Supplementary data for article:

Marjanović-Trajković, J.; Divjakovic, V.; Matovic, R.; Ferjančić, Z.; Saičić, R. Double Asymmetric Induction in Organocatalyzed Aldol Reactions: Total Synthesis of (+)-2-Epi-Hyacinthacine A(2) and (-)-3-Epi-Hyacinthacine A(1). *European Journal of Organic Chemistry* **2013**, *2013* (25), 5555–5560. https://doi.org/10.1002/ejoc.201300716

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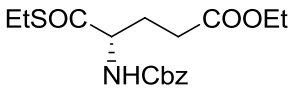
SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201300716
Title: Double Asymmetric Induction in Organocatalyzed Aldol Reactions: Total Synthesis of (+)-2-*epi*-Hyacinthacine A_2 and (–)-3-*epi*-Hyacinthacine A_1
Author(s): Jasna Marjanovic, Vladimir Divjakovic, Radomir Matovic, Zorana Ferjancic,* Radomir N. Saicic*

Experimental Section

Preparation of aldehyde 1:

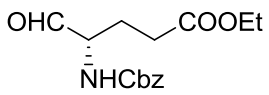
(*S*)-Ethyl 4-(benzyloxycarbonylamino)-5-(ethylthio)-5-oxopentanoate



To a cold solution (-15 °C) of L-glutamic acid (5.0 g, 34.00 mmol) in anhydrous ethanol (38 mL), thionyl chloride (5.1 g, 3.1 mL, 43.00 mmol) was added slowly, by syringe. The solution was stirred at -15 °C for 30 min and then at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in mixture of water (50 ml) and dioxane (50 ml). To the cold (0 °C) resulting solution was added Na_2CO_3 (5.5 g, 51.9 mmol), followed by dropwise addition (over 30 min) of benzyl chloroformate (4.8 g, 4.0 mL, 28.14 mmol) in dioxane (40 ml). The reaction mixture was stirred overnight at rt. The solution was extracted with ethyl acetate (2 x 100 mL) and the aqueous layer was acidified to pH~1 with 6 N HCl. The product was extracted with ethyl acetate (2 x 100 mL), the organic extract was dried over anh. $MgSO_4$, filtered and concentrated in vacuo yielding 7.0 g of the (*S*)-2-(benzyloxycarbonylamino)-5-ethoxy-5-oxopentanoic acid, as pale yellow solid.
Isobutyl chloroformate (1.5 g, 1.4 mL; 10.70 mmol) and triethylamine (1.0 g, 1.4 mL, 10.37 mmol) were added to a cold (0 °C) solution of crude (*S*)-2-(benzyloxycarbonylamino)-5-ethoxy-5-oxopentanoic acid (3.0 g, 9.70 mmol) in freshly distilled THF (30.0 mL), under an argon atmosphere. The reaction mixture was vigorously stirred for 30 min at 0 °C, then ethanethiol (1.2 g, 1.5 mL, 19.97 mmol) and triethylamine (1.0 g, 1.4 mL, 10.37 mmol) were added. The resulting solution was stirred for 30 min at 0 °C and 45 min at rt. The reaction mixture was diluted with dichloromethane, washed with 1.5 M HCl and water, dried over anh. $MgSO_4$ and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) to give 1.7 g (50%) of the (*S*)-ethyl 4-(benzyloxycarbonylamino)-5-(ethylthio)-5-oxopentanoate, as white solid.

Physical data for the title compound: mp 53-54 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 5H), 5.50 (bd, *J* = 8.0 Hz, 1H), 5.13 (s, 2H), 4.45 (td, *J* = 9.0, 5.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.89 (q, *J* = 7.4 Hz, 2H), 2.48 – 2.35 (m, 2H), 2.26 – 2.19 (m, 1H), 2.00 – 1.92 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.3 (C), 172.8 (C), 155.8 (C), 136.1 (C), 128.5 (CH) , 128.2 (CH), 128.1 (CH), 67.2 (CH_2), 60.8 (CH_2), 60.4 (CH), 30.2 (CH_2), 27.8 (CH_2), 23.4 (CH_2), 14.4 (CH_3), 14.1 (CH_3) ppm. IR (ATR): *ν* 3346, 2978, 2935, 1734, 1530, 1453, 1379, 1324, 1255, 1184, 1060 cm^{-1}. HRMS (ESI) for $C_{17}H_{23}NO_5S$ $[M+H]^+$ calculated: 354.1370; found: 354.1376. Anal. calcd. for $C_{17}H_{23}NO_5S$: C 57.77, H 6.56, N 3.96, S 9.07; found: C 57.88, H 6.70, N 4.08, S 9.00. $[\alpha]_D^{20}$ -12.6 (*c* 1.15, $CHCl_3$).

