

Supporting Information

New Monoterpene Glycoside Paeoniflorin Derivatives as NO and IL-1 β Inhibitors: Synthesis and Biological Evaluation

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1. Reaction condition optimization

Among the screening results of Lewis acids, $\text{Sc}(\text{CF}_3\text{SO}_3)_3$ has the fastest reaction speed and the highest yield. $\text{Sc}(\text{CF}_3\text{SO}_3)_3$ is chosen as the catalyst for the experimental reaction. The screening results of Lewis acid are shown in **Table S1**.

Table S1. Lewis acid screening results

Entry	Solvent	Temp. (°C)	Lewis acid	Time (h)	Yield (%)
1	MeOH	65	NiCl_2	6	No reaction
2	MeOH	65	Br_2Cu	6	25
3	MeOH	65	FeCl_3	5	72
4	MeOH	65	BiCl_3	2	86
5	MeOH	65	BiBr_3	5	70
6	MeOH	65	PbCl_2	2	84
7	MeOH	65	InI_3	8	10
8	MeOH	65	$\text{Yb}(\text{CF}_3\text{SO}_3)_3$	8	15
9	MeOH	65	$\text{Cu}(\text{CF}_3\text{SO}_3)_2$	8	12
10	MeOH	65	$\text{Sc}(\text{CF}_3\text{SO}_3)_3$	1	90
11	MeOH	65	$\text{Zn}(\text{CF}_3\text{SO}_3)_2$	8	No reaction
12	MeOH	65	$\text{La}(\text{CF}_3\text{SO}_3)_3$	8	12

The above results are obtained when the molar ratio of paeoniflorin to $\text{Sc}(\text{CF}_3\text{SO}_3)_3$ is 1: 0.5. it is necessary to continue to optimize the molar ratio of paeoniflorin to $\text{Sc}(\text{CF}_3\text{SO}_3)_3$, and select the molar ratios of 1: 0.5, 1: 1, and 1: 1.5 for comparison. The reaction completion time is shortened when the molar ratio is raised to 1: 1. Then the molar ratio is increased to 1:1.5, and the reaction completion time has no significant change compared with the reaction completion time when the molar ratio is 1:1. It was finally determined that the molar ratio of paeoniflorin to Lewis acid was 1:1. The reaction was heated to reflux at the boiling point of the solvent. The screening results of the molar ratio of paeoniflorin to $\text{Sc}(\text{CF}_3\text{SO}_3)_3$ are shown in **Table S2**.

Table S2. Molar ratio screening results

Entry	Proportion	Time (h)	Yield (%)
1	1: 0.5	1.0	90
2	1: 1	0.5	95
3	1: 1.5	0.5	93

2. ^1H NMR and ^{13}C NMR spectra of the synthesized compounds

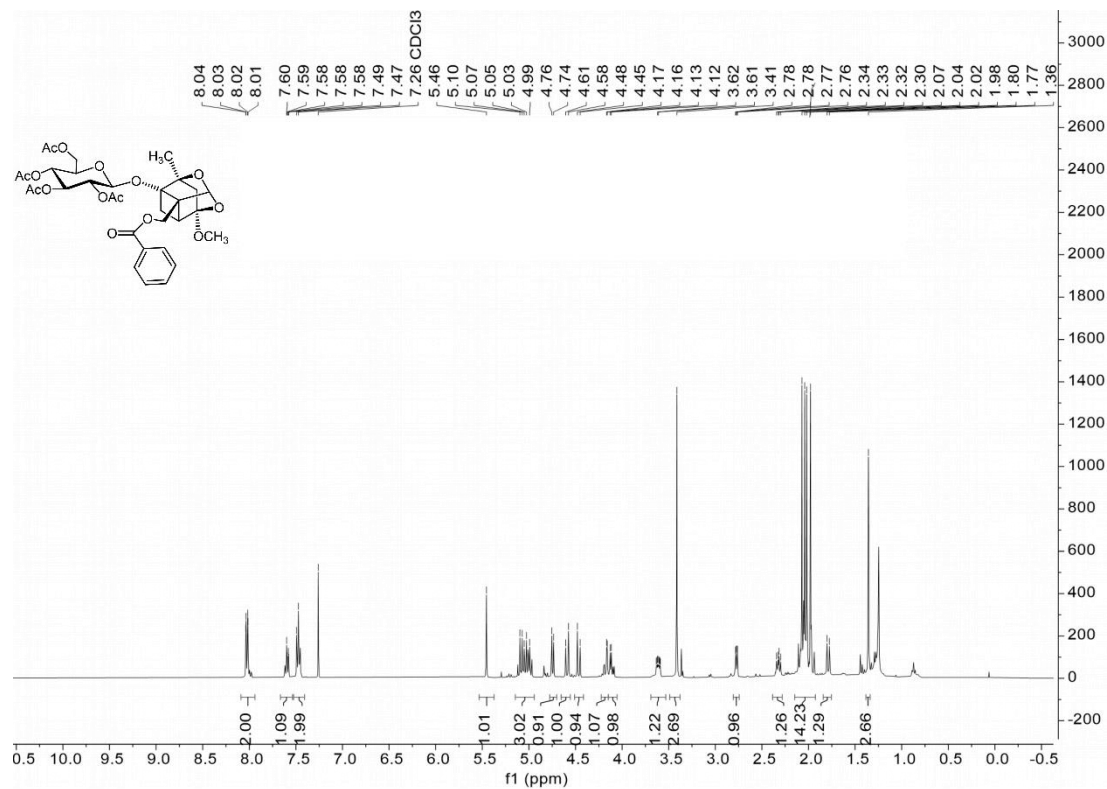


Figure S1. The ^1H NMR of compound 1.

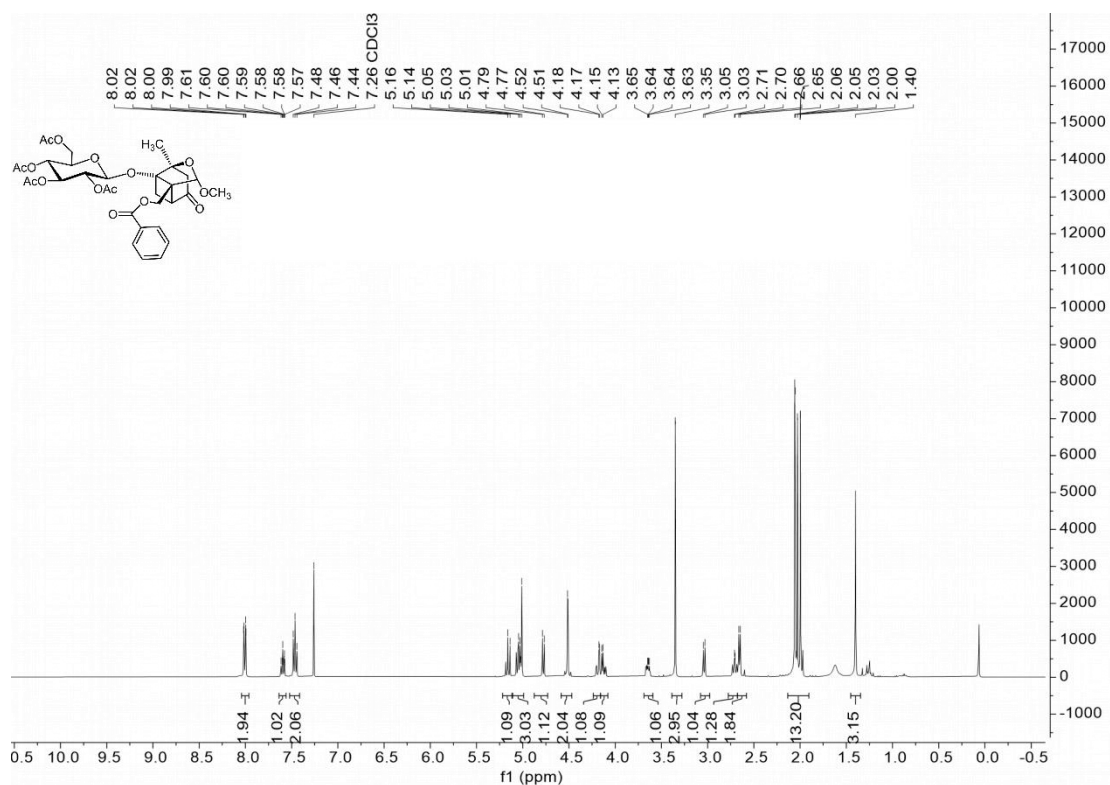


Figure S2. The ¹H NMR of compound **2**.

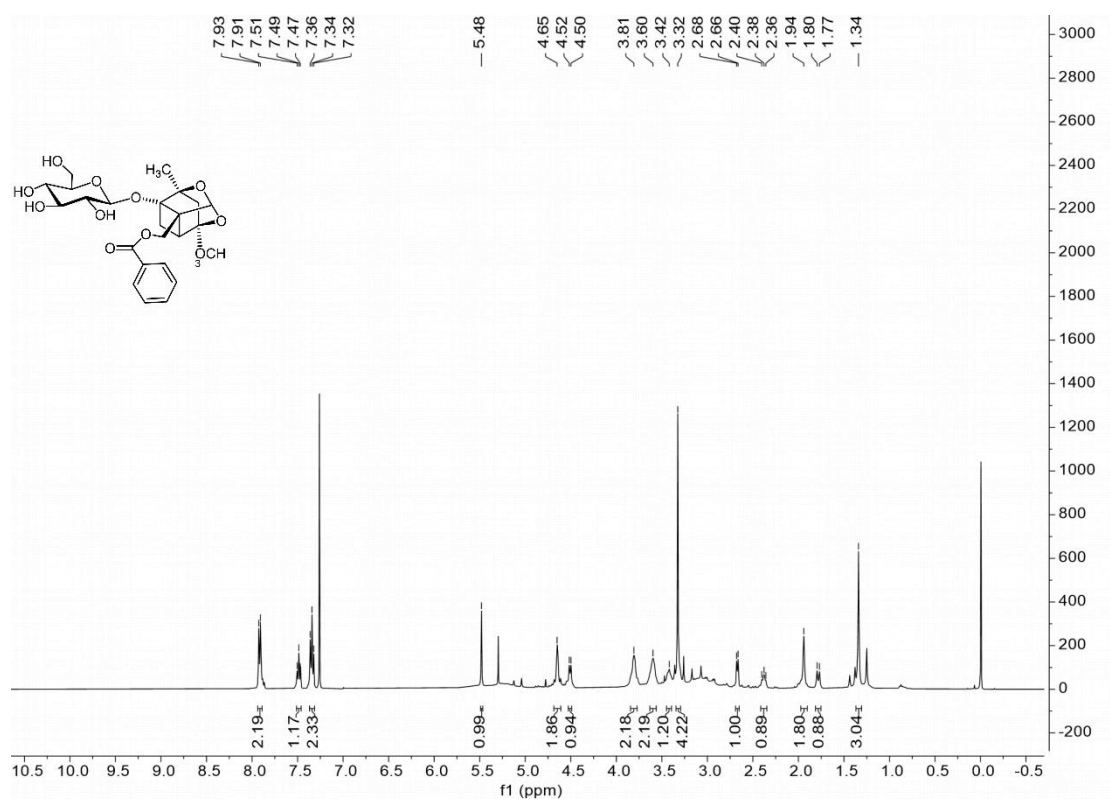


Figure S3. The ¹H NMR of compound **3**.

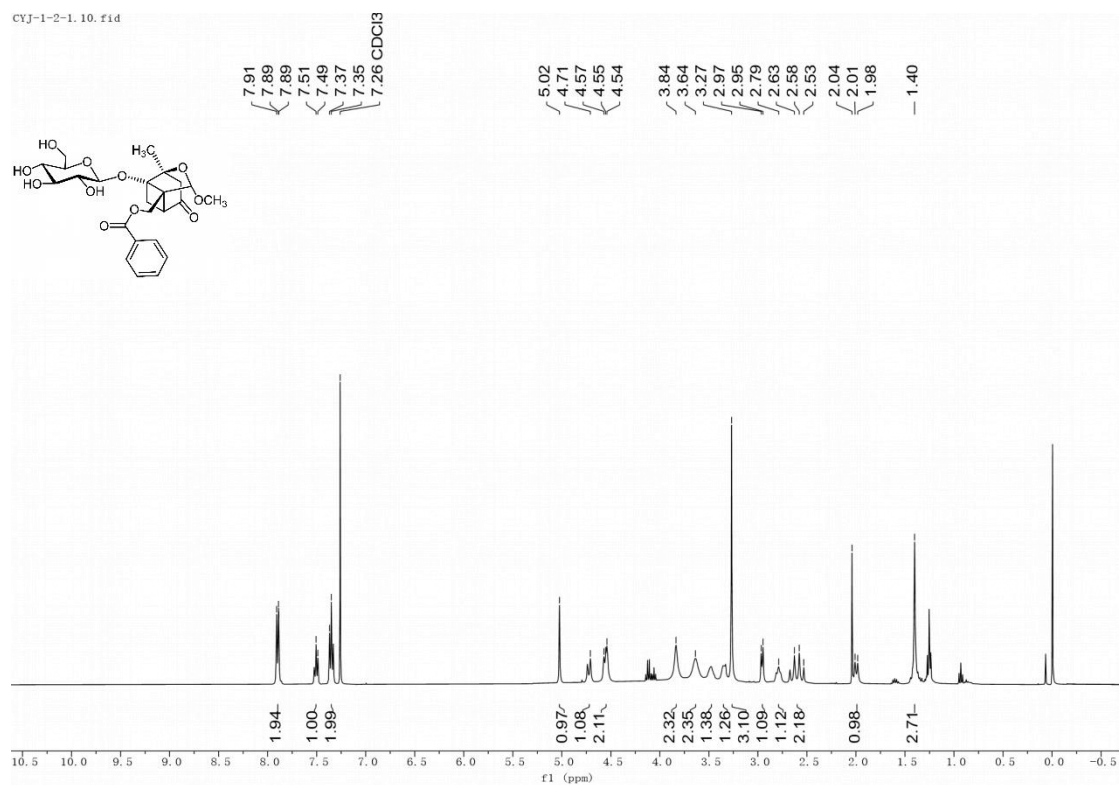


Figure S4. The ¹H NMR of compound **4**.

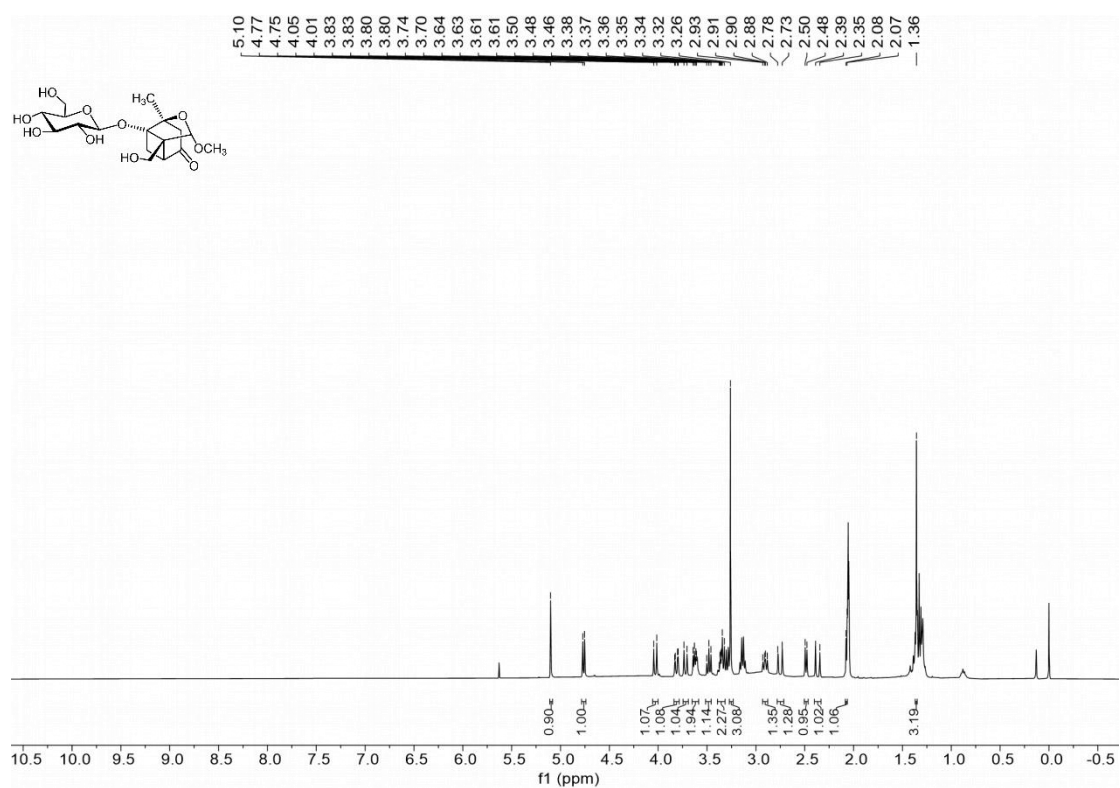


Figure S5. The ¹H NMR of compound **5**.

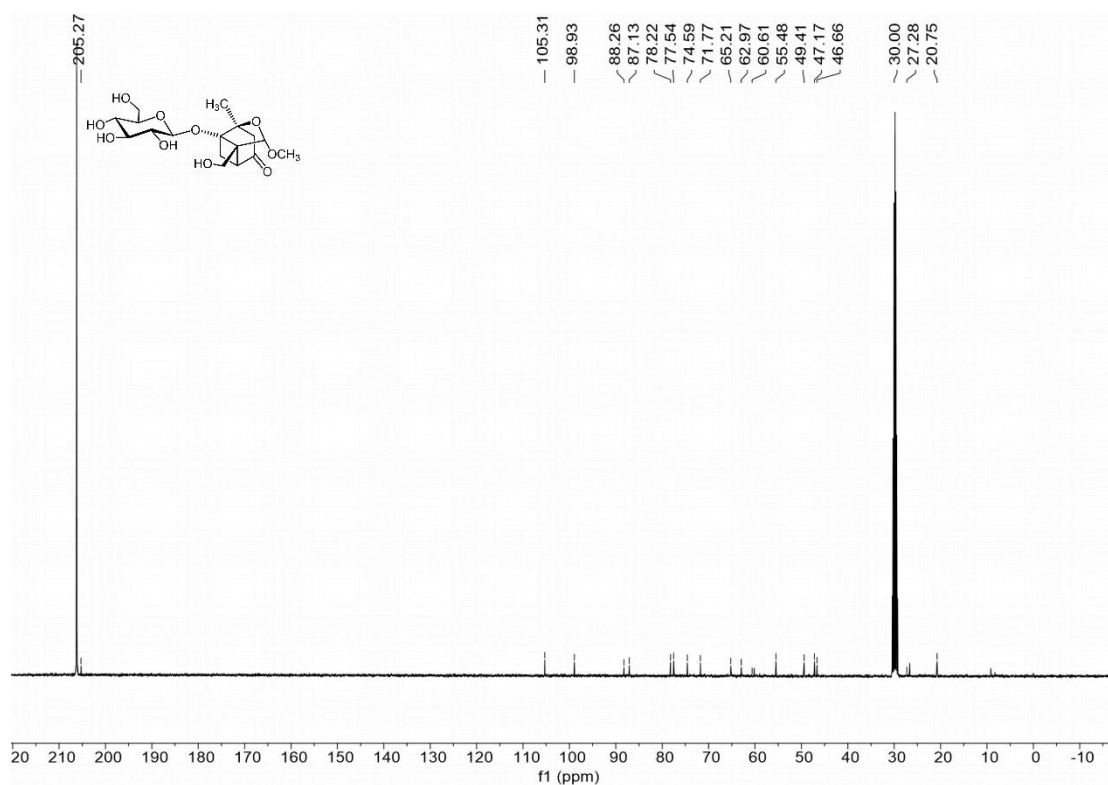


Figure S6. The ¹³C NMR of compound **5**.

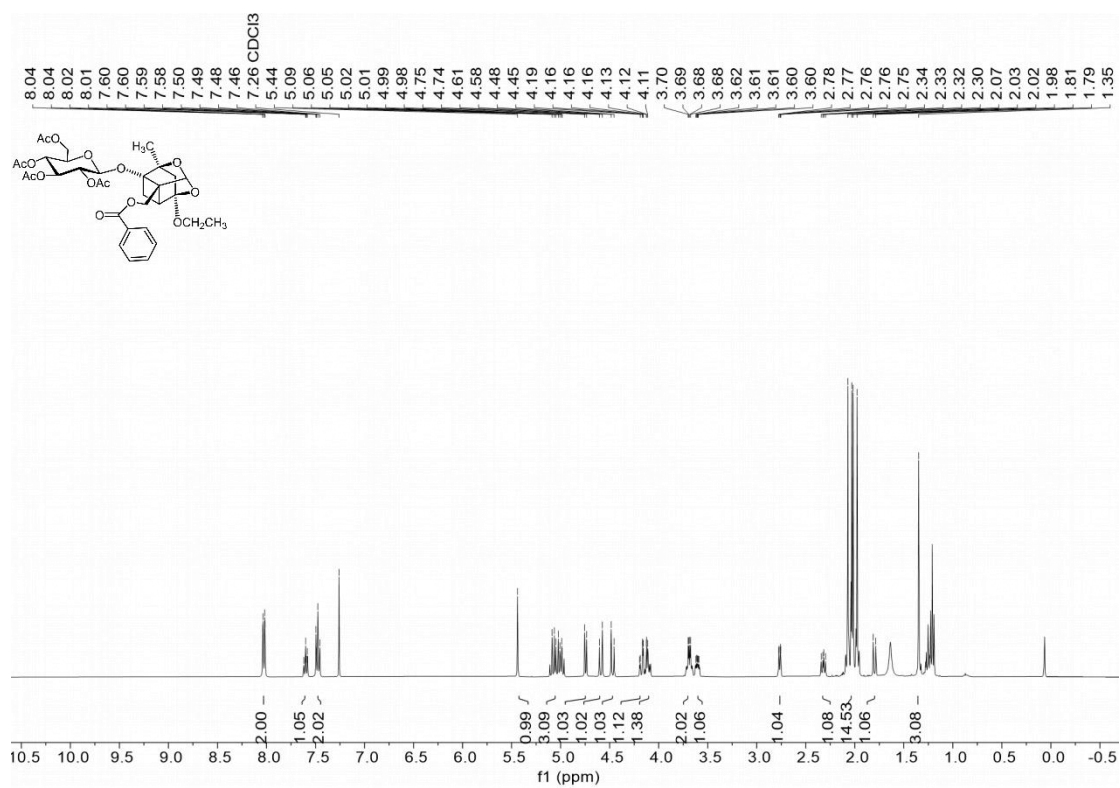


Figure S7. The ¹H NMR of compound **6**.

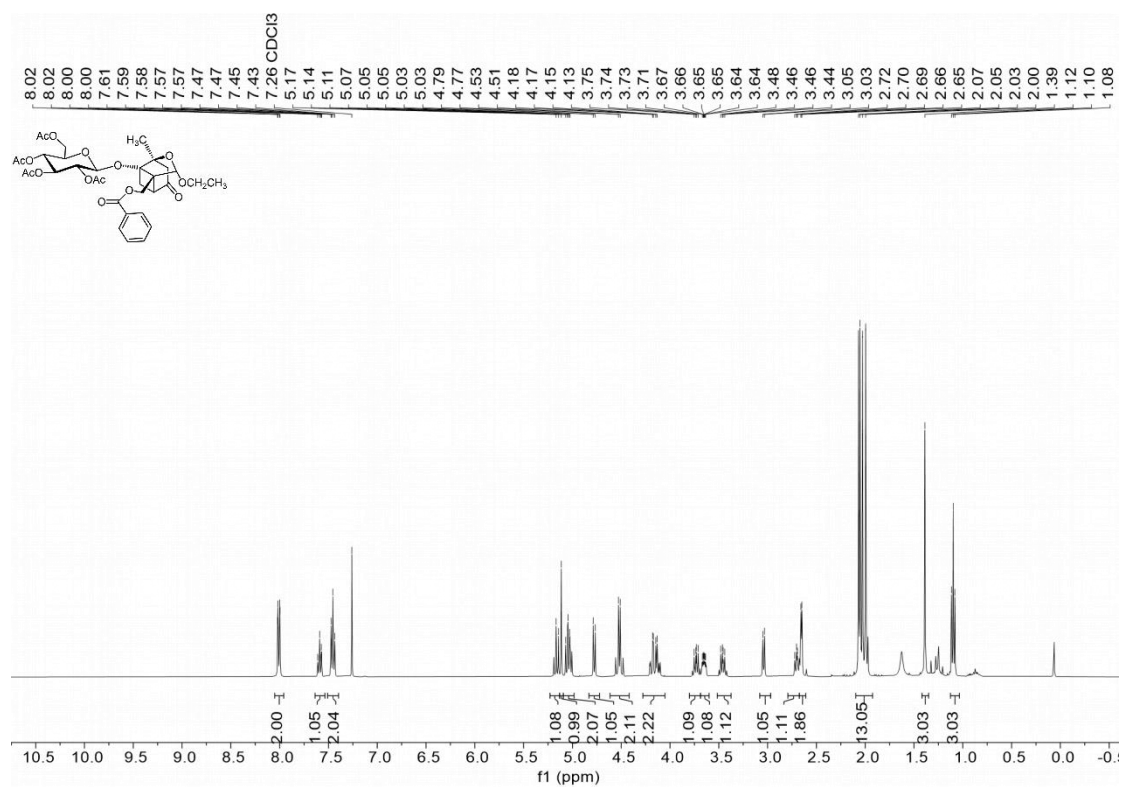


Figure S8. The ¹H NMR of compound 7.

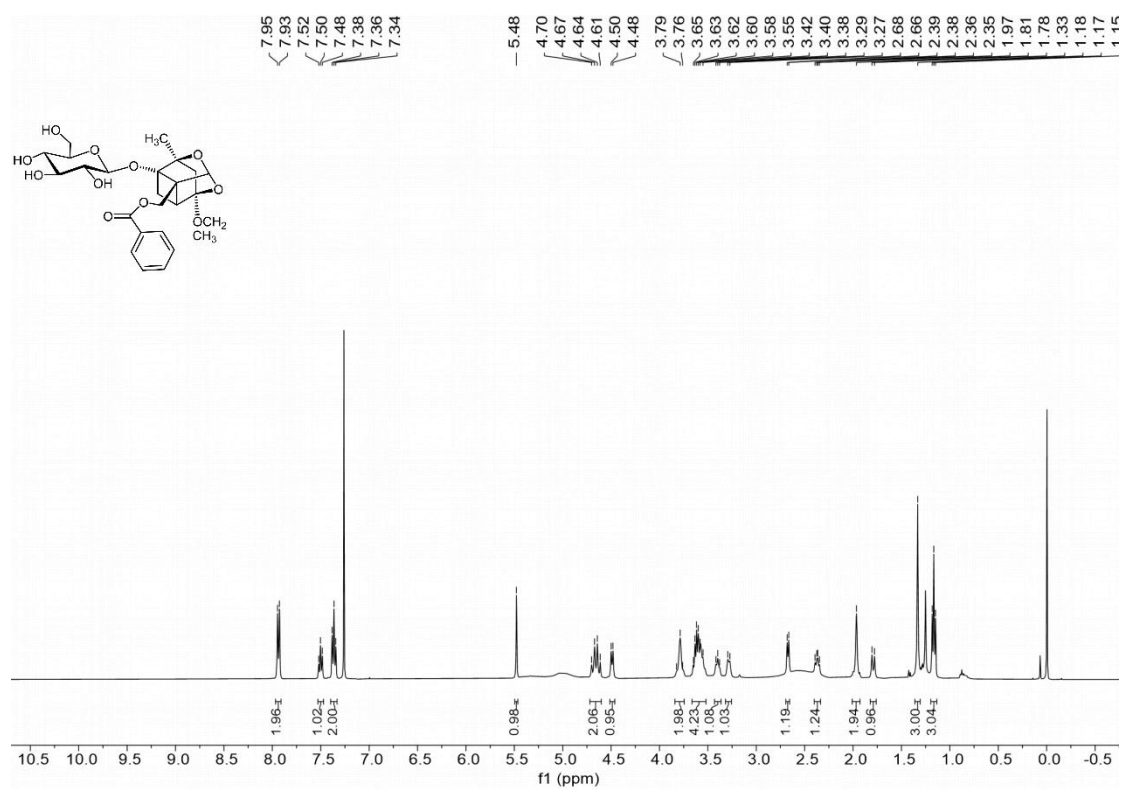


Figure S9. The ¹H NMR of compound 8.

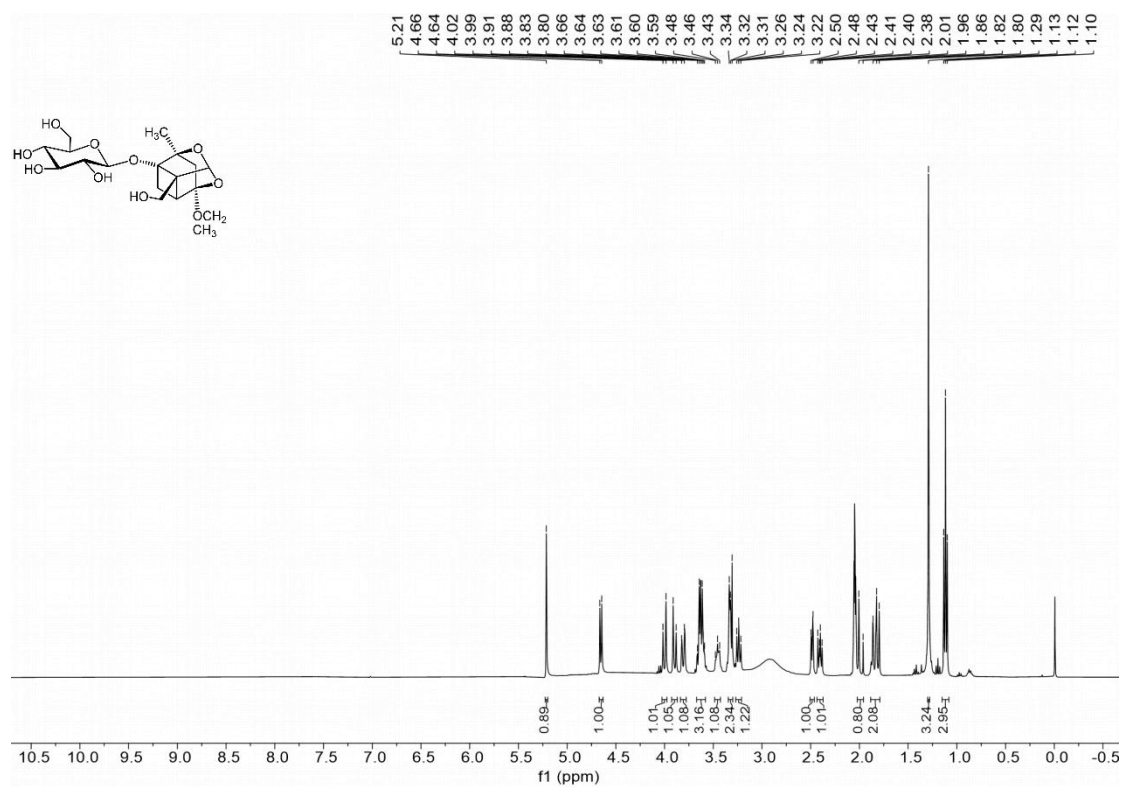


Figure S10. The ¹H NMR of compound **9**.

