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Deleterious effect of 7-methyl group on glycosylation of 2-naphthols

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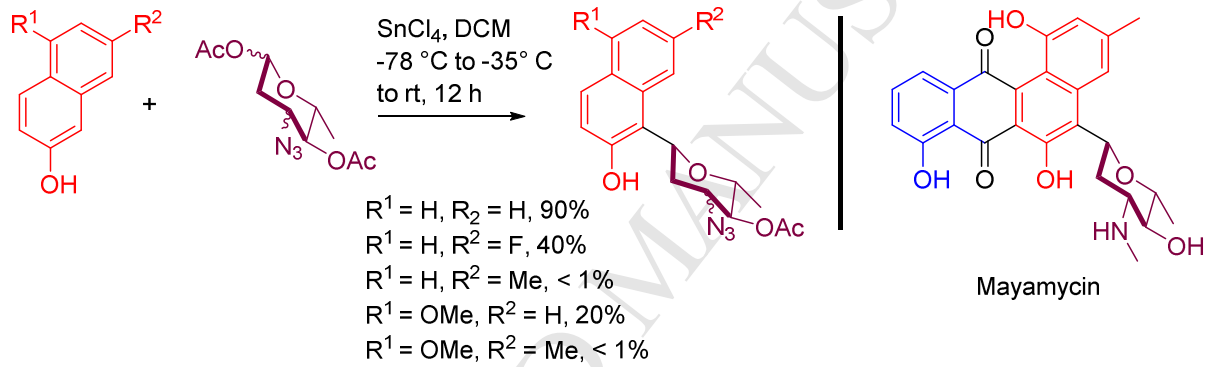
ABSTRACT



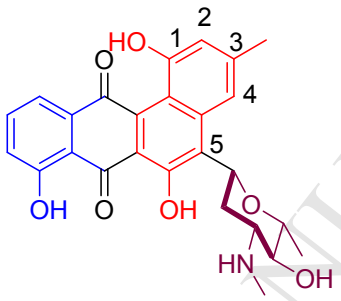
C-Glycosylations of several 2-naphthols with different glycosyl donors have been investigated in the pursuit of the total synthesis of mayamycin (**1**). While glycosylations of the parent 2-naphthol are readily achievable, those of 5-methoxy-7-methyl-2-naphthol (**6**) embodying the target are ineffective under different Lewis acidic conditions. The inefficiency of the glycosylation of **6** has been attributed to the steric effect exerted by C7 methyl group, which was corroborated by glycosylation studies of different 2-naphthols.

Keywords: *C*-Glycosylation, 2-naphthol, Lewis acid, steric effect.

1. Introduction

Mayamycin (**1**)[1] was isolated in 2010 by Imhoff et al. from the culture of marine *Streptomycin sp*. stain HB202. It exhibited potent cytotoxic activities against eight different human cancer cell lines and showed activity against several bacteria including antibiotic-resistant strains with IC_{50} values ranging between 0.13-0.33 μM.

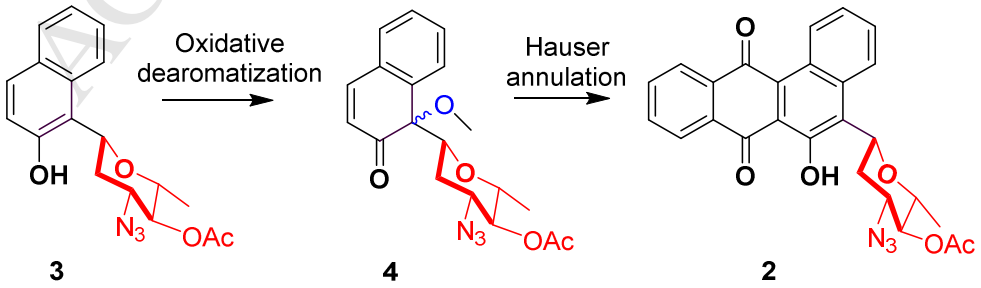
Figure 1. Structure of mayamycin (1)



Mayamycin (**1**)

In addition, it has antiproliferative activities toward the mouse fibroblast cell line NIH-3T3 with an IC_{50} value of 0.22 μM, which is 100-fold more potent than the clinical drug tamoxifen. The unusual structural architecture of **1** along with its remarkable antibacterial and antitumor activities prompted us to undertake its total synthesis. Recently, we reported a route for the synthesis of angucycline C5 glycoside **2** via *C*-glycosylation of 2-naphthols.[2] Oxidative dearomatization of *C*1-glycosyl-2-naphthol **3** and Hauser annulation of **4** were the key steps of the strategy (Scheme 1).

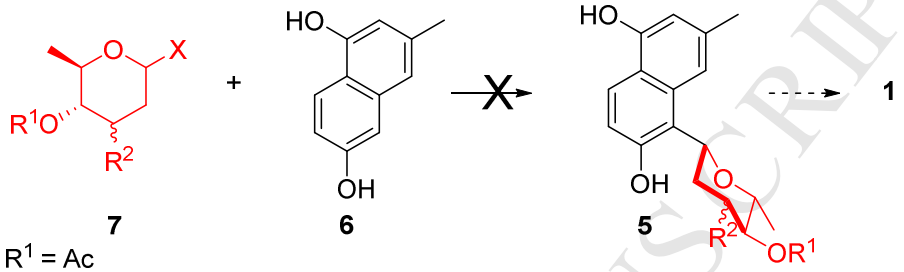
Scheme 1. General synthesis route of angucycline C5 glycosides



3 **4** **2**

Extension of this strategy to the total synthesis of mayamycin (**1**) required the *C*-glycosyl naphthol **5**. However, its synthesis was impeded by the failure of the *C*-glycosylation of the corresponding naphthol **6** with various glycosyl donors **7** (Scheme 2).

Scheme 2. Synthetic analysis of mayamycin (1)



Herein, we report synthesis of the naphthol **6** and its analogs, and their reactivity profiles towards *C*-glycosylation with three glycosyl donors.

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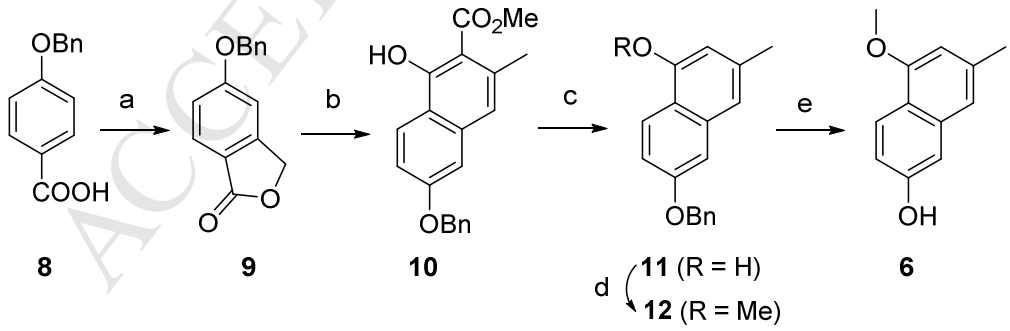
2. Results and discussion

The required naphthol **6** was previously synthesized in 11 steps from commercially available 3,4-dimethylanisole.[3] In the present work, a short synthesis of **6** was achieved by combined

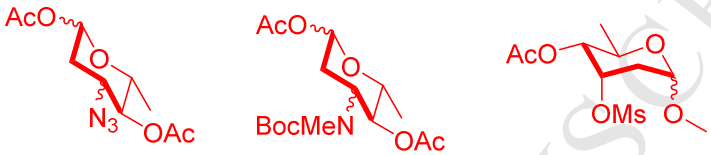
Scheme 3: Synthesis of naphthol 6



Reagents and conditions: a) $Pd(OAc)_2$, K_2HPO_4, CH_2Br_2, 140 °C, 16 h, 80%; b) methyl crotonate, LiHMDS, THF, -78 °C to rt, 12 h; c) aq KOH, MeOH, 80 °C, 4 h, 60% (2 steps); d) MeI, K_2CO_3, acetone, 98%; e) H_2, Pd-C, EtOAc-MeOH (2:1), 12 h, 90%.

application of Yu lactonization[4a] and Sammes annulation[4b] (Scheme 3). Benzyloxybenzoic acid **8** was subjected to Yu lactonization (CH_2Br_2, $Pd(OAc)_2$, K_2HPO_4) to furnish phthalide **9**[5] in 80% yield. Annulation of **9** with methyl crotonate in the presence of LDA provided naphthol **10**. The crude naphthol **10** was heated at reflux with 30% aq KOH-MeOH[6] to give naphthol **11** in 60% overall yield. *O*-Methylation of **11**[3] furnished **12**, which upon debenzylation with H_2, Pd-C furnished naphthol **6**.[3]

Chart 1. **Glycosyl donors used in this study**

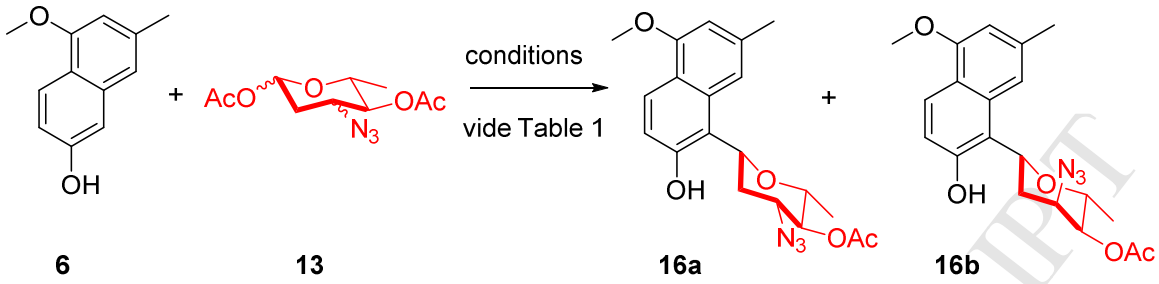


13 **14** **15**

Keeping in mind the structute of mayamycin (**1**), we chose to experiment with three glycosyl donors (**13-15**, Chart 1) for *C*-glycosylation of the naphthol **6**. The choice of the azido acetate **13**[7] owes to it higher reactivity[8] and our success with *C*-glycosylation of the parent 2-naphthol.[1] Strikingly, the reaction between the azido acetate **13** with the naphthol **6** in the presence of $SnCl_4$ furnished a complex mixture of products with small amount of *C*-glycosyl naphthols **16a** and **16b**. Variations of the catalysts, reaction time, concentration and temperature were of no avail (Table 1) to increase the yield of the reaction.

Having failed with the glycosylation with the azido acetate **13**, we turned to *N*-monomethyl *tert*-butylcarbamate **14**. It **14** was prepared in 3 steps from azido acetate**13**. Hydrogenolysis of the azido acetate **13** with H_2/Pd-C in methanol followed by treatment of the crude amine **17** with Boc_2O (1.2 equiv) and DMAP (cat) in DCM produced carbamate **18**. *N*-methylation of **18** using NaH and MeI in DMF gave the *N*-monomethyl-*tert*-butylcarbamate **14** in 65% overall yield (Scheme 4). Glycosylation of 2-naphthol (**19**) with the glycosyl donor **14** in presence of $SnCl_4$ or TMSOTf-$AgClO_4$[9] provided an intractable mixture of products. The complexity of the reactions was possibly due to deprotection of the carbamate group during the reactions.[10]

Table 1. Glycosylation of naphthol 6 with azido acetate 13



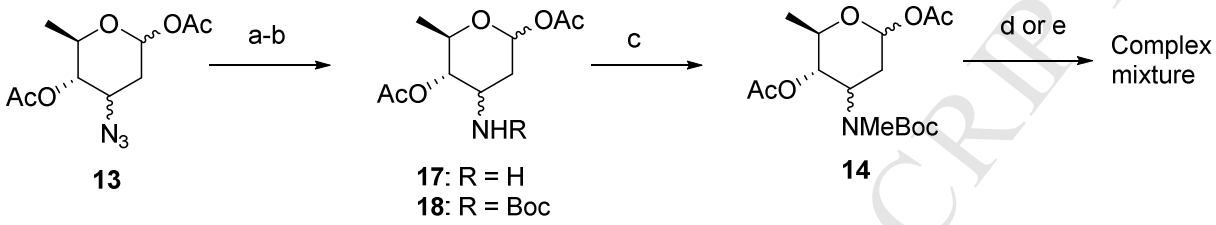
6 **13** **16a** **16b**

Entry	**6** : **13**	Catalyst	Concentration of **6** (mol/L)	Temp/h	Results
1	1.0 : 1.6	$SnCl_4$/DCM	0.027	- 78 °C to – 35 ° C/12	Traces of **16a** and **16 b**
2	1.0 : 1.6	$SnCl_4$/DCM	2.66 x10^{-3}	- 78 °C to to – 35 ° C to rt/ 12	do
3	1.0 : 1.6	$SnCl_4$/DCM	0.027	- 78 °C to – 20 ° C/12	do
4	1.0 : 1.6	$SnCl_4$/DCM	2.66 x10^{-3}	- 78 °C to rt/ 12	do
5	2.0 : 1.0	TMSOTf-$AgClO_4$/DCM	0.06	0 °C to rt/2	IM
6	1.0 : 2.0	Cp_2HfCl_2-$AgClO_4$/DCM	0.018	- 78 °C to rt/ 12	SM
7	1.0 : 4.0	$Sc(OTf)_3$/DCE	0.032	- 30 °C to rt/ 18	SM
8	1.0 : 2.0	$BF_3.Et_2O$/ DCM	0.03	0 °C to rt/ 12	SM

IM = Intractable mixture, SM = Starting naphthol **6** remained unreacted, while **13** decomposed.

Next, glycosyl donor **15** was studied in the place of **14** because it was found to be a better glycosyl donor in the case of 4-*O*-benzyl analogs.[8] For the preparation of **15**, *α*-D-methyl glucopyranoside (**20**) was converted to alcohol **21**[11a] in 4 steps, which was protected as its benzyl

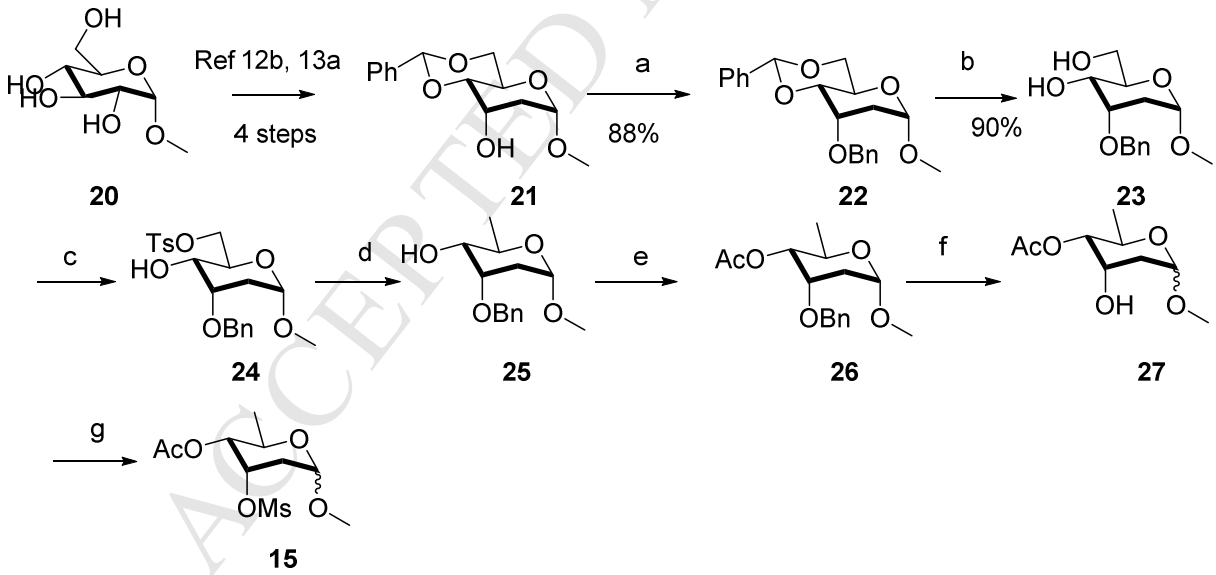
Scheme 4. Synthesis of 14 and glycosylation studies with 2-naphthol (19)



Reagents and conditions: a) Pd-C, H_2, MeOH, 50 psi b) Boc_2O, DMAP (cat) , DCM, rt c) NaH, MeI, DMF, 65% (3 steps) d) **19**, $SnCl_4$, DCM, - 78 °C to - 35° C to rt, 12 h e) **19**, TMSOTf, $AgClO_4$, DCM, 0 °C to rt, 2 h

ether **22** in excellent yield. Deprotection of benzylidene acetal **22** by TFA in DCM to **23**[11b] followed by tosylation furnished monotosyl derivative **24**. The crude tosyl sugar **24** was heated

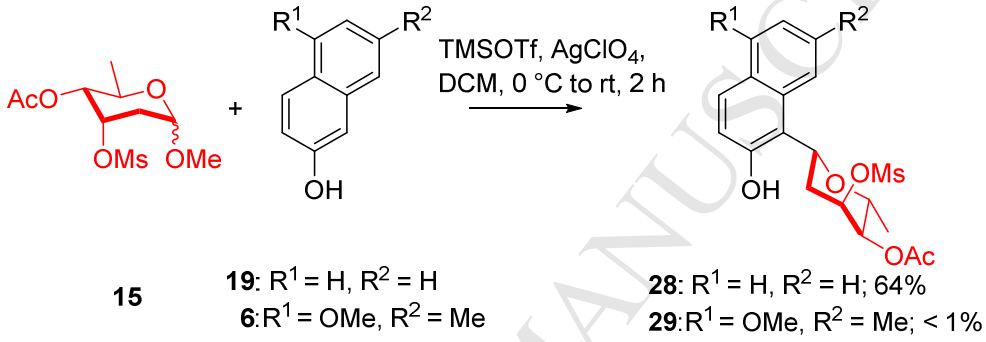
Scheme 5. **Synthesis of 3-mesyloxy carbohydrate 15**



Reagents and conditions: a) BnBr, NaH, DMF, 88%; b) DCM, TFA-H_2O, 90% ; c) TsCl (1.2 equiv.), DCM-Py (1:1) d) LAH, THF, 52% (2 steps); e) Ac_2O, py, quant; f) BBr_3, DCM, 98%; g) MsCl, Py, 95%.

at reflux with excess LAH in dry THF to give 6-deoxy sugar **25**[11c] in 52% yield over two steps (Scheme 5). The sugar **25** was converted into its acetate **26**[11c], and the benzyl ether in **26** was cleaved with BBr_3 in DCM to furnish **27** as an inseparable mixture of two C1 epimers. Reaction of **27** with 1.2 equiv mesyl chloride in pyridine provided the required mesyl sugar **15** in excellent yield. Since the glycosylation is known to proceed through the oxacarbenium intermediate, the stereochemistry at C1 was expected to be of no consequence in the glycosylation.