(*S*)-Ethyl 4-(benzyloxycarbonylamino)-5-oxopentanoate 1



1

Triethylsilane (154.0 mg; 0.2 mL; 1.32 mmol) was added during 30 minute to a suspension of thioester (104.0 mg; 0.29 mmol) and 10% palladium on charcoal (16.7 mg; 0.02 mmol) in acetone (3.8 mL), at rt, under an argon atmosphere. Upon the completion of the addition, the reaction mixture was stirred for additional 15 min, then filtered, concentrated under reduced pressure and purified by dry-flash

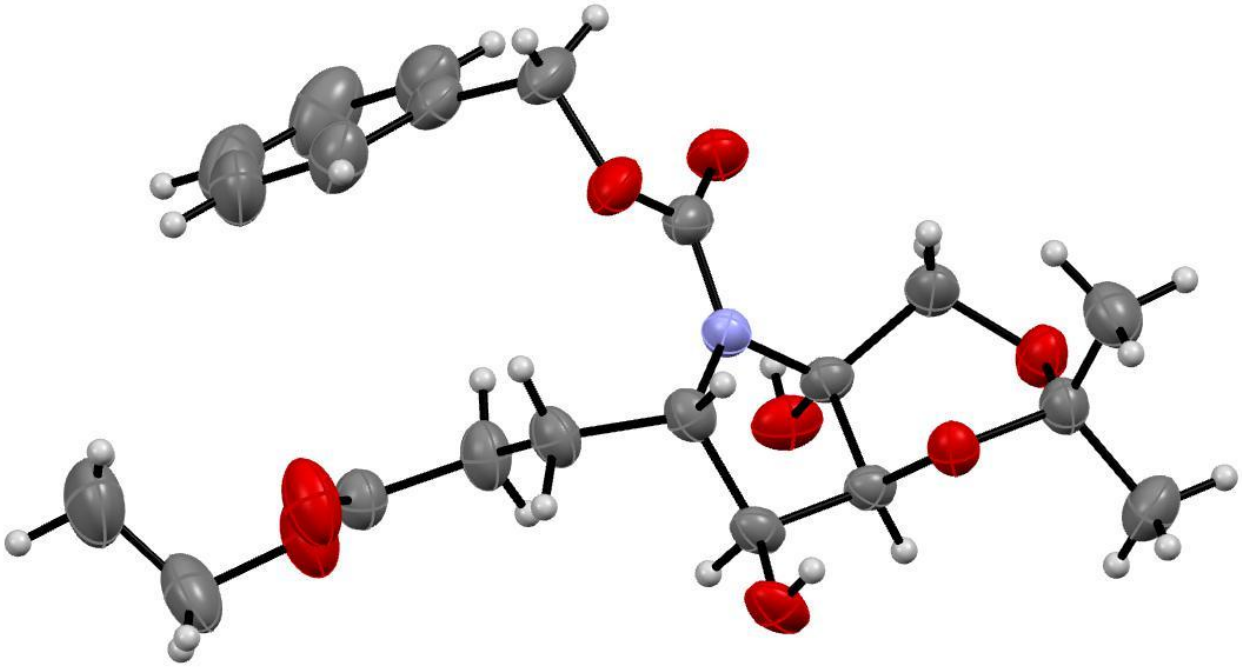
chromatography (SiO_2; eluent: petroleum-ether/EtOAc = 7/3) to give 58.1 mg (67%) of the title compound **1**, as a pale yellow oil.

