

Supporting Information

Anodic Cyclization Reactions and the Mechanistic Strategies that Enable Optimization

Ruozhu Feng, Jake A. Smith, and Kevin D. Moeller*

^aDepartment of Chemistry, Washington University, St. Louis, MO 63130

moeller@wustl.edu

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1. General Information

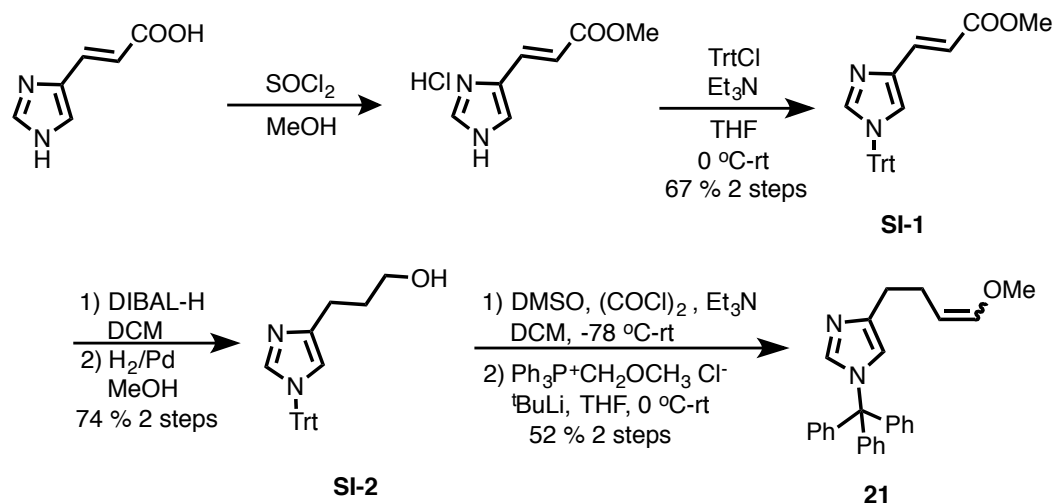
NMR spectra were acquired on either a Varian Mercury 300 or Varian Inova 300 spectrometer at either 300 MHz for ^1H or 75 MHz for $^{13}\text{C}\{^1\text{H}\}$ unless otherwise noted. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (0 ppm) for ^1H and $^{13}\text{C}\{^1\text{H}\}$. Mass spectra were recorded on either a Thermo LTQ-Orbitrap spectrometer under positive ion mode or a Maxis 4G ESI-QTOF spectrometer with flow rate of 3 $\mu\text{L}/\text{min}$. Reactions were run under either an argon or nitrogen atmosphere unless otherwise noted. Tetrahydrofuran was purchased from Sigma-Aldrich Corporation and distilled from sodium benzophenone ketyl under argon atmosphere prior to use. Triethylamine and dichloromethane reaction solvent were purchased from Sigma-Aldrich Corporation and distilled from calcium hydride under argon atmosphere prior to use. Flash column chromatography was performed on 60 Å silica gel purchased from Sorbent Technologies. Thin layer chromatography was performed on Analtec UNIPLATETM and visualized by ultraviolet irradiation, ceric ammonium molybdate, phosphomolybic acid, or 2,4-dinitrophenylhydrazine. Bis(pinacolato)diboron and 4-bromo-2-methylbenzoic acid were purchased from Matrix Scientific and used as received. All other starting materials and reagents were purchased from Sigma-Aldrich Corporation and used as received.

Electrolysis reactions were conducted using a model 630 coulometer, a model 410 potentiostatic controller, and a model 420A power supply purchased from the ElectroSynthesis Company, Inc. (now Electrolytica). Carbon rods and reticulated vitreous carbon (RVC) were also purchased from the Electrolytica



Figure 1 Anodic Cyclization Reaction Apparatus

2. Synthetic scheme of 4-(4-methoxybut-3-en-1-yl)-1-trityl-1H-imidazole (21)



Scheme 1 Synthetic Route to Substrate 21

3. Synthetic Procedures

Synthesis of SI-1

To a solution of (*E*)-3-(1*H*-imidazol-4-yl)acrylic acid (2g, 14.5 mmol, 1.0 eq) in MeOH (15 mL) at 0 °C was added thionyl chloride (1.05 mL) dropwise. The suspension was warmed to room temperature, stirred for 1h, and brought to reflux for 3h. The reaction mixture was then transferred into a 250 mL round bottom flask under argon and diluted with 50 mL of THF (50 mL) and 5.505 mL of triethylamine (2.5eq) was added in at 0 °C. To the resulting solution was added TrtCl (4.67g, 1.15eq) in 50 mL of THF in small portions. The reaction mixture was stirred overnight. Upon completion, the reaction mixture was quenched by water and then diluted with CH₂Cl₂. The organic layer was separated, and the aqueous layer was washed with CH₂Cl₂. The combined organic layers were dried over MgSO₄, concentrated, and the crude product purified by recrystallization with EtOAc to afford **SI-1** (3.87g, 67% yield).