Scheme 6. Glycosylation of 2-naphthol 19 and naphthol 6 with mesyloxy sugar 15



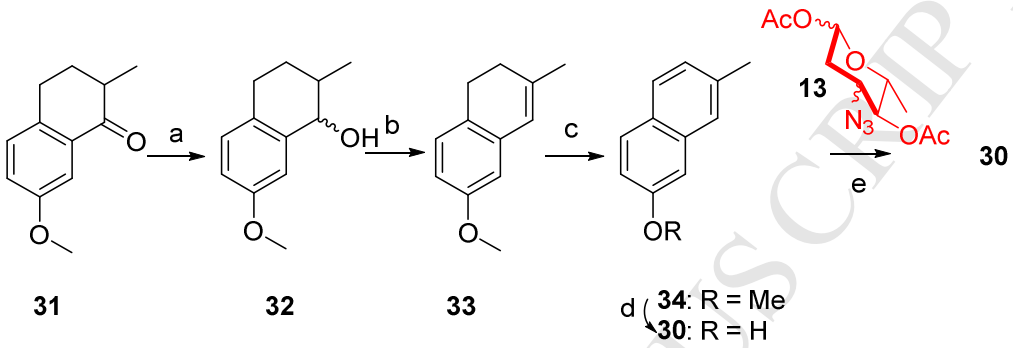
C-Glycosylation of **19** with **15**, when carried out in the presence of TMSOTf-$AgClO_4$ as catalyst, proceeded smoothly to furnish the *β*-*C*-aryl glycoside **28** in 64% isolated yield (Scheme 6). Surprisingly, under the same set of conditions, naphthol **6** produced **29** only in a trace amount (Scheme 6). The above failure intrigued us as to the effect of 7-methyl or 5-methoxy group in the *C*-glycosylation reaction. The marked difference of reactivity of **6** and **19** led us to examine 7-methyl-2-naphthol (**30**) to probe the effect of C5 methoxy group in **6**.

Naphthol **30** was synthesized from tetralone **31** in 4 steps. Reduction of the keto functionality of tetralone **31**[12a] with $NaBH_4$ resulted in the alcohols **32**, which were dehydrated to obtain dihydronaphthalene **33**. Aromatization of **33** to naphthol **34** followed by demethylation using BBr_3 yielded naphthol **30**[12b] in good overall yield (Scheme 7). The reaxction of the naphthol **30** with azido acetate **13** in the presence of $SnCl_4$ in DCM totally failed to give glycosylated product. The naphthol **30** was recovered in good yield . There was no indication of the formation of *C*-glycosides.

Next, we studied the glycosylation of 5-methoxy-2-naphthol (**35**). It was synthesized from tetralone **36**,[13a] which was converted into acetate **37**[13b] and then aromatized with NBS. The

resulting mixture[13c] was *O*-methylated to give methyl ether **38** in an excellent overall yield. Finally, the deacetylation of **38** with MeONa in methanol furnished 2-naphthol **35** in quantitative yield. *C*-Glycosylation of **35** with the azido acetate **13** was then performed in the presence of

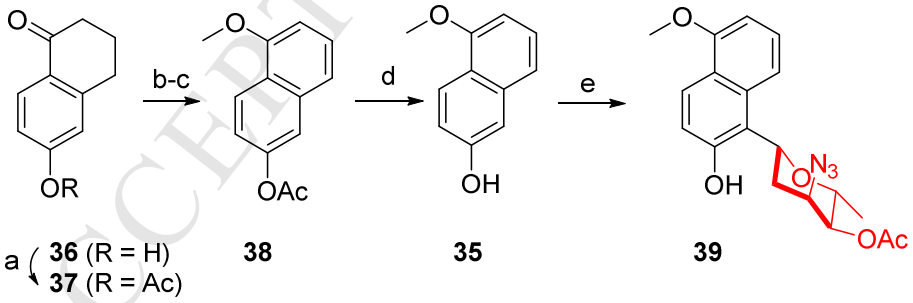
Scheme 7. **Synthesis of 7-methyl-2-naphthol (30) and its glycosylation with 13**



Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C to rt, 6 h, 85%; b) *p*-TsOH, benzene, 80 °C, 4 h, 72%; c) DDQ, benzene, rt, 5 h, 80%; d) BBr_3, DCM, 90%; e) $SnCl_4$, DCM, - 78 °C to - 35° C to rt, 12 h.

$SnCl_4$ in DCM. Although the reaction provided a mixture of two epimeric *C*-glycosides, as evident of its ^{1}H NMR spectrum, but we were able to isolate the C3 epimeric glycoside **39** in 20% yield (Scheme 8).

Scheme 8. Glycosylation of naphthol 35 with glycosyl donor 13

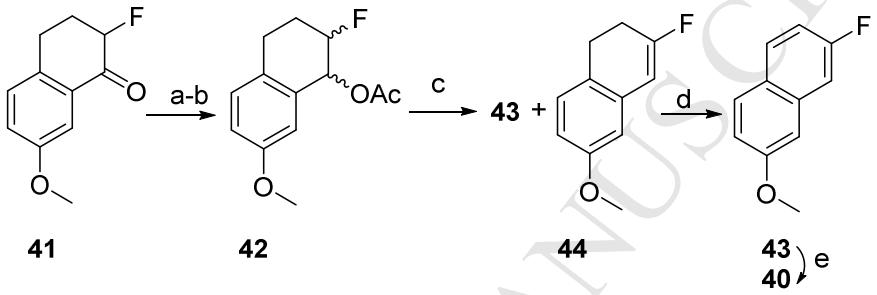


Reagents and conditions: a) Ac_2O, pyridine, 96%; b) NBS, CCl_4; c) MeI, DBU, acetone, 75% (2 steps); d) cat. NaOMe, MeOH, quant; e) **13**, $SnCl_4$, DCM, - 78 °C to - 35° C to rt, 12 h, 20%.

These results imply that the effect of the C7 methyl group of **6** on its *C*-glycosylation of 2-naphthols is quite significant. We anticipated that *peri*-effect might be preventing the *C*-glycosylation as proposed by Parker et al. for 1-naphthol derivatives.[7] Considering the lesser

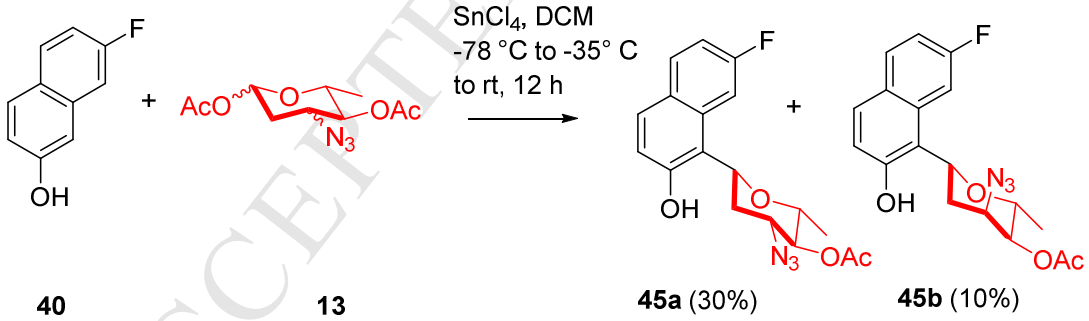
steric bulk of fluorine than methyl, we synthesized fluoronaphthol **40**. Tetralone **41**[14] was reduced with $NaBH_4$ to the corresponding alcohol, which was acetylated to obtain acetate **42** as mixture of isomers (Scheme 9). Treatment of the acetate **42** with *p*-TSA in refluxing toluene produced a mixture of fluoronaphthalenes **43** and **44**. This mixture was then treated with DDQ in dry DCM to provide methyl ether **43** in 40% yield. Treatment of **43** with BBr_3 furnished the desired fluoronaphthol **40** in 85% yield (Scheme 9).

Scheme 9. Preparation of fluoronaphthol 40



Reagents and conditions: a) $NaBH_4$, THF-MeOH; b) Ac_2O, pyridine, 80% (2 steps); c) *p*-TSA, toluene, 120 °C, 2 h; d) DDQ, DCM, rt, 40% (2 steps); e) BBr_3, DCM, 0 °C to rt, 85%.

Scheme 10. Glycosylation of fluoronaphthol 40 with 13

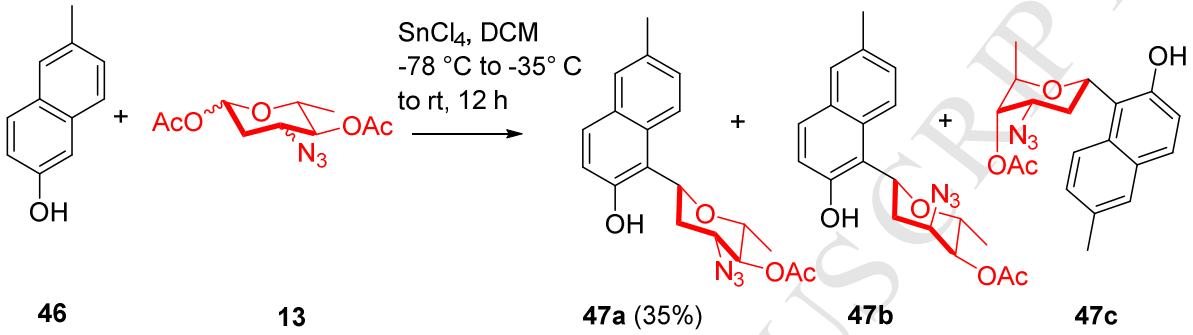


Reaction of fluoronaphthol **40** with the azido acetate **13** in the presence of $SnCl_4$ resulted in a mixture of epimeric *C*-glycosides **45a** (30%) and **45b** (10%). The yield of the glycosylation was relatively lower than with 2-naphthol (**19**), but distinctly better than that with methylnaphthol **30**.

To further ensure the steric perturbation of 7-methyl group of 2-naphthol in the *C*-glycosylation reaction, we carried out glycosylation of 6-methyl-2-naphthol (**46**)[15] with azido acetate **13** in the presence of $SnCl_4$ as Lewis acid. The reaction resulted in a mixture of three *C*-glycosides in 70%

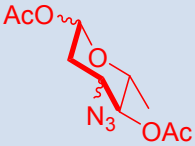
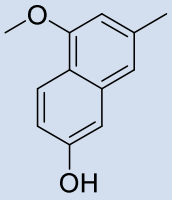
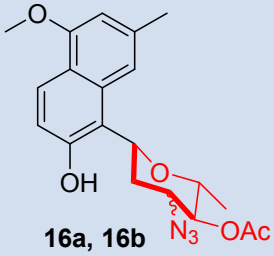
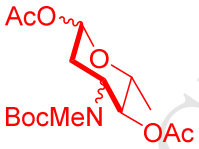
combined yield. Glycoside **47a** was isolated from the mixture in 35% yield, whereas **47b** and **47c** were inseparable (Scheme 11). The structures of **47a** and **47b** were in good agreemrnt with their NMR spectra whereas that of **47c** was tentatively assigned.

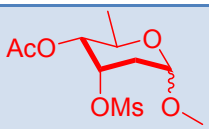
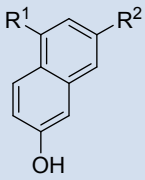
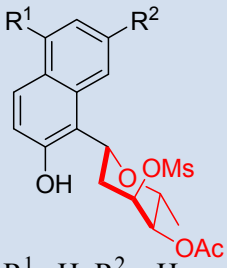
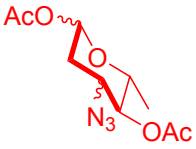
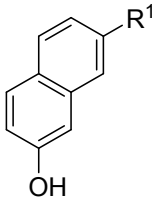
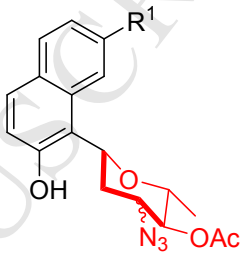
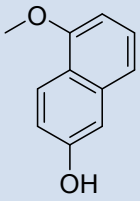
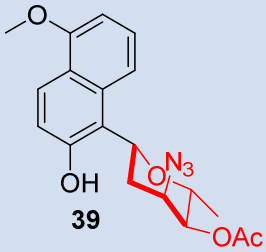
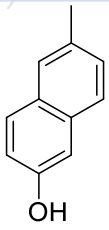
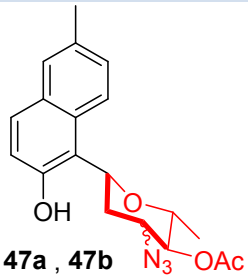
Scheme 11. **Glycosylation of 6-methyl-2-naphthol (46) with azido acetate 13**

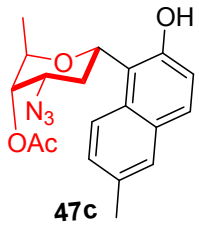


46 **13** **47a** (35%) **47b** **47c**

Table 2. **Summary of *C*-glycosylations of different 2-naphthols**

Entry	Glycosyl donor	Glycosyl acceptor	Conditions	Product	Yield
1	 **13**	 **6**	$SnCl_4$, DCM, - 78 °C to - 35° C to rt, 12 h	 **16a, 16b**	> 1%
2	 **14**	do	do	n.d.	

3	 **15**	 **19**: R^1 =H, R^2 = H **6**:R^1 =OMe, R^2 = Me	TMSOTf, $AgClO_4$, DCM, 0 °C to rt, 2 h	 **28**: R^1 =H, R^2 = H **29**:R^1 =OMe, R^2 = Me	**28**: 64% **29**: < 1%
4	 **13**	 **30**: R^1 = Me **40**: R^1 = F	$SnCl_4$, DCM, - 78 °C to - 35° C to rt, 12 h	 R^1 = Me **45a**, **45b**: R^1 = F	n.d. (R^1 = Me) 40%
5	do	 **35**	do	 **39**	20%
6	do	 **46**	do	 **47a** , **47b**	**47a** 35% **47b** + **47c** 35%



47c

n.d: not detected

3. Conclusion

In summary, several 2-naphthols were synthesized and their *C*-glycosylation with glycosyl donors: azido acetate **13**, *N*-monomethyl *tert*-butylcarbamate sugar **14** and mesyl sugar **15** were studied under Lewis acidic conditions. From these studies it is evident that 7-methyl group in 2-naphthol has a deleterious effect on the *C*-glycosylation under the reaction conditions. This effect is the result of the sensitivity of *C*-glycosylations to the steric effect of the substituents at C7 position.