Spactral data for compound **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.35 (s, 5H), 5.56 (bd, *J* = 5.5 Hz, 1H), 5.12 (s, 2H), 4.38 – 4.30 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.49 – 2.34 (m, 2H), 2.33 – 2.25 (m, 1H), 1.96 – 1.88 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.5 (CH), 172.8 (C), 156.1 (C), 136.0 (C), 128.5 (CH), 128.3(CH), 128.1(CH), 67.2 (CH_2), 60.8 (CH_2), 59.6 (CH), 29.6 (CH_2), 24.0 (CH_2), 14.1 (CH_3) ppm. IR (ATR): *v* 3349, 2930, 1733, 1532, 1453, 1379, 1260, 1186, 1062 cm^{-1}. HRMS (ESI) for $C_{15}H_{19}NO_5$ $[M+H]^+$ calculated: 294.1336; found: 294.1339. $[\alpha]_D^{20}$ -22.7 (*c* 1.14, $CHCl_3$).

Crystallographic data

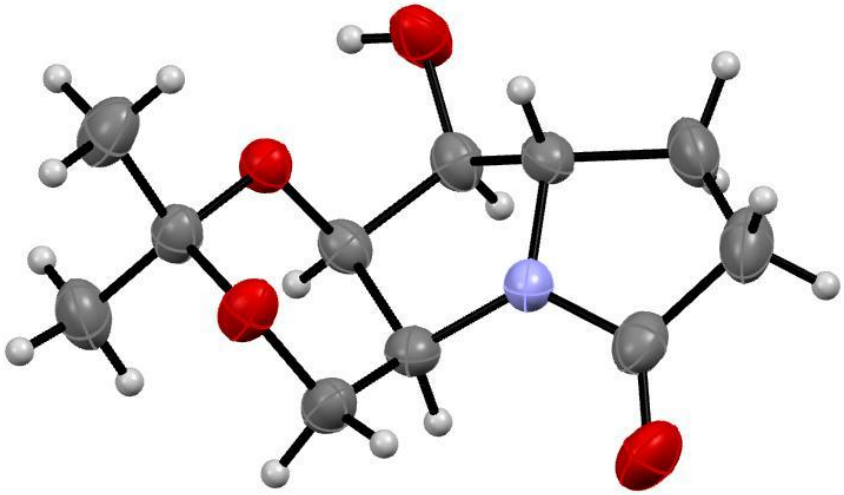
Crystallographic data for **2** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: **CCDC 935825**

ORTEP diagram for hemiaminal **2**



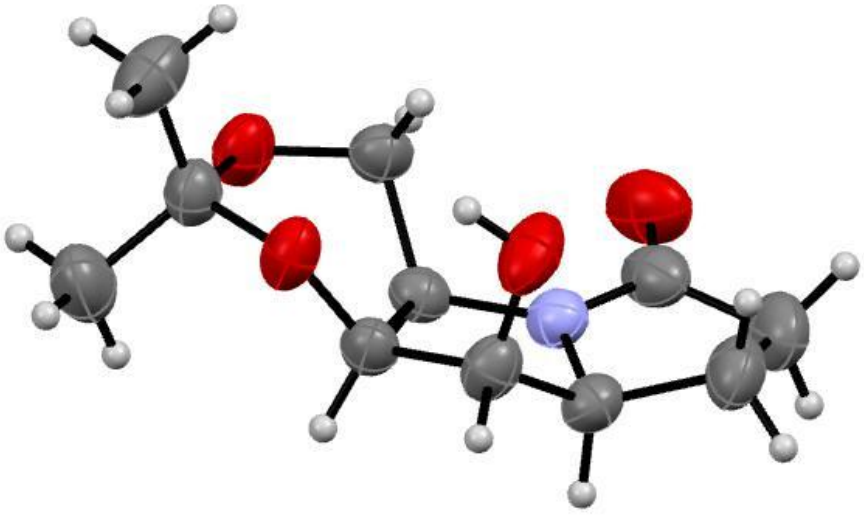
Crystallographic data for **4** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: **CCDC 935822**

ORTEP diagram for lactam **4**

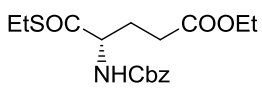


Crystallographic data for **12** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: **CCDC 935850**

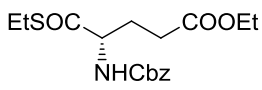
ORTEP diagram for lactam **12**



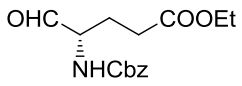
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)