Spectra data for **SI-1**: ¹H NMR (300 MHz, Chloroform-d) δ 7.47 (s, 1H), 7.38 – 7.31 (m, 10H), 7.17 – 7.10 (m, 7H), 7.02 (d, J = 1.3 Hz, 1H), 6.55 (d, J = 15.6 Hz, 1H), 3.75 (s, 3). This data matched the previously published NMR .

Synthesis of SI-2

To a solution of **SI-1** (2.2g, 5.59 mmol, 1.0 eq) in dichloromethane (100 mL) under argon at -78 °C was added DIBAL-H (1M in hexane) dropwise over 1h. Mixture was stirred at rt for 2h. Upon completion, the reaction was diluted with 15 mL of EtOAc and then treated with 30 mL of a saturated Rochelle's salt solution. The mixture was stirred overnight before being quenched with water and then diluted with CH₂Cl₂. The organic layer was separated, and the aqueous layer was washed with CH₂Cl₂. The combined organic layers were dried over MgSO₄, concentrated, and carried onto next step. To this end, the crude mixture was placed into 100 mL round bottom flask under argon and then diluted with 12 mL of methanol. The resulting solution was sonicated for 10 min until everything had been completely dissolved and then treated with 0.12 g of 10% by weight Pd/C. The reaction was then placed under a H₂ atmosphere and was stirred for 20h. Upon completion, the reaction mixture was filtered through celite, washed with CH₂Cl₂, and concentrated. The crude product was purified by chromatography through silica gel using Hexane: EtOAc: MeOH (5:4:1) as the eluent to afford **SI-2** (0.785g, 74% yield).

Spectra data for **SI-2**: ¹H NMR (300 MHz, Chloroform-d) δ 7.43 – 7.30 (m, 10H), 7.19 – 7.05 (m, 7H), 6.55 (s, 1H), 4.33 (s, 1H), 3.74 (t, J = 5.6 Hz, 2H), 2.68 (t, 2H), 1.86 (p, J = 6.0 Hz, 2H). This data matched the previously published NMR.

Synthesis of 21

To a solution of **SI-2** (1.75g, 4.77 mmol, 1.0 eq) in CH₂Cl₂ (30 mL) under argon was added DMSO (0.42 mL, 1.25eq). The mixture was cooled to -78 °C and then freshly distilled oxalyl chloride (0.49 mL, 1.2eq) was added in a dropwise fashion. The solution was allowed warm to -60 ~ -50 °C and stirred for 30 min before triethyl amine (3.3 mL, 5eq) was added to the flask. The reaction was

allowed to warm to was allowed warm to rt before being quenched with water and diluted with CH₂Cl₂. The organic layer was separated, and the aqueous layer was washed with CH₂Cl₂. The combined organic layers were dried over MgSO₄, concentrated, and carried onto next step. To this end, methoxymethyl phosphonium chloride (3.27g, 2 eq) was dissolved in 26 mL of THF and cooled to 0 °C. t-BuLi (5.61mL, 2eq) was added to this solution in a dropwise fashion before stirring the mixture for 1h. At this point the aldehyde from the previous step, was dissolved in 7 mL THF. The resulting aldehyde solution was added into newly generated ylide solution in a dropwise fashion. The resulting solution was stirred overnight. Upon completion, reaction mixture was quenched by water and then diluted with ethyl ether. The organic layer was separated, and the aqueous layer was washed with ethyl ether. The combined organic layers were dried over MgSO₄, concentrated, purified by chromatography through silica gel using Hexane: EtOAc (5:5) as the eluent to afford **21** (0.97g) in a 52% yield.

Spectra data for **21**: ¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.25 (m, 10H), 7.22 -7.09 (m, 6H), 6.55 (s, 0.34H), 6.50 (s, 0.48H), 6.27 (d, *J* = 12.7 Hz, 0.41H), 5.83 (d, *J* = 6.2 Hz, 0.27H), 4.74 – 4.65 (dt, 0.48H), 4.36 (q, *J* = 7.0 Hz, 0.28H), 3.50 (s, 0.87H), 3.45 (s, 1.64H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.44 – 2.09 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 147.4, 146.1, 142.6, 138.2, 129.8, 127.9, 118.1, 106.4, 102.2, 59.4, 55.7, 29.8, 28.7, 27.6, 23.6. IR (neat, cm⁻¹): 3052, 2925, 2847, 2825, 2361, 2157, 1654, 1491, 1445, 1207, 1130, 1107, 1035, 1001, 748, 701. HRMS (ESI) calcd for C₂₇H₂₆N₂O [M + Na]⁺ 395.2110, found 395.2118.