4. Experimental

4.1 General

All commercial reagents were used without further purification. Melting points were determined in open-end capillary tubes. Solvents were dried and distilled following the standard procedures. TLC was carried out on pre-coated plates (Merck silica gel 60, GF254), and the spots were visualized with UV, fluorescent light or by staining with 10% H_2SO_4 in methanol. Column chromatography was performed on silica gel (60-120 or 230-400 mesh). ^{1}H and ^{13}C NMR spectra for the compounds were recorded with 200, 400 and/or 600 MHz spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CHCl_3$; δ_H = 7.26 and δ_C = 77.23, d_6-DMSO; δ_H = 2.50 and δ_C = 39.5). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. IR spectra were recorded on a FT-IR using KBr pellet on a Thermo Nicolet Nexus 870 FT-IR spectrophotometer Mass spectra were taken on a MS-TOF mass spectrometer. The phrase ‘usual work-up’ or ‘worked up in usual manner’ refers

to washing of the organic phase with water (2 × 1/4 the volume of organic phase) and brine (1 × 1/4 the volume of organic phase), and drying (anhydrous Na_2SO_4), filtration, and concentration under reduced pressure. Yields were referred to isolated yields after purification.

6-Benzyloxy-3-methylnaphthalen-1-ol (**11**)[3] To a solution of **9** (720 mg, 3.0 mmol) in dry THF (20 mL) at - 78 °C under argon atmosphere was added LHMDS (11 mL, 1 M in hexane, 11 mmol) and the reaction mixture stirred for 30 min. A solution of methyl crotonate (0.66 mL, 6.0 mmol) in THF (10 mL) was then added in portion and stirred at - 78 °C for another 30 min. After 30 min, the bath was removed and stirring was continued for 12 h at rt. The reaction mixture was cooled to 0 °C, acidified with aq 6 N HCl and extracted with EtOAc (50 × 3 mL) and worked up in usual manner. The crude reaction mixture was dissolved in a mixture of MeOH ( ) and , 30% aq KOH (25 mL) was added and refluxed under inert atmosphere for 4 h. It was cooled to rt, acidified with aq 6 N HCl (ml) and extracted with EtOAc (50 × 3 mL) and worked up in usual manner. The crude compound was subjected to column chromatography on silica gel (using 20% EtOAc/hexanes as eluent) to obtain **11** (500 mg, 60%) as yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.54-7.32 (m, 5H), 7.28-7.11 (m, 3H), 6.50 (s, 1H), 5.38 (s, 1H), 5.18 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.6, 151.6, 137.2, 136.9, 136.5, 128.8, 128.2, 127.8, 123.5, 119.0, 118.3, 117.3, 109.2, 107.0, 70.2, 22.0.

6-Benzyloxy-1-methoxy-3-methylnaphthalene (**12**)[3] To a solution of naphthol **11** (1.1 g, 4.17 mmol) in dry acetone (30 mL), K_2CO_3 (1.73 gm, 12.5 mmol) and MeI (2.4 mL, 17 mmol) were added. The reaction mixture was stirred at rt for 16 h, filtered and acetone was evaporated under reduced pressure. The crude reaction mixture was extracted with ethyl acetate (50 × 3 mL), washed with dil aq sodium thiosulfate solution and worked in usual manner. Chromatography of the residue on silica gel (using 10% EtOAc/hexanes as eluent) provided **12** (1.1 g, 96%) as an off white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 1H), 7.50-7.36 (m, 5H), 7.15-7.10 (m, 3H), 6.52 (s, 1H), 5.16 (s, 2H), 3.97 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.6, 155.6, 137.2, 136.8, 136.2, 128.8, 128.1, 127.8, 123.8, 119.4, 118.6, 117.1, 106.8, 104.6, 70.1, 55.6, 22.5.

5-Methoxy-7-methylnaphthalen-2-ol (**6**)[3] To a stirred solution of **12** (1.0 g, 3.58 mmol) in 3:1 MeOH-EtOAc (80 mL), 10% Pd-C (220 mg) was added and the reaction mixture was

hydrogenated using parr apparatus for 6 h. The reaction mixture was filtered through celite, solvent was evaporated under reduced pressure and purified by column chromatography on silica gel (using 5% EtOAc/hexanes as eluent) to obtain **6** (608 mg, 90%) as pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.6 Hz, 1H),7.05-7.02 (m, 3H), 6.54 (s, 1H), 3.98 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 154.2, 136.9, 136.2, 124.1, 119.3, 118.2, 115.9, 109.1, 104.4, 55.5, 22.4.

6-Acetoxy-4-(tert-butoxycarbonyl-methyl-amino)-2-methyltetrahydropyran-3-yl-acetate (**14**) The azido acetate **13** (550 mg, 2.1 mmol) was hydrogenated in the presence of 10% Pd-C (200 mg) following the procedure used for the preparation of **6** from **12**. The crude amine **17** was dissolved in DCM (20 mL) were added Boc_2O (0.62 mL, 2.7 mmol) and DMAP (10 mg) and stirred at rt for 12 h. Water (40 mL) was added, the reaction mixture was extracted with DCM (50 × 3 mL) and worked up in usual manner to obtain the carbamate **18**. To a solution of **18** in DMF (15 mL) was added NaH (60%, 90 mg, 2 mmol) at 0 °C and stirred for 30 min. Methyl iodide (0.2 mL, 3.2 mmol) was added and the reaction mixture was stirred at rt for 12 h. The reaction mixture was cooled to 0 °C, water was added and extracted with ethyl acetate (50 × 3 mL). After usual work up followed by flash column chromatography (using 20% EtOAc/hexanes as eluent) of the crude product provided **14** (480 mg, 65%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.39 (s), 5.87-5.82 (m), 4.91 (br, s), 4.69 (d, *J* = 11.2 Hz), 4.57 (dd, d, *J* = 11.4 Hz,), 4.44 (ap t, *J* = 4.8 Hz), 2.80 (s), 2.73 (s), 2.68 (s), 2.64 (s), 1.43 (s), 1.40 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.0, 170.5, 170.4, 169.9, 156.3, 156.1, 155.9, 155.6, 98.4, 98.3, 98.0, 97.9, 34.7, 34.0, 33.6, 32.2, 28.8, 28.6, 28.5; HRMS (TOF MS ES+) found $[M+H]^+$ 346.1858, $C_{16}H_{28}O_7N$ calcd 346.1866.

8-(benzyloxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (**22**) To a stirred solution of **21** (1.8 g, 6.76 mmol) in DMF (30 ml), NaH (440 mg, 11 mmol) was added at 0 °C in portion under inert atmosphere and stirred for 30 min. After 30 min benzyl bromide (1.3 mL, 11 mmol) was added to the reaction mixture drop wise manner and the reaction mixture was stirred for overnight at rt. The reaction mixture was cooled to 0 °C, quenched with MeOH (2 ml) and brain (15 mL) was added and it was extracted with ethyl acetate (50 × 3 mL). After usual work up followed by flash column chromatography (using 20% EtOAc/hexanes as eluent) resulted **22** (2.12 g, 86%) as yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54-7.25 (m, 10H), 5.60 (s,

1H), 4.88-4.76 (m, 3H), 4.57-4.33 (m, 2H), 4.01 (brd, 3 Hz), 3.81-3.70 (m, 2H), 3.46 (s, 3H), 2.27 (dd, *J* = 15 Hz, 2.6 Hz, 1H), 2.31-1.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.2, 137.9, 129.1, 128.4, 128.3, 127.6, 127.3, 126.4, 102.3, 98.0, 80.5, 77.9, 77.2, 76.6, 72.2, 70.4, 69.7, 58.3, 55.7, 34.6. HRMS (TOF MS ES+) found $[M+H]^+$ 357.1697, $C_{21}H_{25}O_5$ calcd 357.1702.

4-Benzyloxy-6-methoxy-2-methyltetrahydropyran-3-ol (**25**)[11a] To a solution of **23** (5.1 g, 19 mmol) in dry pyridine (50 mL) was added a solution of tosyl chloride (4.40 g, 23 mmol) at 0 °C in drop wise manner and stirred at rt for 2 h. The reaction mixture was cooled to 0 °C, quenched by adding water, extracted with ethyl acetate (100 × 3 mL). The organic part was washed with dil aq $CuSO_4$ and work up using usual manner to obtain **24** as yellow semisolid. The crude **24** was dissolved in dry THF (100 mL) was added $LiAlH_4$ (440 mg, 122 mmol) at 0 °C in portion under inert atmosphere. The reaction mixture was refluxed for 2 h, cooled to 0 °C and quenched with aq Na_2SO_4. It was passed through celite, washed with ether and concentrated under reduced pressure. The crude **25** was purified by flash column chromatography (using 20% EtOAc/hexanes as eluent) to obtain **25**[12] (2.5 g, 52%) as yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 4.82 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 4.4 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.07-3.93 (m, 1H), 3.83 (d, *J* = 3 Hz, 1H), 3.39 (s, 3H), 3.34-3.26 (m, 1H), 2.67 (d, *J* = 10.4 Hz, 1H), 2.33 (d, *J* = 15 Hz, 1H), 1.82-1.71 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 128.5, 128.0, 127.8, 97.3, 73.0, 72.3, 70.4, 64.6, 55.2, 31.5, 17.9.

4-Benzyloxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**26**)[11b]Acetylation of **25** was carried out using standard procedure (Ac_2O-Py at 0 °C to rt) to obtain **26** in quantitative yield. . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 4.73-4.65 (m, 3H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.41-4.27 (m, 1H), 3.96-3.90 (m, 1H), 3.41 (s, 3H), 2.27-2.17 (m, 1H), 2.09 (s, 3H), 1.91-1.82 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 138.6, 128.4, 127.8, 127.6, 97.7, 74.0, 71.0, 70.8, 62.9, 55.5, 32.5, 21.1, 17.6.

4-Hydroxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**27**) To a solution of **26** (2 g, 6.8 mmol) in DCM (20 mL) at - 90 °C, was added BBr_3 (40.8 mL, 1 M in DCM, 40.8 mmol) and stirred at for 10 min. After which MeOH (15 mL) and saturated aq $NaHCO_3$ (15 mL) were added, extracted with DCM (15 × 3 mL) and work up in usual manner. The reaction mixture was purified by flash column chromatography (using 30% EtOAc/hexanes as eluent) to obtain **27**

(1.36 g, 98%)) was prepared as a yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$, mixture of two anomers) δ 4.72-4.67 (m), 4.52-4.41 (m), 4.14-3.85 (m), 3.40 (s), 3.31 (s), 2.04-1.61 (m), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 170.2, 98.9, 98.5, 75.2, 75.0, 67.3, 65.7, 65.6, 61.2, 56.5, 55.2, 37.4, 35.3, 21,1, 17.9, 17.6. HRMS (TOF MS ES+) found $[M+H]^+$ 205.1081, $C_9H_{17}O_5$ calcd 205.1076.

4-Methanesulfonyloxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**15**) The compound **15** (1.7 g, 95%) was prepared as a yellow semisolid from **27** (1.3 g, 6.4 mmol), following the standard mesylation procedure using mesyl chloride (1.2 mL) in pyridine (20 mL). ^{1}H NMR (200 MHz, $CDCl_3$, mixture of two anomers) δ 5.14-5.10 (m), 5.06-5.01 (m), 4.70-4.65 (m), 4.56-4.46 (m), 4.21-4.10 (m), 3.98-3.84 (m), 3.43 (s), 3.29 (s), 2.99 (s), 2.24-1.79 (m), 1.20-1.10 (m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 170.1, 98.4, 96.6, 76.1, 74.1, 72.2, 71.9, 67.7, 61.1, 56.6, 55.3, 38.9, 38.6, 36.6, 34.3, 20.9. 17.8, 17.3; HRMS (TOF MS ES+) found $[M+H]^+$ 283.0844, $C_{10}H_{19}O_7S$ calcd 283.0852.

6-(2-Hydroxy-naphthalen-1-yl)-4-methanesulfonyloxy-2-methyltetrahydropyran-3-yl-acetate (**28**) To a stirred solution of 2-naphthol (**19**) (180 mg, 1.25 mmol) and hexopyranoside **15** (300 mg, 1.06 mmol) in methylene chloride (20 mL) were added TMSOTf (50 µL, 2.7 mmol) and $AgClO_4$ (260 mg, 2.7 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then the temperature was gradually increased to rt and stirred for 1 h. The reaction was quenched with triethyl amine (0.2 mL) and DCM was evaporated under reduced pressure. The reaction mixture was purified by flash column chromatography (using 20% EtOAc/hexanes as eluent) to obtain **28** (268 mg, 64%) as yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.78-7.64 (m, 3H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 5.89 (dd, *J* = 10.6 Hz, *J* = 3.2 Hz, 1H), 5.29 (d, *J* = 2.6 Hz, 1H), 4.83 (dd, *J* = 10.2 Hz, *J* = 2.8 Hz, 1H), 4.34-4.20 (m, 2H), 3.15 (s, 3H), 2.43-2.25 (m, 2H), 2.17 (s, 3H), 1.39 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 154.0, 130.8, 130.4, 129.2, 129.0, 127.4, 123.4, 120.5, 120.0, 113.9, 76.1, 72.9, 72.3, 72.0, 38.9, 36.6, 21.8, 18.2. HRMS (TOF MS ES+) found $[M+Na]^+$ 417.0994, $C_{19}H_{22}O_7SNa$ calcd 417.0984.

6-Methoxy-3-methyl-1,2-dihydronaphthalene (**33**) To a solution of **31** (5 g, 26.3 mmol) in dry MeOH, was added sodium borohydride (1.12 g, 31.6 mmol) at 0 °C in portion and stirred at rt

for 12 h. The reaction was quenched by adding water (5 mL) at 0 °C and MeOH was evaporated under reduced pressure. Water (50 mL) was added and it was extracted with ethyl acetate (3 x 100 mL) and worked up in usual manner to obtain the crude alcohol **31** (4.3 g, 85%). The crude alcohol **31** (4 g, 20.8 mmol) was dissolved in dry benzene (80 mL), *p*-toluenesulfonic acid (200 mg) was added and the reaction mixture was refluxed for 2 h using a Dean-Stark apparatus. The reaction mixture was concentrated under reduced pressure, water (50 mL) was added, extracted with EtOAc (3 x 100 mL) and work up in usual manner. The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as eluent) to afford **33** (2.6 g, 72%) as clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8 Hz, 1H), 6.70 (dd, *J* = 8 Hz, *J* = 2.6 Hz 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 6.25 (s, 1H), 3.84 (s, 3H), 2.82 (t, *J* = 8 Hz, 2H), 2.29 (t, *J* = 8.2 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.5, 139.2, 136.3, 128.0, 126.4, 123.0, 111.1, 111.0, 55.4, 29.4, 27.4, 23.7. HRMS (TOF MS ES+) found $[M+H]^+$ 175.1120, $C_{12}H_{15}O$ calcd 175.1123.

2-Methoxy-7-methylnaphthalene (**34**)[13a] To a solution of **33** (500 mg, 1.63 mmol) in dry DCM (20 mL), DDQ (450 mg, 2 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was passed through basic alumina column to obtain pure ether **31** (395 mg, 80%, pale yellow solid). mp 96 - 98 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 7 Hz, 1H), 7.37-7.29 (m, 3H), 4.03 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5, 135.0, 134.4, 128.2, 126.4, 126.9, 125.5, 124.7, 118.4, 106.6, 55.3, 19.5.

7-Methylnaphthalen-2-ol (**27**)[12b] To a solution of **31** (110 mg, 0.64 mmol) in DCM (10 mL) at 0 °C, was added BBr_3 (1.3 mL, 1 M in DCM, 1.3 mmol) and stirred at rt for 12 h. The reaction mixture was cooled to 0 °C and quenched with aq $NaHCO_3$, extracted with DCM (15 × 3 mL) and work up in usual manner. The reaction mixture was purified by flash column chromatography (using 10% EtOAc/hexanes as eluent) to obtain **27** (91 mg, 90%) was prepared as a yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73-7.69 (m, 2H), 7.44 (s, 1H), 7.21 (d, *J* = 6.4 Hz, 1H), 7.11-7.07 (m, 2H), 5.36 (s, 1H), 2.51 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.4, 136.4, 135.0, 129.8, 127.7, 127.4, 126.1, 125.7, 117.0, 109.3, 21.9.

5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl-acetate (**37**)[13b] A solution of **36** (900 mg, 4.4 mmol) in dry pyridine (20 mL) at 0 °C, was added acetic anhydride (0.63 mL, 6.6 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was cooled to 0 °C, quenched by adding water, extracted with ethyl acetate (3 x 50 mL). The organic part was washed with dil aq $CuSO_4$ and work up using usual manner to obtain **37** (1.08 g, 96%) as yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2 Hz, *J* = 2 Hz, 1H), 7.00-6.86 (m, 2H), 2.91 (t, *J* = 6 Hz, 2H), 2.60 (t, *J* = 6 Hz, 2H), 2.26 (s, 3H), 2.15-2.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.2, 168.9, 154.4, 146.4, 130.4, 129.1, 121.5, 120.2, 38.9, 29.8, 23.1, 21.1.