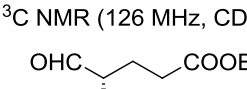


^{1}H NMR (500 MHz, $CDCl_3$)



1

^{13}C NMR (126 MHz, $CDCl_3$)



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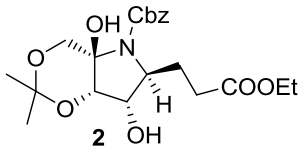
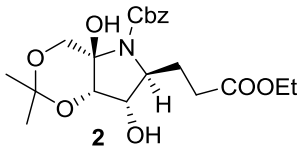
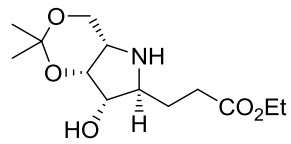
^{1}H NMR (500 MHz, DMSO-d_6, 65 °C)



^{13}C NMR (126 MHz, DMSO-d_6, 65 °C)



^{1}H NMR (500 MHz, $CDCl_3$)



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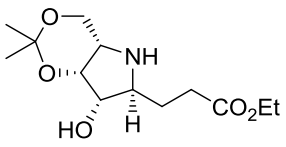
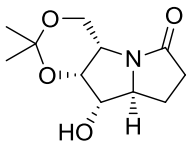
^{13}C NMR (126 MHz, $CDCl_3$)



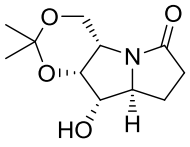
3

^{1}H NMR (500 MHz, $CDCl_3$)



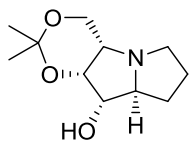
4

^{13}C NMR (126 MHz, $CDCl_3$)



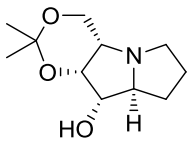
4

^{1}H NMR (500 MHz, CD_3OD)



5

^{13}C NMR (126 MHz, CD_3OD)



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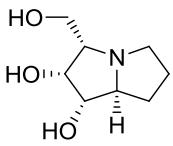
^{1}H NMR (500 MHz, D_2O)



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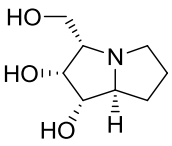
^{13}C NMR (126 MHz, D_2O)



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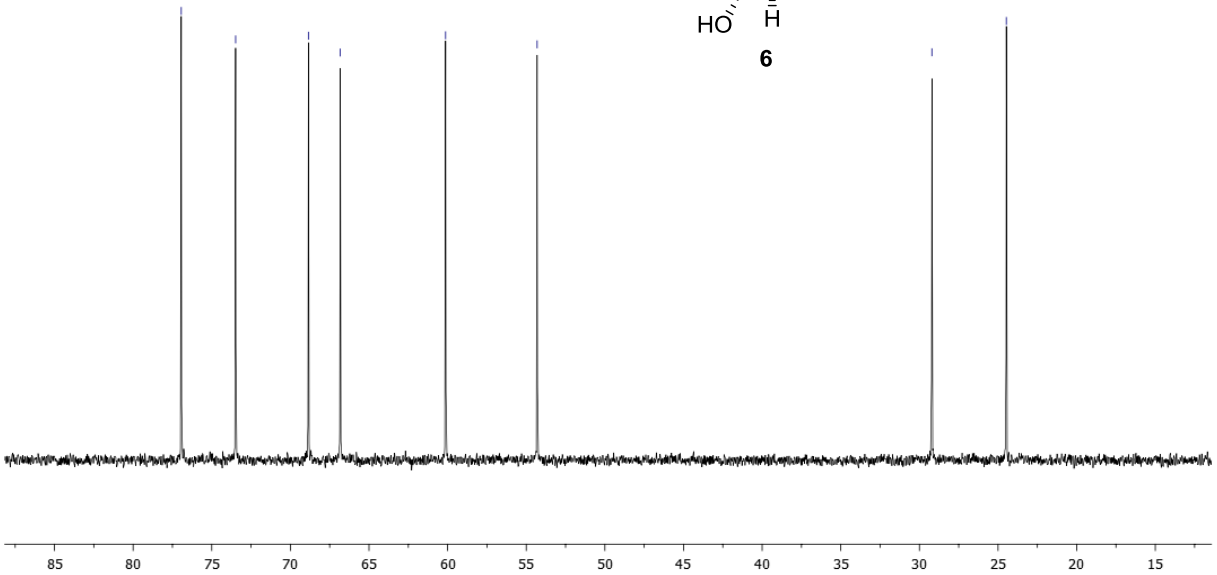

