gave **44b** (81% yield) as a colorless oil: $[\alpha]^{20}_D$ –38.4° (*c* 1.05, $CHCl_3$); ^{1}H NMR δ 7.10 (d, 1H, *J* = 7.9), 6.41 (m, 2H,), 5.85- 5.63 (m, 2H), 5.41 (d, 1H, *J* = 8.7), 5.06-4.92 (m, 5H), 4.63 (d, 1H, *J* = 15.5), 4.30 (d, 1H, *J* = 15.5), 4.01 (dd, 1H, J = 5.5, 9.0), 3.79 (s, 6H), 3.56 (s, 3H), 2.70 (m, 1H), 2.58 (m, 1H), 2.13 (m, 2H), 1.83 (m, 1H), 1.66 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ 172.4, 170.5, 160.9, 158.8, 155.0, 137.4, 134.3, 130.6, 117.5, 115.7, 115.0, 103.4, 98.2, 79.0, 58.1, 55.1, 54.9, 51.7, 50.0, 47.7, 33.2, 33.1, 29.1, 28.1; MS (ESI, *m/z*) 513.2 $(MNa)^+$.

***N*-(Fmoc)-L-homoallylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-allylglycine Methyl Ester (44c).** Using General Procedure **B**, followed by chromatography of the product from **38b** (1.5 mmol) and **40a** (1.0 mmol) using 30:70 EtOAc/hexanes as eluant gave **44c** (82% yield) as a colorless oil: $[\alpha]^{20}_{D}$ –6.0 (*c* 1.32, $CHCl_3$); ^{1}H NMR δ 7.75 (d, 2H, *J* = 7.4), 7.61 (dd, 2H, *J* = 3.2, 3.1), 7.38 (t, 2H, *J* = 7.3), 7.30 (t, 2H, *J* = 7.3), 7.10 (d, 1H, *J* = 8.2), 6.40 (dd, 2H, *J* =2.1, 2.2), 5.87- 5.66 (m, 3H), 5.12-4.87 (m, 5H), 4.64 (d, 1H, *J* = 15.5), 4.44-4.20 (m, 4H), 4.04 (m, 1H), 3.76 (s, 6H), 3.56 (s, 3H), 2.74 (m, 1H), 2.61 (m, 1H), 2.15 (m, 2H), 1.89 (m, 1H), 1.72 (m, 1H); ^{13}C NMR δ 172.0, 170.5, 160.9, 158.8, 155.6, 143.7, 141.1, 137.2, 134.3, 130.5, 127.5, 126.9, 125.0, 119.8, 117.7, 115.6, 115.3, 103.5, 98.3, 66.6, 58.2, 55.1, 55.0, 51.8, 50.7, 47.7, 47.0, 33.3, 32.9, 29.0; HRMS calcd for $C_{36}H_{41}N_2O_7$ $(MH)^+$ 613.29083, found 613.29071.

***N*-(Boc)-L-Homoallylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-homoallylglycine Methyl Ester (45b).** Using General Procedure **B**, followed by chromatography of the product from **38a** (0.8 mmol) and **41a** (0.4 mmol) using 30:70 EtOAc/hexanes as eluant gave **45b** (74% yield) as a gum: ^{1}H NMR δ 7.05 (d, 1H, *J* = 8.0), 6.39 (m, 2H,), 5.79 (m, 1H), 5.66 (m, 1H), 5.43 (d, 1H, *J* = 8.6), 5.04-4.86 (m, 4H), 4.60 (d, 1H, *J* = 15.5), 4.34 (d, 1H, *J* = 15.5), 4.01 (dd, 1H, *J* = 6.1, 7.7), 3.76 (s, 6H), 3.54 (s, 3H), 2.15-1.95 (m, 5H), 1.85-1.71 (m, 2H), 1.70-1.55 (m, 2H),1.41 (s, 9H); ^{13}C NMR δ 172.8, 171.1, 160.8, 158.7, 155.1, 137.3, 130.3, 116.0, 115.2, 115.1, 103.5, 98.3, 79.1, 57.4, 55.1, 54.9, 51.7, 50.1, 46.9, 33.0, 30.4, 29.5, 29.1, 28.1, 28.0. MS (ESI, *m/z*) 527.3 (MNa^+).

General Procedure G: Peptide Coupling using Symmetrical Anhydrides. The *N*-Boc protected amino acid **38a** (3.0 eq) and DCC (1.5 eq) were dissolved in CH_2Cl_2 (0.2 M) and stirred for 2h. The mixture was filtered and *N*-(2-hydroxybenzyl) amino ester **40b** or **41b** (1.0 eq) was added

to the filtrate which was then stirred overnight at rt. The mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, 10% HCl and with brine, dried over $MgSO_4$, filtered and concentrated to a residue that was purified by chromatography.

***N*-(Boc)-L-Homoallylglycinyl-*N*-(2-hydroxy-6-nitrobenzyl)-L-allylglycine Methyl Ester (44d).** Using General Procedure **G**, followed by chromatography of the product from **38a** (0.69 mmol) and **40b** (0.23 mmol) using 30:70 EtOAc/hexanes as eluant gave **44d** (87% yield) as a greenish oil in 4.6:1 mixture of isomers: ^{1}H NMR (major isomer) 9.31 (s, 1H), 7.33 (m, 3H), 5.82 (m, 2H), 5.47 (m, 1H), 5.22 (m, 1H), 5.04 (m, 4H), 4.77 (m, 2H), 3.77 (m, 1H), 3.58 (s, 3H), 2.80 (m, 2H), 2.10 (m, 2H), 1.82 (m, 2H), 1.48 (s, 9H); ^{13}C NMR δ 172.5, 170.9, 158.7, 156.6, 151.2, 137.6, 134.7, 130.2, 122.6, 121.1, 118.9, 116.3, 115.9, 80.9, 58.7, 52.4, 51.0, 44.0, 33.8, 33.6, 29.6, 28.8.

***N*-(Boc)-L-Homoallylglycinyl-*N*-(2-hydroxy-4-methoxybenzyl)-L-homoallylglycine Methyl Ester (45c).** Using General Procedure **G**, followed by chromatography of the product from **38a** (1.08 mmol) and **41b** (0.36 mmol) using 30:70 EtOAc/hexanes as eluant gave **45c** (86% yield) as an oil: ^{1}H NMR δ 9.51 (s, 1H), 6.92 (d, 1H, J = 8.4 Hz,), 6.43 (d, 1H, J = 2.51), 6.31 (dd, 1H, J = 8.4, 2.5 Hz), 5.76 (m, 2H), 5.21 (d, 1H, J = 9.2 Hz), 5.00 (m, 4H), 4.62 (m, 2H), 4.45 (m, 1H), 4.35 (m, 1H), 3.73 (s, 3H), 3.43 (s, 3H), 2.04 (m, 6H), 1.71 (m, 2H), 1.40 (s, 9H).

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylate (47b). Using General Procedure **C**, followed by chromatography of the product from **43b** (0.6 mmol) using 20:80 EtOAc/hexanes eluant gave **47b** (80% yield) as a brown gum: $[\alpha]^{20}_D$ −38.5° (*c* 2.53, $CHCl_3$); ^{1}H NMR δ 7.21 (d, 1H, J = 8.3), 6.41 (m, 2H,), 6.17 (d, 1H, J = 6.6), 6.09 (q, 1H, J = 9.4), 5.58 (q, 1H, J = 9.2), 4.62-4.49 (m, 4H,), 3.78 (s, 3H), 3.77 (s, 3H), 3.45 (s, 3H), 2.61 (m, 1H), 2.28-2.17 (m, 2H), 1.91-1.87 (m, 2H), 1.70 (m, 1H), 1.47 (s,

9H); ^{13}C NMR δ 173.6, 170.5, 159.7, 157.4, 154.7,130.6, 129.9, 129.2, 117.6. 104.0, 97.8, 79.3, 60.1, 56.8, 55.1, 51.9, 51.3, 39.8, 34.9, 28.2, 27.9, 22.0; HRMS calcd for $C_{24}H_{34}N_2O_7Na$ 485.22582, found 485.22543.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylate (48b). Using General Procedure **C**, followed by chromatography of the product from **44b** (0.5 mmol) using 30:70 EtOAc/hexanes as eluant gave **48b** (81% yield) as gum; $[\alpha]^{20}_D$ −27.3° (*c* 1.21, $CHCl_3$); ^{1}H NMR δ 7.13 (d, 1H, *J* = 8.1), 6.41 (m, 2H), 5.77-5.50 (m, 2H), 4.90 (t, 1H, *J* = 7.8), 4.72 (t, 1H, *J* = 8.5), 4.62 (d, 1H, *J* = 15.5), 4.16 (d, 1H, *J* = 15.5), 3.78 (s, 3H), 3.76 (s, 3H), 3.42 (q, 1H), 3.38 (s, 3H), 2.65 (m, 2H), 2.06 (m, 3H), 1.70 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 174.0, 169.9, 159.7, 157.6, 154.8,133.4, 129.8, 124.7, 116.9, 103.8, 97.6, 79.3, 58.3, 55.1, 55.0, 52.0, 50.5, 40.0, 34.6, 28.2, 26.5, 25.2; HRMS calcd for $C_{24}H_{35}N_2O_7$ $(MH)^+$ 463.24388, found 463.24259.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylate (48c). Using General Procedure **C**, followed by chromatography of the product from **44c** (0.4 mmol) using 30:70 EtOAc/hexanes as eluant gave **48c** (71% yield) as an oil; $[\alpha]^{20}_D$ −24.3° (*c* 0.90, $CHCl_3$); ^{1}H NMR δ 7.76 (d, 2H, *J* = 7.4), 7.61 (d, 2H, *J* = 7.5), 7.40 (t, 2H, *J* = 7.3), 7.31 (t, 2H, *J* = 7.2), 7.13 (d, 1H, *J* = 8.0), 5.95 (d, 1H, *J* = 7.5), 5.63 (q, 1H, *J* = 8.7), 5.53 (m, 1H), 4.90 (t, 1H, *J* = 7.7), 4.81 (m, 1H), 4.67 (d, 1H, *J* = 15.3), 4.36-4.32 (m, 2H), 4.30-4.10 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.54 (q, 1H, *J* = 35.0), 3.39 (s, 3H), 2.65 (m, 1H), 2.16 (m, 3H), 1.79 (m, 1H); ^{13}C NMR δ 173.5, 169.8, 159.8, 157.6, 155.2, 143.8, 141.1, 133.4, 129.8, 127.5, 126.9, 125.04, 119.8, 116.7, 103.8, 97.7, 66.8, 58.1, 55.1, 55.0, 52.1, 51.1, 47.0, 40.3, 34.7, 29.5, 26.2, 25.2; HRMS calcd for $C_{34}H_{37}N_2O_7$ $(MH)^+$ 585.25953, found 585.25807.

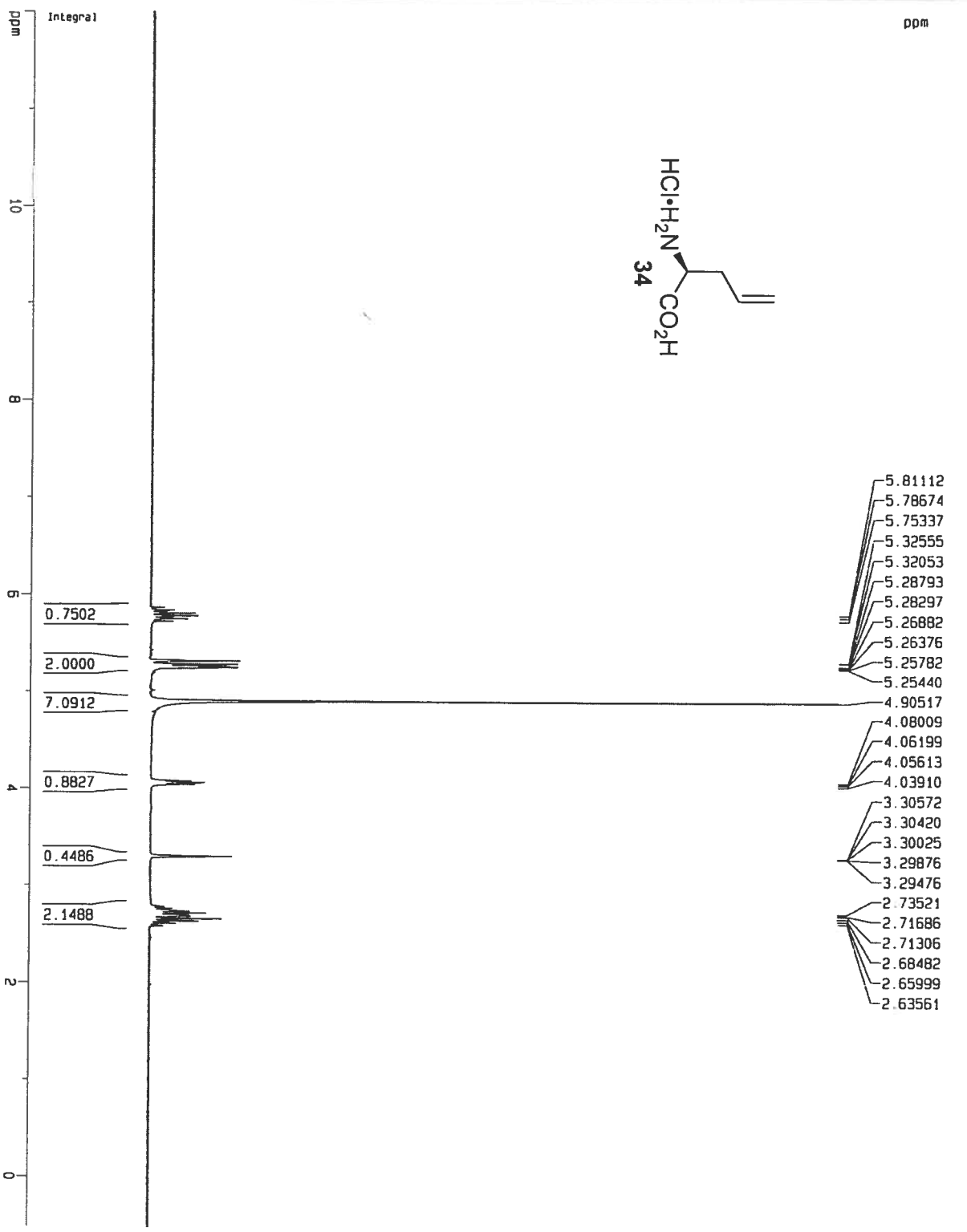
Methyl (*E*, 3*S*, 10*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxylate (49b). Using General Procedure **C**, followed by chromatography of the product from **45b** (0.3 mmol) using 30:70 EtOAc/hexanes as eluant gave **49b** (87%

yield) as an oil; ^{1}H NMR δ 7.40 (d, 1H, *J* = 8.4), 6.41 (m, 2H,), 5.58 (dt, 1H, *J* = 4.1, 11.4), 5.40 (dt, 1H, *J* = 4.2, 10.6), 5.29 (d, 1H, *J* = 9.2), 4.81 (m, 2H,), 4.57 (q, 2H, *J* = 15.1), 3.77 (s, 3H), 3.76 (s, 3H), 3.40 (s, 3H), 2.26 (m, 1H), 2.20-1.79 (m, 7H),1.43 (s, 9H); ^{13}C NMR δ 175.1, 171.0, 159.8, 157.5, 154.7,131.6, 131.2, 128.9, 118.0, 104.2, 97.6, 79.2, 57.6, 55.1, 55.0, 51.8, 47.6, 38.5, 33.8, 28.1, 26.5, 23.3, 21.8; MS (ESI, *m/z*) 499.2 $(MNa)^+$.

Methyl (*E*, 3*S*, 10*S*)-3-*N*-(Boc)Amino-1-(2-hydroxy-4-methoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxylate (49c). Using General Procedure **C**, followed by chromatography of the product from **45c** (0.09 mmol) using 30:70 EtOAc/hexanes as eluant gave **49c** (86% yield) as an oil; ^{1}H NMR δ 9.77 (s, 1H), 6.92 (d, 1H, *J* = 8.4 Hz), 6.43 (d, 1H, *J* = 2.6 Hz), 6.33 (dd, 1H, *J* = 8.4, 2.6 Hz), 5.56 (m, 1H), 5.43 (m, 1H), 5.23 (d, 1H, *J* = 9.6 Hz), 4.87 (m, 2H), 4.43 (m. 2H), 3.75 (s, 3H), 3.37 (s, 3H), 2.35 (m, 1H),1.96 (m, 7H), 1.40 (s, 9H). MS (ESI, *m/z*) 463.0 $(MH)^+$.

Methyl (3*S*, 9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2, 3, 4, 5, 8, 9-hexahydro-1*H*-azonine-9-carboxylate (51). Using General Procedure **D**, followed by chromatography of the product from **48c** (0.5 mmol) using EtOAc as eluant gave **51** (90% yield) as a brown gum: ^{1}H NMR δ 7.74 (d, 2H, *J* = 7.4), 7.57 (d, 2H, *J* = 6.8), 7.38 (t, 2H, *J* = 7.0), 7.27 (t, 2H, *J* = 7.3), 6.71 (d, 1H, *J* = 7.7), 5.87 (q, 1H, *J* = 9.1), 5.80 (m, 1H), 5.7 (d, 1H, *J* = 8.1), 5.52 (m, 1H), 4.48 (m, 1H), 4.32 (m, 2H), 4.17 (m, 1H), 3.8 (s, 3H), 2.51 (m, 2H), 2.28 (m, 1H), 2.15 (m, 1H), 2.0 (m, 1H), 1.87 (m, 1H); ^{13}C NMR 173.7, 171.4.0, 155.5, 143.6, 143.5, 141.1, 133.1, 127.5, 126.9, 126.5, 124.9, 119.8, 66.9, 54.6, 52.9, 49.5, 46.9, 33.9, 24.1; HRMS calcd for $C_{25}H_{27}N_2O_5$ $(MH)^+$ 435.19145, found 435.19201.

(*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylic Acid (53). Using General Procedure **E**, hydrolysis of **51** (0.15 mmol) gave **53** (99% yield) as a white solid: mp 170-171°C; $[\alpha]^{20}_{D}$ −12.6° (*c* 0.42, CH_3OH); ^1H NMR δ 8.85 (d, 1H, *J* = 7.0), 7.73 (d, 2H, *J* = 7.5), 7.54 (t, 2H, *J* = 6.9), 7.36 (t, 2H, *J* = 7.4), 7.28 (d, 1H, *J* = 7.4), 5.95 (q, 1H, J = 9.3), 5.80 (q, 1H, *J* = 9.0), 5.45 (d, 1H, J = 8.7), 4.51 (m, 1H), 4.35 (m, 3H), 4.18 (t, 1H, *J* = 7.0), 2.72-2.62 (m, 2H), 2.18-2.15 (m, 2H), 1.84 (m, 1H), 1.29 (bs, 1H); ^{13}C NMR δ 177.0, 175.3, 156.3, 144.4, 144.3, 141.9, 133.4, 128.3, 127.7, 125.8, 125.6, 120.6, 67.8, 55.8, 50.6, 47.7, 34.5, 30.3; HRMS calcd for $C_{24}H_{25}N_2O_5$ $(MH)^+$ 421.17580, found 421.17591.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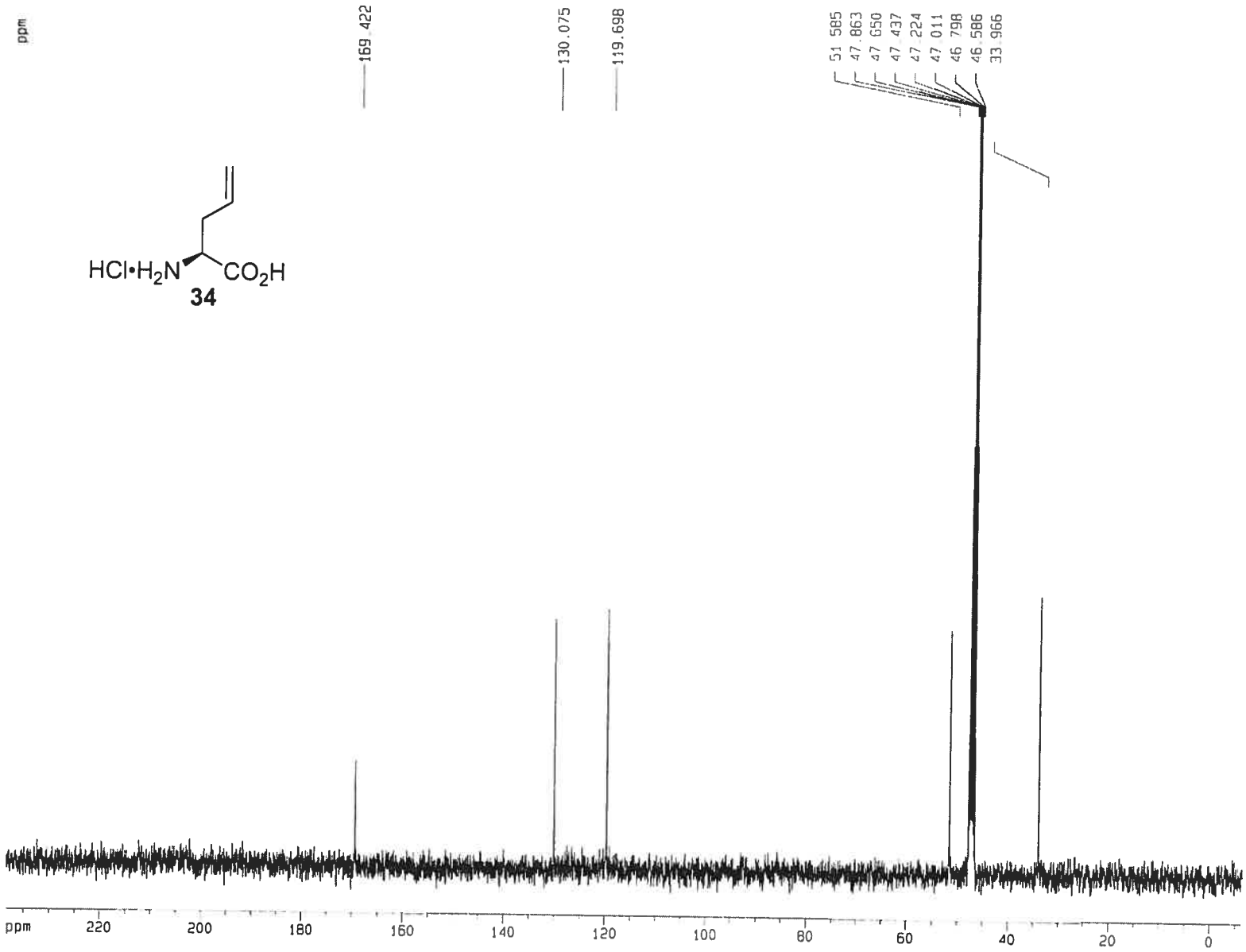
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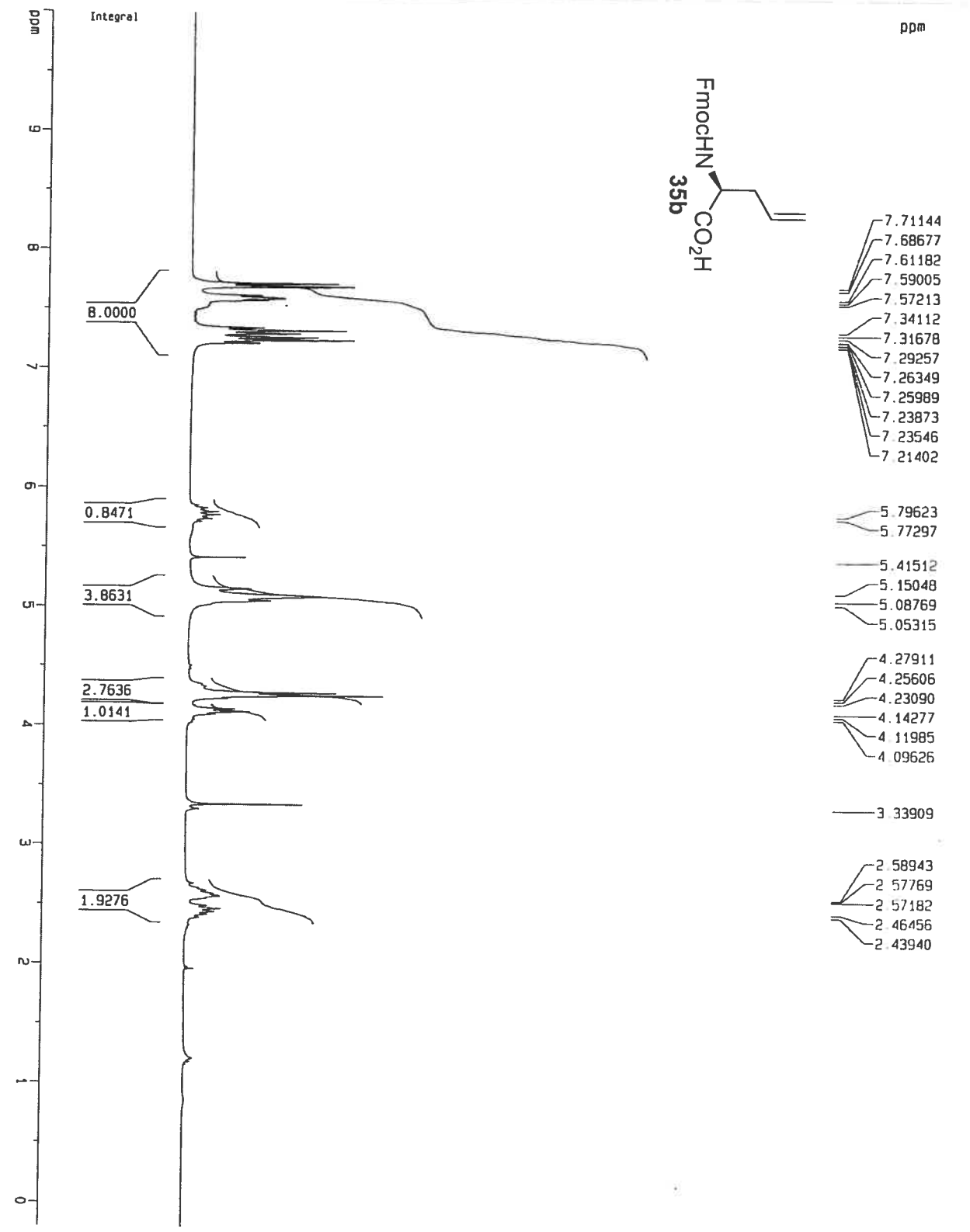
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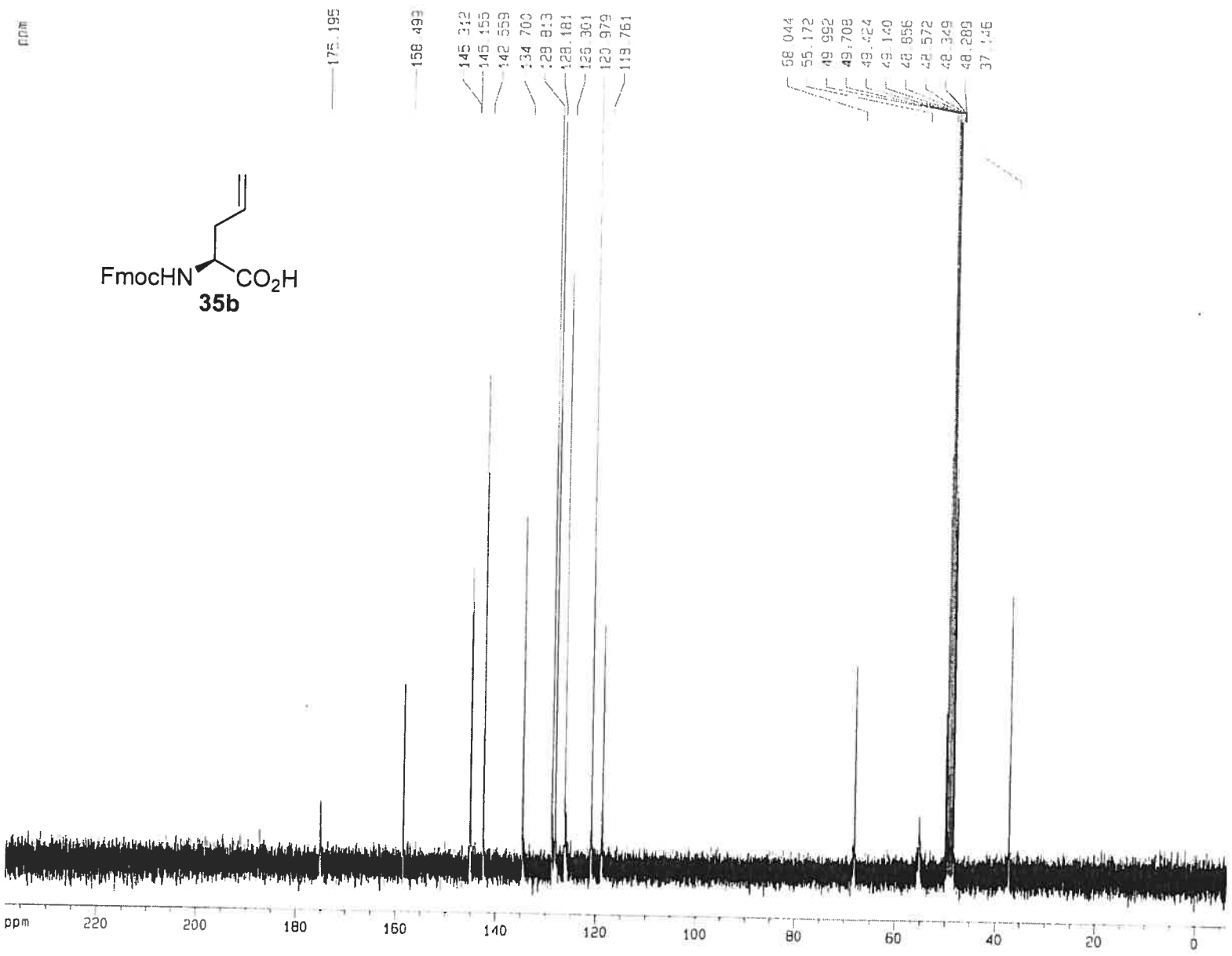
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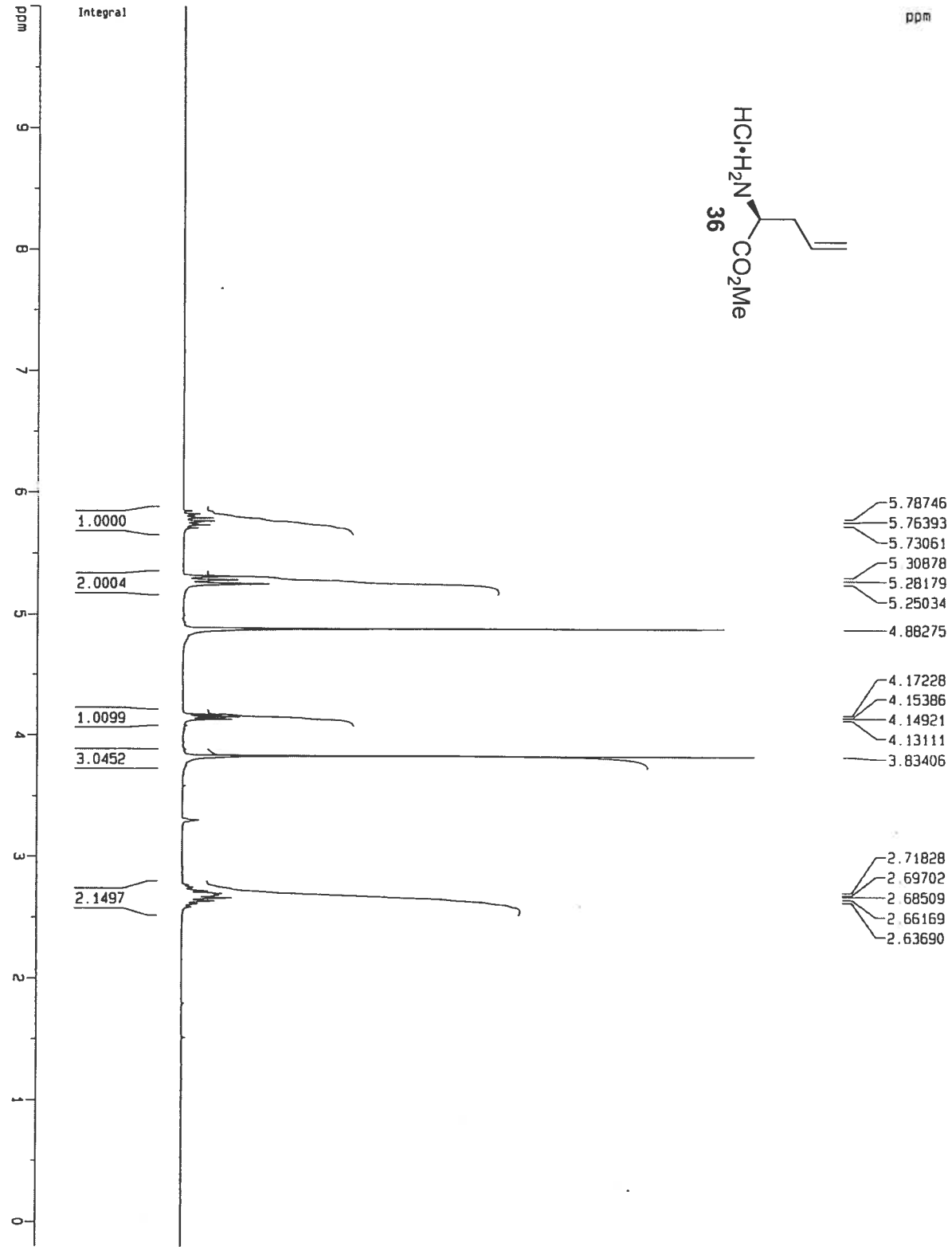
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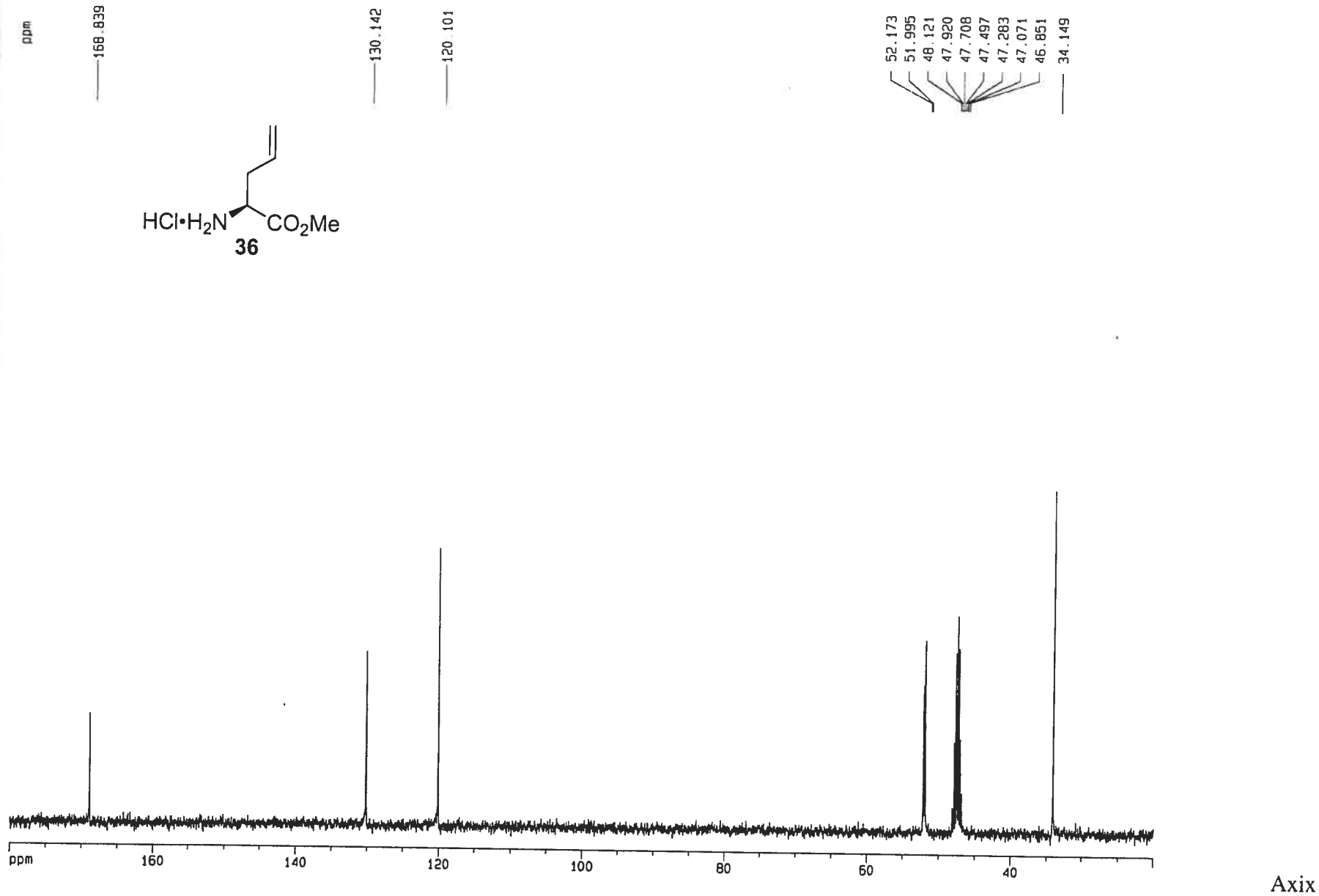
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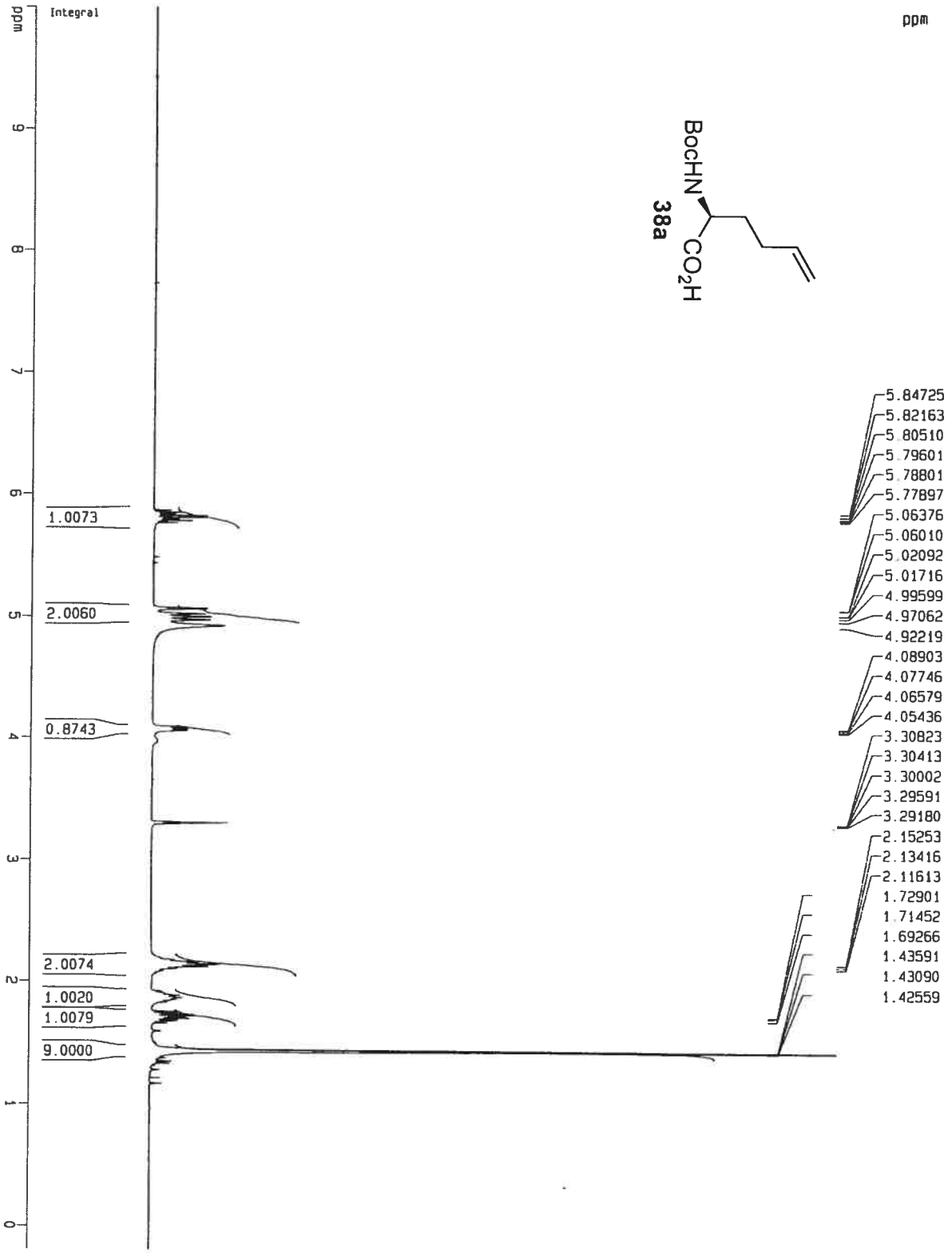
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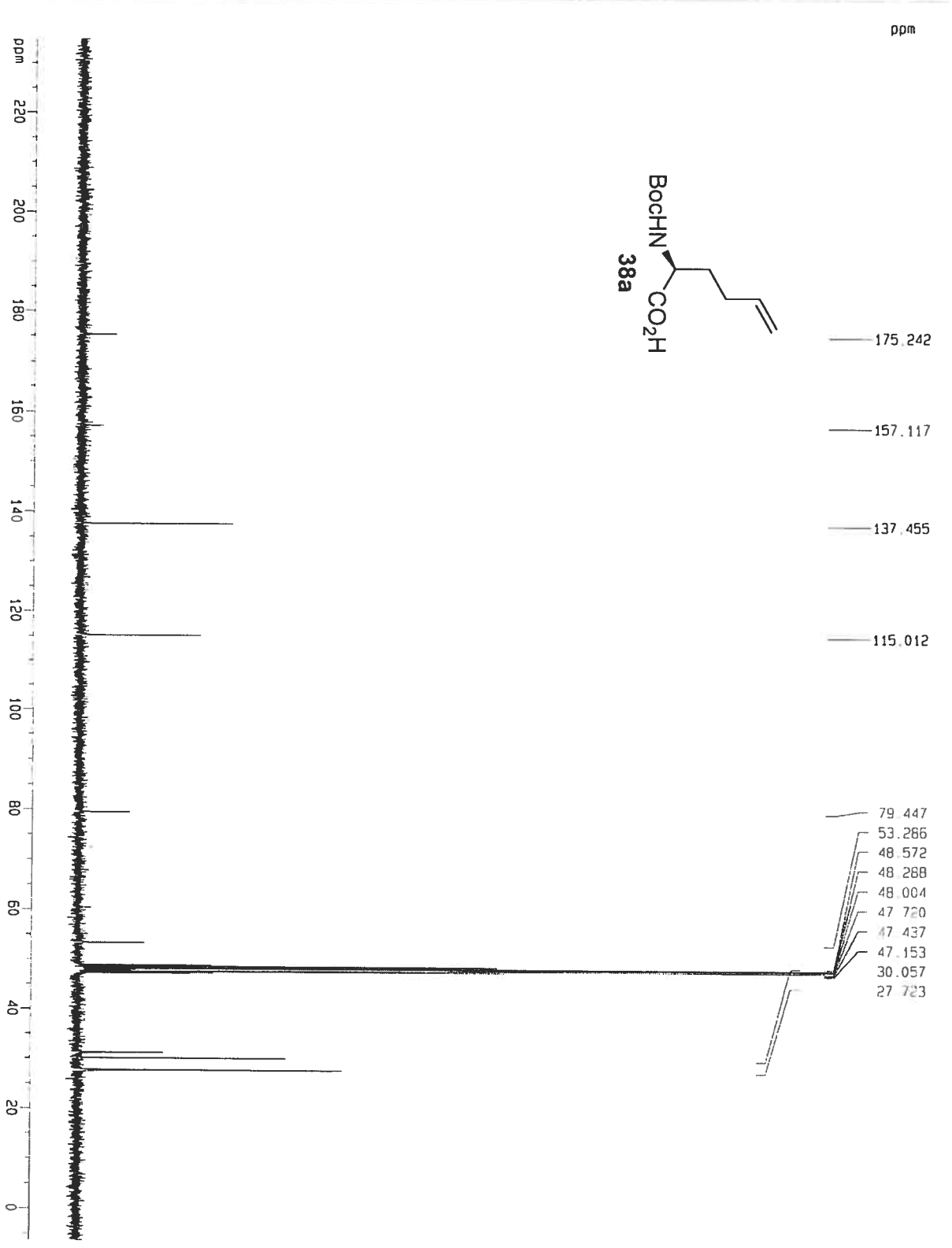
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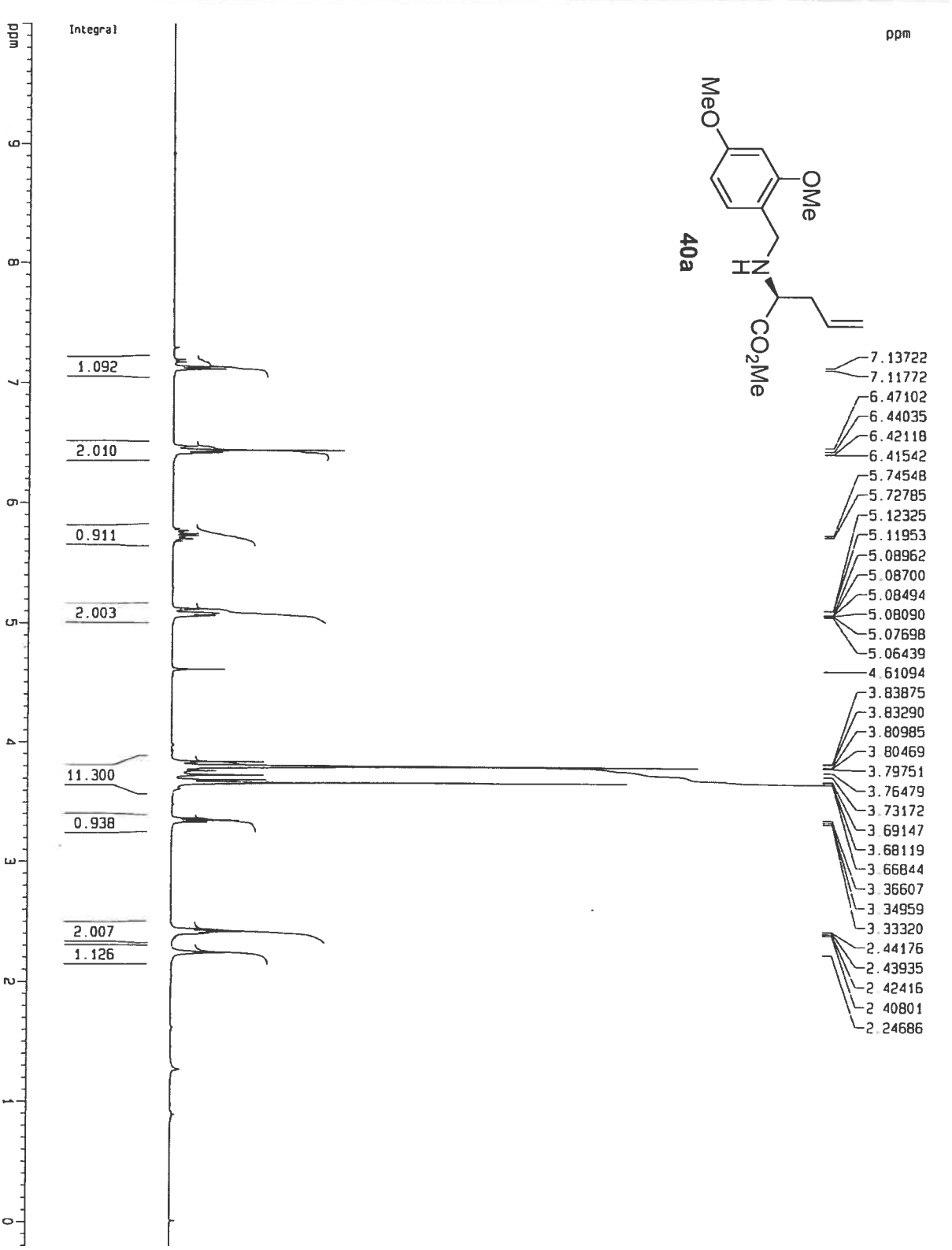
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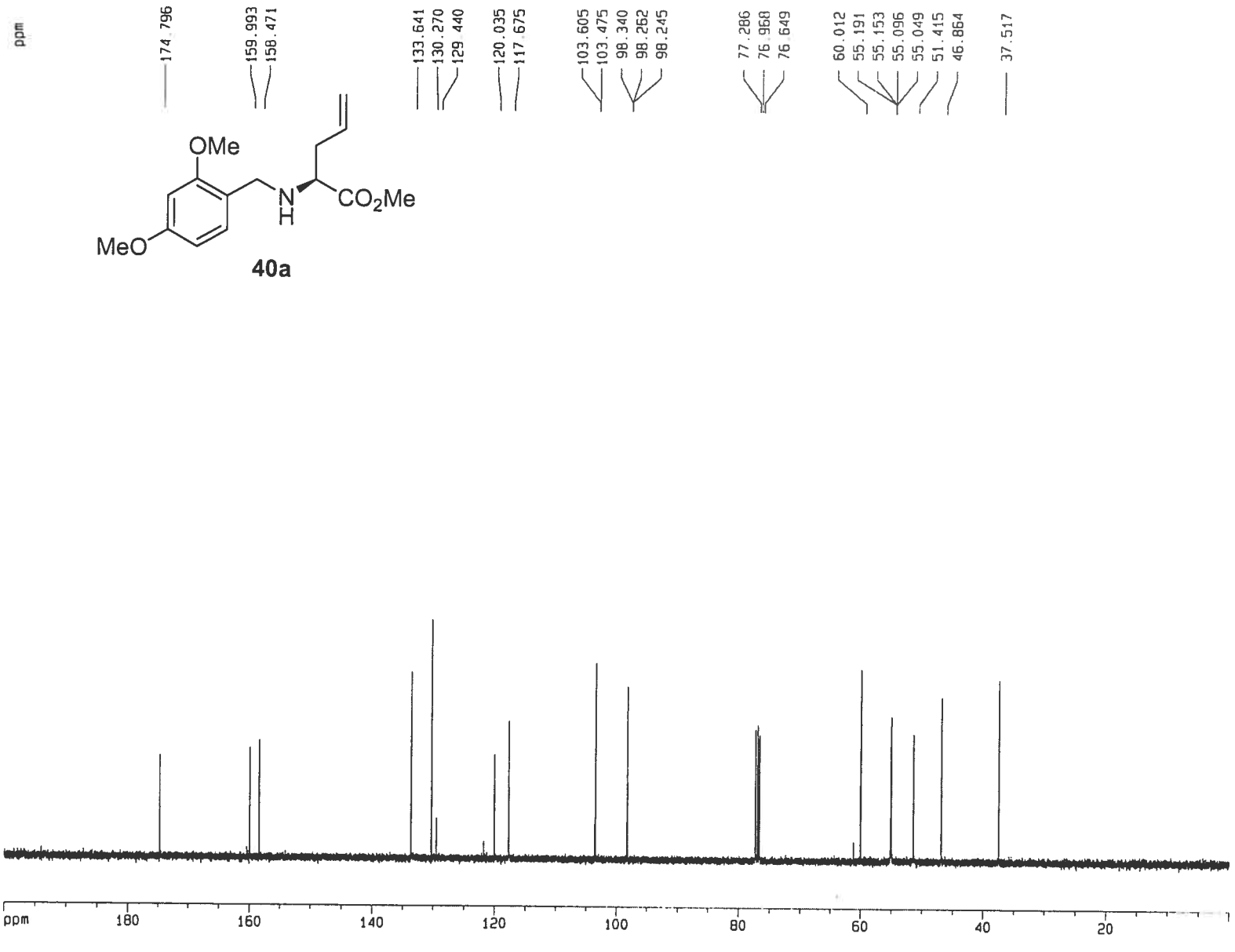
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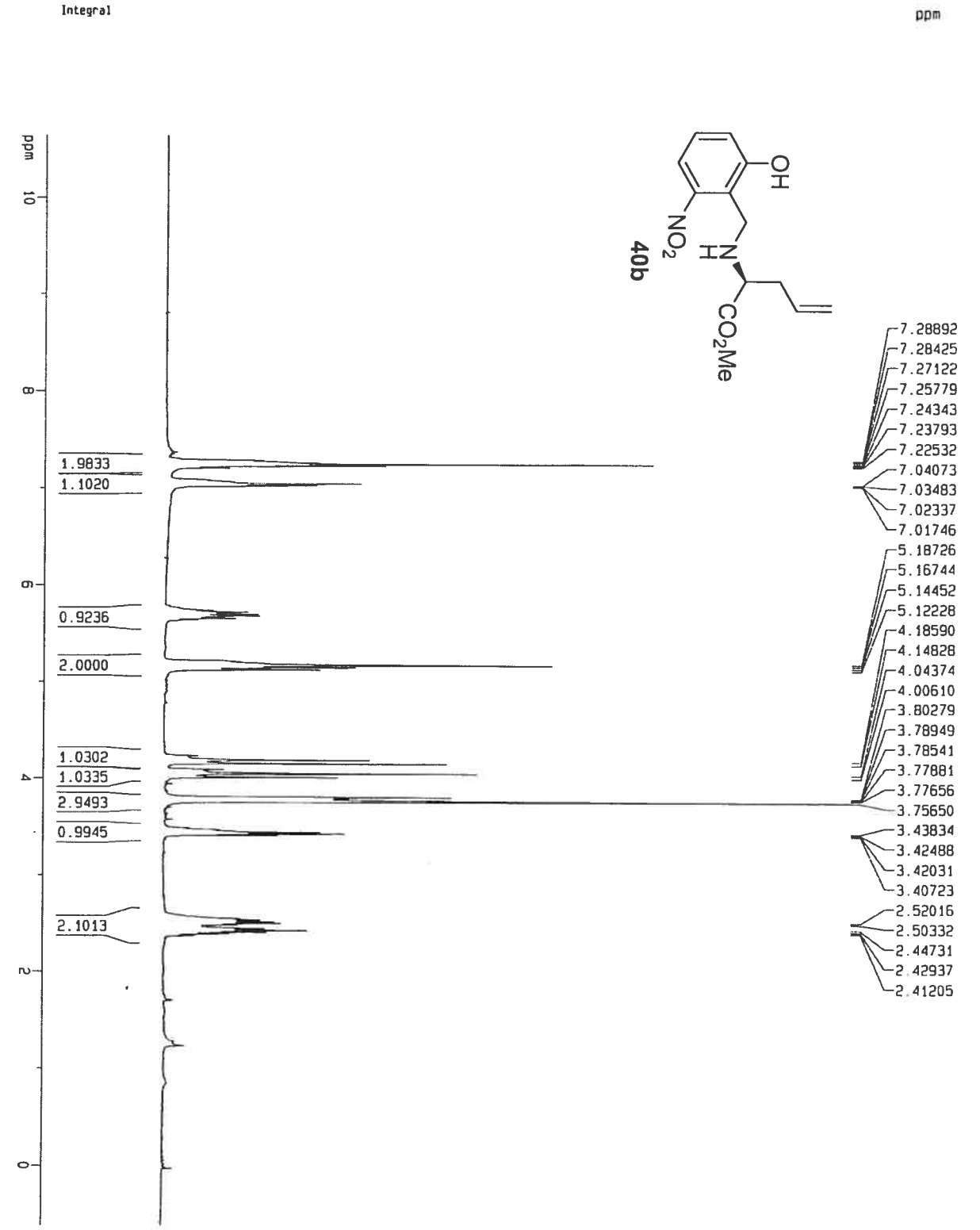
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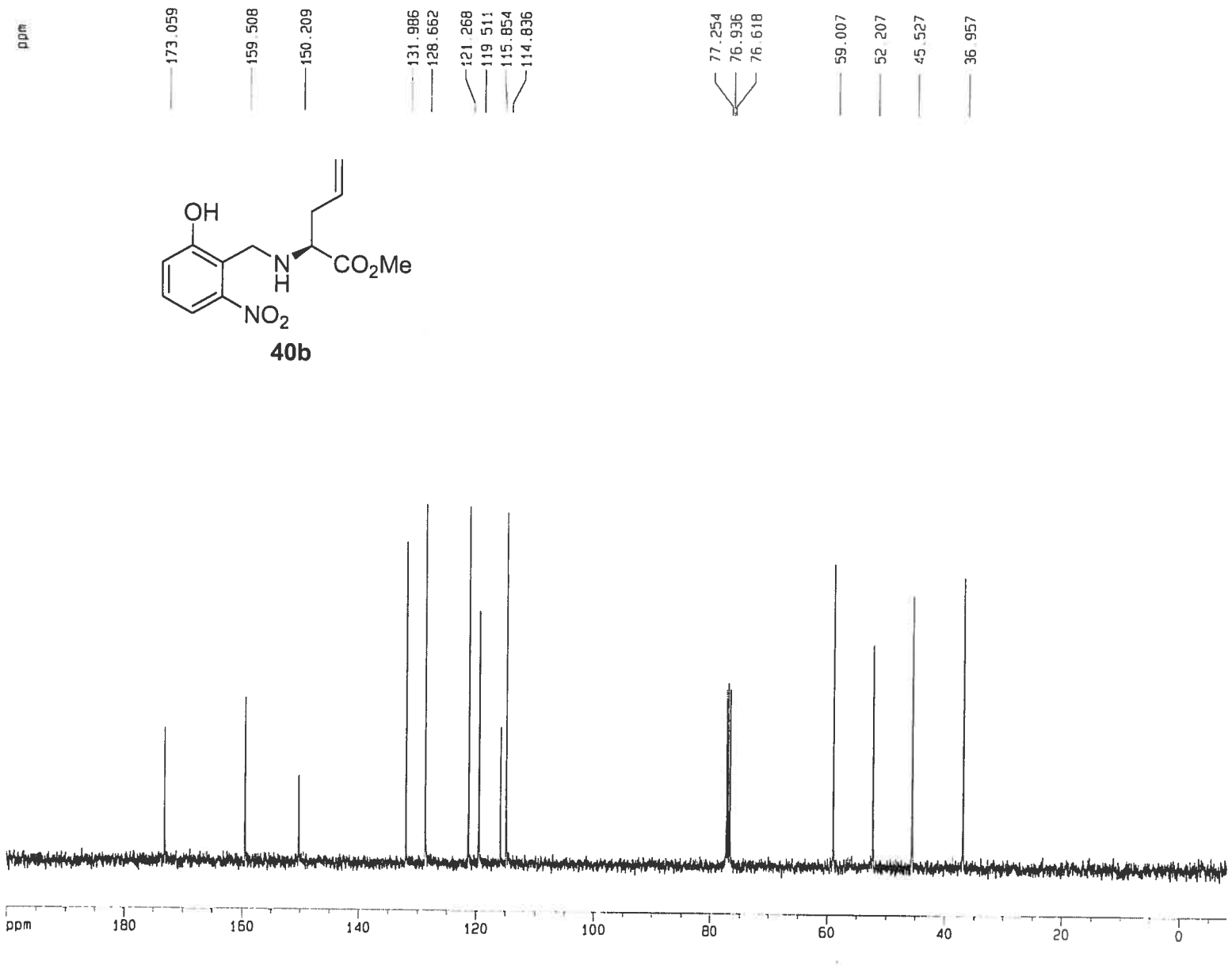
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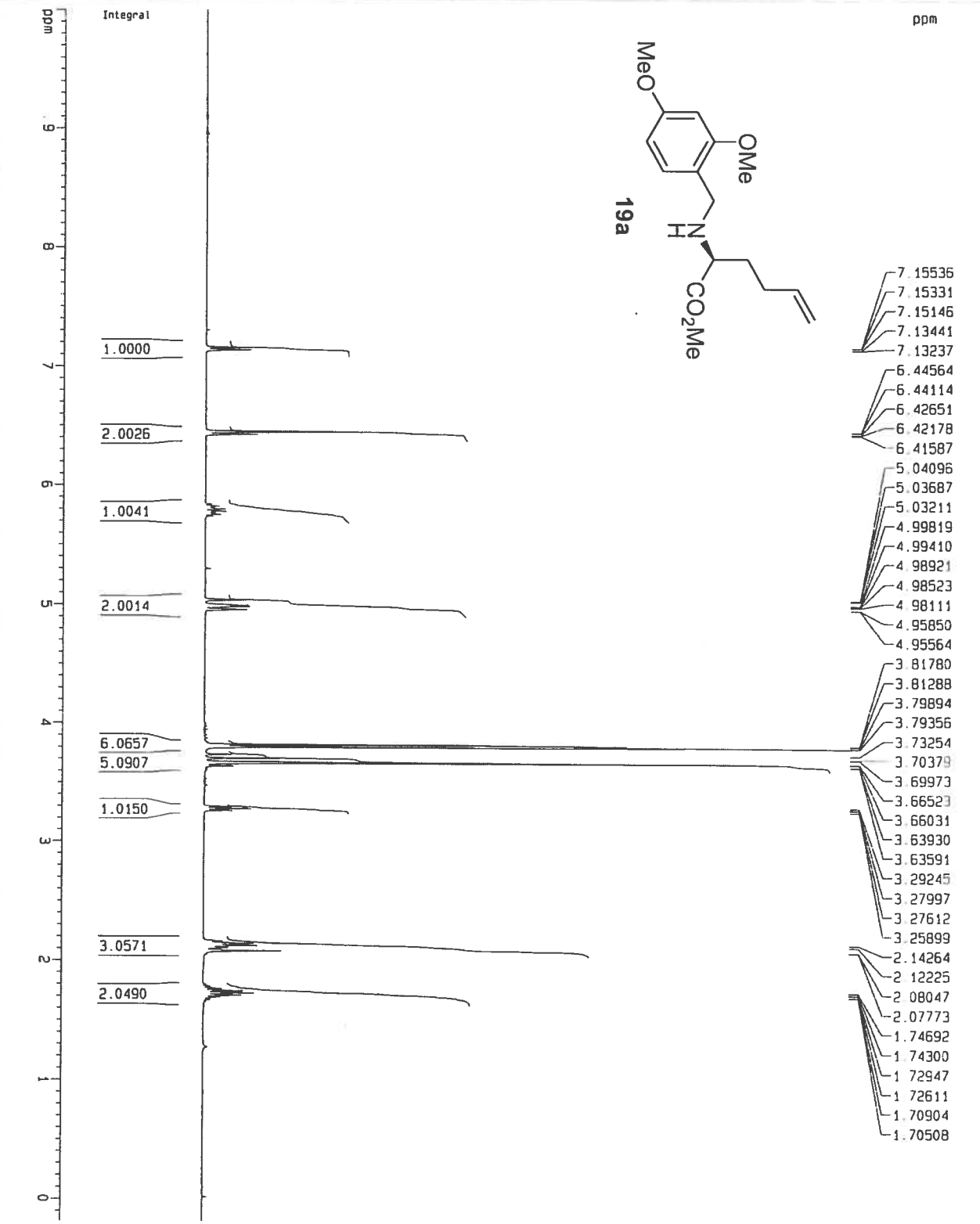
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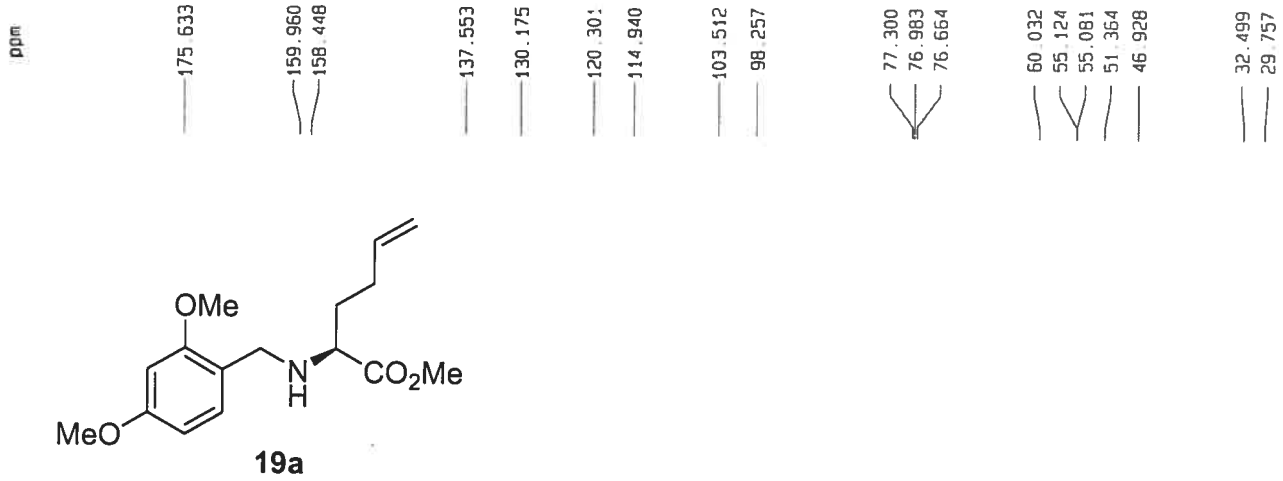
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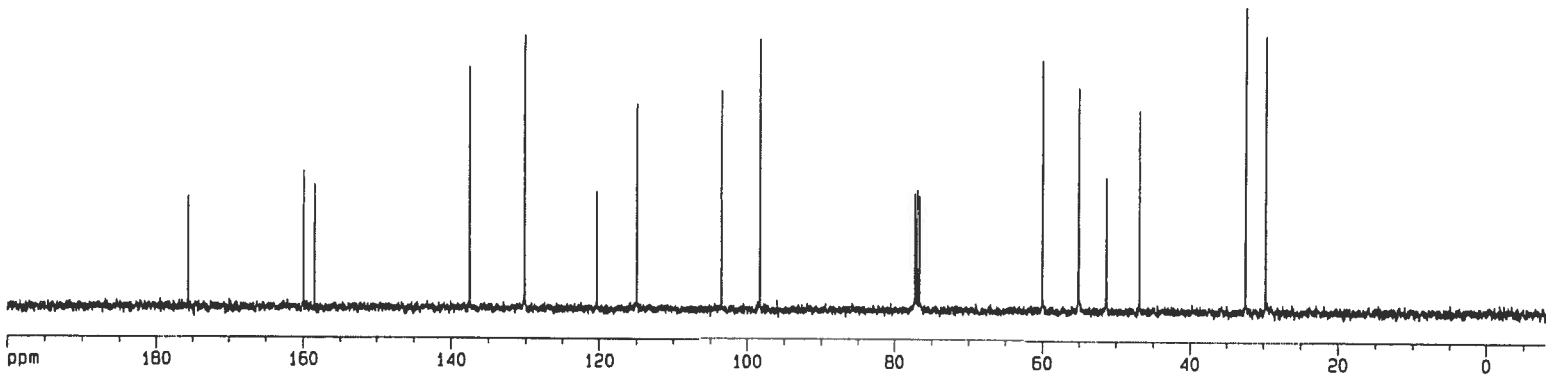
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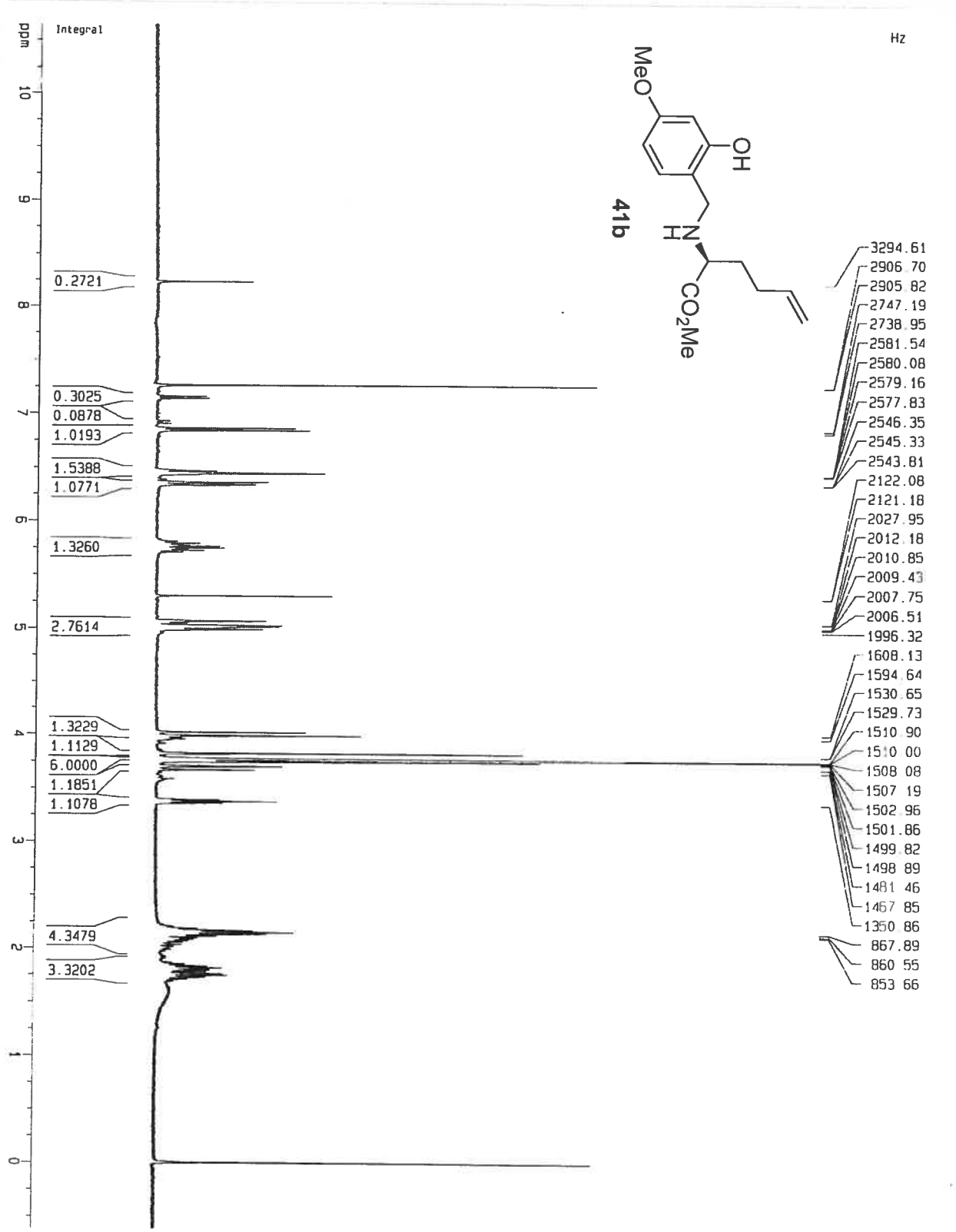
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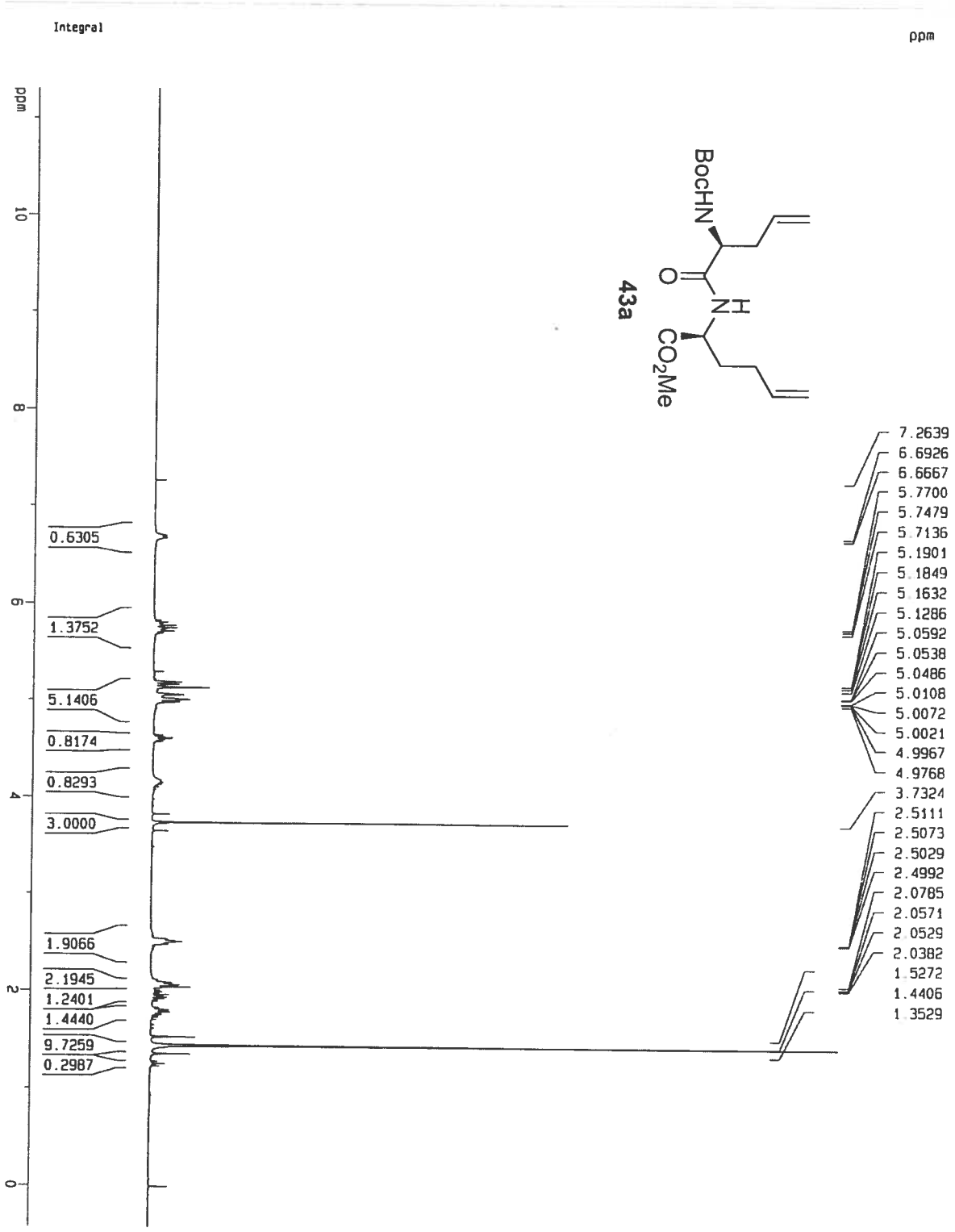
Integral
ppm
BocHN
O
H
N
CO2Me
43a
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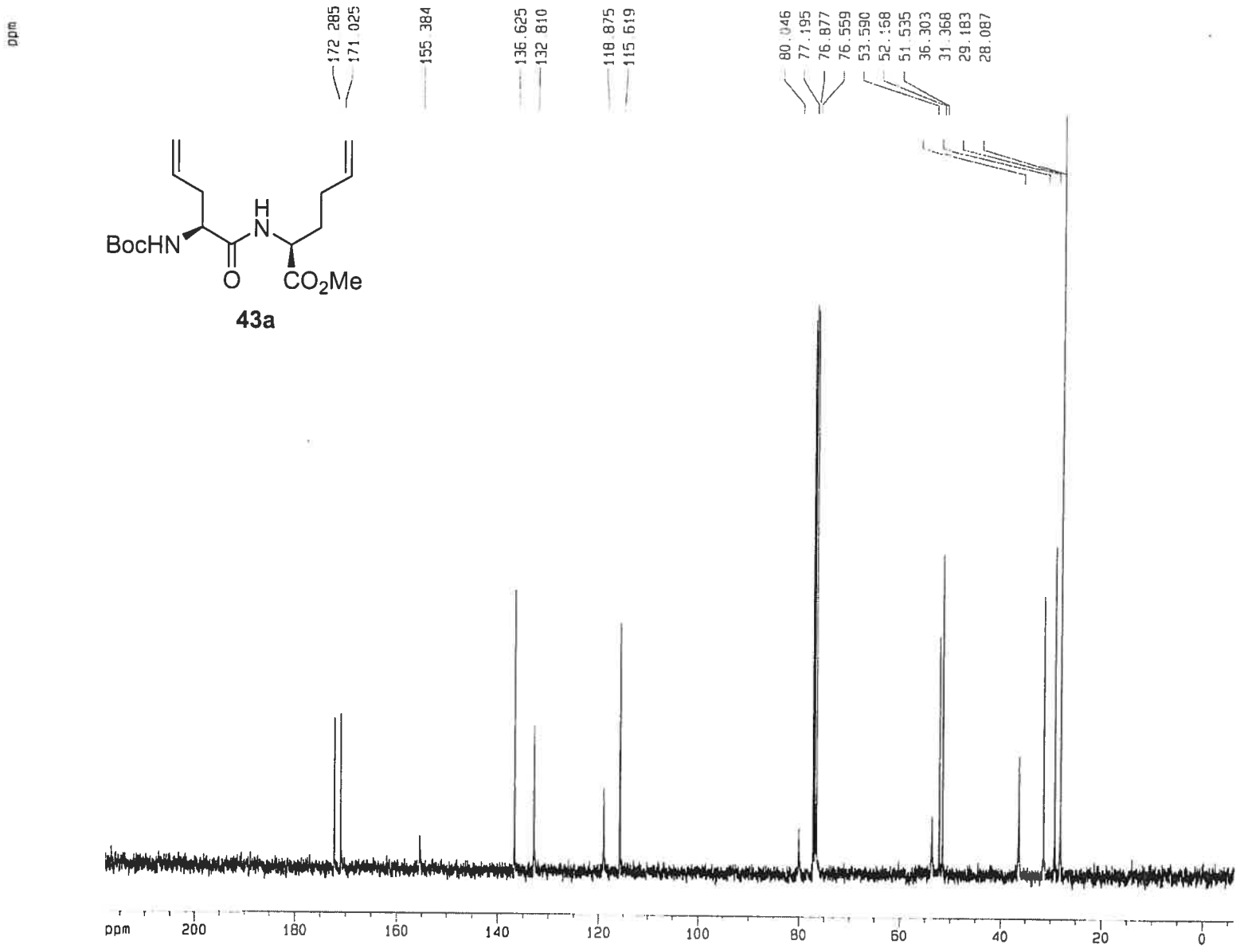
1.3752
5.1406
0.8174
0.8293
3.0000
1.9066
2.1945
1.2401
1.4440
9.7259
0.2987
7.2639
6.6926
6.6667
5.7700
5.7479
5.7136
5.1901
5.1849
5.1632
5.1286
5.0592
5.0538
5.0486
5.0108
5.0072
5.0021
4.9967
4.9768
3.7324
2.5111
2.5073
2.5029
2.4992
2.0785
2.0571
2.0529
2.0382
1.5272
1.4406
1.3529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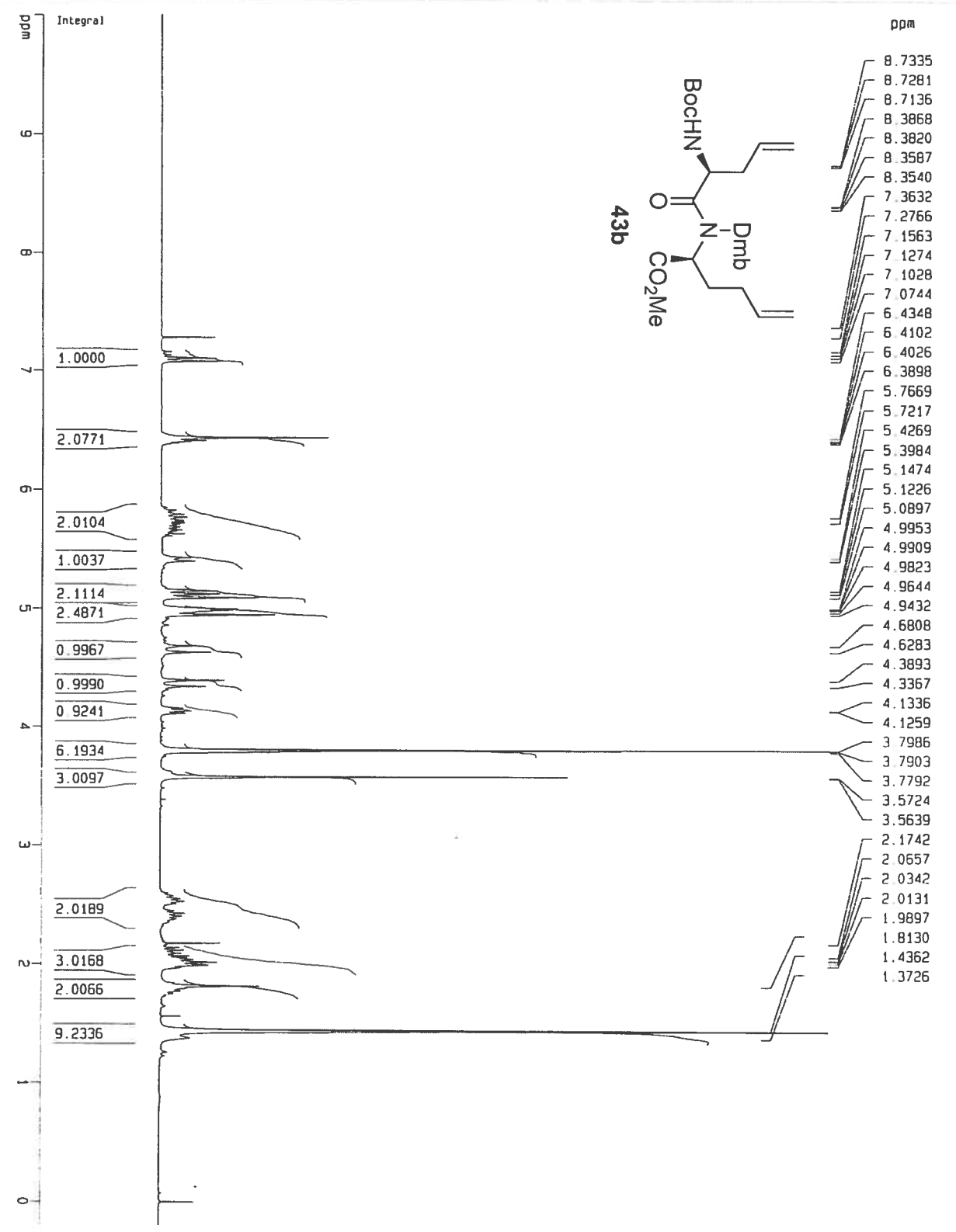
136.625
132.810
118.875
115.619
80.046
77.195
76.877
76.559
53.590
52.158
51.535
36.303
31.368
29.183
28.087
BocHN
H
N
O
CO2Me
43a
ppm
200
180
160
140
120
100
80
60
40
20
0