5-Methoxynaphthalen-2-yl-acetate (**38**) To a solution of **37** (1.0 g, 4.9 mmol) in dry CCl_4 (40 mL), were added NBS (850 mg, 4.75 mmol) and AIBN (10 mg) and refluxed for 4 h in the presence of 200 W electric bulb. The reaction mixture was cooled to 0 °C, filtered through regular filter paper and the filtrate was evaporated under reduced pressure to obtain the crude naphthol. The crude naphthol was dissolved in dry acetone (30 mL), were added DBU (0.9 mL, 6 mmol) and MeI (0.6 mL, 10 mmol) and stirred at rt for 12 h. Acetone was evaporated under reduced pressure, extracted with ethyl acetate (3 x 50 mL) and work up in usual manner to obtain the crude **38**. The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as eluent) to afford **38** (790 mg, 75%) as yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9 Hz, 1H), 7.36 (s, 1H), 7.25 (d, *J* = 4.4 Hz, 2H), 7.07 (dd, *J* = 8.6 Hz, *J* = 1.2 Hz, 1H), 6.58 (t, *J* = 4.4 Hz, 1H), 3.77 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.6, 155.6, 149.1, 135.11, 127.0, 123.9, 123.6, 120.2, 119.9, 118.2, 103.7, 55.5, 21.2. HRMS (TOF MS ES+) found $[M+H]^+$ 217.0858, $C_{13}H_{13}O_3$ calcd 217.0865.

5-Methoxynaphthalen-2-ol (**35**) To a solution of **38** (864 mg, 4 mmol) in methanol (20 mL), was added NaOMe (20 mg) and the reaction mixture was stirred at rt for 1 h. The reaction was quenched by adding amberlyst-15, filtered through regular filter paper and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (using 10% EtOAc/hexanes as eluent) to afford **35** (690 mg, 99%) as pale yellow semisolid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.8 Hz, 1H), 7.22-7.06 (m, 2H), 6.96-6.91 (m, 2H), 6.51 (d, *J* = 7.4 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.8, 154.2, 136.1, 126.9, 124.3, 121.0, 119.1, 117.0, 109.6, 102.1, 55.6; HRMS (TOF MS ES+) found $[M+Na]^+$ 197.0570, $C_{11}H_{10}O_2Na$ calcd 197.0578.

4-Azido-6-(2-hydroxy-5-methoxy-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-acetate (**39**) To a stirred solution of naphthol **35** (100 mg, 0.57 mmol) and azido acetate **13** (300 mg, 1.15 mmol)) and $4A^0$ molecular sieves in methylene chloride (40 mL) was added tin (IV) chloride (3.5 mL, 1 M in DCM, 3.5 mmol) at - 78 °C. The reaction mixture was stirred at - 78 °C for 10 min and then the temperature was gradually increased to - 35 °C and kept overnight. The reaction was quenched with saturated sodium sulfate and the mixture was extracted with methylene chloride. The organic phase was dried and concentrated and purified by flash column chromatography (using 20% EtOAc/hexanes as eluent) to obtain **39** (43 mg, 20%) as yellow semisolid. $[\alpha]^{35}_{D}$ = + 56.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.72 (dd, *J* = 6.8 Hz, 1H), 4.90 (dd, *J* = 9.6 Hz, *J* = 3.2 Hz, 1H), 4.31-4.22 (m, 2H), 3.97 (s, 3H), 2.21-2.15 (m, 5H), 1.36 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3, 156.5, 154.6, 132.3, 127.5, 124.2, 120.8, 118.9, 114.2, 113.4, 101.9, 74.9, 73.6, 72.1, 58.7, 55.8, 35.8, 20.9, 18.3; HRMS (TOF MS ES+) found $[M+Na]^+$ 394.1370, $C_{19}H_{21}O_5NNa$ calcd 394.1379.

2-Fluoro-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl-acetate (**42**) The compound **42** (585 mg, 80%) was prepared as a white semisolid from **41** (600 mg, 3 mmol), following the procedure for the preparation of compound **32** from **31** using $NaBH_4$ (130 mg, 3.6 mmol) followed by acetylation using acetic anhydride (0.43 mL, 4.5 mmol) and pyridine (10 mL). ^{1}H NMR (200 MHz, $CDCl_3$, mixture of four isomers) δ 7.07-7.05 (m, 1H), 6.86-6.75 (m, 2H), 6.16-6.08 (m, 1H), 5.07-4.79 (m, 1H), 3-68 (s, 3H), 3.05-2.75 (m, 2H), 2.39-1.95 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of four isomers) δ 170.9, 158.4, 133.4, 133.3, 129.8, 129.7, 128.4, 115.7, 115.1, 113.9, 113.6, 91.0, 89.6, 87.8, 71.7, 71.5, 70.1, 69.9, 55.56, 55.5, 26.3, 26.1, 25.6, 25.5, 25.0, 24.8, 24.7,24.6, 21.4; ^{19}F NMR (188 MHz, $CDCl_3$, mixture of four isomers) δ - 198.1, - 202.6, - 203.6, - 204.0; HRMS (TOF MS ES+) found $[M\text{-}HOAc+H]^+$ 179.0847, $C_{11}H_{12}OF$ calcd 179.0872.

2-Fluoro-7-methoxynaphthalene (**43**) The compound **42** (500 mg, 2.6 mmol) was dissolved in dry benzene (20 mL), *p*-toluenesulfonic acid (30 mg) was added and the reaction mixture was refluxed for 2 h using a Dean-Stark apparatus. The reaction mixture was concentrated under reduced pressure, diluted with water (50 mL), extracted with EtOAc (3 x 100 mL) and work up

in usual manner. The crude product was dissolved in DCM (20 mL), DDQ (450 mg, 2 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was passed through basic alumina column to obtain pure **43** (147 mg, 40%) as a brown solid. m.p. 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.35 (d, *J* = 10 Hz, 1H), 7.13-7.07 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J_{C-F} = 243.8 Hz), 158.7, 135.8 (d, J_{C-F} = 9.8 Hz), 130.2 (d, J_{C-F} = 9.6 Hz), 129.6, 126.1, 118.1 (d, J_{C-F} = 2.8 Hz), 113.8 (d, J_{C-F} = 25 Hz), 110.2 (d, J_{C-F} = 21 Hz), 105.5 (d, J_{C-F} = 5 Hz). 55.5; HRMS (TOF MS ES+) found $[2M-H]^+$ 351.1181, $C_{22}H_{17}O_2F_2$ calcd 351.1197.

7-Fluoronaphthalen-2-ol (**40**) The compound **40** (125 mg, 85%) was prepared as a yellow semisolid from **43** (160 mg, 0.91 mmol), following the procedure for the preparation of compound **30** from **34** using BBr_3 (2.0 mL, 1 M in DCM, 2.0 mmol) in DCM (10 mL). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.28-7.25 (m, 1H), 7.15-7.08 (m, 3H), 6.02 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (d, J_{C-F} = 244 Hz), 154.2, 135.7 (d, J_{C-F} = 9.5 Hz), 130.3 (d, J_{C-F} = 10 Hz), 130.1, 126.1, 117.1 (d, J_{C-F} = 2.5 Hz), 114.0 (d, J_{C-F} = 25.5 Hz), 109.9, 109.4 (d, J_{C-F} = 9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ - 115.2; HRMS (TOF MS ES+) found $[M+H]^+$ 163.0560, $C_{10}H_8OF$ calcd 163.0559.

4-(*R*)-Azido-6-(7-fluoro-2-hydroxynaphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (**45a**) The compound **45a** (54 mg, 30%) was prepared as a yellow semisolid from the reaction of **40** (81 mg, 0.5 mmol) with **13** (250 mg, 1.0 mmol) following the procedure for the preparation of compound **39** from **35** using $SnCl_4$ (1.7 mL, 1 M in DCM, 1.7 mmol) in DCM (10 mL). $[\alpha]^{35}_D$ = + 62.6 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3367, 2099, 1744, 1630, 1220, 1048, 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.75 (dd, *J* = 8.8 Hz, J_{H-F} = 6 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 10 Hz, 1H), 7.13-7.05 (m, 2H), 5.36 (dd, *J* = 11.6 Hz, *J* = 1.6 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 3.86-3.73 (m, 2H), 2.41-2.36 (m, 1H), 2.20 (s, 3H), 2.10-2.00 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.0 (d, J_{C-F} = 244 Hz), 154.9, 131.89 (d, J_{C-F} = 9 Hz), 131.6 (d, J_{C-F} = 9.8 Hz), 130.4, 125.9, 119.4 (d, J_{C-F} = 2.6 Hz), 113.7 (d, J_{C-F} = 5.5 Hz), 113.3 (d, J_{C-F} = 24.8 Hz), 77.6, 76.7, 76.4, 75.1, 61.0, 35.98, 21.0, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 113.5; HRMS (TOF MS ES+) found $[M+Na]^+$ 382.1183, $C_{18}H_{18}FN_3O_4Na$ calcd 382.1179.

4-(*S*)-Azido-6-(7-fluoro-2-hydroxynaphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (**45b**) The compound **45b** (18 mg, 10%) was obtained along with **45a** as a yellow semisolid. $[\alpha]^{35}_{D}$ = + 98.4 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3353, 217, 1744, 1629, 1220, 1050, 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.73 (dd, *J* = 8.8 Hz, J_{H-F} = 6 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.28 (d, *J* = 12 Hz, 1H), 7.11-7.03 (m, 2H), 5,58 (dd, *J* = 10.4 Hz, *J* = 3.6 Hz, 1H), 4.91 (dd, *J* = 10 Hz, *J* = 3.2 Hz, 1H), 4.31-4.23 (m, 2H), 2.20-2.16 (m, 5H), 1.37 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 161.9 (d, J_{C-F} = 243.9 Hz), 155.0, 132.1 (d, J_{C-F} = 8.8 Hz), 131.5 (d, J_{C-F} = 9.6 Hz), 130.2, 125.9, 119.3, 114.0 (d, J_{C-F} = 5.2 Hz), 113.3 (d, J_{C-F} = 25 Hz), 105.1 (d, J_{C-F} = 22.6 Hz), 74.8, 73.3, 72.2, 58.5, 35.7, 20.9, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 113.3; HRMS (TOF MS ES+) found $[M+Na]^+$ 382.1188, $C_{18}H_{18}FN_3O_4Na$ calcd 382.1179.

4-(*S*)-Azido-6-(2-hydroxy-6-methyl-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (47a)

The compound **47a** (28 mg, 35%) was prepared as a yellow semisolid from the reaction of **46** (36 mg, 0.23 mmol) with **13** (100 mg, 0.39 mmol) following the procedure for the preparation of compound **39** from **35** using $SnCl_4$ (1.3 mL, 1 M in DCM, 1.3 mmol) in DCM (10 mL). $[\alpha]^{35}_{D}$ = + 60.4 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3369, 2098, 1744, 1606, 1375, 1227, 1046, 913, 744; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.65 (d, *J* = 9 Hz, 1H), 7.57 (s, 1H), 7.55 (d, *J* = 9 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 9 Hz, 1H), 5.52 (d, *J* = 11.4 Hz, 1H), 4.91 (t, *J* = 9.6 Hz, 1H), 3.86-3.77 (m, 2H), 2.49 (s, 3H), 2.44-2.41 (m, 1H), 2.21 (s, 3H), 2.19-2.06 (m, 1H), 1.39 (d, *J* = 6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170, 153, 132.6, 129.6, 129.1, 129.0, 128.7, 128.2, 120.2, 119.9, 113.7, 76.5, 76.1, 75, 61, 35.9, 21.1, 20.9, 18. HRMS (TOF MS ES+) found $[M+Na]^+$ 378.1431, $C_{19}H_{21}N_3O_4Na$ calcd 378.1430.

4-(*R*)-Azido-6-(2-hydroxy-6-methyl-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (47b, major) and **(3S,4R,6S)-4-azido-6-(2-hydroxy-6-methylnaphthalen-1-yl)-2-methyltetrahydro-2H-pyran-3-yl acetate (47c, minor)**

47b + 47c (29 mg) were obtained along with **47a** as yellow semisolid. IR (KBr, cm^{-1}) 3356, 2116, 1743, 1376, 1227, 1051, 813, 744; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, major), 8.59 (s, minor), 7.64 - 7.55 (m), 7.34 (d, *J* = 8.4 Hz), 7.09 - 7.07 (m), 5.92 (dd, *J* = 10.8 Hz, *J* = 4.8 Hz,

minor), 5.75 (dd, *J* = 10.2 Hz, *J* = 3 Hz, major), 5.30 (d, *J* = 3 Hz, minor), 4.92 (dd, *J* = 10.2 Hz, *J* = 3.6 Hz, major), 4.40 (d, *J* = 3.6 Hz, minor), 4.39 (s, major), 4.38 - 4.27 (m, major), 4.05-4.04 (m, minor), 2.48 (s), 2.23 - 2.18 (m), 1.45 (d, *J* = 6.6 Hz, minor), 1.39 (d, *J* = 6.6 Hz, major); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 170.0, 153.2, 153.0, 132.53, 132.5, 129.4, 129.3, 129.1, 129.08, 128.9, 128.8, 128.0, 120.6, 120.5, 119.8, 119.8, 114.0, 112.3, 96.1, 87.1, 79.2, 74.6, 73.0, 71.8, 69.3, 61.4, 58.4, 39.5, 35.6, 21.2, 21.1, 20.7, 18.1, 16.5. HRMS (TOF MS ES+) found $[M+Na]^+$ 378.1432, $C_{19}H_{21}N_3O_4Na$ calcd 378.1430.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds associated with this article.

Acknowledgement

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Deleterious effect of 7-methyl group on glycosylation of 2-naphthols

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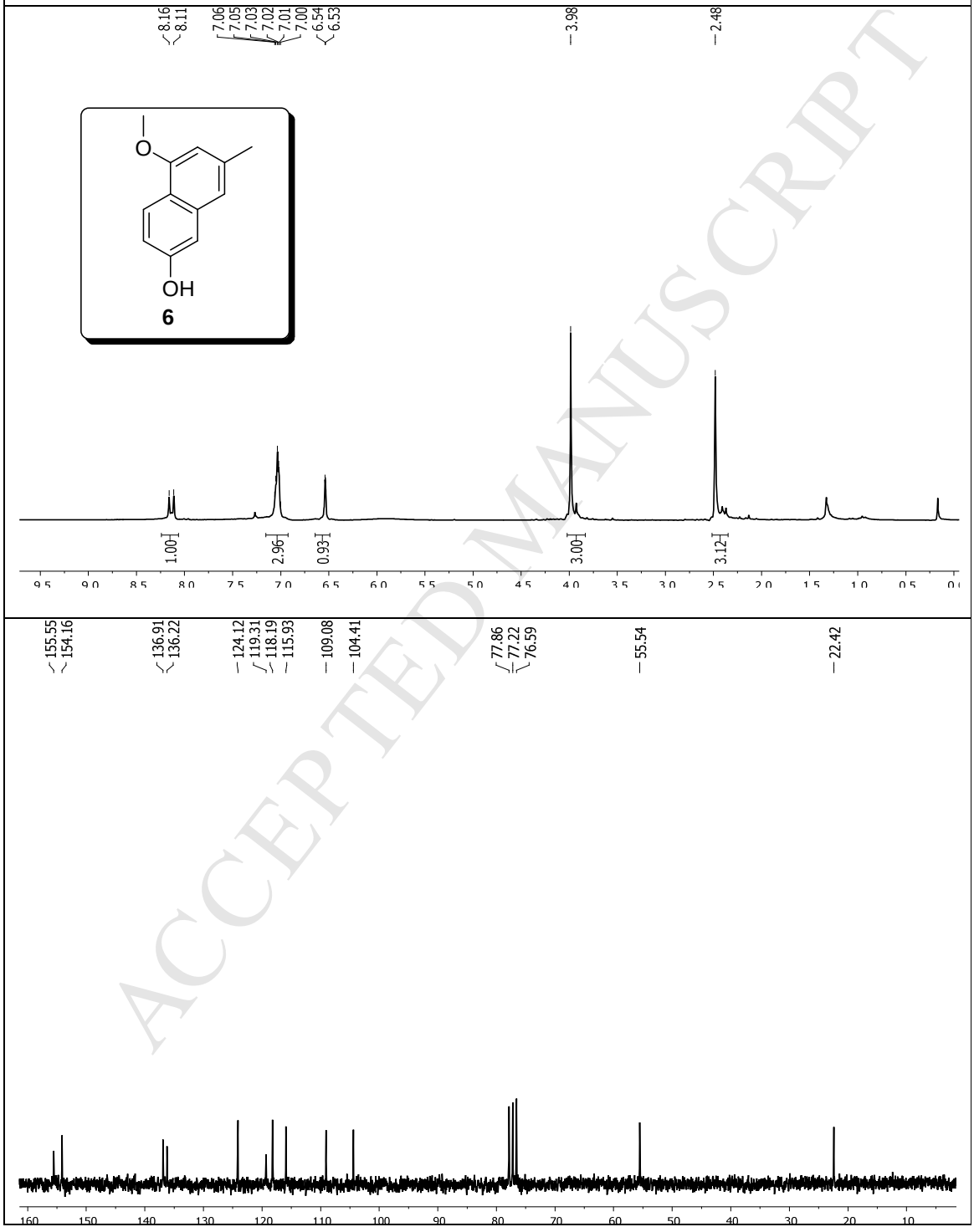
Supporting Information