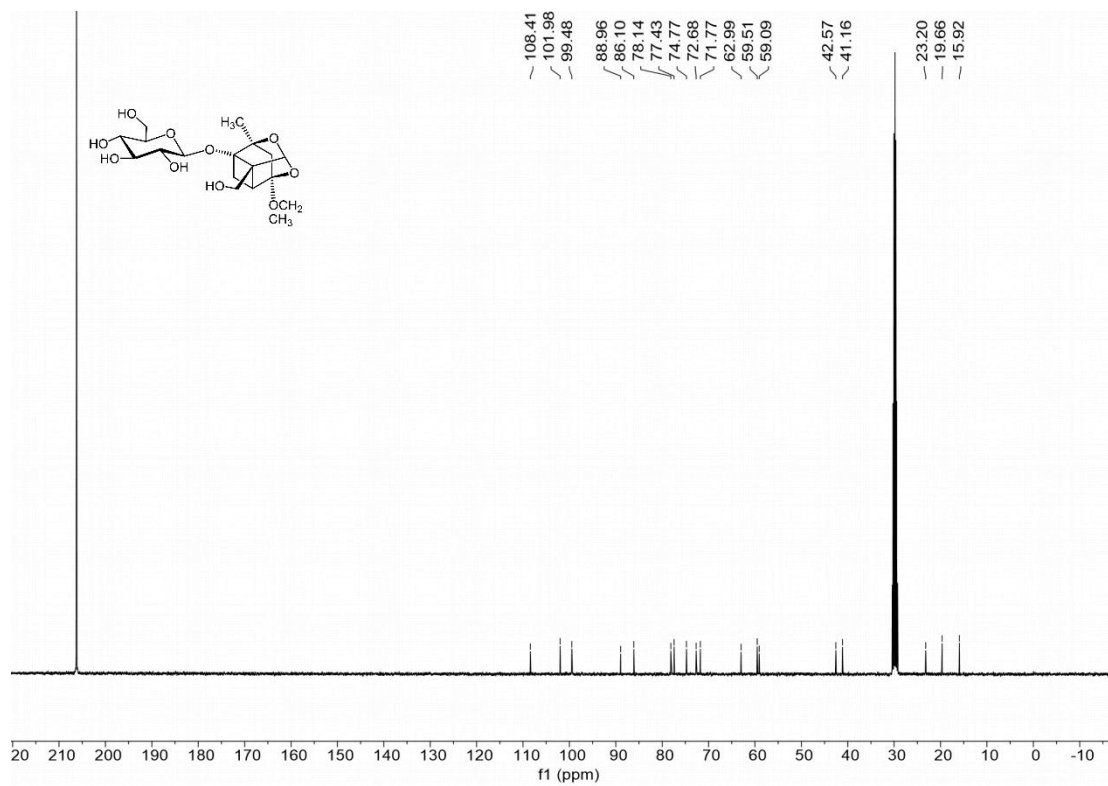


Figure S11. The ¹³C NMR of compound **9**.

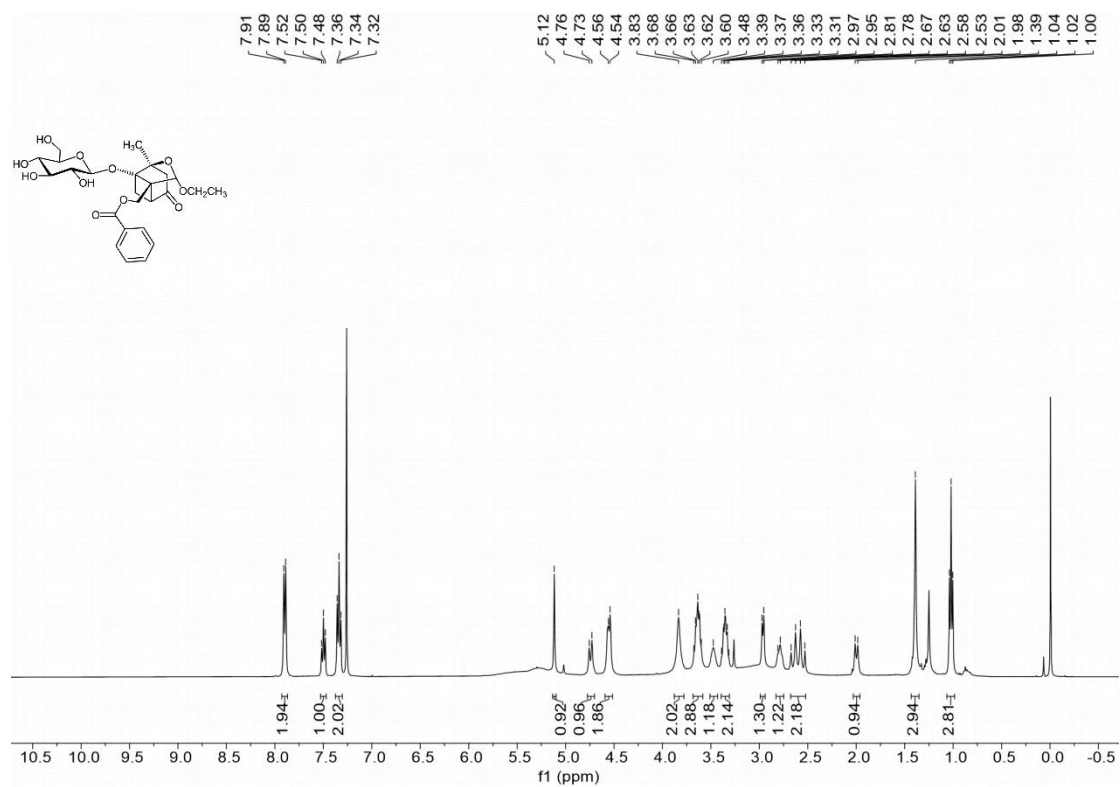


Figure S12. The ¹H NMR of compound 10.

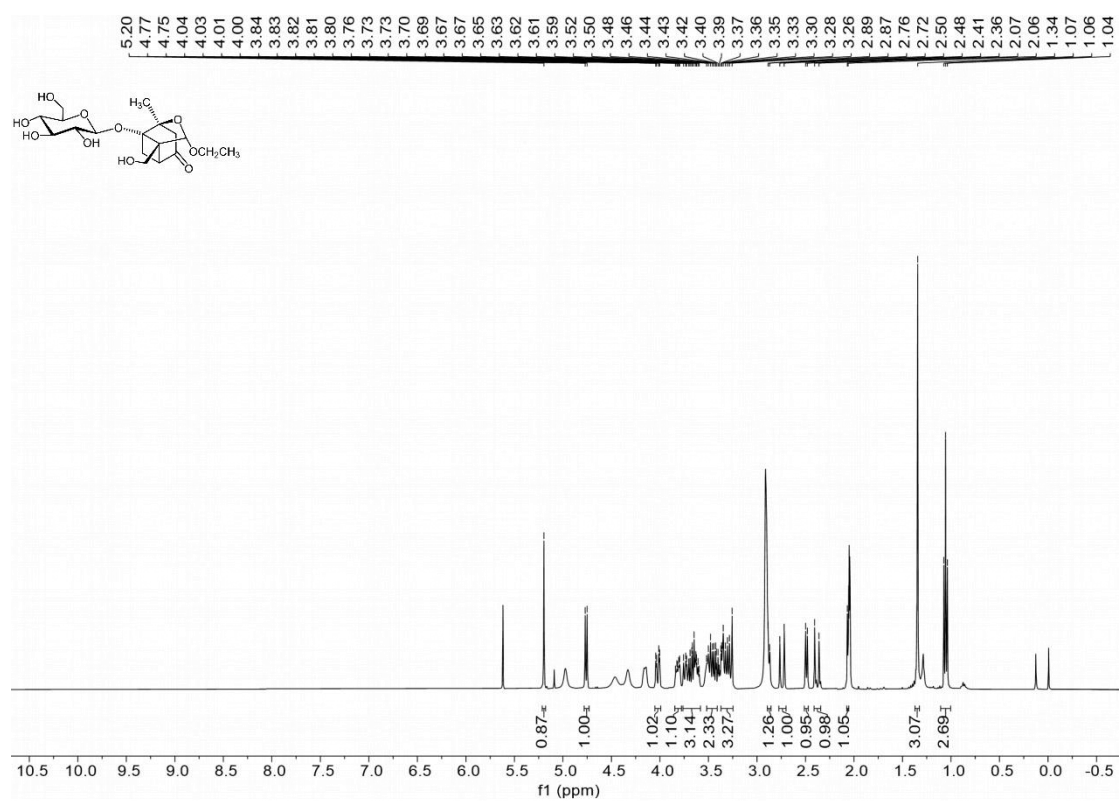


Figure S13. The ¹H NMR of compound 11.

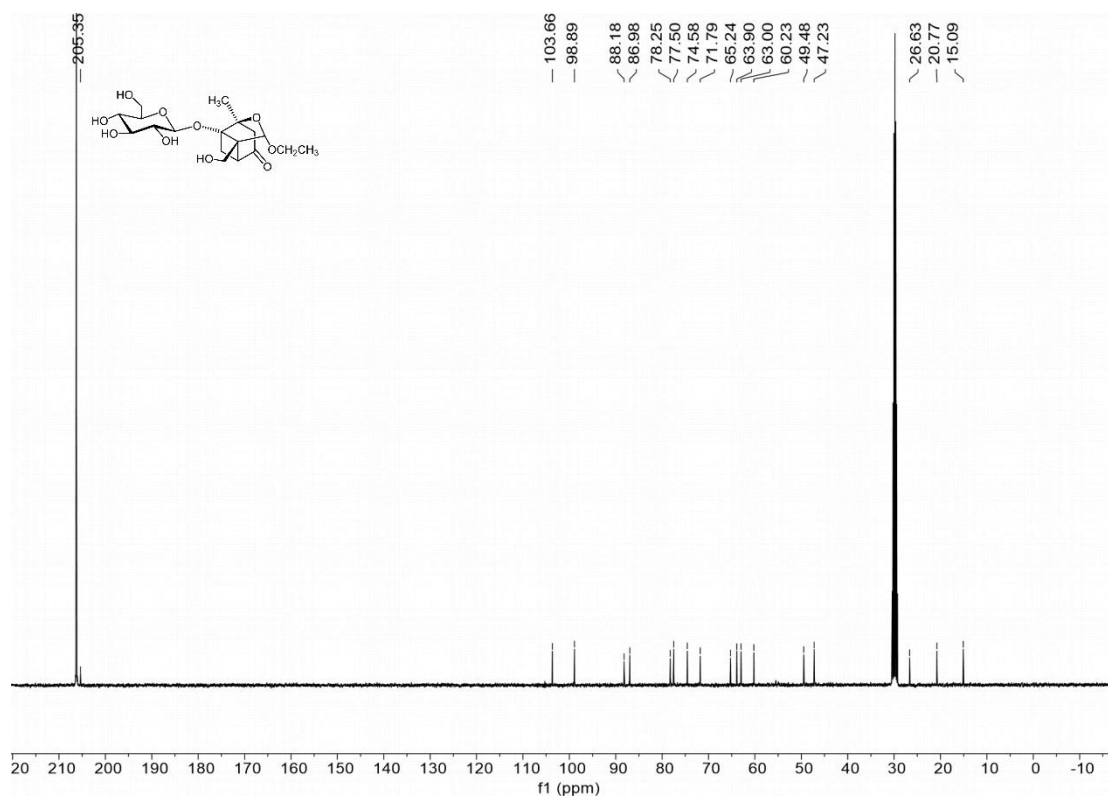


Figure S14. The ¹³C NMR of compound 11.

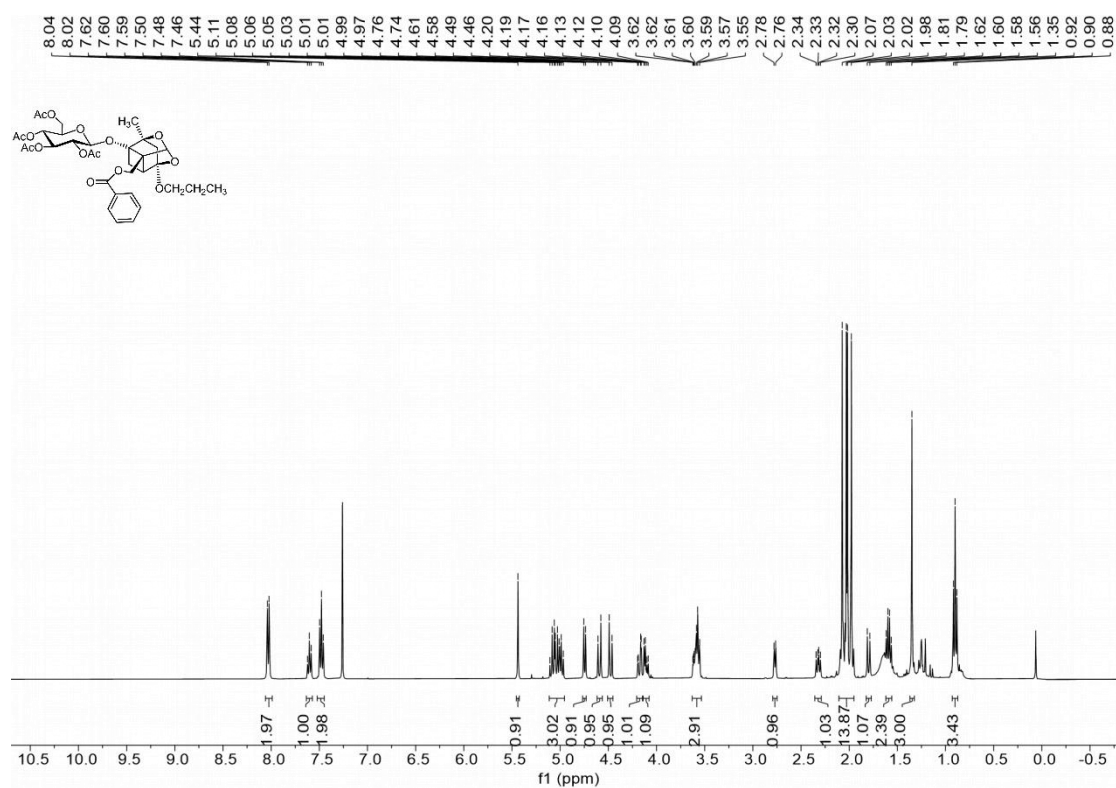
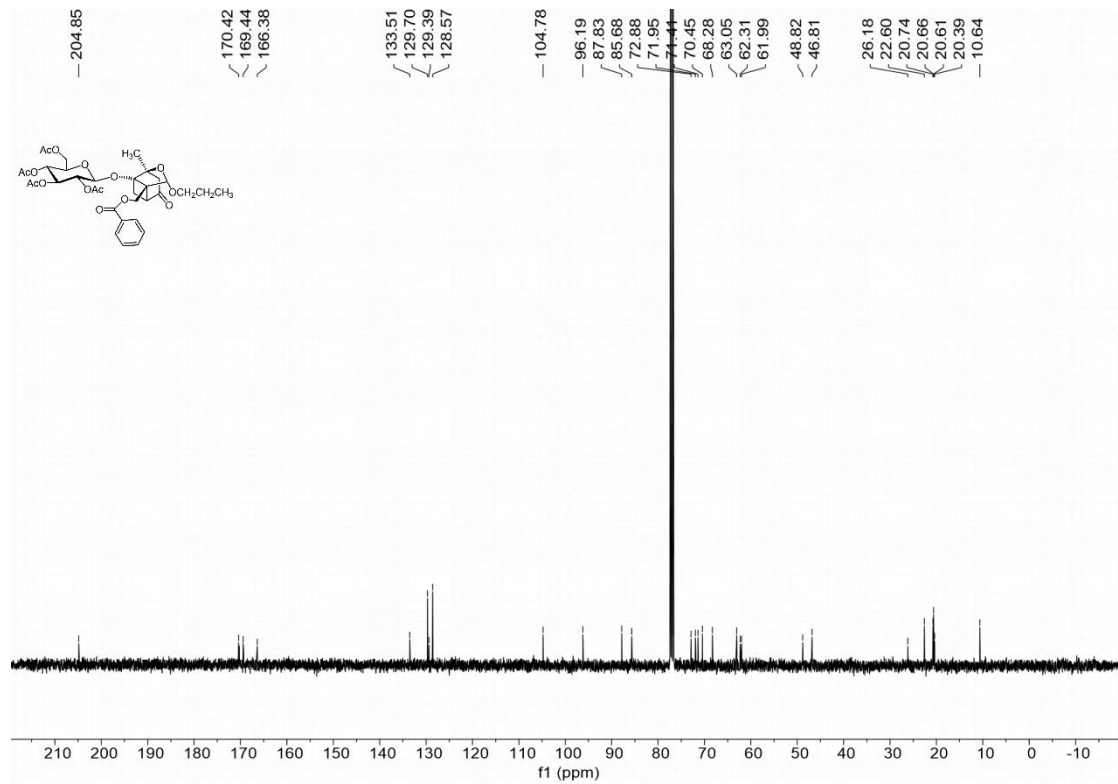
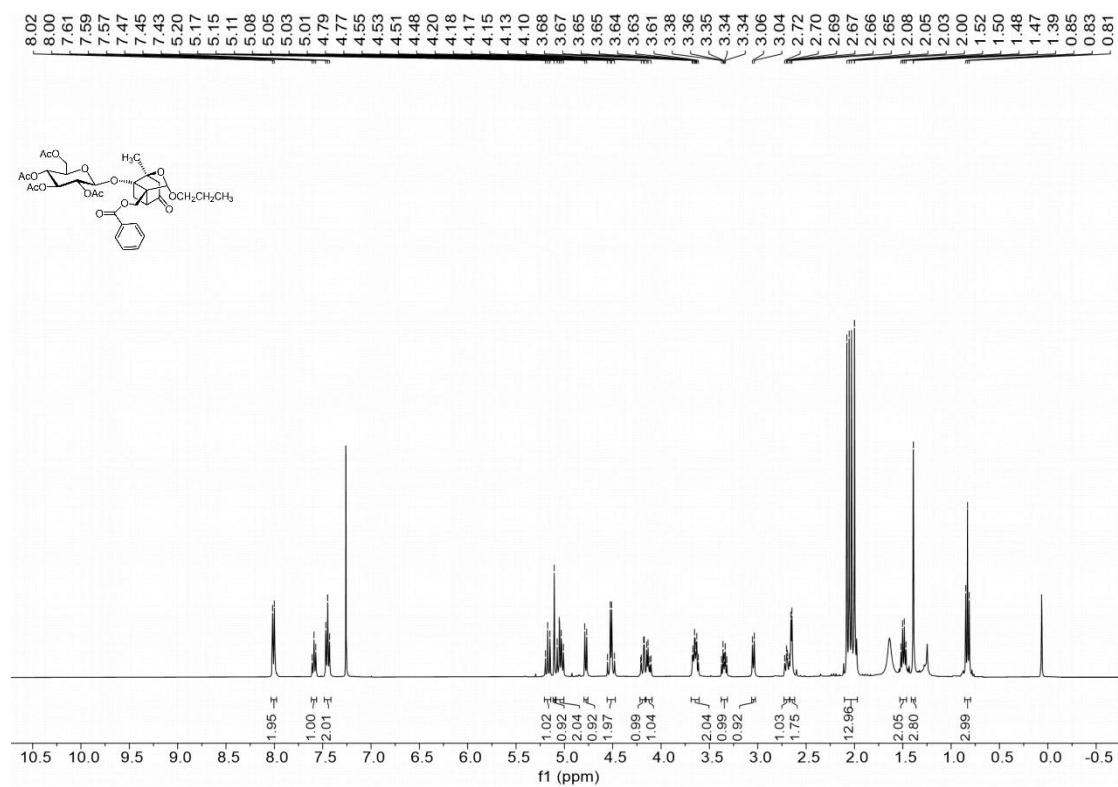


Figure S15. The ¹H NMR of compound 12.



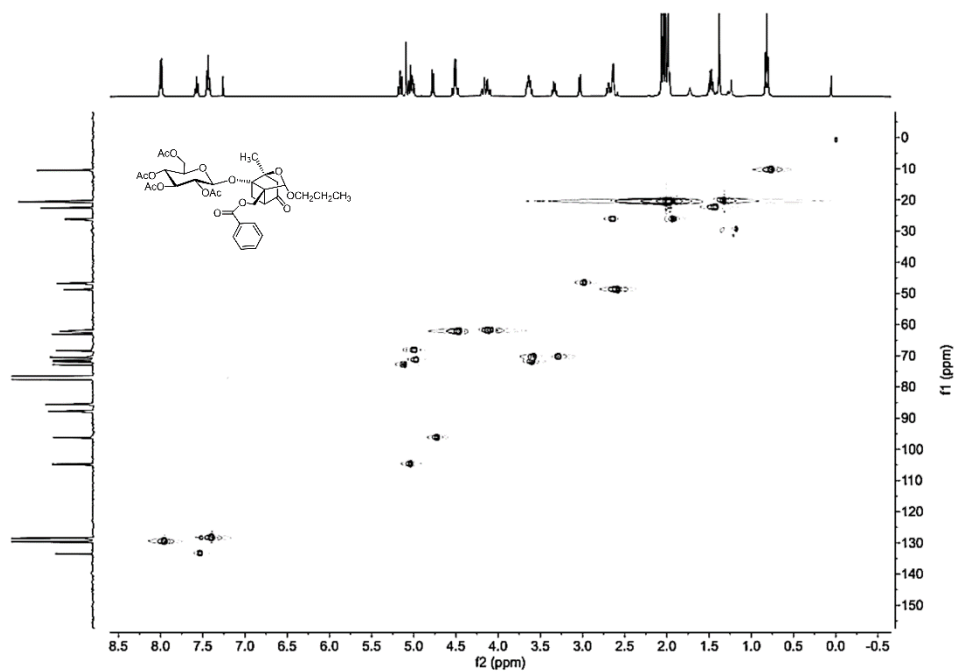


Figure S20. The HSQC-NMR of compound **13**.

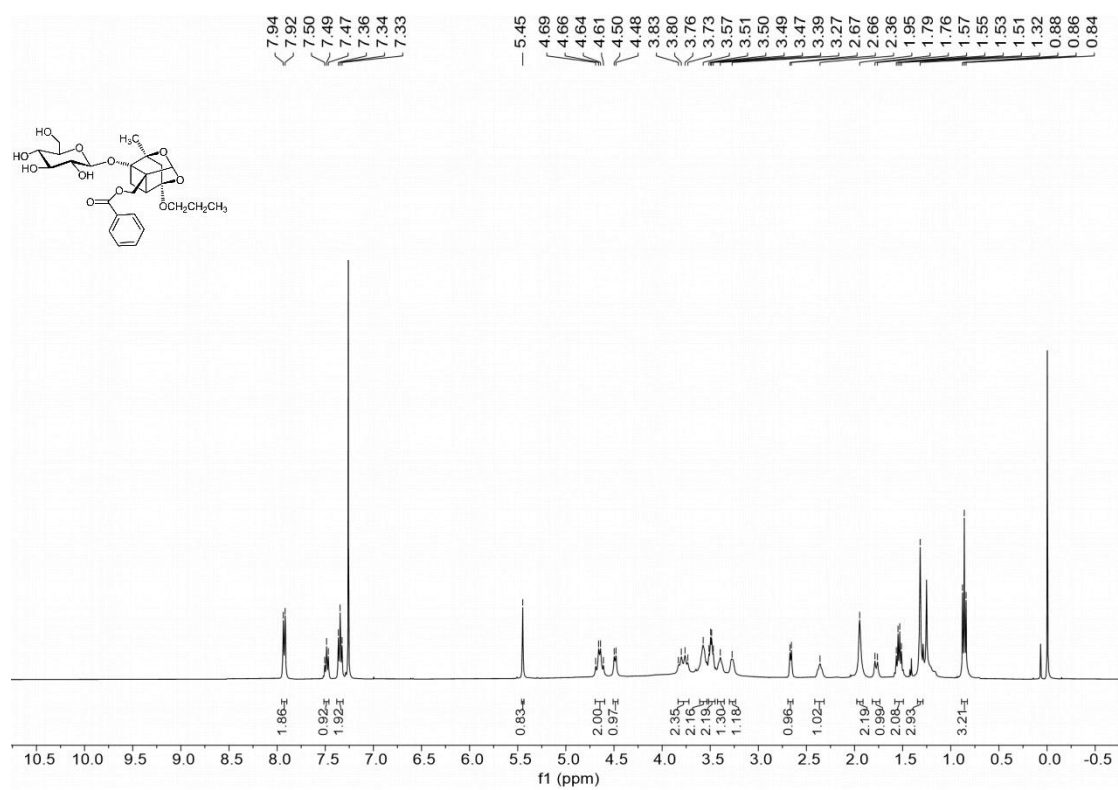


Figure S21. The ^1H NMR of compound **14**.

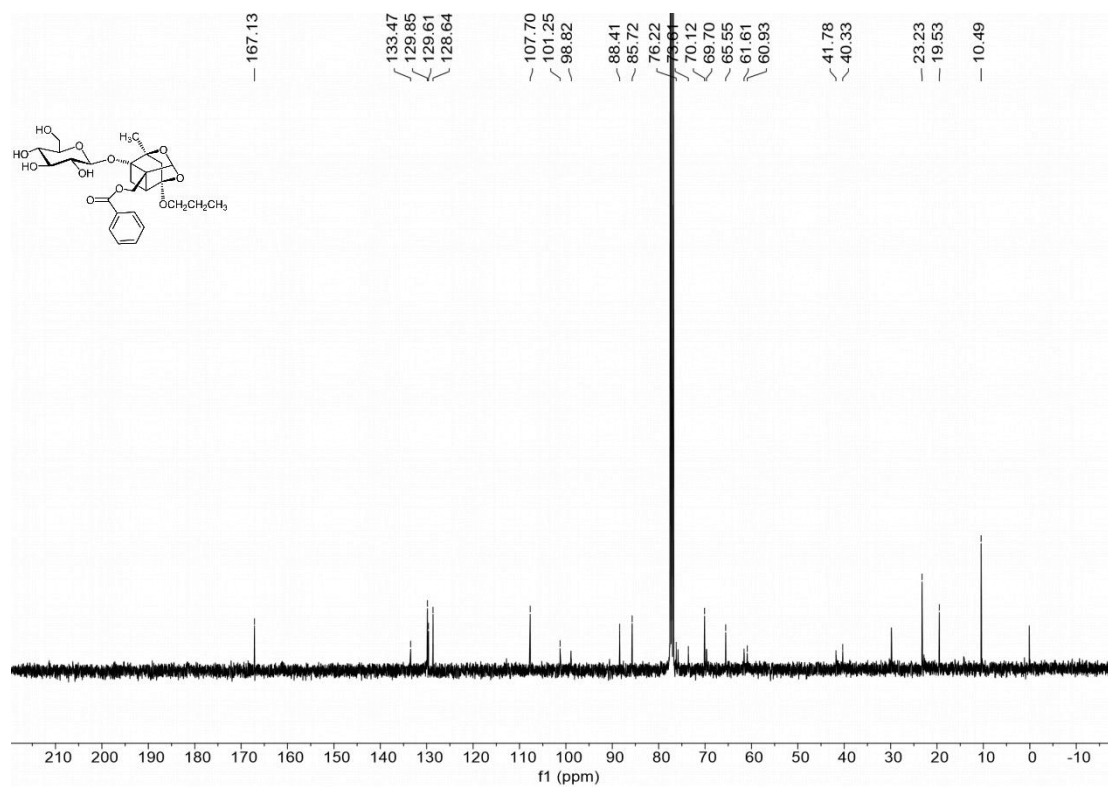


Figure S22. The ¹³C NMR of compound **14**.