Axxx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1.0037
2.1114
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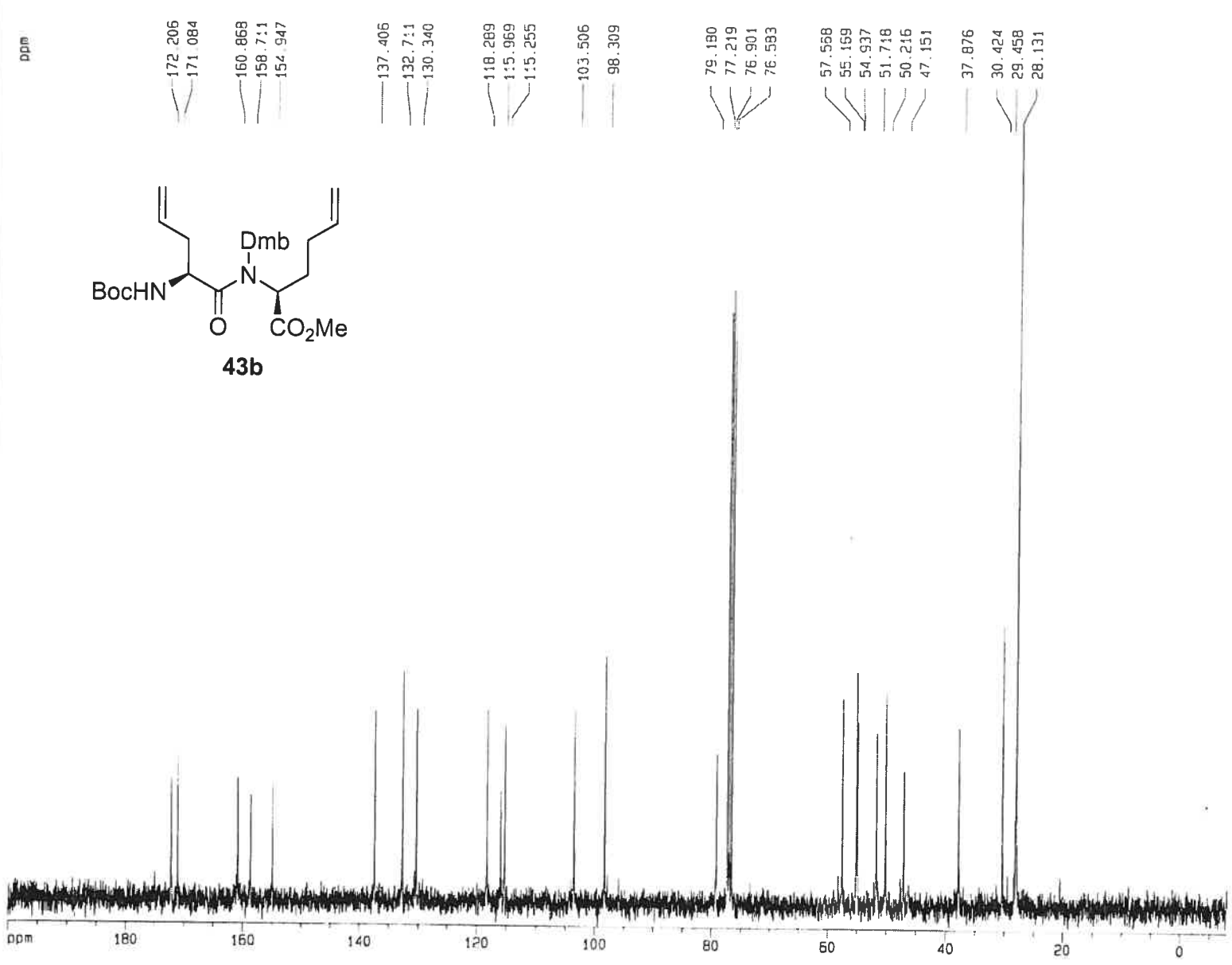
0.9967
0.9990
0 9241
6.1934
3.0097
2.0189
3.0168
2.0066
9.2336
BocHN
O
N
Dmb
CO2Me
43b
ppm
8.7335
8.7281
8.7136
8.3868
8.3820
8.3587
8.3540
7.3632
7.2766
7.1563
7.1274
7.1028
7.0744
6.4348
6.4102
6.4026
6.3898
5.7669
5.7217
5.4269
5.3984
5.1474
5.1226
5.0897
4.9953
4.9909
4.9823
4.9644
4.9432
4.6808
4.6283
4.3893
4.3367
4.1336
4.1259
3 7986
3.7903
3.7792
3.5724
3.5639
2.1742
2 0657
2 0342
2 0131
1.9897
1.8130
1.4362
1.3726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154.947
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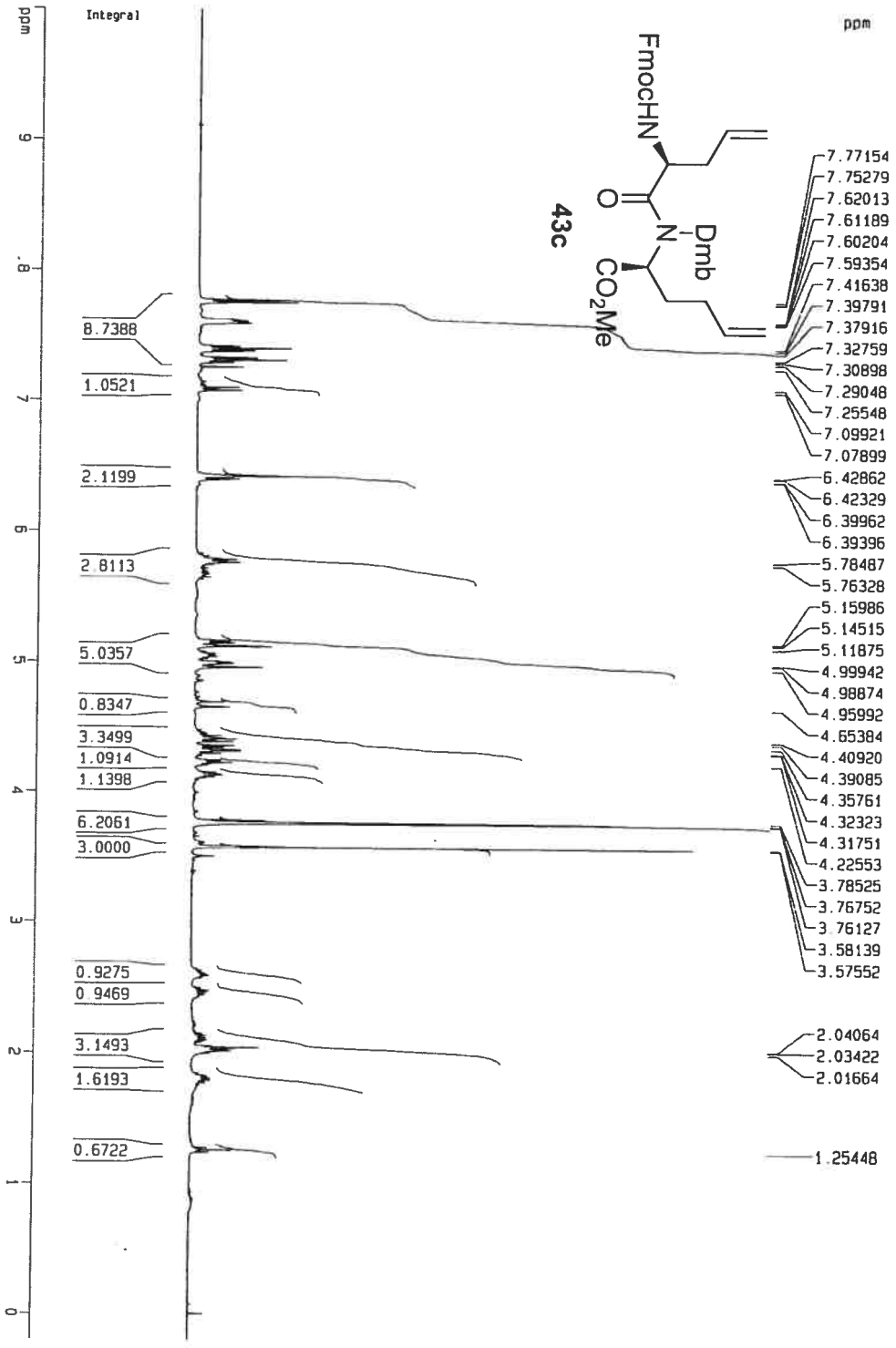
118.289
115.969
115.255
103.506
98.309
79.180
77.219
76.901
76.583
57.558
55.159
54.937
51.718
50.216
47.151
37.876
30.424
29.458
28.131
Dmb
N
BocHN
O
CO2Me
43b
ppm
180
160
140
120
100
80
60
40
20
0


ppm
Integral
ppm
FmocHN
O
N
Dmb
CO2Me
43c
8.7388
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2.1199
2.8113
5.0357
0.8347
3.3499
1.0914
1.1398
6.2061
3.0000
0.9275
0.9469
3.1493
1.6193
0.6722
7.77154
7.75279
7.62013
7.61189
7.60204
7.59354
7.41638
7.39791
7.37916
7.32759
7.30898
7.29048
7.25548
7.09921
7.07899
6.42862
6.42329
6.39962
6.39396
5.78487
5.76328
5.15986
5.14515
5.11875
4.99942
4.98874
4.95992
4.65384
4.40920
4.39085
4.35761
4.32323
4.31751
4.22553
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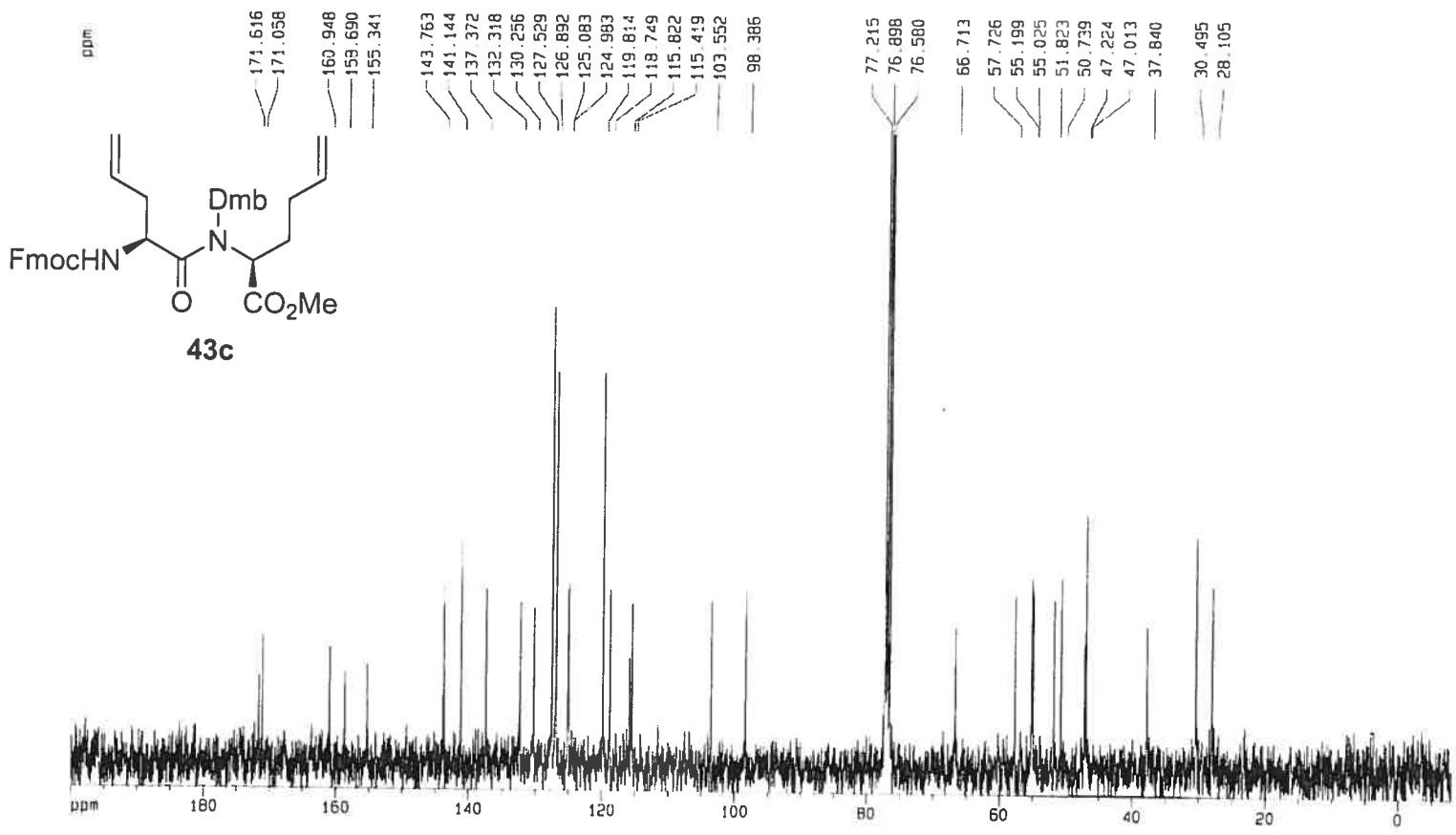
3.76752
3.76127
3.58139
3.57552
2.04064
2.03422
2.01664
1.25448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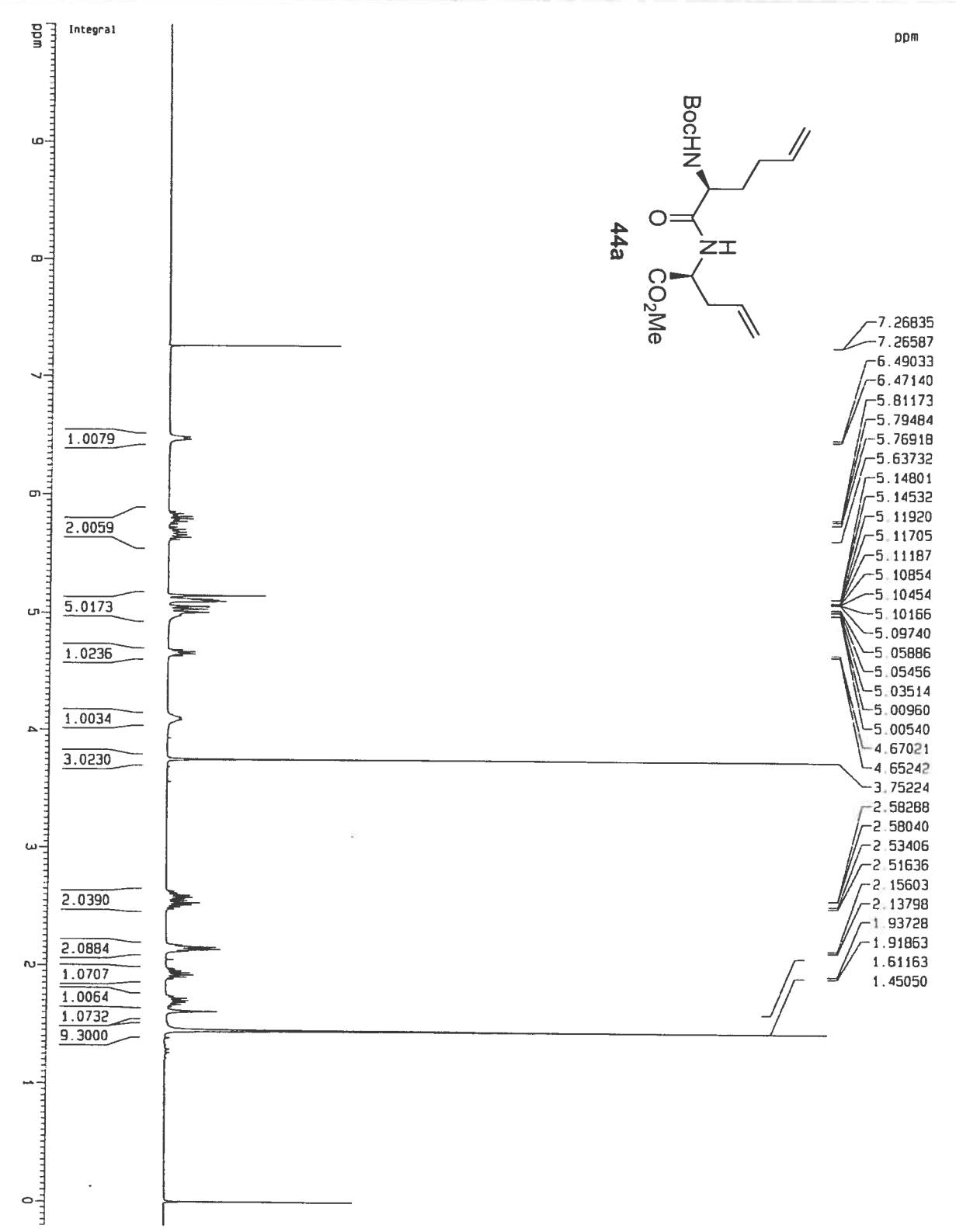
160.948
159.690
155.341
143.763
141.144
137.372
132.318
130.256
127.529
126.892
125.083
124.983
119.814
118.749
115.822
115.419
103.552
98.386
77.215
76.898
76.580
66.713
57.726
55.199
55.025
51.823
50.739
47.224
47.013
37.840
30.495
28.105
Dmb
N
FmocHN
O
CO2Me
43c
ppm
180
160
140
120
100
80
60
40
20
0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Integral
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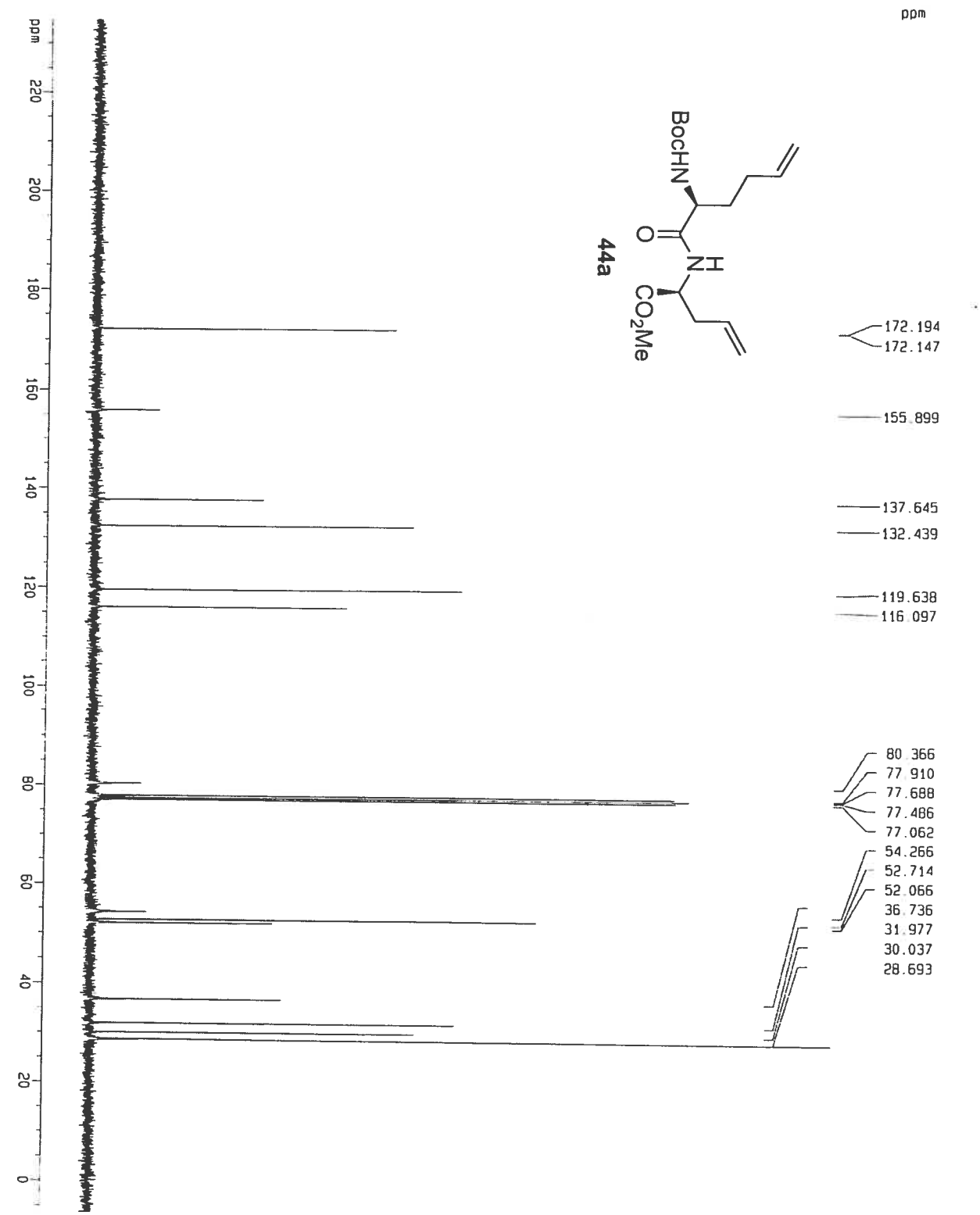
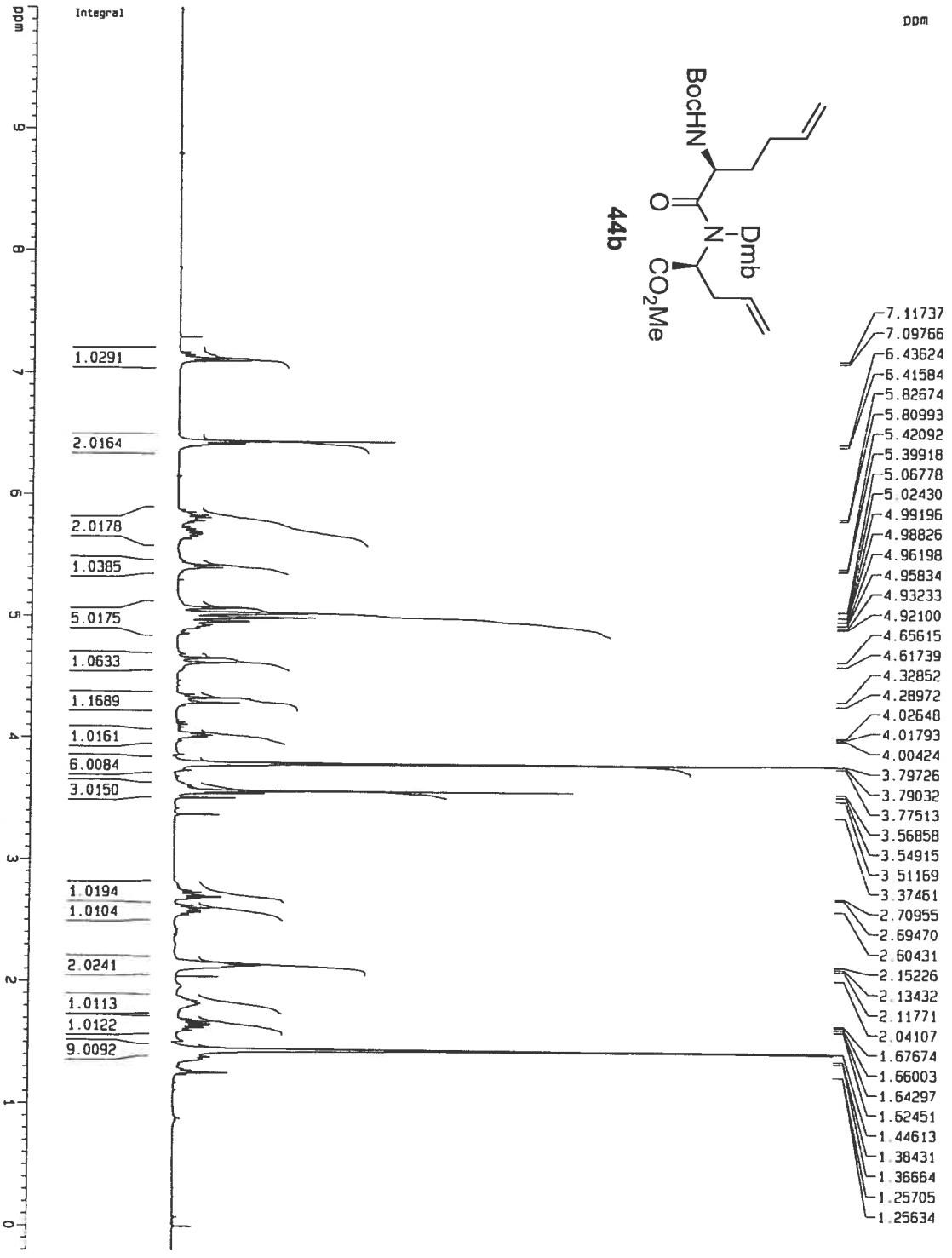
8
7
6
5
4
3
2
1
0
1.0079
2.0059
5.0173
1.0236
1.0034
3.0230
2.0390
2.0884
1.0707
1.0064
1.0732
9.3000
BocHN
O
H
N
CO2Me
44a
ppm
7.26835
7.26587
6.49033
6.47140
5.81173
5.79484
5.76918
5.63732
5.14801
5.14532
5.11920
5.11705
5.11187
5.10854
5.10454
5.10166
5.09740
5.05886
5.05456
5.03514
5.00960
5.00540
4.67021
4.65242
3.75224
2.58288
2.58040
2.53406
2.51636
2.15603
2.13798
1.93728
1.91863
1.61163
1.45050


ppm
220
200
180
160
140
120
100
80
60
40
20
0
BocHN
O
H
N
CO2Me
44a
ppm
172.194
172.147
155.899
137.645
132.439
119.638
116.097
80.366
77.910
77.688
77.486
77.062
54.266
52.714
52.066
36.736
31.977
30.037
28.693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ppm
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2.0178
1.0385
5.0175
1.0633
1.1689
1.0161
6.0084
3.0150
1.0194
1.0104
2.0241
1.0113
1.0122
9.0092
BocHN
O
N
Dmb
CO2Me
44b
ppm
7.11737
7.09766
6.43624
6.41584
5.82674
5.80993
5.42092
5.39918
5.06778
5.02430
4.99196
4.98826
4.96198
4.95834
4.93233
4.92100
4.65615
4.61739
4.32852
4.28972
4.02648
4.01793
4.00424
3.79726
3.79032
3.77513
3.56858
3.54915
3 51169
3.37461
2.70955
2.69470
2.60431
2.15226
2.13432
2.11771
2.04107
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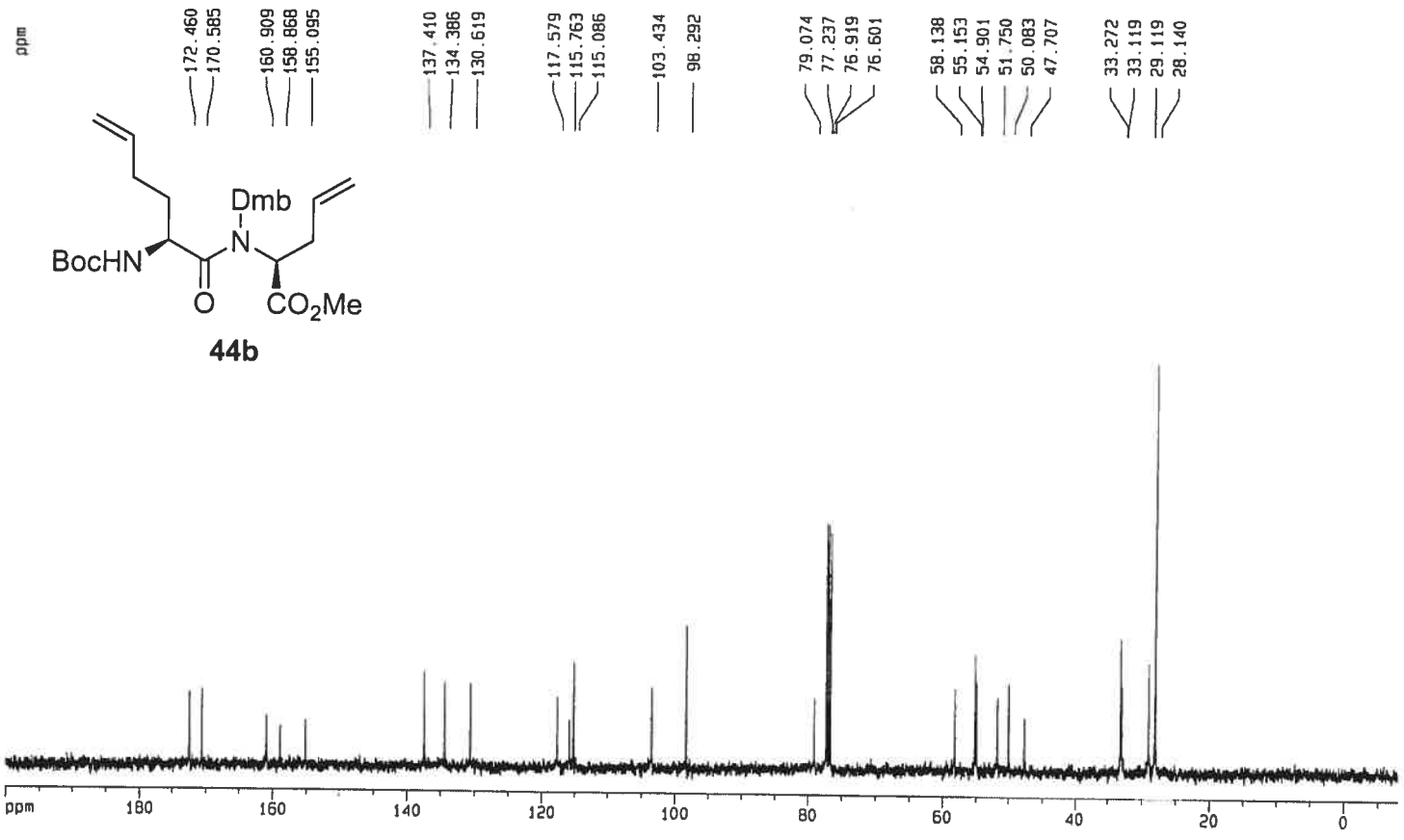
1.66003
1.64297
1.62451
1.44613
1.38431
1.36664
1.25705
1.25634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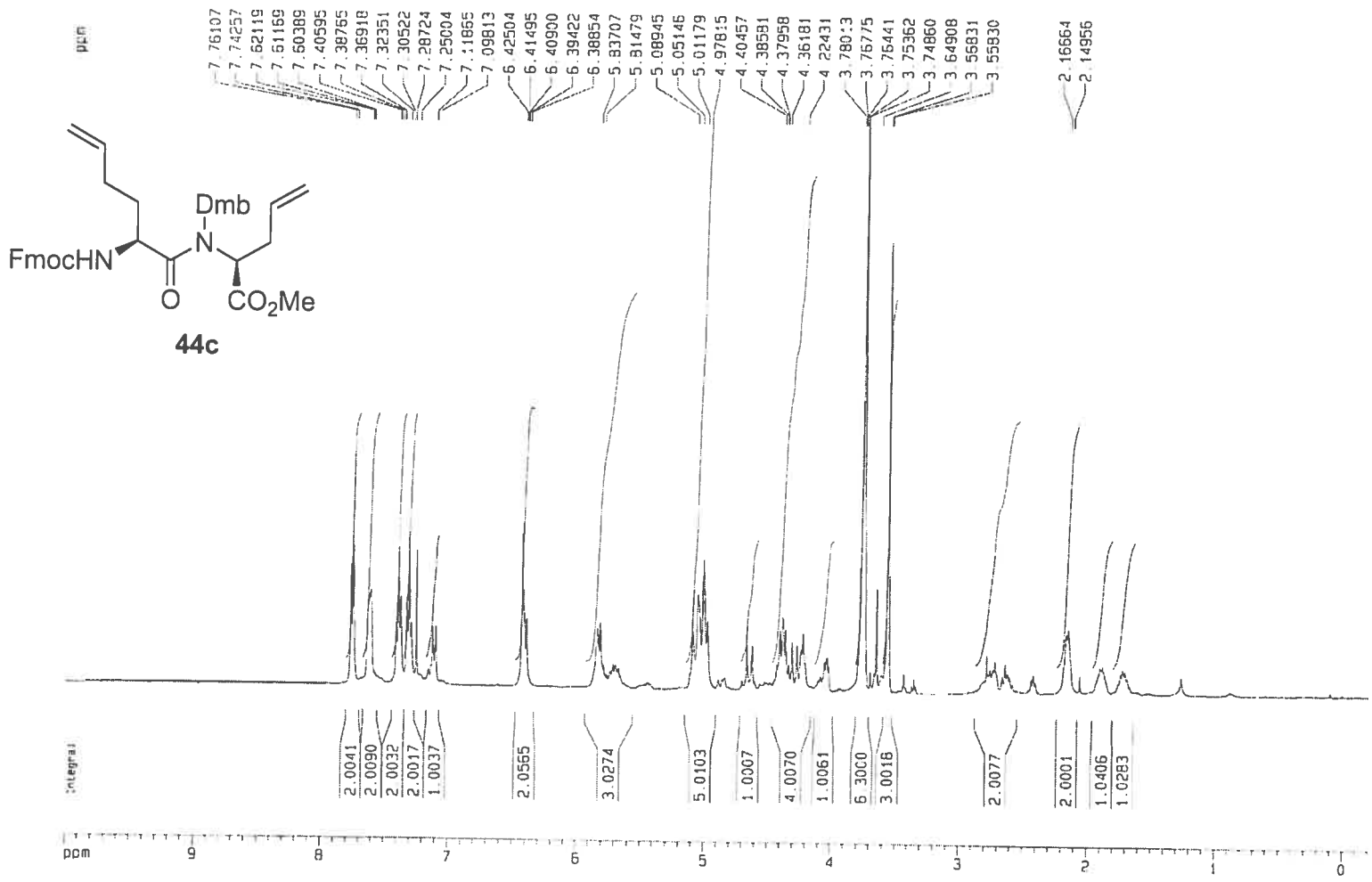
158.868
155.095
137.410
134.386
130.619
117.579
115.763
115.086
103.434
98.292
79.074
77.237
76.919
76.601
58.138
55.153
54.901
51.750
50.083
47.707
33.272
33.119
29.119
28.140
Dmb
N
BocHN
O
CO2Me
ppm
180
160
140
120
100
80
60
40
20
0