Contains

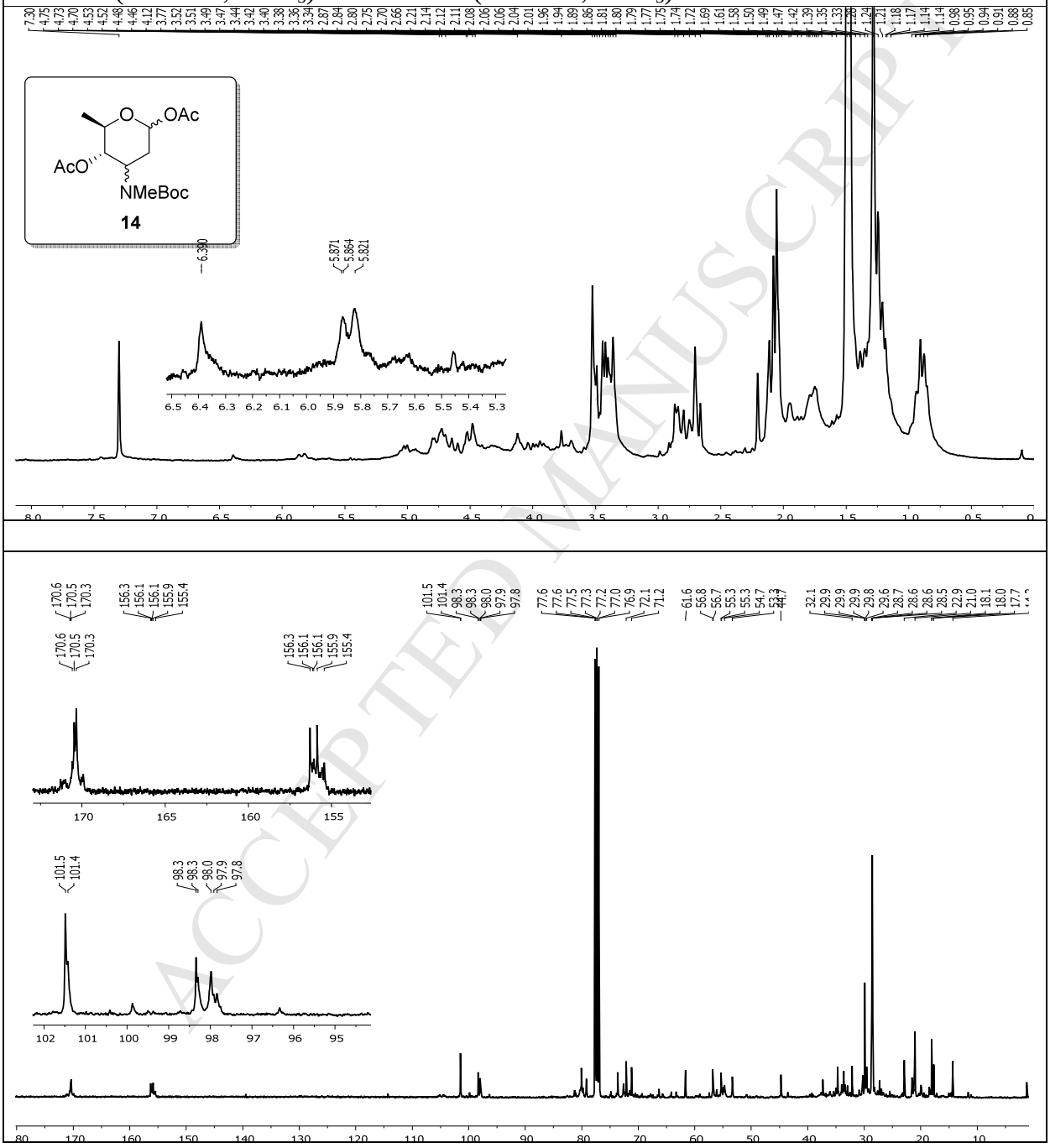
1. ^{1}H and ^{13}C NMR spectra of selected compounds

5-Methoxy-7-methylnaphthalen-2-ol (**6**)
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



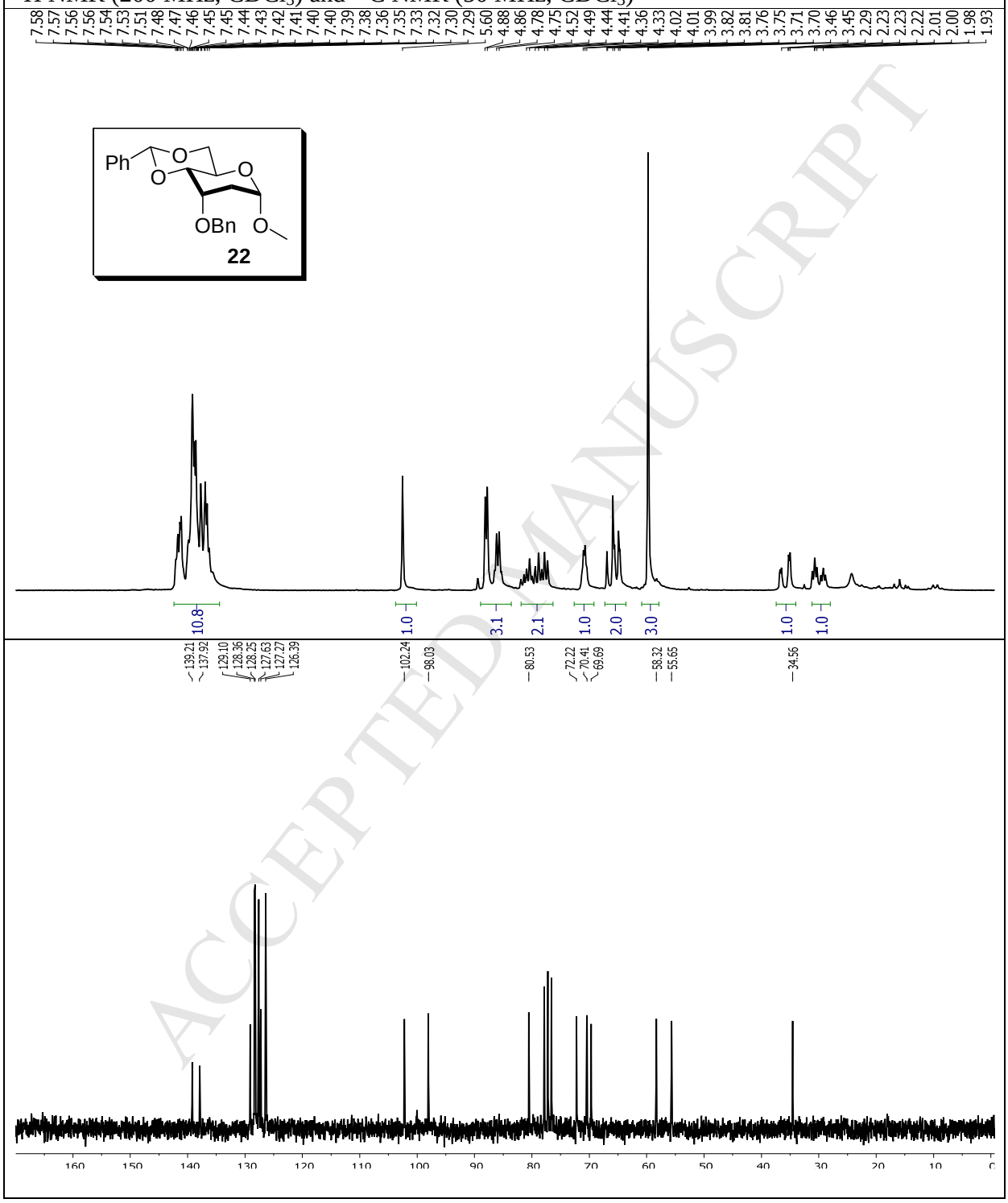
6-Acetoxy-4-(tert-butoxycarbonyl-methyl-amino)-2-methyltetrahydropyran-3-yl-acetate (14)

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)



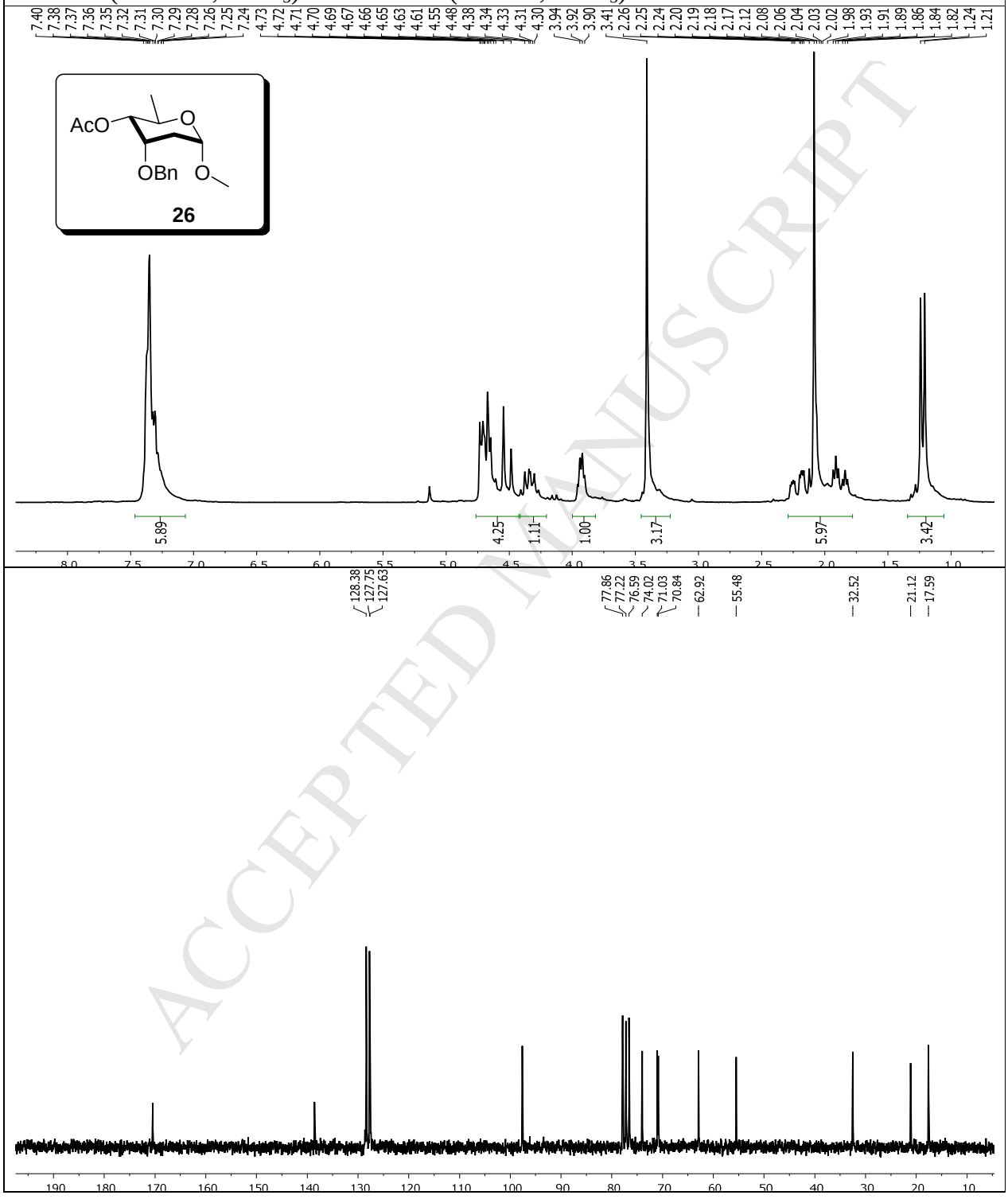
8-(Benzyloxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (**22**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



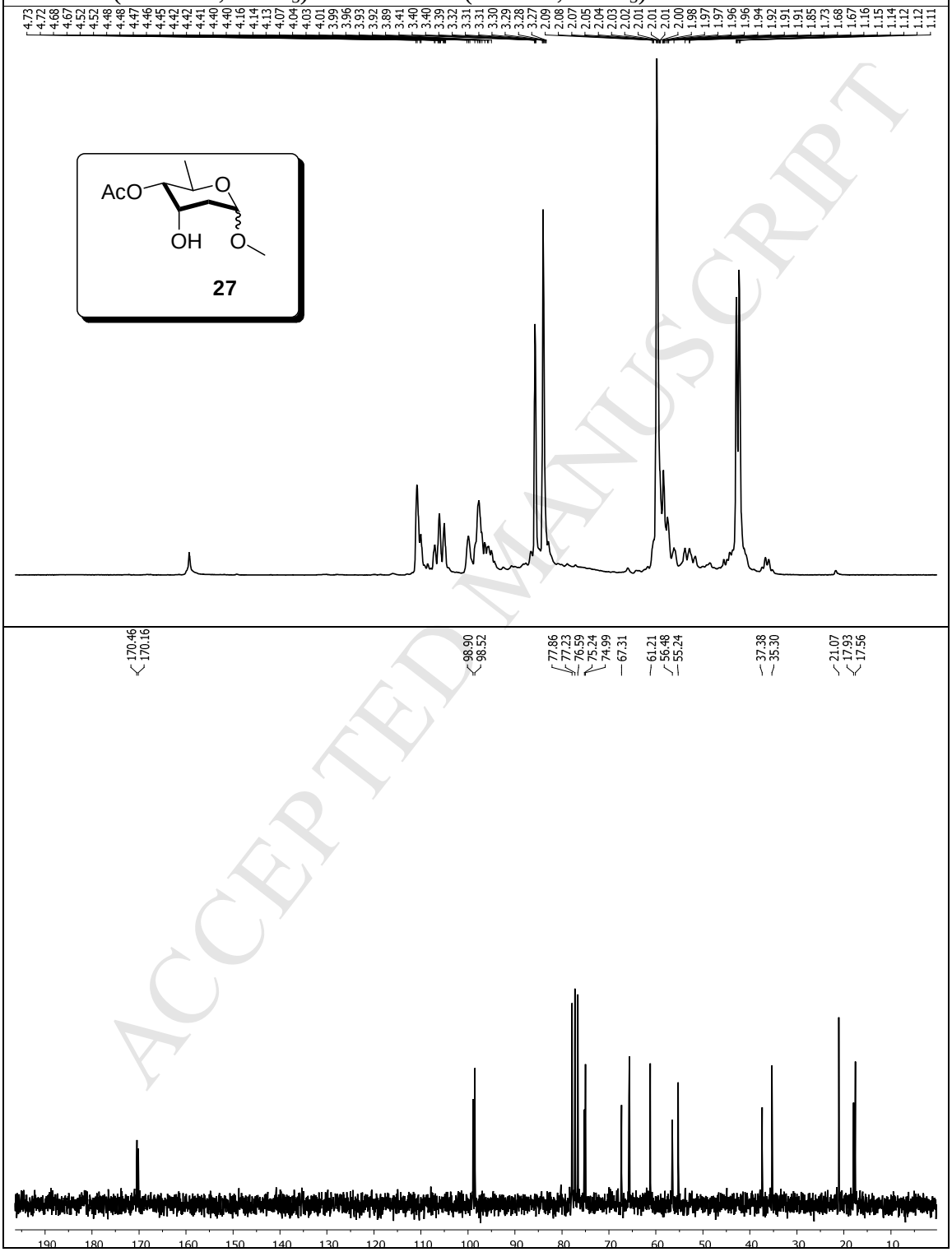
4-Benzyloxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**26**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