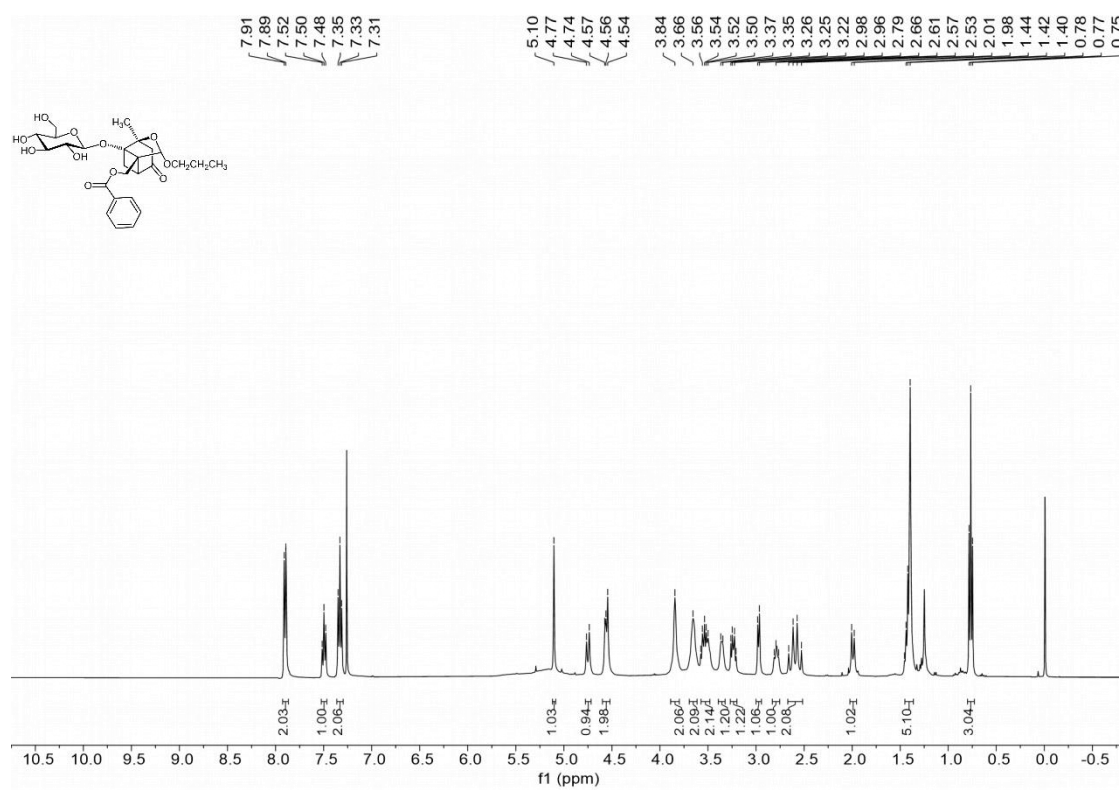


Figure S23. The ¹H NMR of compound **15**

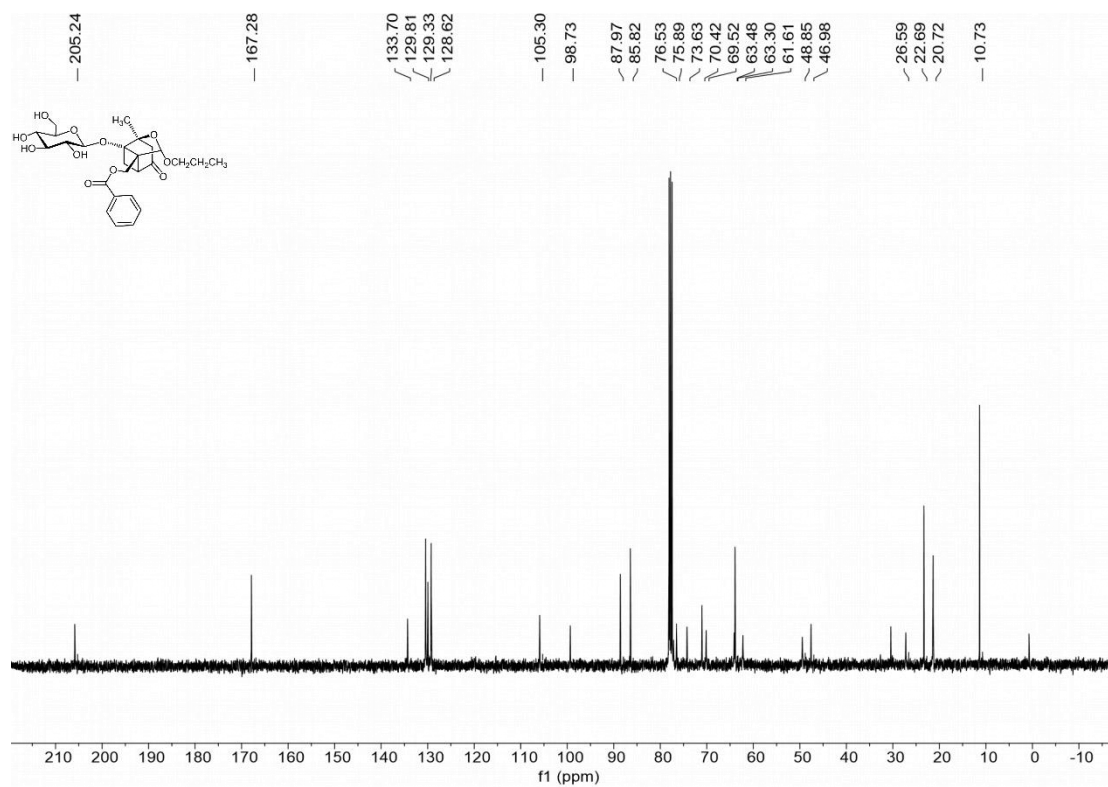


Figure S24. The ¹³C NMR of compound **15**.

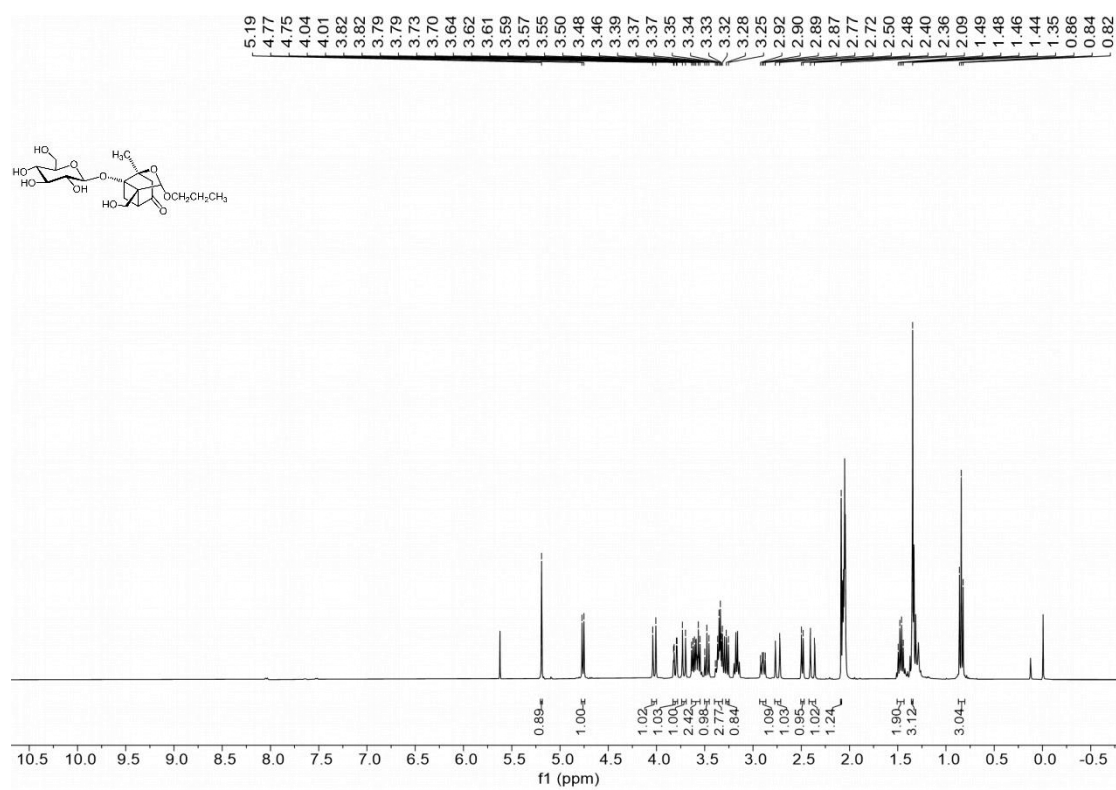


Figure S25. The ¹H NMR of compound **16**.

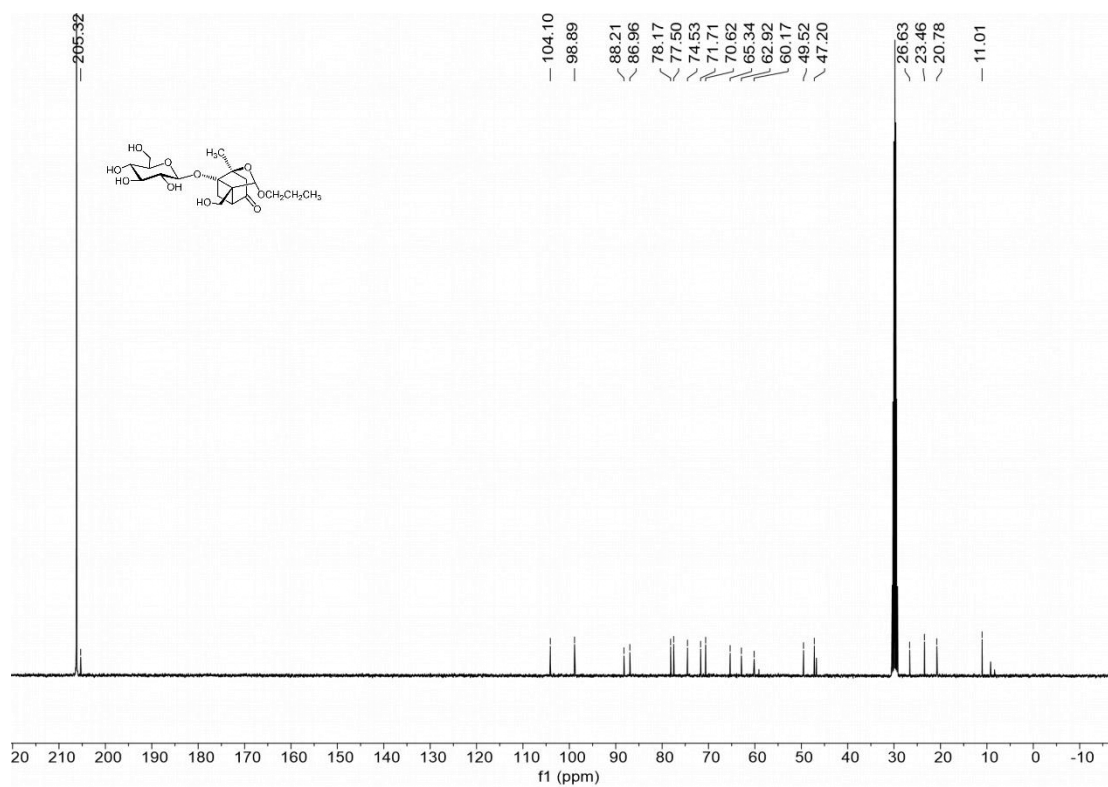


Figure S26. The ¹³C NMR of compound 16.

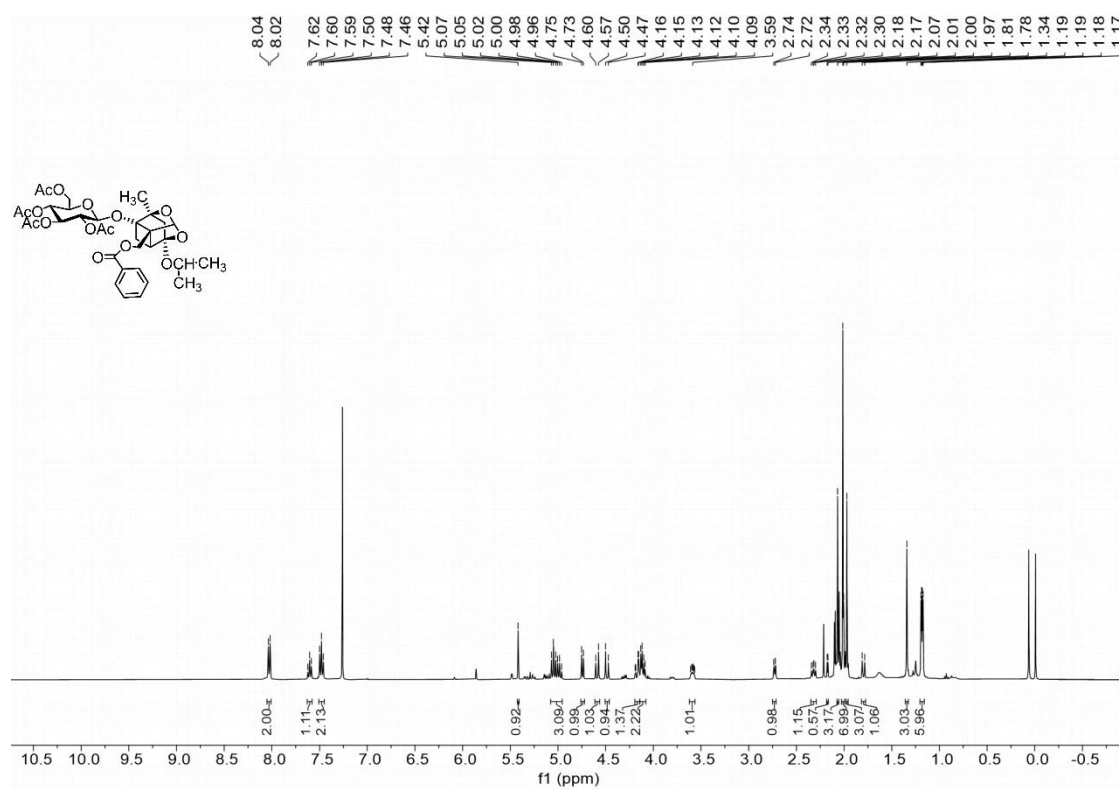


Figure S27. The ¹H NMR of compound 17.

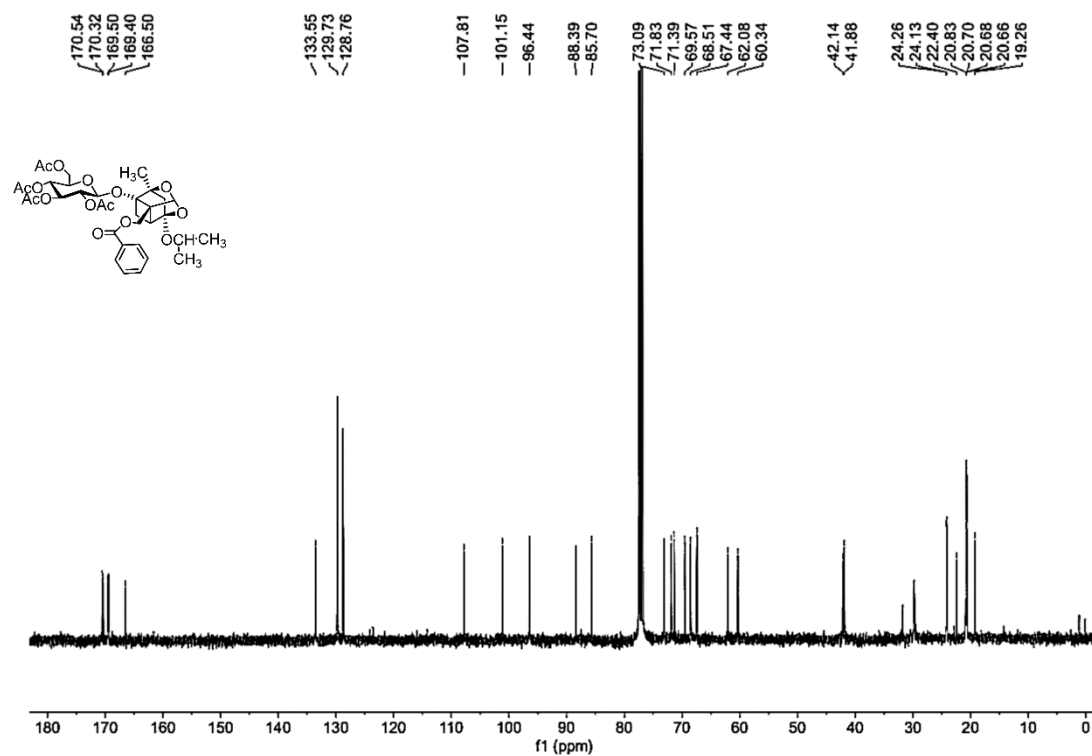


Figure S28. The ¹³C NMR of compound 17.

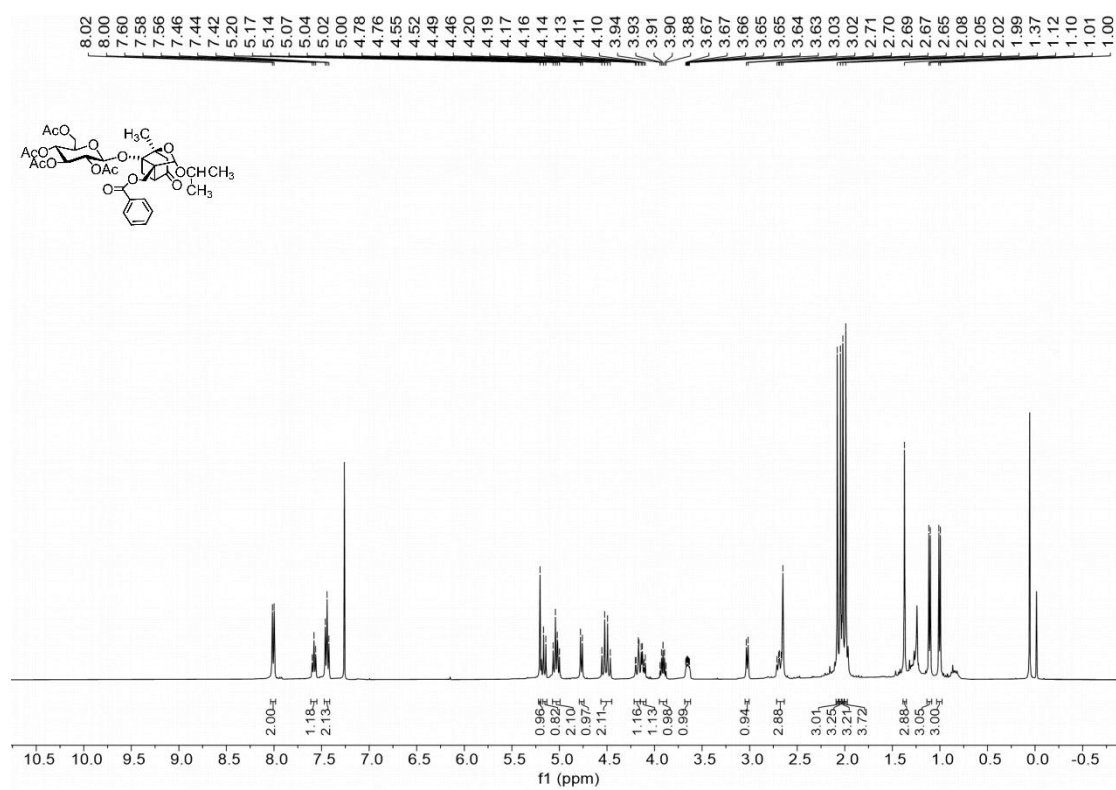


Figure S29. The ¹H NMR of compound 18.

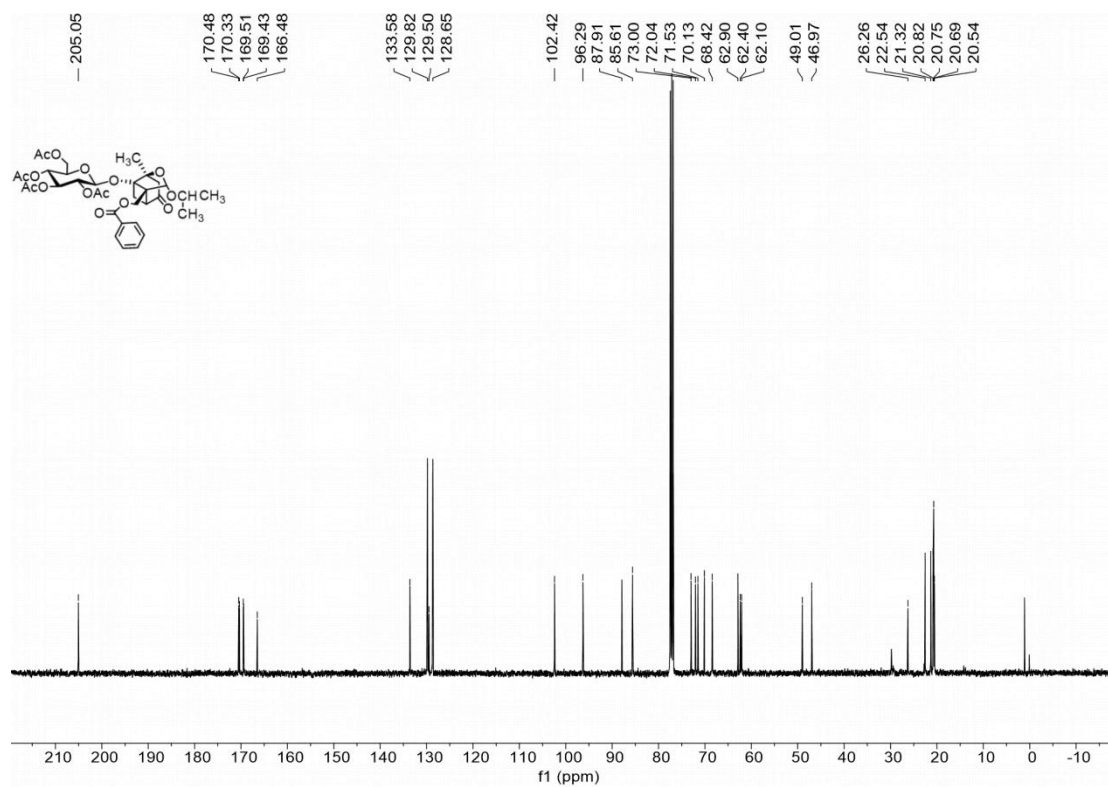


Figure S30. The ¹³C NMR of compound 18.

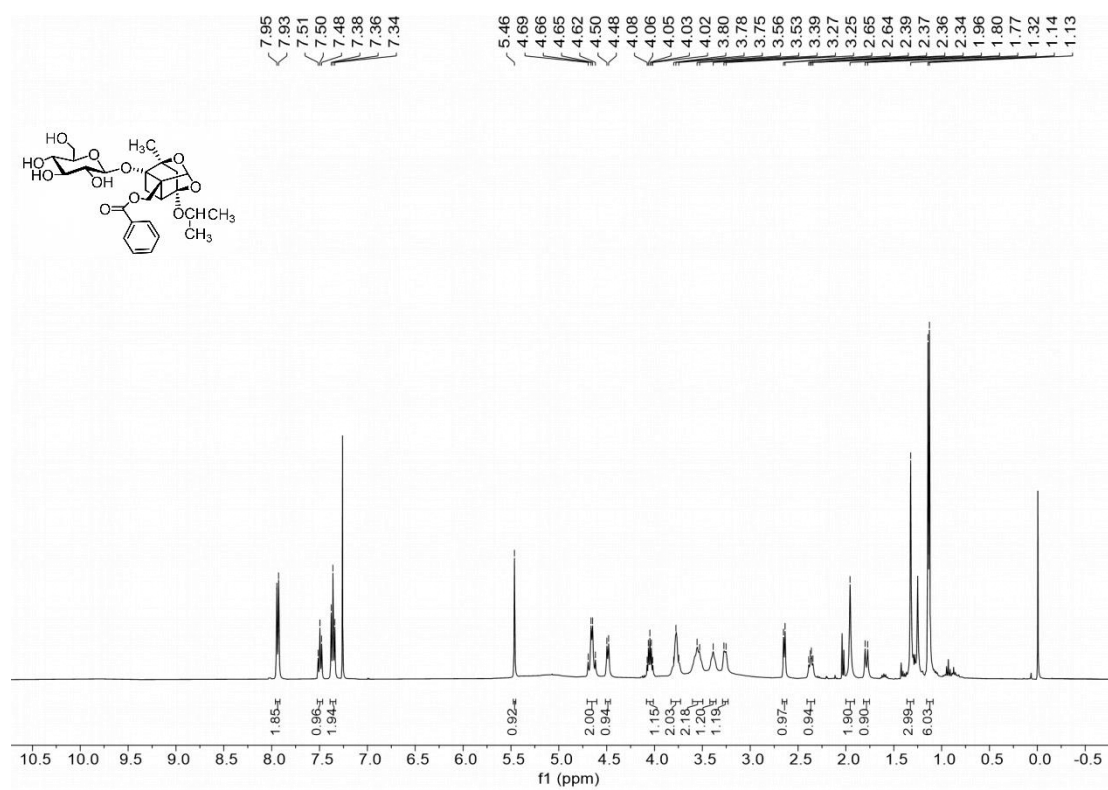


Figure S31. The ¹H NMR of compound 19.

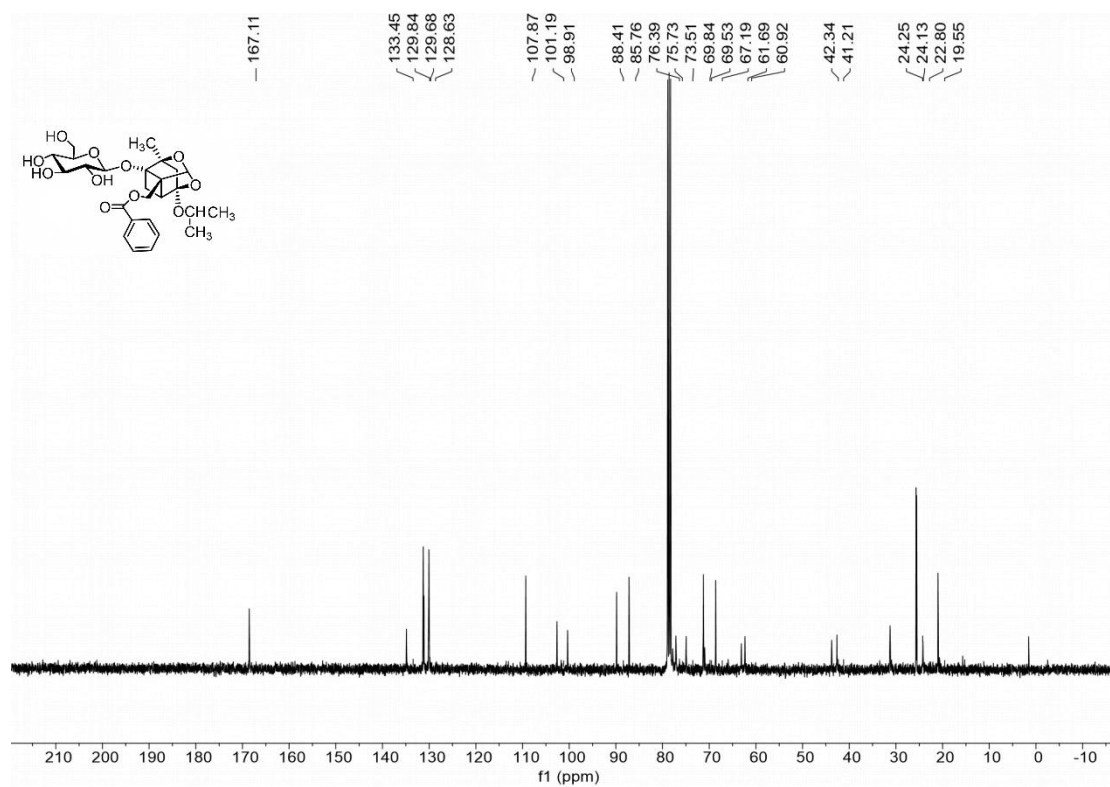


Figure S32. The ^{13}C NMR of compound **19**.

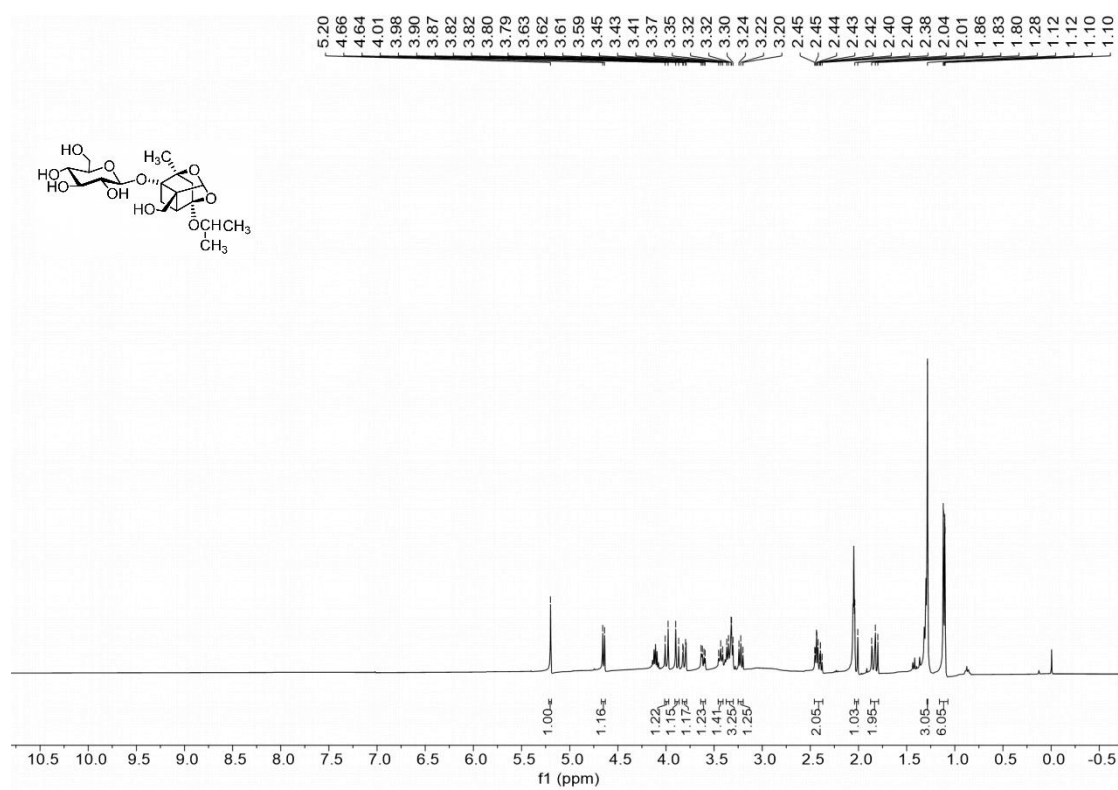


Figure S33. The ^1H NMR of compound **20**.

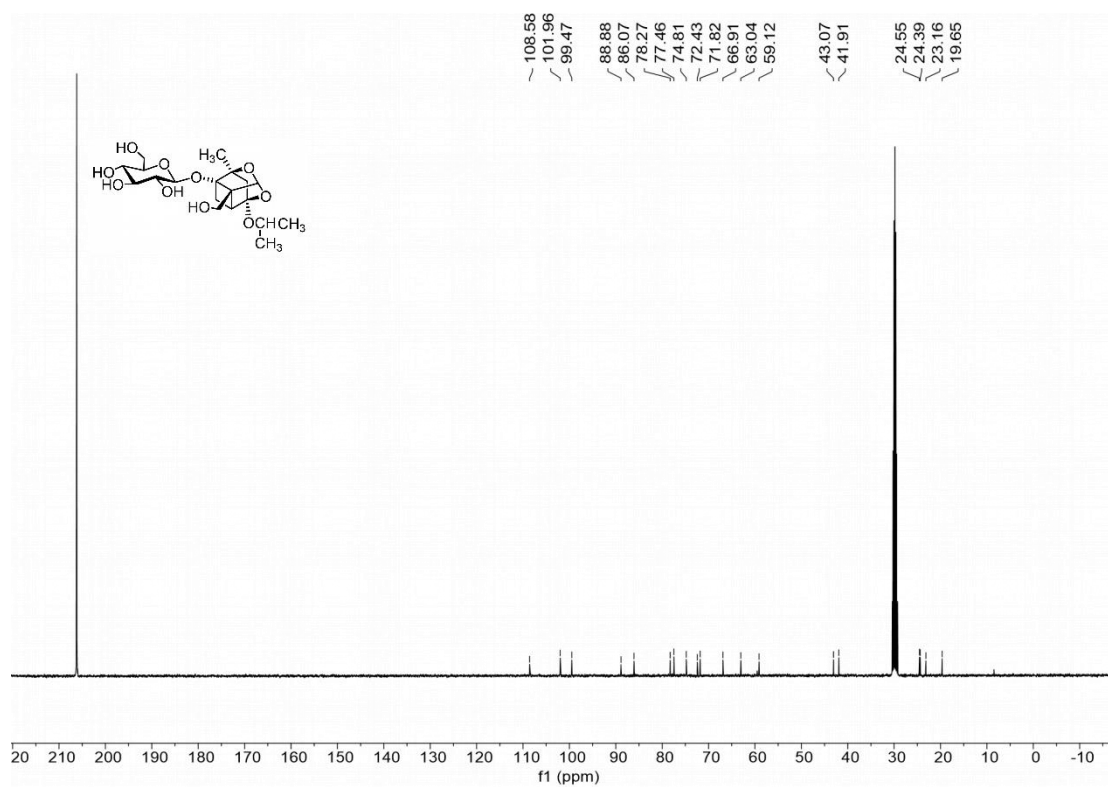


Figure S34. The ¹³C NMR of compound **20**.