44b


FmocHN
Dmb
N
O
CO2Me
44c
ppm
Integral
7.76107
7.74257
7.62119
7.61169
7.60389
7.40595
7.38765
7.36918
7.32351
7.30522
7.28724
7.25004
7.11865
7.09813
6.42504
6.41495
6.40900
6.39422
6.38854
5.83707
5.81479
5.08945
5.05146
5.01179
4.97815
4.40457
4.38581
4.37958
4.36181
4.22431
3.78013
3.76775
3.75441
3.75362
3.74860
3.64908
3.55831
3.55830
2.16664
2.14956
2.0041
2.0090
2.0032
2.0017
1.0037
2.0565
3.0274
5.0103
1.0007
4.0070
1.0061
6.3000
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2.0077
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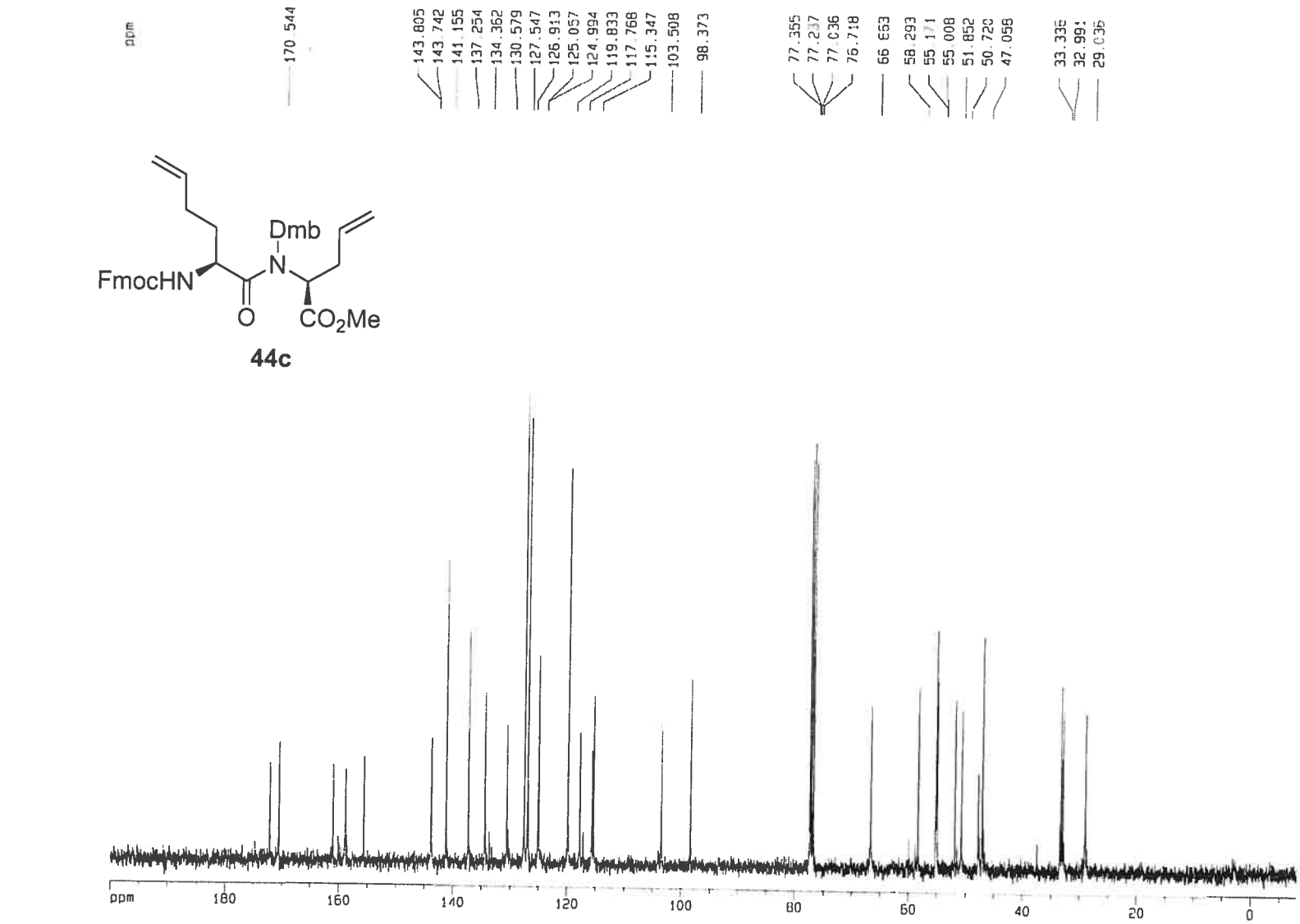
1.0406
1.0283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137.254
134.362
130.579
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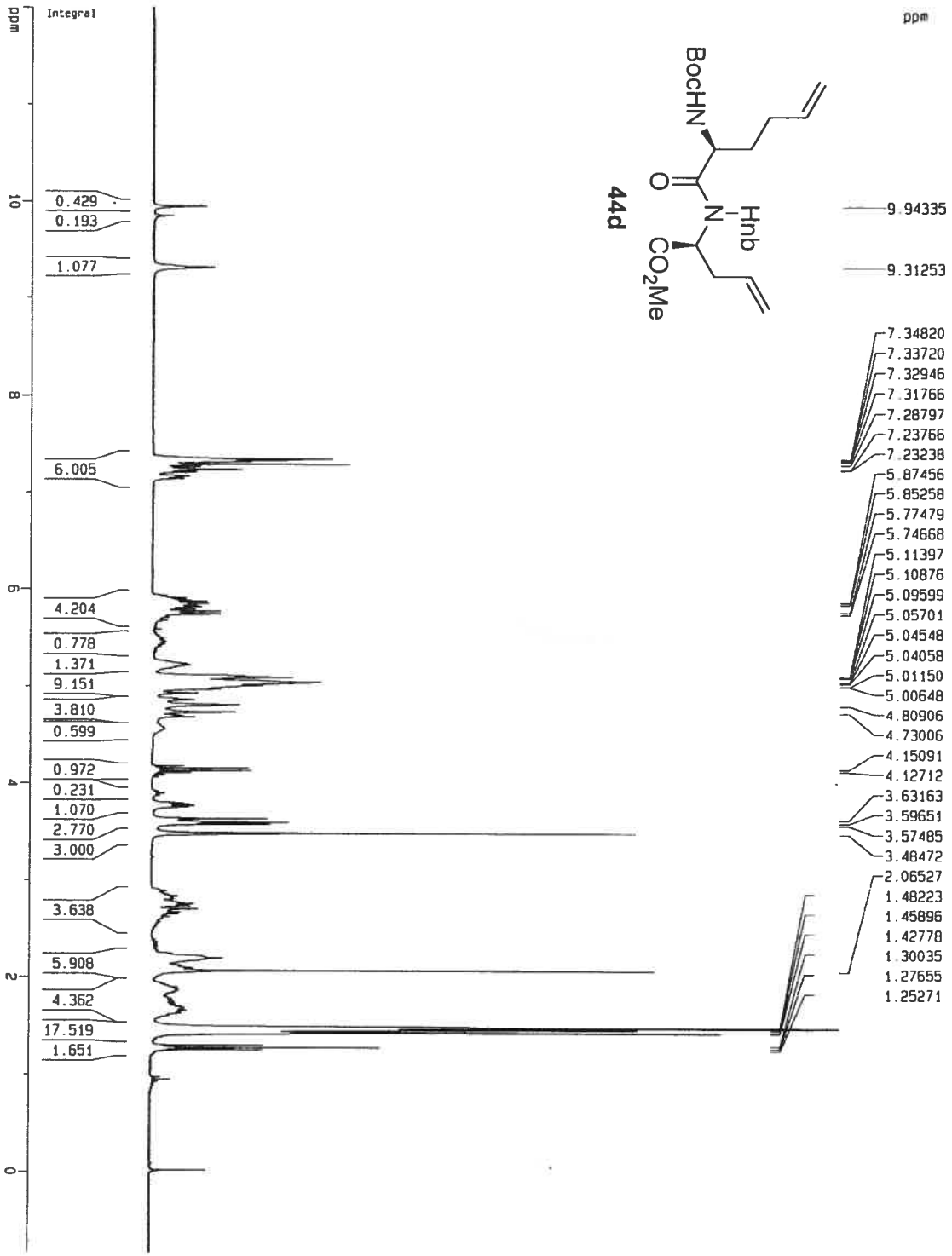
126.913
125.057
124.994
119.833
117.768
115.347
103.508
98.373
77.355
77.237
77.036
76.718
66.653
58.293
55.171
55.008
51.852
50.720
47.058
33.336
32.991
29.036
Dmb
N
FmocHN
O
CO2Me
44c
ppm
180
160
140
120
100
80
60
40
20
0

Axl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Integral
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4.204
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1.371
9.151
3.810
0.599
0.972
0.231
1.070
2.770
3.000
3.638
5.908
4.362
17.519
1.651
BocHN
O
N
Hnb
CO2Me
44d
ppm
9.94335
9.31253
7.34820
7.33720
7.32946
7.31766
7.28797
7.23766
7.23238
5.87456
5.85258
5.77479
5.74668
5.11397
5.10876
5.09599
5.05701
5.04548
5.04058
5.01150
5.00648
4.80906
4.73006
4.15091
4.12712
3.63163
3.59651
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2.06527
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1.30035
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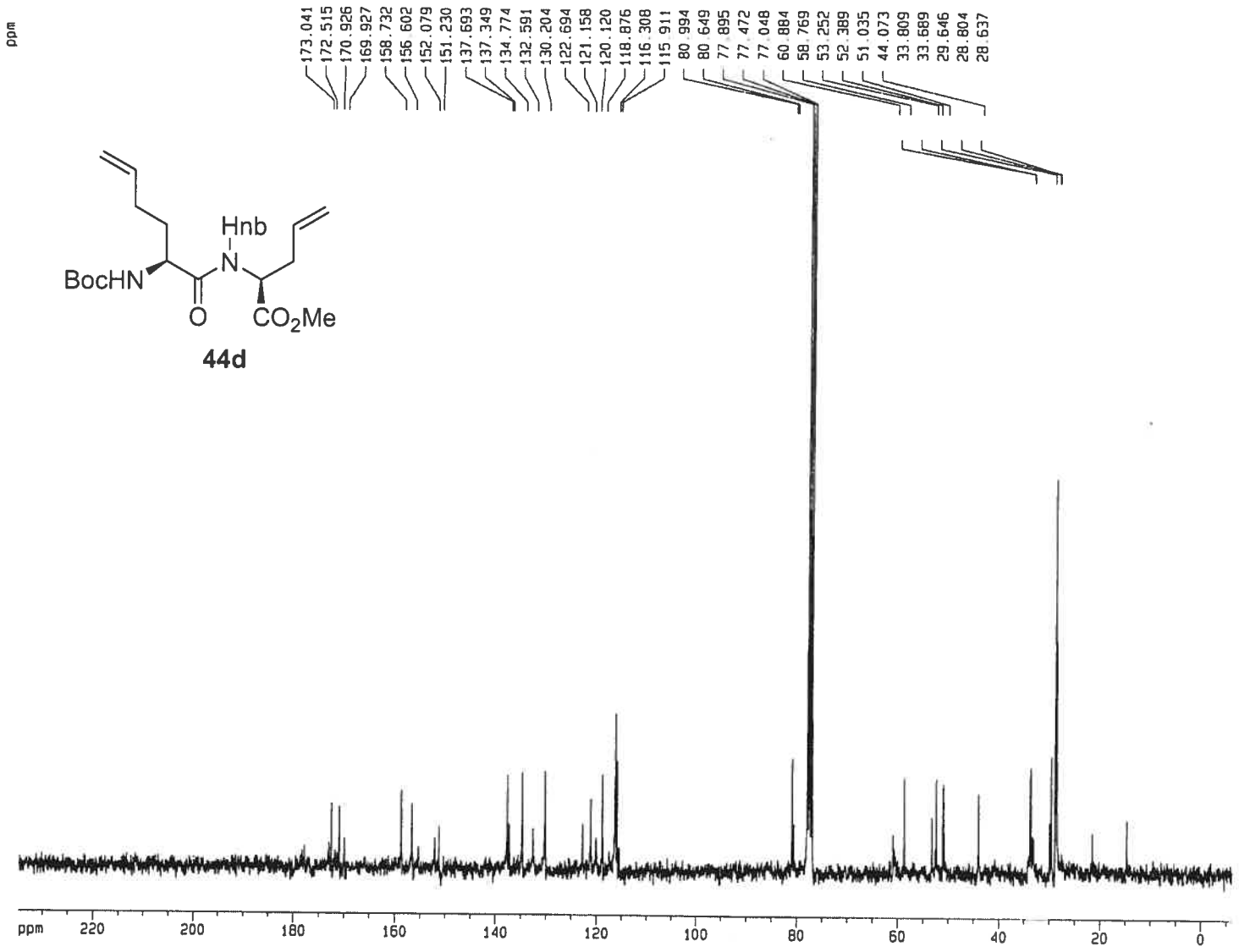
1.25271

Axli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151.230
137.693
137.349
134.774
132.591
130.204
122.694
121.158
120.120
118.876
116.308
115.911
80.994
80.649
77.895
77.472
77.048
60.884
58.769
53.252
52.389
51.035
44.073
33.809
33.689
29.646
28.804
28.637
Hnb
N
BocHN
O
CO2Me
44d
ppm
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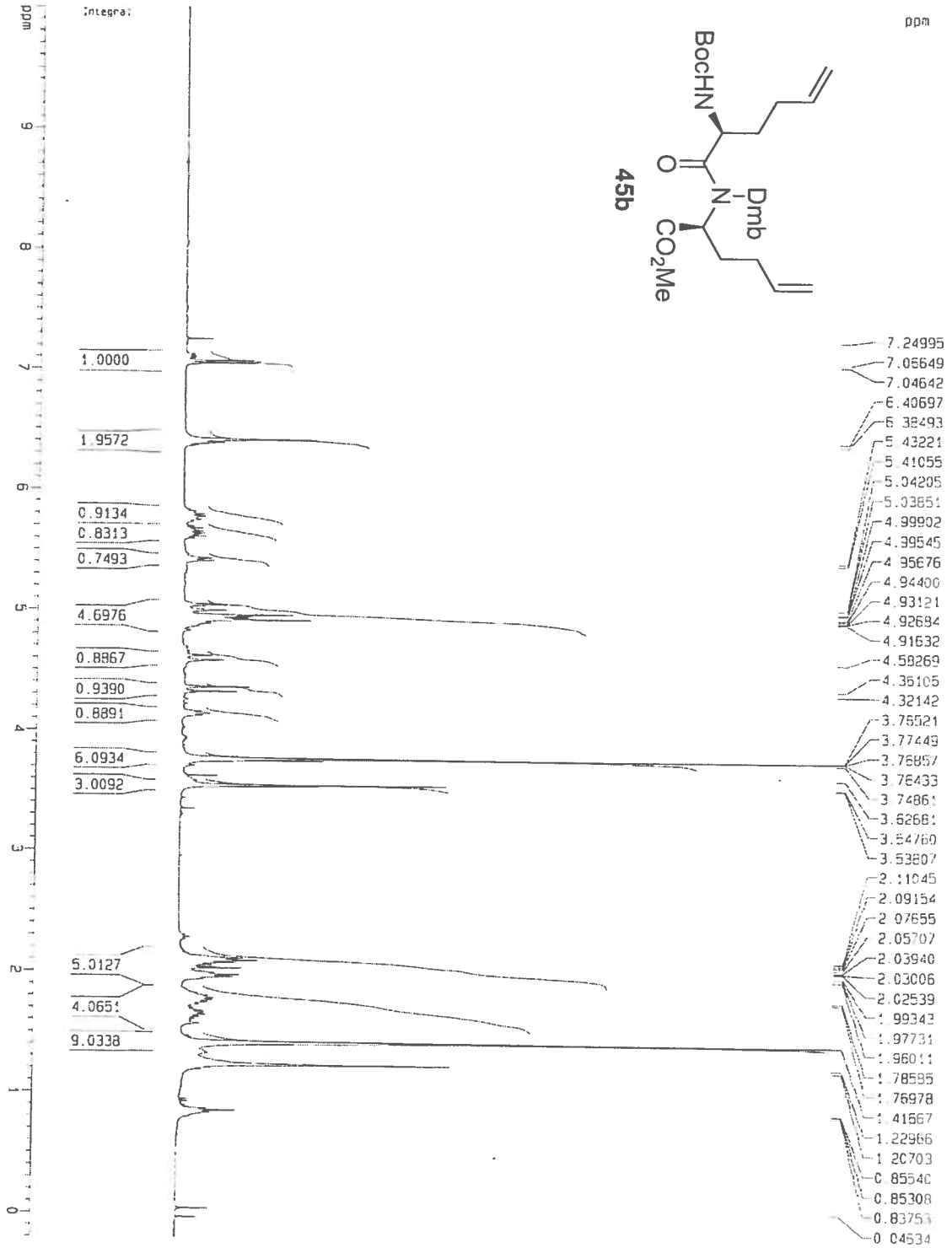
200
180
160
140
120
100
80
60
40
20
0


BocHN
O
N
Dmb
CO2Me
45b
ppm
Integral
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1.9572
0.9134
0.8313
0.7493
4.6976
0.8867
0.9390
0.8891
6.0934
3.0092
5.0127
4.0651
9.0338
7.24995
7.06649
7.04642
6.40697
6.38493
5.43221
5.41055
5.04205
5.03851
4.99902
4.99545
4.95676
4.94400
4.93121
4.92684
4.91632
4.58269
4.36105
4.32142
3.76521
3.77449
3.76857
3.76433
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3.62681
3.54760
3.53807
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2.09154
2.07655
2.05707
2.03940
2.03006
2.02539
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1.97731
1.96011
1.78595
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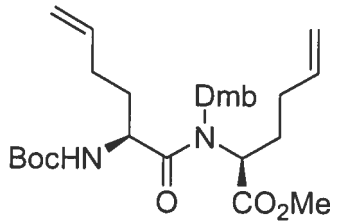
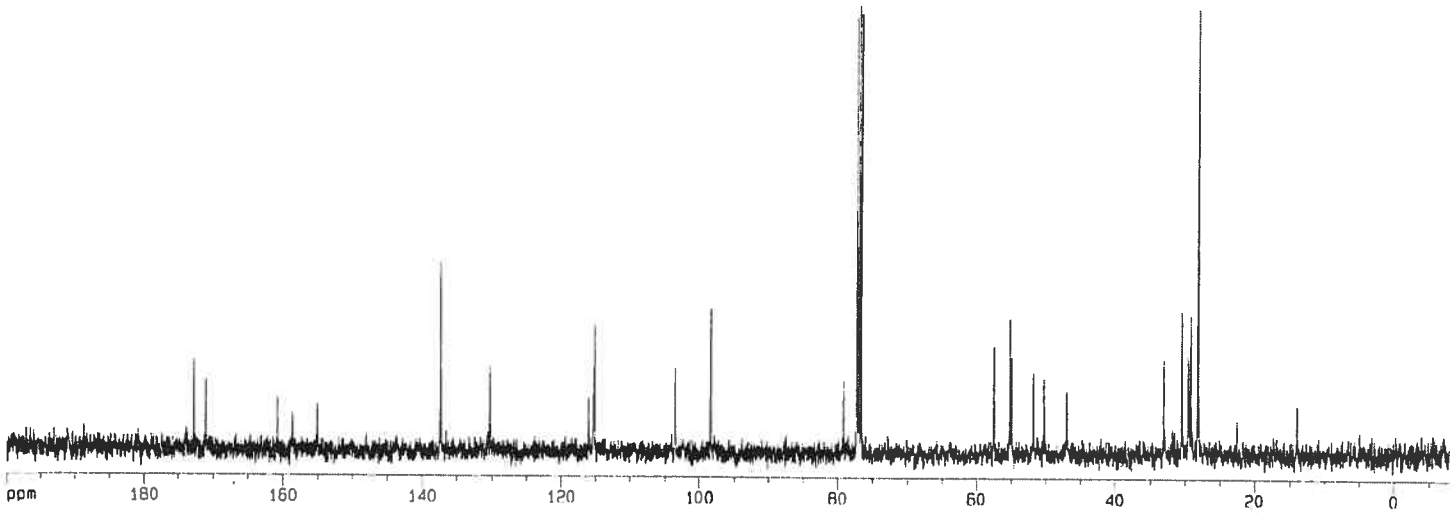
1.41567
1.22966
1.20703
0.85540
0.85308
0.83753
0.04534

Axliii


ppm
172.879
171.153
160.856
158.708
155.121
137.392
130.312
116.021
115.279
115.143
103.509
98.317
79.145
77.204
76.886
76.568
57.458
55.178
54.934
51.744
50.194
46.965
33.037
30.432
29.511
29.138
28.151
28.083
22.505
13.935


Dmb
N
BocHN
O
CO2Me

45b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160
140
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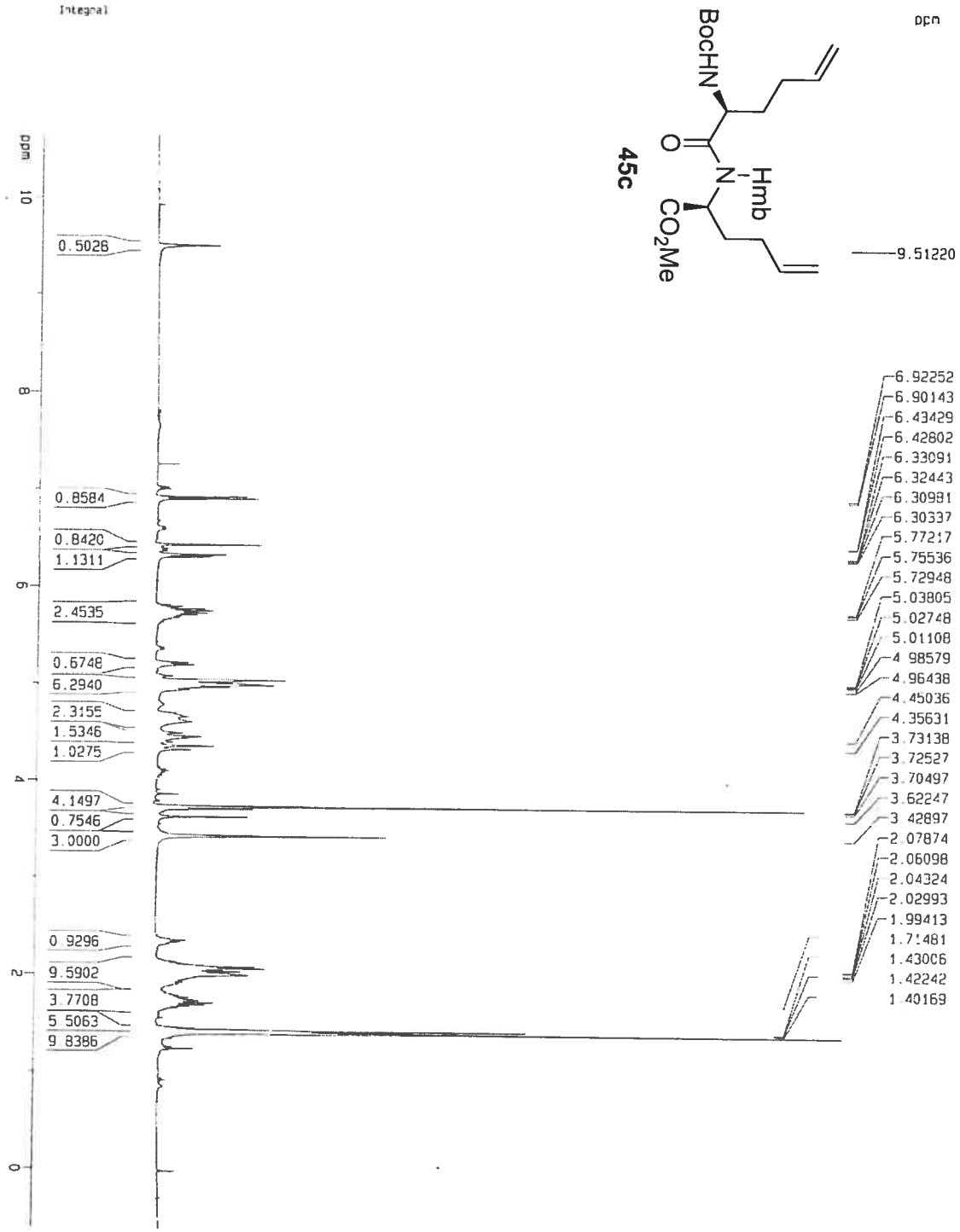
100
80
60
40
20
0


Integral
ppm
BocHN
O
N
Hmb
CO2Me
45c
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6.90143
6.43429
6.42802
6.33091
6.32443
6.30981
6.30337
5.77217
5.75536
5.72948
5.03805
5.02748
5.01108
4.98579
4.96438
4.45036
4.35631
3.73138
3.72527
3.70497
3.62247
3.42897
2.07874
2.06098
2.04324
2.02993
1.99413
1.71481
1.43006
1.42242
1.40169
0.5026
0.8584
0.8420
1.1311
2.4535
0.6748
6.2940
2.3155
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4.1497
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3.0000
0.9296
9.5902
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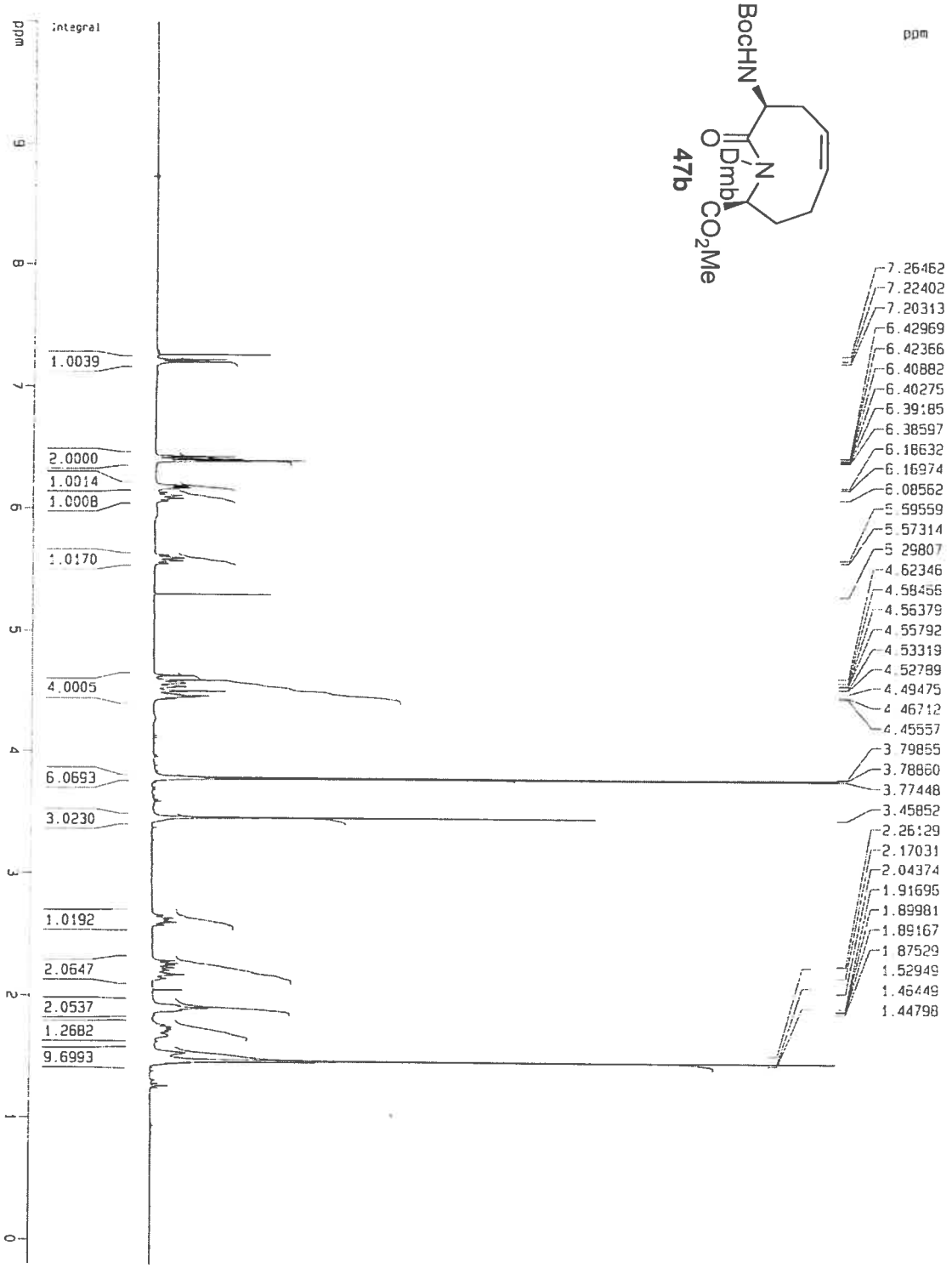
5.5063
9.8386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1.0170
4.0005
6.0693
3.0230
1.0192
2.0647
2.0537
1.2682
9.6993
BocHN
N
Dmb
O
CO2Me
47b
ppm
7.26462
7.22402
7.20313
6.42969
6.42366
6.40882
6.40275
6.39185
6.38597
6.18632
6.16974
6.08562
5.59559
5.57314
5.29807
4.62346
4.58466
4.56379
4.55792
4.53319
4.52789
4.49475
4.46712
4.45557
3.79855
3.78860
3.77448
3.45852
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2.17031
2.04374
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1.87529
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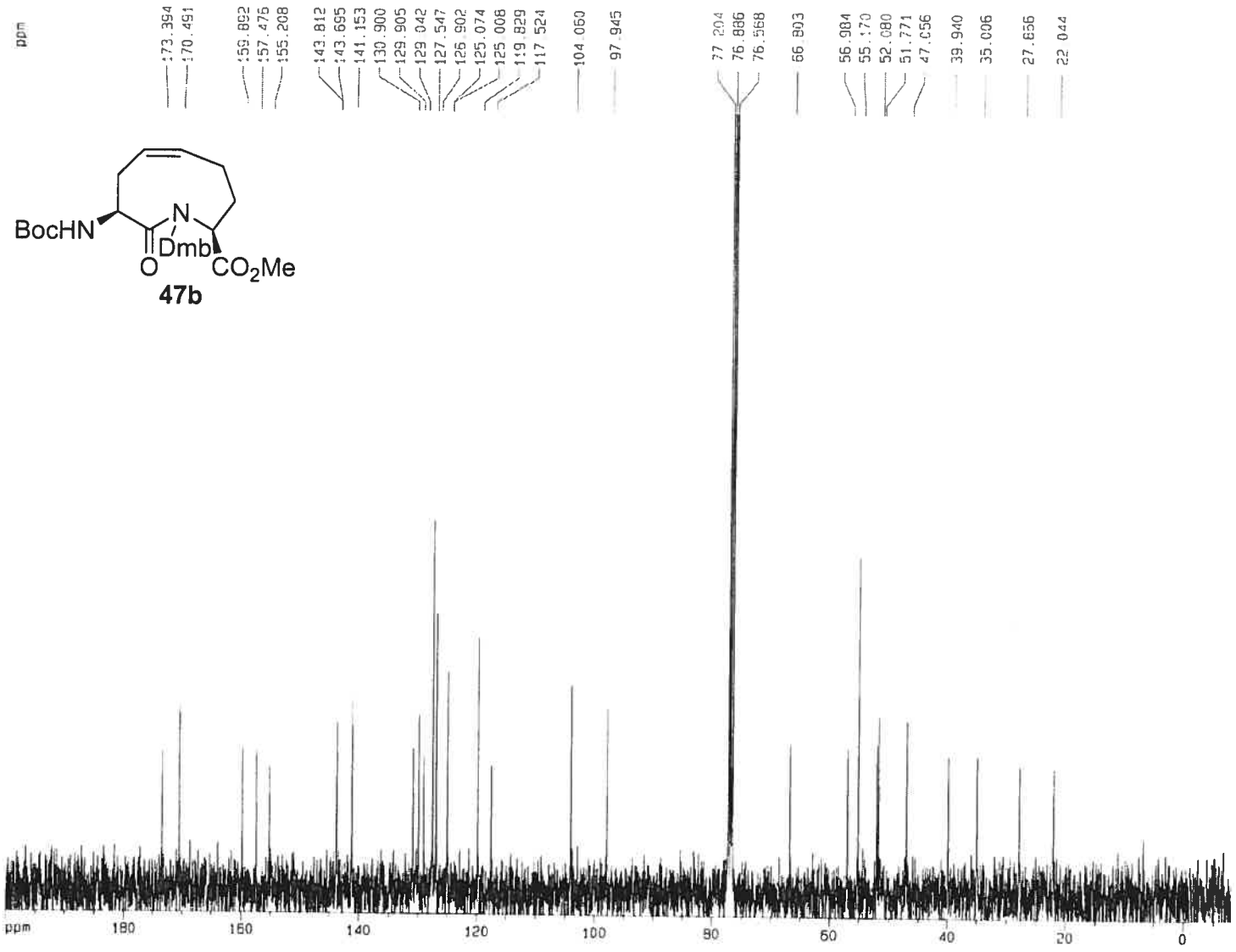
1.44798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141.153
130.900
129.905
129.042
127.547
126.902
125.074
125.008
119.829
117.524
104.060
97.945
77.204
76.886
76.568
66.803
56.984
55.170
52.080
51.771
47.056
39.940
35.006
27.656
22.044
BocHN
N
Dmb
O
CO2Me
47b
ppm
180
160
140
120
100
80
60
40
20
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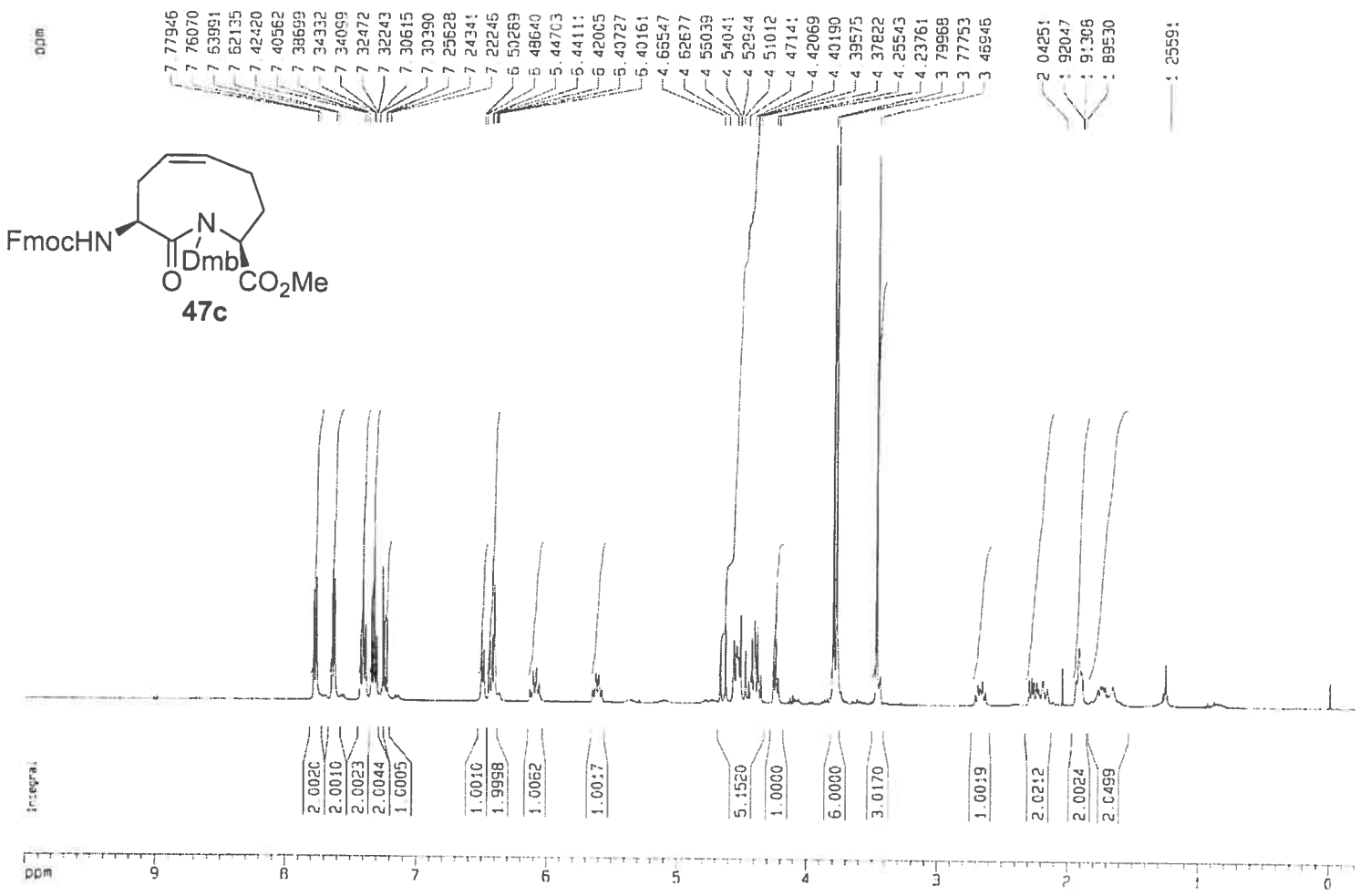
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Dmb
O
CO2Me
47c
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7.34099
7.32472
7.32243
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7.30390
7.25628
7.24341
7.22245
6.50269
6.48640
5.44703
5.44111
6.42005
5.40727
5.40161
4.66547
4.62677
4.55039
4.54041
4.52944
4.51012
4.47141
4.42069
4.40190
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1.25591
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2.0010
2.0023
2.0044
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1.0010
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1.0062
1.0017
5.1520
1.0000
6.0000
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2.0212
2.0024
2.0499
ppm
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8
7
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3
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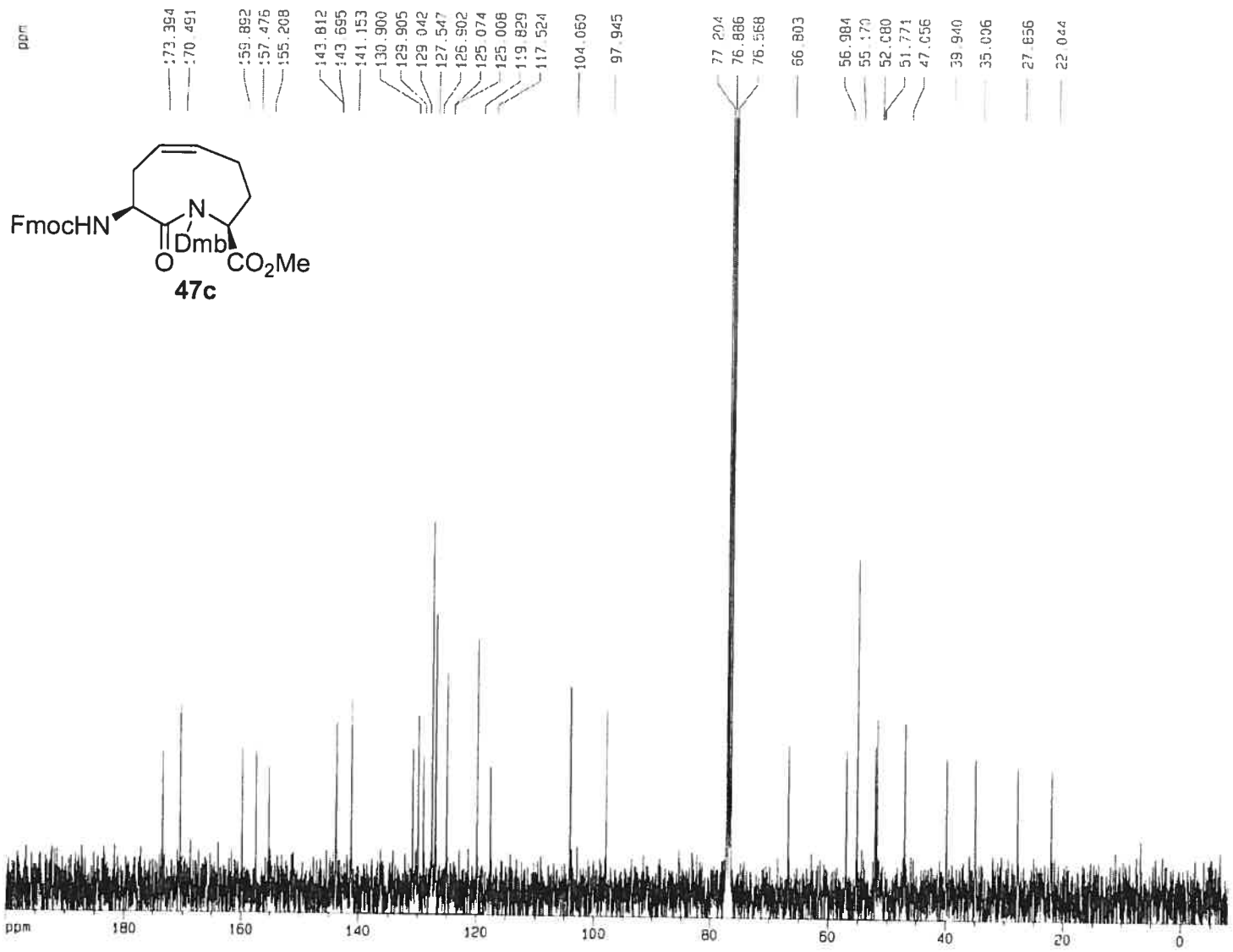
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143.812
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129.042
127.547
126.902
125.074
125.008
119.829
117.524
104.060
97.945
77.204
76.886
76.568
66.803
56.984
55.170
52.080
51.771
47.056
39.940
35.006
27.856
22.044
FmocHN
N
Dmb
O
O
CO2Me
47c
ppm
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140
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100
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60
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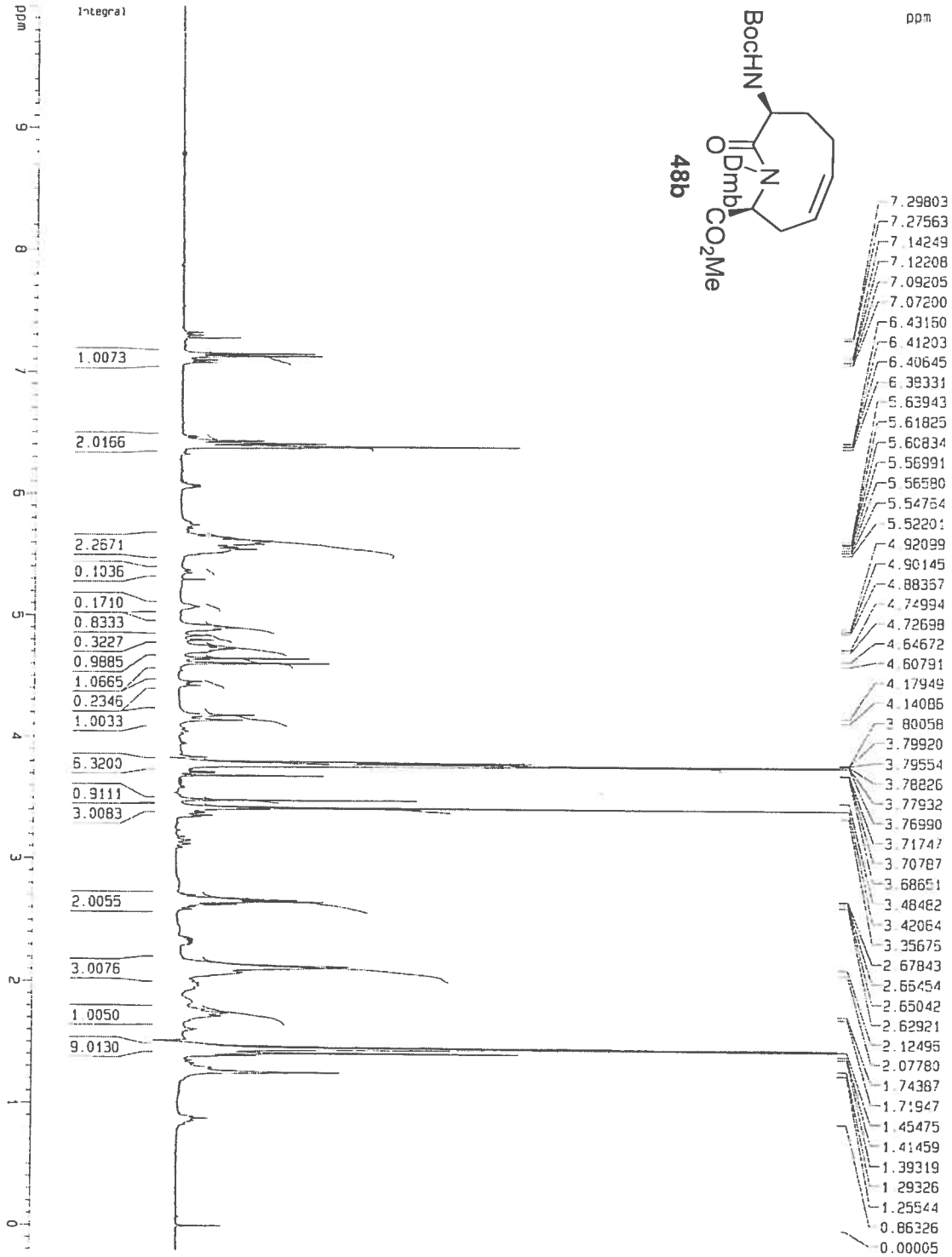
20
0


BocHN
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Dmb
O
CO2Me
48b
Integral
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2.0166
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0.1710
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0.3227
0.9885
1.0665
0.2346
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6.3200
0.9111
3.0083
2.0055
3.0076
1.0050
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6.38331
5.63943
5.61825
5.60834
5.56991
5.56580
5.54764
5.52201
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4.90145
4.88357
4.74994
4.72698
4.64672
4.60791
4.17949
4.14086
3.80058
3.79920
3.79554
3.78826
3.77932
3.76990
3.71747
3.70787
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3.48482
3.42064
3.35675
2.67843
2.66454
2.65042
2.62921
2.12495
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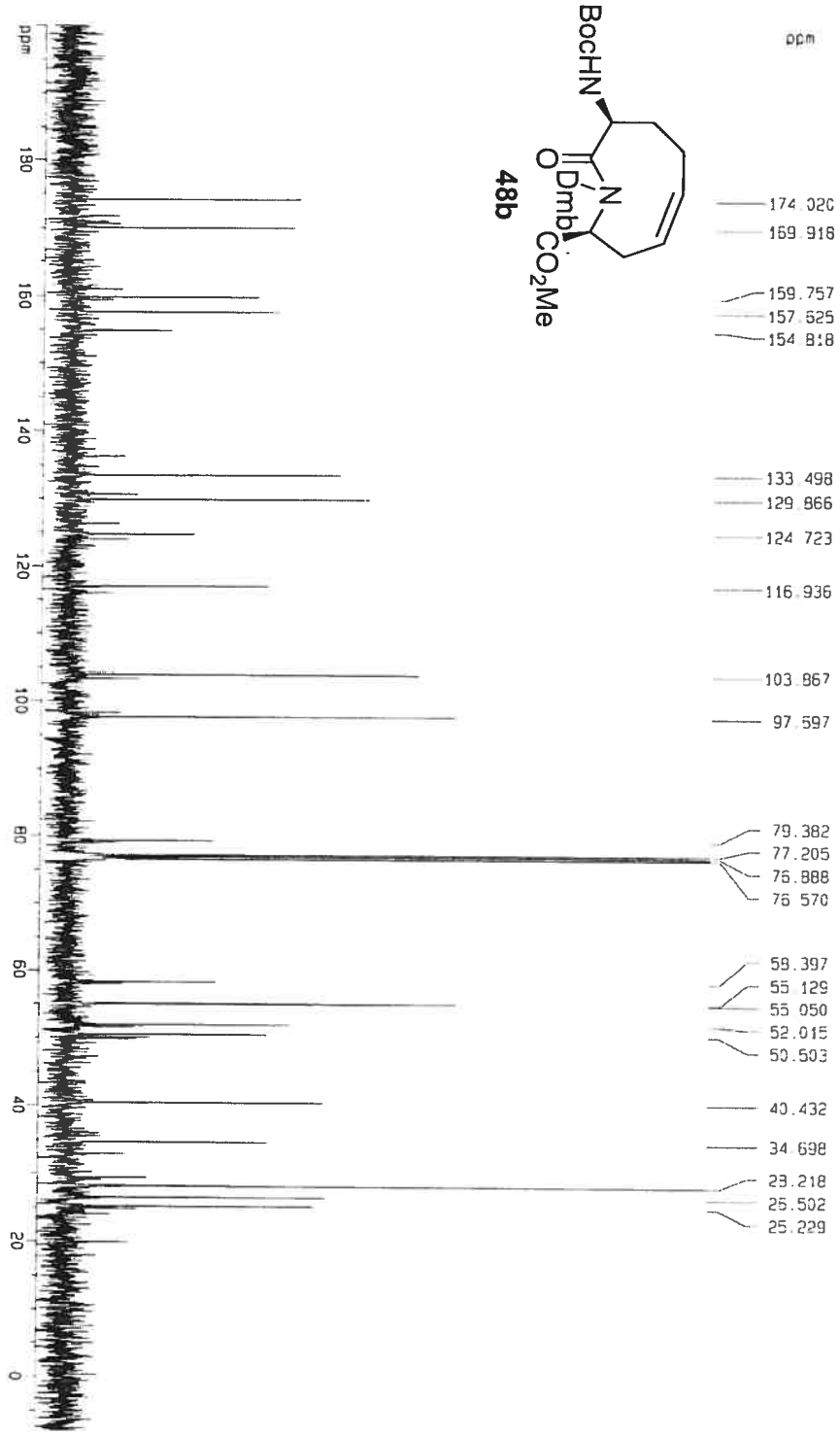
0.86326
0.00005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O
N
Dmb
CO2Me
48b
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154.818
133.498
129.866
124.723
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103.967
97.597
79.382
77.205
76.888
76.570
58.397
55.129
55.050
52.015
50.503
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34.698
28.218
25.502
25.229
ppm
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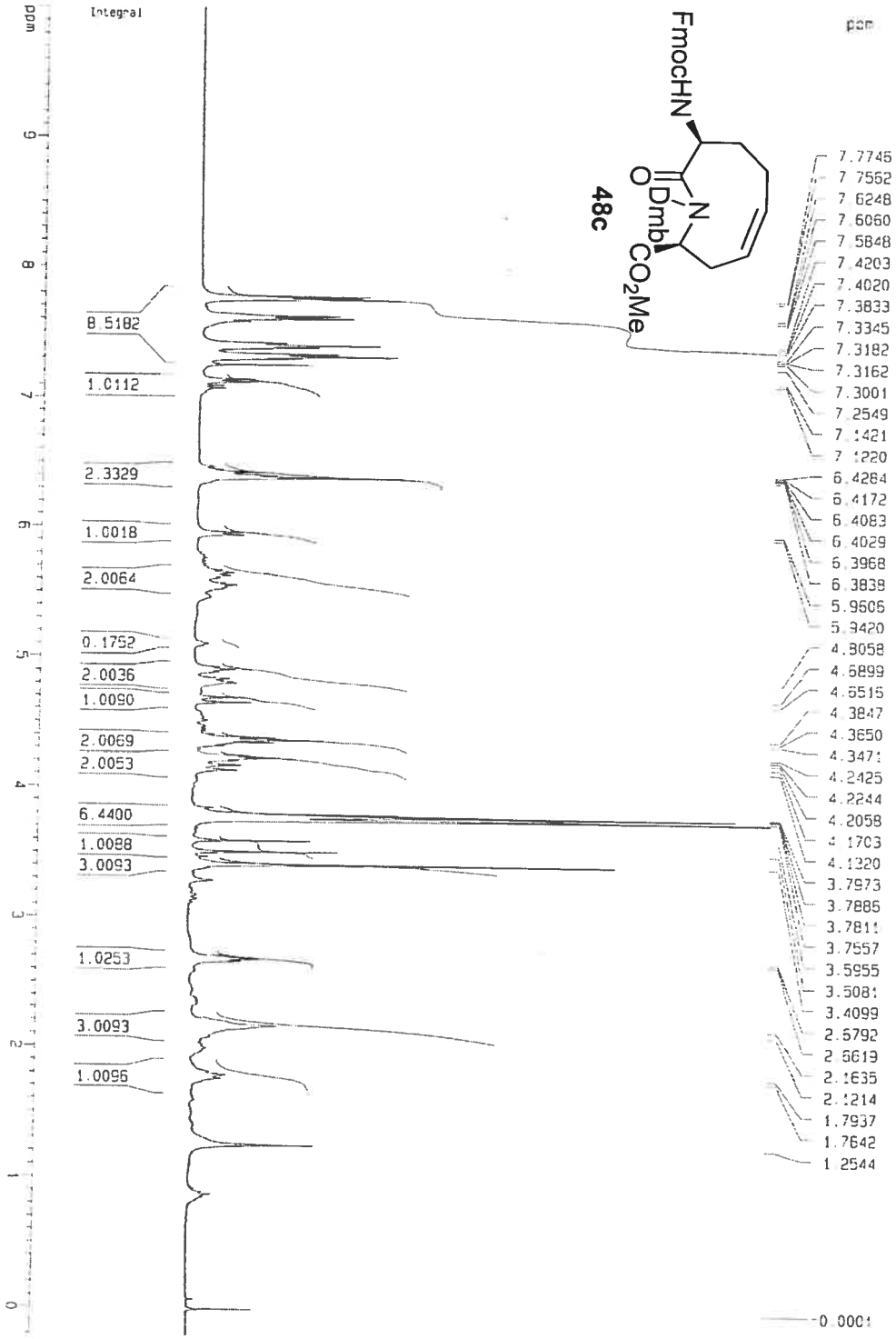
160
140
120
100
80
60
40
20
0