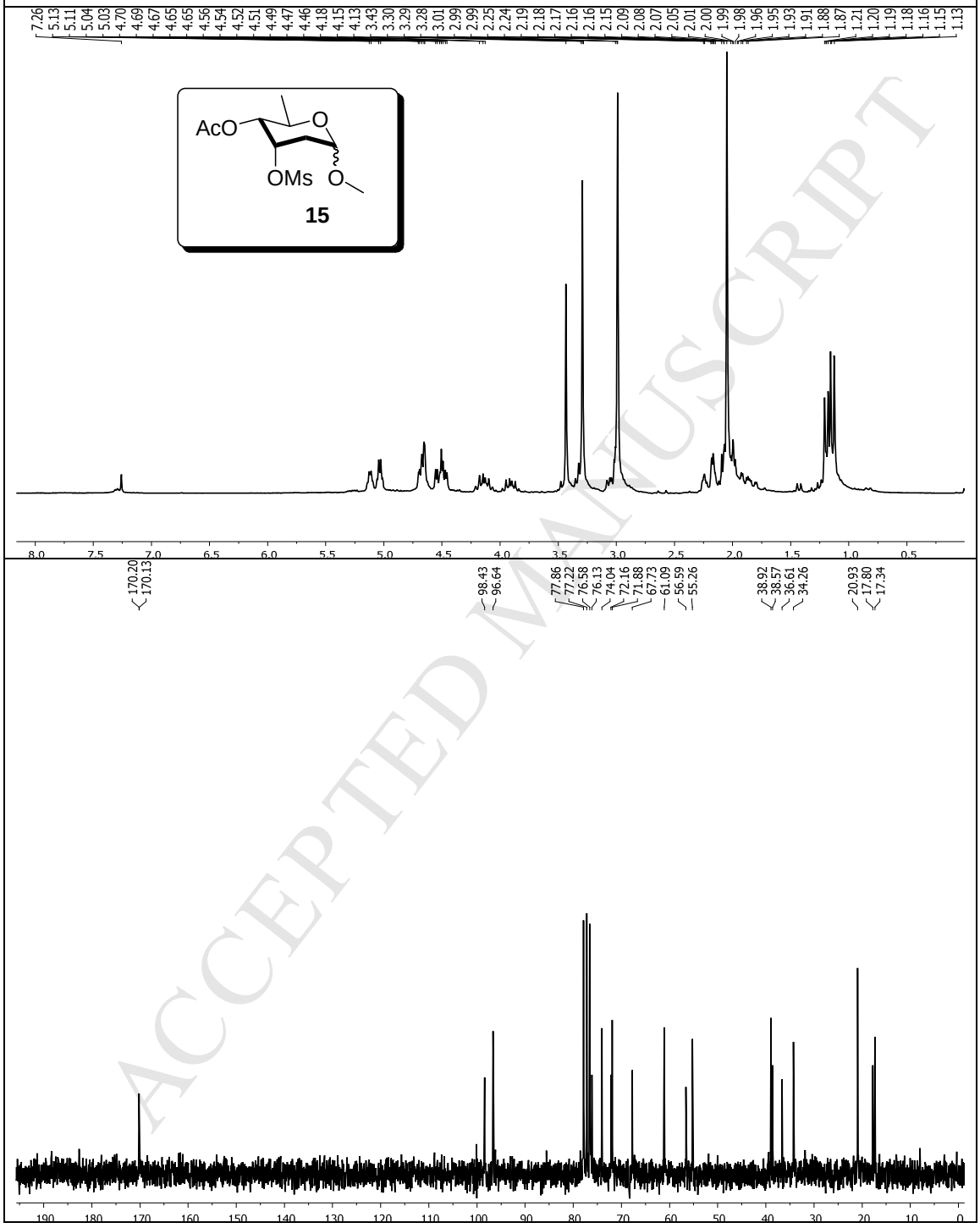


4-Hydroxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**27**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

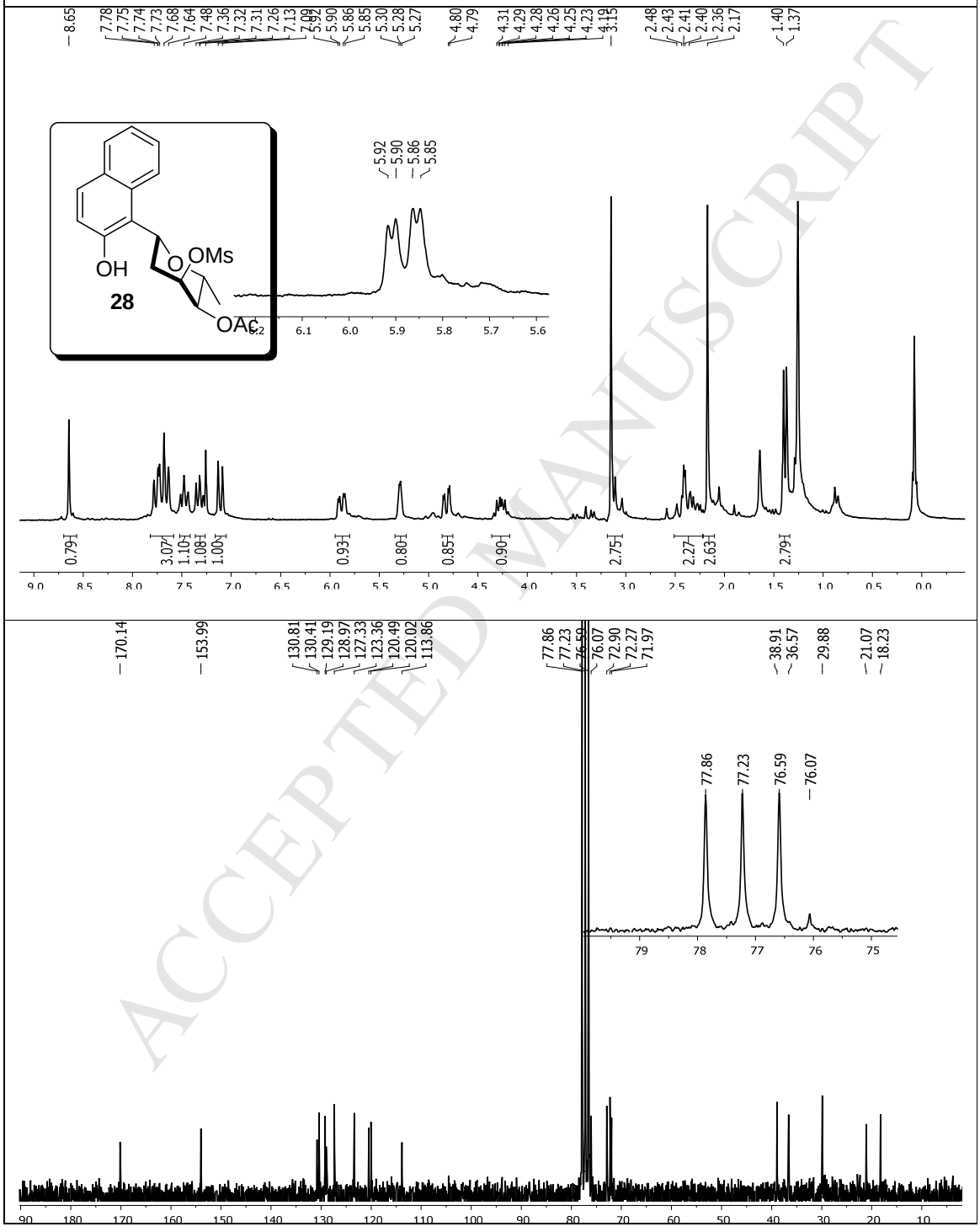


4-Methanesulfonyloxy-6-methoxy-2-methyltetrahydropyran-3-yl-acetate (**15**)
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

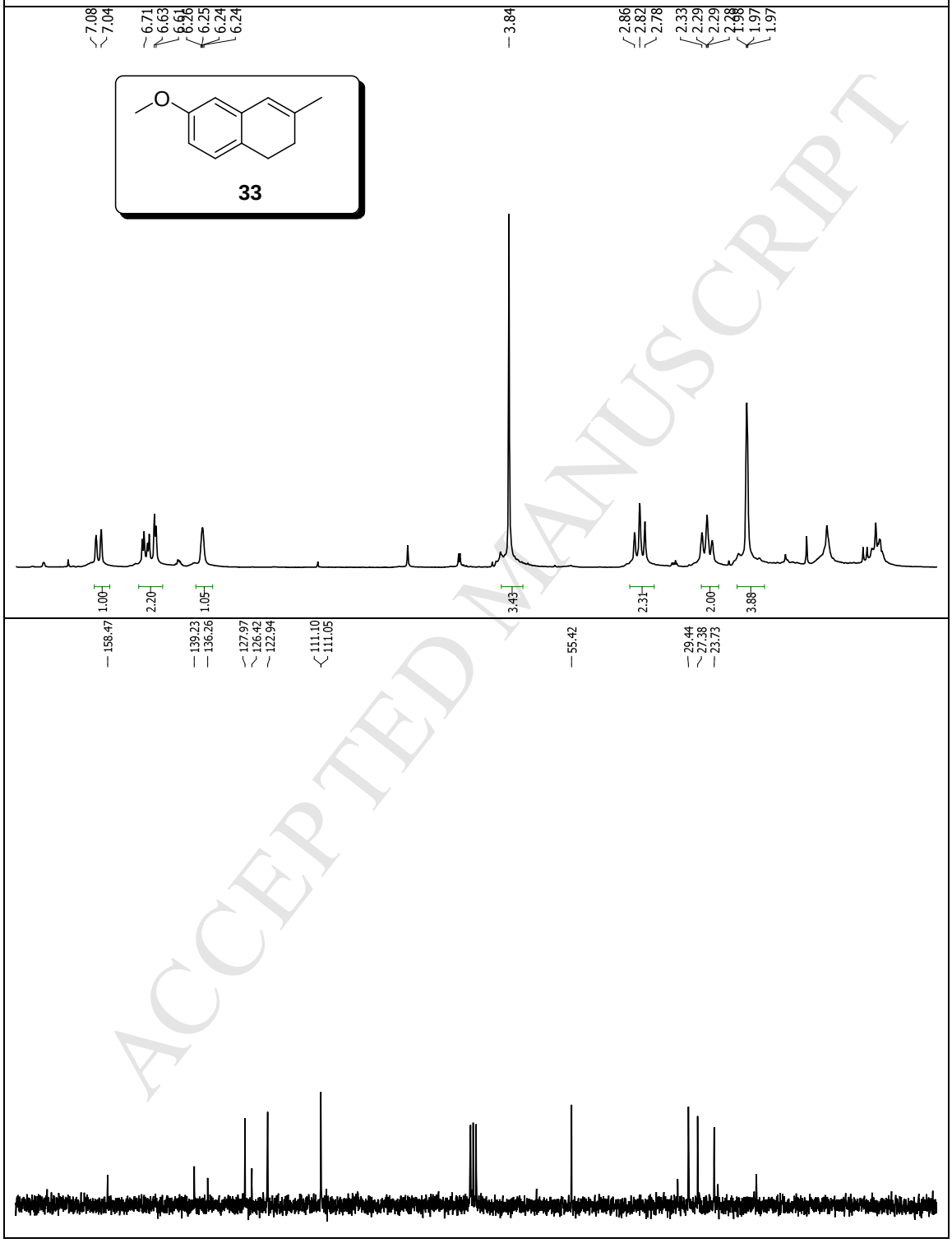


6-(2-Hydroxy-naphthalen-1-yl)-4-methanesulfonyloxy-2-methyltetrahydropyran-3-yl-lacetate (**28**)

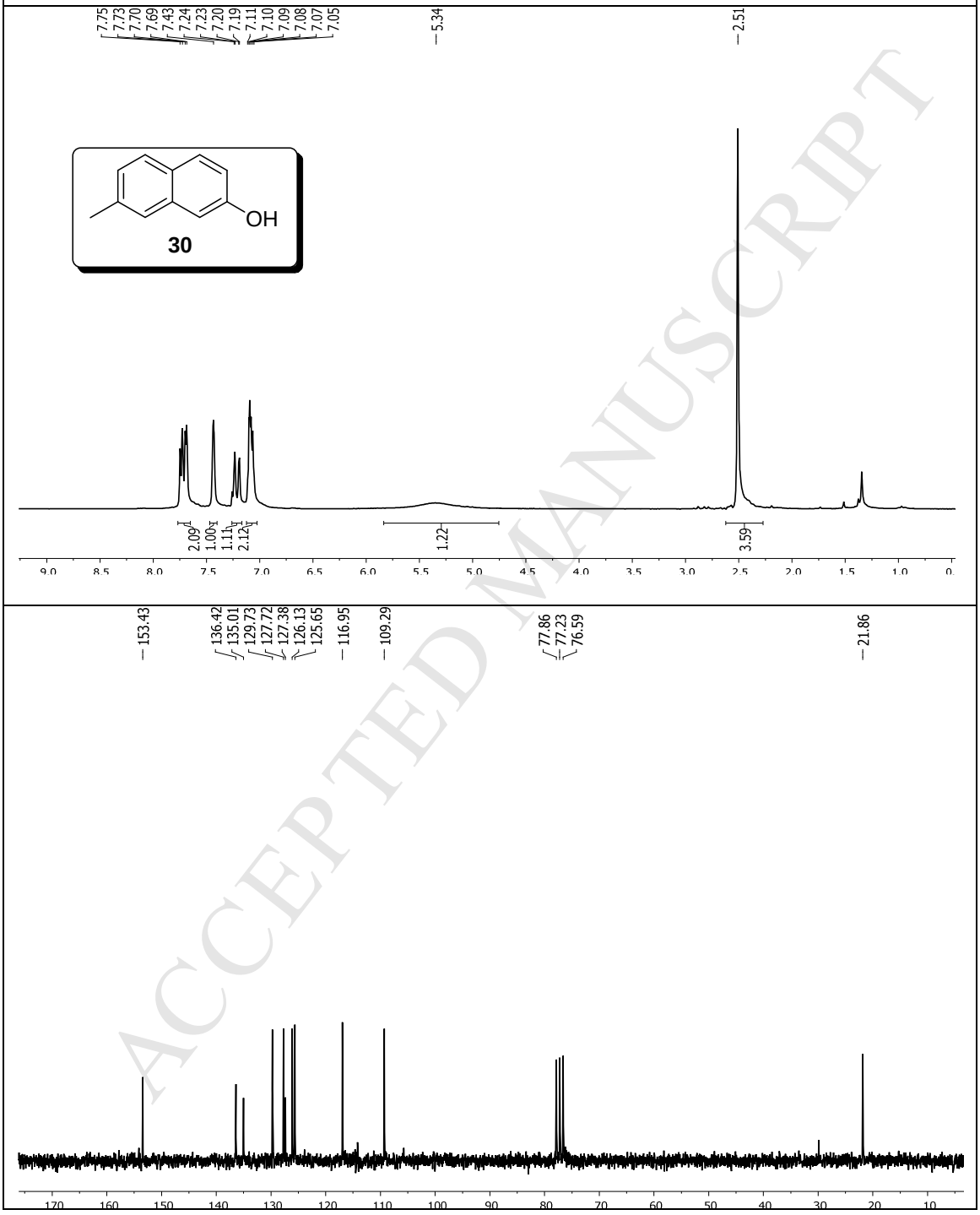
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



6-Methoxy-3-methyl-1,2-dihydronaphthalene (**33**)
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

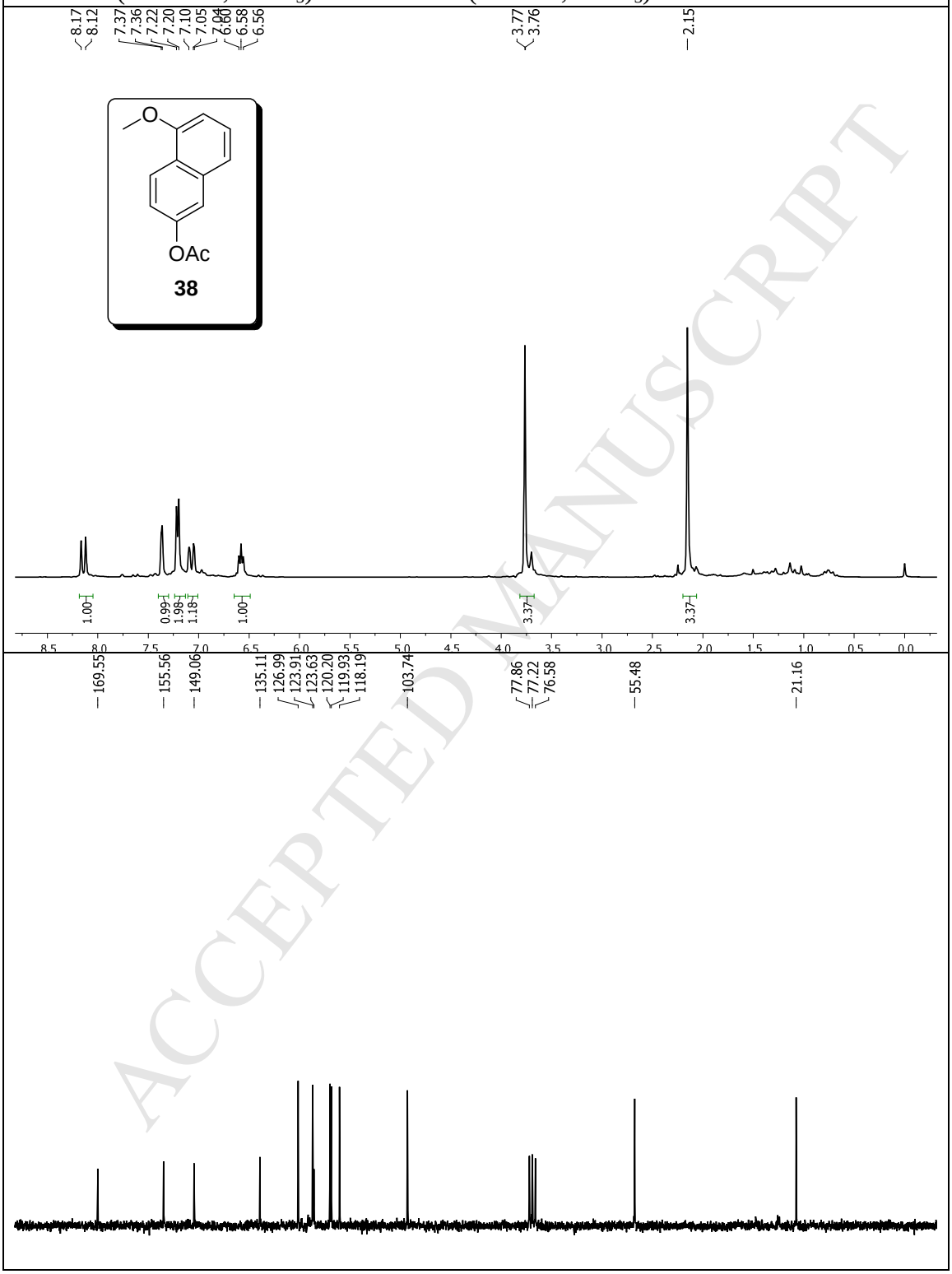


7-Methylnaphthalen-2-ol (**30**)
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