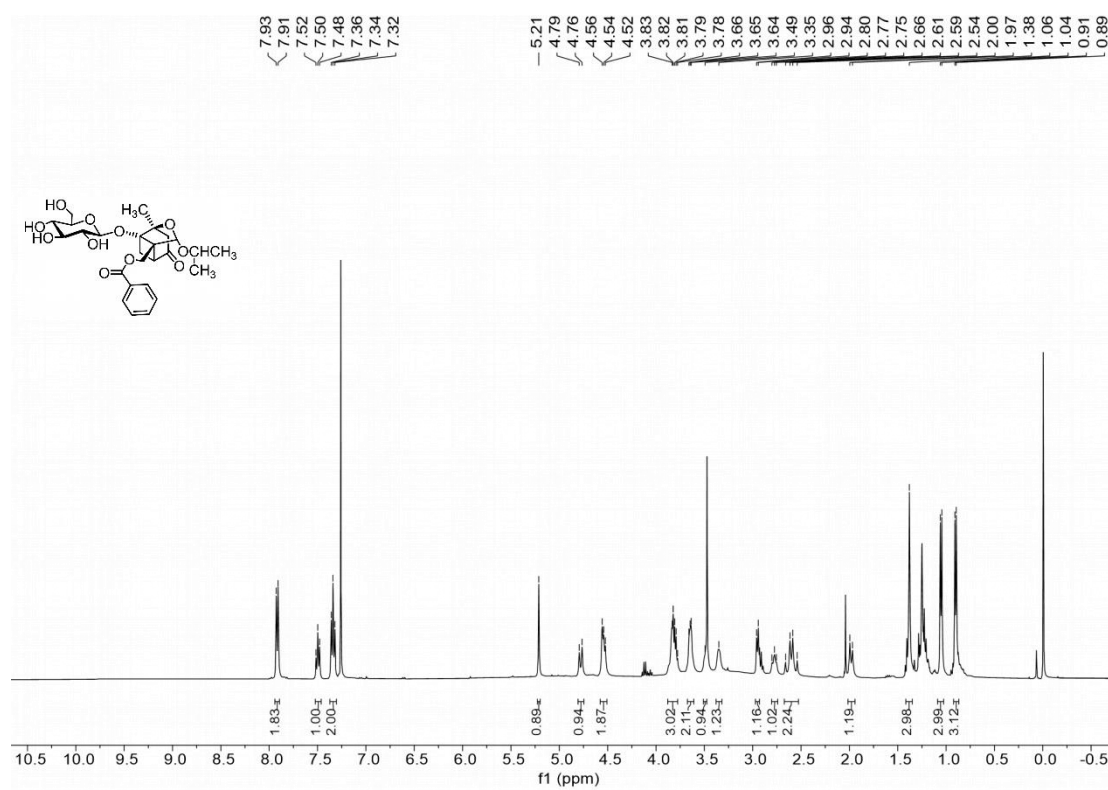


Figure S35. The ¹H NMR of compound **21**.

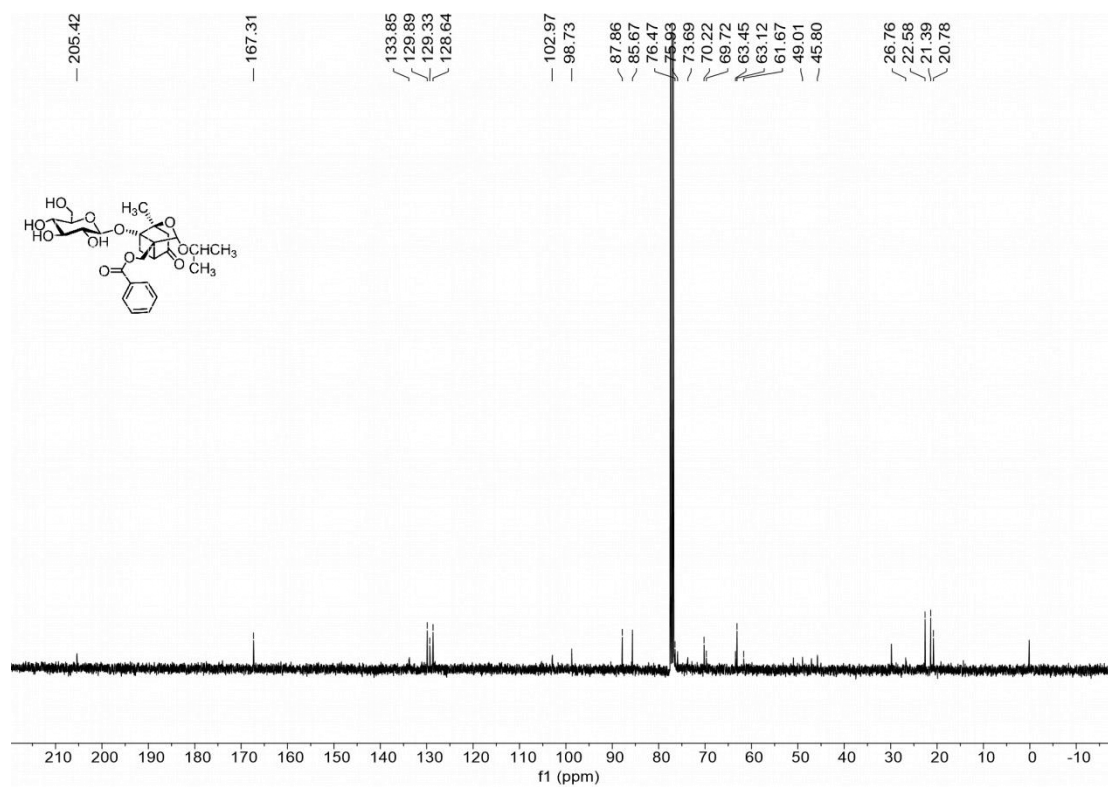


Figure S36. The ¹³C NMR of compound 21.

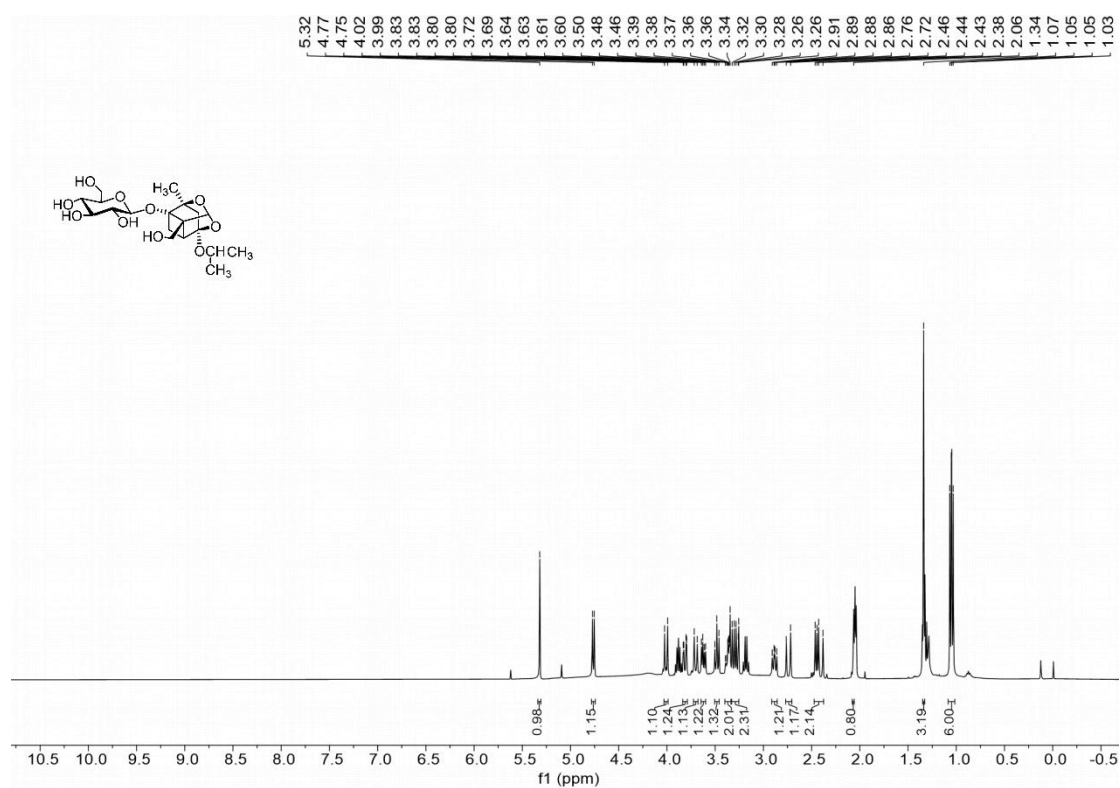


Figure S37. The ¹H NMR of compound 22.

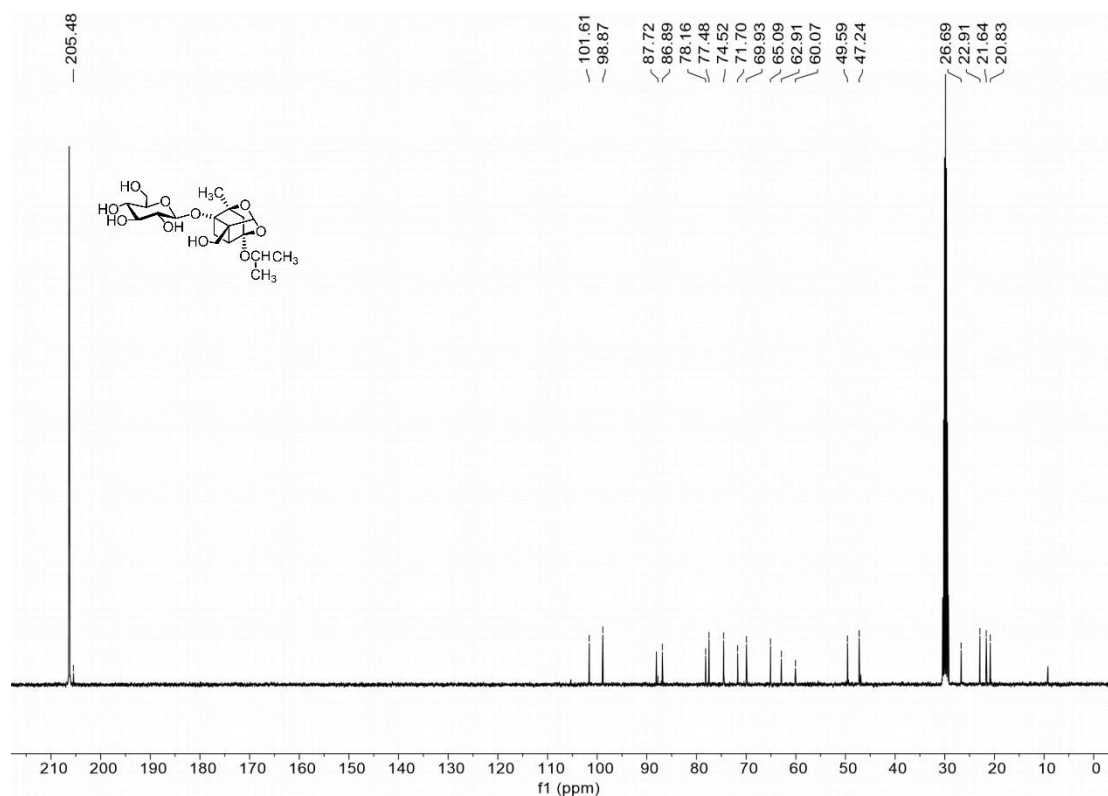


Figure S38. The ¹³C NMR of compound **22**.

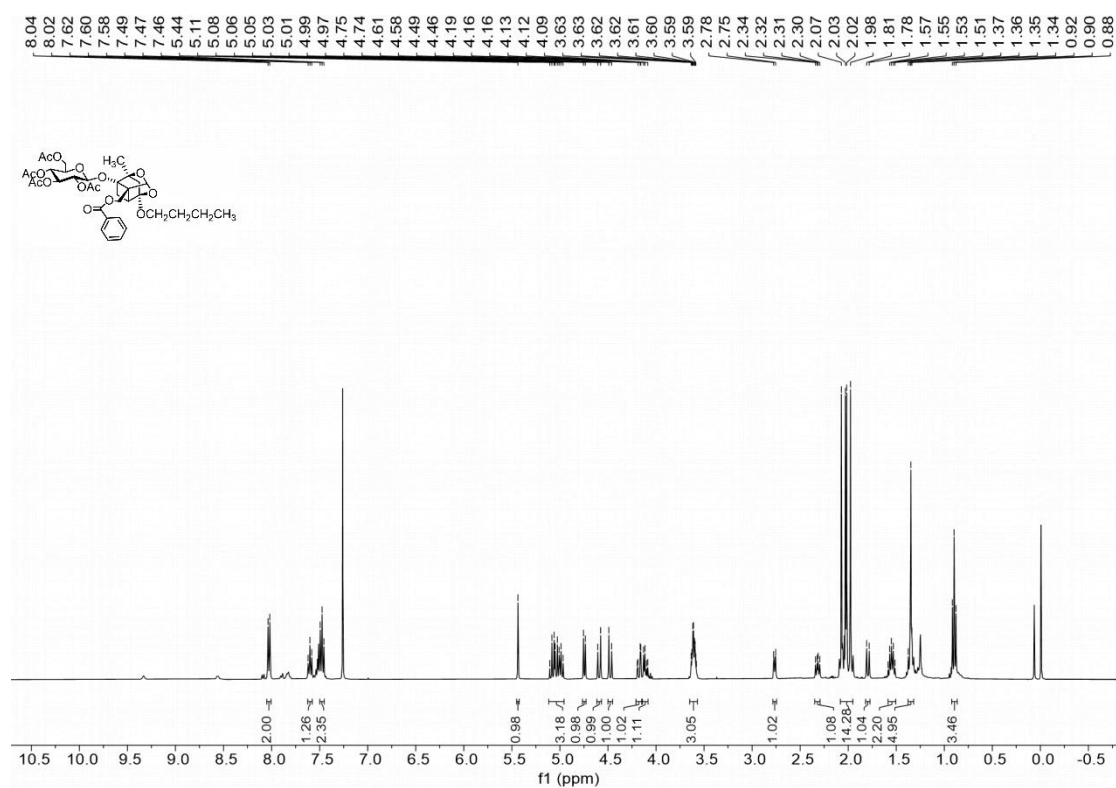


Figure S39. The ¹H NMR of compound **23**.

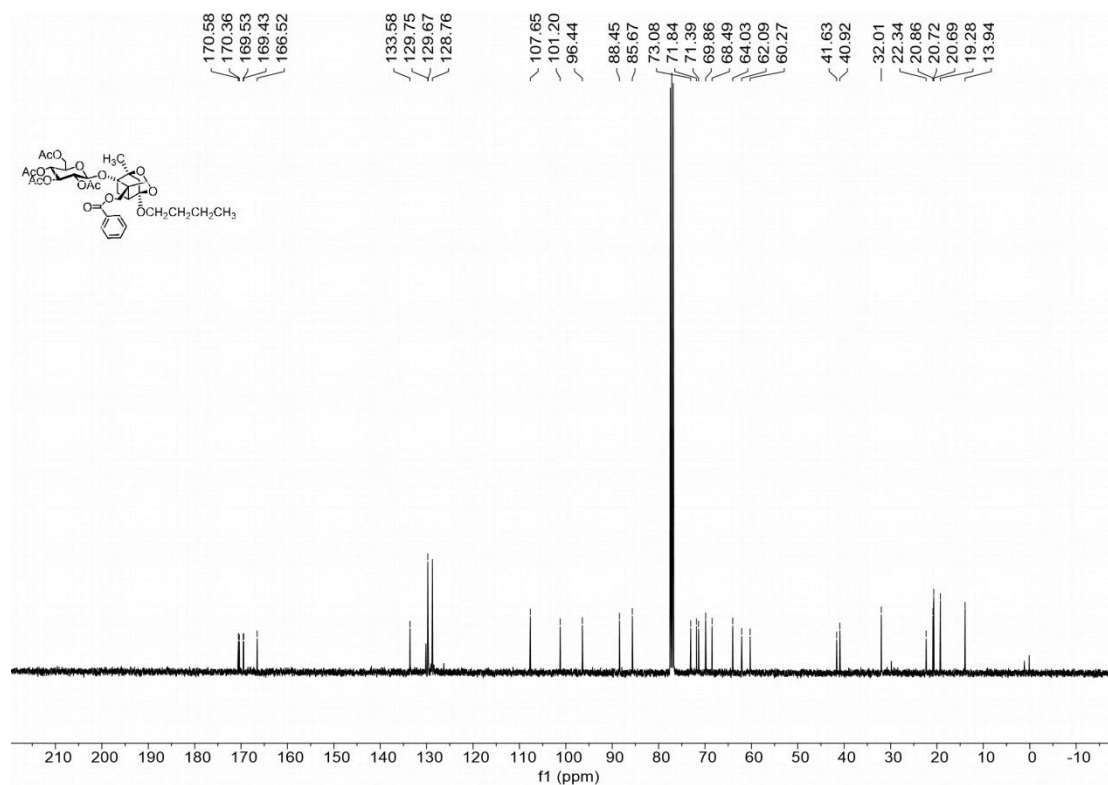


Figure S40. The ¹³C NMR of compound 23.

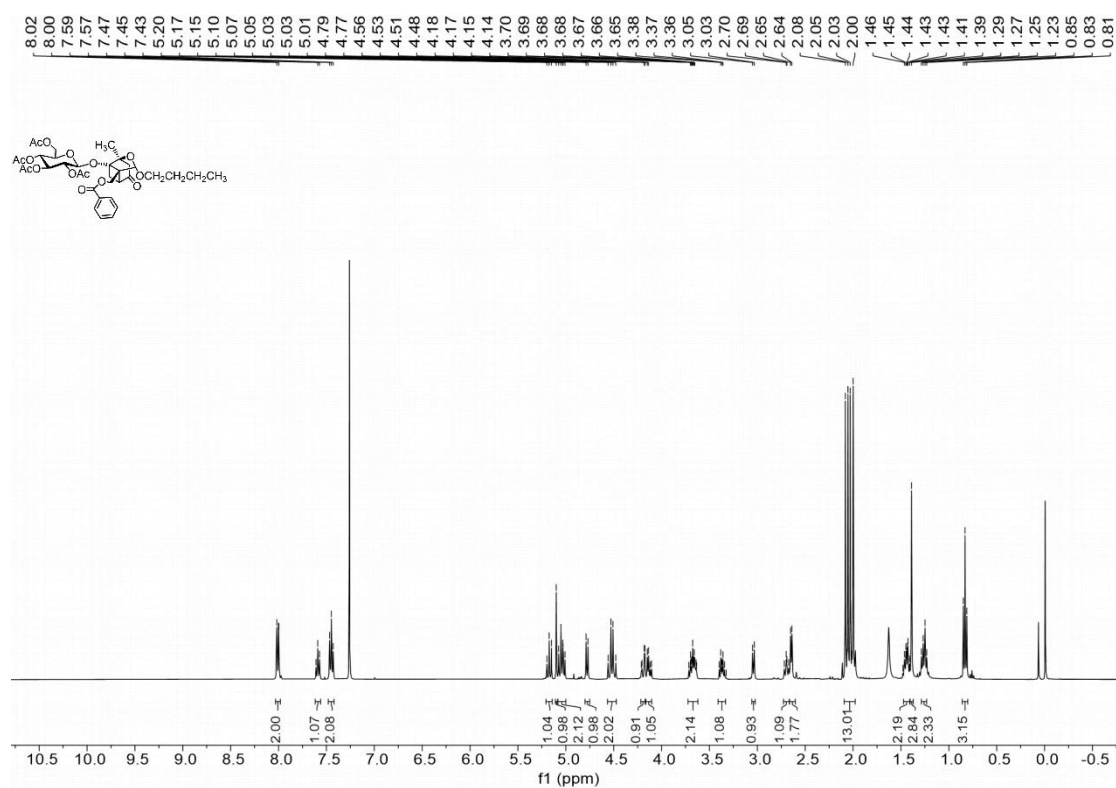


Figure S41. The ¹H NMR of compound 24.

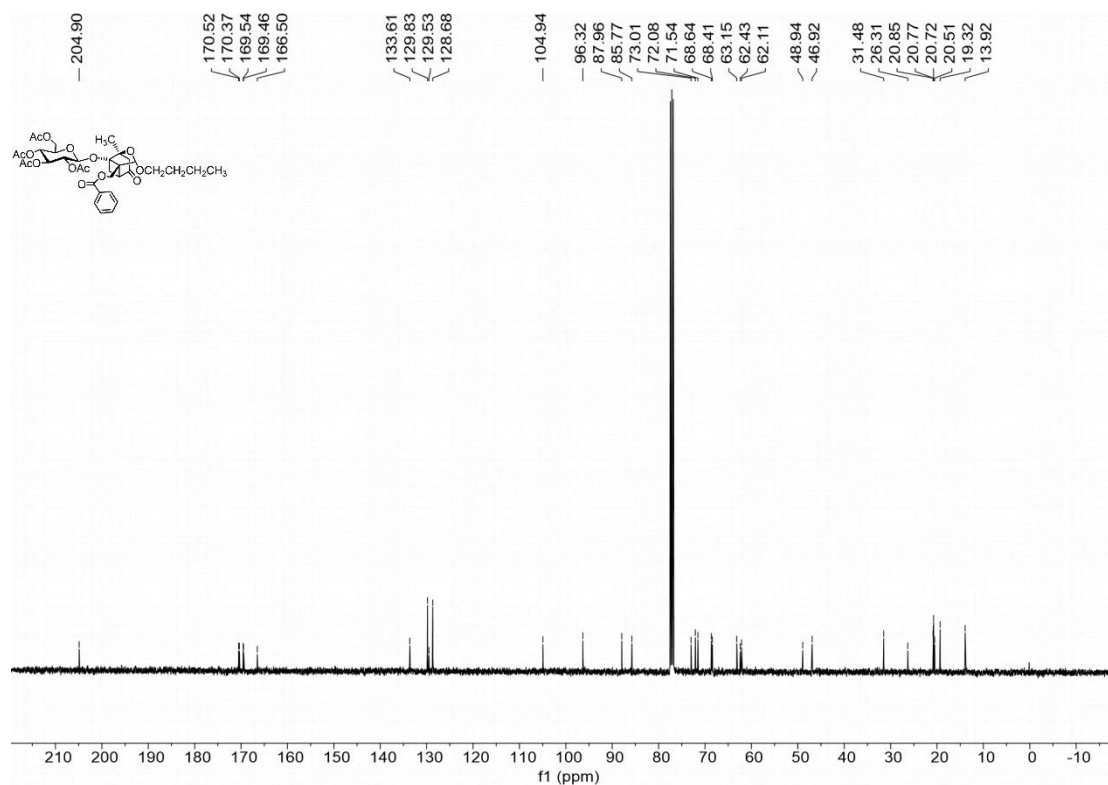


Figure S42. The ^{13}C NMR of compound **24**.

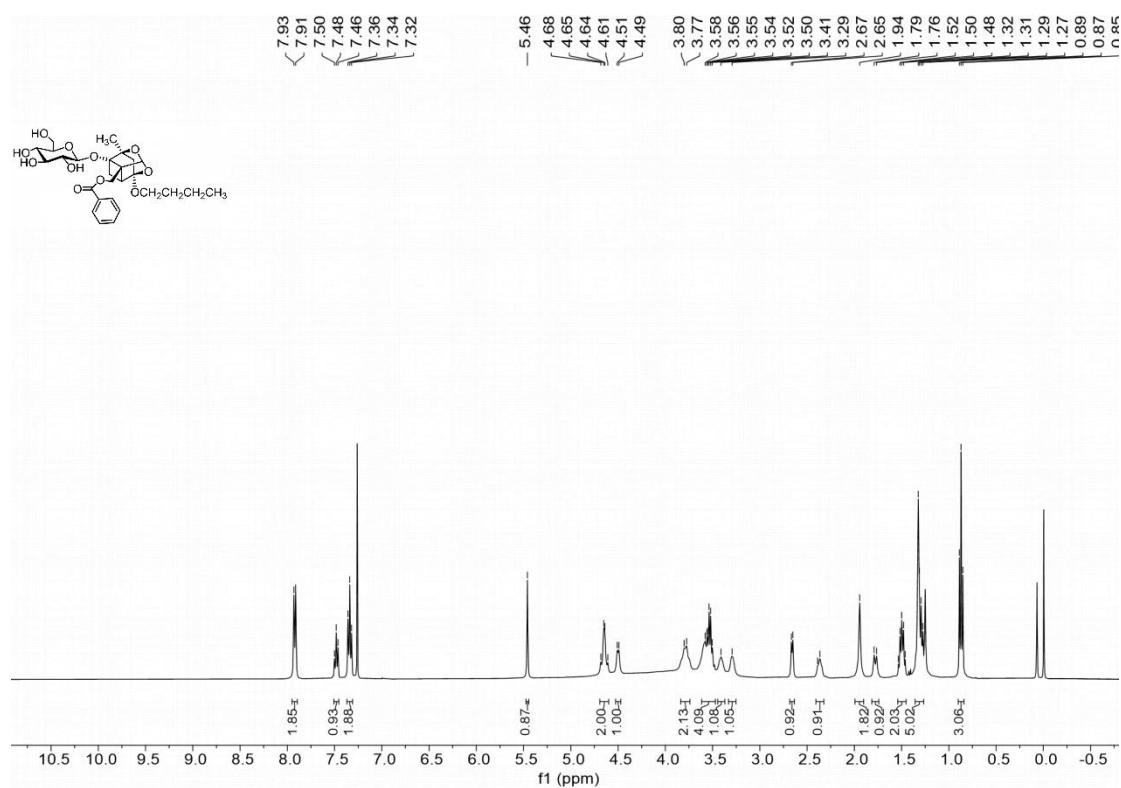


Figure S43. The ^1H NMR of compound **25**.

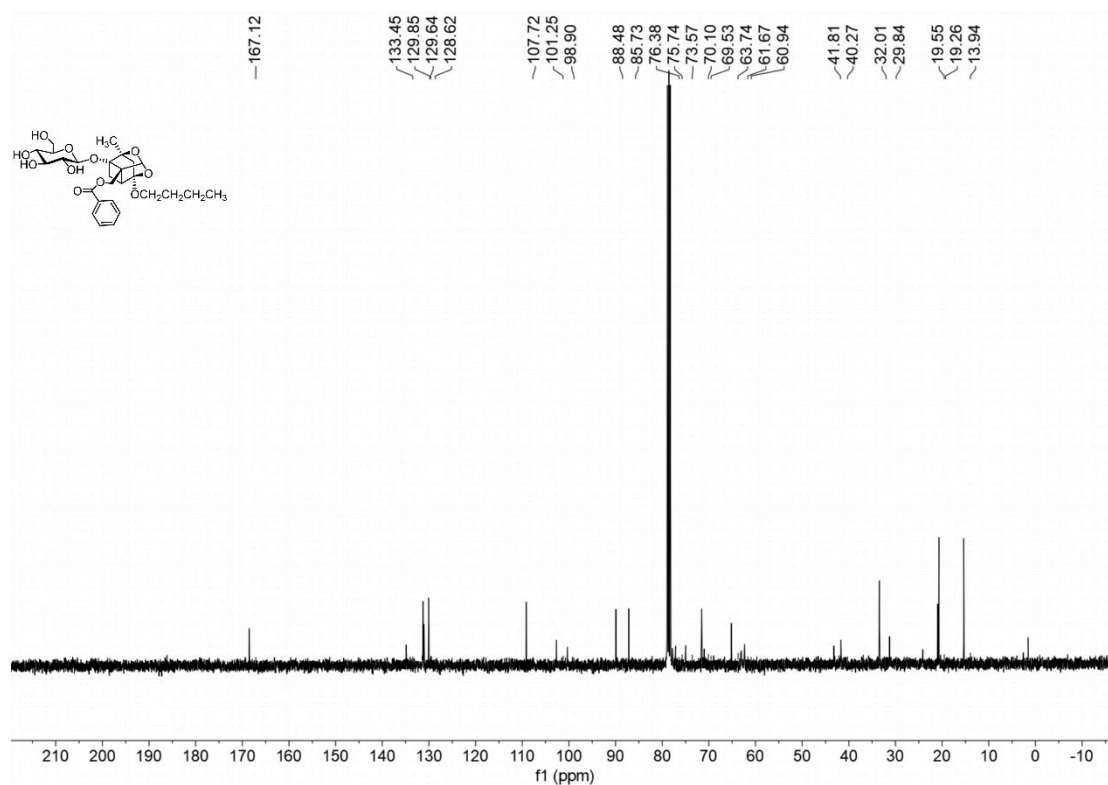


Figure S44. The ¹³C NMR of compound **25**.