Ali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N
Dmb
CO2Me
48c
ppm
Integral
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2.0064
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2.0036
1.0090
2.0069
2.0053
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1.0088
3.0093
1.0253
3.0093
1.0096
7.7745
7.7552
7.6248
7.6060
7.5848
7.4203
7.4020
7.3833
7.3345
7.3182
7.3162
7.3001
7.2549
7.1421
7.1220
6.4284
6.4172
6.4083
6.4029
6.3968
6.3838
5.9505
5.9420
4.8058
4.5899
4.5515
4.3847
4.3650
4.3471
4.2425
4.2244
4.2058
4.1703
4.1320
3.7973
3.7886
3.7811
3.7557
3.5955
3.5081
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1.7642
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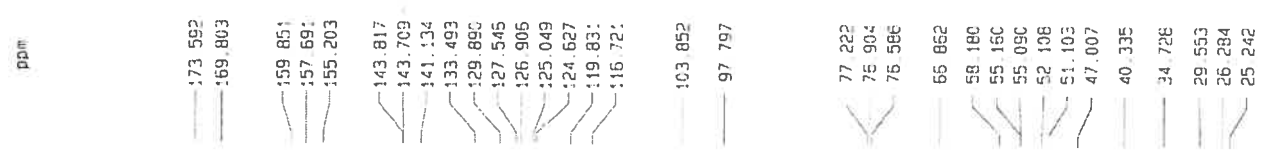
Alii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141.134
133.493
129.890
127.545
126.905
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124.627
119.831
116.721
103.852
97.797
77.222
75.904
76.586
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58.180
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55.090
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51.103
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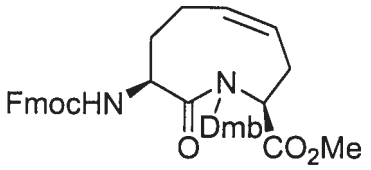
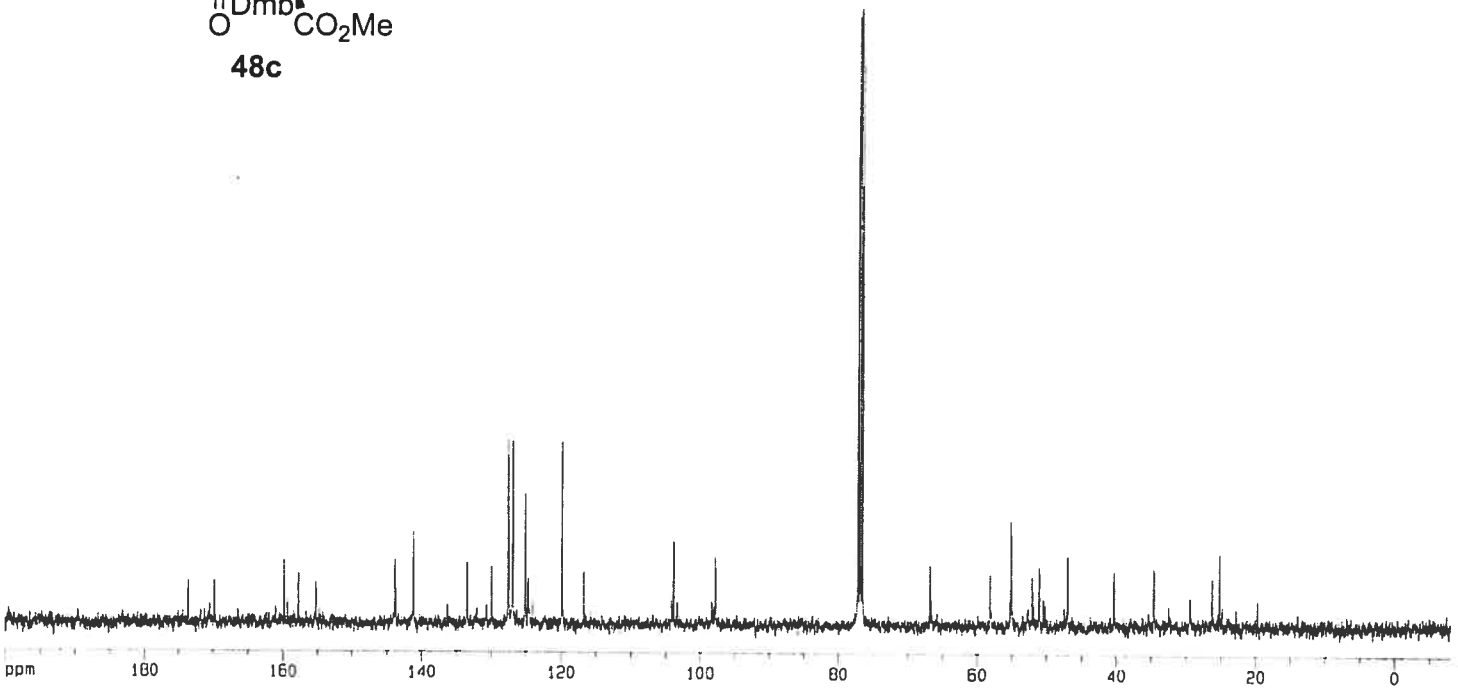
26.284
25.242


FmocHN
N
Dmb
O
O
CO2Me

48c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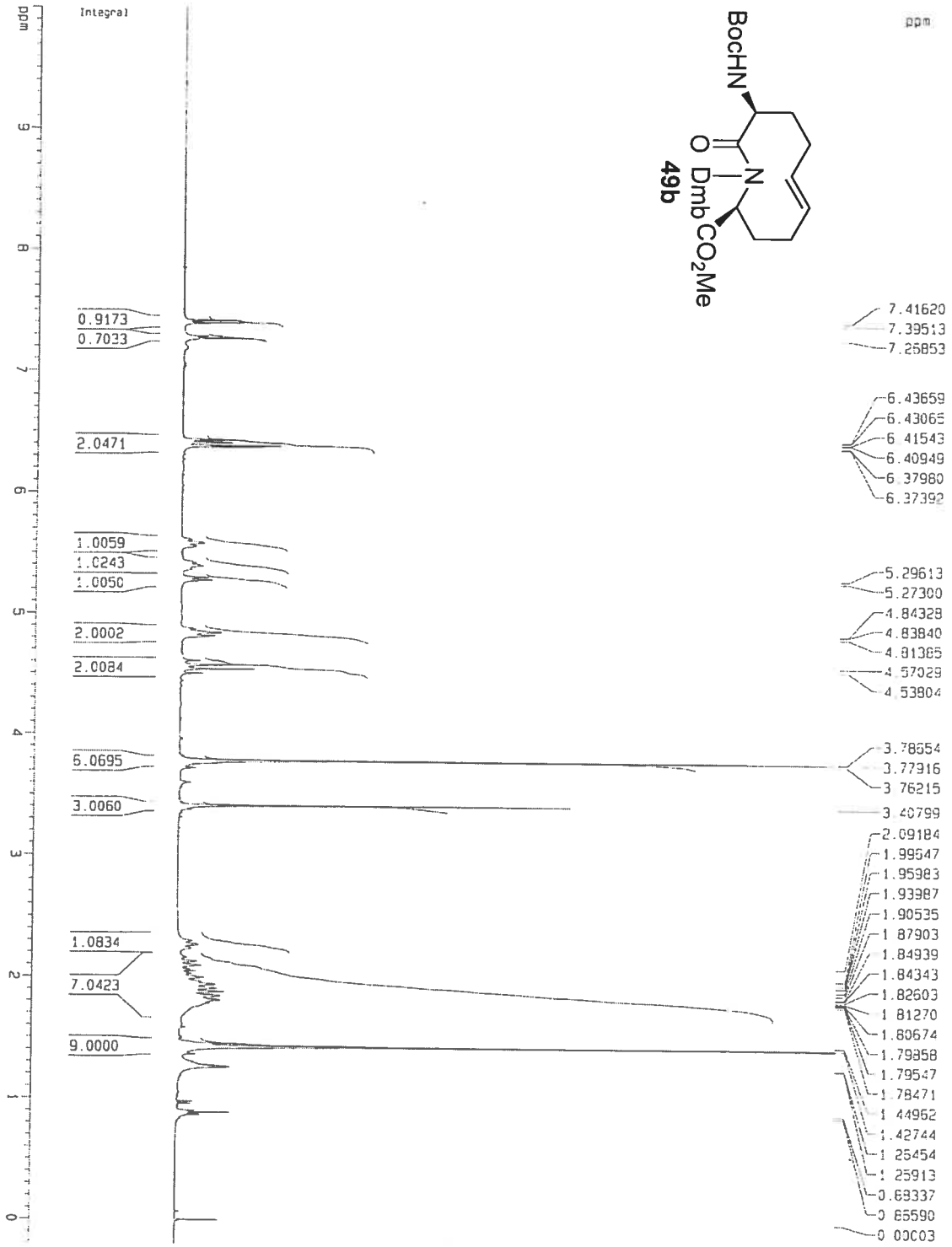
140
120
100
80
60
40
20
0

Aliii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O
N
Dmb
CO2Me
49b
ppm
Integral
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1.0243
1.0050
2.0002
2.0084
5.0695
3.0060
1.0834
7.0423
9.0000
7.41620
7.39513
7.25853
6.43659
6.43065
6.41543
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6.37980
6.37392
5.29613
5.27300
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4.83840
4.81385
4.57029
4.53804
3.78654
3.77916
3.76215
3.40799
2.09184
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1.84939
1.84343
1.82603
1.81270
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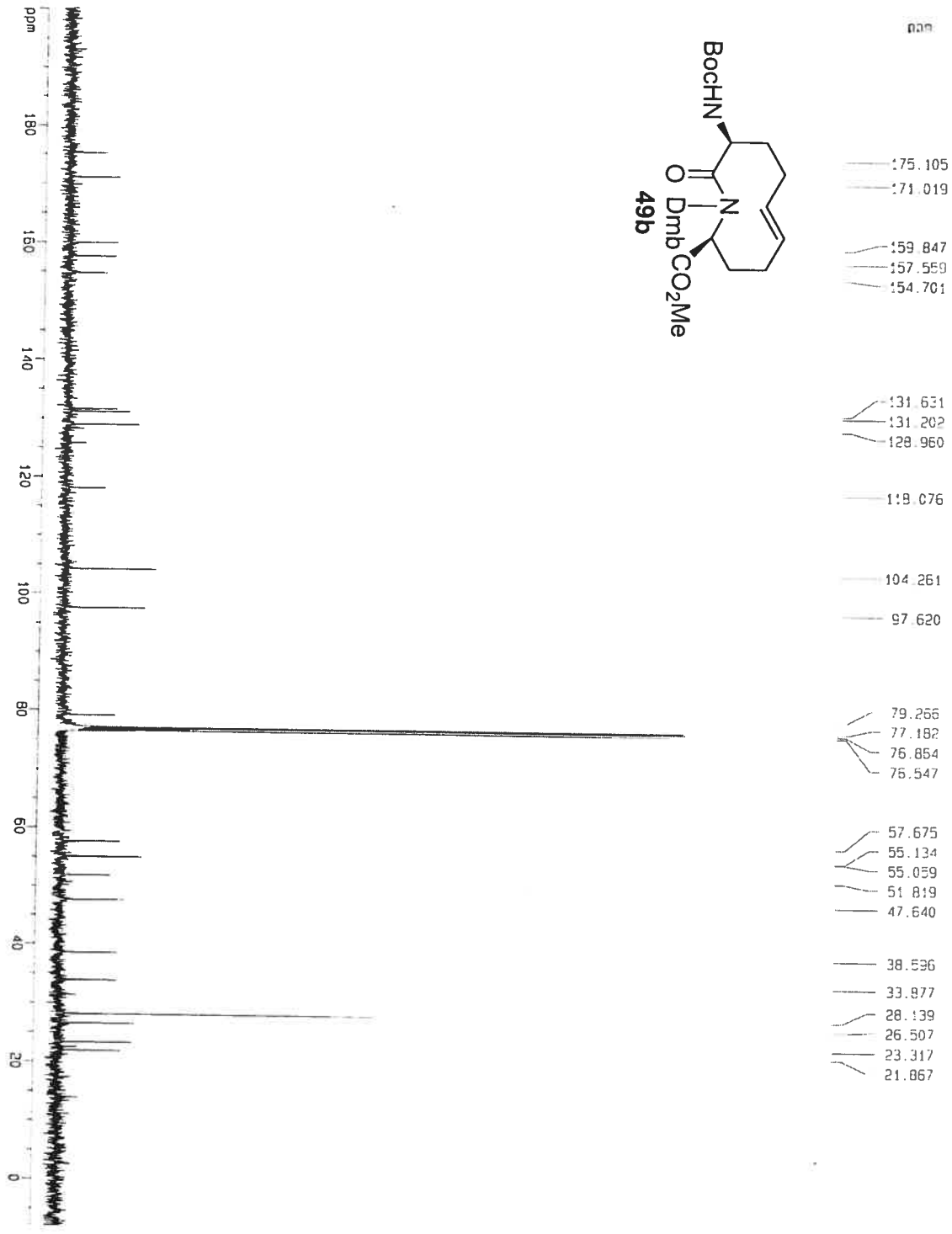
Aliv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Dmb
CO2Me
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ppm
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80
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40
20
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159.847
157.559
154.701
131.631
131.202
128.960
119.076
104.261
97.620
79.266
77.182
76.854
76.547
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51.819
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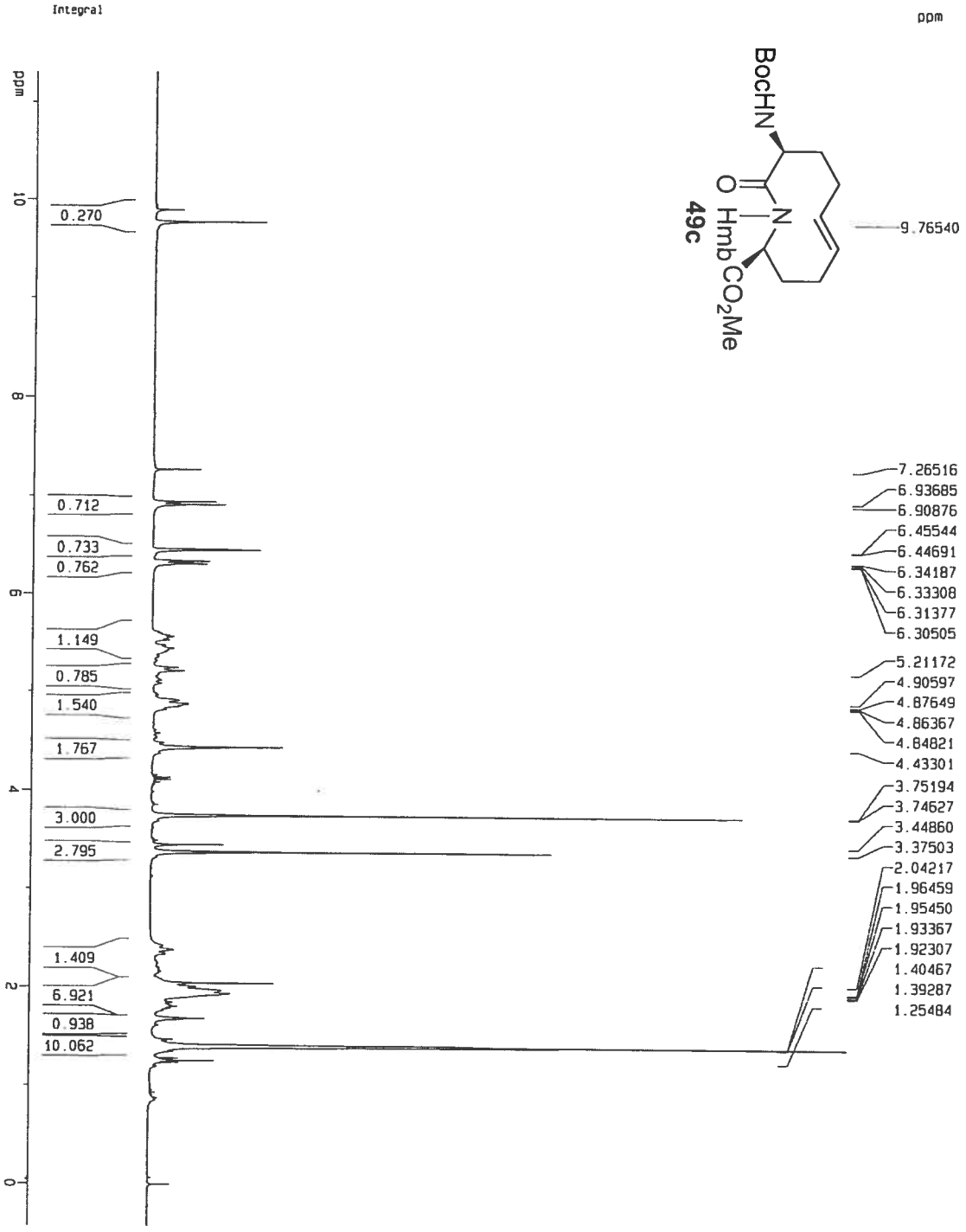
Alv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Hmb
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6.44691
6.34187
6.33308
6.31377
6.30505
5.21172
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4.86367
4.84821
4.43301
3.75194
3.74627
3.44860
3.37503
2.04217
1.96459
1.95450
1.93367
1.92307
1.40467
1.39287
1.25484
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0.712
0.733
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1.540
1.767
3.000
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1.409
6.921
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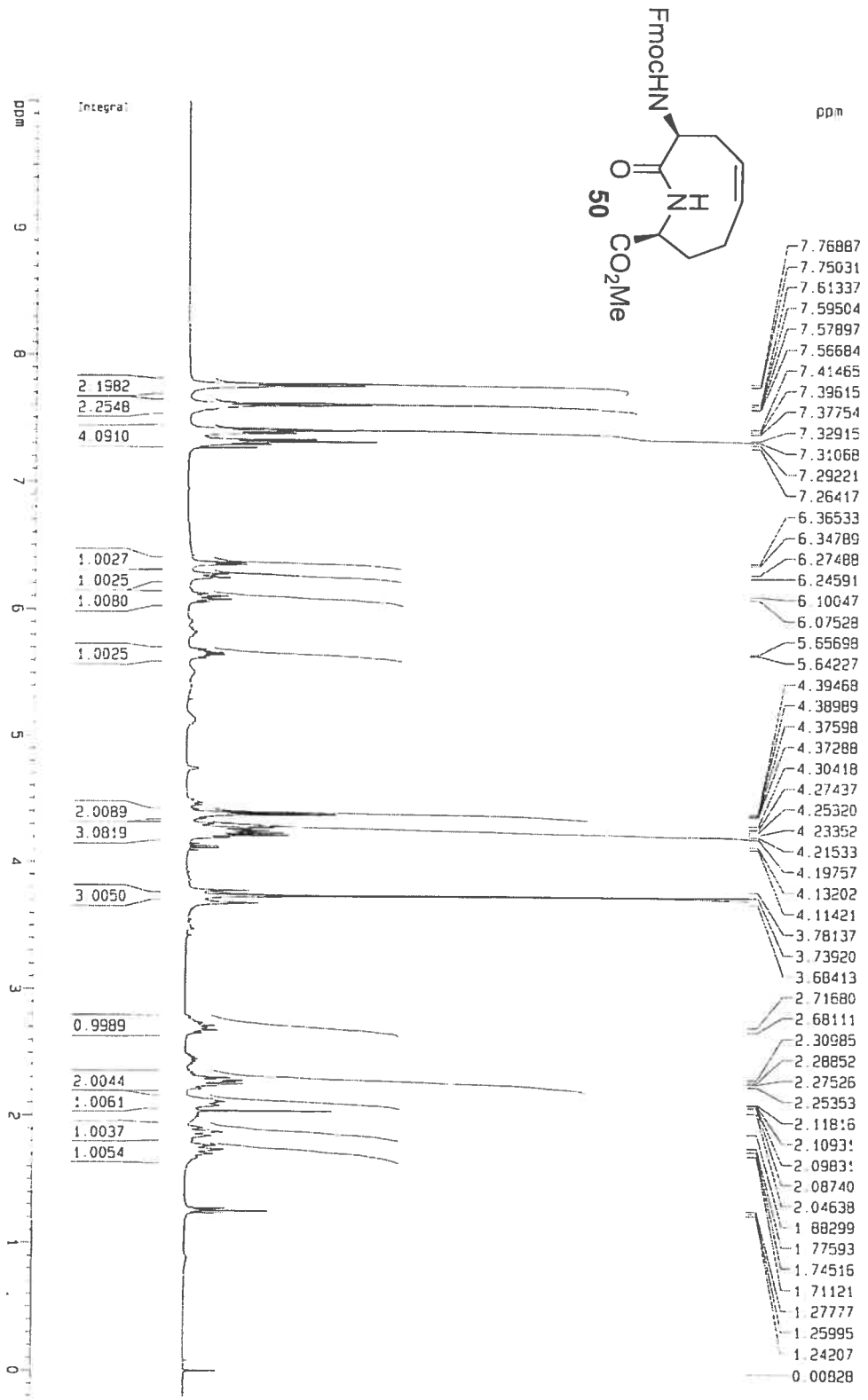
10.062

Alvi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N
O
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CO2Me
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1.0080
1.0025
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3.0819
3.0050
0.9989
2.0044
1.0061
1.0037
1.0054
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7.75031
7.61337
7.59504
7.57897
7.56684
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5.65698
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4.30418
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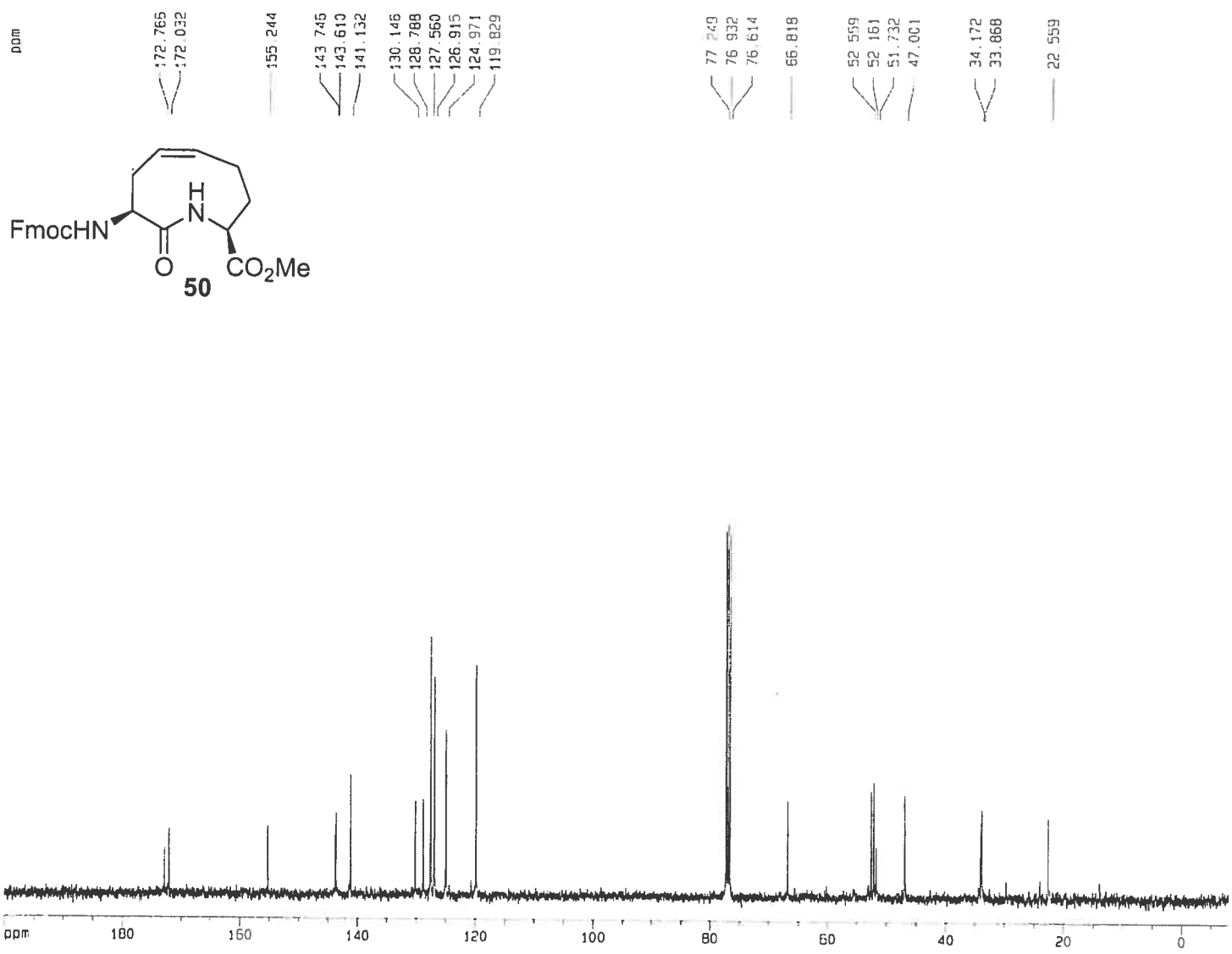
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124.971
119.829
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76.932
76.614
66.818
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52.161
51.732
47.001
34.172
33.868
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FmocHN
H
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O
CO2Me
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20
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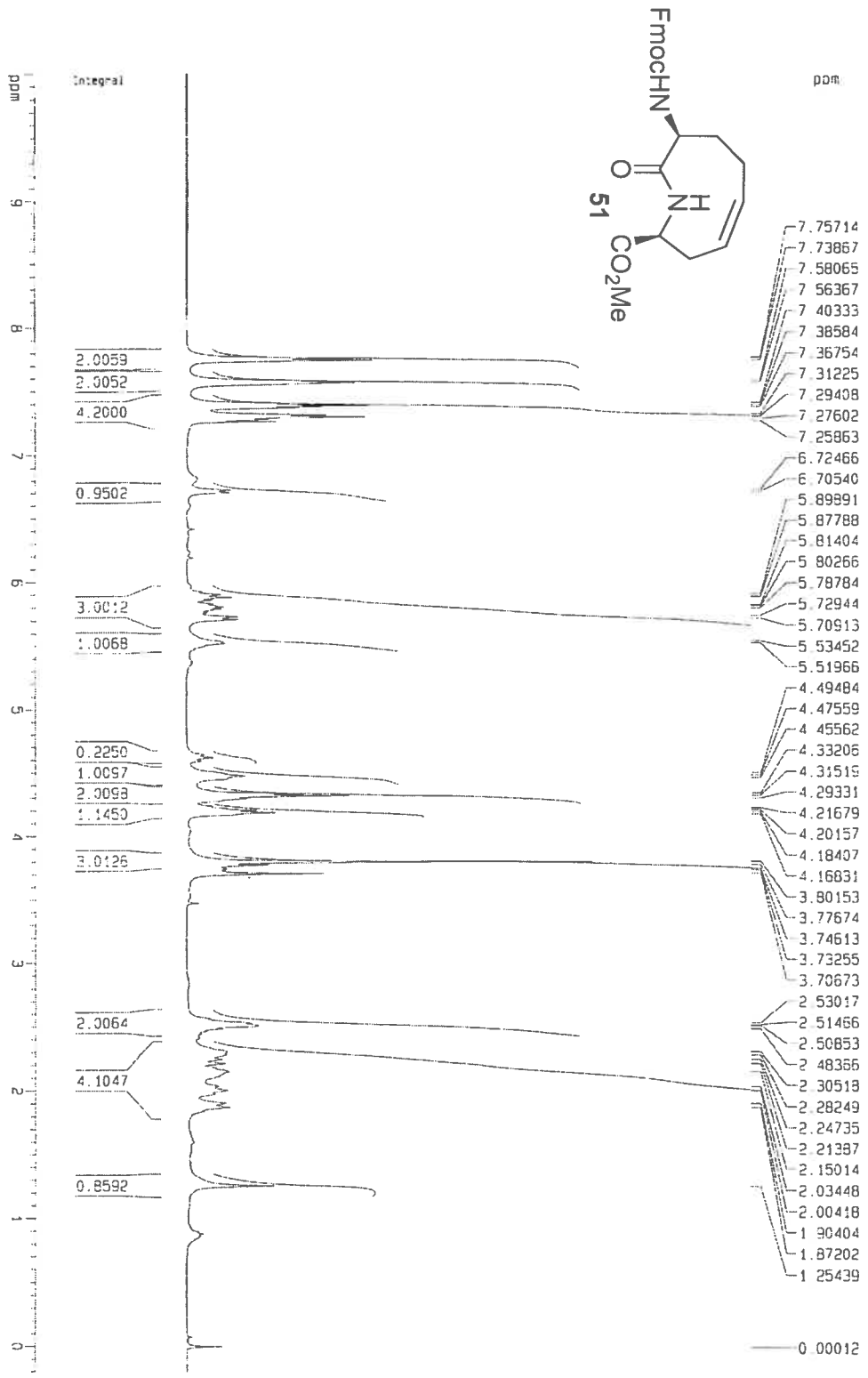
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O
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Integral
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7.36754
7.31225
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7.27602
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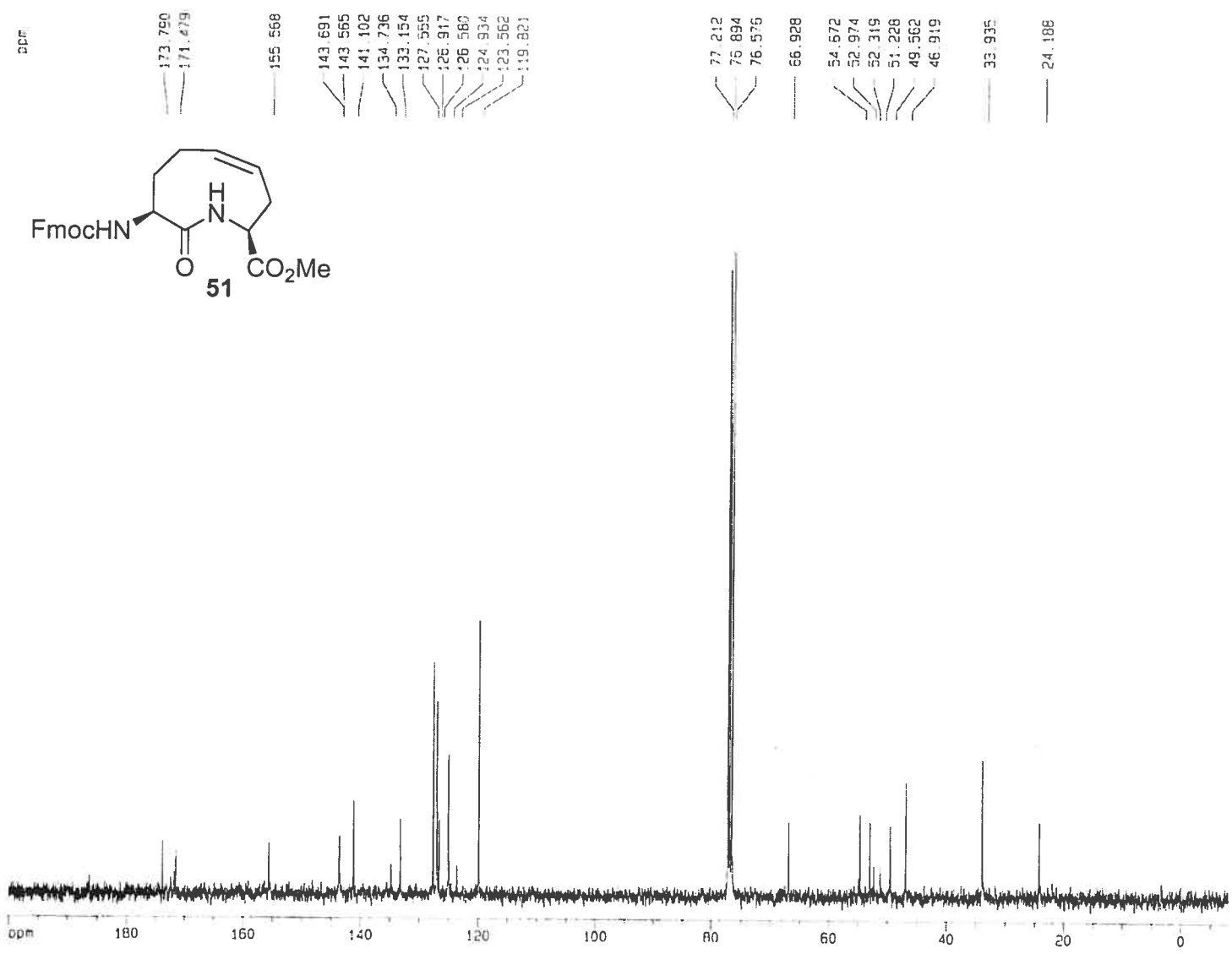
Alix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123.562
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76.894
76.576
66.928
54.672
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52.319
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46.919
33.935
24.188
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CO2Me
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120
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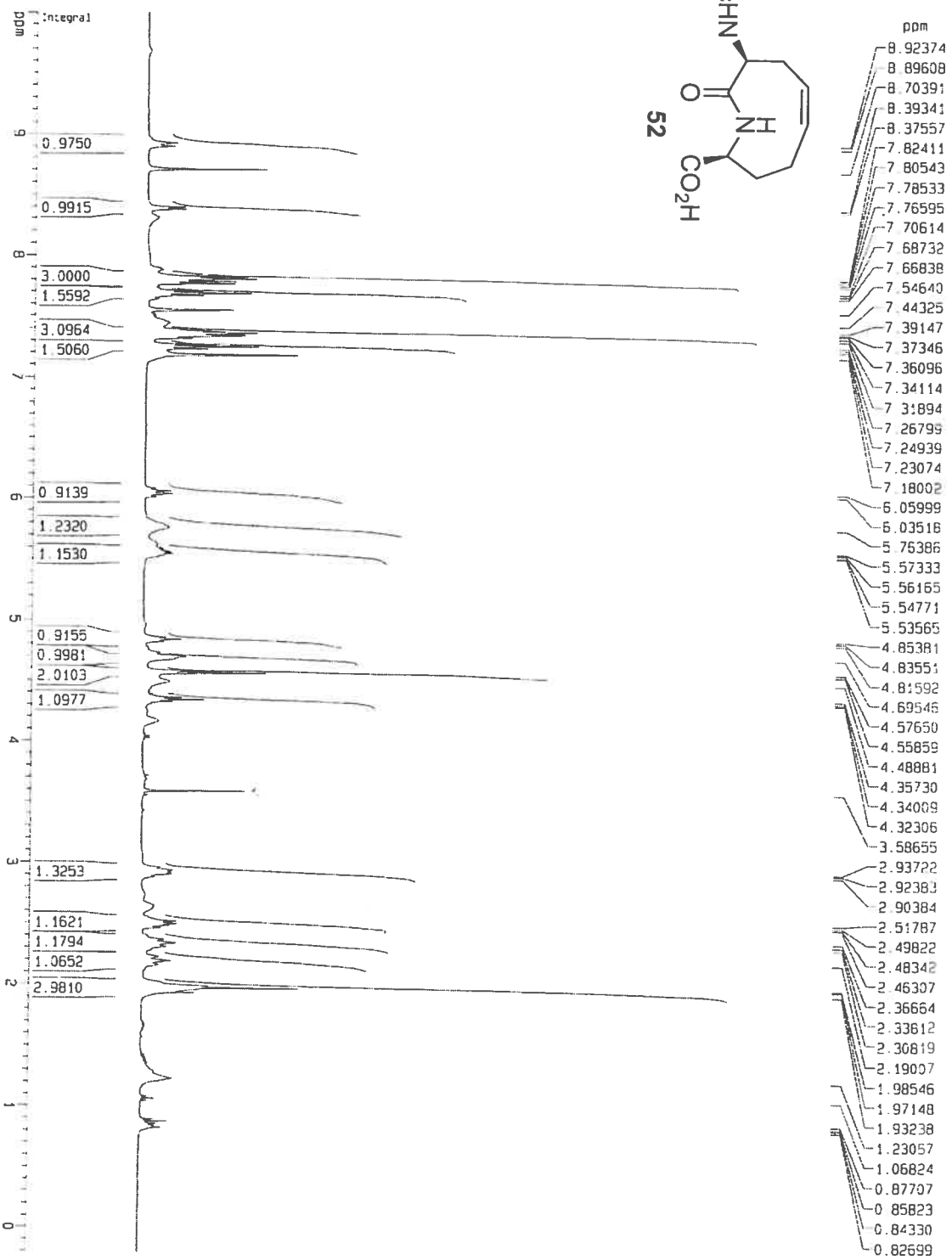
Alx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CO2H
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7.54640
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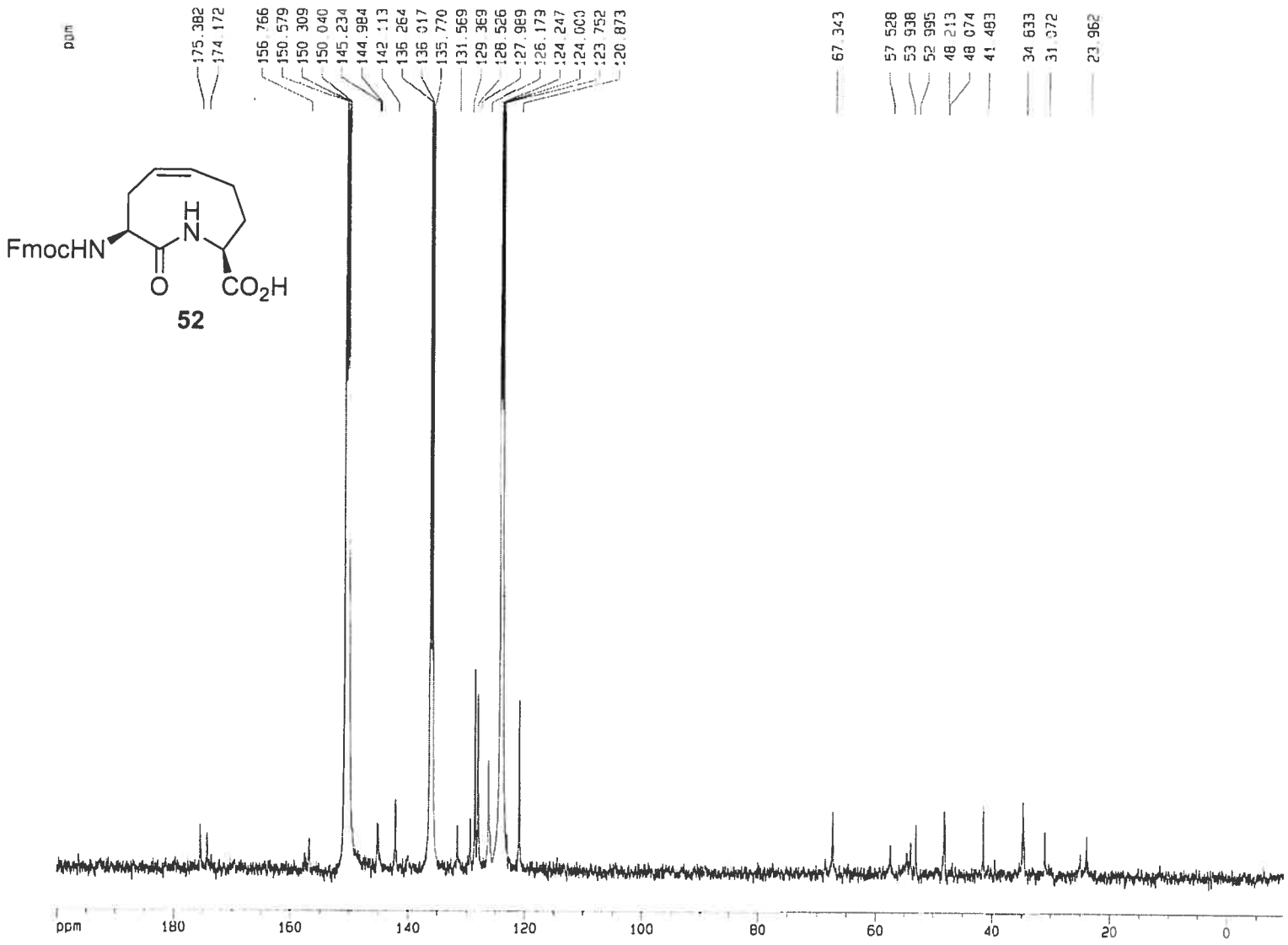
Alxi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128.526
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31.072
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O
CO2H
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140
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100
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60
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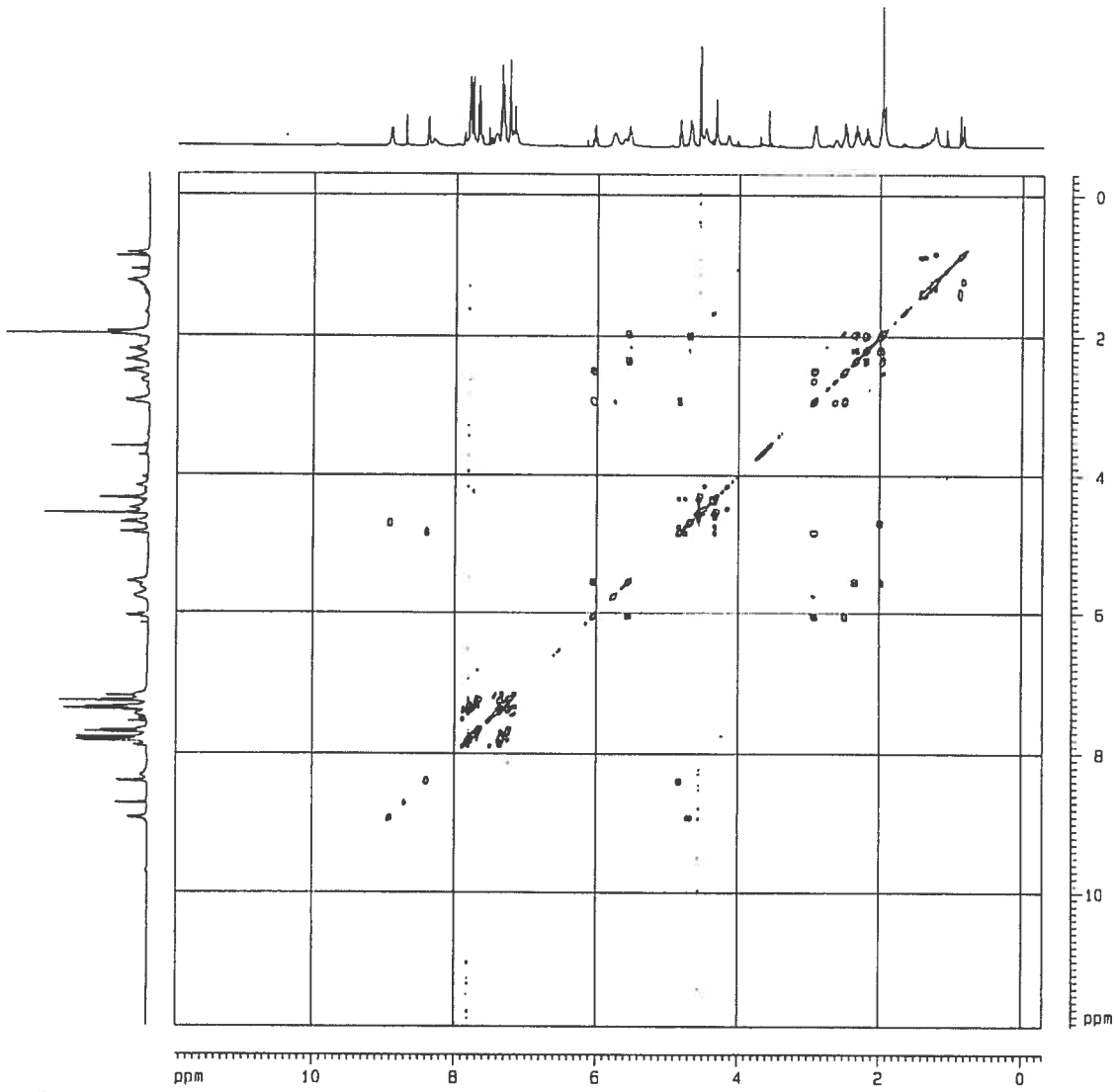


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EXPNO                 1
PROCNO                1

                    F2 - Acquisition Parameters
Date_           20041208
Time                14.23
INSTRUM             av500
PROBHD     5 mm TBI 1H/13
PULPROG             coesgpsf
TD                  2048
SOLVENT             CDCl3
NS                    1
DS                   16
SWH              6127.451 Hz
FIDRES           2.991920 Hz
AQ               0.1672484 sec
RG                   57
DW                 81.600 usec
DE                 6.00 usec
TE                 293.2 K
D0               0.00050300 sec
D1               2.00000000 sec
d13              0.00000400 sec
D16              0.00075000 sec
IN0              0.00018320 sec
NCREST           0.00000000 sec
NCWRK            2.00000000 sec

                    ======== CHANNEL f1 ========
NUC1                1H
P0                  3.00 usec
P1                  8.00 usec
PL1                 0.00 dB
SFO1           500.1325132 MHz

                    ======== GRADIENT CHANNEL ========
GPNAM1              SINE.100
GPNAM2              SINE.100
GPZ1                0.00 %
GPZ2                0.00 %
GPZ3                0.00 %
GPZ4                0.00 %
GPZ12              10.00 %
GPZ13              15.00 %
P16              1000.00 usec

                    F1 - Acquisition parameters
NS                    1
TD                  512
SFO1           500.1325 MHz
FIDRES          11.957676 Hz
SW              12.258 ppm
FnMODE              QF

                    F2 - Processing parameters
SI                  2048
SF             500.1300000 MHz
WDW                 SINE
SSB                   0
LB                  0.00 Hz
GB                    0
PC                 1.00

                    F1 - Processing parameters
SI                  1024
MC2                 QF
SF             500.1300000 MHz
WDW                 SINE
SSB                   0
LB                  0.00 Hz
GB                    0

                    2D nmr plot parameters
CX2                15.00 cm
CY1                15.00 cm
F2PLO           11.981 ppm
F2LO            5975.01 Hz
F2PH1           -0.301 ppm
F2H1            -150.54 Hz
F1PLO           11.981 ppm
F1LO            5975.01 Hz
F1PH1           -0.301 ppm
F1H1            -150.54 Hz
F2PPMCM         0.81676 ppm/cm
F2HZCM          408.49873 Hz/cm
F1PPMCM         0.81676 ppm/cm
F1HZCM          408.49873 Hz/cm
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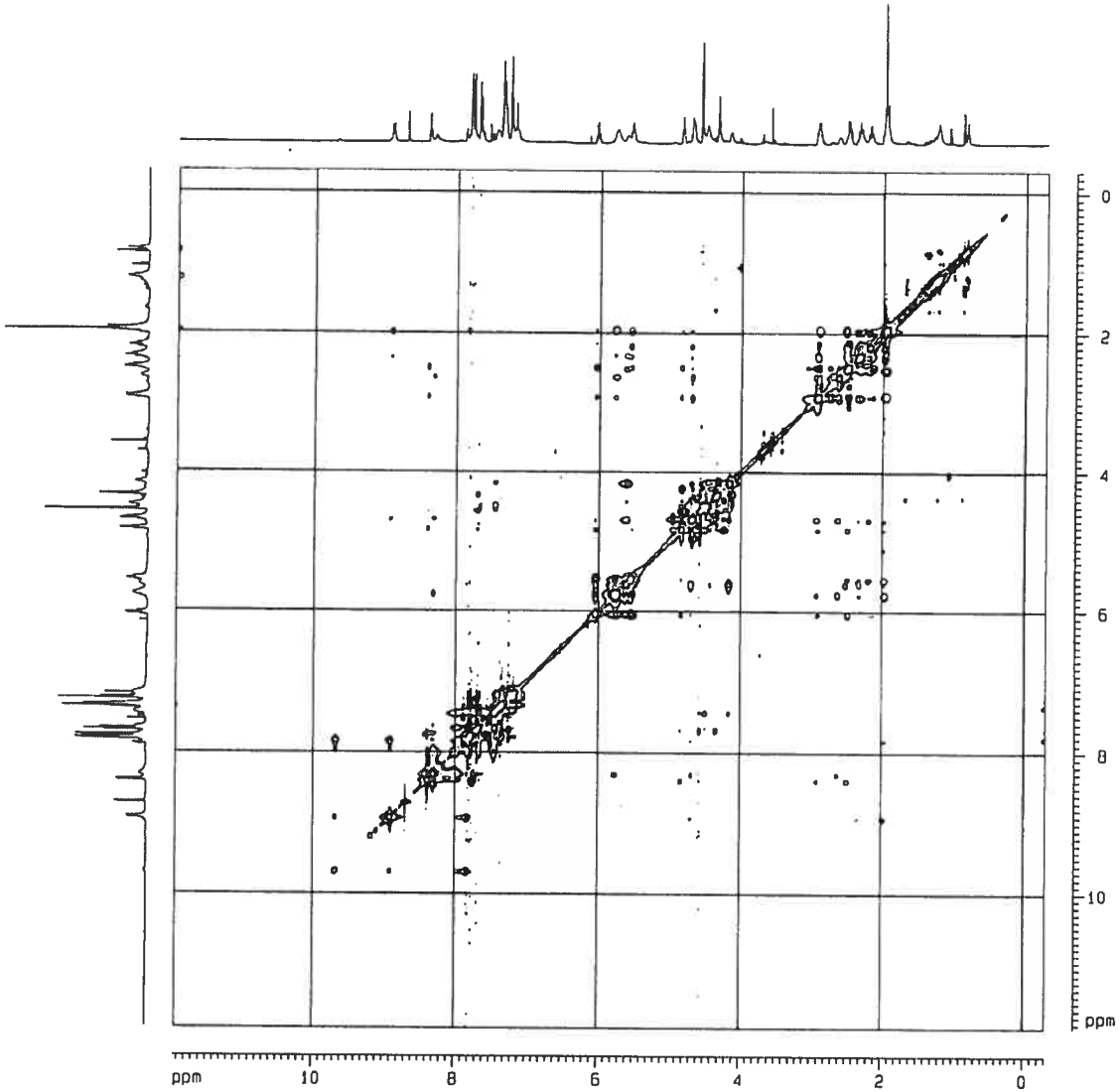

NOESY

Current Data Parameters

NAME	tan
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20041208
Time	18.14
INSTRUM	av500
PROBHD	5 mm TBI 1H/13
PULPROG	noesygpph
TD	2048
SOLVENT	CDCl3
NS	16
DS	16
SWH	6127.451 Hz
FIDRES	2.991529 Hz
AQ	0.1672454 sec
RG	181.6
DW	81.600 usec
DE	6.00 usec
TE	293.2 K
d0	0.00007422 sec
D1	2.00000095 sec
D8	0.40000001 sec
D16	0.00020000 sec
IN0	0.00016320 sec
MCREST	0.00000000 sec
MCWRN	1.10000002 sec
STSHI	256
TAU	0.10000001 sec

CHANNEL f1

NUC1	1H
P1	5.00 usec
P2	11.00 usec
PL1	0.00 dB
SFO1	500.1329192 MHz

GRADIENT CHANNEL

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GPNAM2	SINE.100
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GPZ2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	40.00 %
GPZ2	-40.00 %
P16	1000.00 usec

F1 - Acquisition parameters

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SFO1	500.1329 MHz
FIDRES	11.987670 Hz
SW	12.757 ppm
FnMODE	States-TPPI

F2 - Processing parameters

SI	2048
SF	500.1300000 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

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MC2	States-TPPI
SF	500.1300000 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

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CY1	19.00 cm
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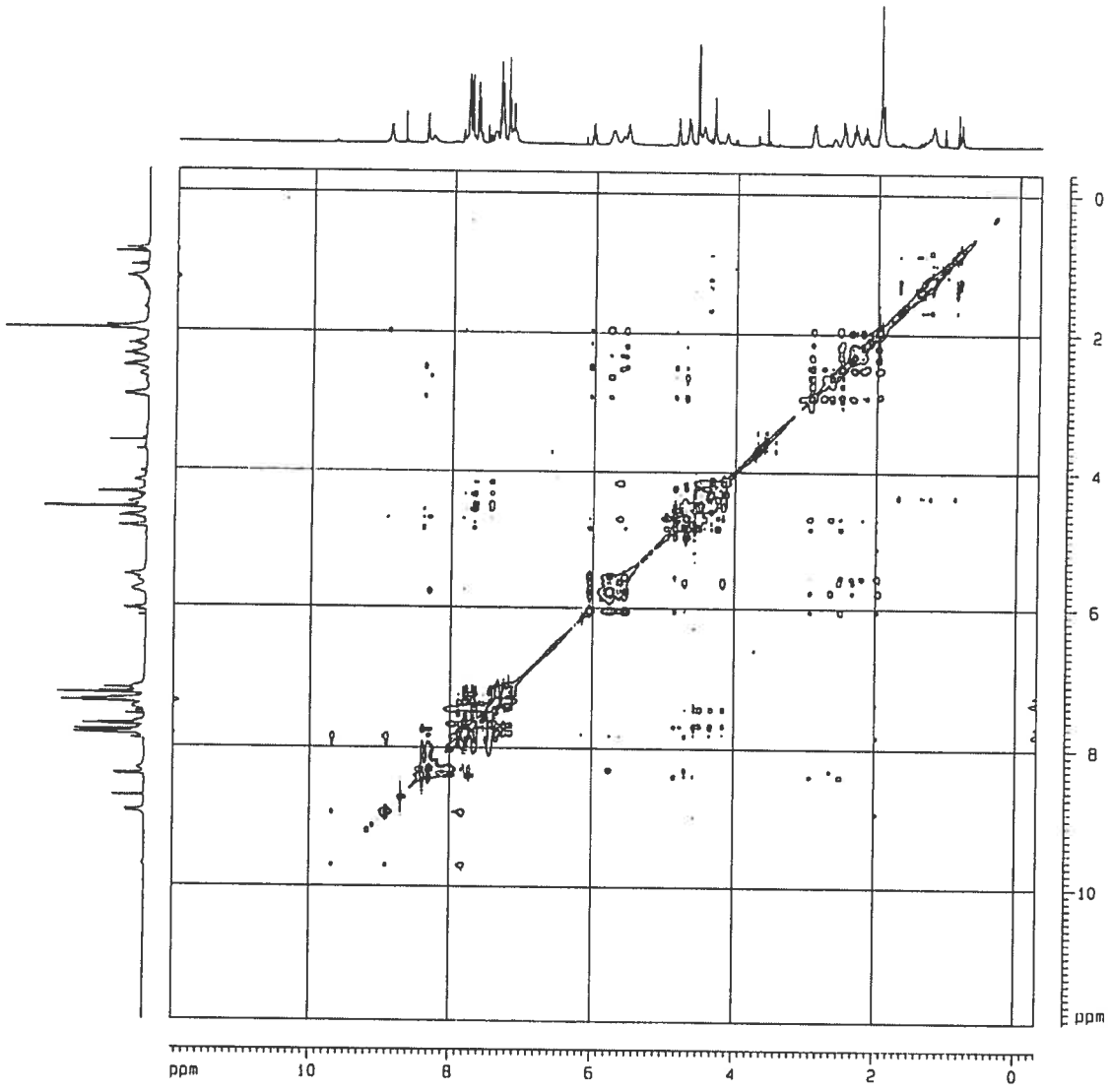
F2LO	5676.01 Hz
F2PHI	-0.301 ppm
F2HI	-150.54 Hz
F1PLO	11.051 ppm
F1LO	5676.01 Hz
F1PHI	-0.301 ppm
F1HI	-150.54 Hz
F2PPMCM	0.61670 ppm/cm
F2HZCM	488.49873 Hz/cm
F1PPMCM	0.61670 ppm/cm
F1HZCM	488.49873 Hz/cm

Alxiv



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PROCNO 1

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TD 2048
SOLVENT CDCl3
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SWH 8127.451 Hz
FIDRES 3.961620 Hz
AQ 0.1572464 sec
RG 98.3
DW 61.600 usec
DE 6.00 usec
TE 293.2 K
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D1 3.79999995 sec
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TAU 0.30000001 sec

CHANNEL f1
NUC1 1H
P1 9.98 usec
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PL1 0.00 dB
SFO1 500.1329132 MHz

GRADIENT CHANNEL
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GPNAM2 SINE.100
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GPZ2 0.00 %
GPZ11 0.00 %
GPZ2 -0.00 %
GPZ11 -40.00 %
GPZ12 -40.00 %
P16 1000.00 usec

F1 - Acquisition parameters
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SFO1 500.1329 MHz
FIDRES 11.987679 Hz
SW 12.252 ppm
FnMODE States-TPPI

F2 - Processing parameters
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WDW SINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
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MC2 States-TPPI
SF 500.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