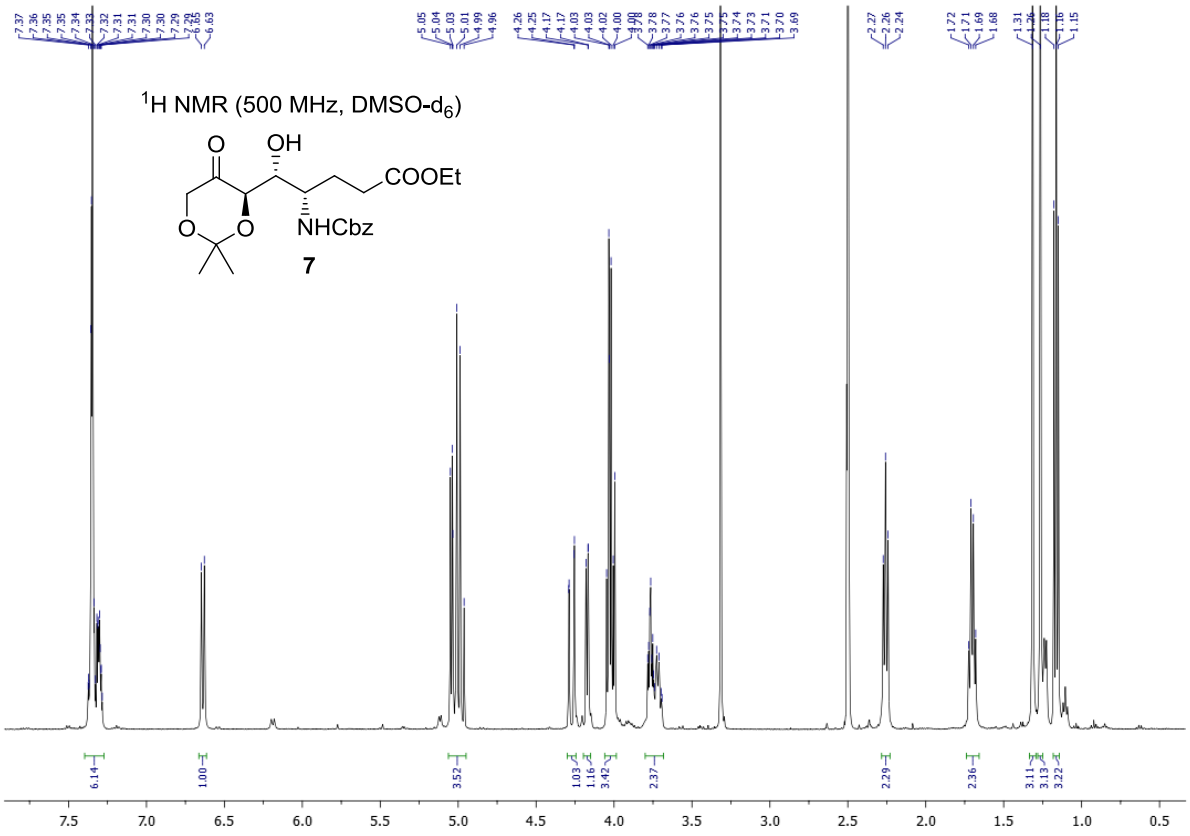
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