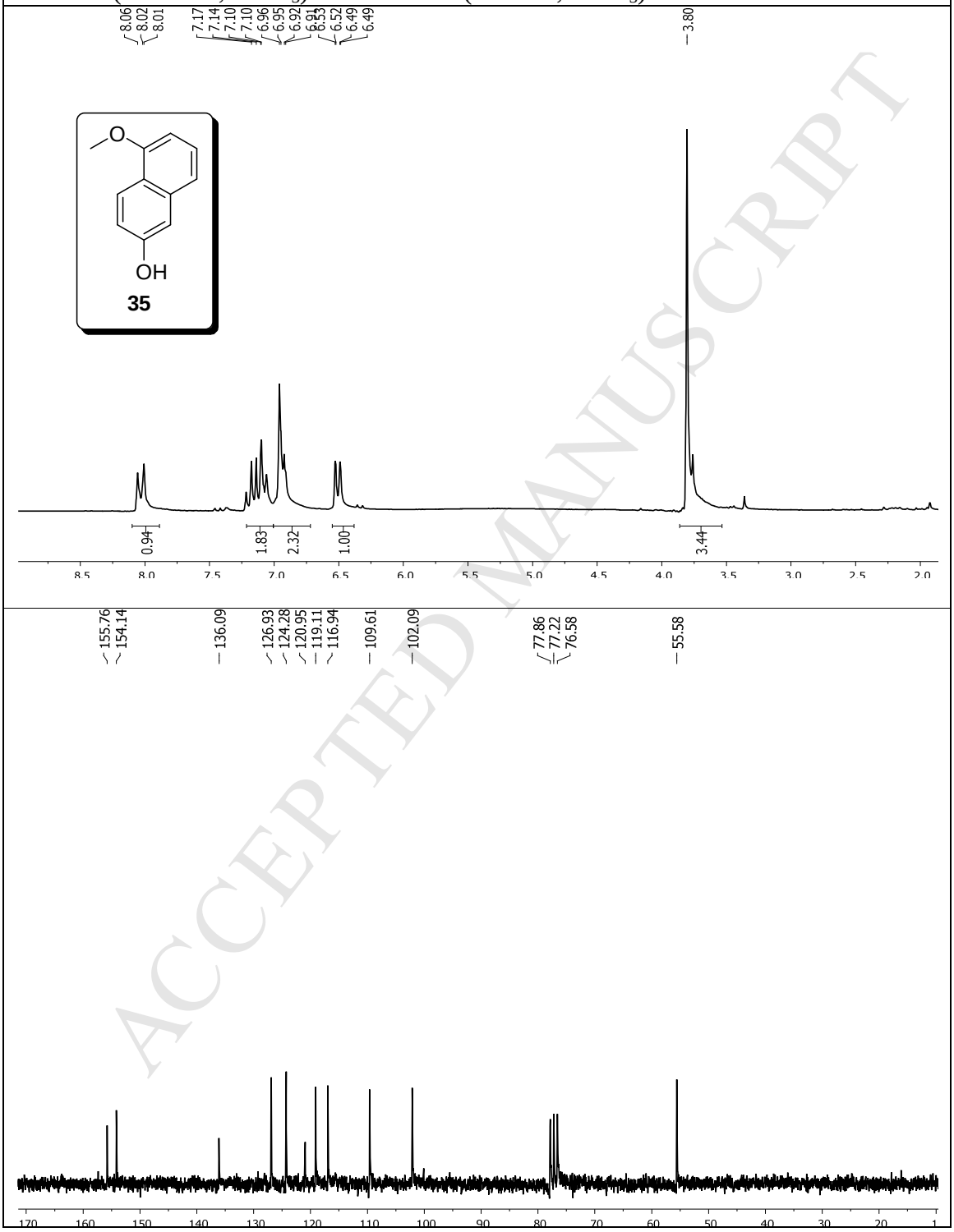
5-Methoxy-naphthalen-2-yl-acetate (**38**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



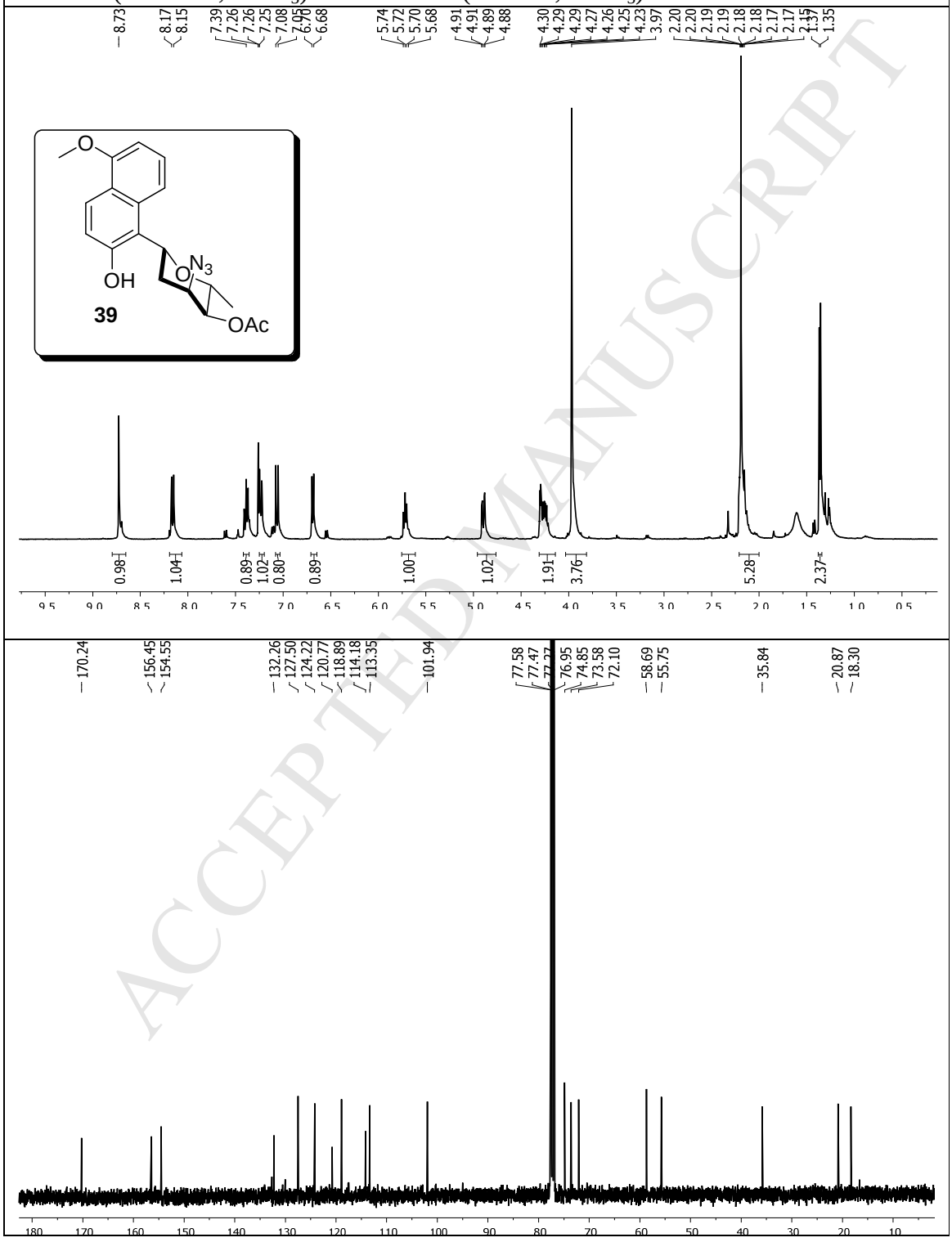
5-Methoxynaphthalen-2-ol (**35**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

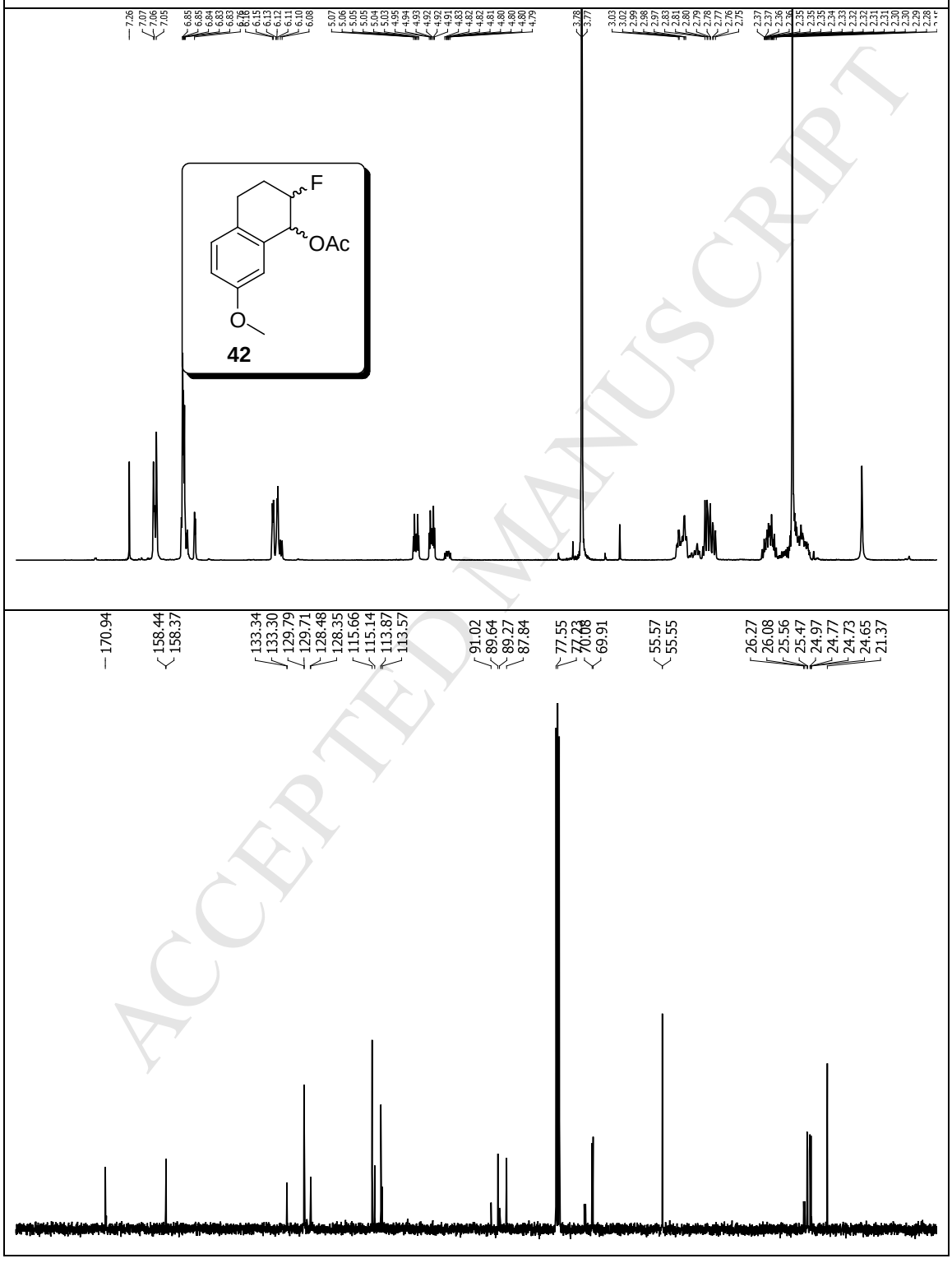


4-Azido-6-(2-hydroxy-5-methoxy-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-acetate (**39**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

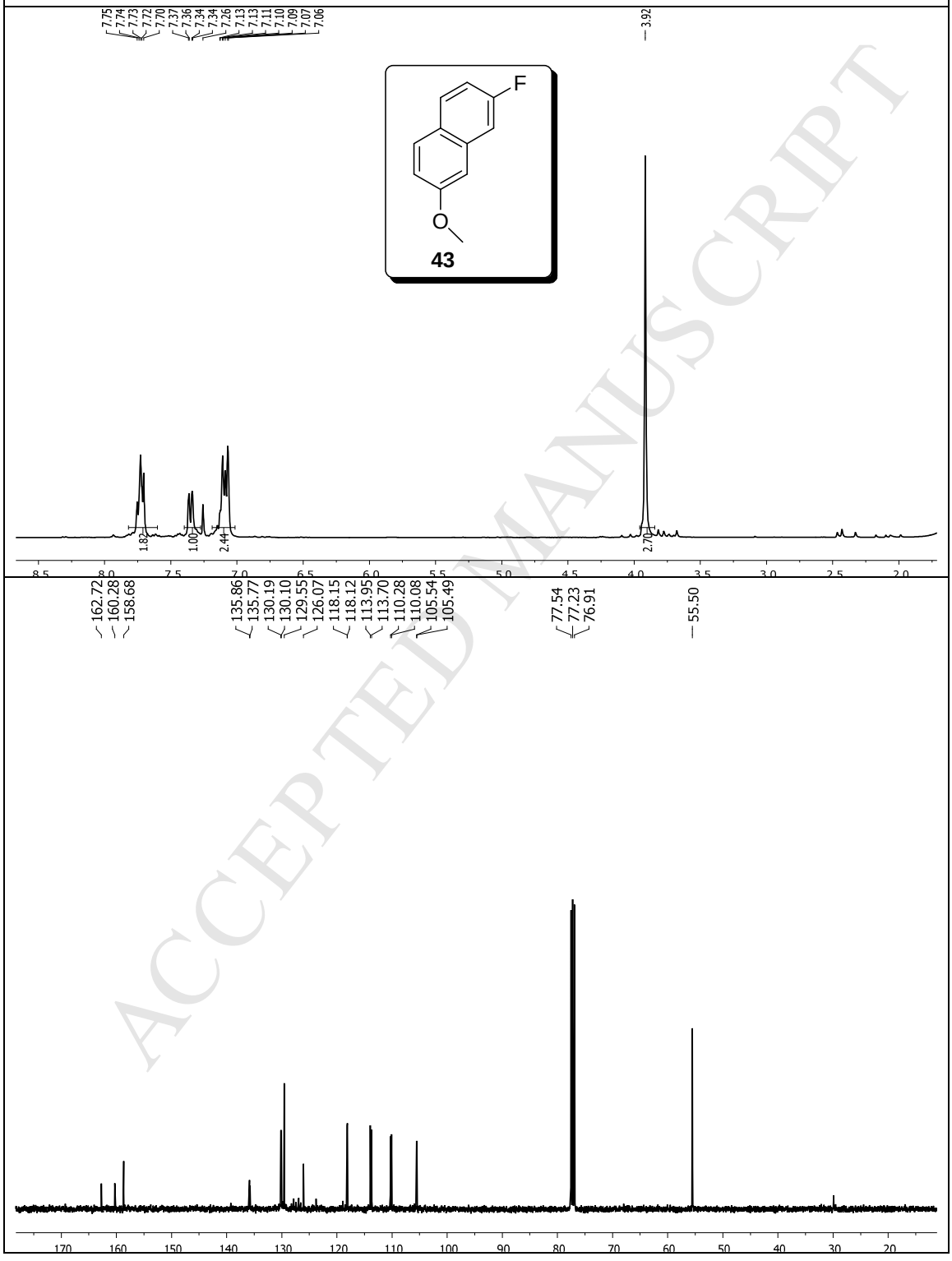


2-Fluoro-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl-acetate (**42**)
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)