2D NMR plot parameters
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CY 15.00 cm
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F2LO 5576.91 Hz
F2PHI -0.301 ppm
F2HI -150.54 Hz
F1PLO 11.051 ppm
F1LO 5576.91 Hz
F1PHI -0.301 ppm
F1HI -150.54 Hz
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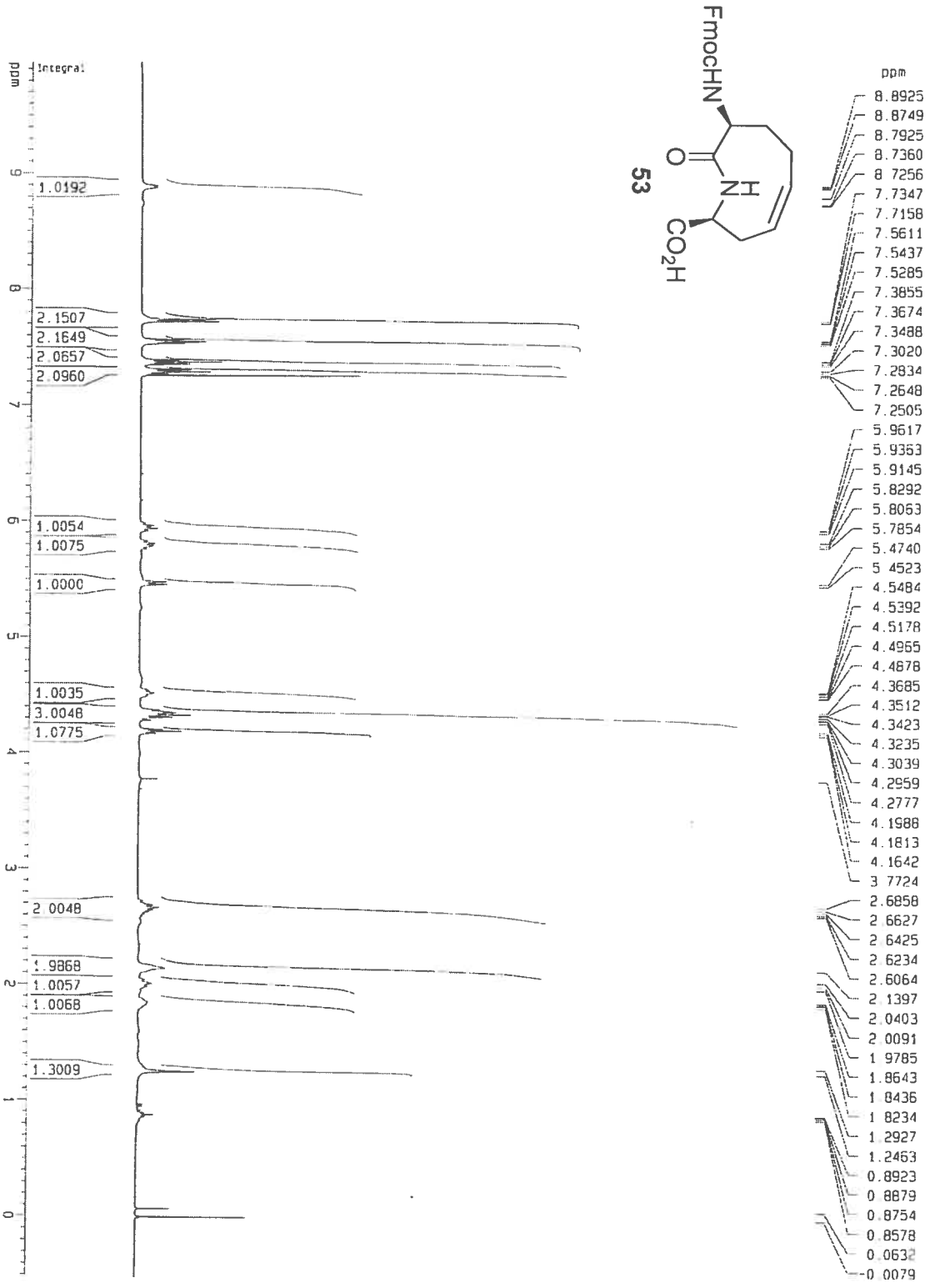
F2HZCM 408.49873 Hz/cm
F1PPMCM 0.81678 ppm/cm
F1HZCM 408.49873 Hz/cm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4.4965
4.4878
4.3685
4.3512
4.3423
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4.2959
4.2777
4.1988
4.1813
4.1642
3.7724
2.6858
2.6627
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2.6064
2.1397
2.0403
2.0091
1.9785
1.8643
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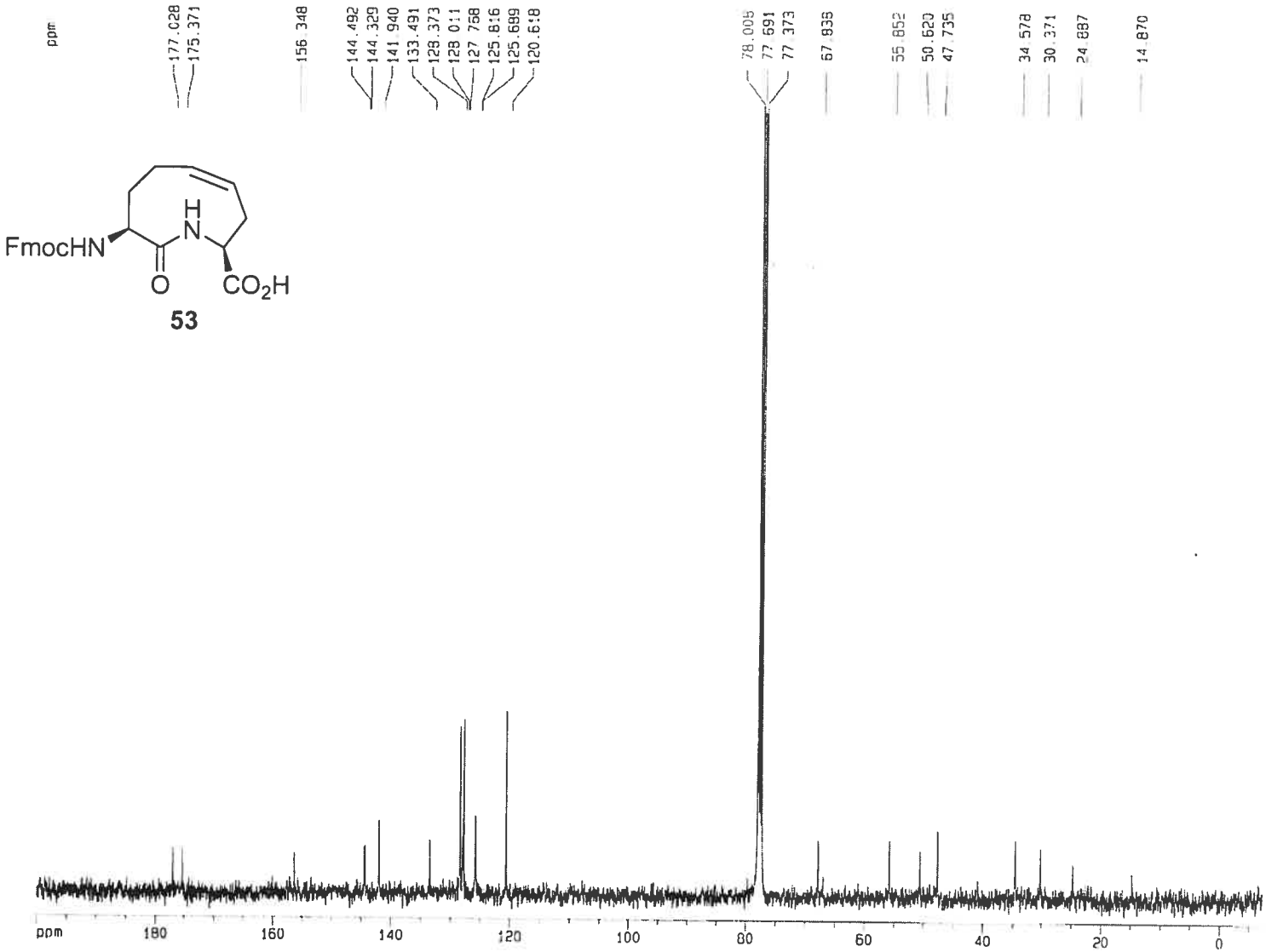
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N
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CO2H
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ppm
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140
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40
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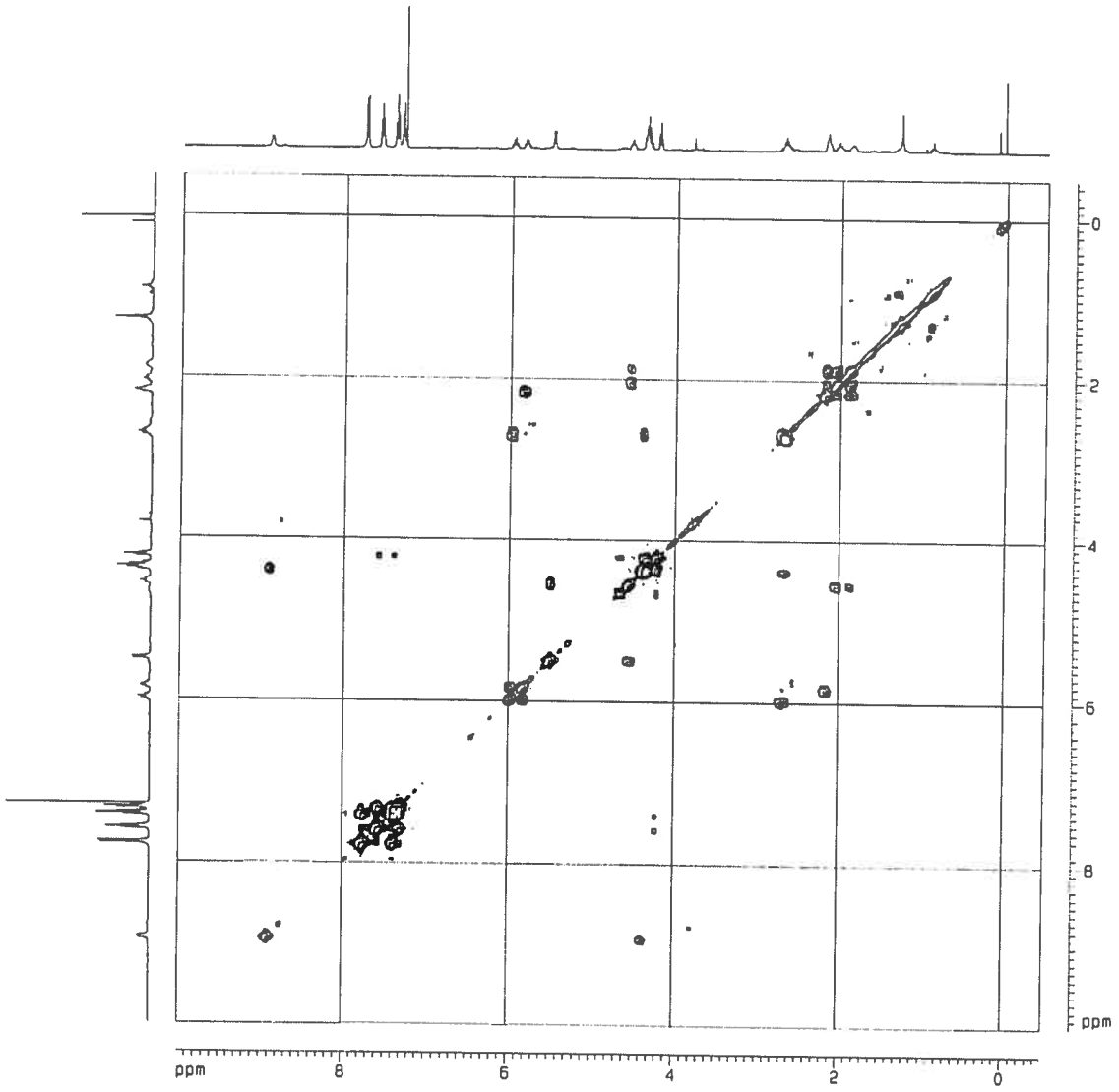

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EXPNO	2
PROCNO	1

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TD	2048
SOLVENT	CDCl3
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SWH	4194 631 Hz
FIDRES	2 048160 Hz
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RG	181
DW	119 200 usec
DE	6 00 usec
TE	294 0 K
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D1	1 50000000 sec
d13	0 00000400 sec
D16	0 00005000 sec
IN0	0 00023840 sec
MCREST	0 00000000 sec
MCWRK	1 50000000 sec

-------- CHANNEL f1 --------

NUC1	1H
P0	4 50 usec
P1	9 40 usec
PL1	-3 00 dB
SFO1	400 1318066 MHz

====== GRADIENT CHANNEL =====

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GPNAM2	sine 100
GPZ1	0 00 %
GPZ2	0 00 %
GPZ11	0 00 %
GPZ12	0 00 %
GPZ21	15 00 %
GPZ22	15 00 %
P16	1000 00 usec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	400 1318 MHz
FIDRES	16 385277 Hz
SW	10 483 ppm

F2 - Processing parameters

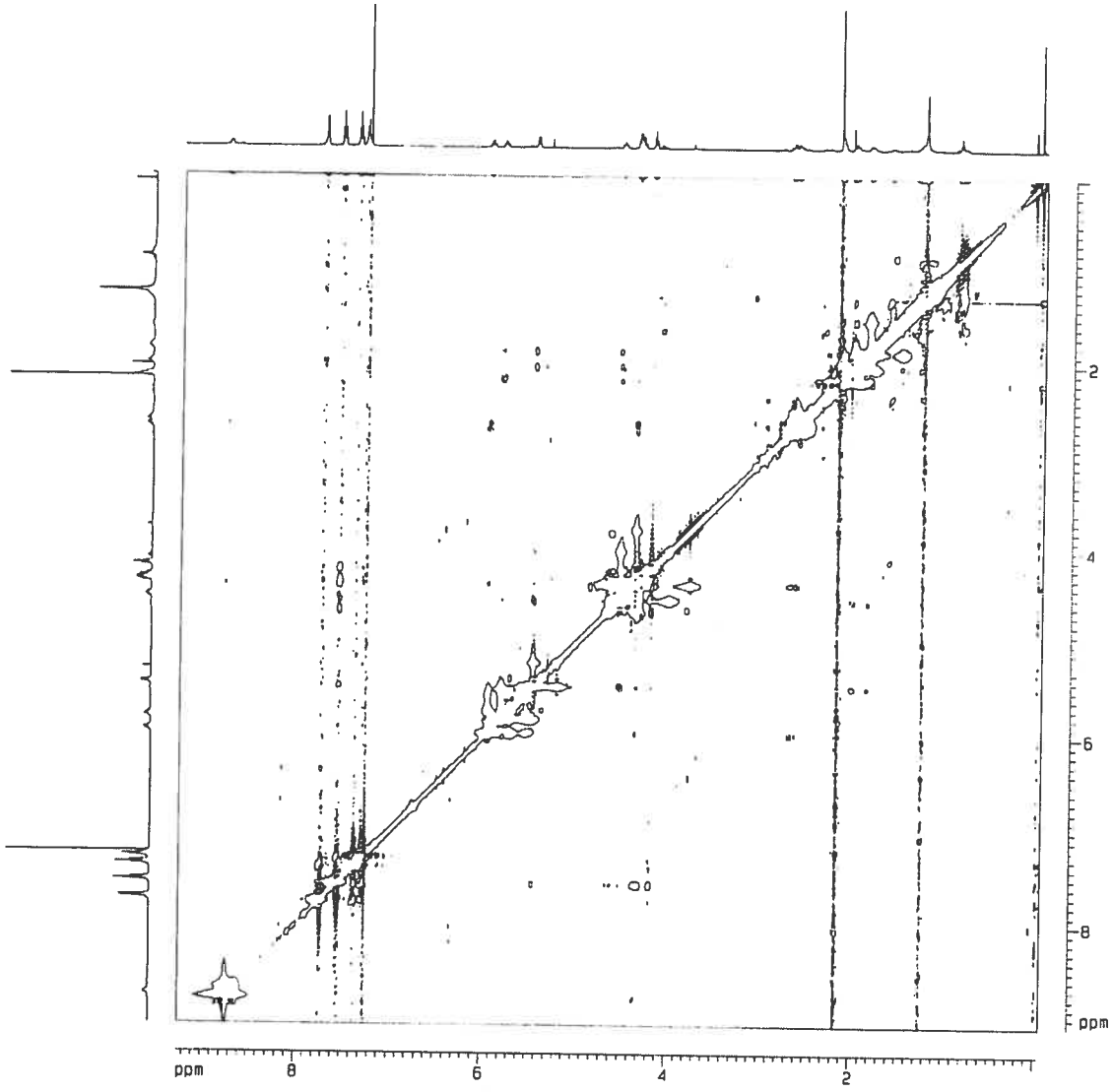
SI	2048
SF	400 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0
PC	1 00

F1 - Processing parameters

SI	1024
MC2	QF
SF	400 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	15 00 cm
CX1	15 00 cm
F2PLO	9 992 ppm
F2LO	3997 73 Hz
F2PHI	-0 492 ppm
F2HI	-198 70 Hz
F1PLO	9 992 ppm
F1LO	3997 73 Hz
F1PHI	-0 492 ppm
F1HI	196 70 Hz
F2PPMCM	0 68998 ppm/cm
F2HZCM	279 64266 Hz/cm
F1PPMCM	0 68998 ppm/cm
F1HZCM	279 64266 Hz/cm

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EXPNO                     12
PROCNO                     1

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Time                   18 57
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PULPROG             mesvqpph
TD                      2048
SOLVENT                  THF
NS                        64
DS                        16
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FIDRES              2 564502 Hz
AQ                  0 1950196 sec
RG                       128
DW                   95 200 usec
DE                    6 00 usec
TE                    298 2 K
D0                  0 00006782 sec
D1                  1 00000000 sec
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D16                 0 00005000 sec
IN0                 0 00019040 sec
MCREST              0 00000000 sec
MCWRK               0 50000000 sec
SFOCH1                   750
TAU                 0 24852000 sec

                ======== CHANNEL f1 ========
NUC1                      1H
P1                    5 80 usec
P2                   11 60 usec
PL1                   0 00 dB
SFO1              500 1323571 MHz

            ====== GRADIENT CHANNEL =====
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GPNAM2                sine 100
GPZ1                  0 80 %
GPZ2                  0 00 %
GPZ3                  0 00 %
GPZ4                  0 00 %
GPZ5                 40 00 %
GPZ6                -40 00 %
P16                 1000 00 usec

                F1 - Acquisition parameters
MDD                       1
TD                      400
SFO1              500 1324 MHz
FIDRES             17 130252 Hz
SW                 10 501 ppm

                F2 - Processing parameters
SI                      2048
SF                500 1300186 MHz
WDW                     SINE
SSB                        2
LB                    0 00 Hz
GB                         0
PC                    1 00

                F1 - Processing parameters
SI                      1024
MC2                 States TPPI
SF                500 1300000 MHz
WDW                     SINE
SSB                        2
LB                    0 00 Hz
GB                         0