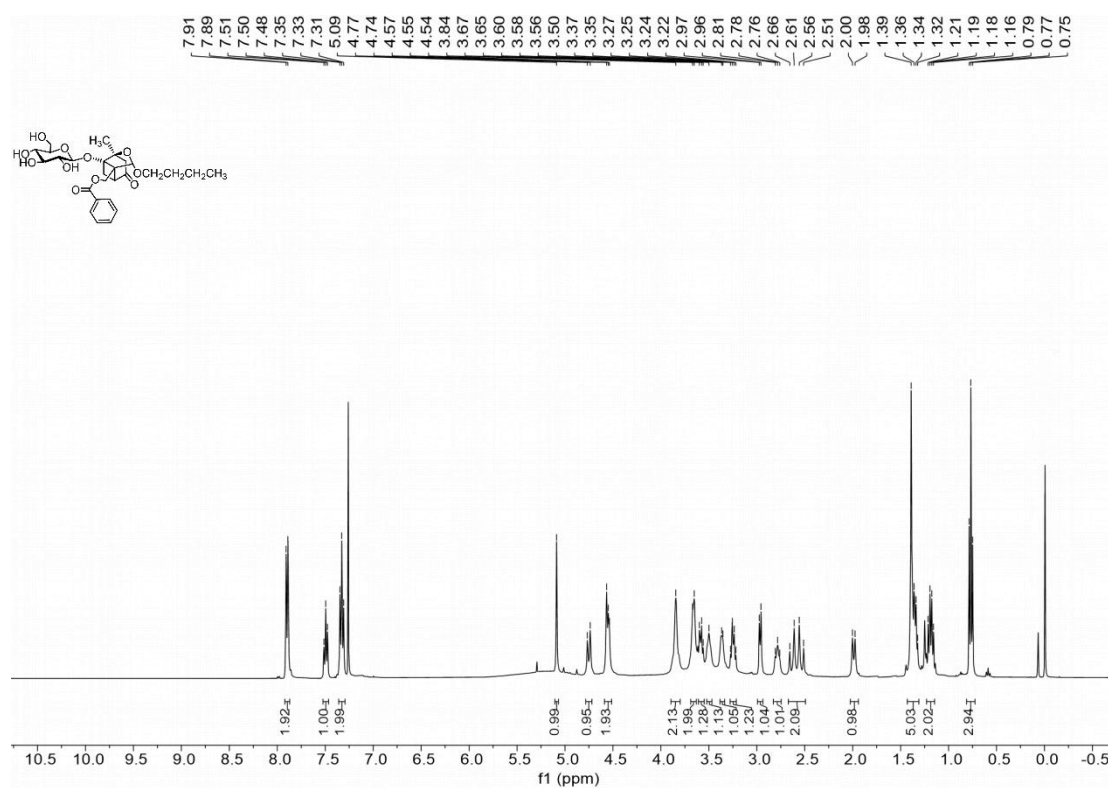


Figure S45. The ¹H NMR of compound **26**.

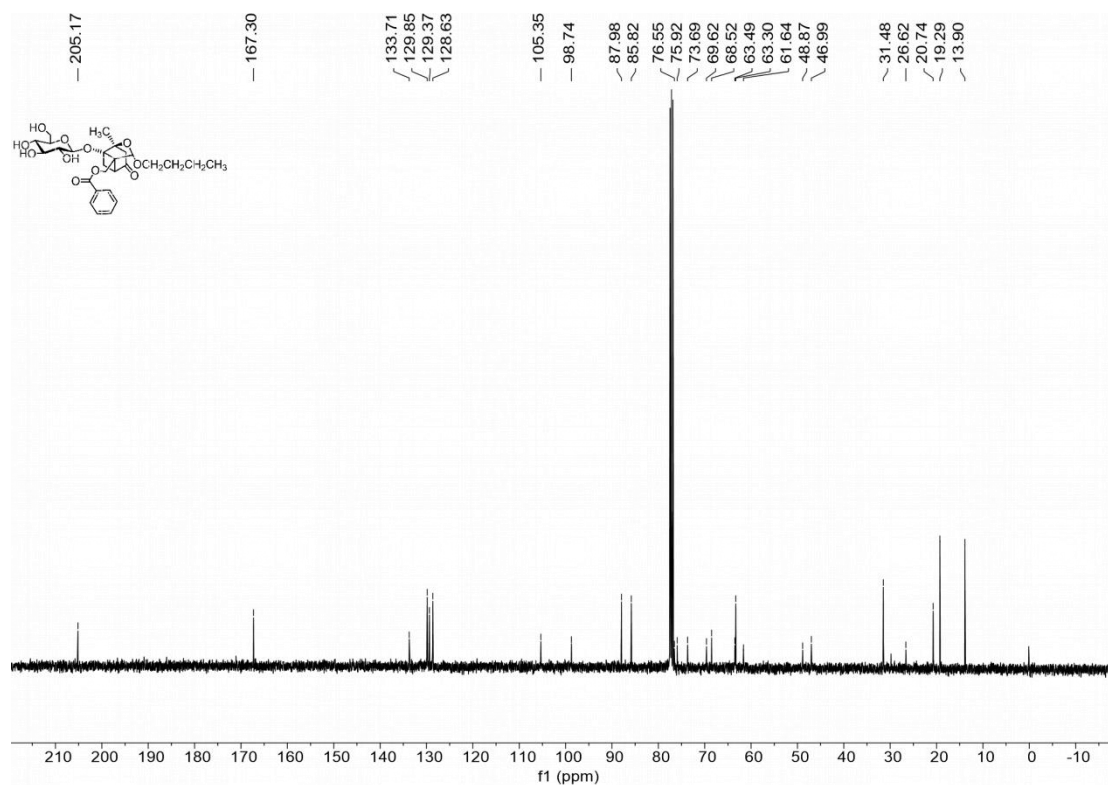


Figure S46. The ¹³C NMR of compound 26.

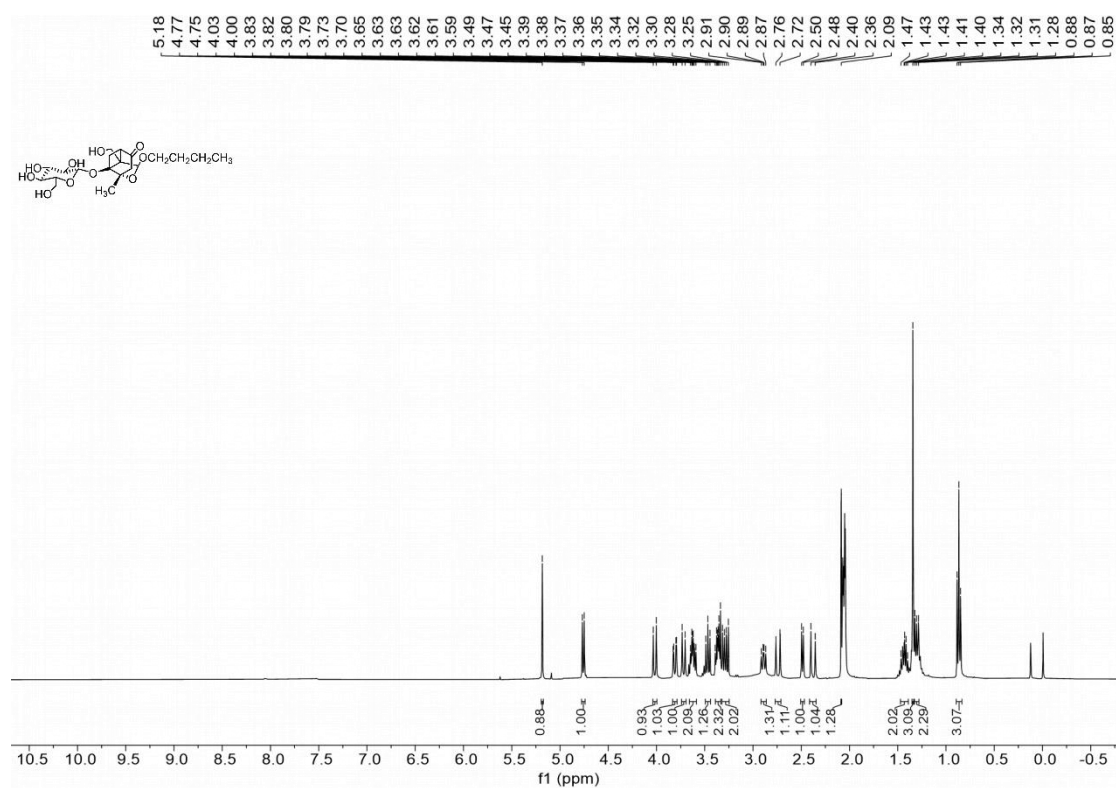
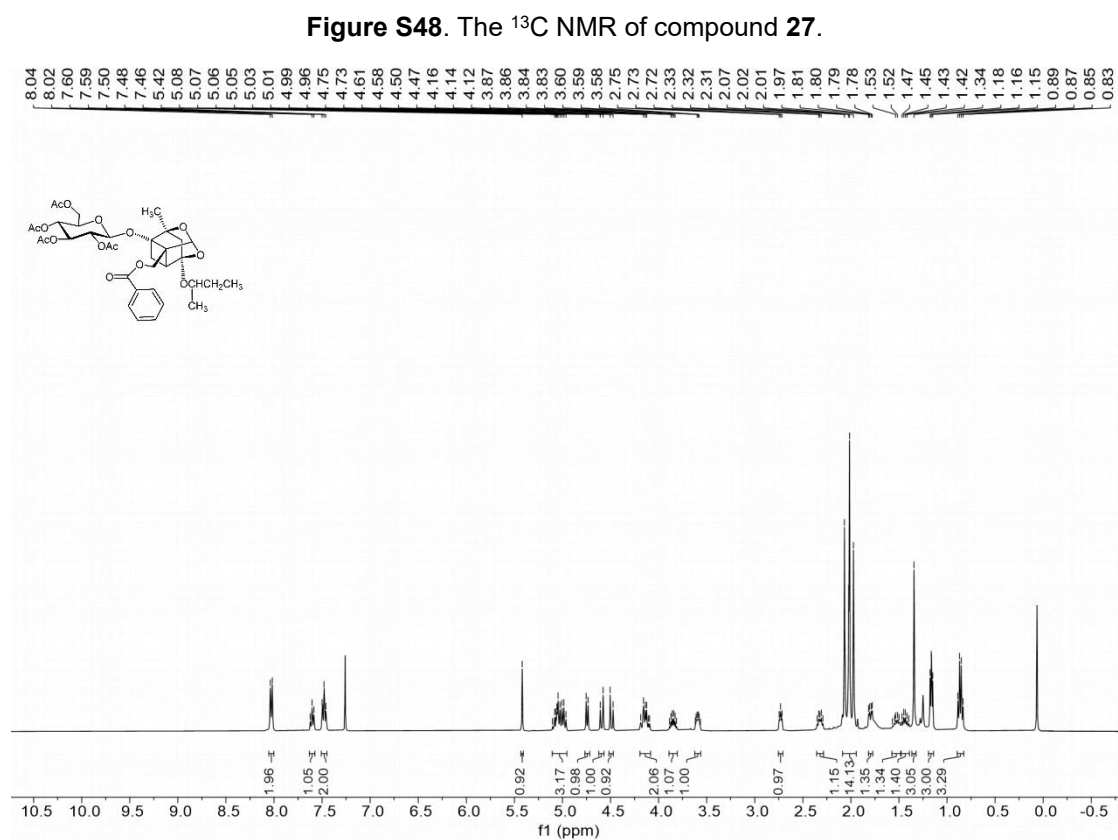
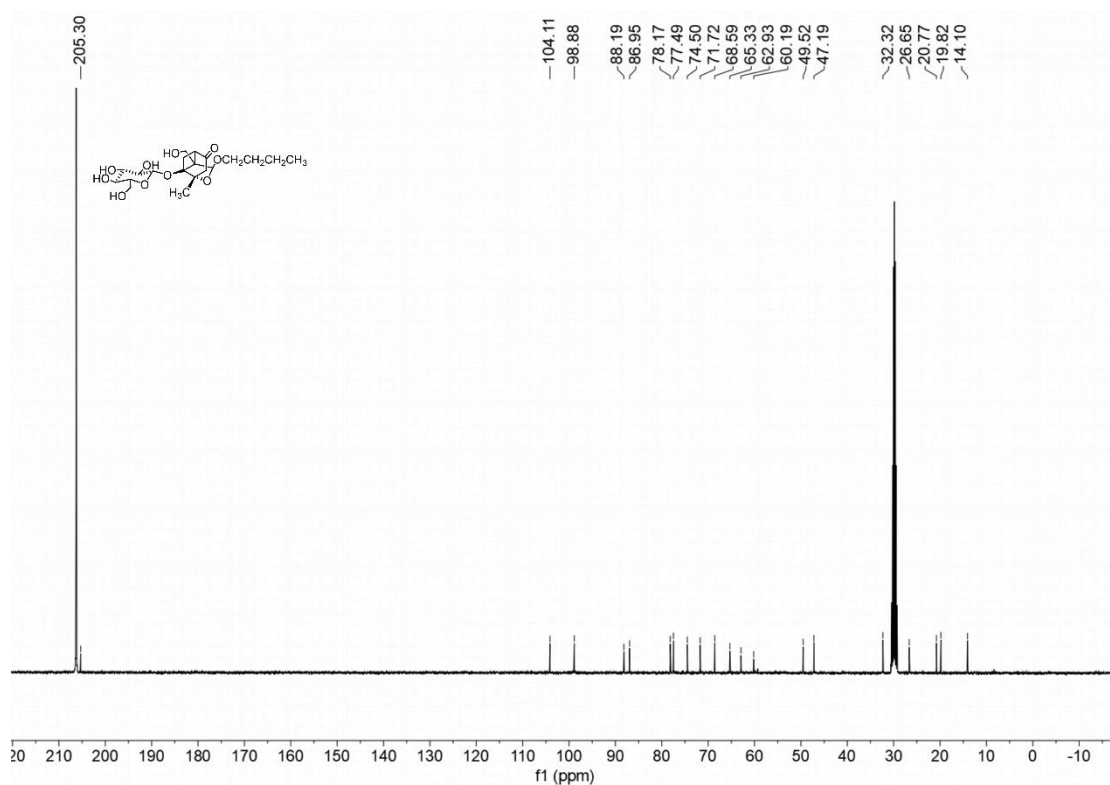


Figure S47. The ¹H NMR of compound 27.



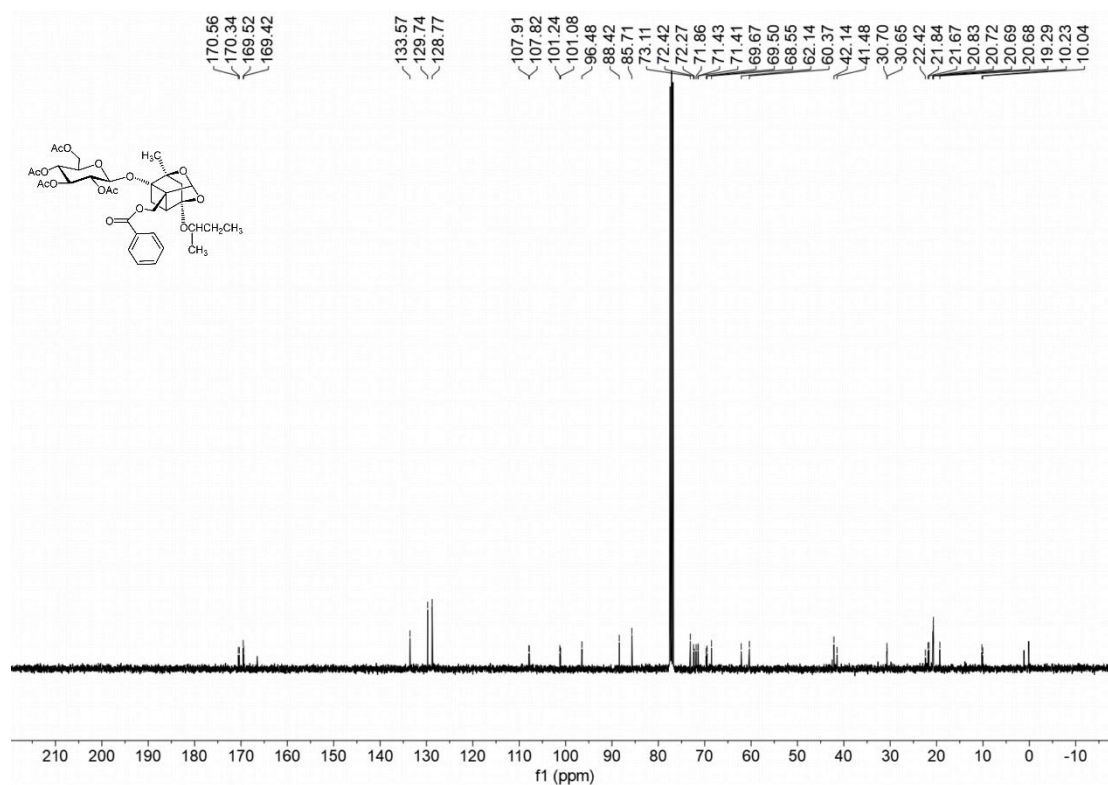


Figure S50. The ^{13}C NMR of compound **28**.

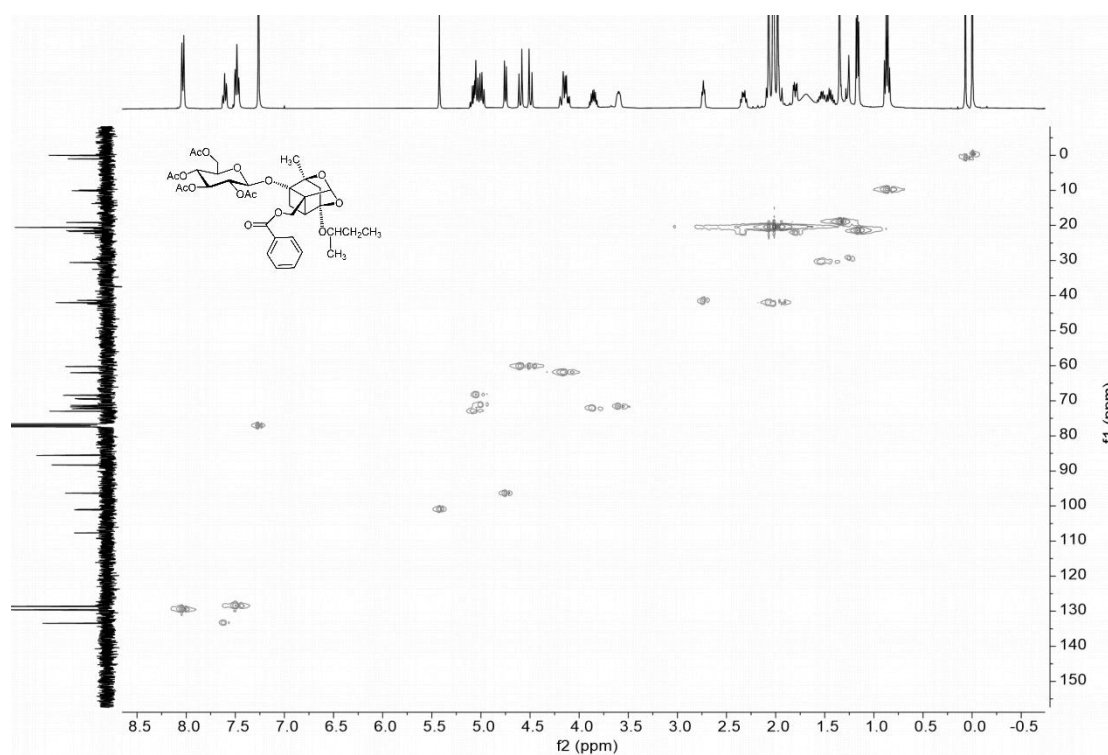


Figure S51. The HSQC-NMR of compound **28**.

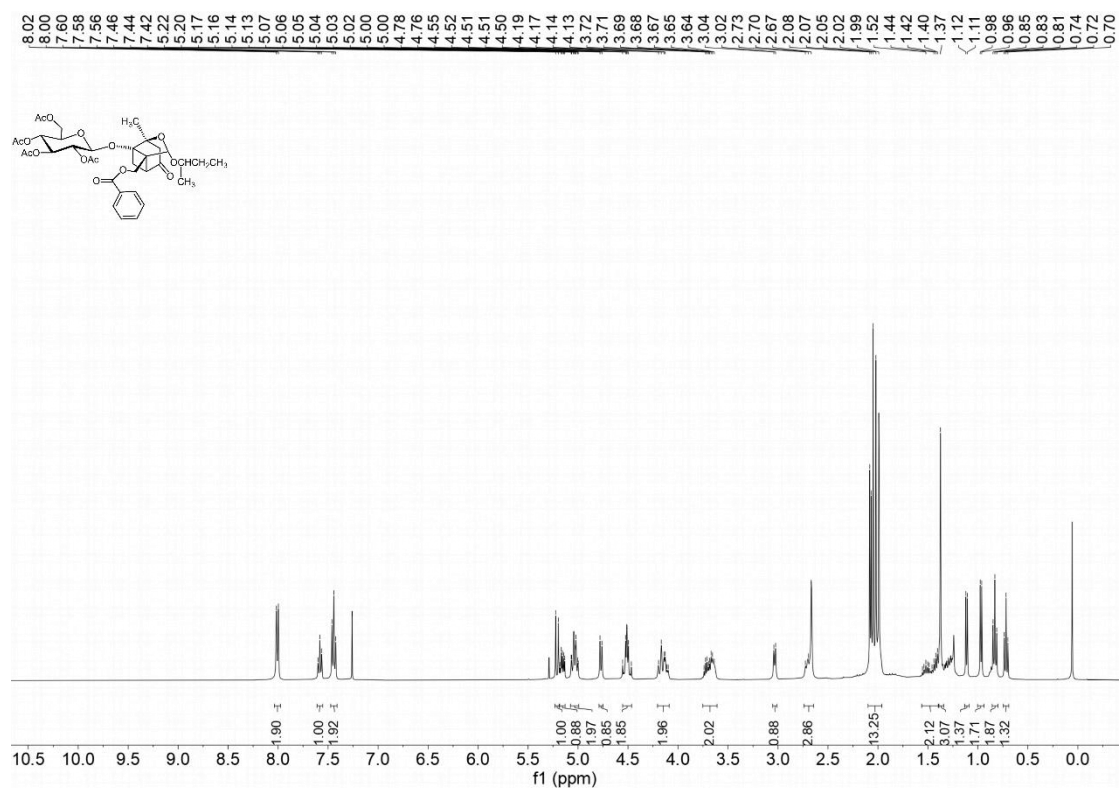


Figure S52. The ¹H NMR of compound **29**.

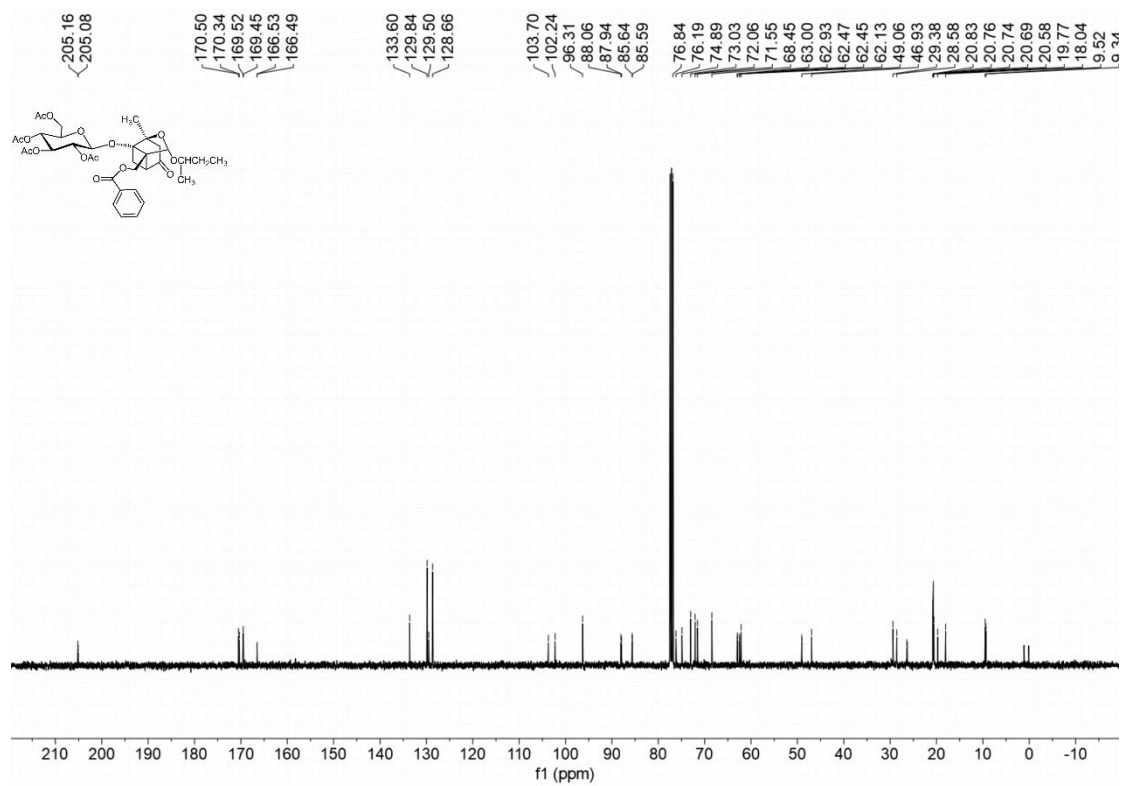


Figure S53. The ¹³C NMR of compound **29**.

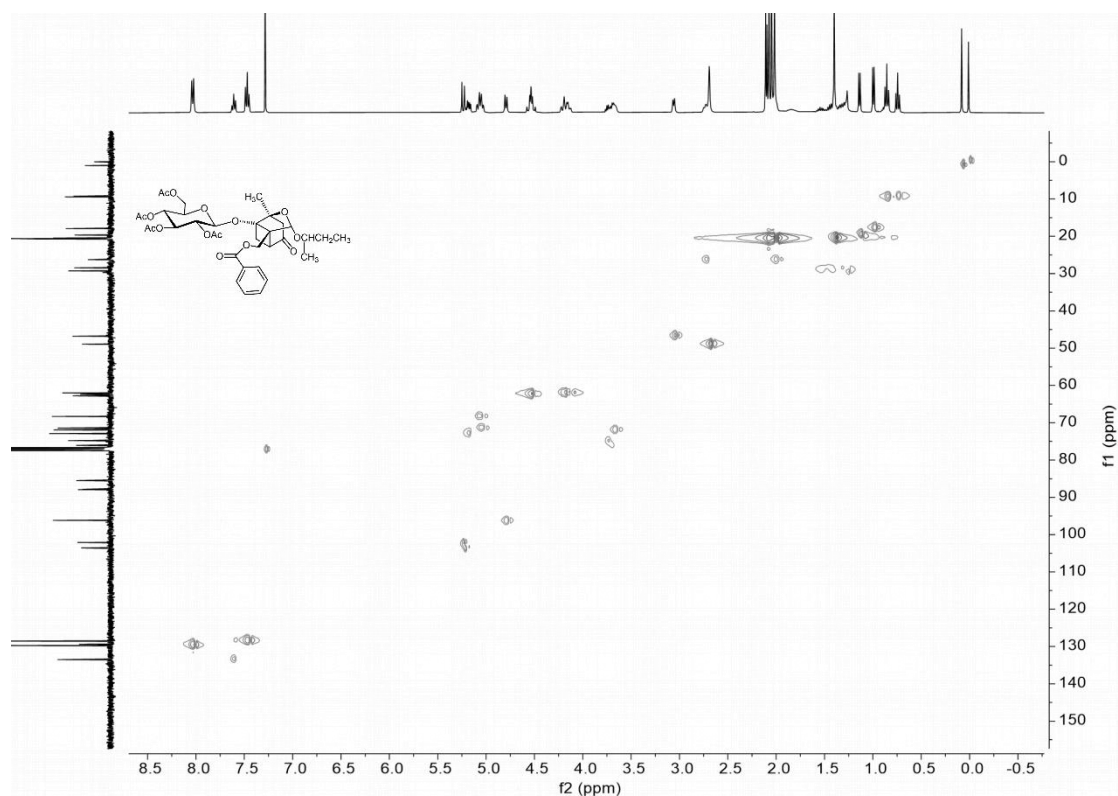


Figure S54. The HSQC-NMR of compound **29**.

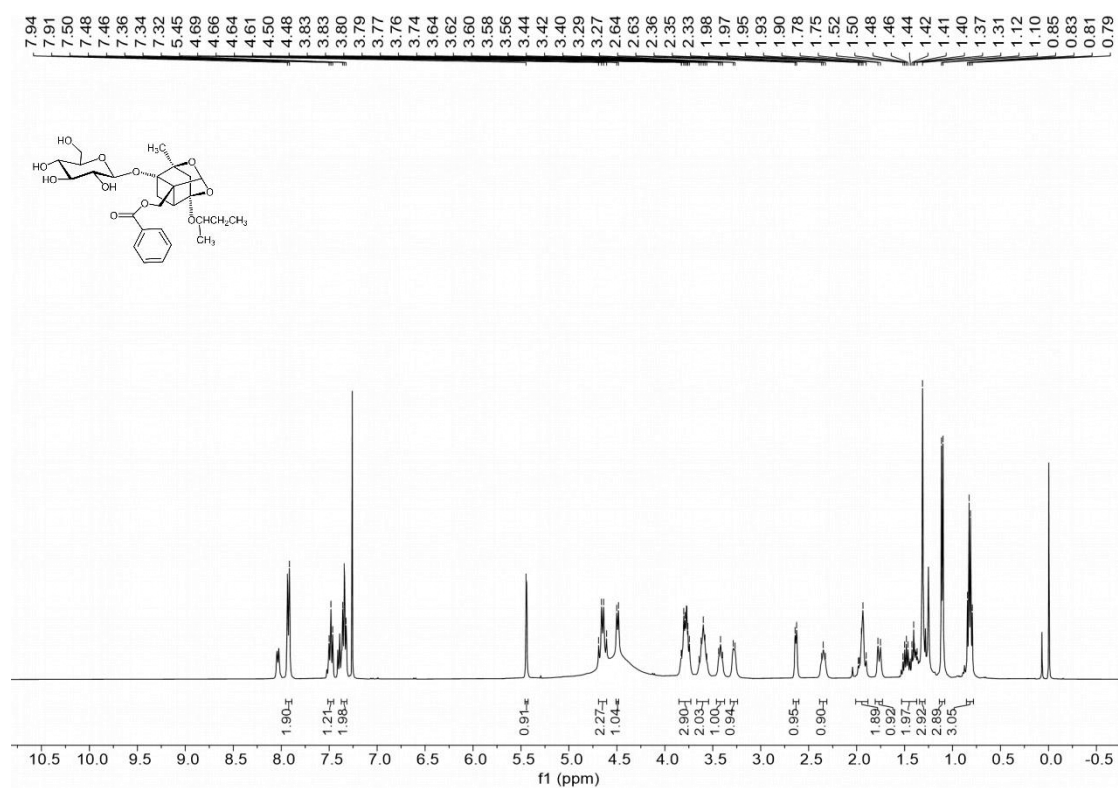


Figure S55. The ^1H NMR of compound **30**.