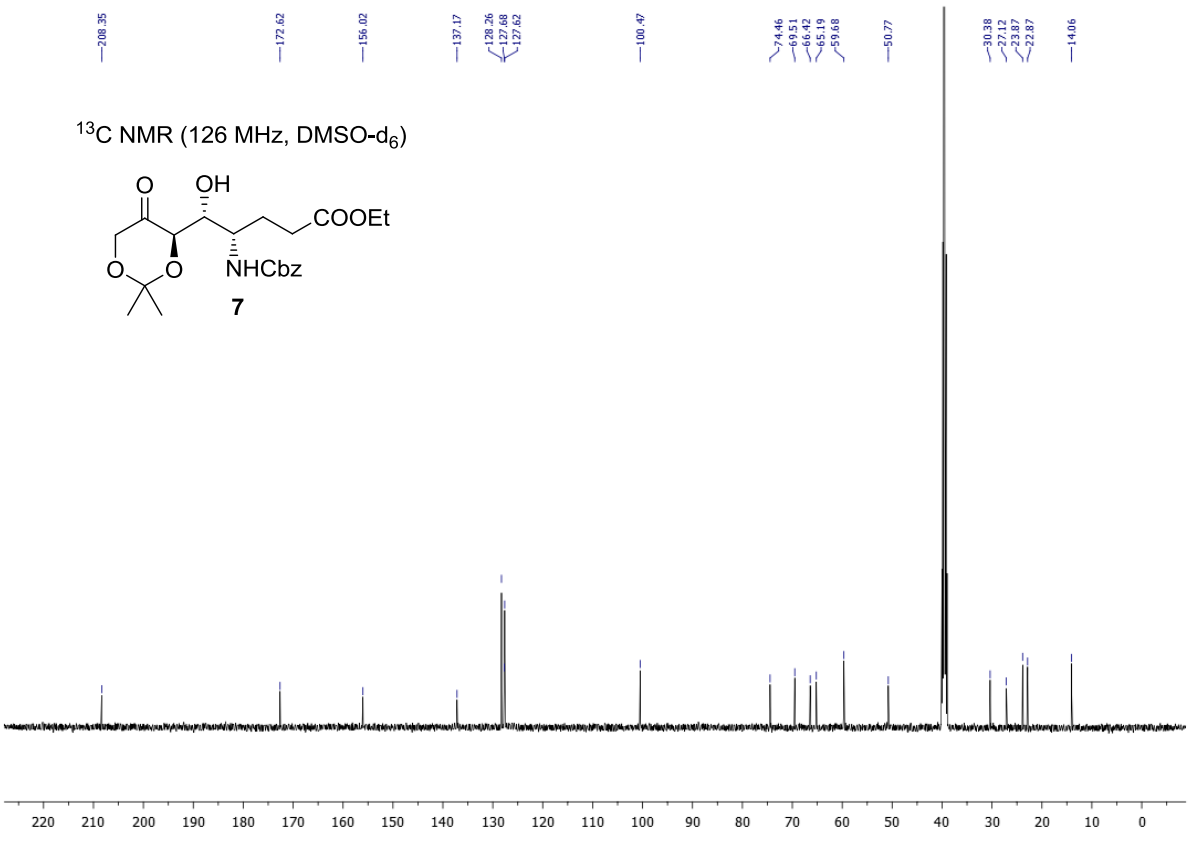
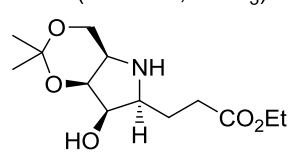
O
OH
COOEt
O
O
NHCbz
7