                2D plot parameters
CX2                   15 00 cm
CY1                   15 00 cm
F2PLO                 9 265 ppm
F2LO                 4833 82 Hz
F2PH1                -0 057 ppm
F2H1                 -78 44 Hz
F1PLO                 9 092 ppm
F1LO                 4547 31 Hz
F1PH1                 0 004 ppm
F1H1                  -2 13 Hz
F2PPMCM             0 62147 ppm/cm
F2HZCM            310 81769 Hz/cm
F1PPMCM             0 60843 ppm/cm
F1HZCM            303 28517 Hz/cm
```

Alxix

Data File:	COMPD-30
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Acquisition Date:	02/06/05 09:35:59
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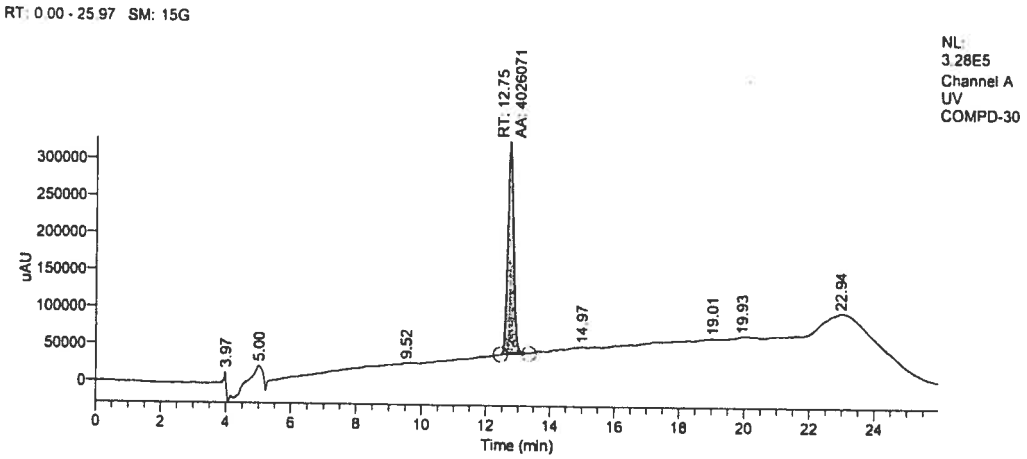
Injection Volume (µl):	10.00



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Alxx

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Run Time (min):	25
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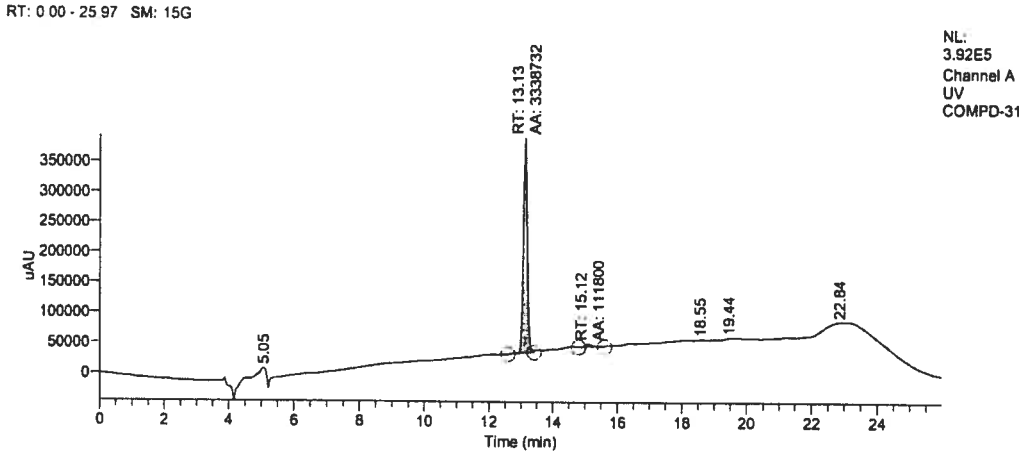
Injection Volume (µl):	10.00



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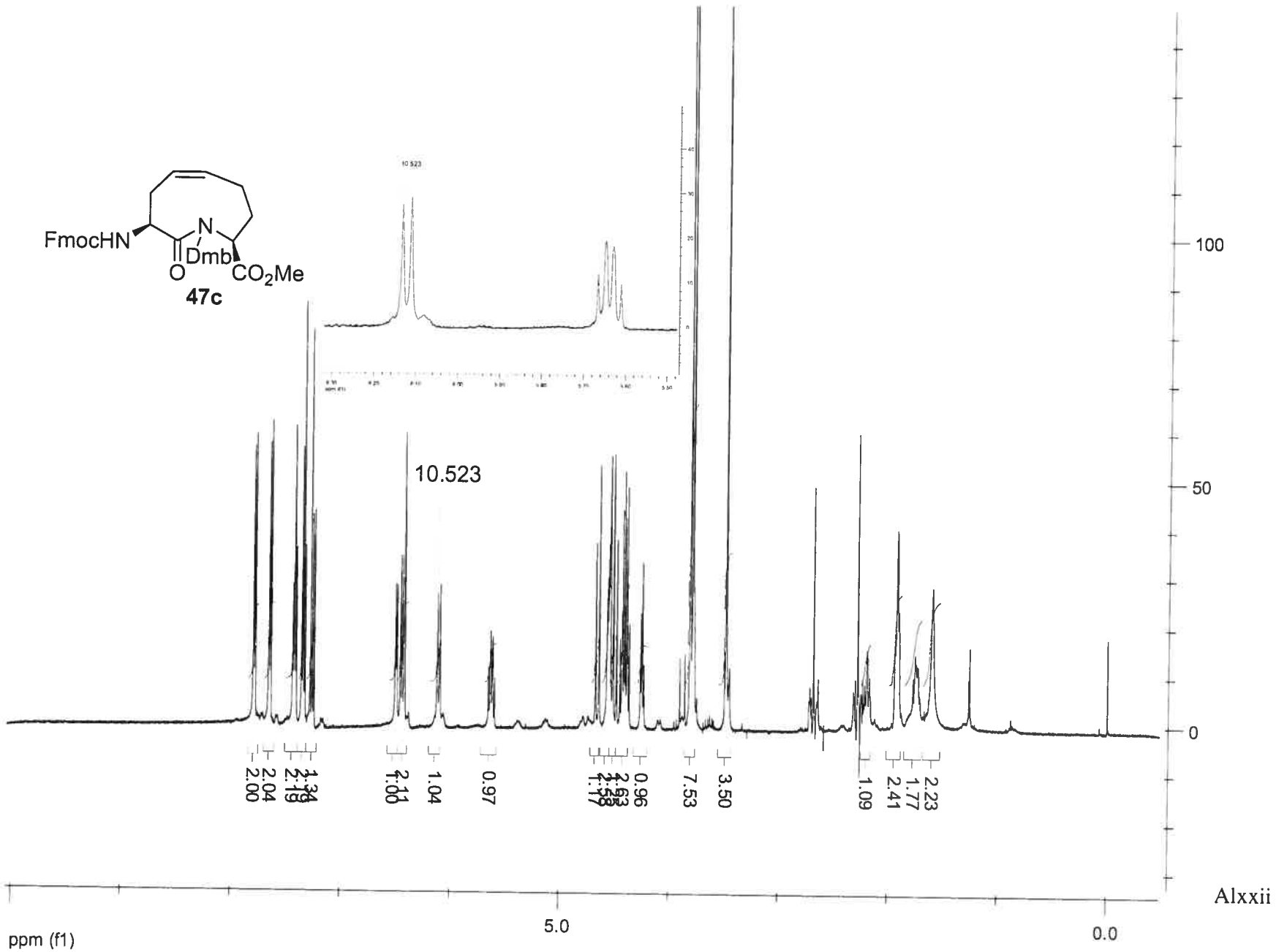
15.12	111800	5628	3.24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2.41
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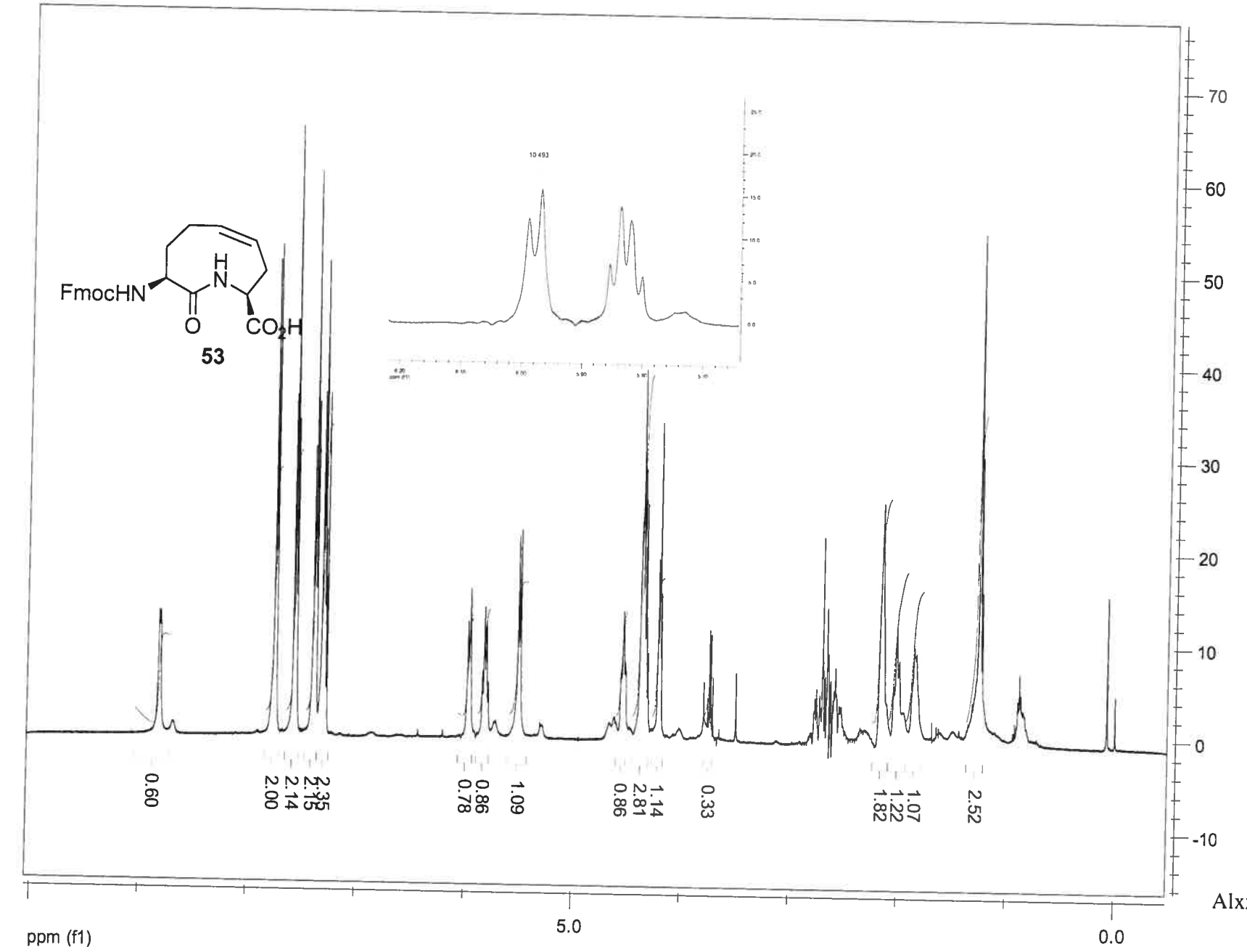
50
0
5.0
0.0
ppm (f1)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N
O
CO2H
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0.33
1.82
1.22
1.07
2.52
70
60
50
40
30
20
10
0
-10
ppm (f1)
5.0
0.0

From Macrocycle Dipeptide Lactams To Azabicyclo[X.Y.0]alkanone Amino Acids, A Transannular Cyclization Route For Peptide Mimic Synthesis

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[redacted]

Supporting Information

Table of contents

General procedure for electrophilic transannular cyclization. A refluxing THF solution of macrocyle (0.02 M) was treated with the electrophile (iodine or phenylselenium bromide). The resulting solution was stirred for 2 h and the volatiles were removed. The crude product was taken in CH_2Cl_2, and applied on a silica gel column and eluted with 70% EtOAc/Hex to obtain a brownish oil that solidified on standing to afford a brownish gummy solid.

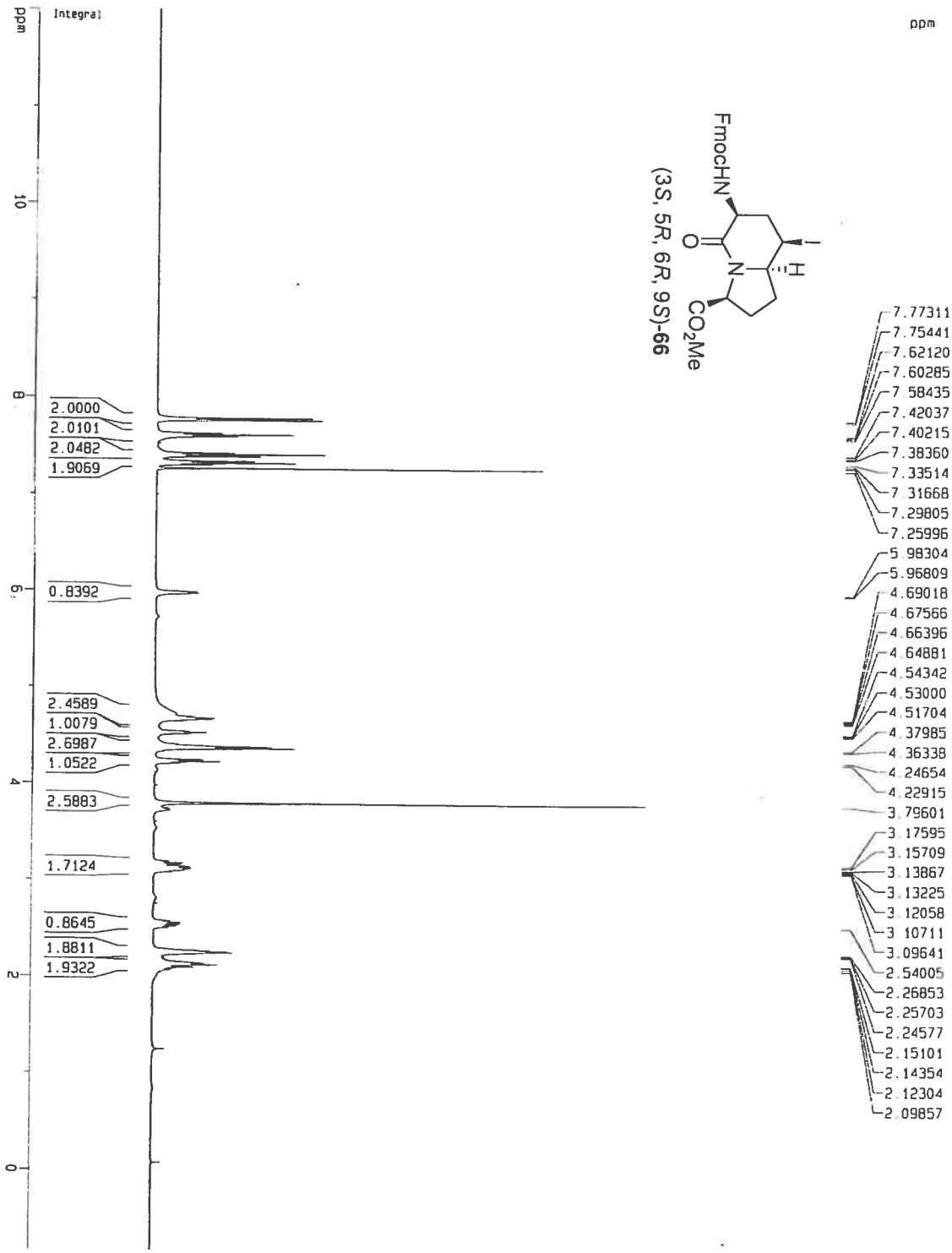
(3*S*,5*R*,6*R*,9*S*)-Methyl 2-oxo-3-*N*-(Fmoc)amino-5-iodo-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*R*,6*R*,9*S*)-66). $[\alpha]_D^{20}$ 21.9° (*c* 1.67 MeOH) ; ^{1}H NMR ($CDCl_3$) ppm 7.76 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 5.98 (d, J = 5.9 Hz, 1H), 4.67 (dd, J = 10.6, 5.9 Hz, 1H), 4.53 (m, 1H), 4.39 (m, 3H), 4.23 (t, J = 7.2, 1H), 3.80 (s, 3H), 3.18 (m, 1H), 3.10 (m, 1H), 2.55 (m, 1H), 2.26 (m, 2H), 2.12 (m, J = 2H) ; ^{13}C NMR ppm 170.9, 156.1, 143.8, 143.5, 141.2, 127.7, 127.0, 125.1, 119.9, 67.4, 60.6, 58.2, 52.4, 50.1, 46.9, 40.7, 35.6, 28.2, 24.3; HRMS calcd for $C_{25}H_{26}IN_2O_5$ $[M + H]^+$ 561.0881, found 561.0887.

(3*S*,5*S*,6*S*,9*S*)-Methyl 2-oxo-3-*N*-(Fmoc)amino-5-iodo-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*S*,6*S*,9*S*)-66). $[\alpha]_D^{20}$ –117.8° (*c* 1.10 MeOH); ^{1}H NMR (acetone-d6) ppm 7.87 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 6.98 (d, J = 7.9 Hz, 1H), 5.07 (s, 1H), 4.65 (m, 1H), 4.32 (m, 4H), 3.67 (s, 3H), 3.34 (m, 1H), 2.62 (m, 1H), 2.50 (m, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 1.89 (m, 1H), 1.77 (m, 1H) ; ^{13}C NMR ppm 174.0, 167.8, 158.2, 146.0, 143.0, 129.4, 128.9, 127.2, 121.7, 68.2, 64.4, 60.4, 53.1, 48.9, 40.1, 36.8, 35.8, 33.2, 28.9, 24.2; HRMS calcd for $C_{25}H_{26}IN_2O_5$ $[M + H]^+$ 561.0881, found 561.0887.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-oxo-3-*N*-(Fmoc)amino-6-iodo-1-azabicyclo[5.3.0]decane-10-carboxylate((3*S*,6*R*,7*S*,10*S*)-67). Rerystallized from acetone/hexanes mp. 138-140°C; $[\alpha]_D^{20}$ –68.4° (*c* 0.79 MeOH); ^{1}H NMR (CDCl3) ppm 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.1 Hz, 2H), 5.85 (m, 1H), 4.65 (m, 1H), 4.52 (m, 1H), 4.42 (m, 2H), 4.32 (m, 1H), 4.24 (t, J = 6.5 Hz, 2H), 3.69 (s, 3H), 2.48 (m, 3H), 2.15 (m, 4H), 1.87 (m, 1H) ; ^{13}C NMR ppm 172.7, 170.5, 156.3, 144.2, 141.7, 128.1, 127.5, 125.5, 120.4, 67.4, 63.5, 63.1, 54.5, 52.8, 47.6, 37.8, 37.4, 30.9, 28.9, 26.2 ; HRMS calcd for $C_{26}H_{28}IN_2O_5$ $[M + H]^+$ 575.1037, found 575.1039.

(3*S*,6*R*,7*S*,10*S*)-Methyl 2-oxo-3-*N*-(Boc)amino-6-iodo-1-azabicyclo[5.3.0]decane-10-carboxylate((3*S*,6*R*,7*S*,10*S*)-68). Rerystallized from EtOAc/hexanes mp. 136-138°C $[\alpha]_D^{20}$ –89.2° (*c* 2.01 MeOH); ^{1}H NMR (CDCl3) ppm 5.42 (bs, 1H), 4.62 (dd, J = 8.2, 5.3 Hz, 1H), 4.40(m, 1H), 4.28 (dd, J = 11.8, 6.3 Hz, 1H), 4.19 (m, 1H), 3.71 (s, 3H), 2.49 (m, 3H), 2.18 (m, 1H), 2.04 (m, 3H), 1.85 (td, J = 6.3, 12.2 Hz, 1H), 1.45 (s, 9H) ; ^{13}C NMR ppm 172.1, 170.4, 155.3, 79.9, 62.7, 62.3, 53.9, 52.2, 37.0, 36.8, 31.1, 28.6, 28.1, 25.7 ; HRMS calcd for $C_{16}H_{26}IN_2O_5$ $[M + H]^+$ 453.0881, found 453.0878.

(3*S*,5*R*,6*R*,9*S*)-Methyl 2-oxo-3-*N*-(Fmoc)amino-5-phenylselenyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*R*,6*R*,9*S*)-69). $[\alpha]_D^{20}$ –41.5° (*c* 2.48 MeOH); ^{1}H NMR (CDCl3) ppm 7.79 (d, J = 7.4 Hz, 2H), 7.64 (dd, J = 12.4, 7.5 Hz, 2H), 7.58 (d, J = 6.4 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.38-7.23 (m, 5H), 6.11 (d, J = 5.9 Hz, 1H), 4.55 (m, 1H), 4.44(m, 2H), 4.34 (t, J = 8.9 Hz, 1H), 4.25 (t, J = 7.1 Hz, 1H), 4.03 (m, 1H), 3.94 (m, 1H), 3.84 (s, 3H), 2.89 (m, 1H), 2.46 (m, 1H), 2.25 (m, 2H), 2.12 (m, 2H) ; ^{13}C NMR ppm 171.4, 168.6, 156.2, 143.9, 143.6, 141.2, 141.2, 134.1, 129.3, 129.0, 127.8, 127.6, 127.6, 127.0, 125.2, 125.0, 119.9, 67.4, 61.1, 58.2, 52.5, 50.0, 47.0, 41.0, 36.3, 30.5, 28.6 ; HRMS calcd for $C_{31}H_{31}N_2O_5Se$ $[M + H]^+$ 591.1393, found 591.1393.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FmocHN
O
N
H
CO2Me
(3S, 5R, 6R, 9S)-66
ppm
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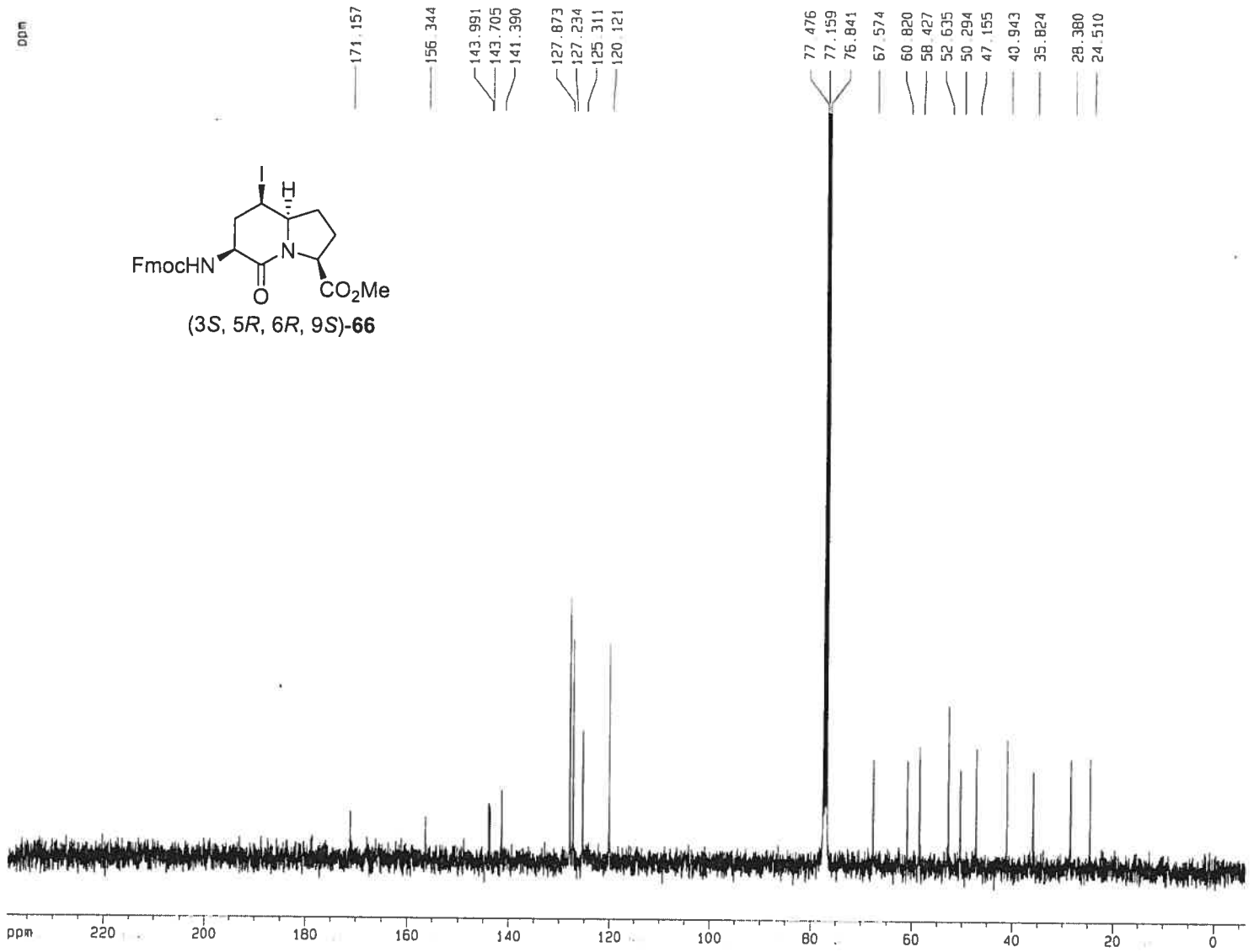
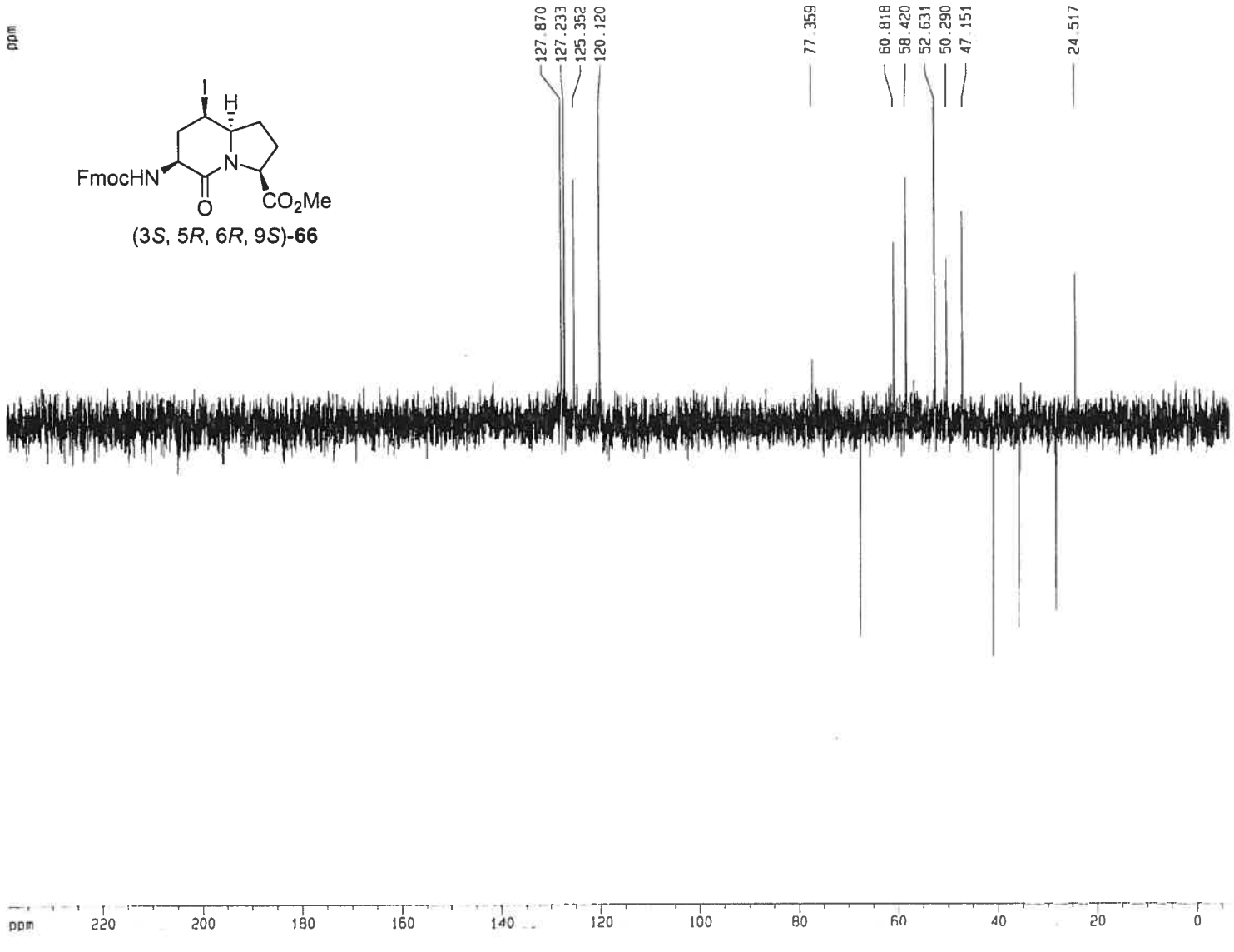
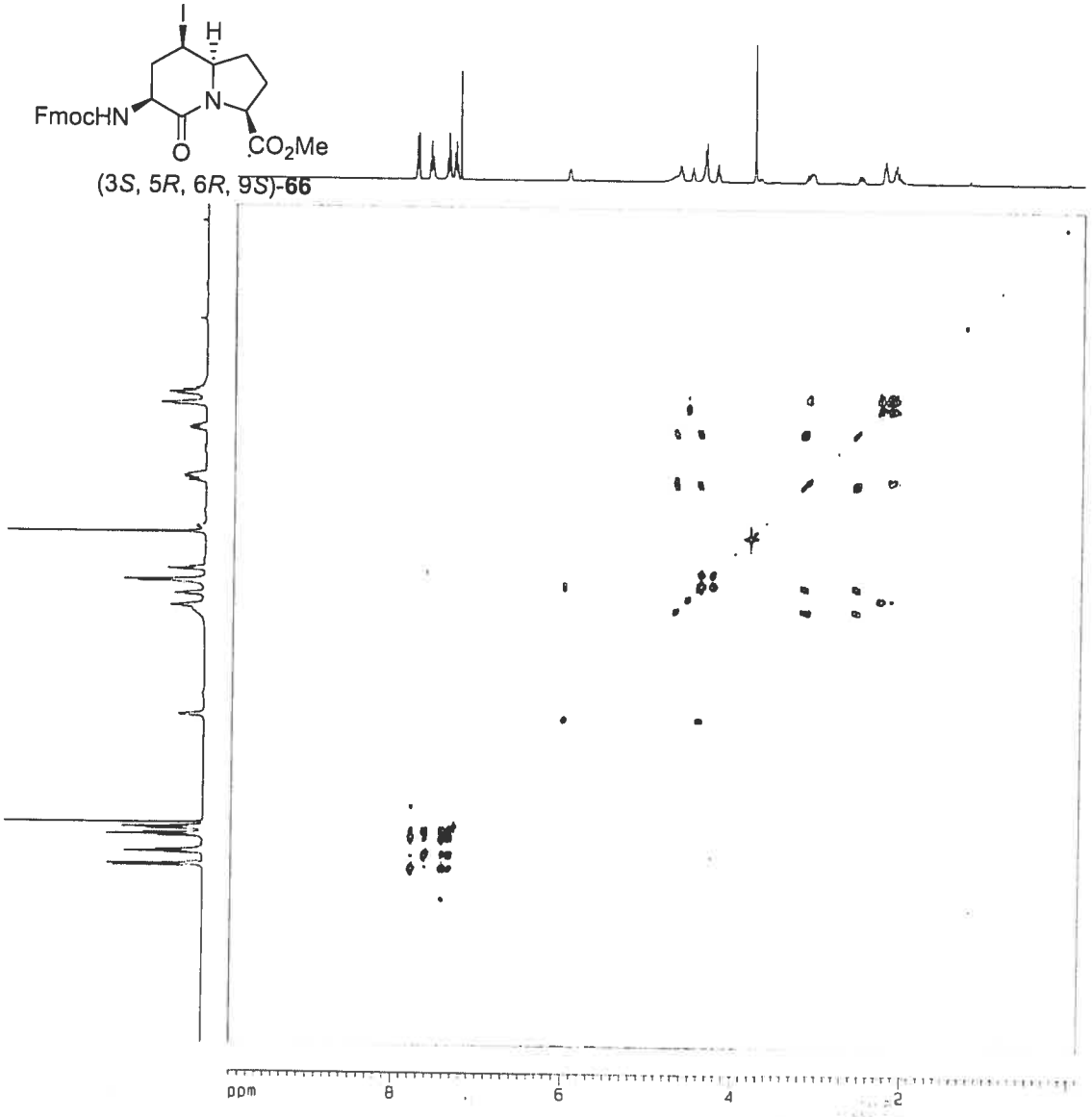
2.09857

Bvi


ppm
171.157
156.344
143.991
143.705
141.390
127.873
127.234
125.311
120.121
77.476
77.159
76.841
67.574
60.820
58.427
52.635
50.294
47.155
40.943
35.824
28.380
24.510
FmocHN
O
N
H
CO2Me
ppm
220
200
180
160
140
120
100
80
60
40
20
0

(3*S*, 5*R*, 6*R*, 9*S*)-**66**


ppm
127.870
127.233
125.352
120.120
77.359
60.818
58.420
52.631
50.290
47.151
24.517
FmocHN
O
N
CO2Me
(3S, 5R, 6R, 9S)-66
ppm
220
200
180
160
140
120
100
80
60
40
20
0



Current Data Parameters

NAME	99-3-1cos
EXPNO	2
PROCNO	1

F2 Acquisition Parameters

Date_	20060111
Time	12 21
INSTRUM	av400
PROBHD	5 mm PABBO BB-
PULPROG	cosydqf
TD	2048
SOLVENT	CDCl3
NS	1
DS	16
SWH	4006 410 Hz
FIDRES	1 956255 Hz
AQ	0 2558404 sec
RG	256
DW	124 800 usec
DE	6 00 usec
TE	293 3 K
d0	0 00000300 sec
D1	1 50000000 sec
d13	0 00000403 sec
D16	0 00020000 sec
IN0	0 00624960 sec
MCREST	0 00000000 sec
MCWRK	1 50000000 sec

======== CHANNEL f1 ========

NUC1	1H
P0	4 80 usec
P1	9 75 usec
PL1	-3 00 dB
SFO1	400 1319606 MHz

====== GRADIENT CHANNEL =====

GPNAM1	sine.100
GPNAM2	sine.100
GPZ1	0 00 %
GPZ2	0 00 %
GPY1	0 00 %
GPY2	0 00 %
GPZ1	15 00 %
GPZ2	15 00 %
P16	1000 00 usec

F1 - Acquisition parameters

NDO	1
TD	512
SFO1	400 132 MHz
FIDRES	7 825020 Hz
SW	10 013 ppm

F2 - Processing parameters

SI	2048
SF	400 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0
PC	1 00

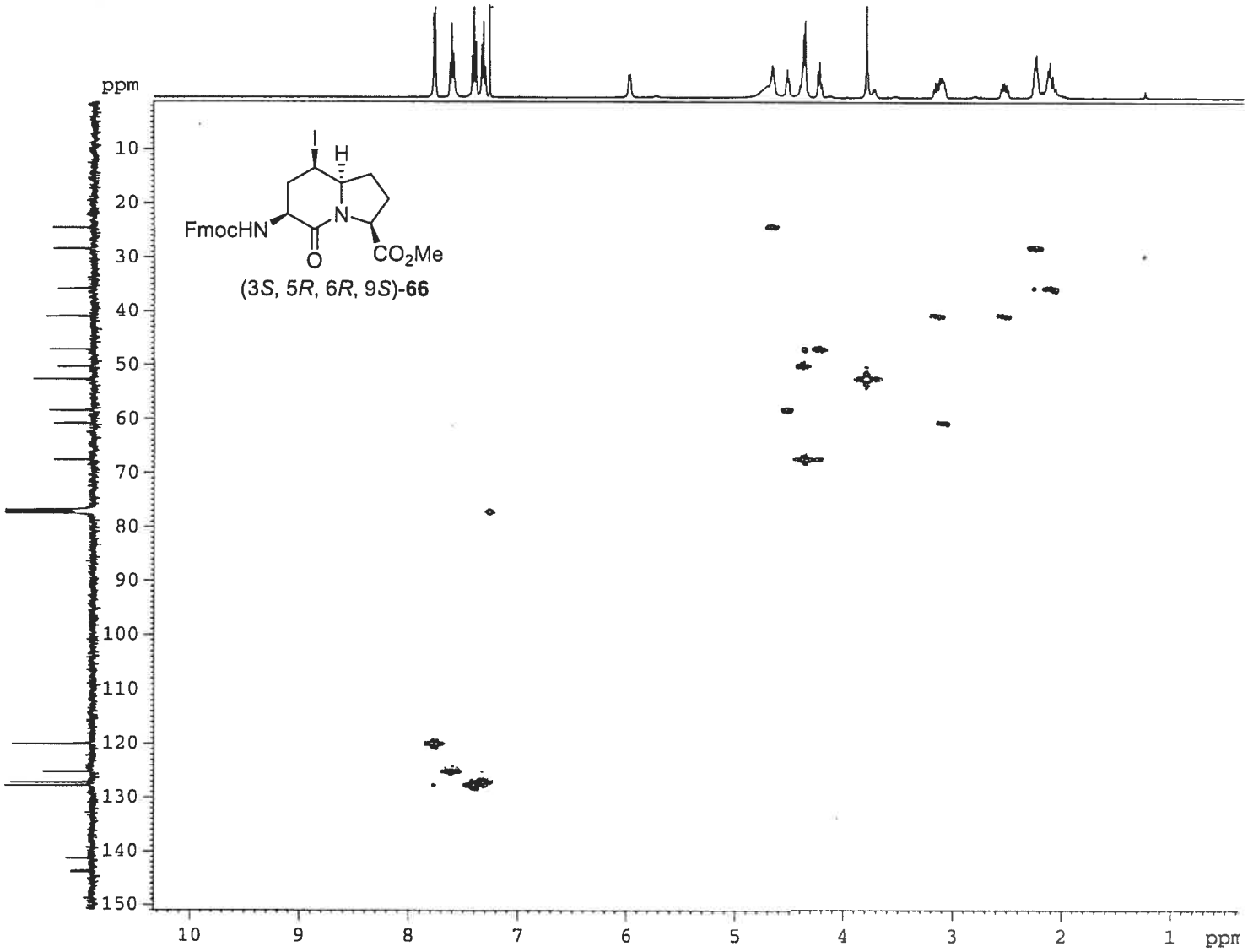
F1 - Processing parameters

SI	1024
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0

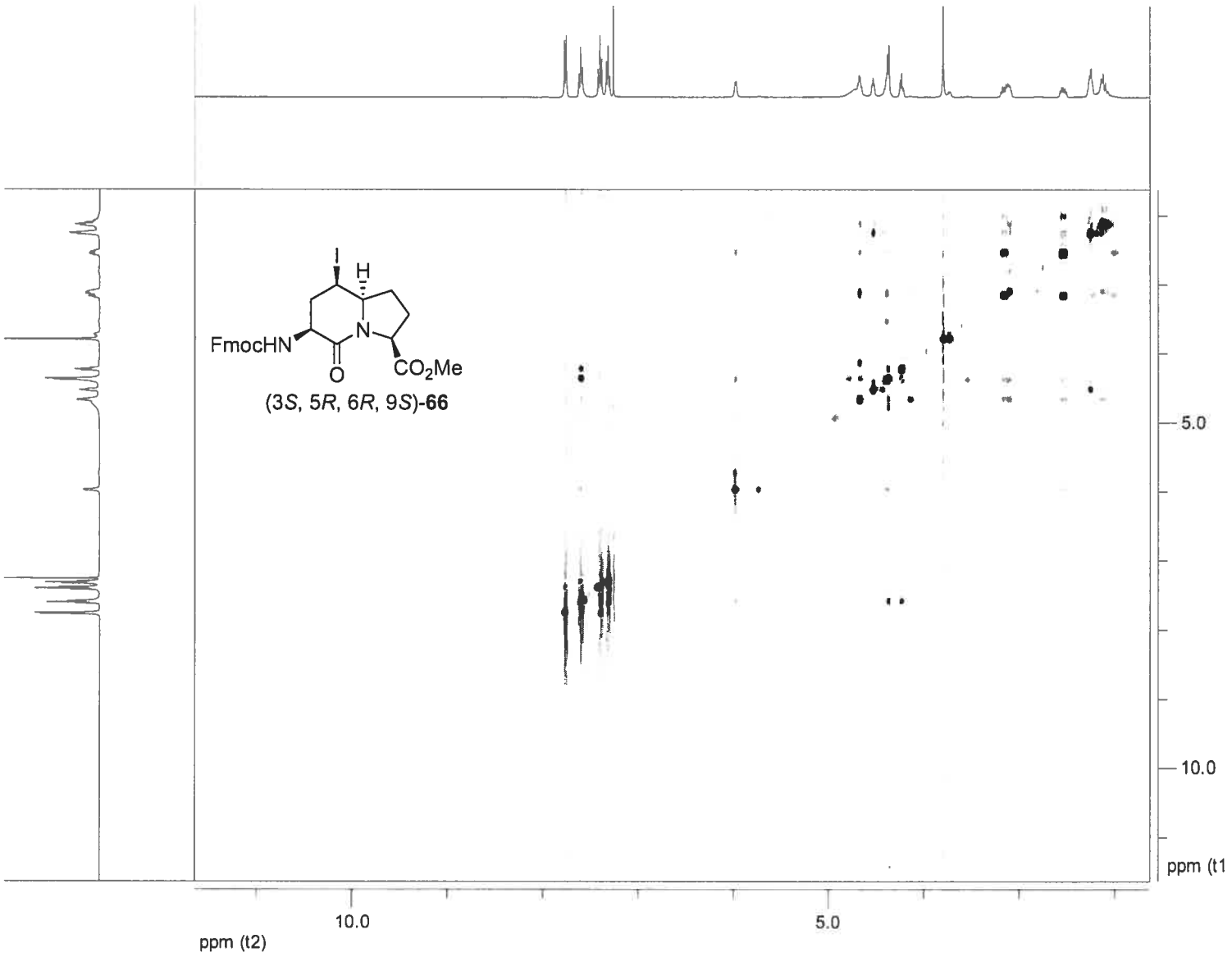
2D NMR plot parameters

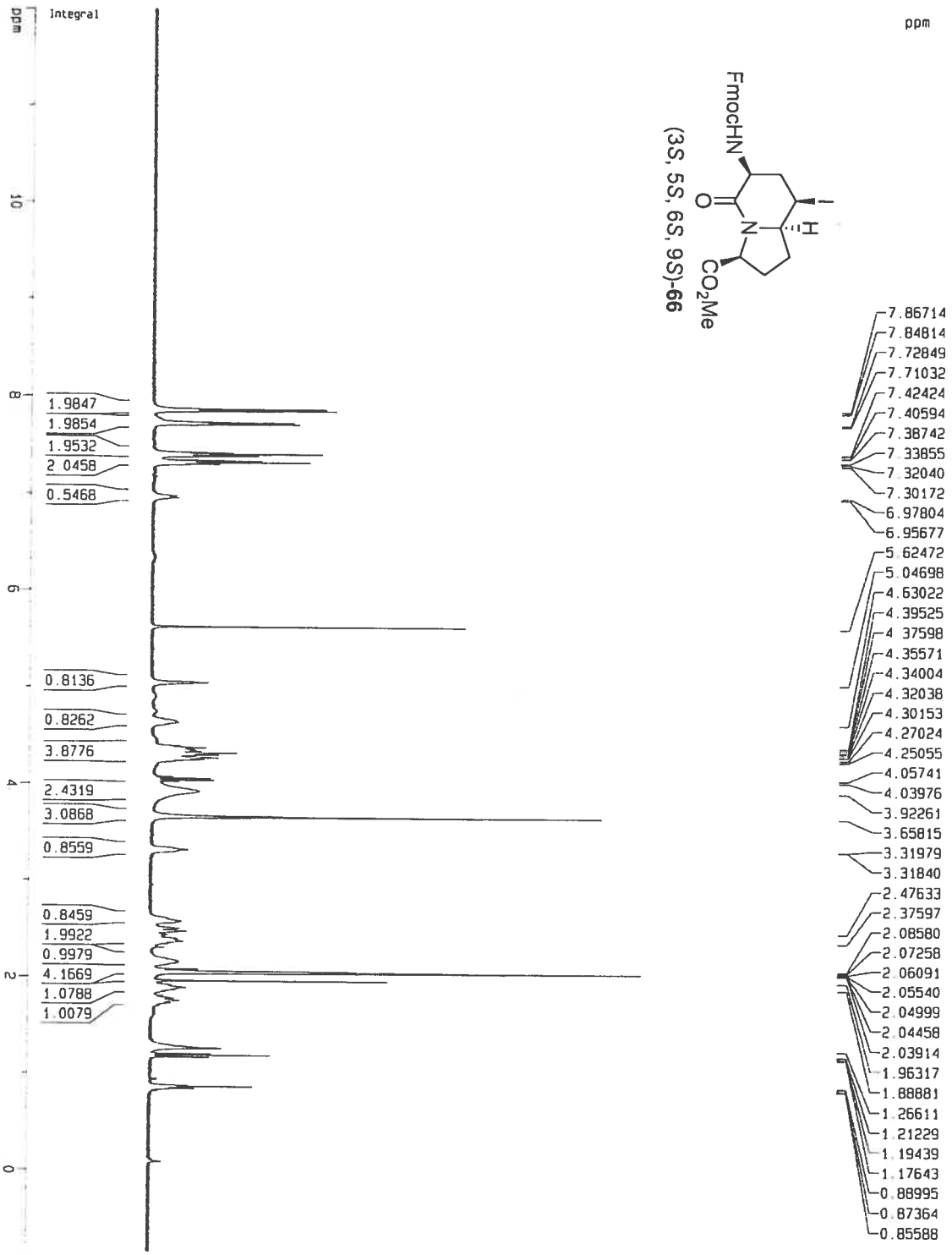
CX2	15 00 cm
CX1	15 00 cm
F2PLO	9 906 ppm
F2LO	3961 84 Hz
F2PHI	-0 106 ppm
F2HI	-42 57 Hz
F1PLO	9 906 ppm
F1LO	3963 84 Hz
F1PHI	0 106 ppm
F1HI	-42 57 Hz
F2PPMCM	0 66752 ppm/cm
F2HZCM	267 09402 Hz/cm
F1PPMCM	2 66752 ppm/cm
F1HZCM	1067 09402 Hz/cm

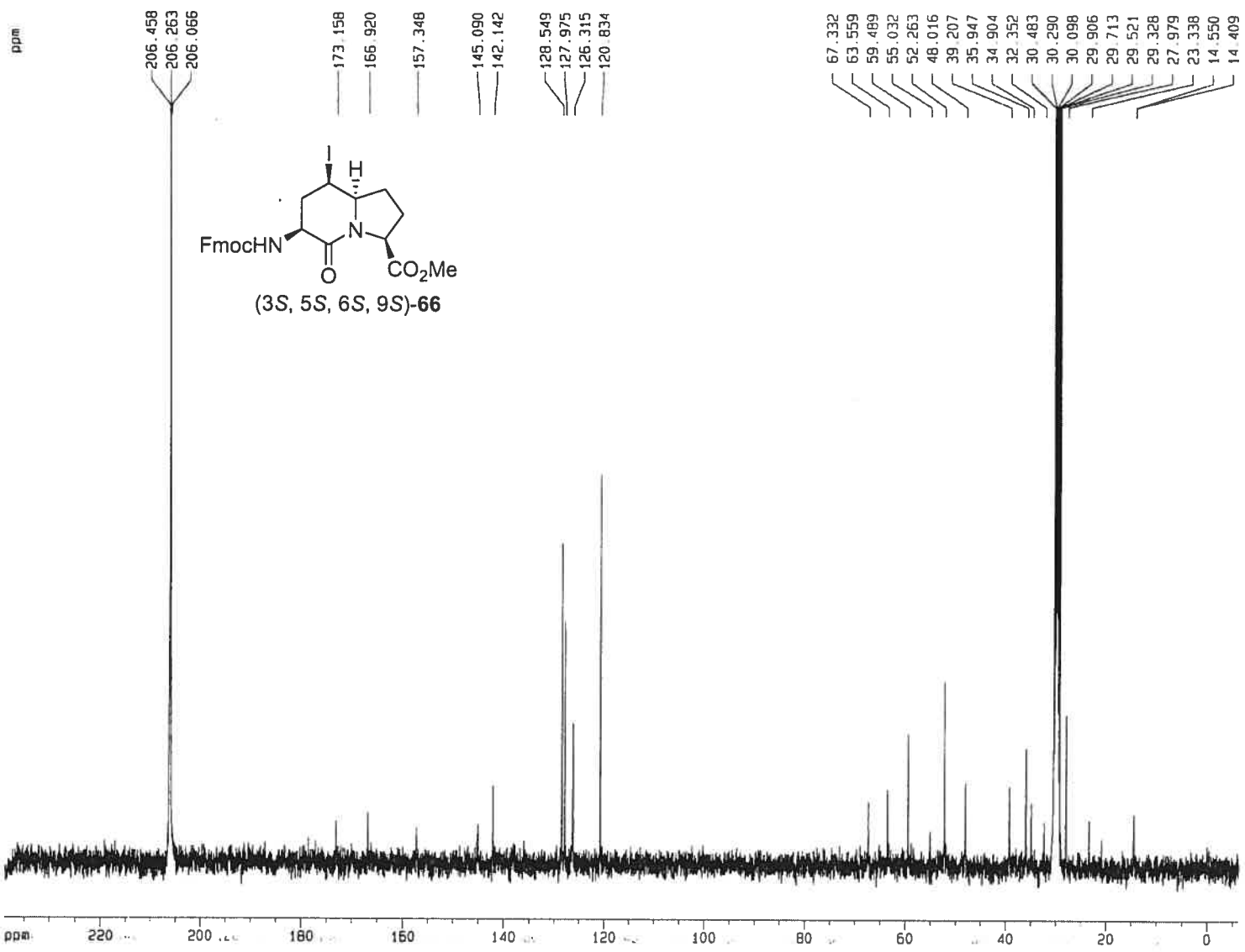
Bix