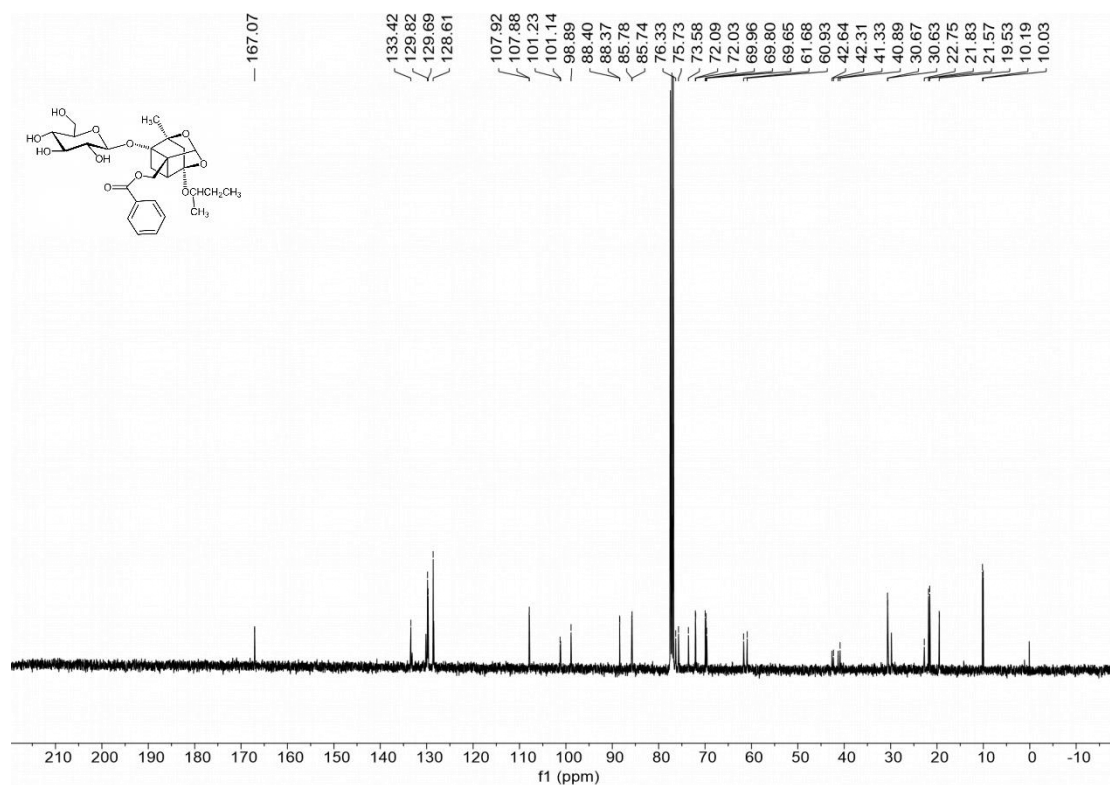


Figure S56. The ¹³C NMR of compound **30**.

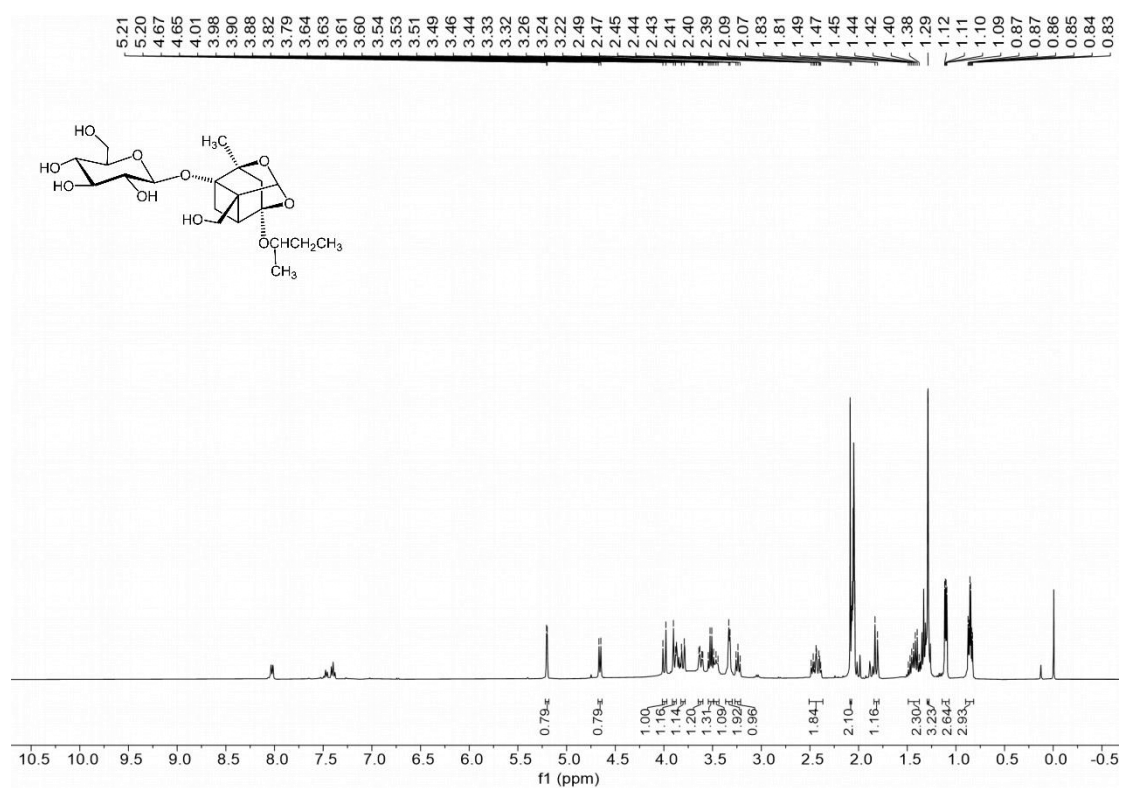


Figure S57. The ¹H NMR of compound **31**.

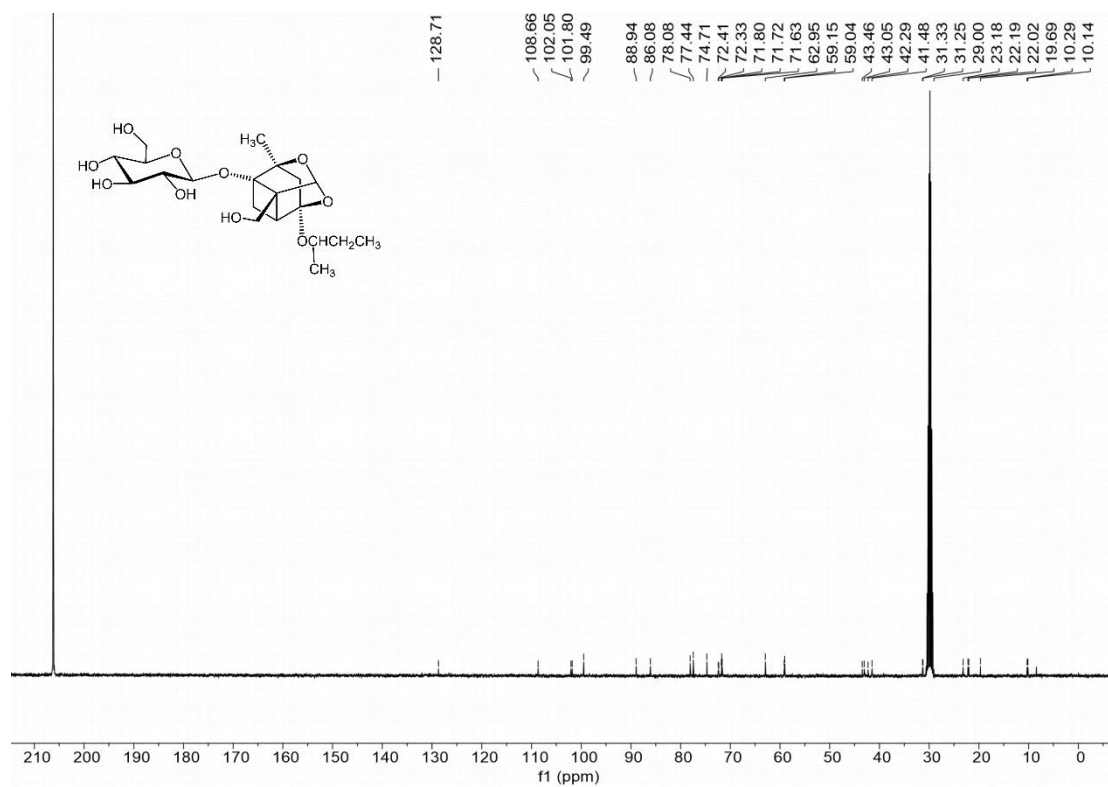


Figure S58. The ¹³C NMR of compound **31**.

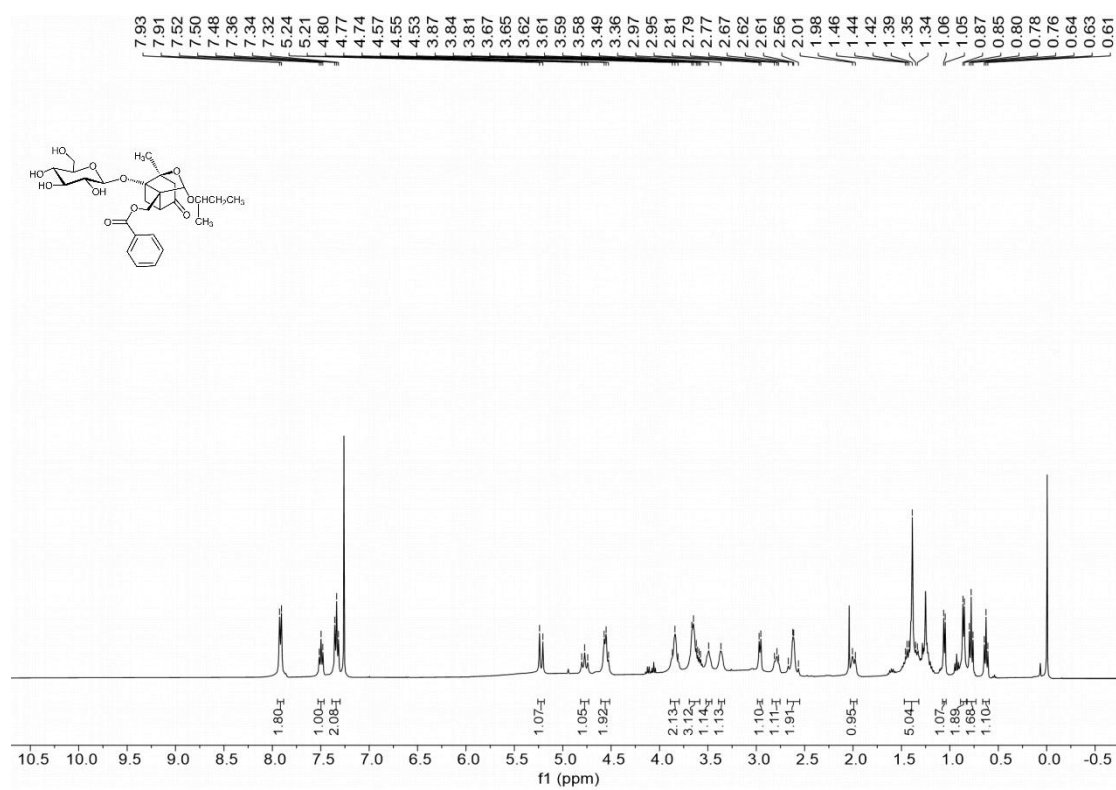


Figure S59. The ¹H NMR of compound **32**.

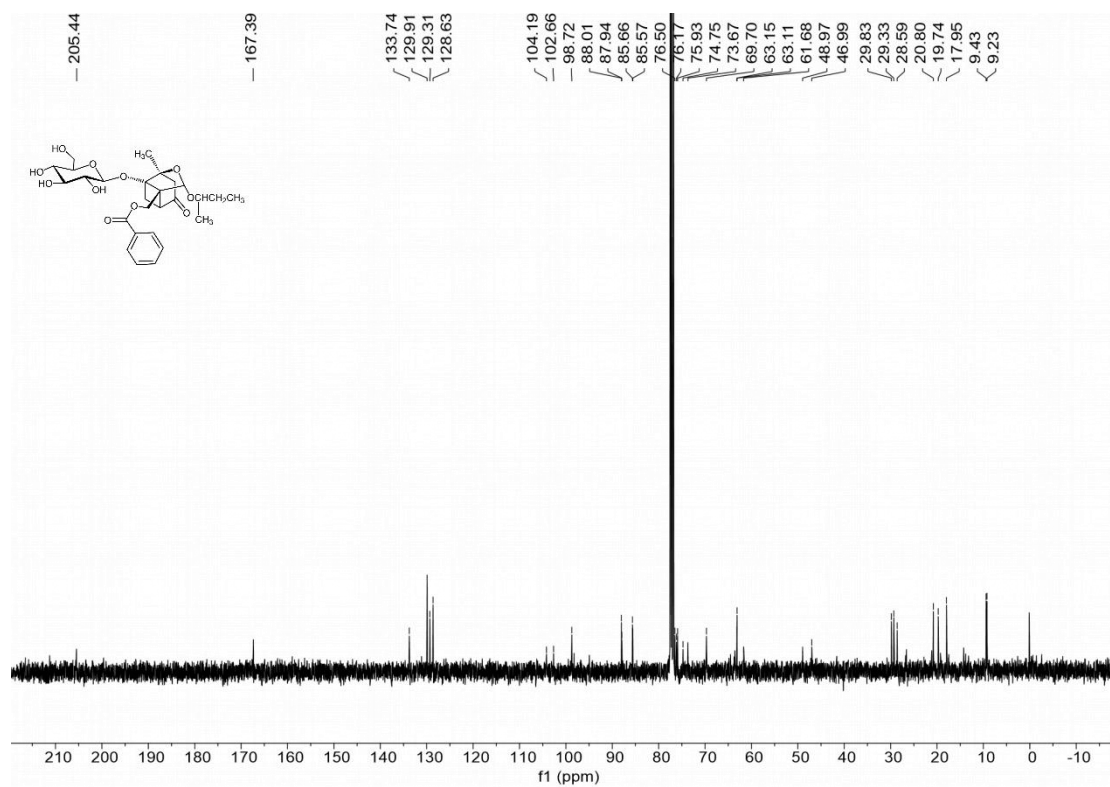


Figure S60. The ¹³C NMR of compound **32**.

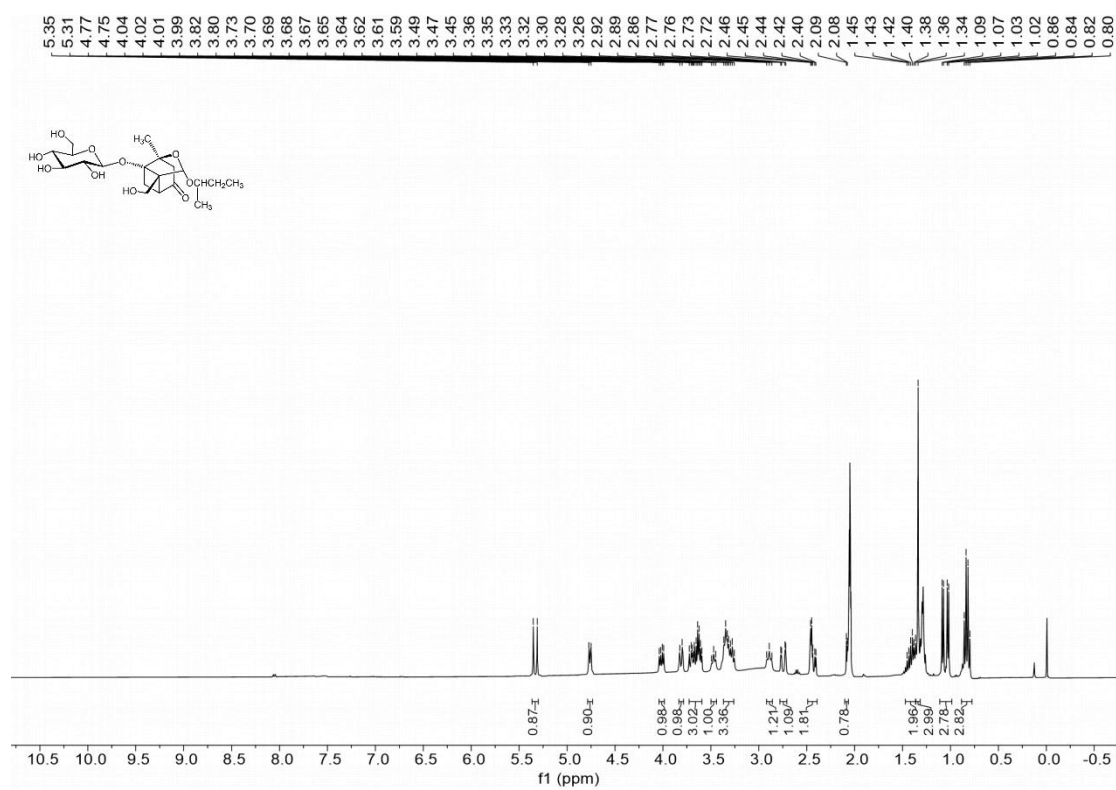


Figure S61. The ¹H NMR of compound **33**.

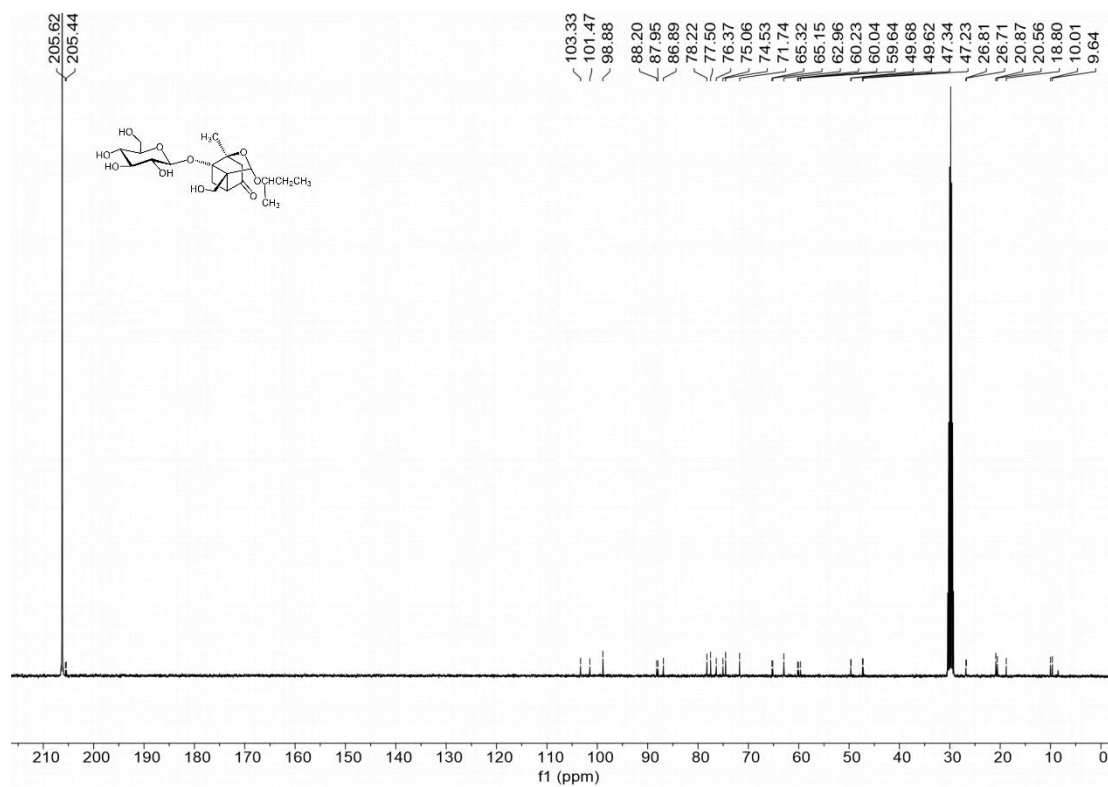


Figure S62. The ^{13}C NMR of compound **33**.

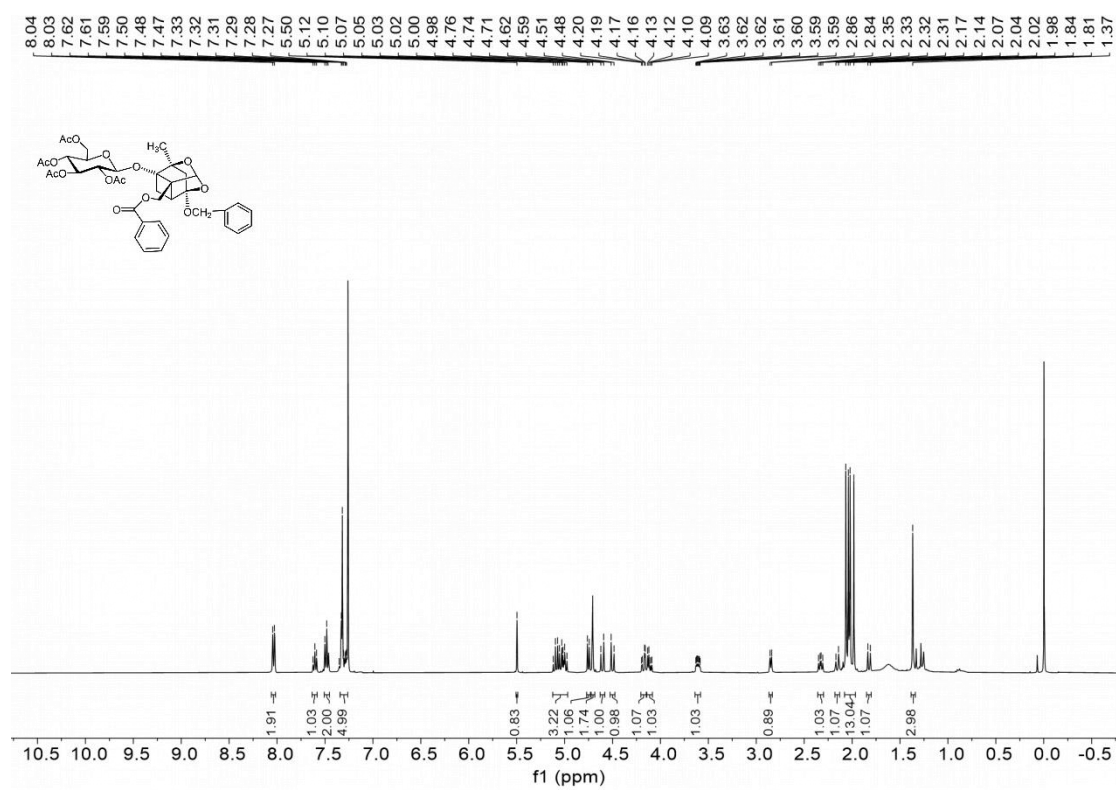


Figure S63. The ^1H NMR of compound **34**.

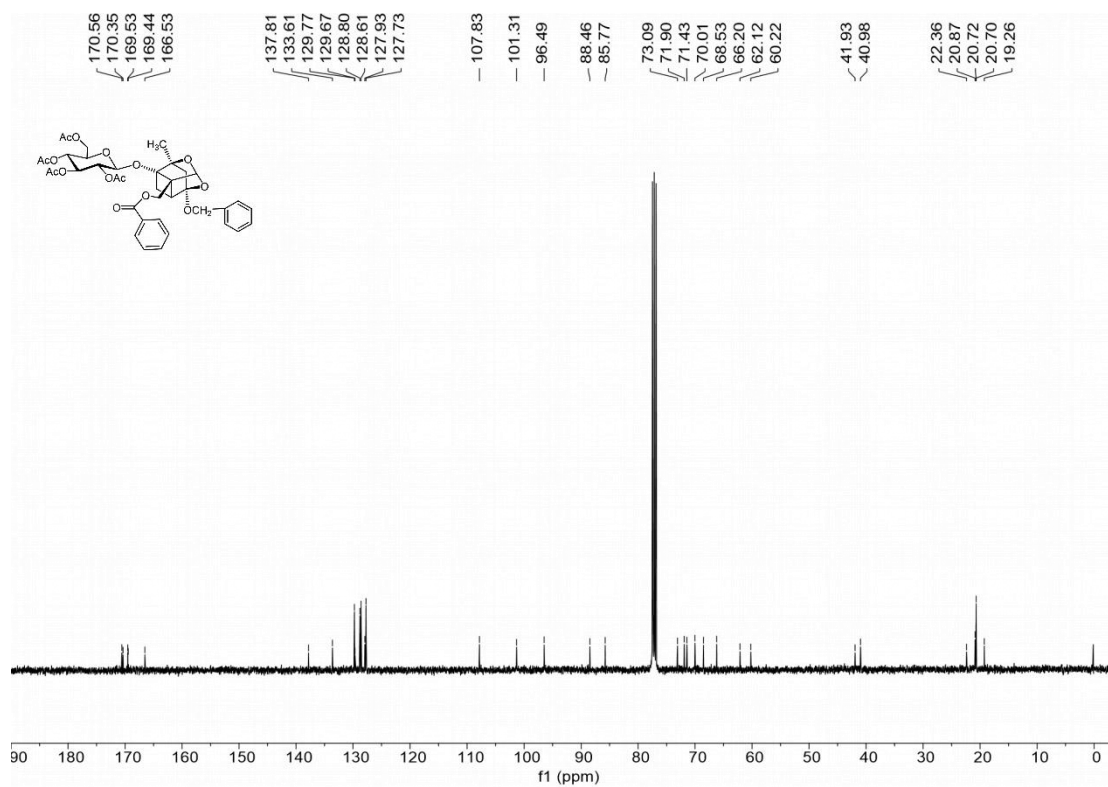


Figure S64. The ^{13}C NMR of compound **34**.

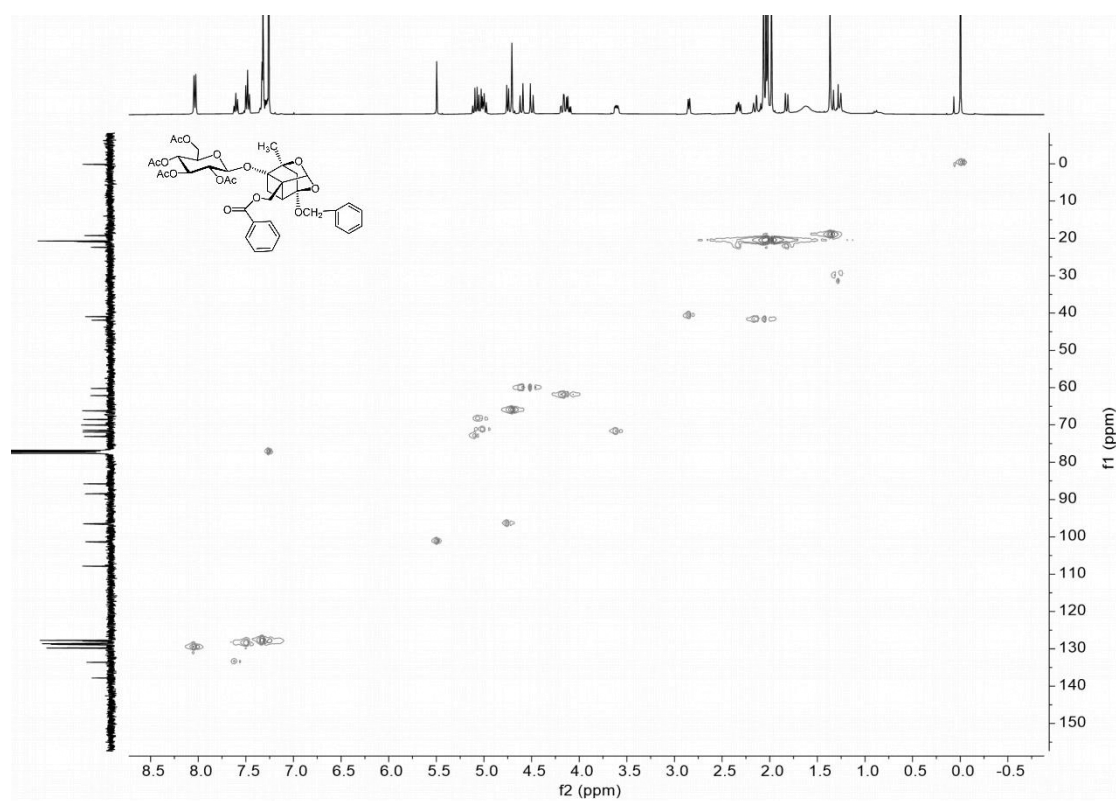


Figure S65. The HSQC-NMR of compound **34**.

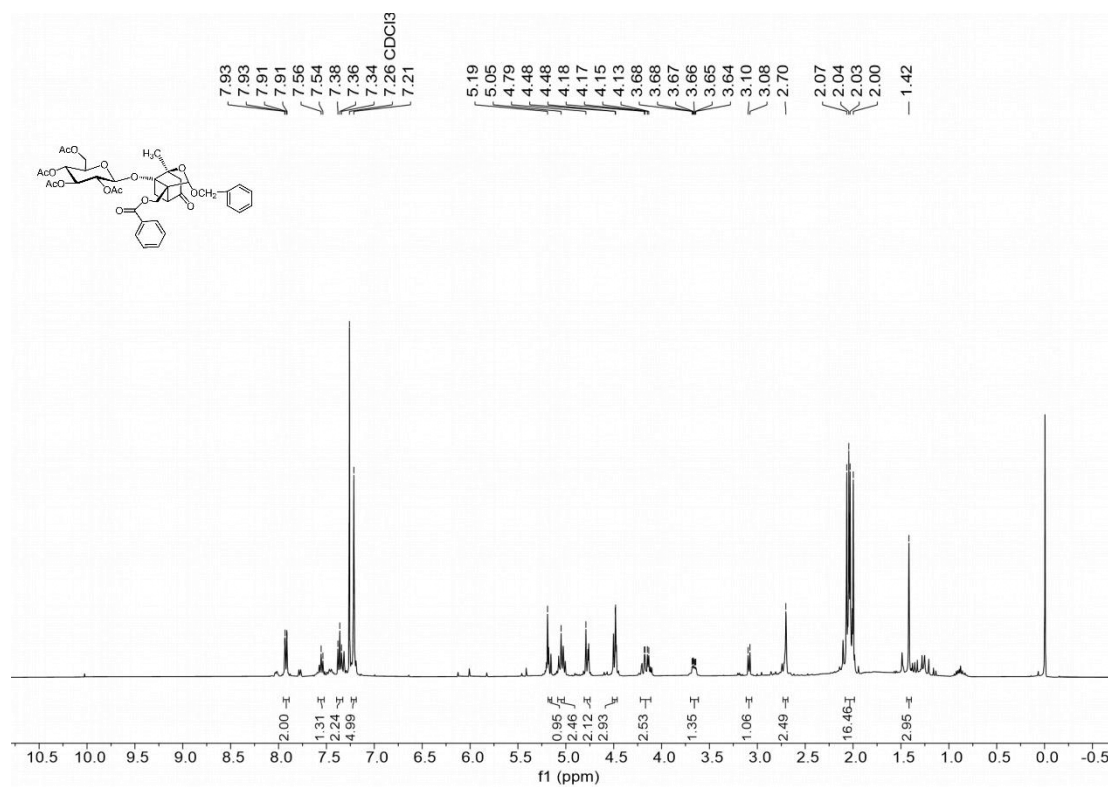


Figure S66. The ^1H NMR of compound **35**.