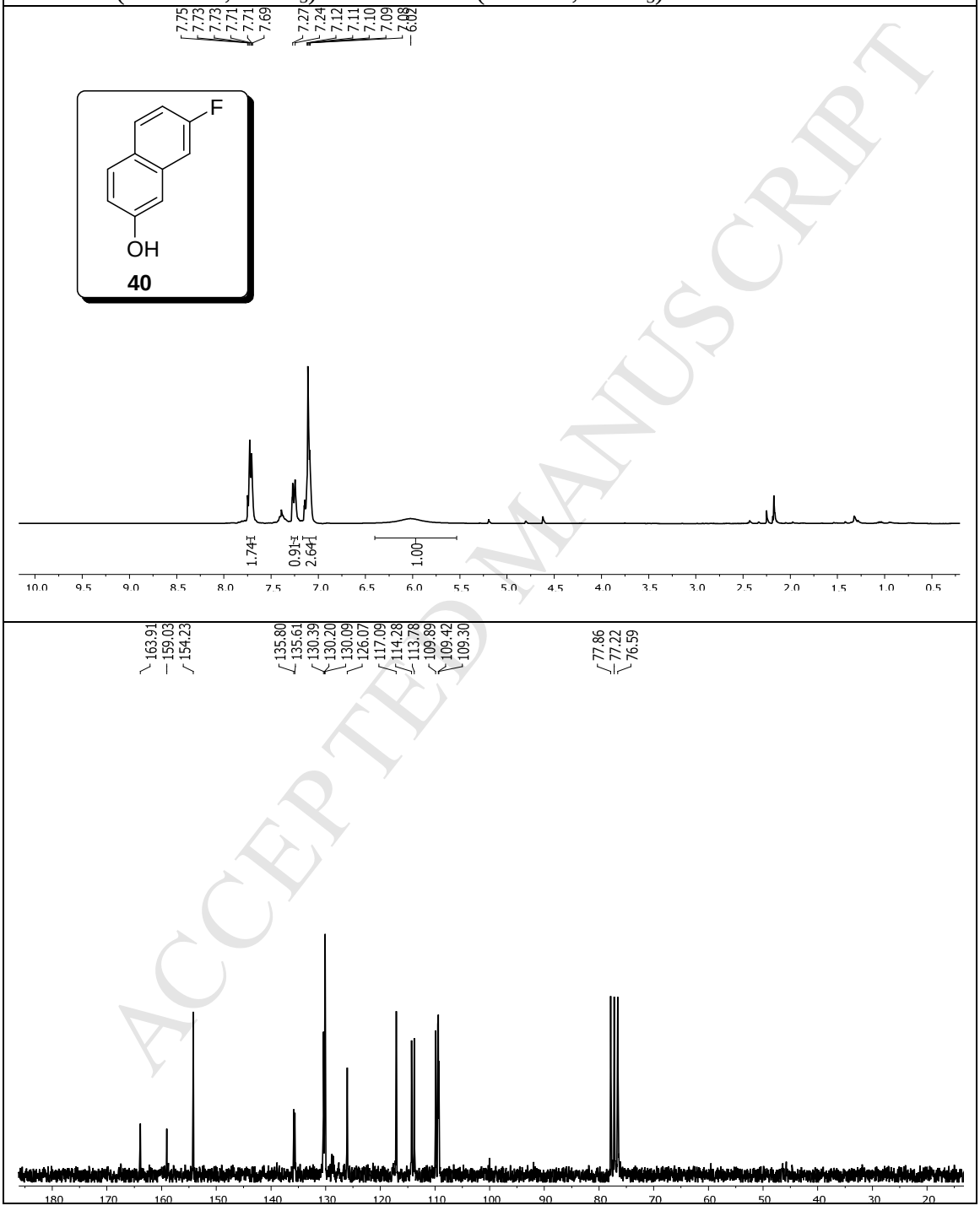
2-Fluoro-7-methoxynaphthalene (**43**)

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



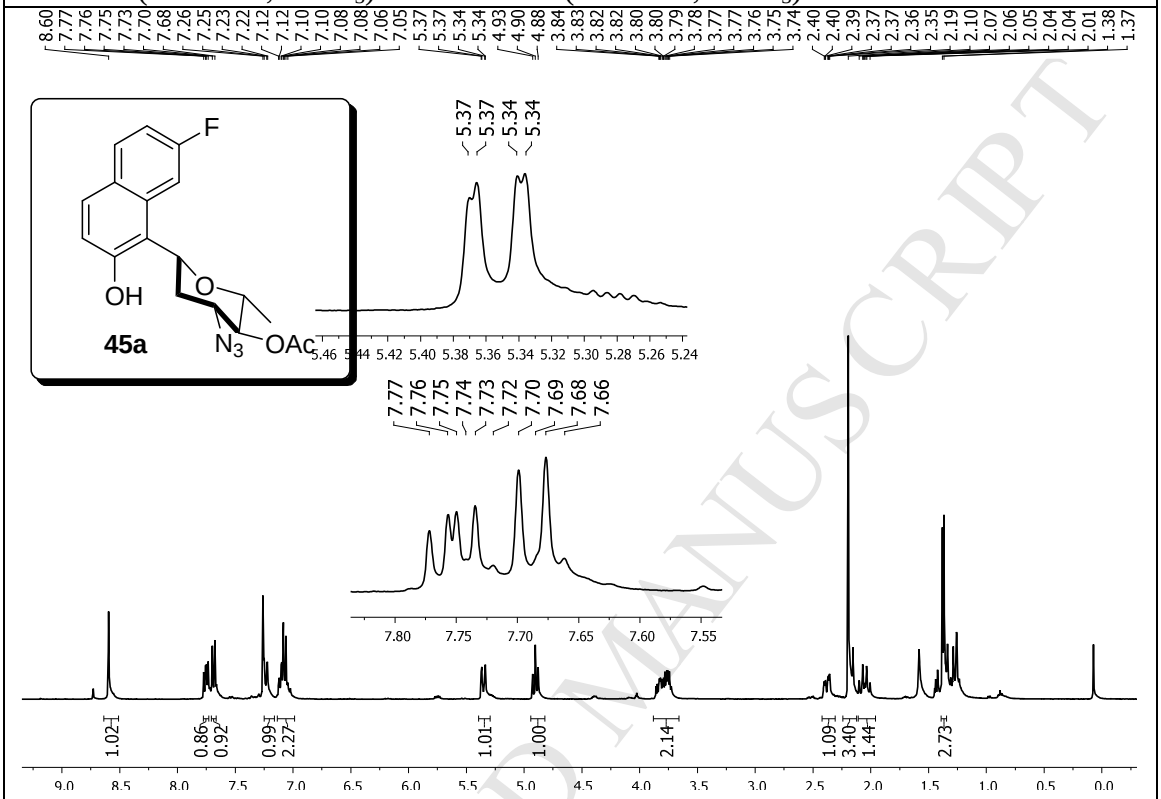
7-Fluoronaphthalen-2-ol (**40**)

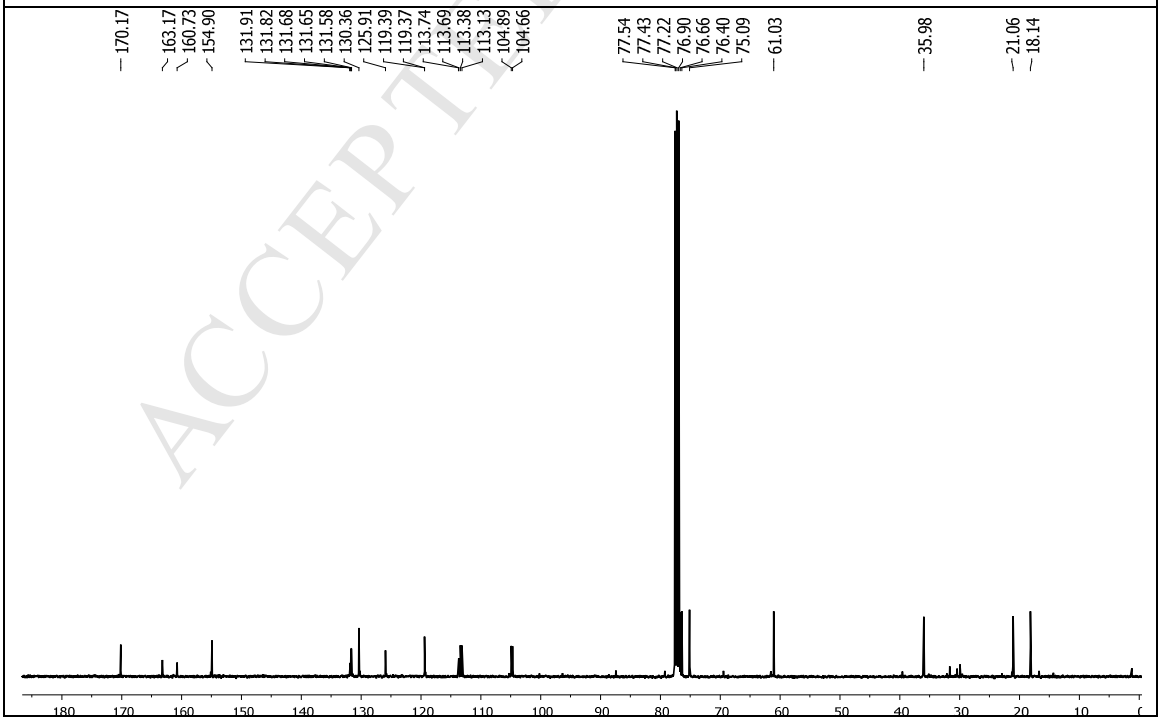
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



4-Azido-6-(7-fluoro-2-hydroxy-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (**45a**)

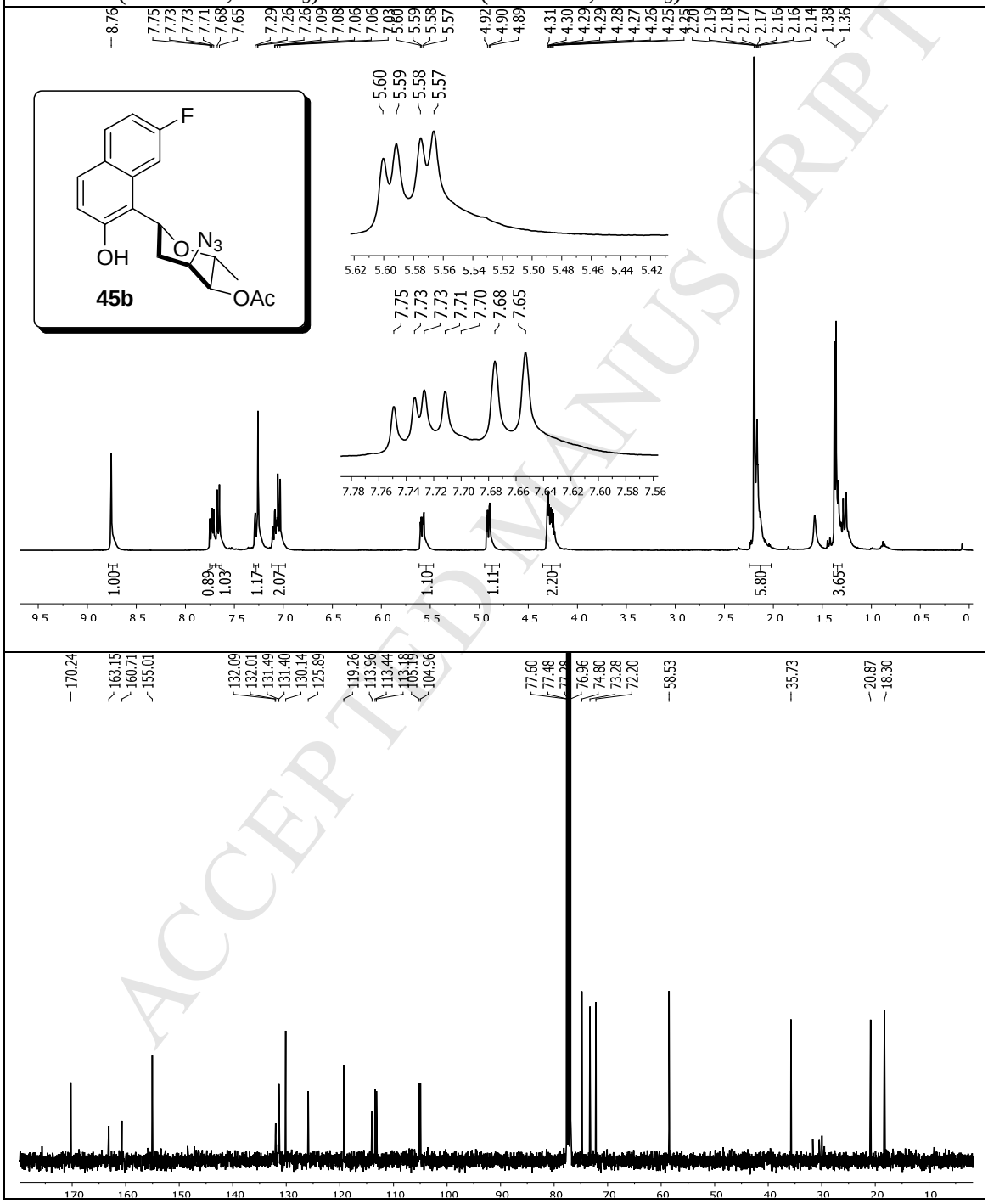
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)





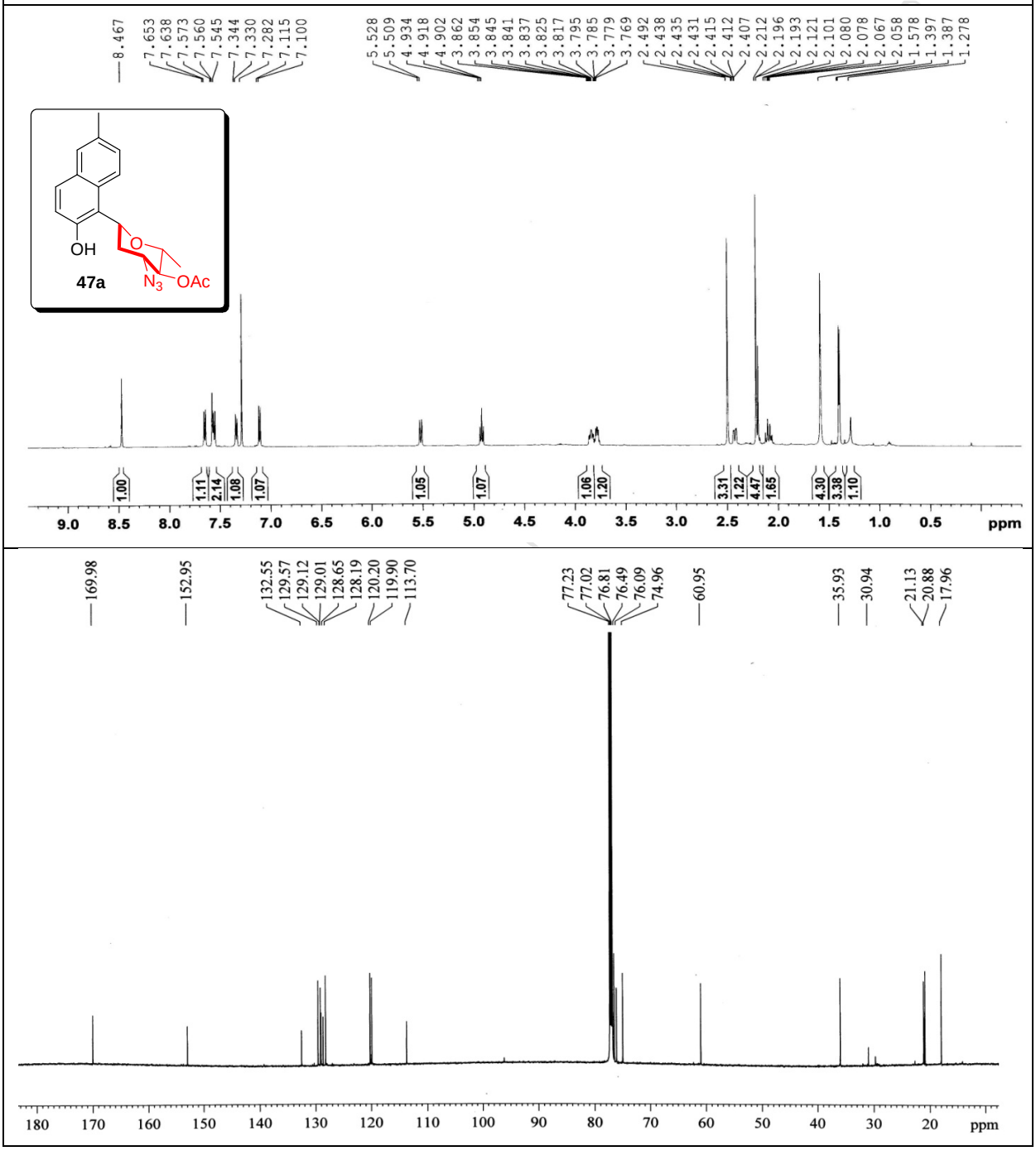
4-Azido-6-(7-fluoro-2-hydroxy-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (45b)

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)



4-(*S*)-Azido-6-(2-hydroxy-6-methyl-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (47a)

^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$)



4-(*R*)-Azido-6-(2-hydroxy-6-methyl-naphthalen-1-yl)-2-methyltetrahydropyran-3-yl-methylester (47b, major) and **(3S,4R,6S)-4-azido-6-(2-hydroxy-6-methylnaphthalen-1-yl)-2-methyltetrahydro-2H-pyran-3-yl acetate (47c, minor)**

^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$)