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
FmocHN
H
N
O
CO2Me
(3S, 5R, 6R, 9S)-66
10
9
8
7
6
5
4
3
2
1
ppm

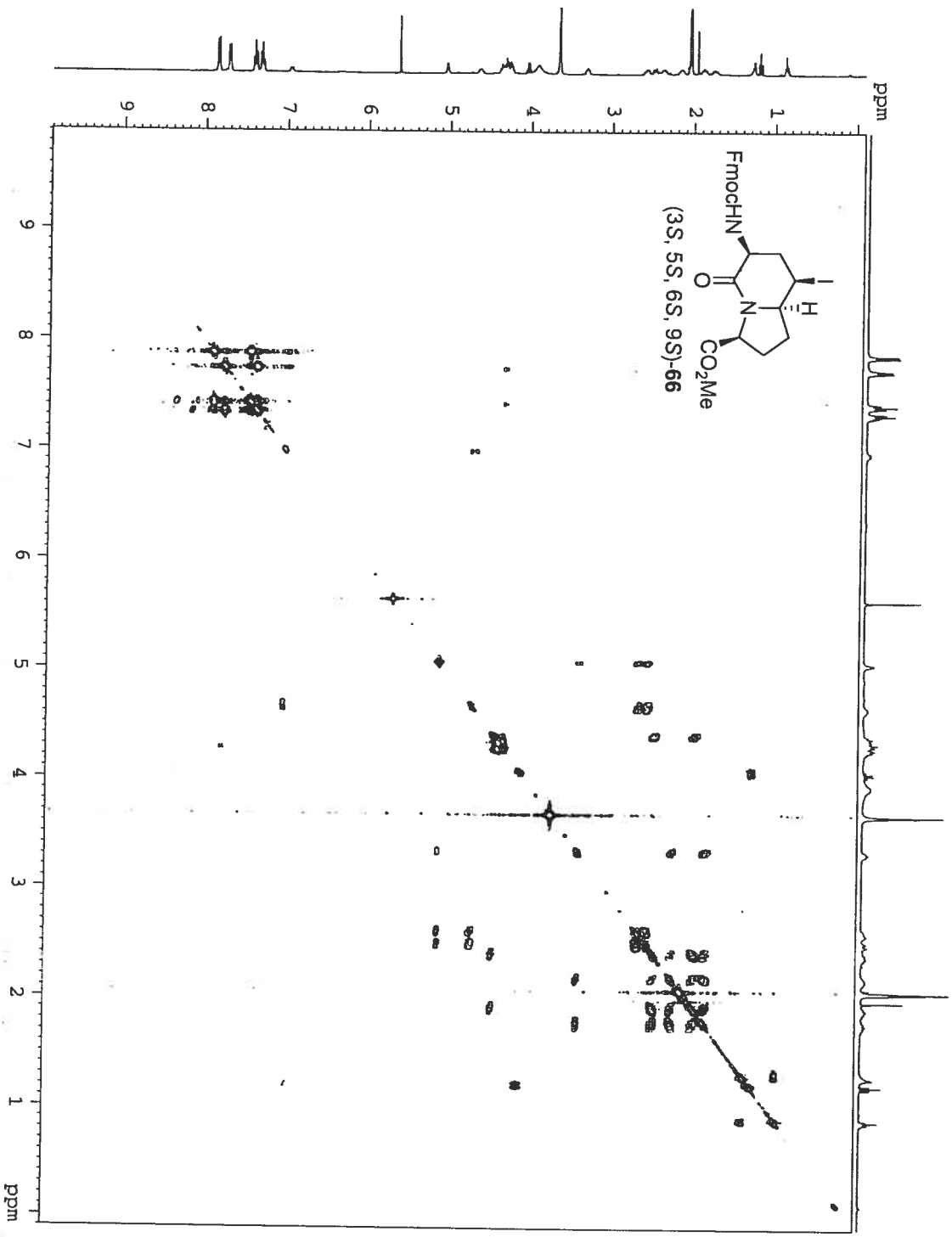
Bx

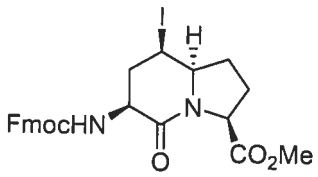

I
H
FmocHN
N
O
CO_2Me
(3S, 5R, 6R, 9S)-66
5.0
10.0
ppm (t1
10.0
5.0
ppm (t2)


ppm
Integral
1.9847
1.9854
1.9532
2.0458
0.5468
0.8136
0.8262
3.8776
2.4319
3.0868
0.8559
0.8459
1.9922
0.9979
4.1669
1.0788
1.0079
FmocHN
O
N
H
CO2Me
(3S, 5S, 6S, 9S)-66
ppm
7.86714
7.84814
7.72849
7.71032
7.42424
7.40594
7.38742
7.33855
7.32040
7.30172
6.97804
6.95677
5.62472
5.04698
4.63022
4.39525
4.37598
4.35571
4.34004
4.32038
4.30153
4.27024
4.25055
4.05741
4.03976
3.92261
3.65815
3.31979
3.31840
2.47633
2.37597
2.08580
2.07258
2.06091
2.05540
2.04999
2.04458
2.03914
1.96317
1.88881
1.26611
1.21229
1.19439
1.17643
0.88995
0.87364
0.85588

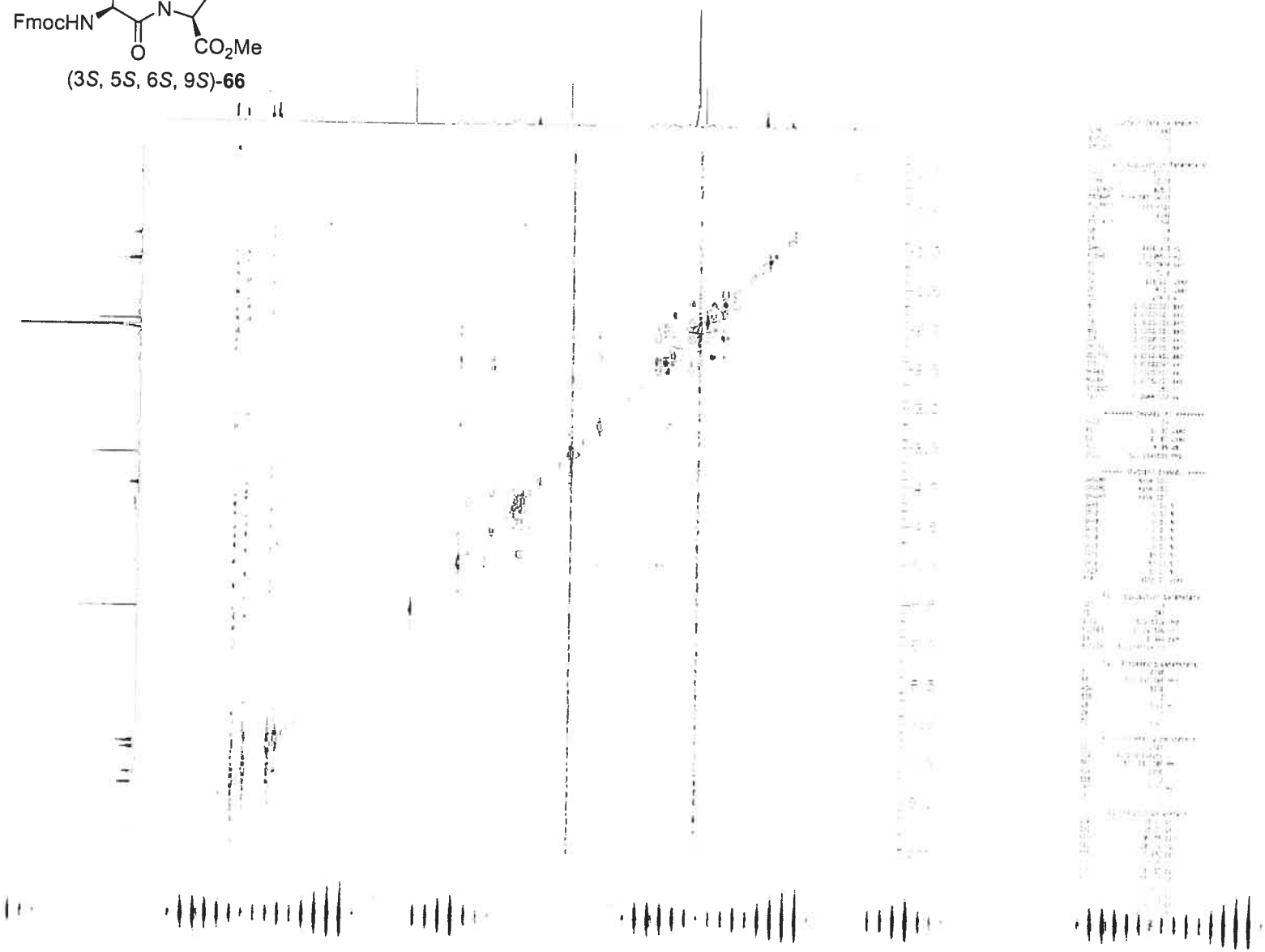

ppm
206.458
206.263
206.066
173.158
166.920
157.348
145.090
142.142
128.549
127.975
126.315
120.834
67.332
63.559
59.489
55.032
52.263
48.016
39.207
35.947
34.904
32.352
30.483
30.290
30.098
29.906
29.713
29.521
29.328
27.979
23.338
14.550
14.409
FmocHN
N
H
O
CO2Me
ppm
220
200
180
160
140
120
100
80
60
40
20
0

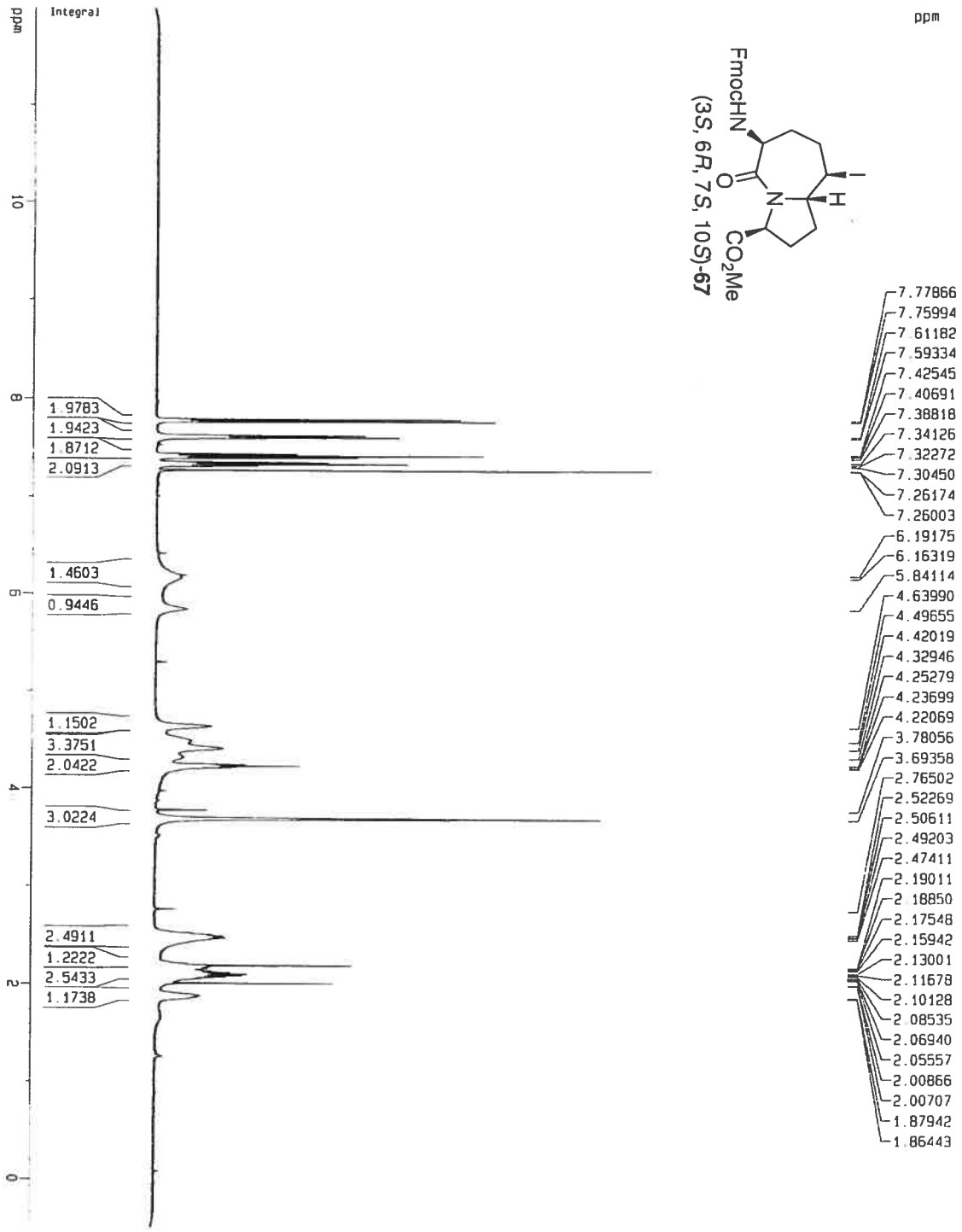
(3*S*, 5*S*, 6*S*, 9*S*)-**66**

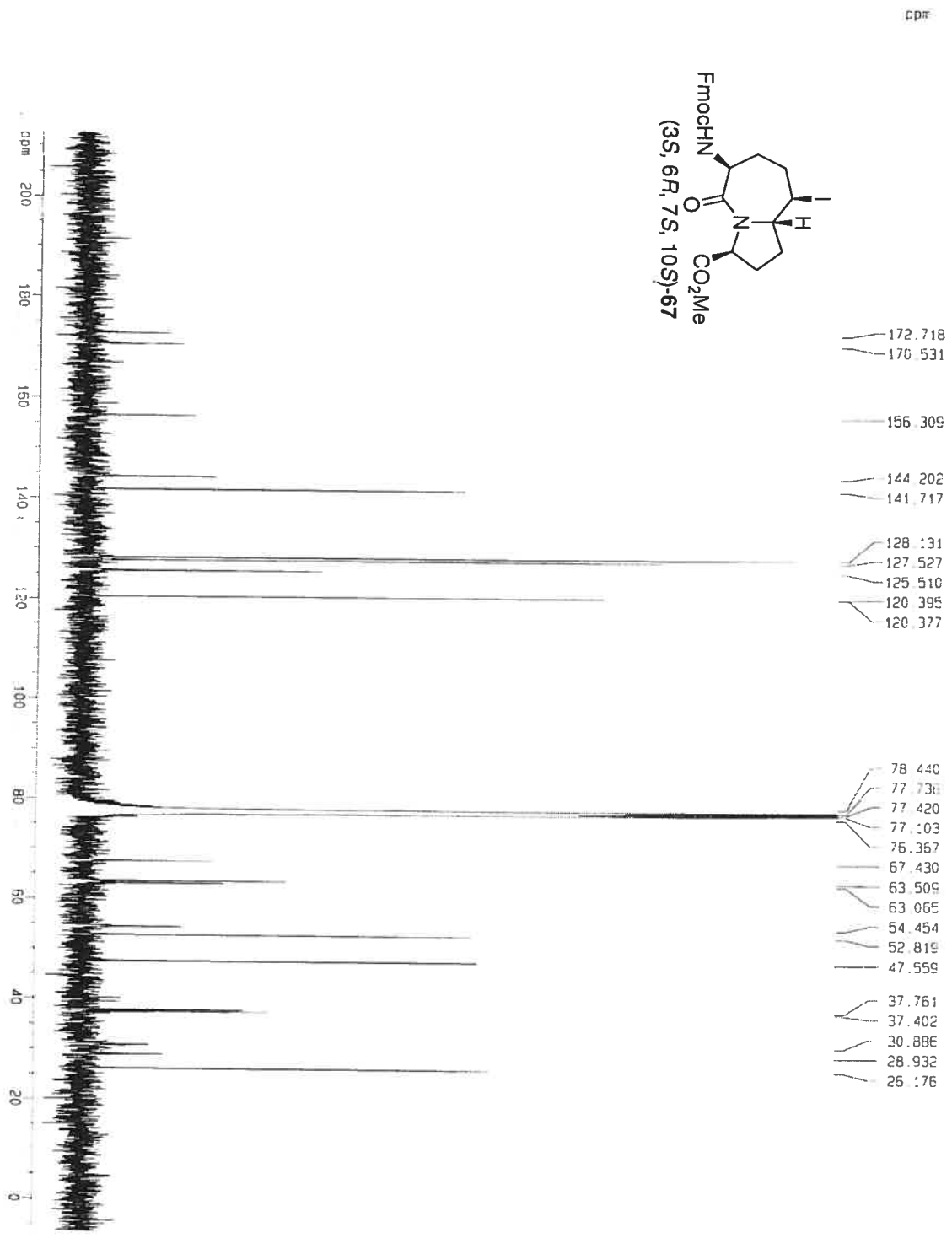

FmocHN
O
N
H
CO2Me
(3S, 5S, 6S, 9S)-66
ppm
ppm

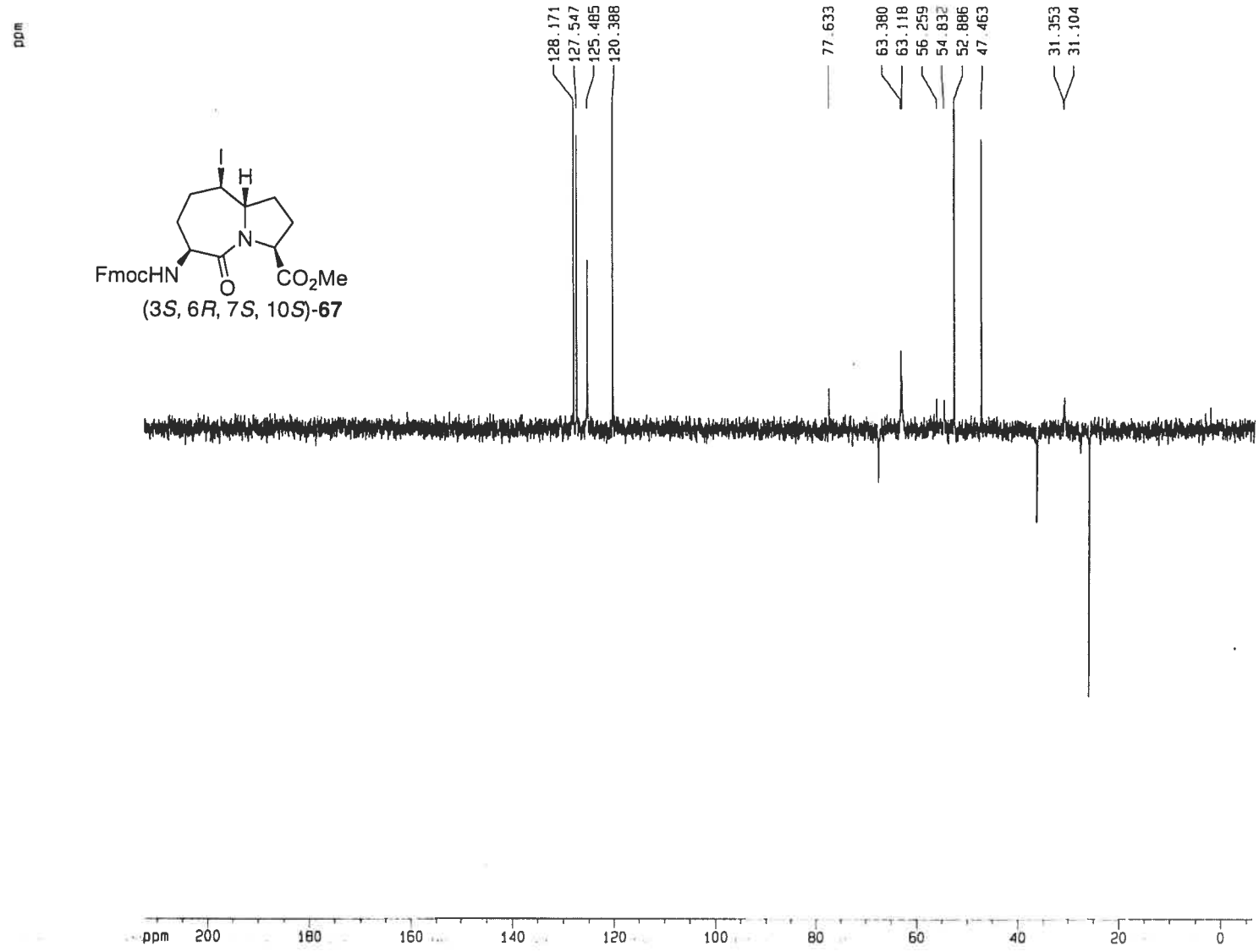


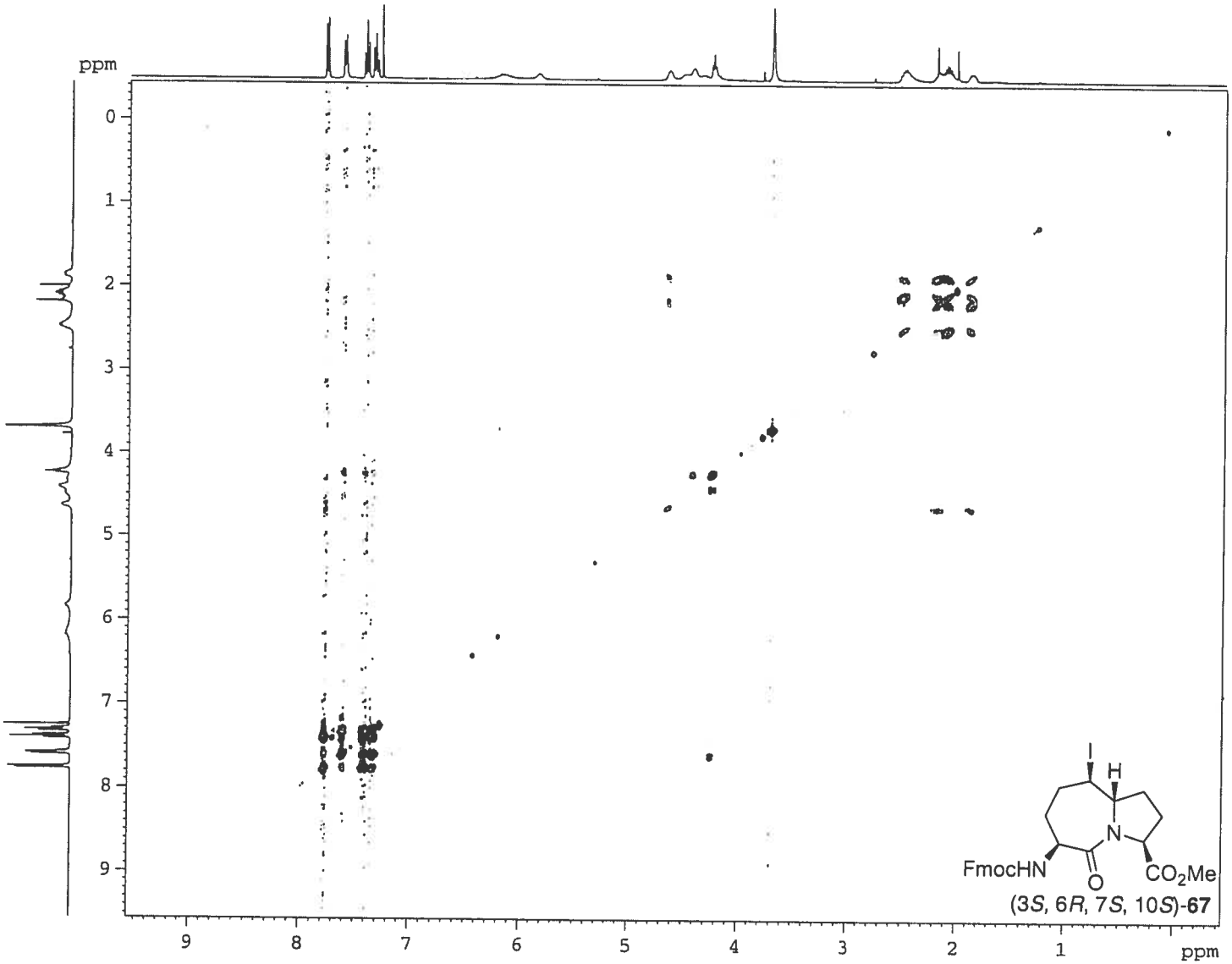
(3*S*, 5*S*, 6*S*, 9*S*)-**66**

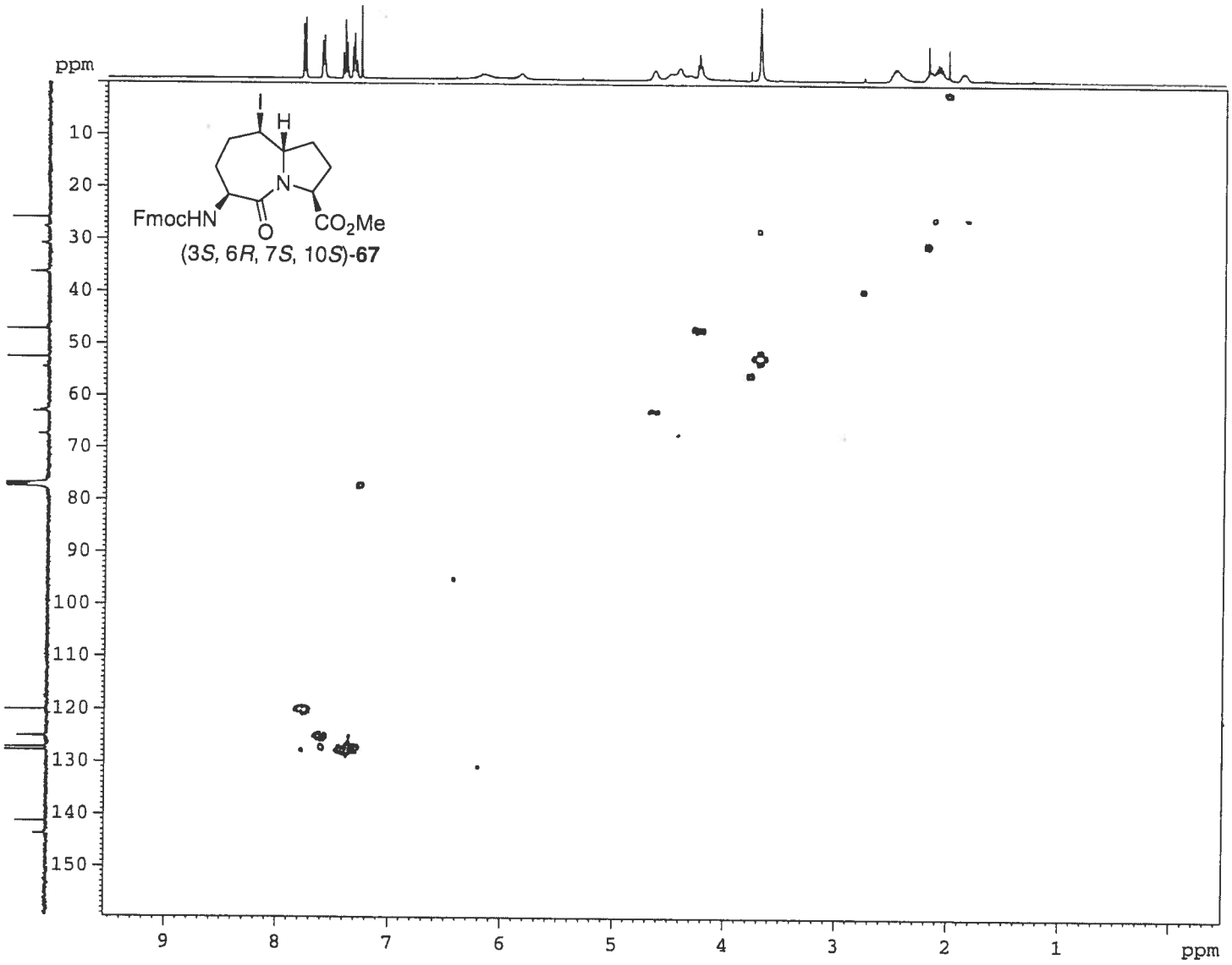


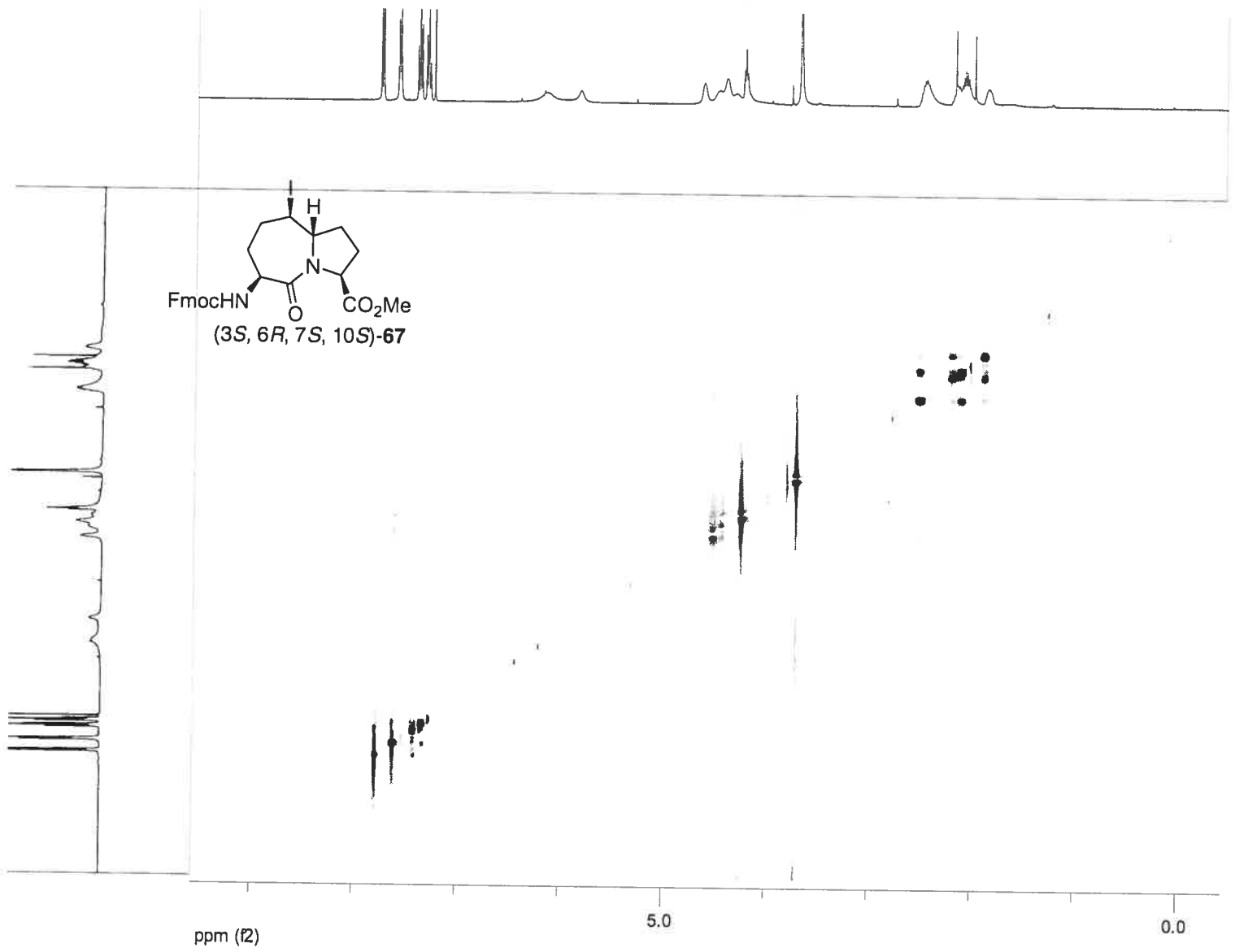

ppm
Integral
10
8
6
4
2
0
1.9783
1.9423
1.8712
2.0913
1.4603
0.9446
1.1502
3.3751
2.0422
3.0224
2.4911
1.2222
2.5433
1.1738
FmocHN
O
N
H
I
CO2Me
(3S, 6R, 7S, 10S)-67
ppm
7.77866
7.75994
7.61182
7.59334
7.42545
7.40691
7.38818
7.34126
7.32272
7.30450
7.26174
7.26003
6.19175
6.16319
5.84114
4.63990
4.49655
4.42019
4.32946
4.25279
4.23699
4.22069
3.78056
3.69358
2.76502
2.52269
2.50611
2.49203
2.47411
2.19011
2.18850
2.17548
2.15942
2.13001
2.11678
2.10128
2.08535
2.06940
2.05557
2.00866
2.00707
1.87942
1.86443

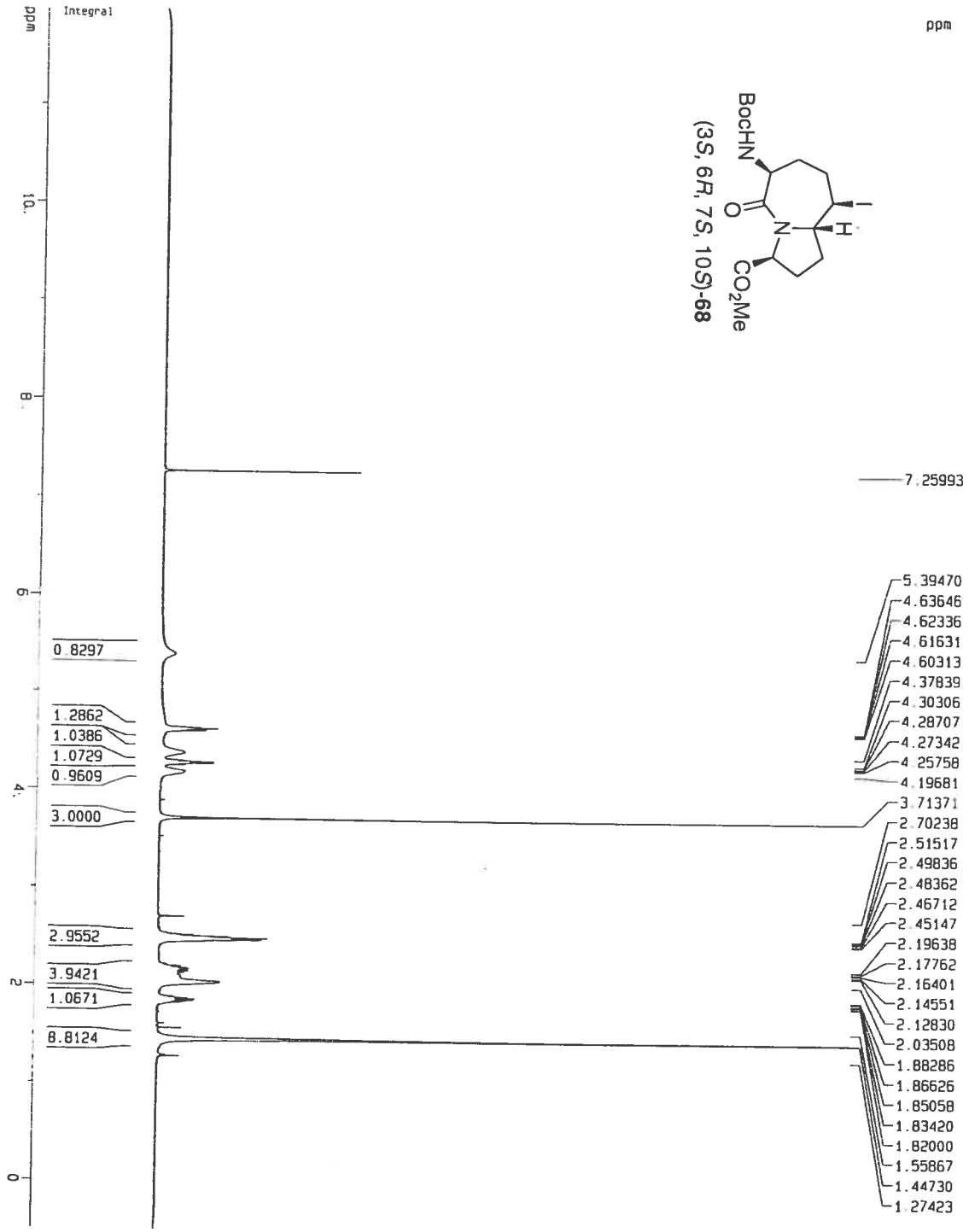

ppm
FmocHN
O
N
H
CO2Me
(3S, 6R, 7S, 10S)-67
172.718
170.531
156.309
144.202
141.717
128.131
127.527
125.510
120.395
120.377
78.440
77.738
77.420
77.103
76.367
67.430
63.509
63.065
54.454
52.819
47.559
37.761
37.402
30.886
28.932
25.176

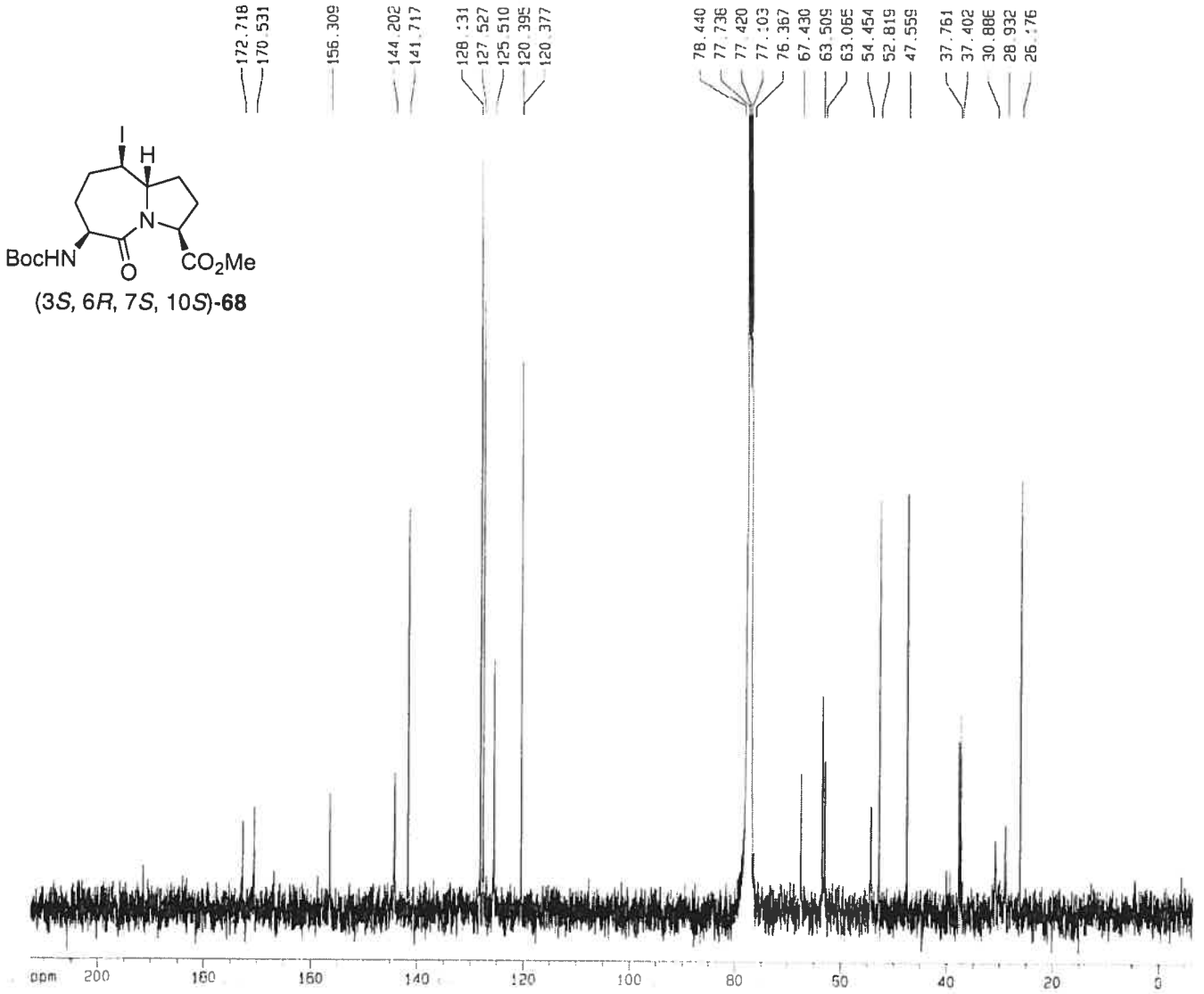

ppm
128.171
127.547
125.485
120.388
77.633
63.380
63.118
56.259
54.832
52.886
47.463
31.353
31.104
I
H
N
FmocHN
O
CO2Me
(3S, 6R, 7S, 10S)-67
ppm 200 180 160 140 120 100 80 60 40 20 0


ppm
0
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
ppm
I
H
N
O
FmocHN
CO2Me
(3S, 6R, 7S, 10S)-67

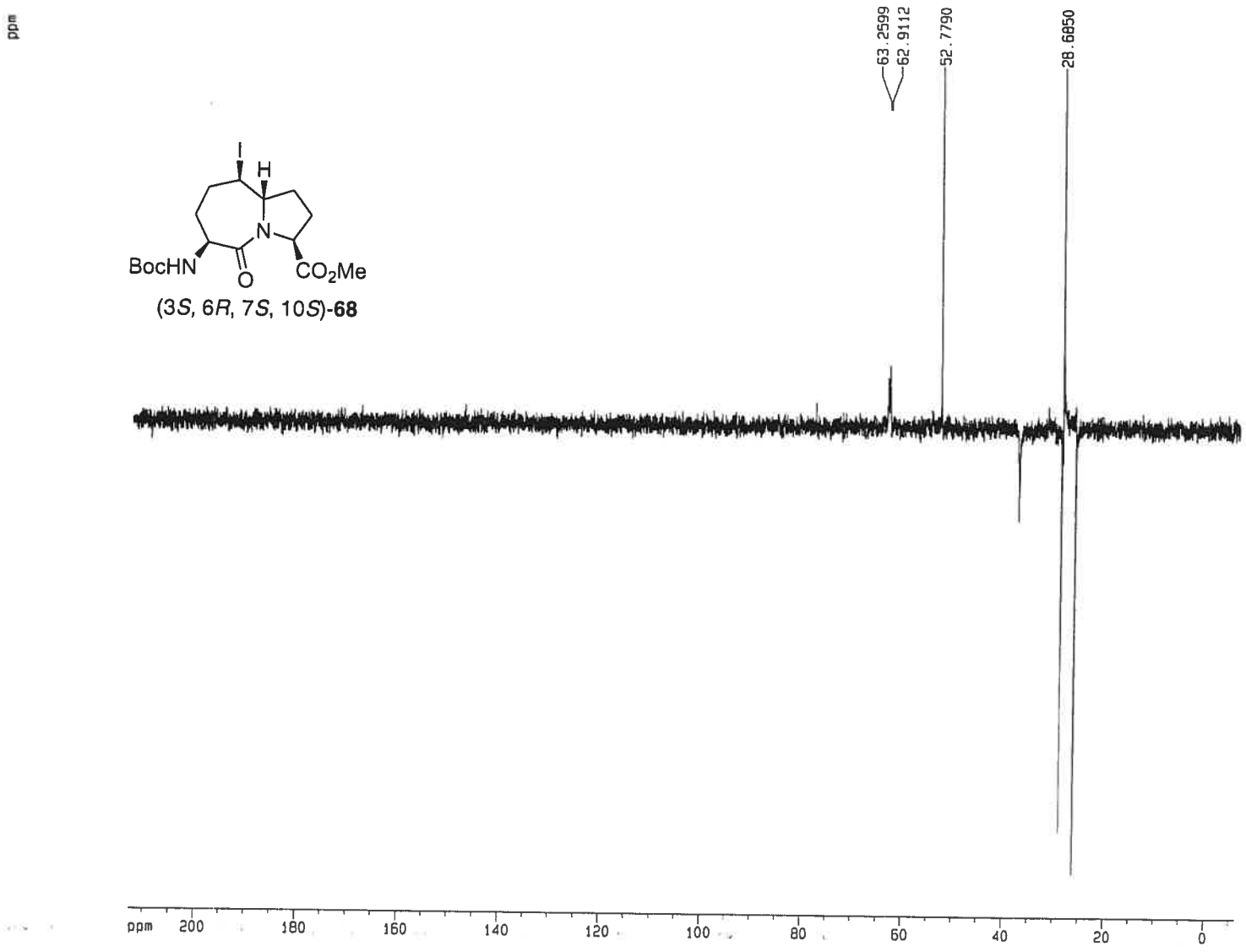

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9
8
7
6
5
4
3
2
1
ppm
H
N
FmocHN
O
CO2Me
(3S, 6R, 7S, 10S)-67

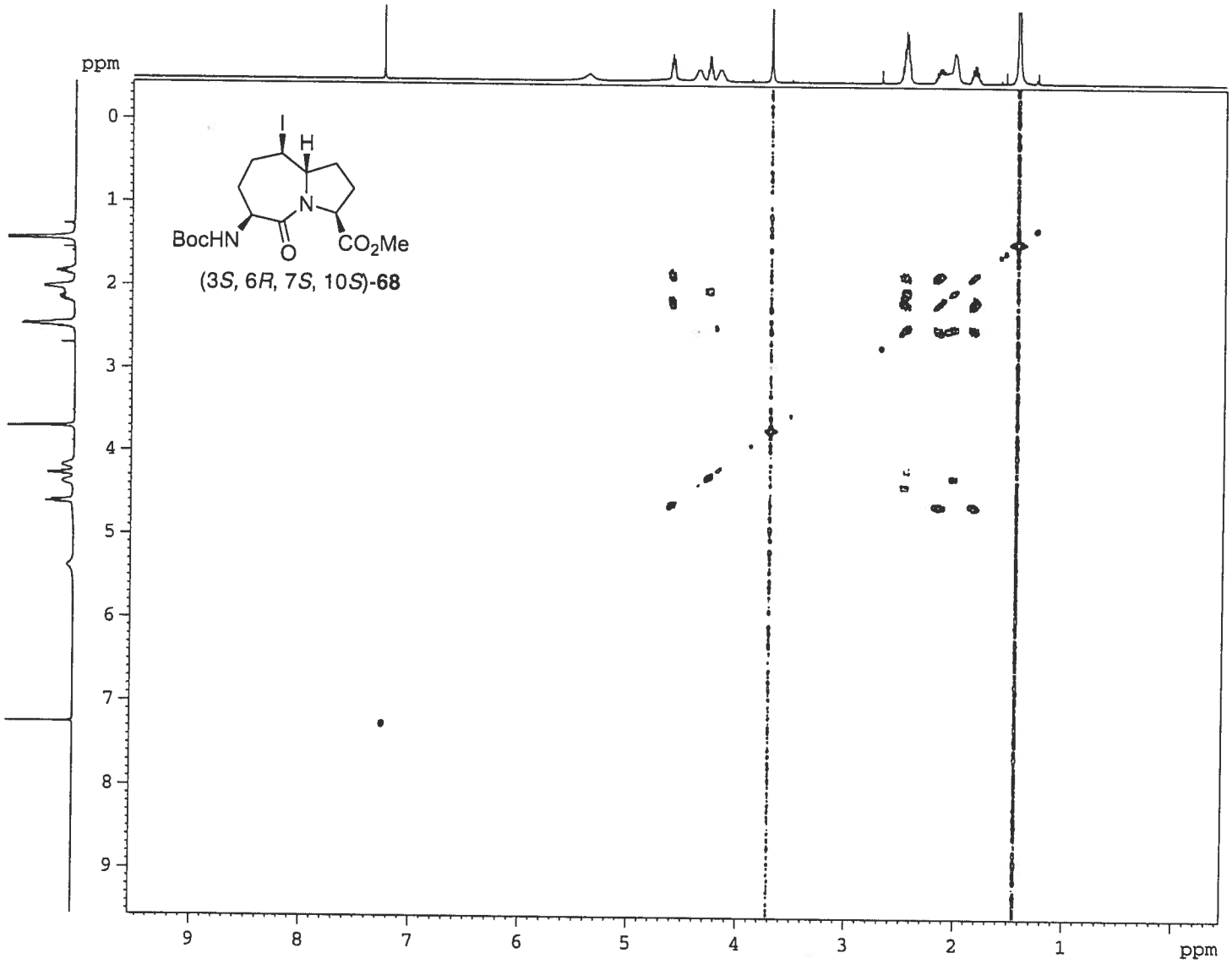

H
N
FmocHN
O
CO2Me
(3S, 6R, 7S, 10S)-67
ppm (f2)
5.0
0.0

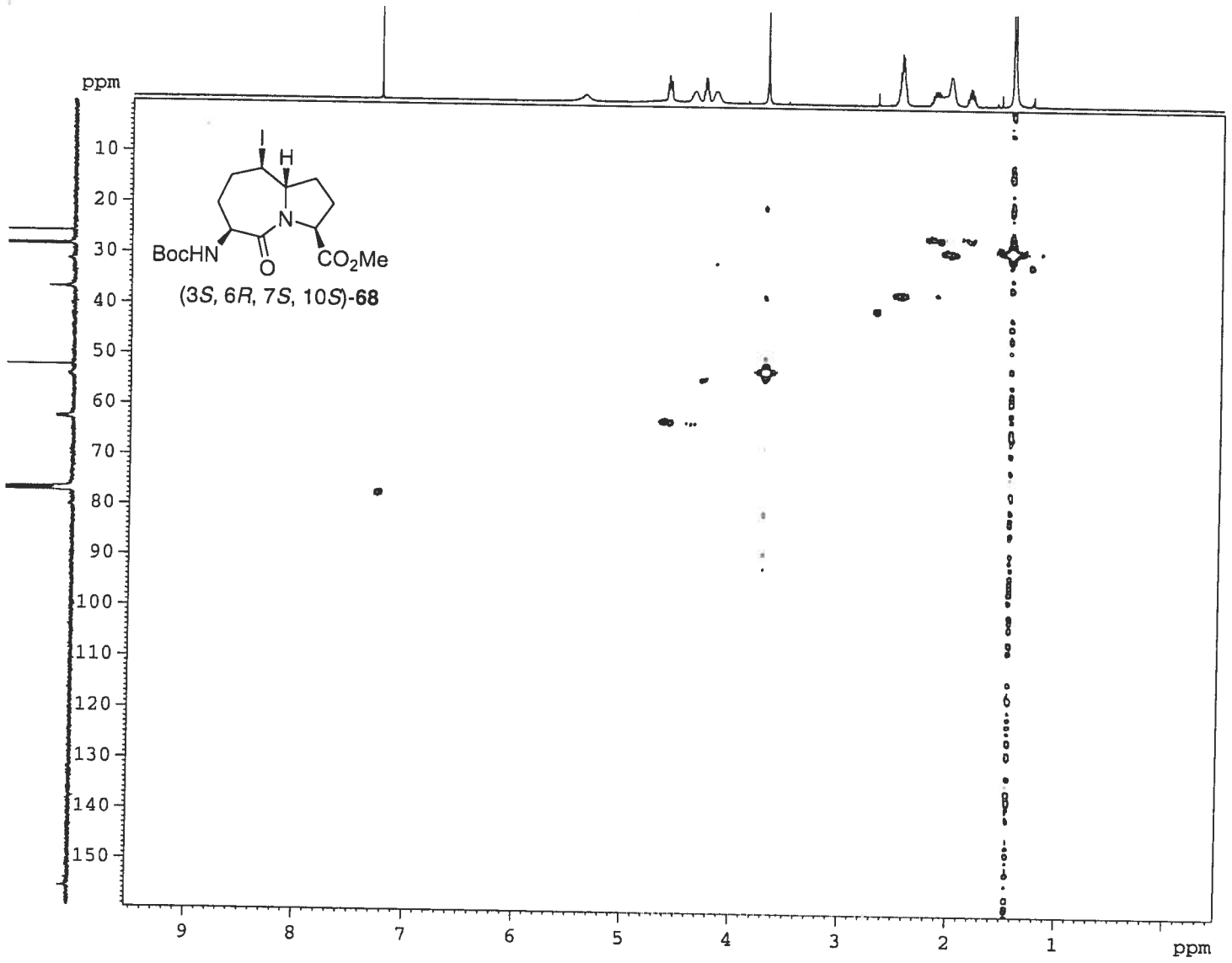

ppm
Integral
10.
8
6
4
2
0
0.8297
1.2862
1.0386
1.0729
0.9609
3.0000
2.9552
3.9421
1.0671
8.8124
ppm
BocHN
O
N
H
CO2Me
(3S, 6R, 7S, 10S)-68
7.25993
5.39470
4.63646
4.62336
4.61631
4.60313
4.37839
4.30306
4.28707
4.27342
4.25758
4.19681
3.71371
2.70238
2.51517
2.49836
2.48362
2.46712
2.45147
2.19638
2.17762
2.16401
2.14551
2.12830
2.03508
1.88286
1.86626
1.85058
1.83420
1.82000
1.55867
1.44730
1.27423

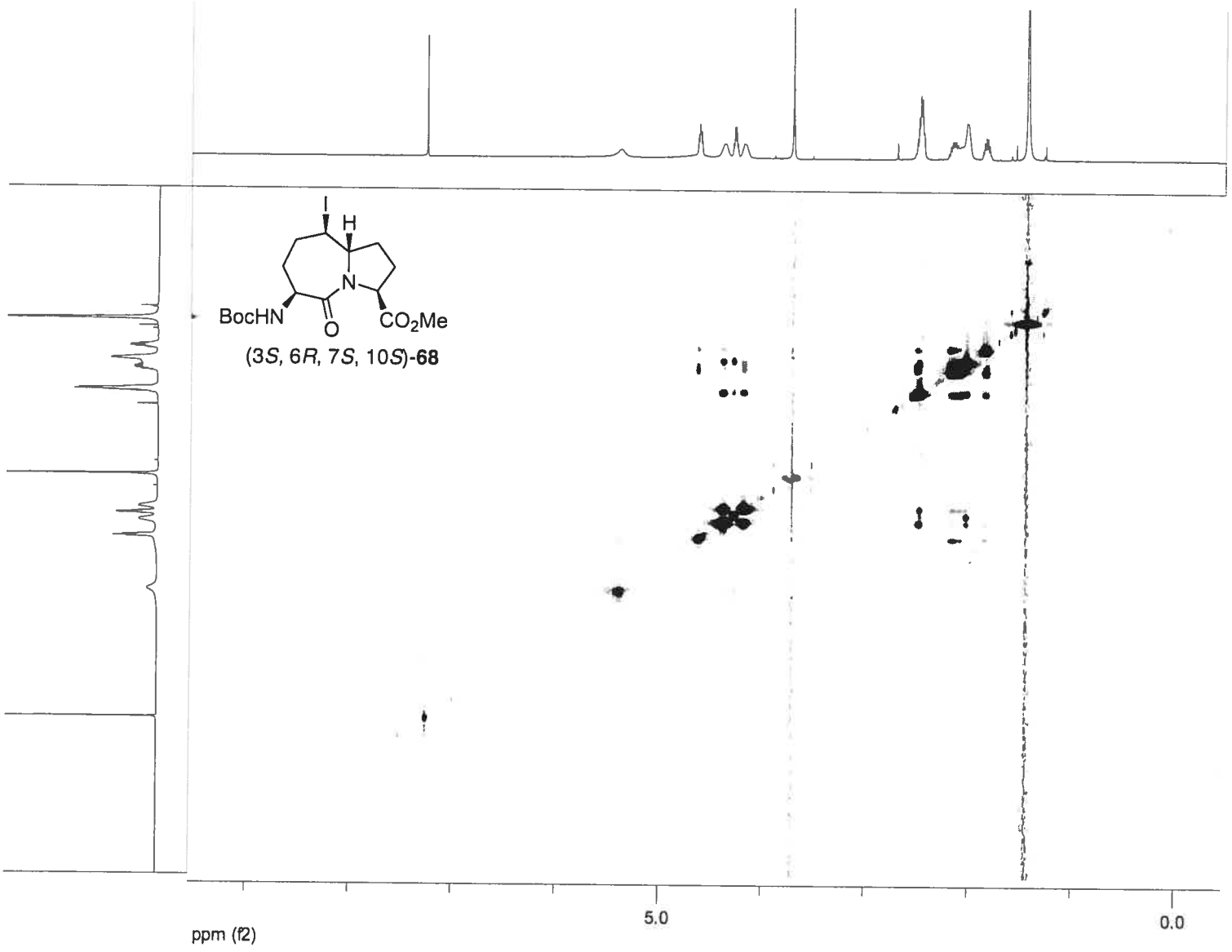


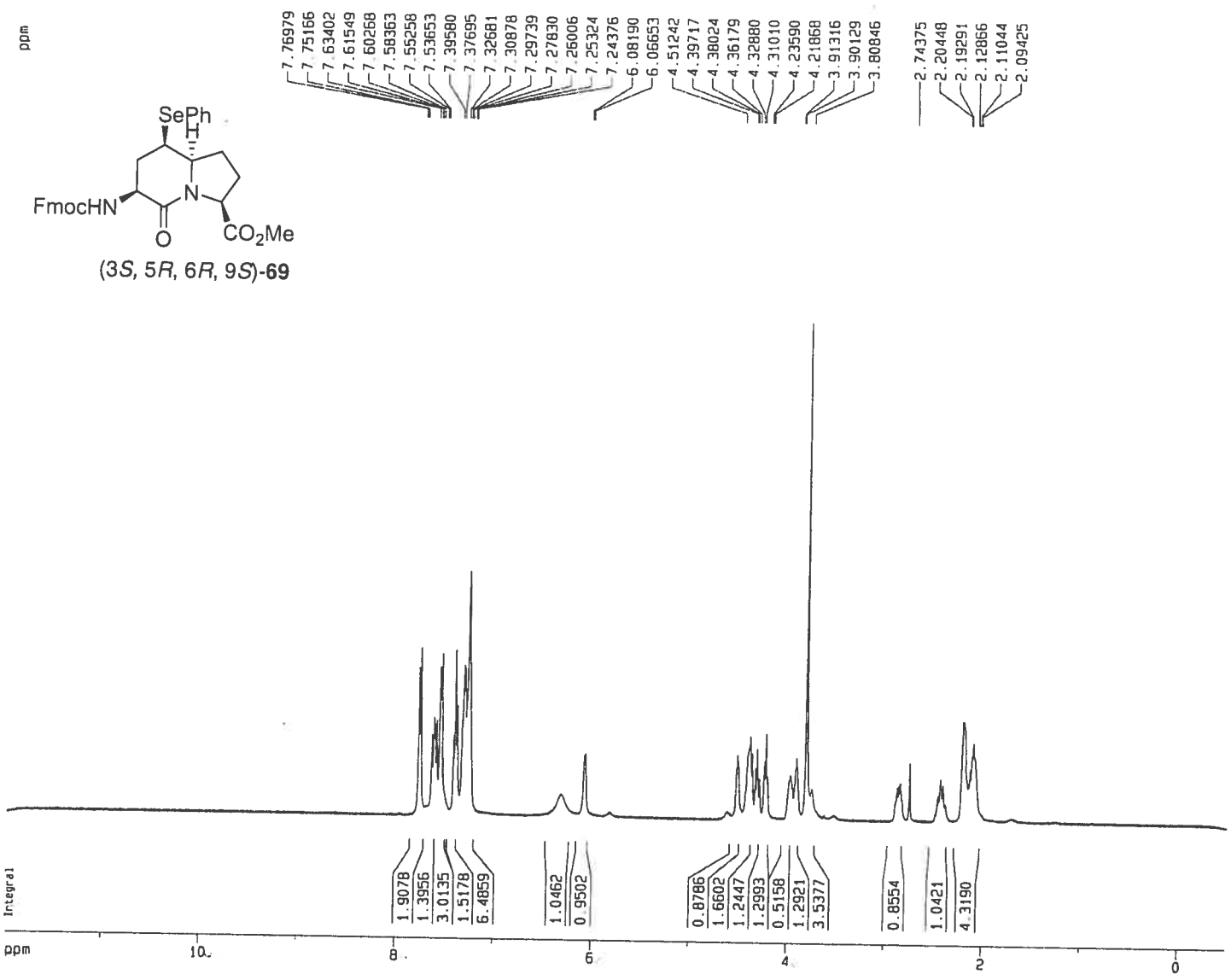
(3*S*, 6*R*, 7*S*, 10*S*)-**68**


ppm
63.2599
62.9112
52.7790
28.6850
I
H
N
BocHN
O
CO2Me
(3S, 6R, 7S, 10S)-68
ppm 200 180 160 140 120 100 80 60 40 20 0

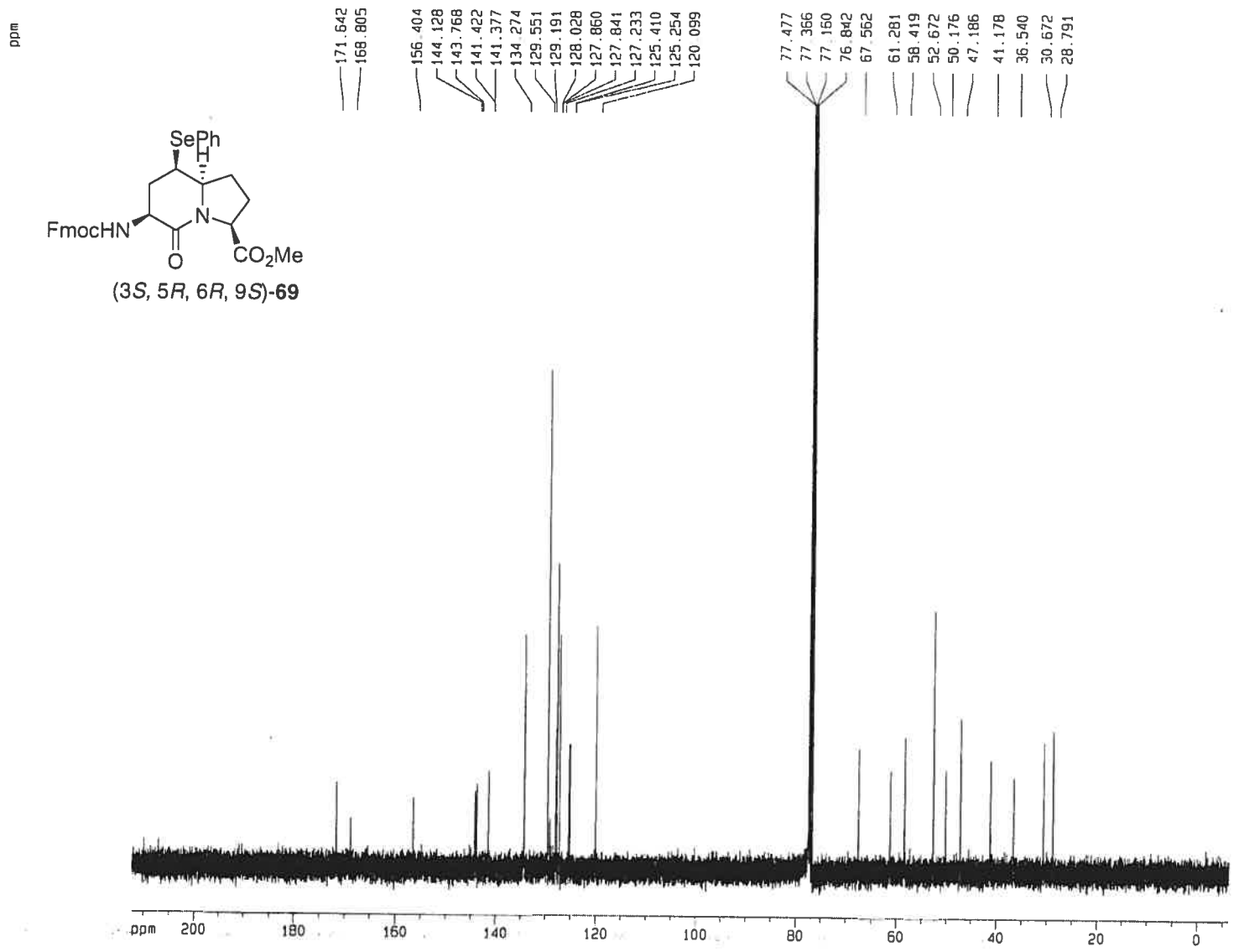

ppm
0
1
2
3
4
5
6
7
8
9
ppm
9
8
7
6
5
4
3
2
1
I
H
N
BocHN
O
CO2Me
(3S, 6R, 7S, 10S)-68

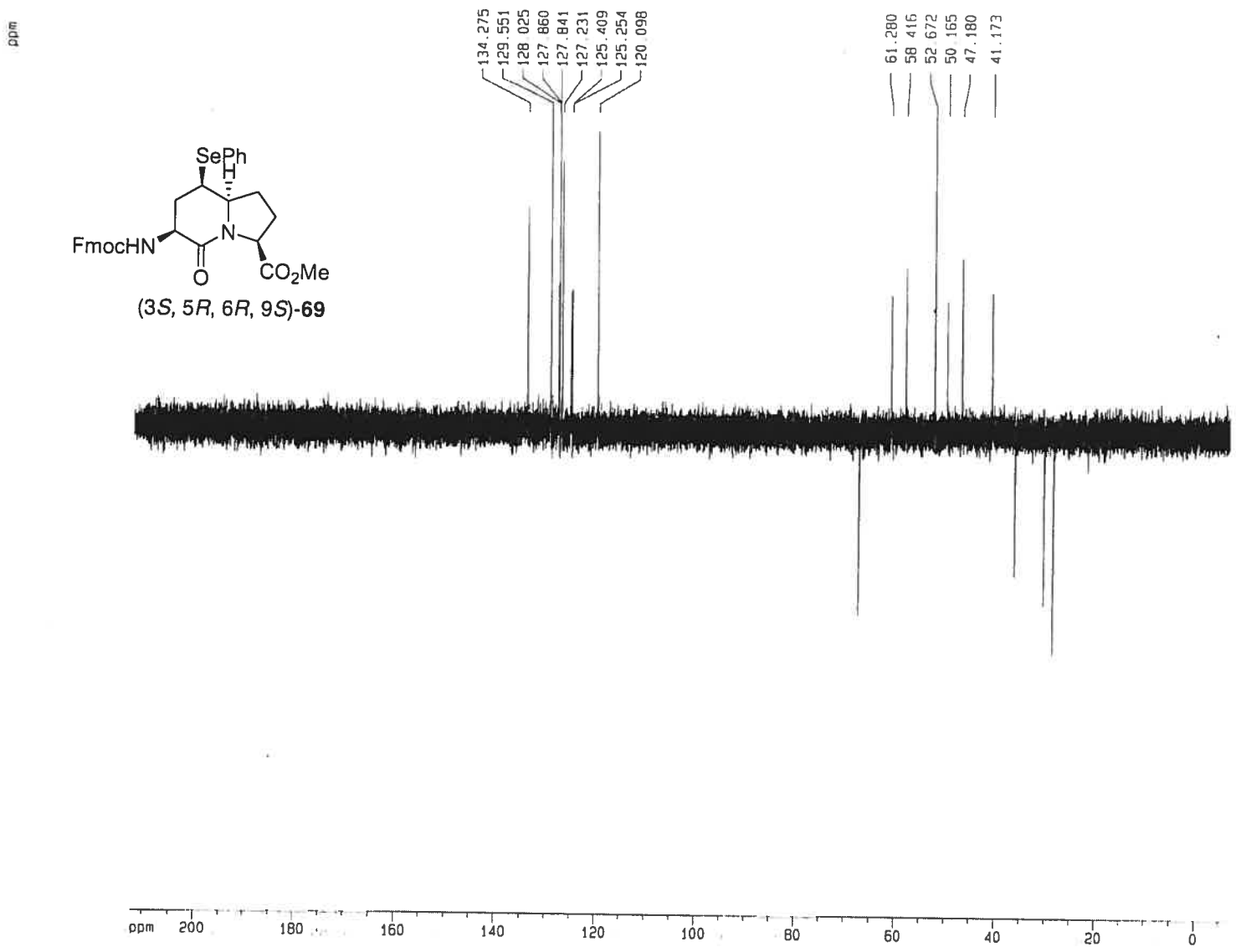

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
I
H
N
BocHN
O
CO2Me
(3S, 6R, 7S, 10S)-68
9
8
7
6
5
4
3
2
1
ppm


I
H
N
BocHN
O
CO2Me
(3S, 6R, 7S, 10S)-68
5.0
0.0
ppm (f2)

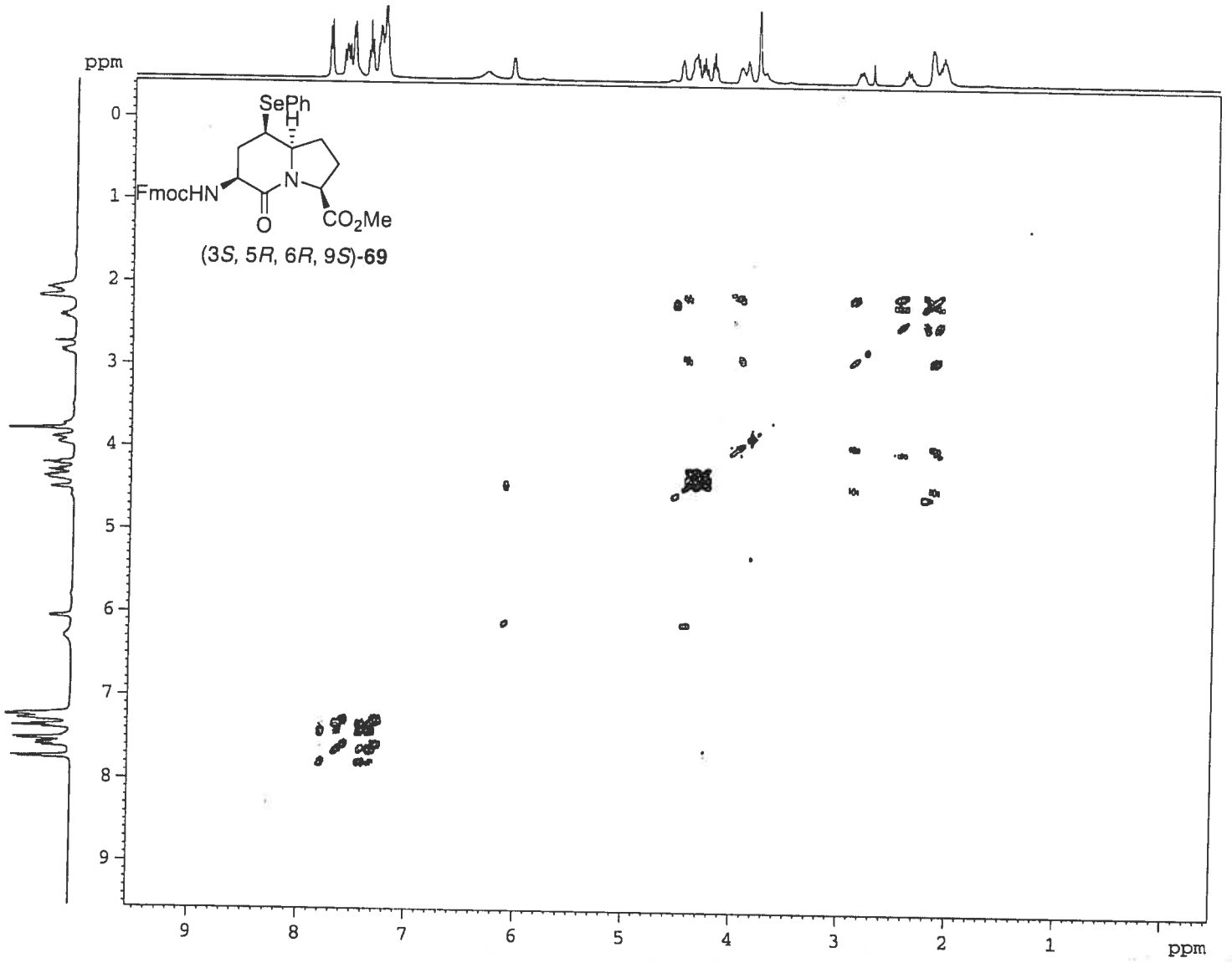

ppm
7.76979
7.75166
7.63402
7.61549
7.60268
7.58363
7.55258
7.53653
7.39580
7.37695
7.32681
7.30878
7.29739
7.27830
7.26006
7.25324
7.24376
6.08190
6.06653
4.51242
4.39717
4.38024
4.36179
4.32880
4.31010
4.23590
4.21868
3.91316
3.90129
3.80846
2.74375
2.20448
2.19291
2.12866
2.11044
2.09425
SePh
H
N
FmocHN
O
CO2Me
Integral
1.9078
1.3956
3.0135
1.5178
6.4859
1.0462
0.9502
0.8786
1.6602
1.2447
1.2993
0.5158
1.2921
3.5377
0.8554
1.0421
4.3190
ppm
10
8
6
4
2
0

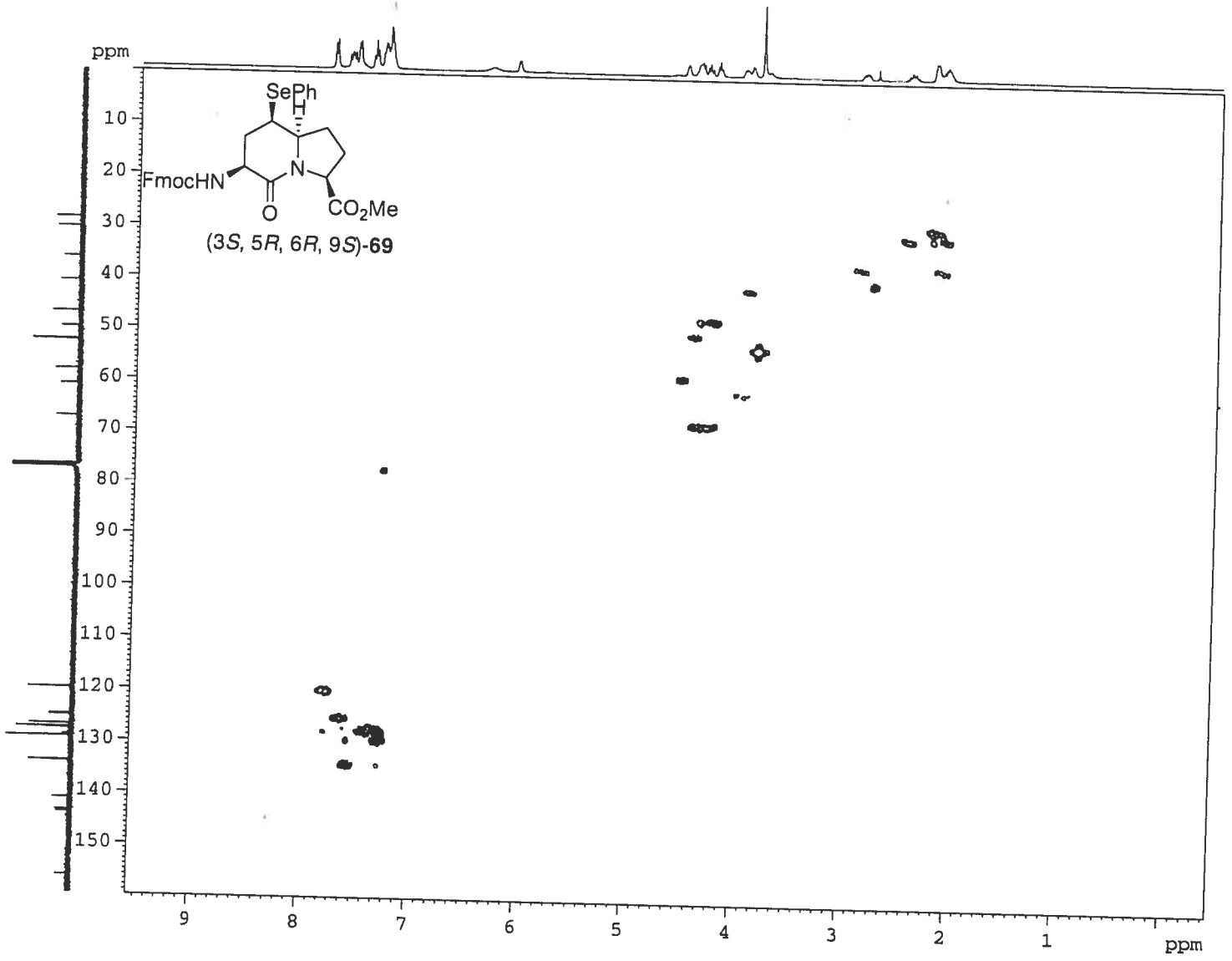
(3*S*, 5*R*, 6*R*, 9*S*)-**69**

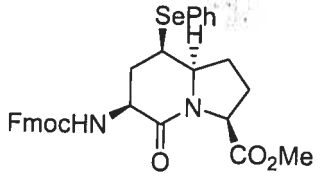

ppm
171.642
168.805
156.404
144.128
143.768
141.422
141.377
134.274
129.551
129.191
128.028
127.860
127.841
127.233
125.410
125.254
120.099
77.477
77.366
77.160
76.842
67.562
61.281
58.419
52.672
50.176
47.186
41.178
36.540
30.672
28.791
SePh
H
FmocHN
N
O
CO2Me
(3S, 5R, 6R, 9S)-69
ppm 200 180 160 140 120 100 80 60 40 20 0


ppm
134.275
129.551
128.025
127.860
127.841
127.231
125.409
125.254
120.098
61.280
58.416
52.672
50.165
47.180
41.173
SePh
H
FmocHN
N
O
CO2Me
(3S, 5R, 6R, 9S)-69
ppm 200
180
160
140
120
100
80
60
40
20
0

Bxxx


ppm
SePh
H
N
FmocHN
O
CO_2Me
(3S, 5R, 6R, 9S)-69
0
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
ppm


ppm
SePh
H
FmocHN
N
O
CO2Me
(3S, 5R, 6R, 9S)-69
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9
8
7
6
5
4
3
2
1
ppm



(3*S*, 5*R*, 6*R*, 9*S*)-**69**

9-(4-Bromophenyl)-9-fluorenyl as a Safety-Catch Nitrogen Protecting Group

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Supporting Information

Table of contents

General Experimental Section. Unless otherwise noted, all reactions were performed under argon atmosphere and distilled solvents were transferred by syringe. Anhydrous CH_2Cl_2 was obtained from a solvent filtration system. Final reaction mixture solutions were dried over anhydrous $MgSO_4$, filtered and rotary-evaporated under reduced pressure. Unless otherwise noted, ^1H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane ($(CH_3)_4Si$), residual $CHCl_3$ (δ 7.27 and 77.2 ppm), C_6D_6 (δ 7.16 and 128.1 ppm), CD_3OD (3.31 and 49.0 ppm) or D_2O (4.79). Aromatic carbons of compounds having a PhF group or a derivative are reported as seen on spectra. Analytical thin-layer chromatography (TLC) was performed by using glass-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Compounds were purified by column chromatography using 230-400 mesh silica gel.

(2*S*)-*N*-(MPF)Alanine *tert*-Butyl Ester (75) Chromatography of the product from **74** (230 mg, 0.50 mmol) using 20 % EtOAc in hexanes as eluant gave **75** (186 mg, 79 % yield) as a white foam: mp 63-65°C; $[\alpha]^{20}_D$ −115.7° (*c* 1.1, CH_3OH); ^1H NMR δ 7.69 (dd, *J* = 7.6 Hz, 1.1 Hz, 2H), 7.36-7.23 (m, 8H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.83 (t, *J* = 4.8 Hz, 4H), 3.11 (t, *J* = 4.8 Hz, 4H), 2.78 (q, *J* = 7.1 Hz, 1H), 1.23 (s, 9H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 176.4, 150.5, 141.0, 140.5, 128.4, 128.2, 128.1, 127.5, 126.3, 125.6, 120.3, 120.1, 115.6, 80.7, 73.1, 67.3, 52.4, 49.6, 28.3, 22.6; HRMS calcd for $C_{30}H_{34}N_2O_3Na$ $[M + Na]^+$ 493.2461, found 493.2459.

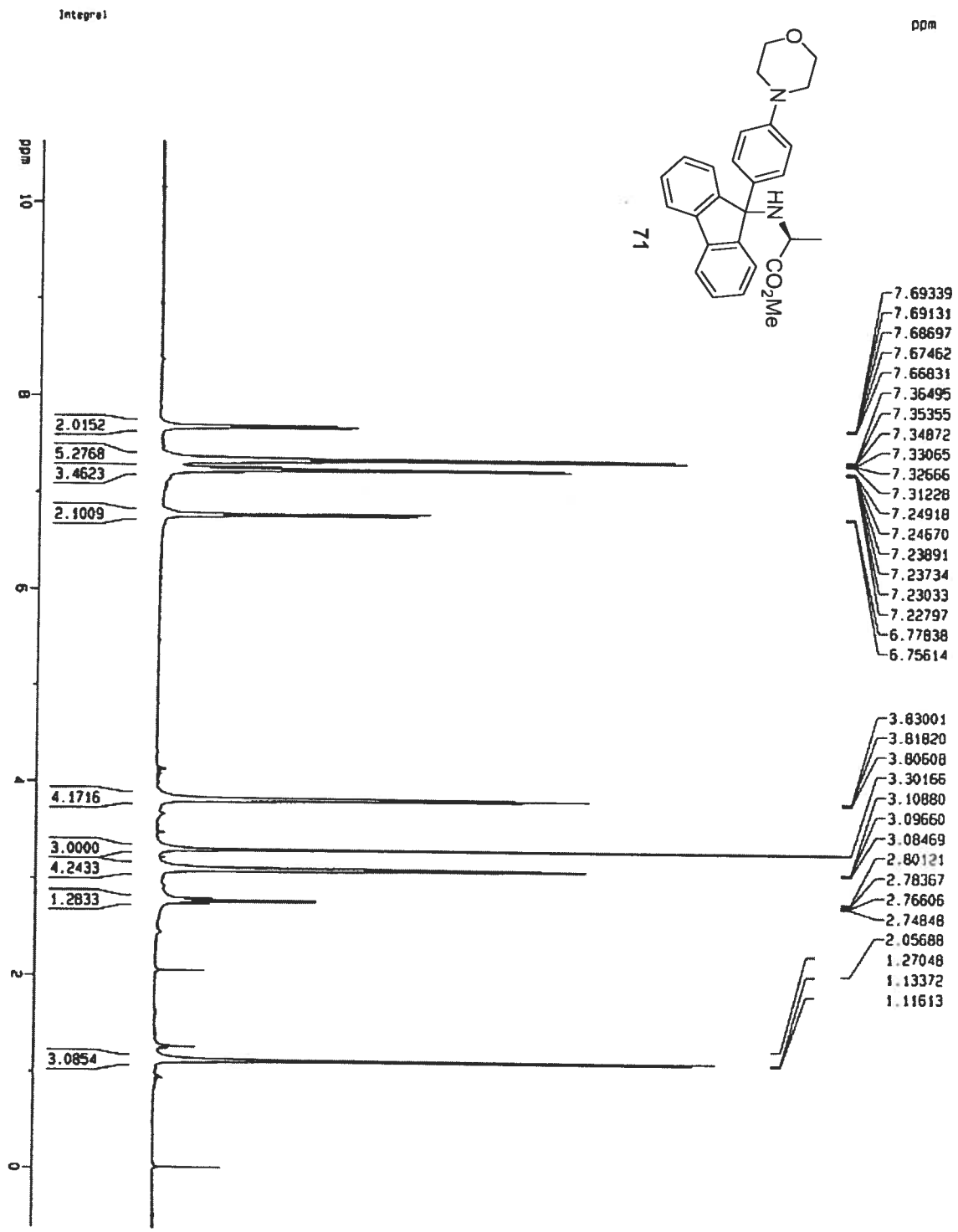
***N*-(MPF)-Alaninyl-(ω-Boc)lysine *tert*-butyl ester (81)** Chromatography of the product from **80** (300 mg, 0.43 mmol) using 50 % EtOAc in hexanes as eluant gave **81** (235 mg, 78 % yield) as a yellowish oil; $[\alpha]^{20}_D$ 12.5° (*c* 1.0, CH_3OH); ^1H NMR (C_6D_6) δ 7.88 (m, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.61 (m, 3H), 7.37-7.18 (m, 5H), 6.72 (d, *J* = 8.9 Hz, 2H), 4.68 (m, 1H), 4.47 (m, 1H), 3.60 (t, *J* = 4.8 Hz, 4H), 3.11 (m, 2H), 2.84 (m, 1H), 2.77 (t, *J* = 4.8 Hz, 4H), 1.89 (m, 1H), 1.66 (m, 1H), 1.55 (s, 9H), 1.47 (s, 9H), 1.35 (m, 4H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (C_6D_6) δ

175.2, 172.7, 151.2, 150.7, 149.4, 141.8, 140.5, 135.9, 128.8, 128.7, 127.6, 127.4, 126.8, 125.1, 120.5, 120.4, 116.0, 81.6, 78.4, 73.6, 67.0, 53.3, 52.3, 49.4, 40.7, 33.5, 28.7, 28.2, 28.1, 22.7, 22.2; HRMS calcd for $C_{41}H_{54}N_4O_6Na$ $[M + Na]^+$ 721.39356, found 721.39346.