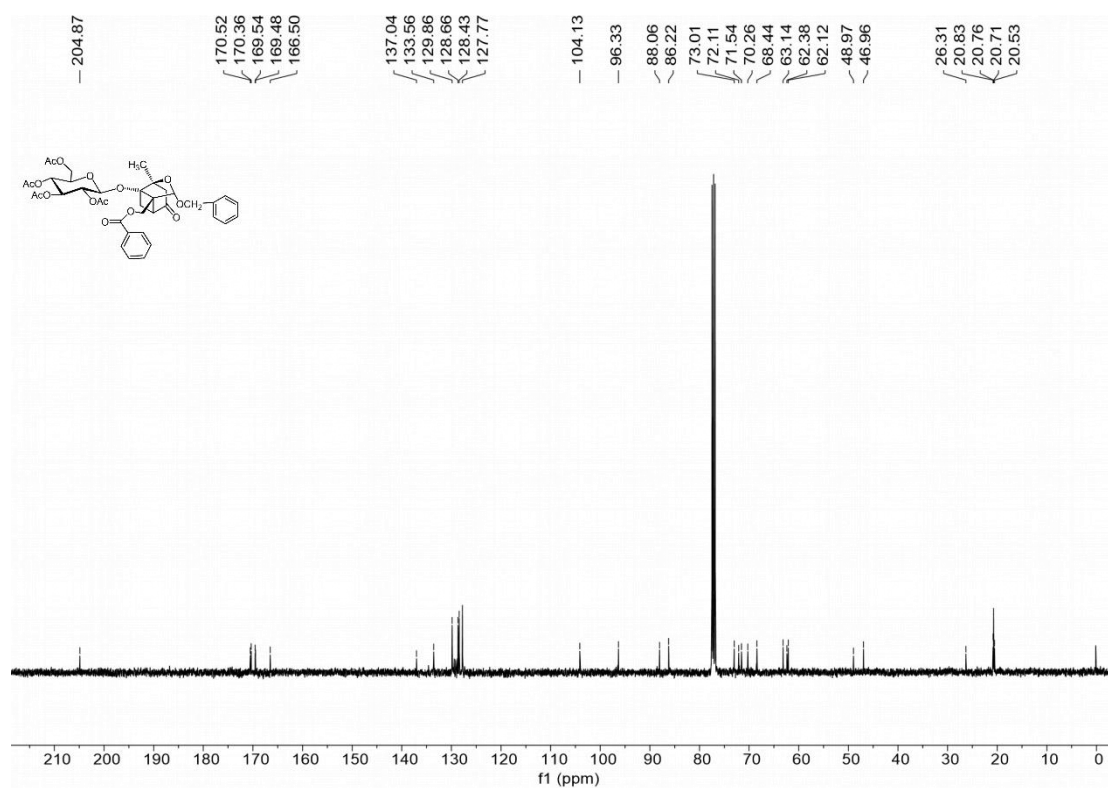


Figure S67. The ^{13}C NMR of compound **35**.

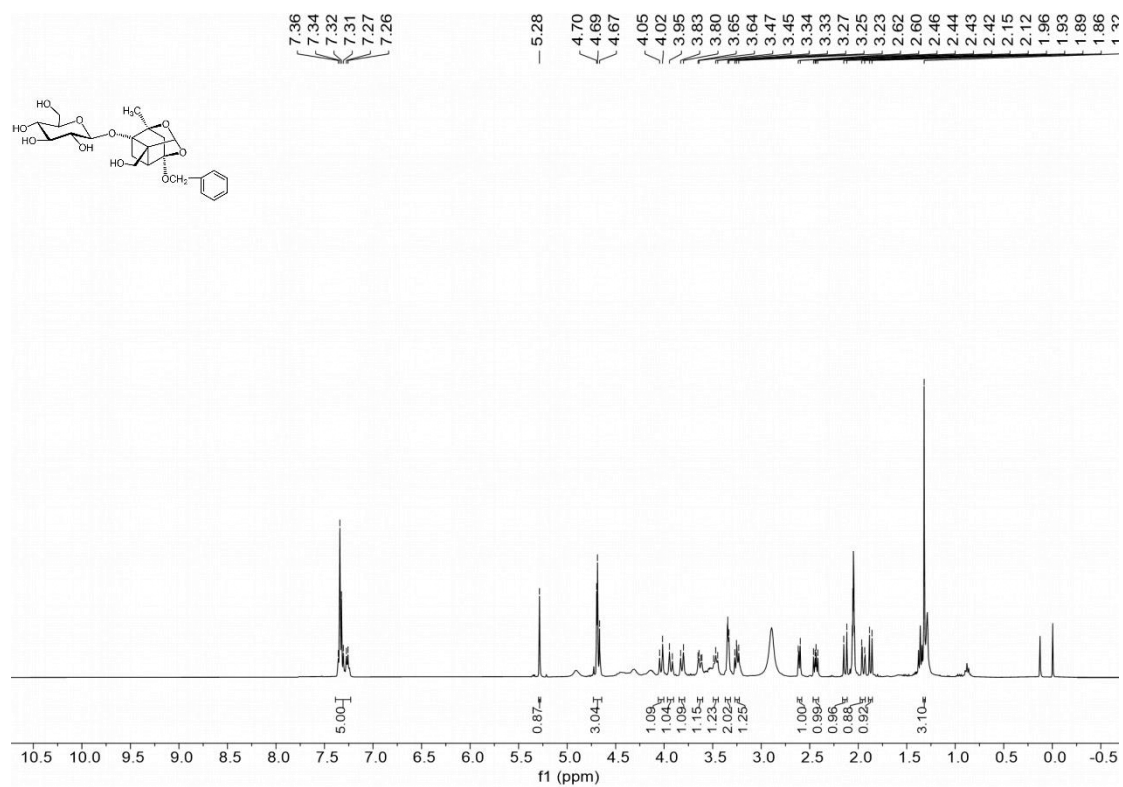


Figure S68. The ¹H NMR of compound **36**.

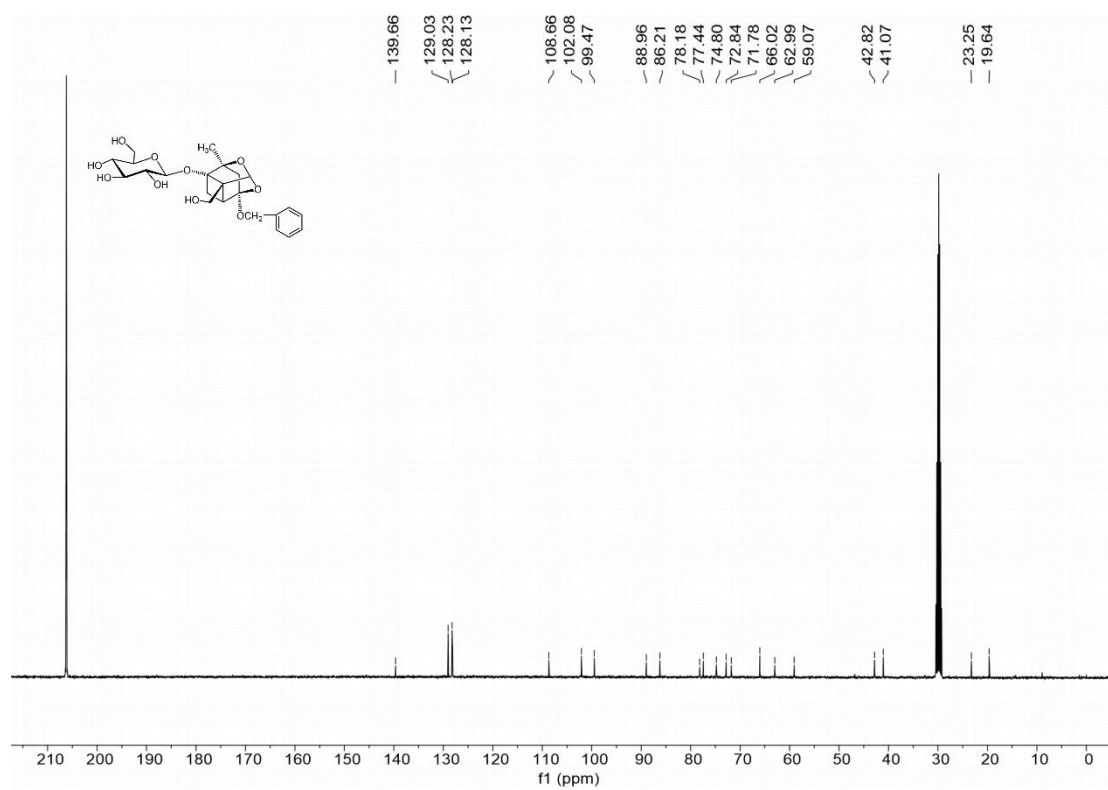


Figure S69. The ¹³C NMR of compound **36**.

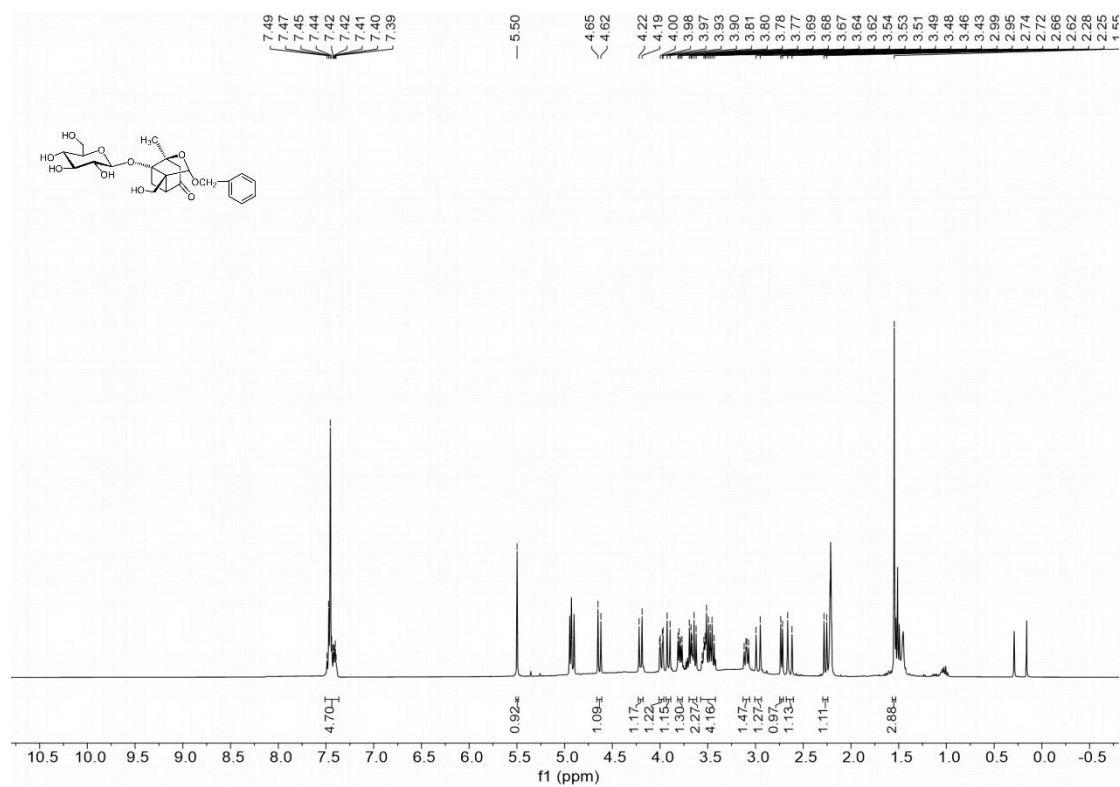


Figure S72. The ¹H NMR of compound **38**.

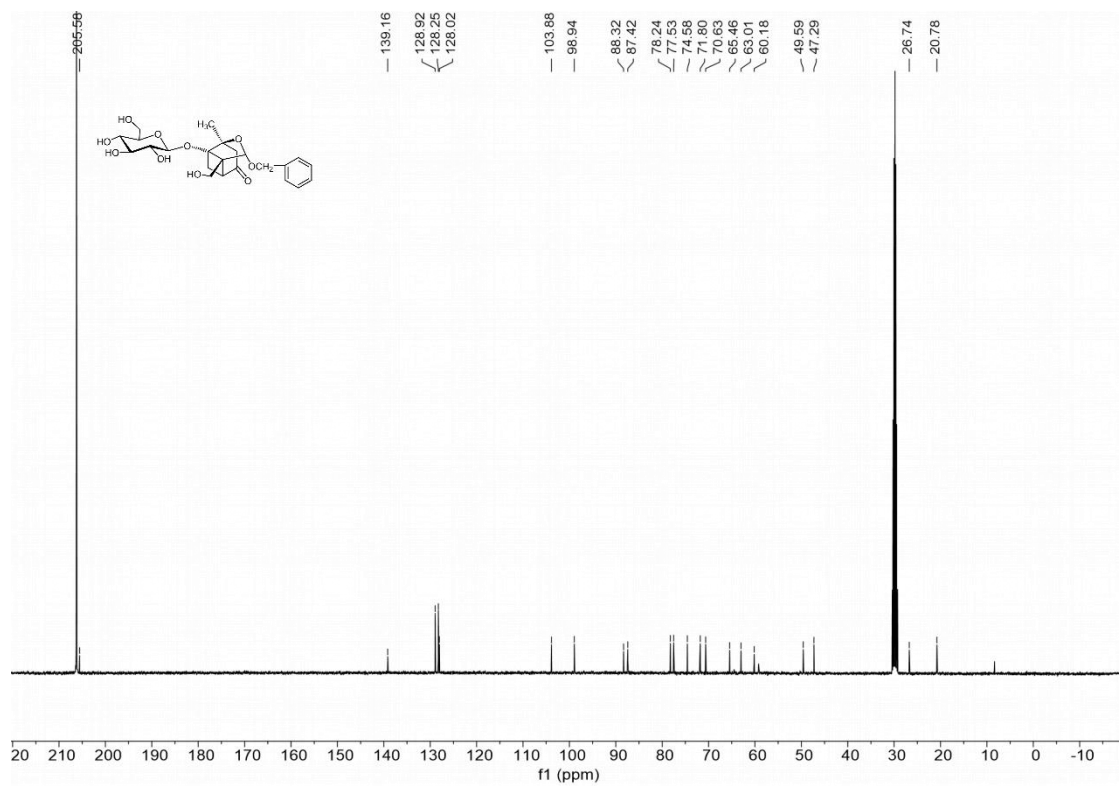


Figure S73. The ¹³C NMR of compound **38**.

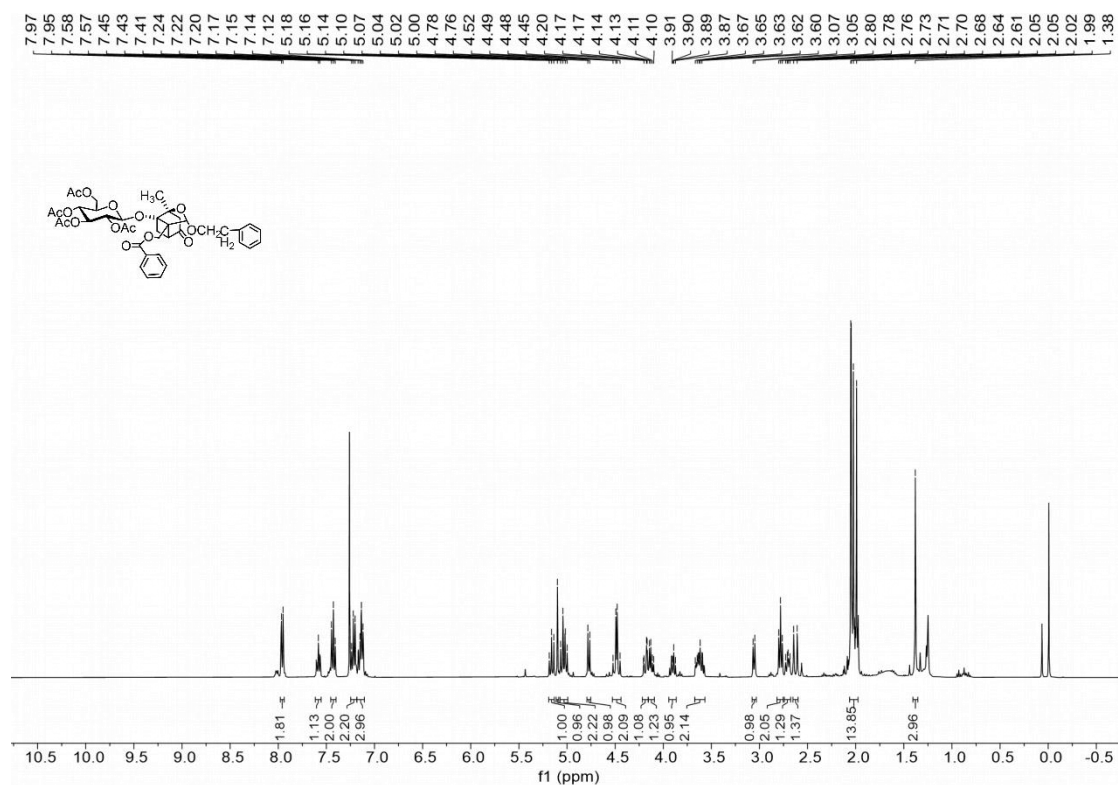


Figure S76. The ^1H NMR of compound **40**.

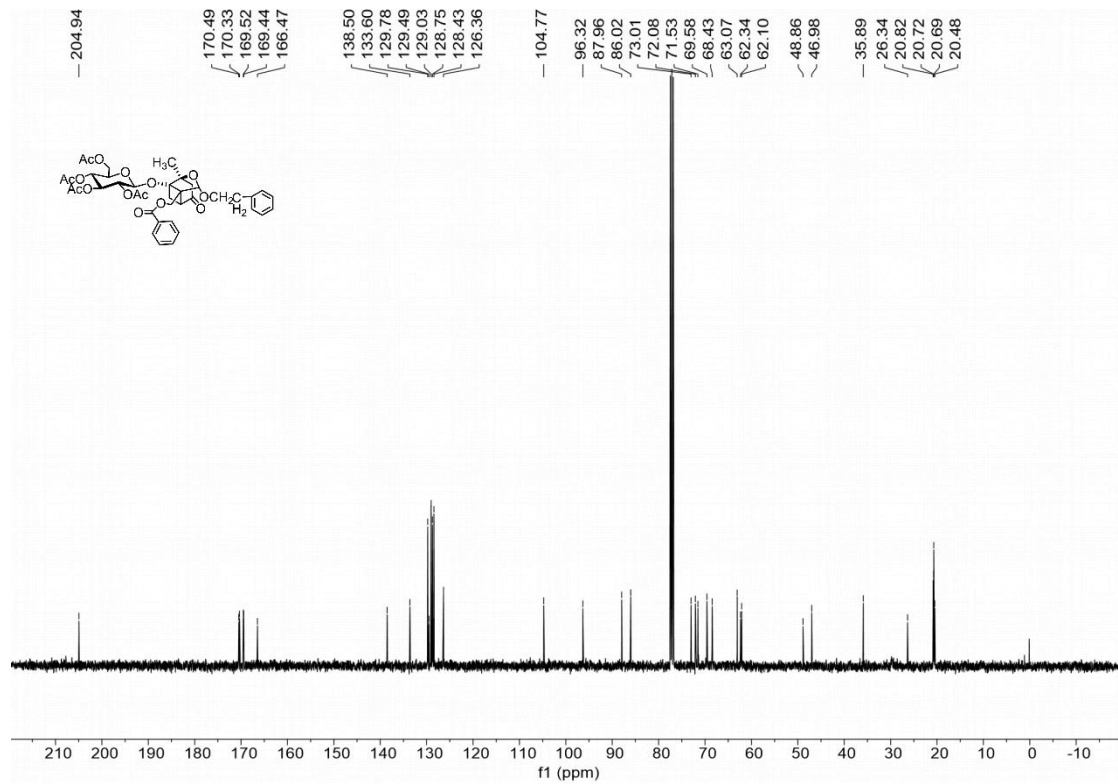


Figure S77. The ^{13}C NMR of compound **40**.

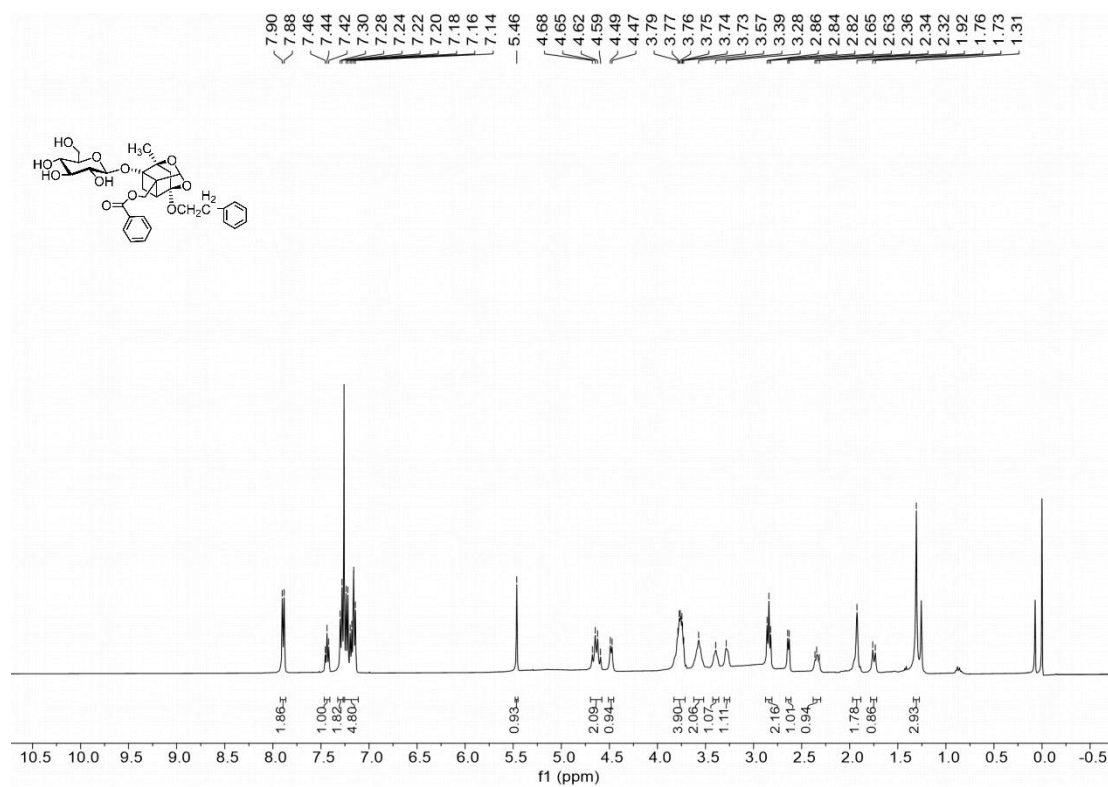


Figure S78. The ^1H NMR of compound **41**.

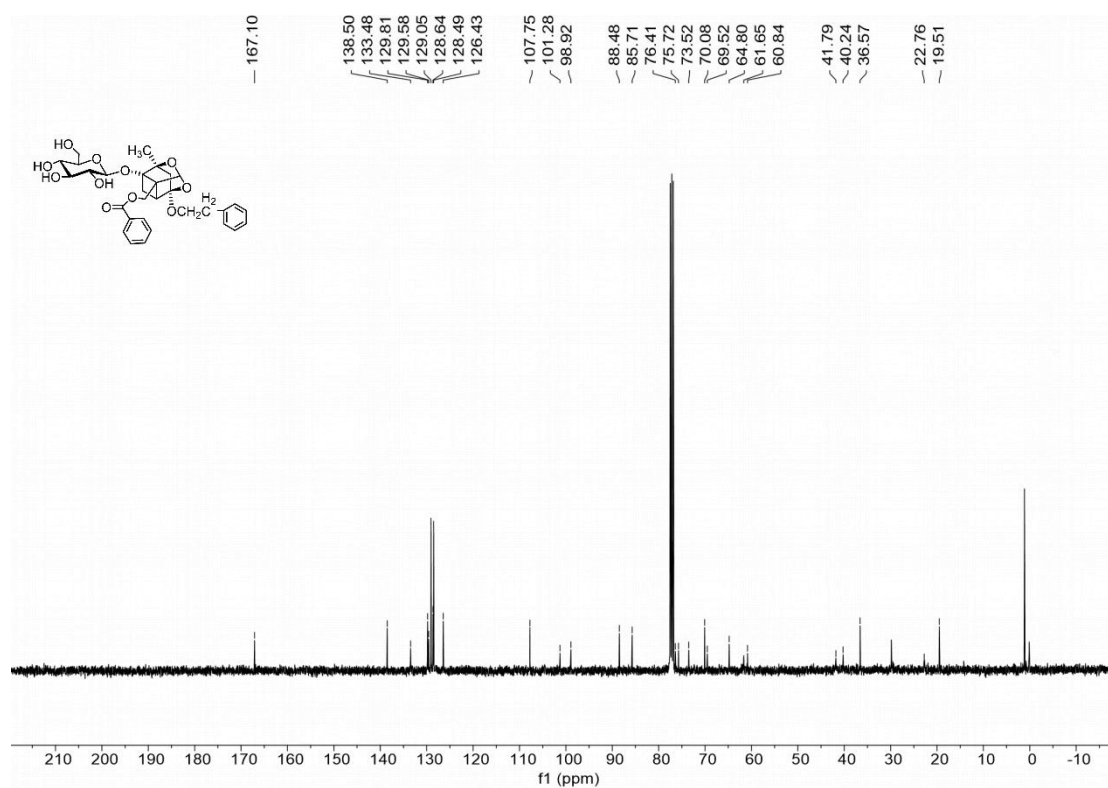


Figure S79. The ^{13}C NMR of compound **41**.

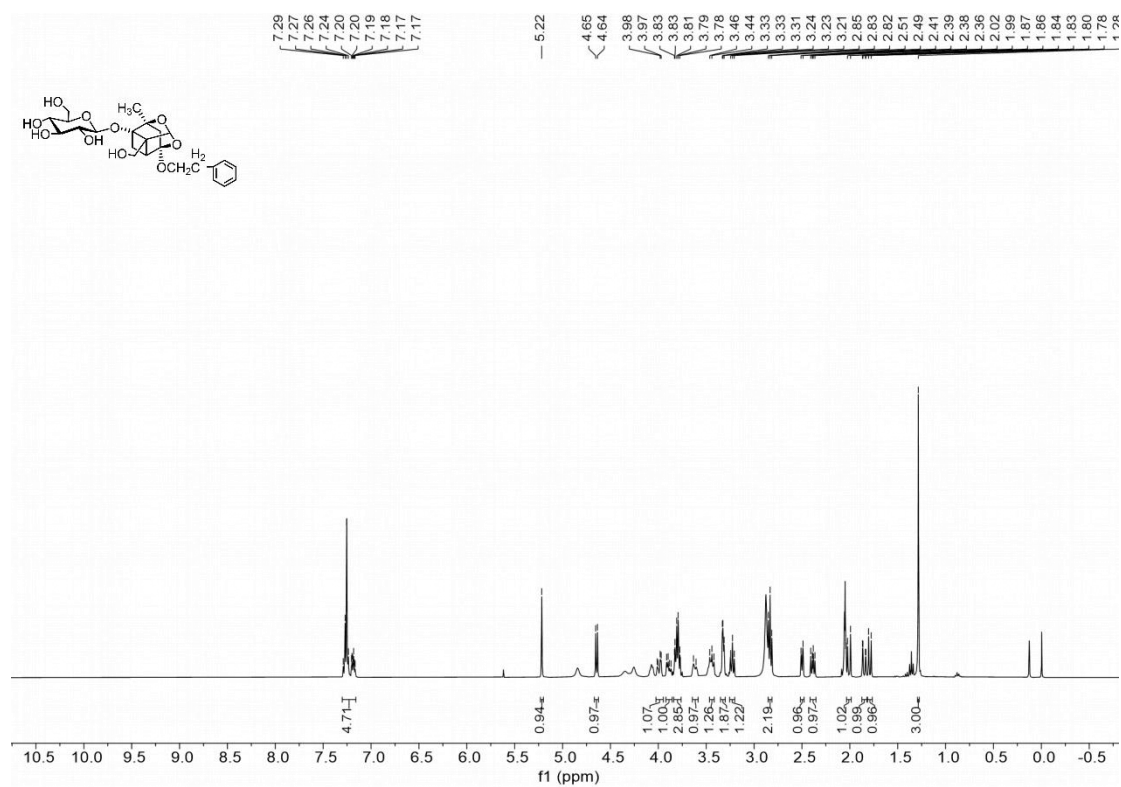


Figure S80. The ¹H NMR of compound **42**.