^{13}C NMR (126 MHz, DMSO-d$_6$)
O
OH
COOEt
O
O
NHCbz
7

^{1}H NMR (500 MHz, $CDCl_3$)



8

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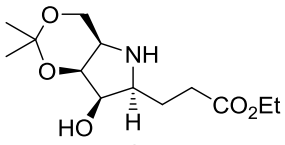

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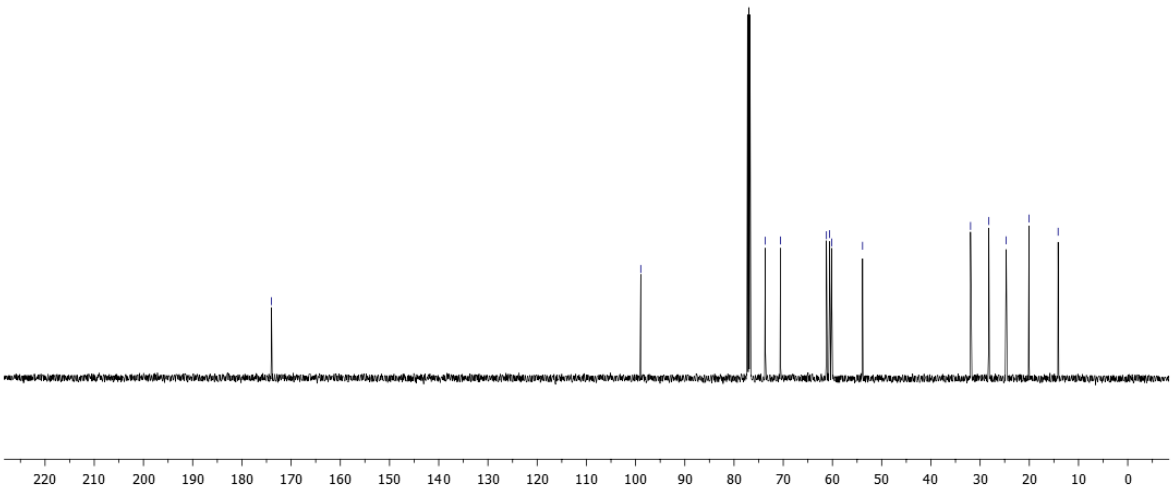
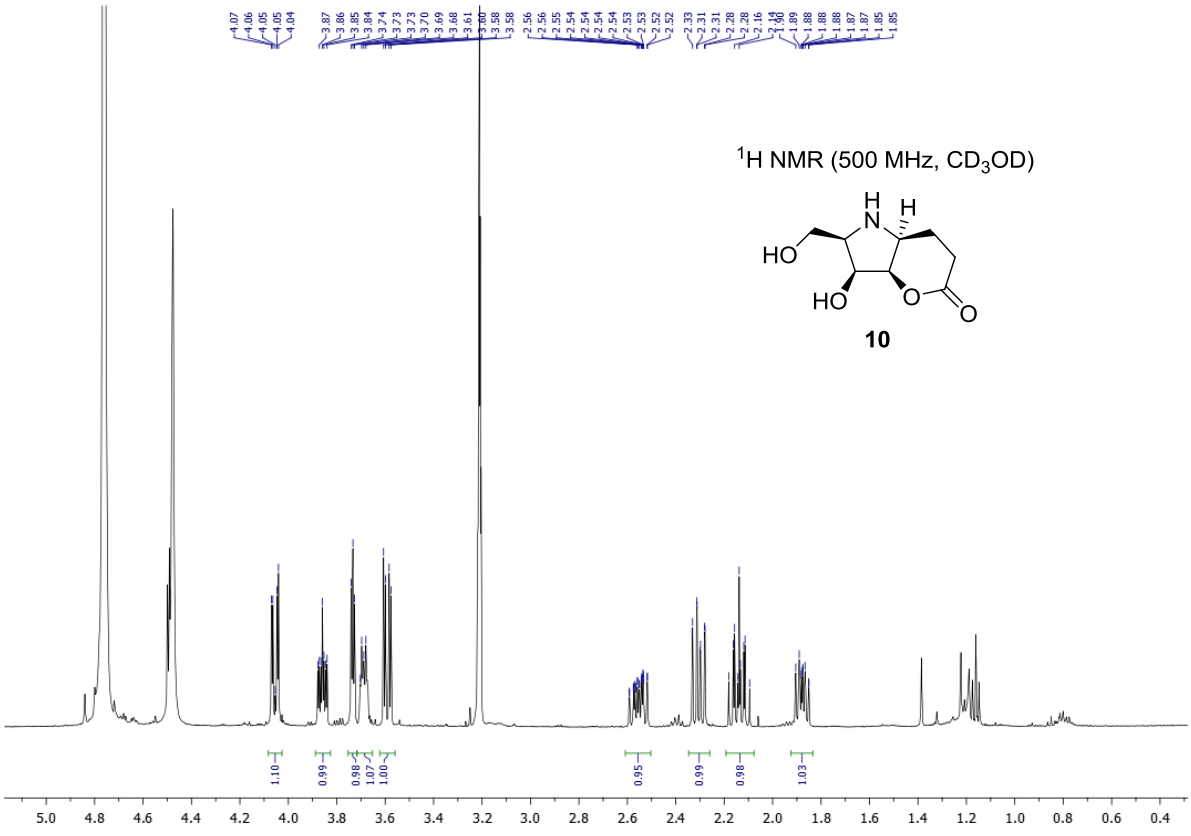
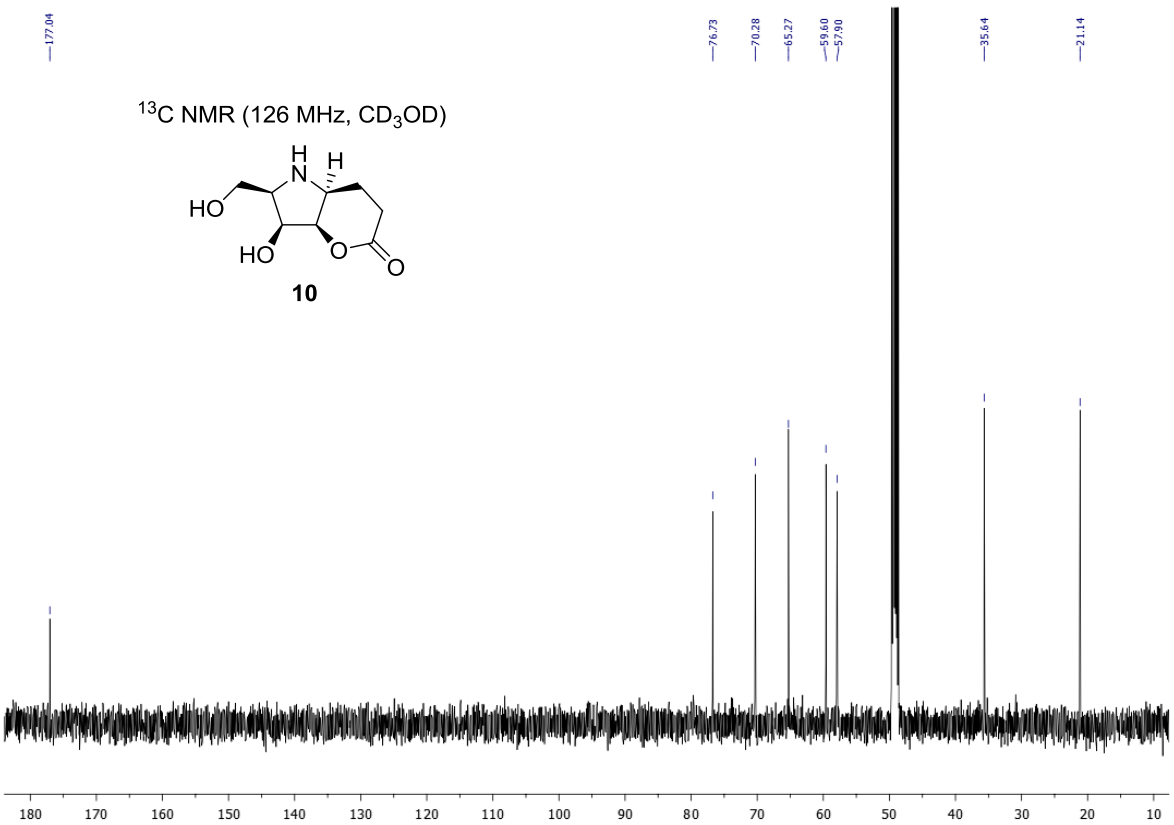




^{1}H NMR (500 MHz, CD_3OD)

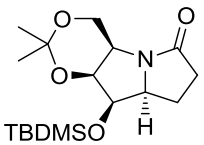
10



^{13}C NMR (126 MHz, CD_3OD)

10

^{1}H NMR (500 MHz, $CDCl_3$)



11

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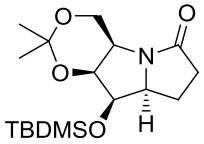

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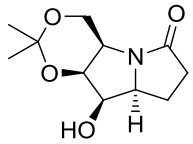

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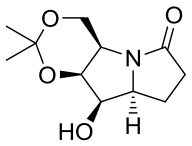

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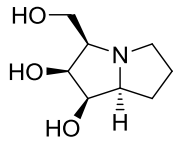

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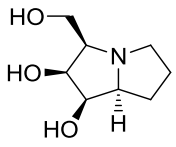

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