(2*S*)-*N*-(Boc)Alanine Methyl Ester (77) Chromatography of the product from **71** (50 mg, 0.12 mmol) using 10 % EtOAc in hexanes as eluant gave **77** as a white solid (19.0 mg, 79 % yield): mp 31-33°C, lit.[21] mp 30°C; $[\alpha]^{20}_D$ –45.1° (*c* 1.0, CH_3OH), lit.[21] $[\alpha]^{20}_D$ –44° (*c* 1.0, CH_3OH). The ^1H and ^{13}C NMR spectral data were consistent with the literature.[21]

(2*S*)-*N*-(Boc)Alanine *tert*-Butyl Ester (79) Chromatography of the product from **75** (50 mg, 0.11 mmol) using 10 % EtOAc in hexanes as eluant gave **79** as a clear oil (22.8 mg, 84 % yield): $[\alpha]^{20}_D$ –36.7° (*c* 1.0, CH_3OH), lit.[22] $[\alpha]^{20}_D$ –38.1° (*c* 1.0, CH_3OH). The ^1H and ^{13}C NMR spectral data were consistent with the literature.[23]

***N*-(Methyl carbamoyl)alaninyl-ω-(Boc)lysine *tert*-butyl ester (82)** Chromatography of the product from **81** (20 mg, 0.029 mmol) using 60 % EtOAc in hexanes as eluant gave **82** as a yellowish oil (10.1 mg, 82 % yield): mp 105-106°C $[\alpha]^{20}_D$ –11.7° (*c* 1.1, $CHCl_3$); ^1H NMR (C_6D_6) δ 7.40 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 5.33 (bs, 1H), 4.76 (m, 1H), 4.44 (t, J = 6.9 Hz, 1H), 3.58 (s, 3H), 3.21 (m, 1H), 3.13 (m, 1H), 1.89 (m, 1H), 1.71 (m, 1H), 1.43 (s, 9H), 1.47 (d, J = 7.1 Hz, 3H) 1.43 (s, 9H), 1.45-1.40 (m, 4H); ^{13}C NMR (C_6D_6) δ 172.6, 171.1 156.7, 155.6, 80.7, 77.9, 52.6, 51.4, 50.1, 39.8, 31.6, 29.2, 28.0, 27.3, 22.3, 18.5; HRMS calcd for $C_{20}H_{37}N_3O_7Na$ $[M + Na]^+$ 454.25237, found 454.25195.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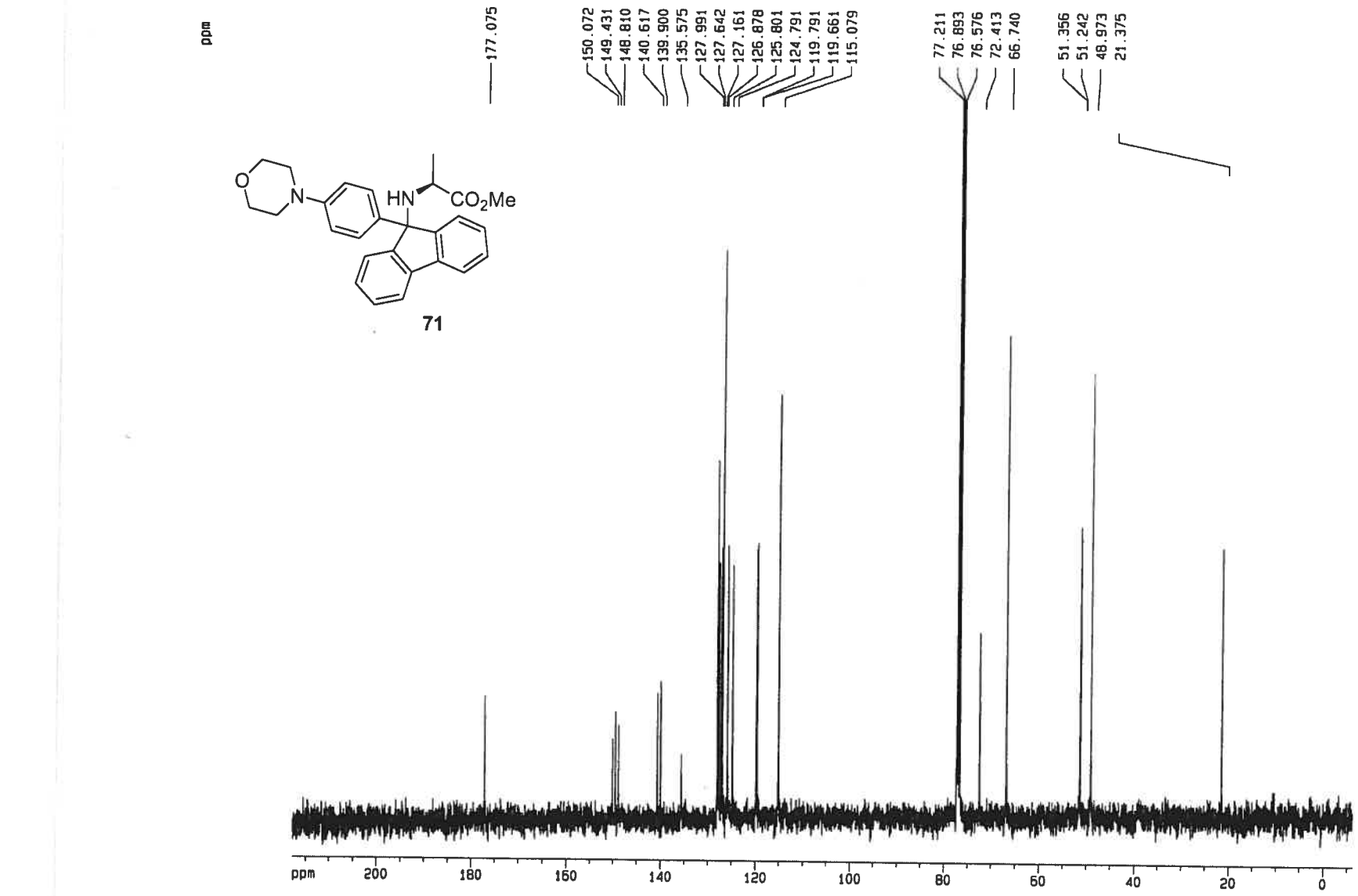
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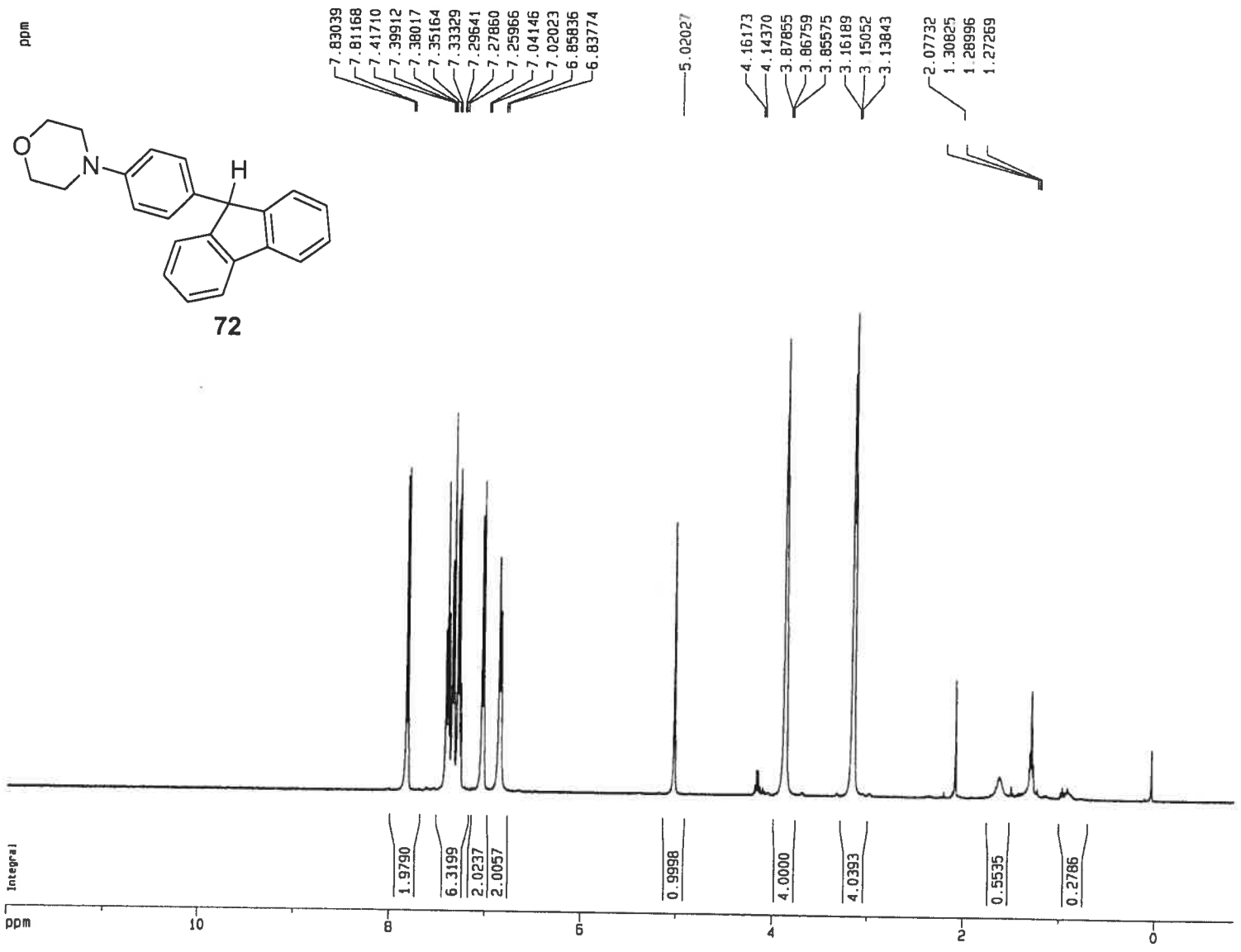
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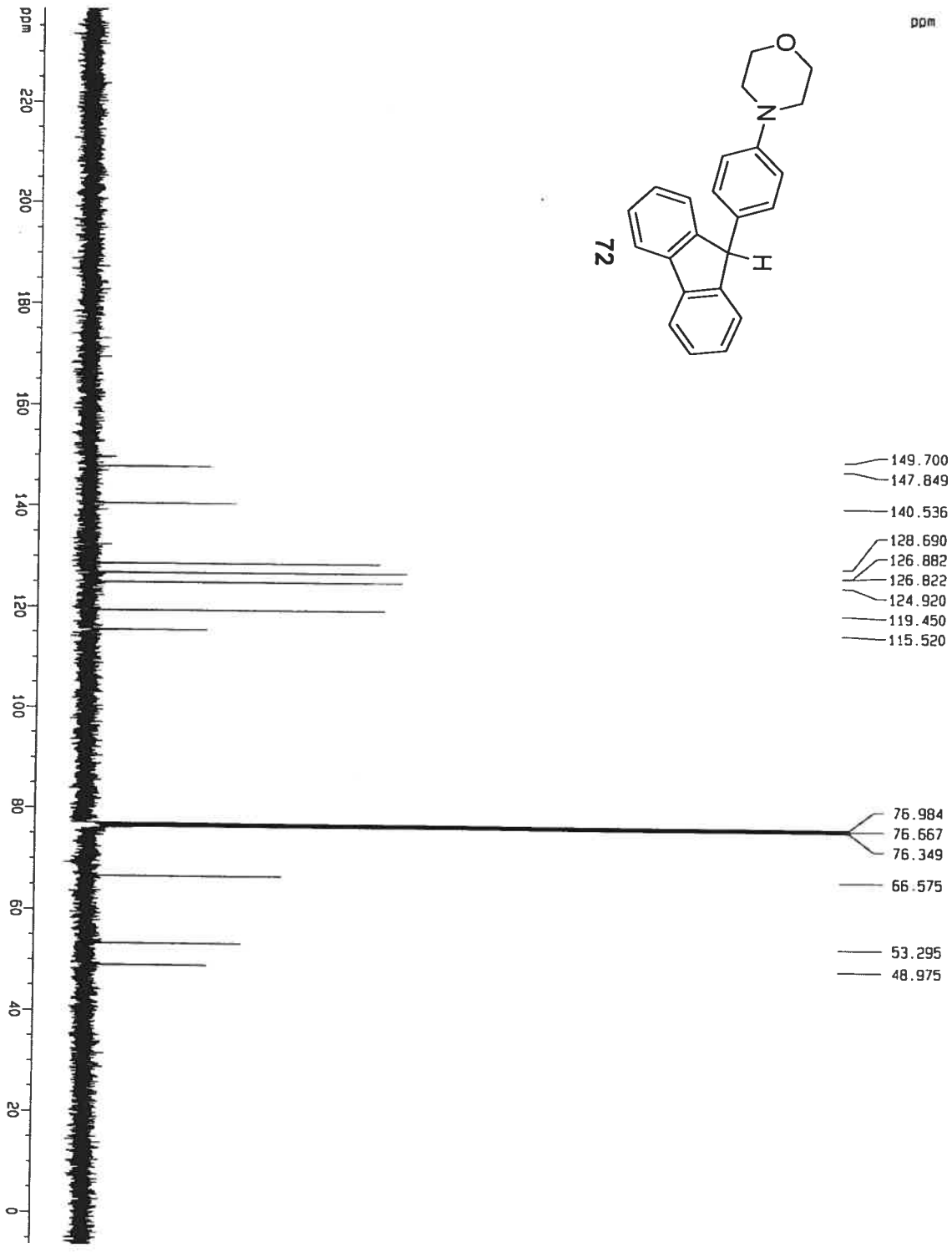
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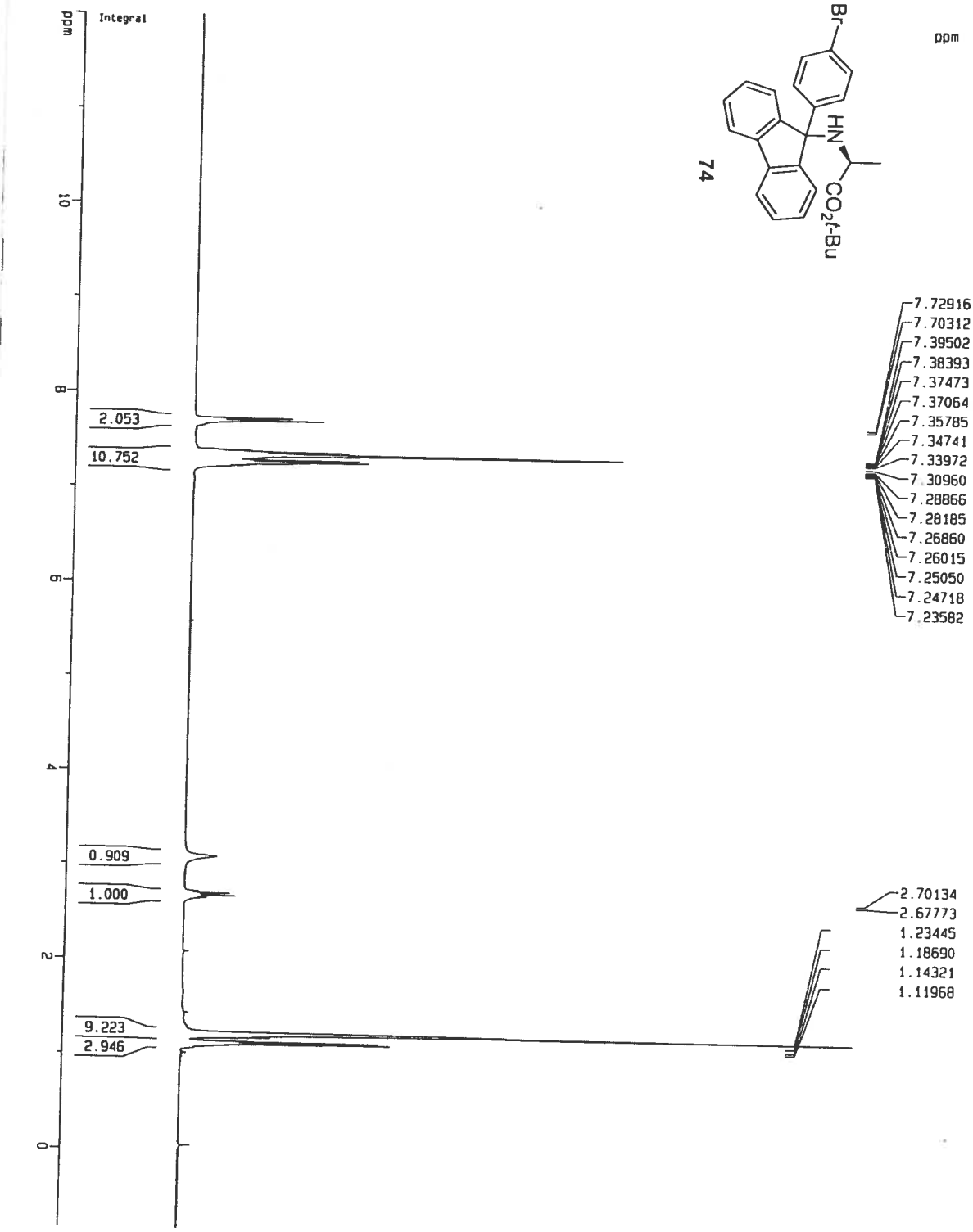
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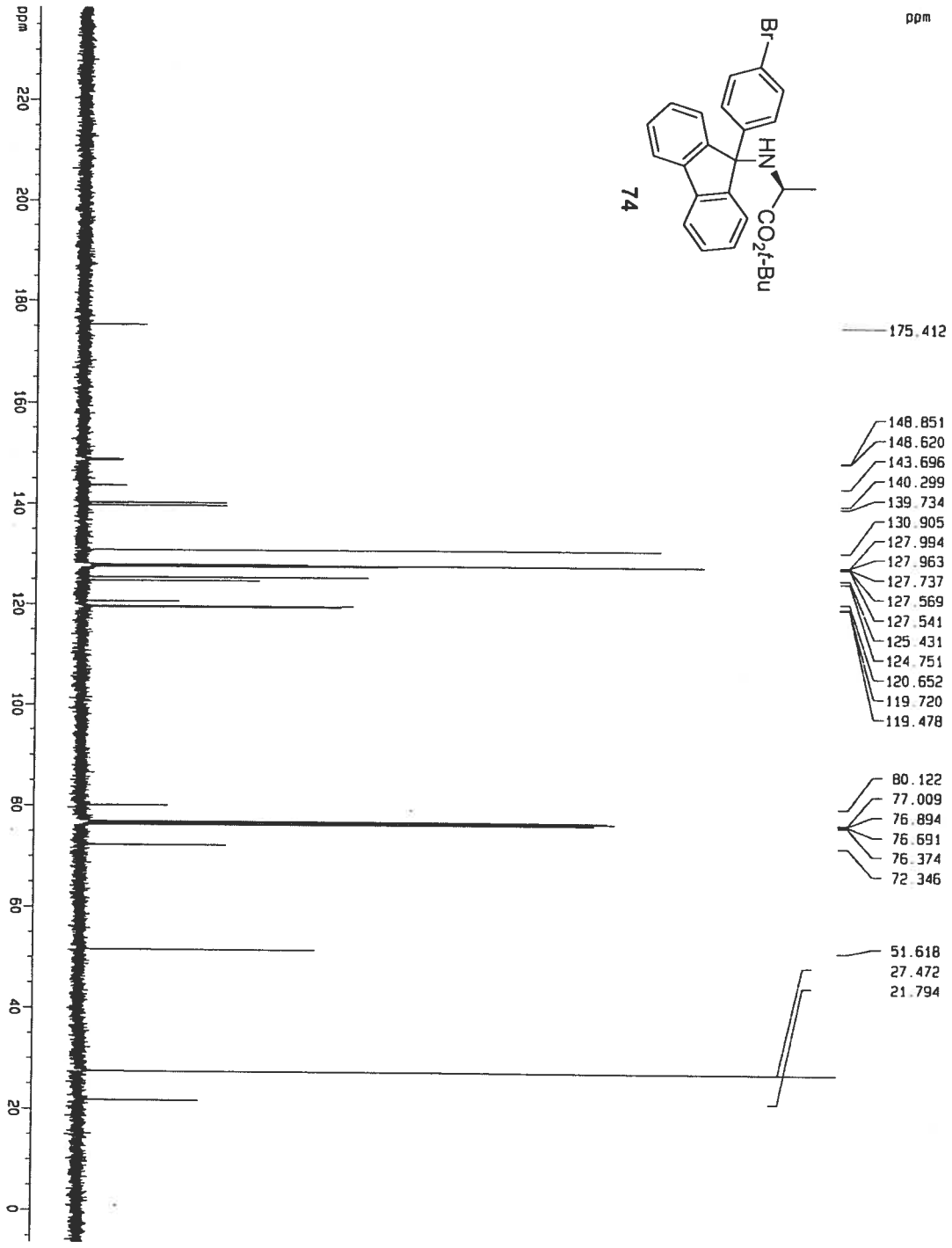
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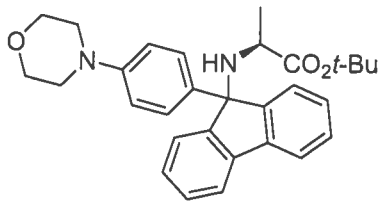
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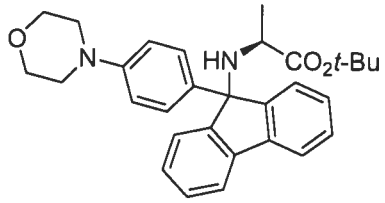

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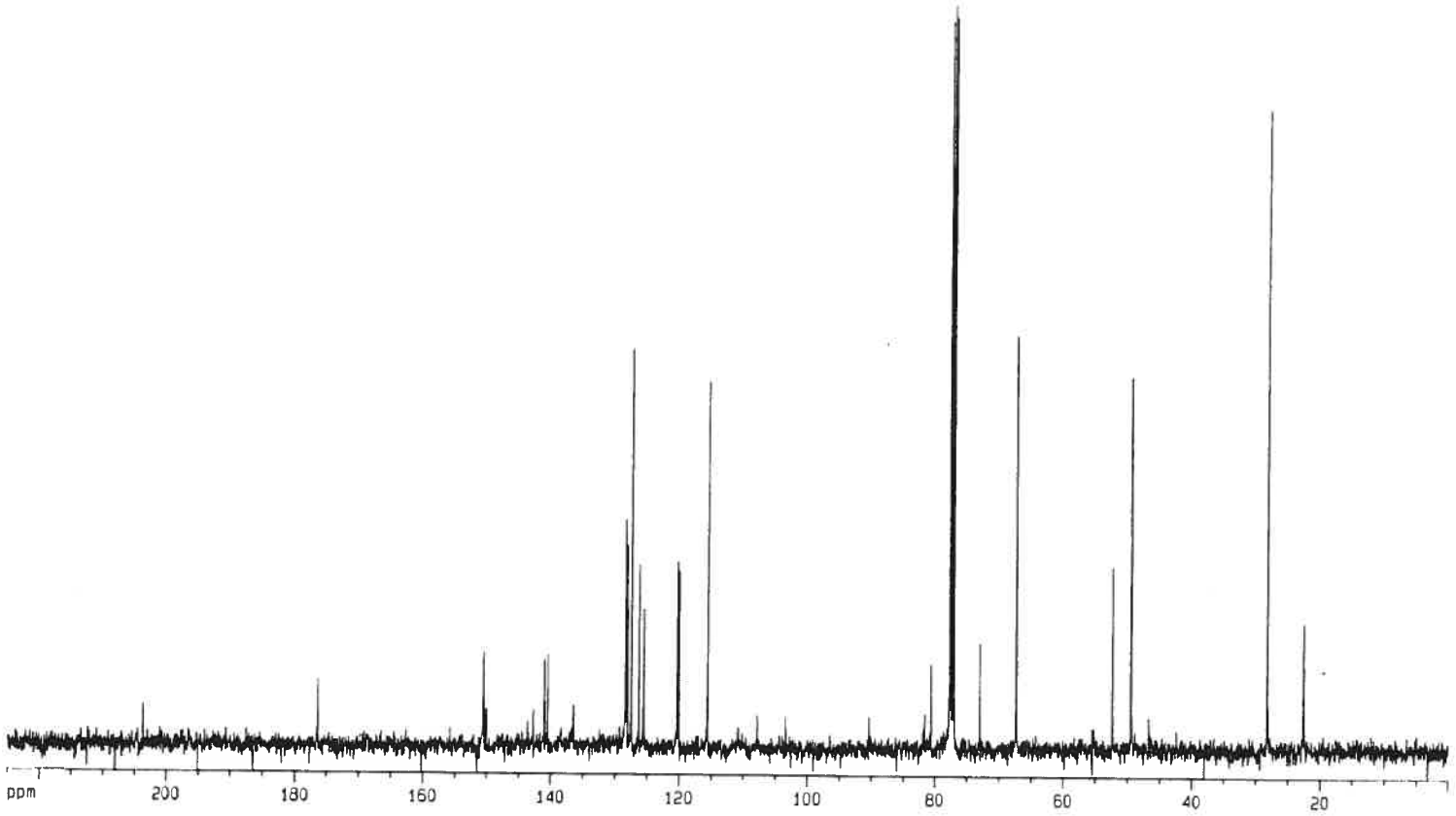

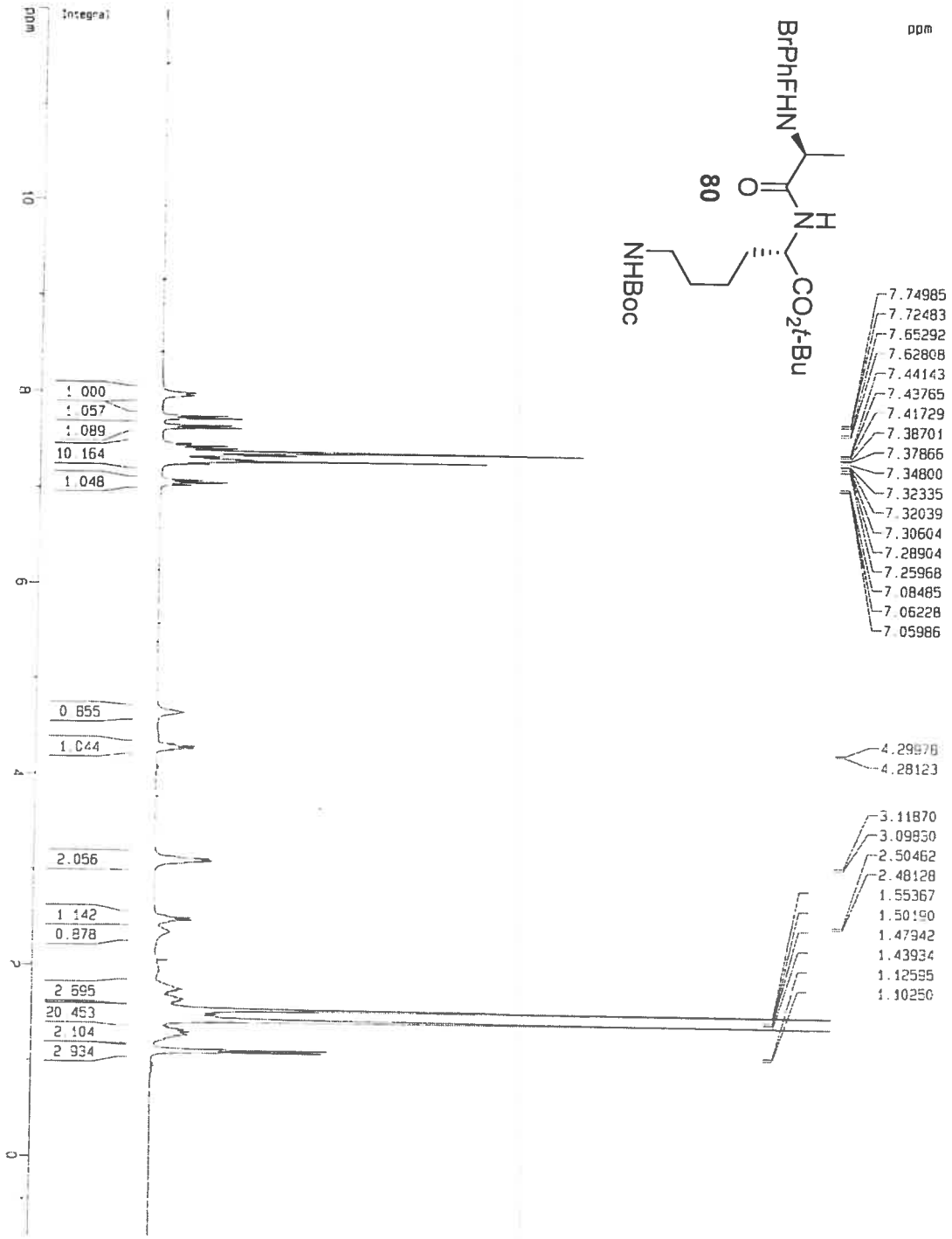
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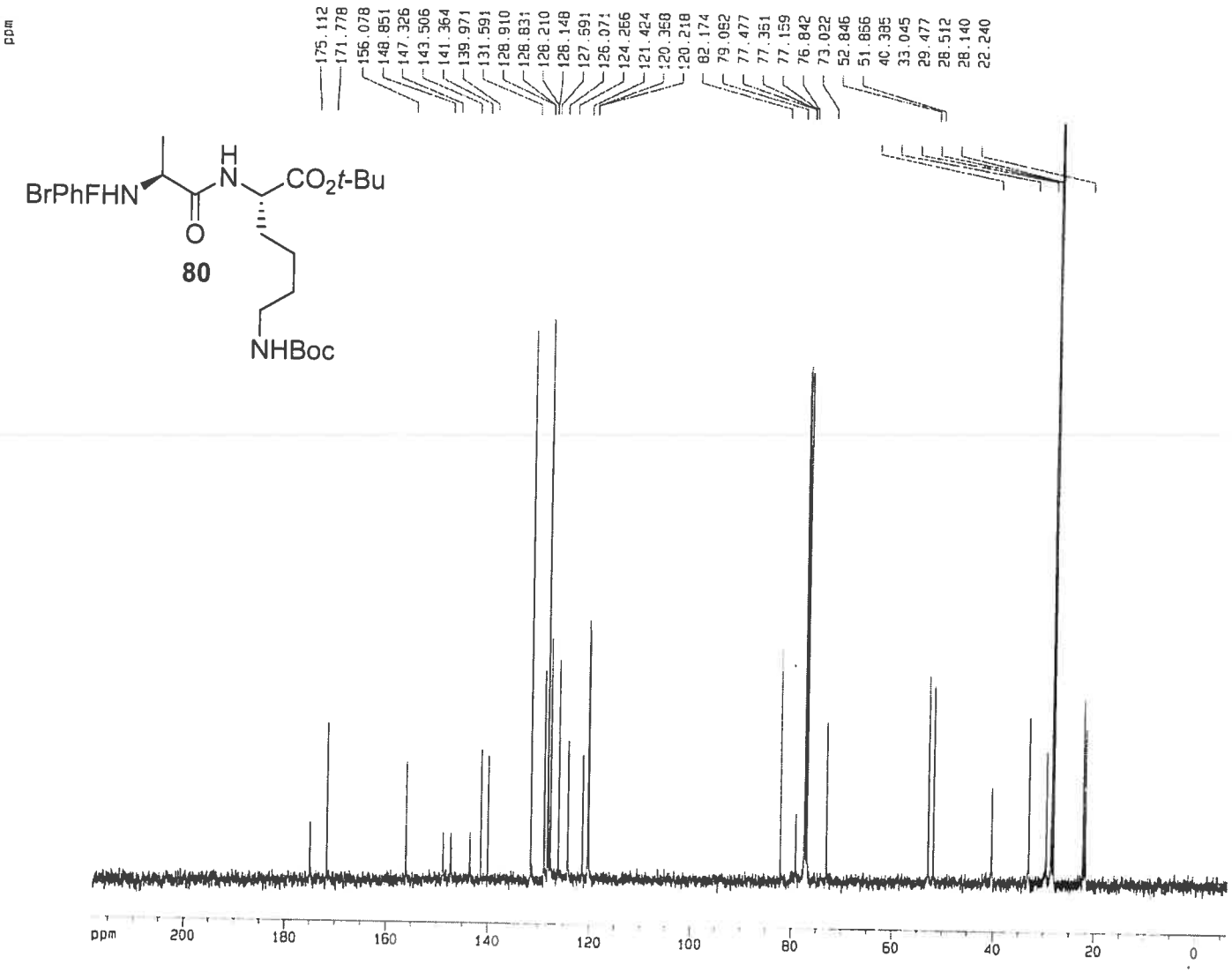
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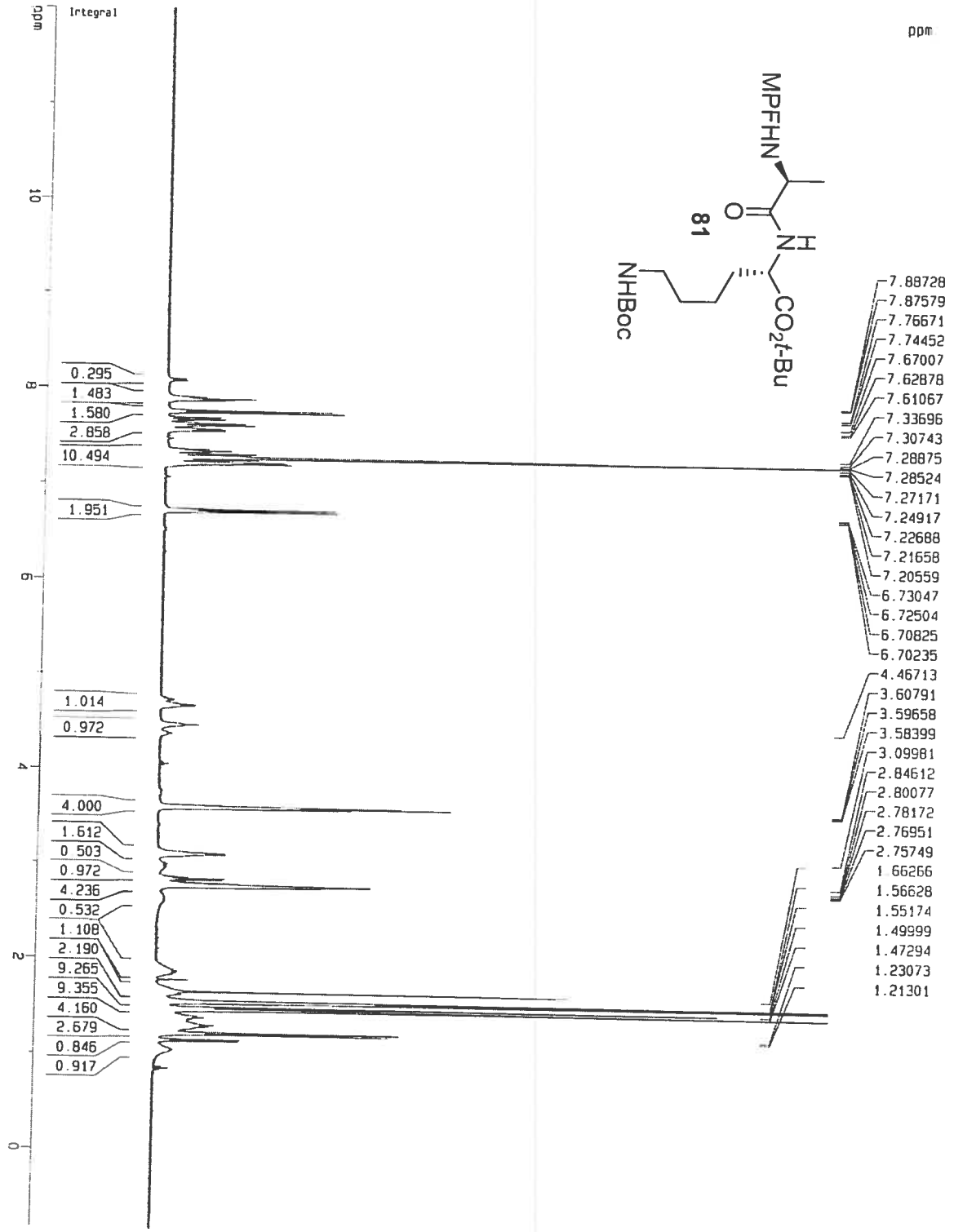
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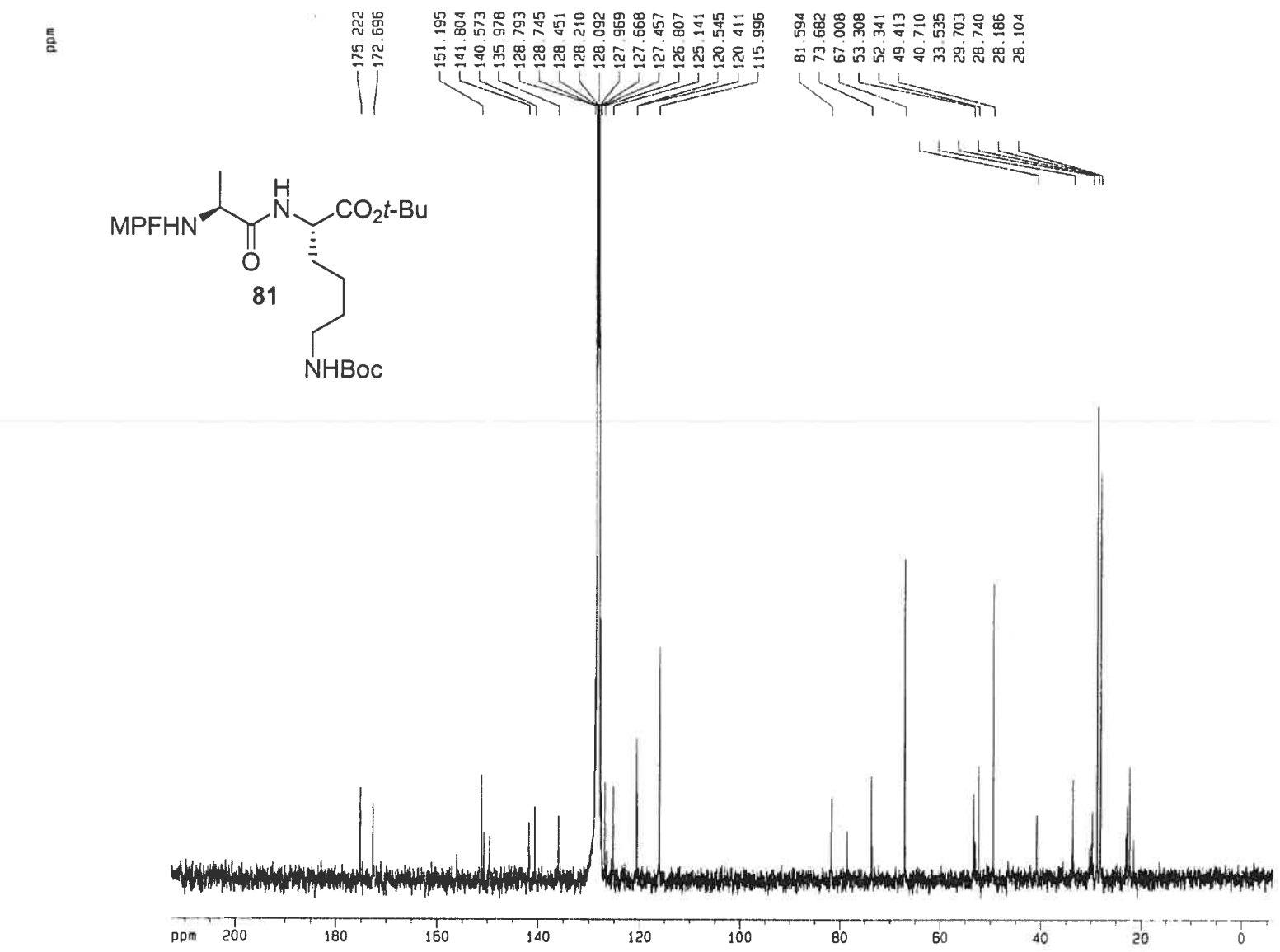
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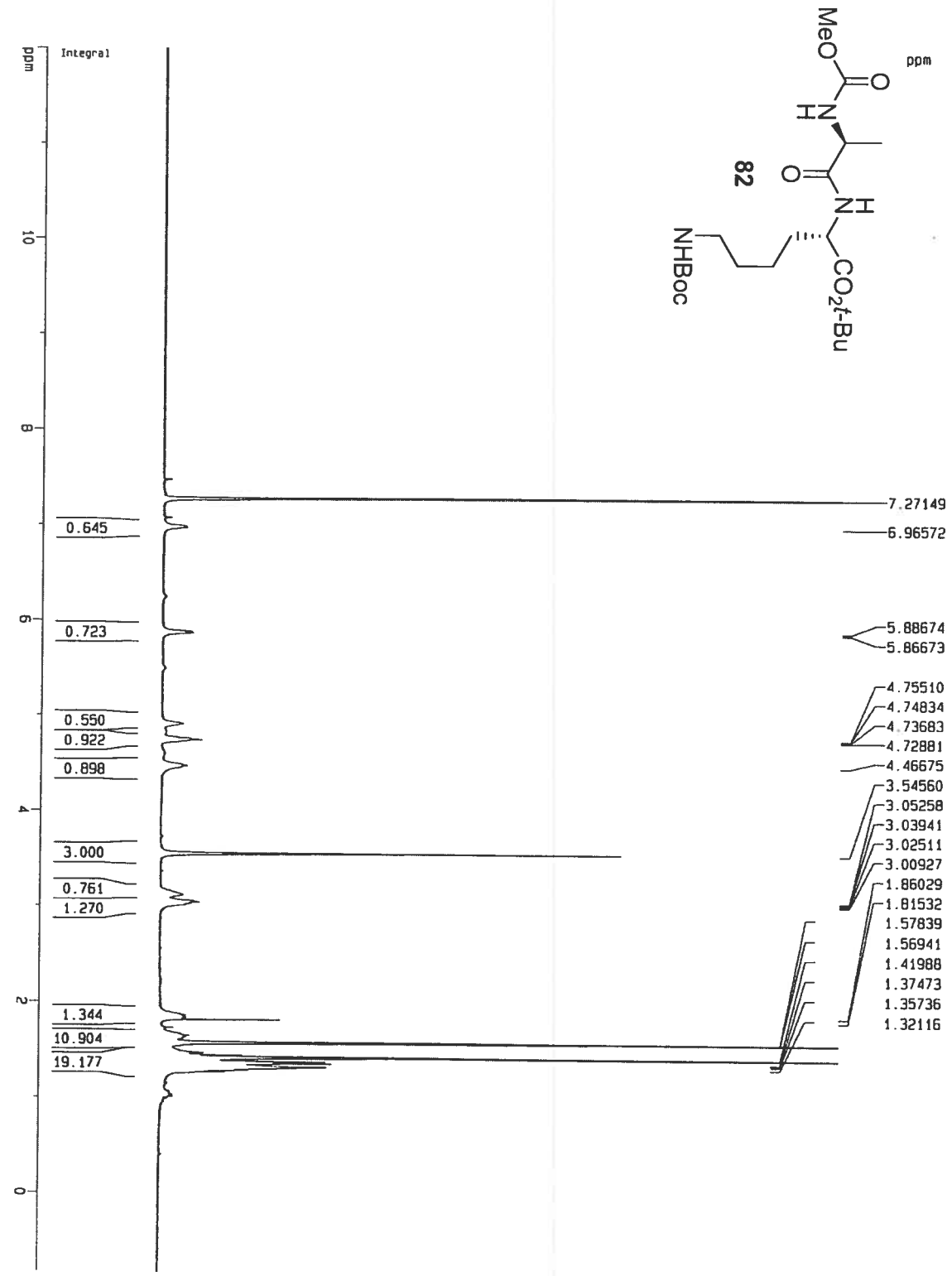
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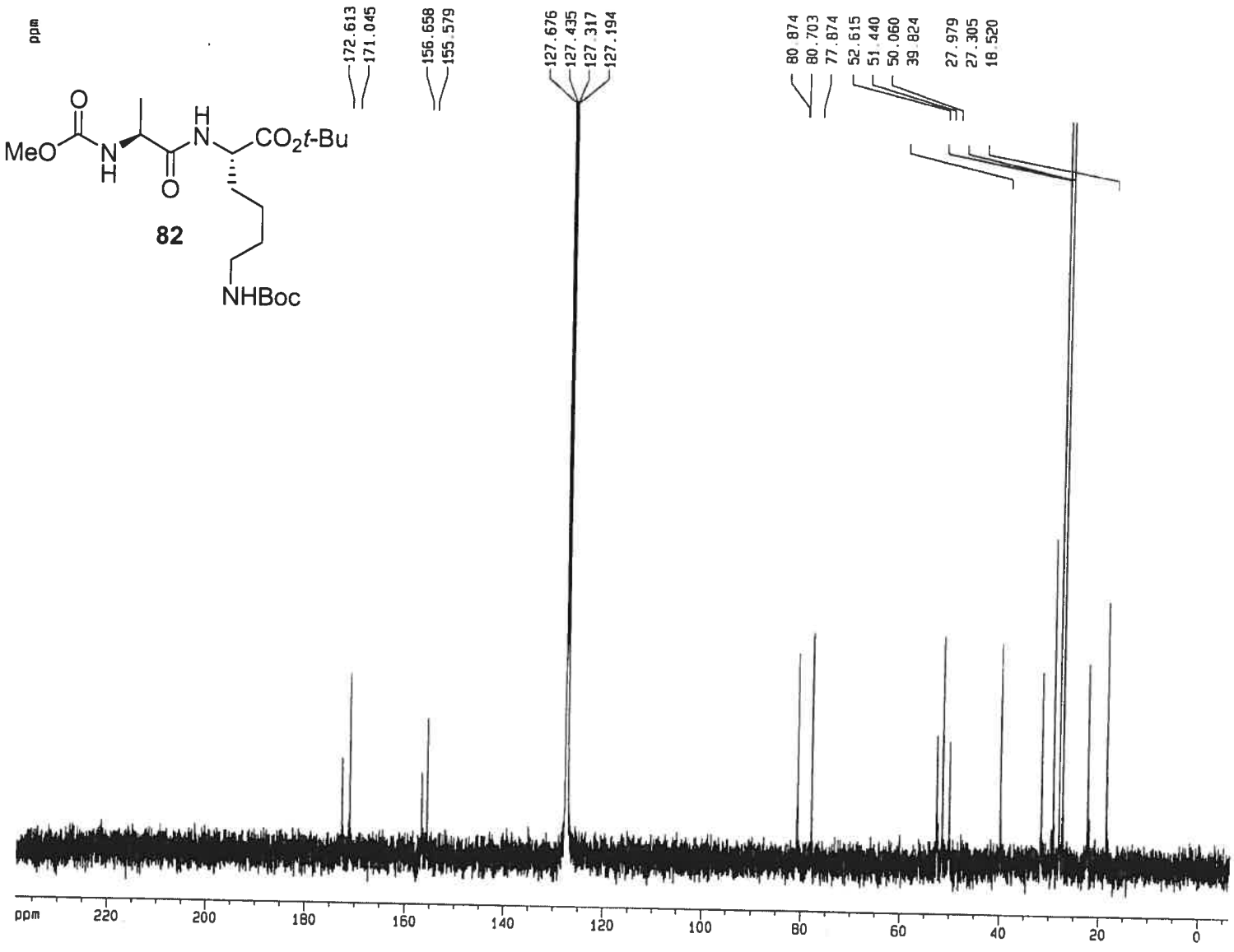
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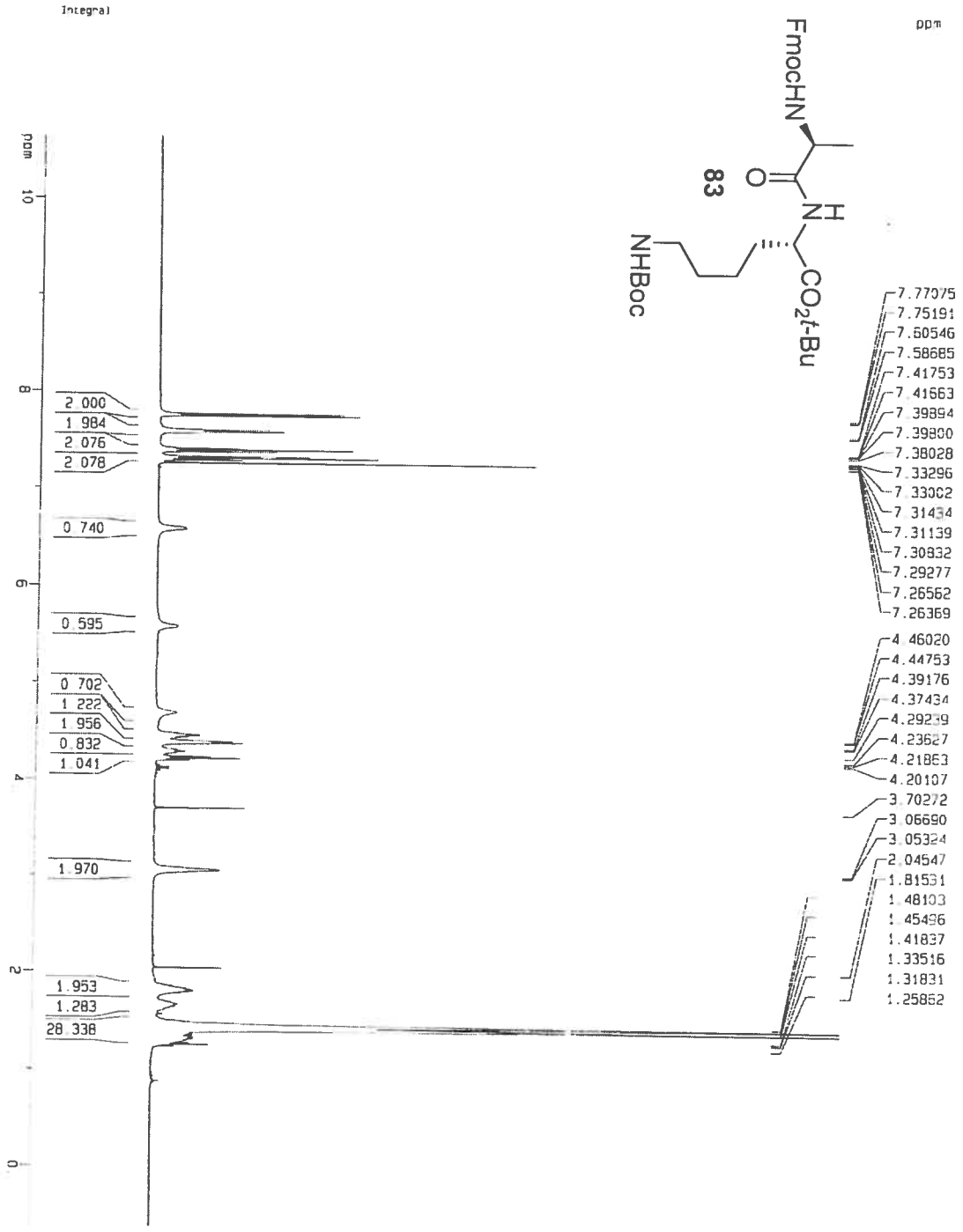
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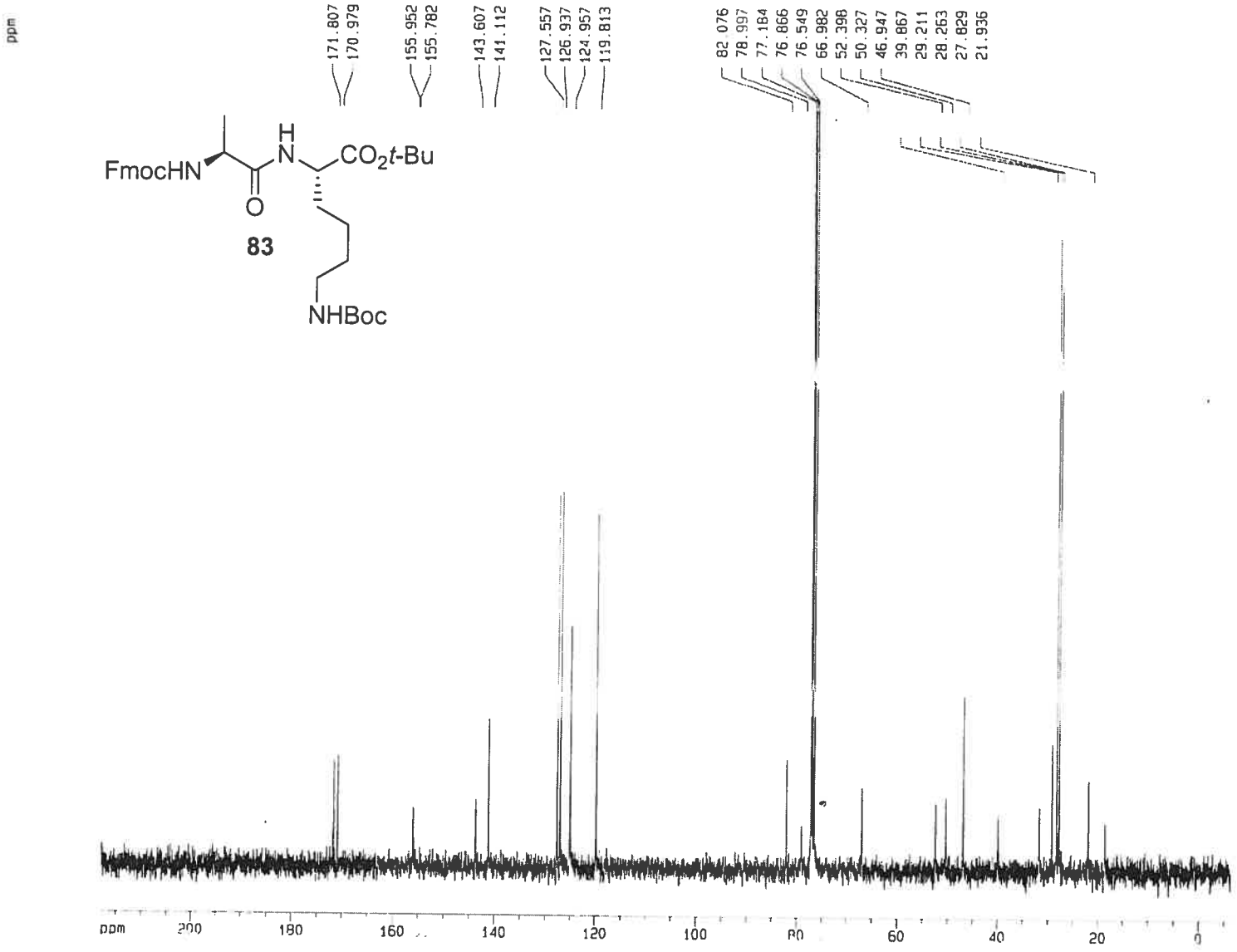
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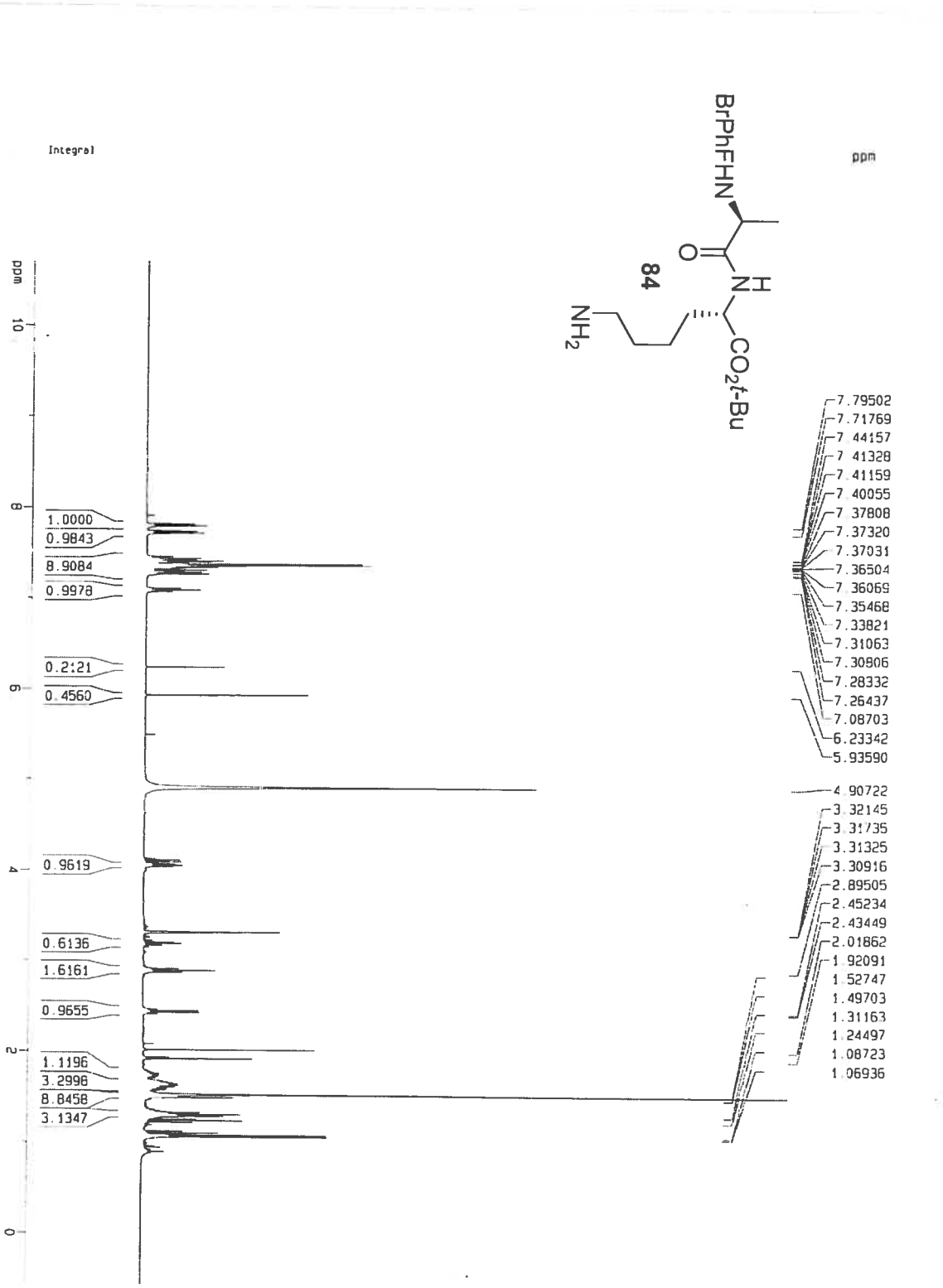
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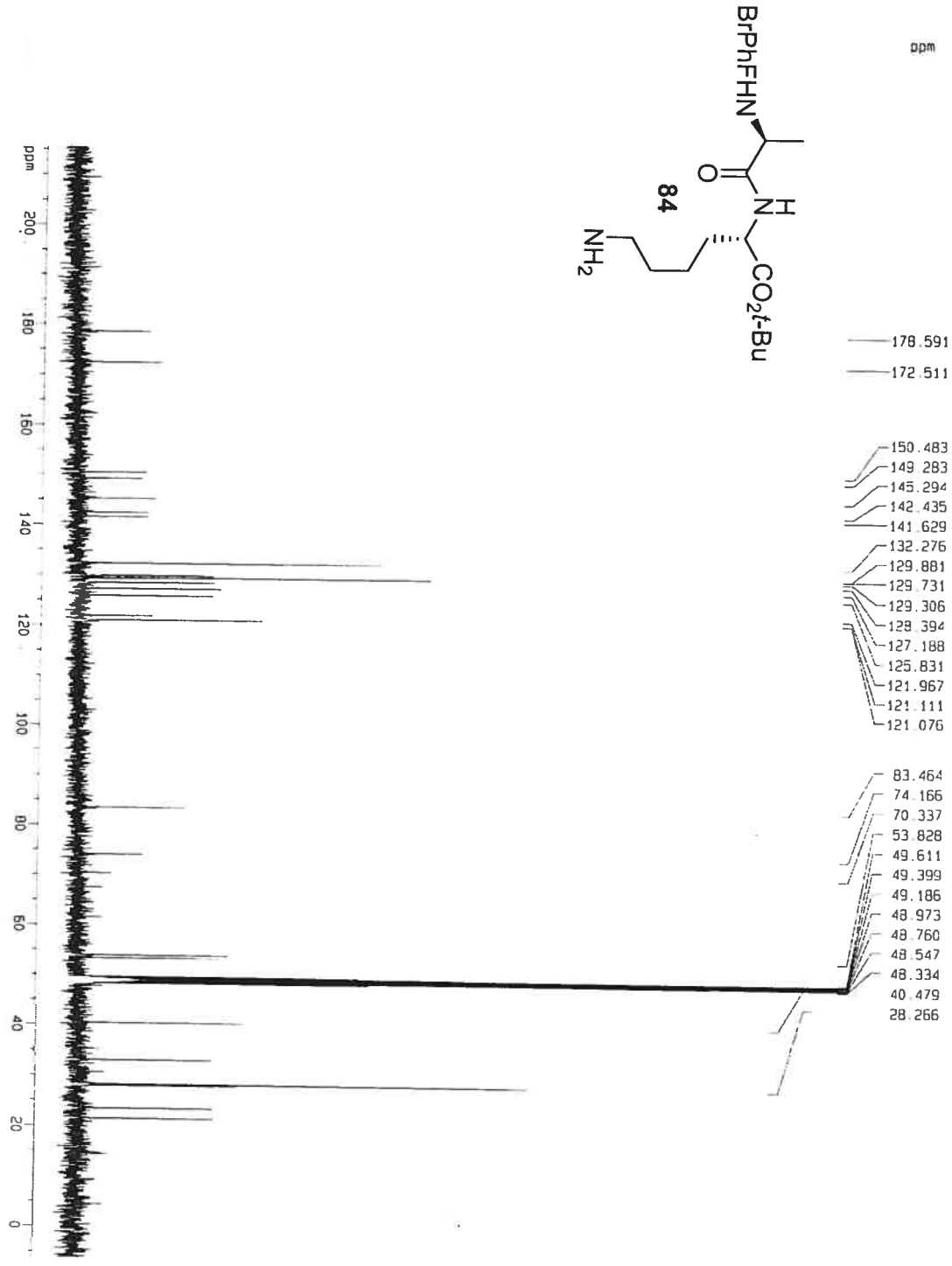
3.31735
3.31325
3.30916
2.89505
2.45234
2.43449
2.01862
1.92091
1.52747
1.49703
1.31163
1.24497
1.08723
1.06936


BrPhFHN
O
N
H
84
NH2
CO2t-Bu
ppm
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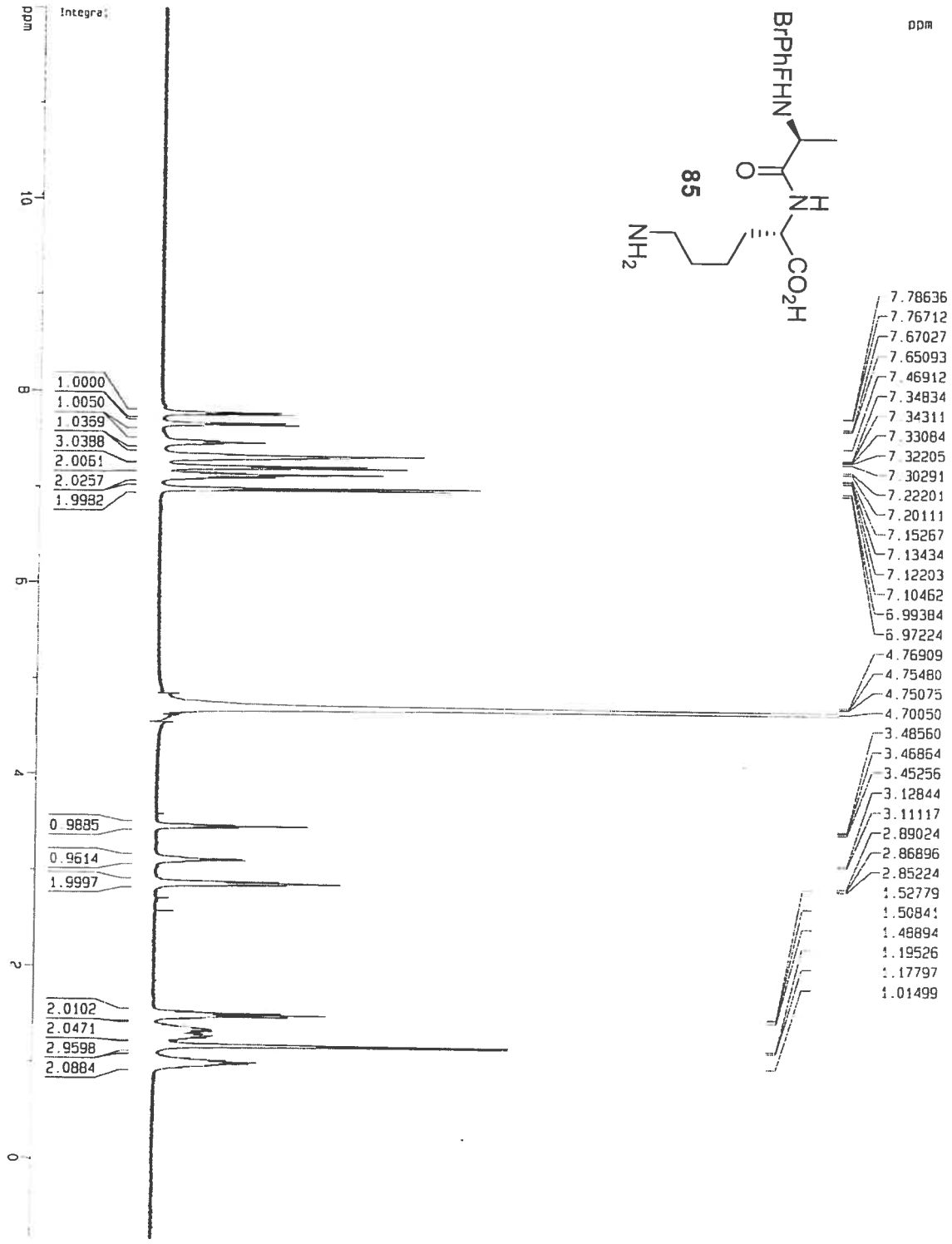
172.511
150.483
149.283
145.294
142.435
141.629
132.276
129.881
129.731
129.306
128.394
127.188
125.831
121.967
121.111
121.076
83.464
74.166
70.337
53.828
49.611
49.399
49.186
48.973
48.760
48.547
48.334
40.479
28.266
ppm
200
180
160
140
120
100
80
60
40
20
0


ppm
Integral
BrPhFHN
O
H
N
85
NH2
CO2H
ppm
7.78636
7.76712
7.67027
7.65093
7.46912
7.34834
7.34311
7.33084
7.32205
7.30291
7.22201
7.20111
7.15267
7.13434
7.12203
7.10462
6.99384
6.97224
4.76909
4.75480
4.75075
4.70050
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3.46864
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3.12844
3.11117
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2.85224
1.52779
1.50841
1.48894
1.19526
1.17797
1.01499
1.0000
1.0050
1.0359
3.0388
2.0051
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1.9982
0.9885
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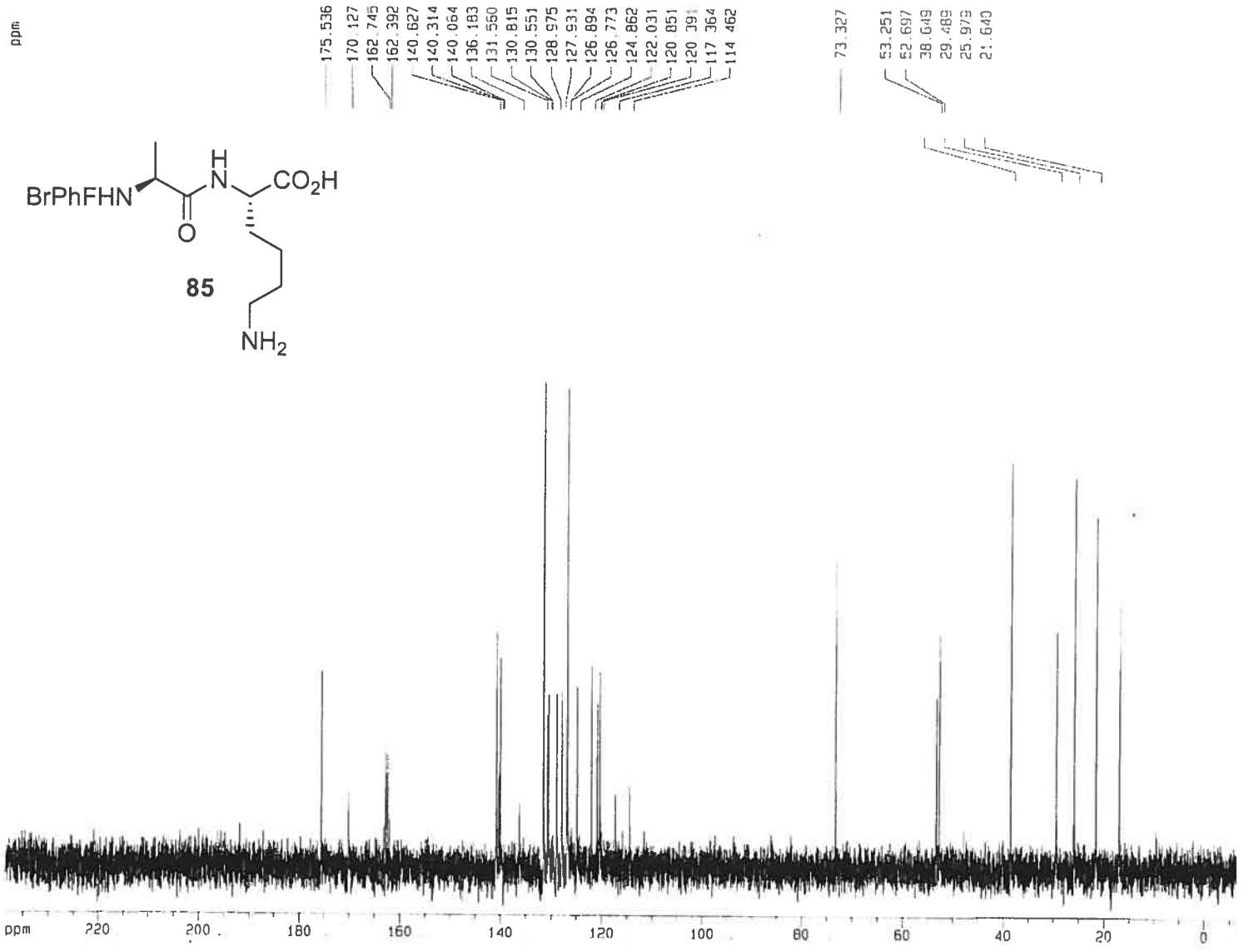
1.9997
2.0102
2.0471
2.9598
2.0884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162.392
140.627
140.314
140.064
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130.551
128.975
127.931
126.894
126.773
124.862
122.031
120.851
120.391
117.364
114.462
73.327
53.251
52.697
38.649
29.489
25.973
21.640
BrPhFHN
H
N
CO2H
O
85
NH2
ppm
220
200
180
160
140
120
100
80
60
40
20
0

Initial mixture

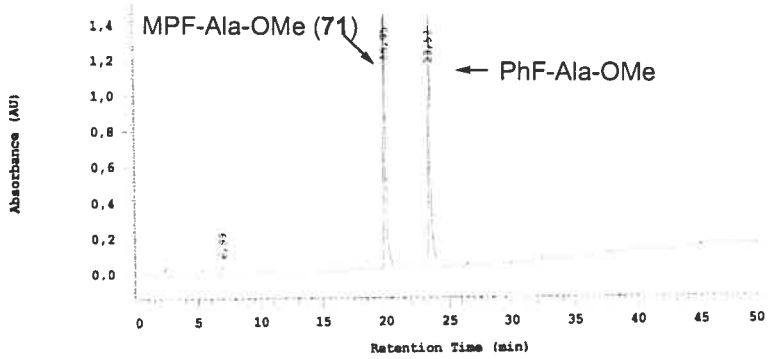
Series: 0877

D-7000 HPLC System Manager Report

Analyzed: 03/10/04 17:00 Reported: 04/10/04 10:32
Processed: 03/10/04 17:51

Data Path: D:\WIN32APP\HSM\samples\DATA\0877\
Processing Method :DAM OBTO100B-40min
Sample Name: Mix
Sample Description:

Chrom Type: Fixed WL Chromatogram, 214 nm



Acquisition Method: DAM
Gradient : OBTO100B-40min
0% B (100% A) to 100% B (0% A) in 40 min then 10 min at 100% B.
(A : H2O 0.1% TFA, B : ACN 0.1% TFA).

Developed by: DAM

Pump A Type: L-7100
Solvent A: H2O 0.1% TFAA Solvent B: ACN 0.1%TFAB
Solvent C: Solvent D:
Method Description: gradient 0B-100B_40 min_50min

Chrom Type: Fixed WL Chromatogram, 214 nm

After 20 min of solvolysis

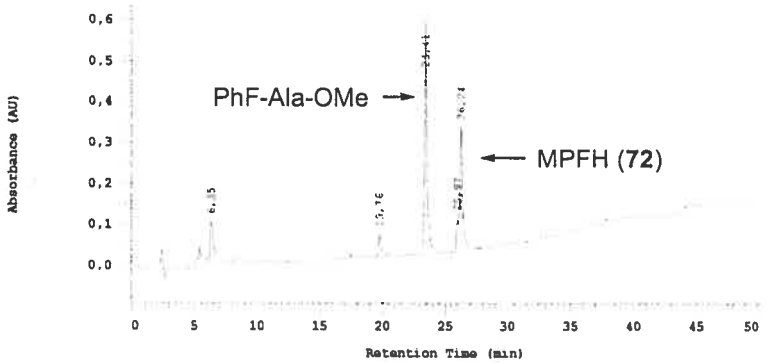
Series: 0883

D-7000 HPLC System Manager Report

Analyzed: 03/10/04 23:41 Reported: 04/10/04 10:26
Processed: 04/10/04 00:32

Data Path: D:\WIN32APP\HSM\samples\DATA\0883\
Processing Method :DAM OBTO100B-40min
Sample Name: 20 min
Sample Description:

Chrom Type: Fixed WL Chromatogram, 214 nm



Acquisition Method: DAM
Gradient : OBTO100B-40min
0% B (100% A) to 100% B (0% A) in 40 min then 10 min at 100% B.
(A : H2O 0.1% TFA, B : ACN 0.1% TFA).

Developed by: DAM

Pump A Type: L-7100
Solvent A: H2O 0.1% TFAA Solvent B: ACN 0.1%TFAB
Solvent C: Solvent D:
Method Description: gradient 0B-100B_40 min_50min

Chrom Type: Fixed WL Chromatogram, 214 nm

Initial mixture

Series: 1028

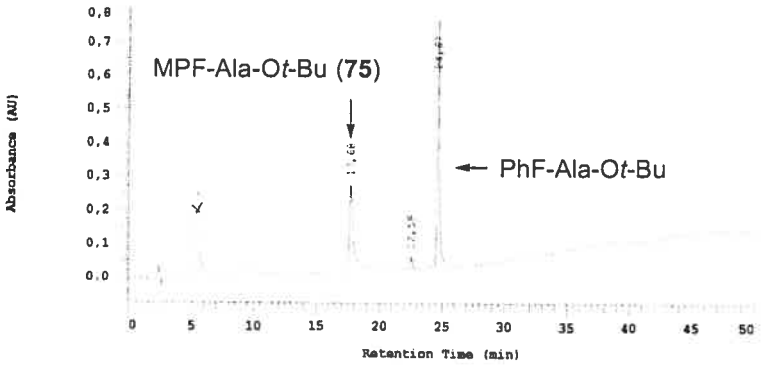
D-7000 HPLC System Manager Report

Analyzed: 21/10/04 23:10 Reported: 22/10/04 12:12
Processed: 22/10/04 00:01

Data Path: D:\WIN32APP\HSM\samples\DATA\1028\
Processing Method :DAM OBTO100B-40min

Sample Name: mix
Sample Description:

Chrom Type: Fixed WL Chromatogram, 214 nm



Acquisition Method: DAM
Gradient : OBTO100B-40min
0% B (100% A) to 100% B (0% A) in 40 min then 10 min at 100% B.
(A : H2O 0.1% TFA, B : ACN 0.1% TFA).

Developed by: DAM

Pump A Type: L-7100
Solvent A: H2O 0.1% TFAA Solvent B: ACN 0.1%TFAB
Solvent C: Solvent D:
Method Description: gradient 0B-100B_40 min_50min

Chrom Type: Fixed WL Chromatogram, 214 nm

After 5 min of solvolysis

Series: 1029

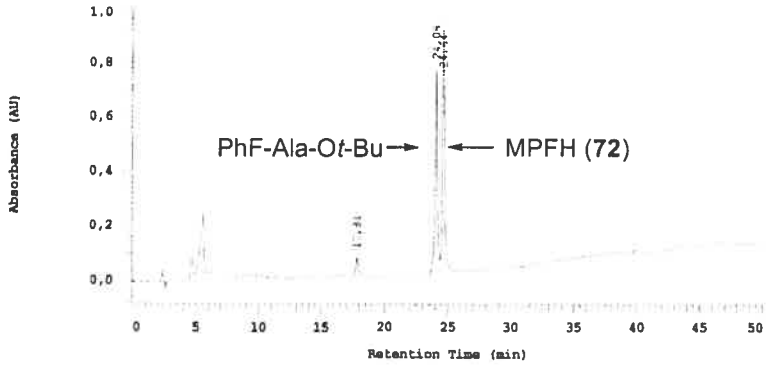
D-7000 HPLC System Manager Report

Analyzed: 22/10/04 00:16 Reported: 22/10/04 12:14
Processed: 22/10/04 01:07

Data Path: D:\WIN32APP\HSM\samples\DATA\1029\
Processing Method :DAM OBTO100B-40min

Sample Name: 5 min
Sample Description:

Chrom Type: Fixed WL Chromatogram, 214 nm



Acquisition Method: DAM
Gradient : OBTO100B-40min
0% B (100% A) to 100% B (0% A) in 40 min then 10 min at 100% B.
(A : H2O 0.1% TFA, B : ACN 0.1% TFA).

Developed by: DAM

Pump A Type: L-7100
Solvent A: H2O 0.1% TFAA Solvent B: ACN 0.1%TFAB
Solvent C: Solvent D:
Method Description: gradient 0B-100B_40 min_50min

Chrom Type: Fixed WL Chromatogram, 214 nm