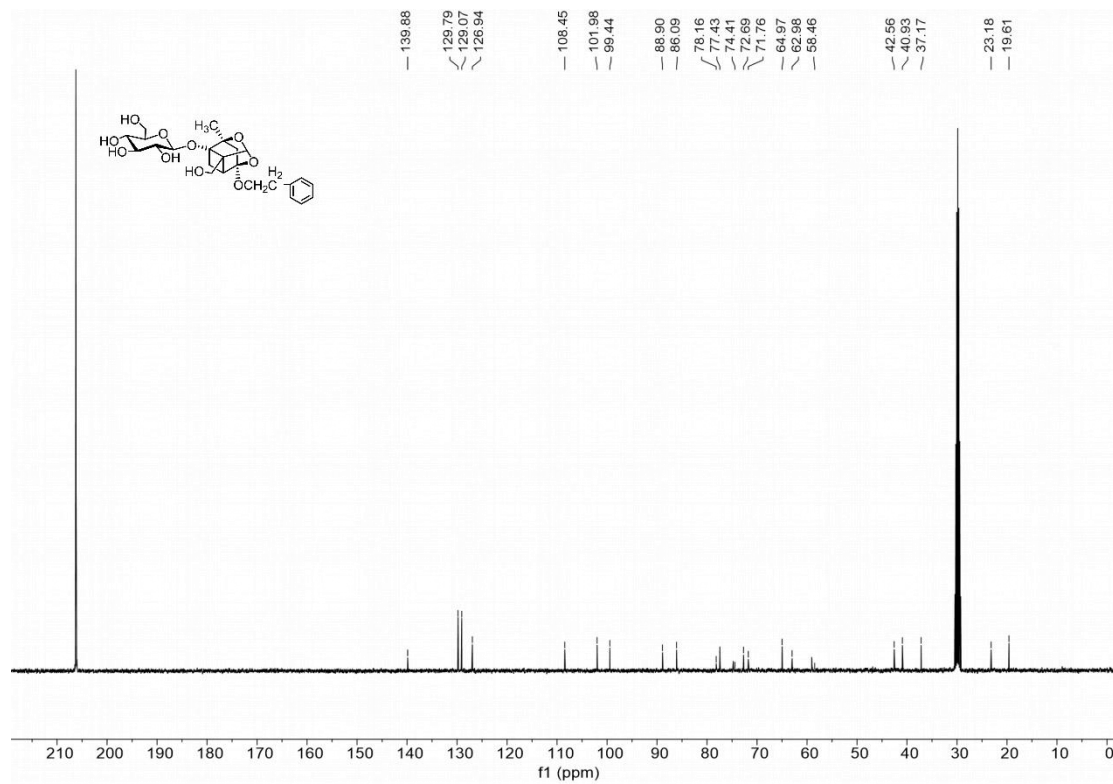


Figure S81. The ¹³C NMR of compound **42**.

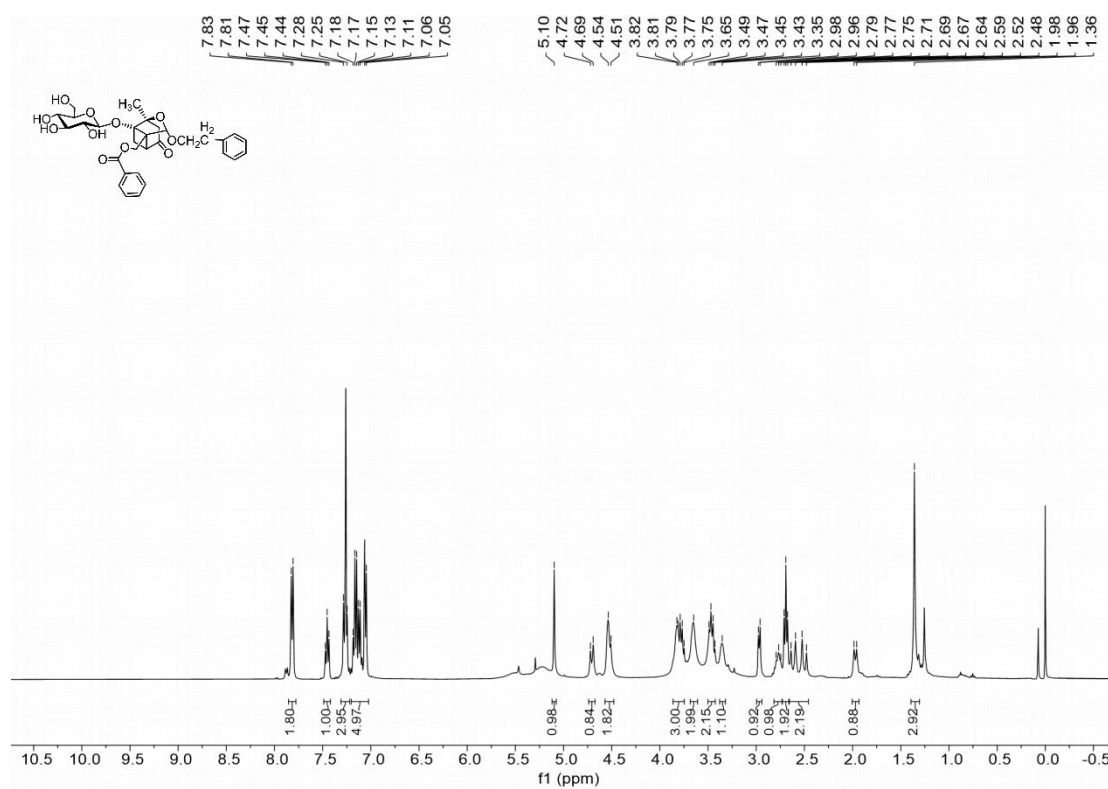


Figure S82. The ¹H NMR of compound **43**.

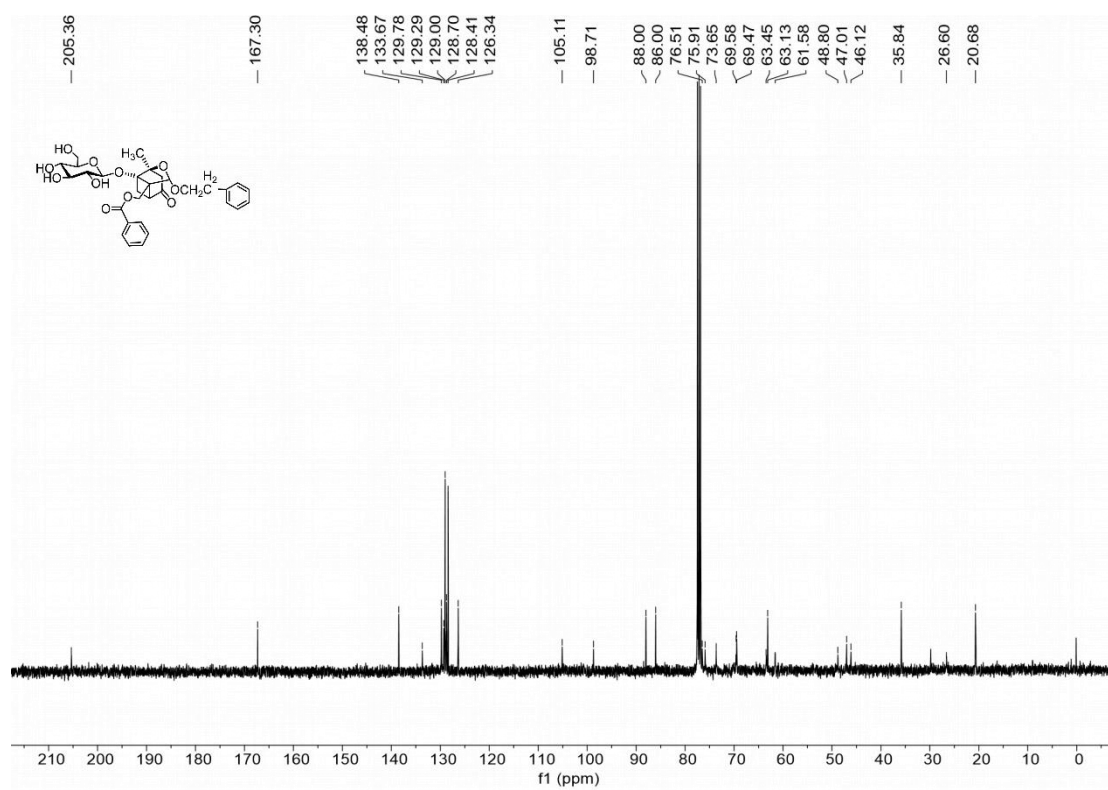


Figure S83. The ¹³C NMR of compound **43**.

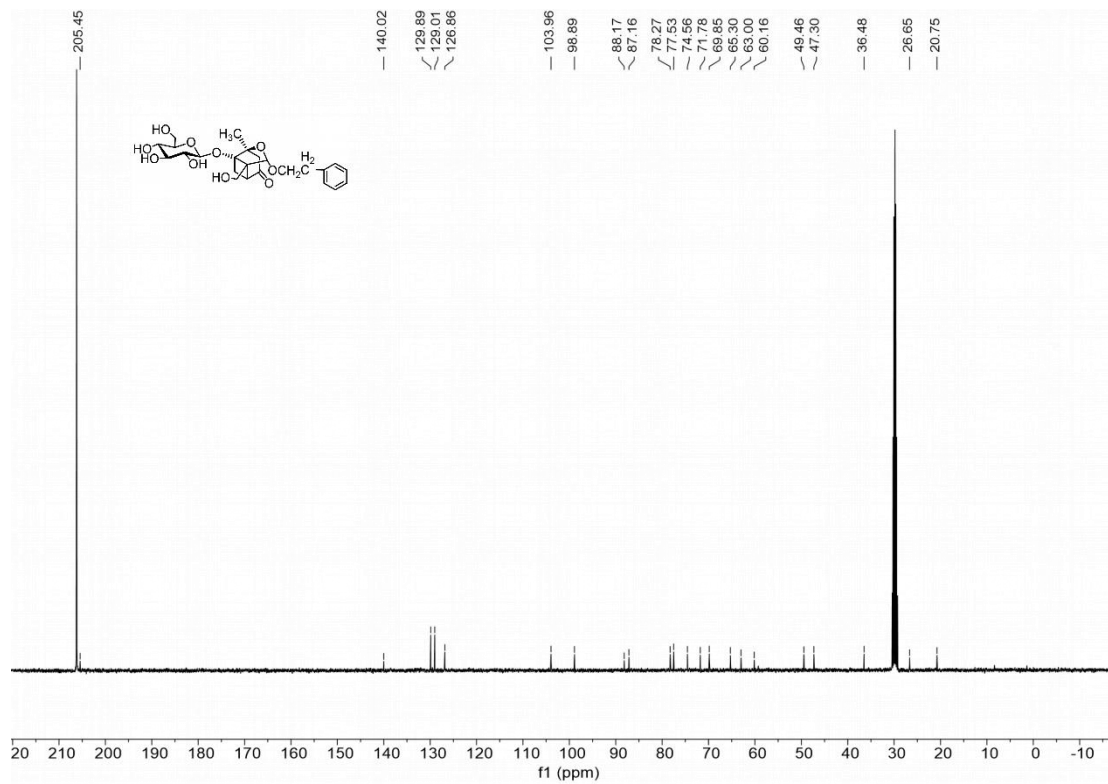
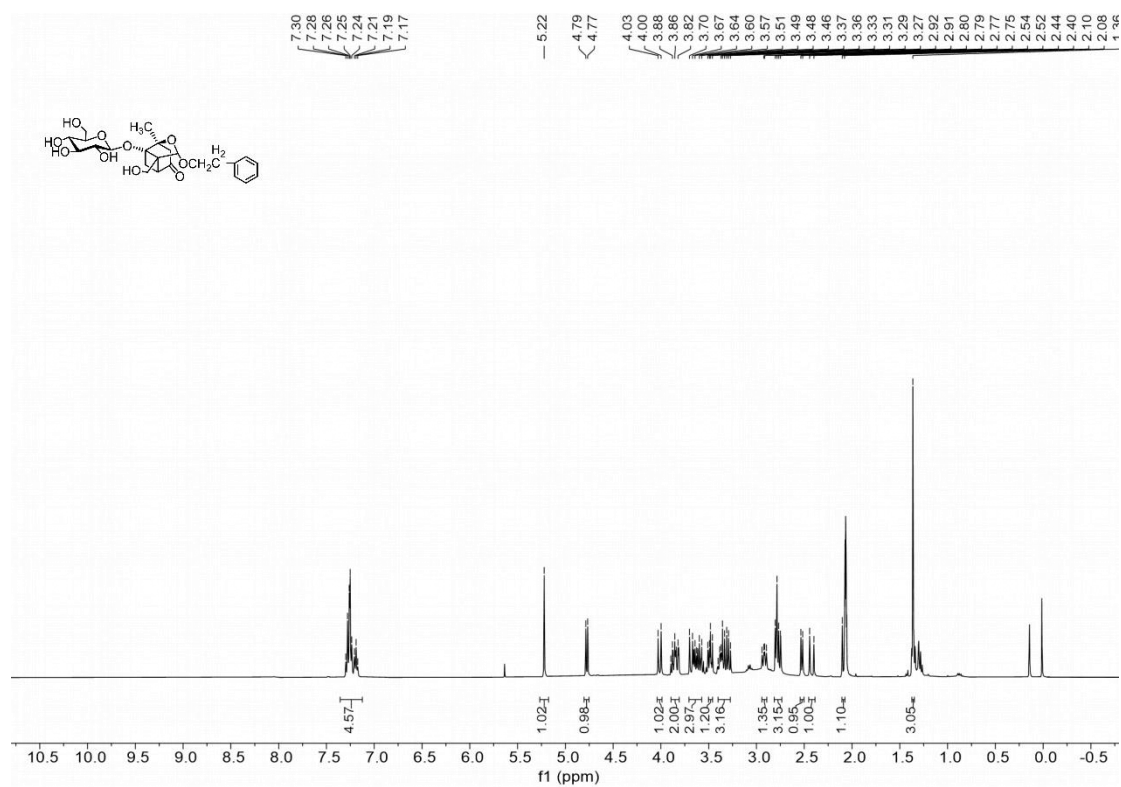


Figure S85. The ^{13}C NMR of compound **44**.

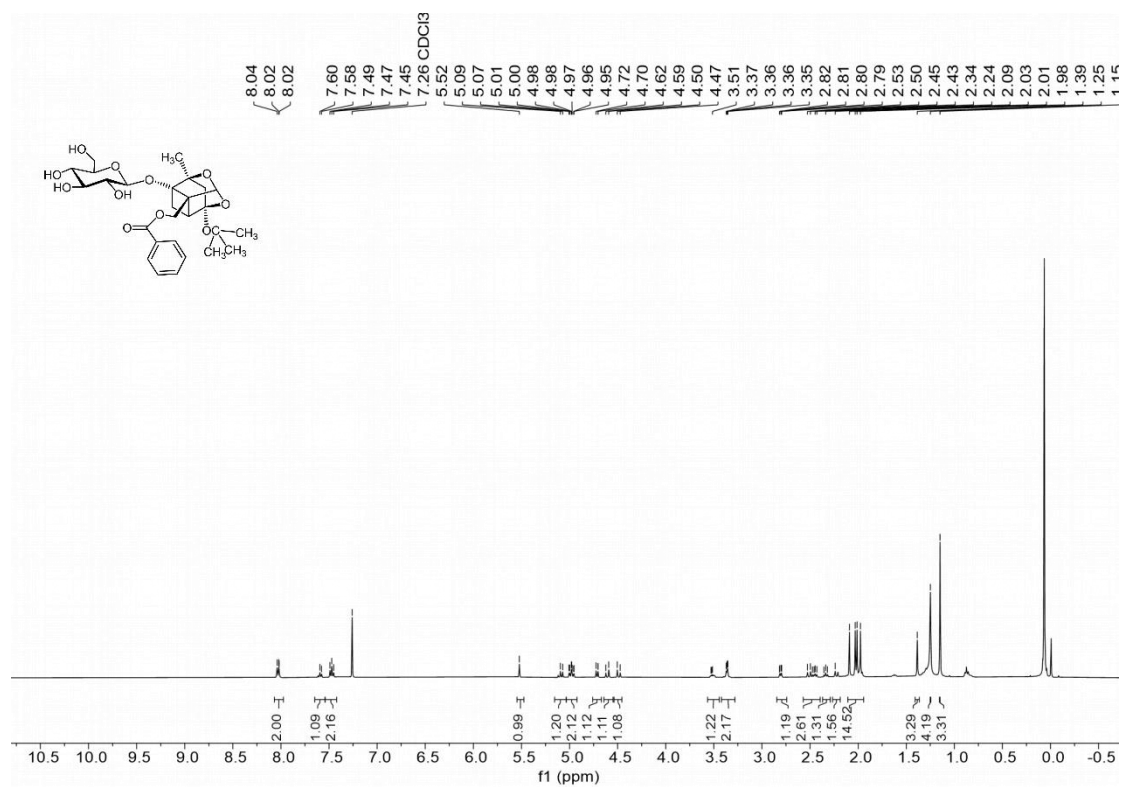


Figure S86. The ¹H NMR of compound 45.

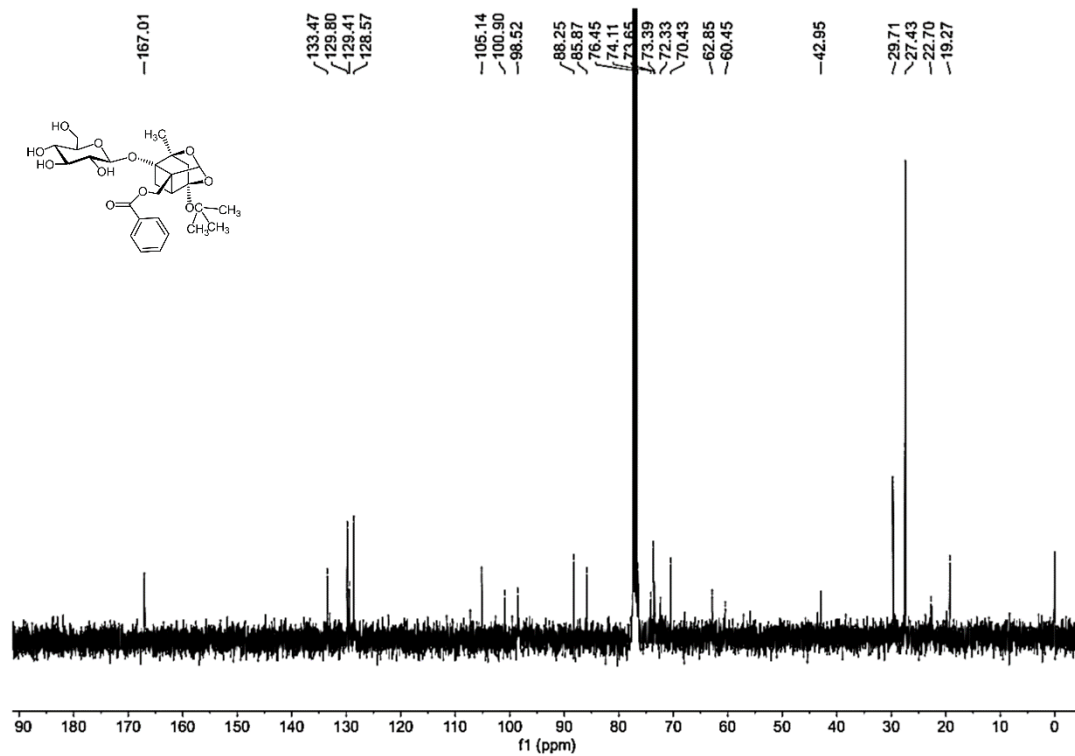


Figure S87. The ¹³C NMR of compound 45.

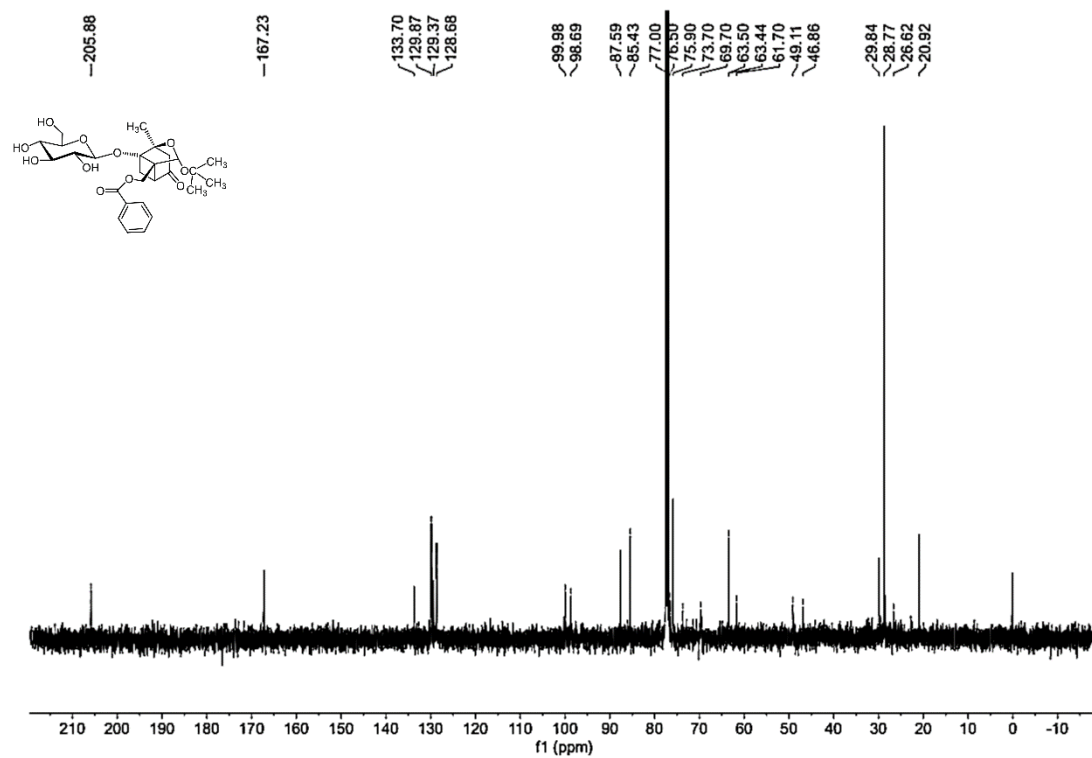
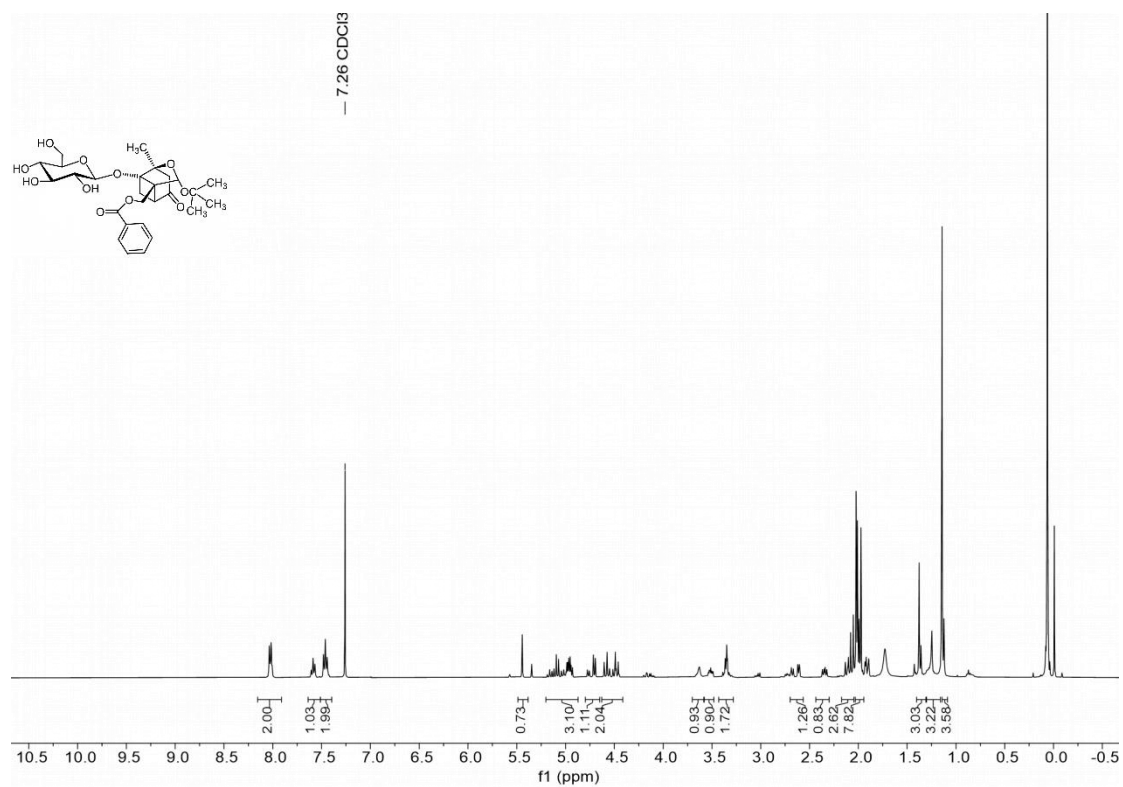


Figure S89. The ^{13}C NMR of compound **46**.

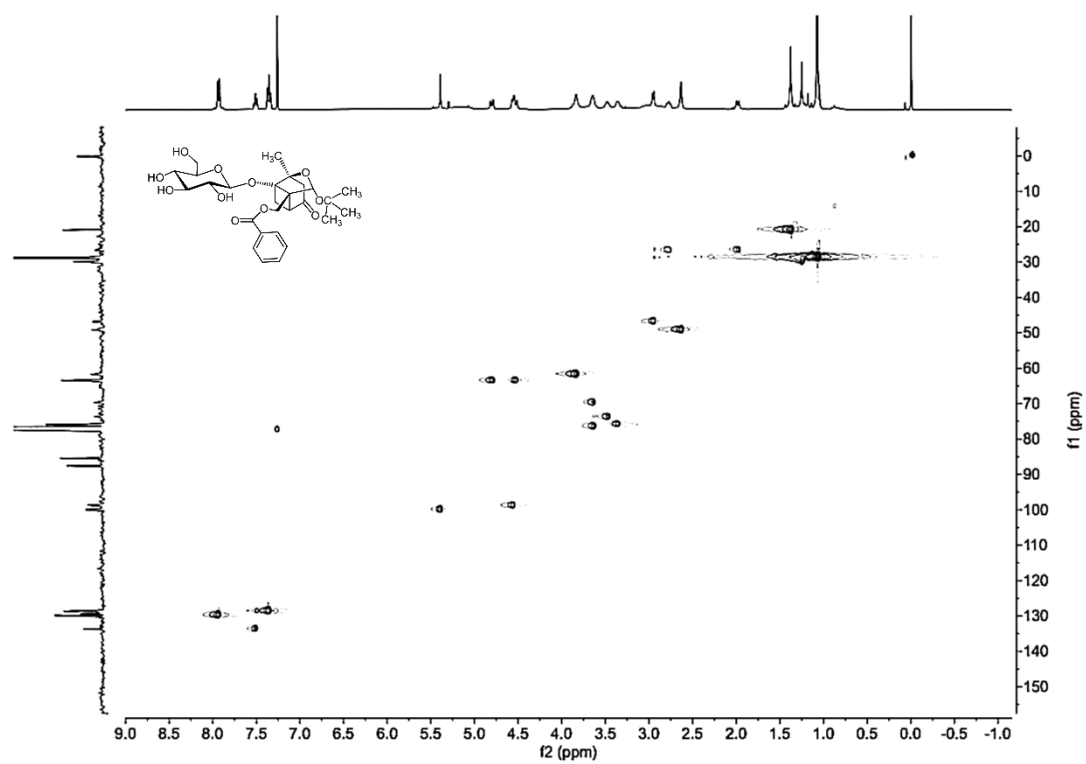


Figure S90. The HSQC-NMR of compound **46**.

3. Single crystal structure and data

CCDC 2249825 (Compound **11**), 2249824 (Compound **17**), and 2249823 (Compound **18**) containing the supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/search>

Compounds single crystal data

Table S3 Crystal data and structure refinement for compound 11 .	
Empirical formula	C ₁₈ H ₂₈ O ₁₀
Formula weight	404.40
Temperature/K	293.15
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	9.9334(8)
b/Å	13.2276(8)
c/Å	14.4439(14)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1897.9(3)
Z	4
ρ _{calc} /cm ³	1.415
μ/mm ⁻¹	0.116
F(000)	864.0
Crystal size/mm ³	0.35 × 0.3 × 0.25
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	6.16 to 52.732
Index ranges	-12 ≤ h ≤ 12, -16 ≤ k ≤ 11, -17 ≤ l ≤ 18
Reflections collected	5755
Independent reflections	3597 [R _{int} = 0.0249, R _{sigma} = 0.0589]
Data/restraints/parameters	3597/0/260
Goodness-of-fit on F ²	1.037
Final R indexes [I >= 2σ (I)]	R ₁ = 0.0673, wR ₂ = 0.1612
Final R indexes [all data]	R ₁ = 0.0919, wR ₂ = 0.1791
Largest diff. peak/hole / e Å ⁻³	0.70/-0.29
Flack parameter	0.6(10)

Table S4 Crystal data and structure refinement for compound **17**.

Empirical formula	C ₃₄ H ₄₂ O ₁₅
Formula weight	690.67
Temperature/K	293.15
Crystal system	monoclinic
Space group	C2
a/Å	20.613(3)
b/Å	5.9223(6)
c/Å	29.982(3)
α/°	90
β/°	100.058(12)
γ/°	90
Volume/Å ³	3603.8(7)
Z	4
ρ _{calc} /cm ³	1.273
μ/mm ⁻¹	0.100
F(000)	1464.0
Crystal size/mm ³	0.35 × 0.1 × 0.05
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	6.234 to 52.744
Index ranges	-25 ≤ h ≤ 25, -7 ≤ k ≤ 4, -29 ≤ l ≤ 37
Reflections collected	7962
Independent reflections	5359 [R _{int} = 0.0214, R _{sigma} = 0.0581]
Data/restraints/parameters	5359/1/449
Goodness-of-fit on F ²	0.934
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0693, wR ₂ = 0.1838
Final R indexes [all data]	R ₁ = 0.1128, wR ₂ = 0.2076
Largest diff. peak/hole / e Å ⁻³	0.59/-0.26
Flack parameter	-1.2(8)

Table S5 Crystal data and structure refinement for compound 18 .	
Empirical formula	C ₃₄ H ₄₂ O ₁₅
Formula weight	690.67
Temperature/K	293.15
Crystal system	monoclinic
Space group	C2
a/Å	19.019(3)
b/Å	6.4924(8)
c/Å	29.815(3)
α/°	90

$\beta/^\circ$	95.370(11)
$\gamma/^\circ$	90
Volume/ \AA^3	3665.3(8)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.252
μ/mm^{-1}	0.099
F(000)	1464.0
Crystal size/ mm^3	$0.35 \times 0.3 \times 0.25$
Radiation	MoK α ($\lambda = 0.71073$)
2 θ range for data collection/ $^\circ$	6.634 to 52.742
Index ranges	$-21 \leq h \leq 23$, $-8 \leq k \leq 8$, $-37 \leq l \leq 37$
Reflections collected	14487
Independent reflections	7000 [$R_{\text{int}} = 0.0238$, $R_{\text{sigma}} = 0.0387$]
Data/restraints/parameters	7000/1/471
Goodness-of-fit on F^2	1.015
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0572$, $wR_2 = 0.1347$
Final R indexes [all data]	$R_1 = 0.0916$, $wR_2 = 0.1577$
Largest diff. peak/hole / e \AA^{-3}	0.17/-0.17
Flack parameter	-0.9(5)