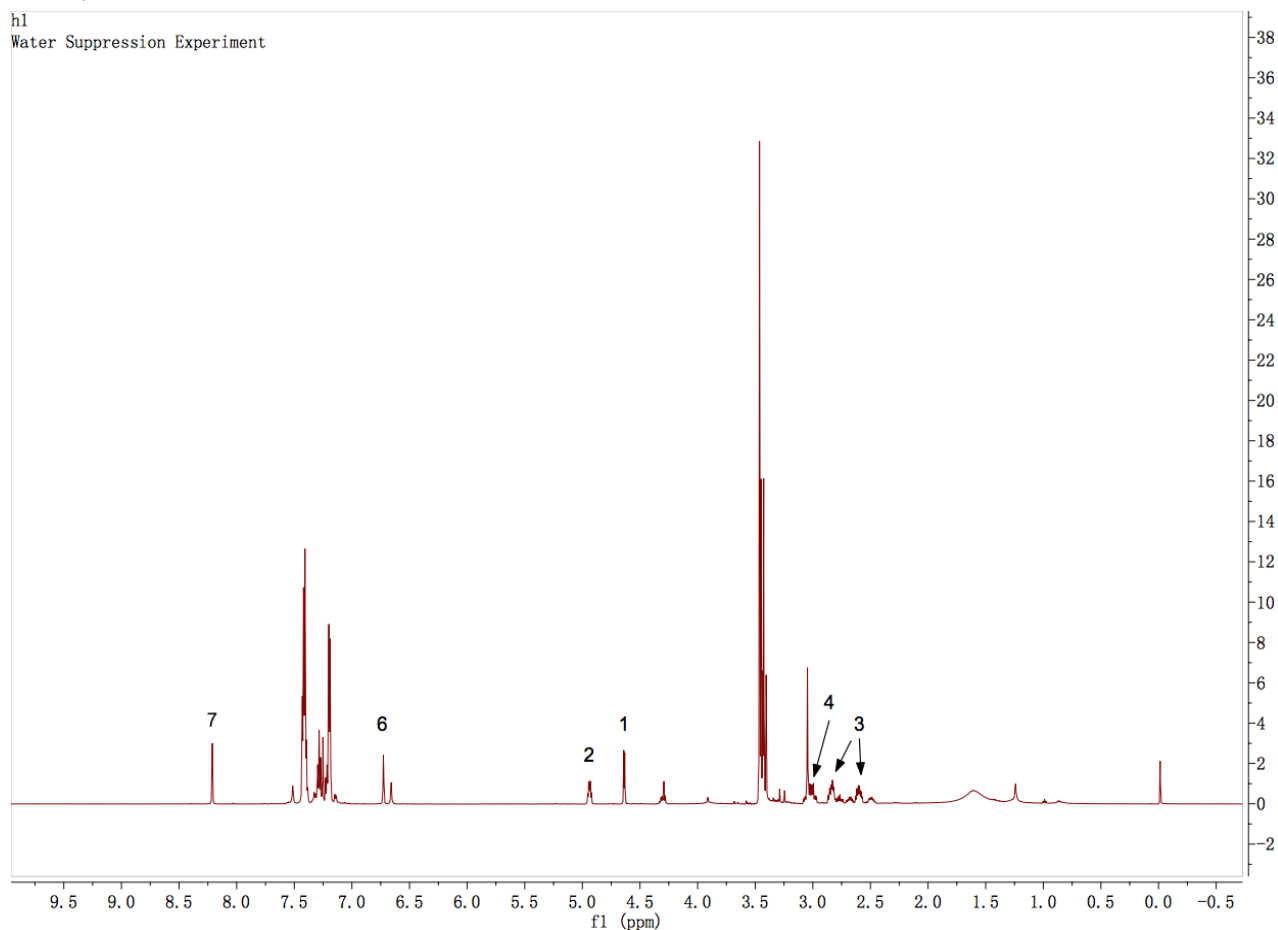
4. Electrolysis of 4-(4-methoxybut-3-en-1-yl)-1-trityl-1H-imidazole (21)

Compound **21** (72.9 mg, 0.184 mmol) and 5mL of a 0.65 M LiClO₄ in THF were placed in a 25 mL, 3-neck round bottom flask. To this solution was added LiOMe (0.5 mmol). The mixture was sonicated for 10 min, and then the flask equipped with carbon cathode and RVC anode. Current (10 mA , 10 F/mol) was passed through the cell until the starting material disappeared by TLC. At that point, the reaction mixture was diluted with NaHCO₃ (sat. aq), the layers separated, and the aqueous layer washed three times with CH₂Cl₂. The combined organic layer was dried over MgSO₄ and then concentrated. A proton NMR was taken of the crude product and the yield of the product present calculated to be 74% using 2,6-ludidine which had been added to the crude material following the reaction as internal standard. The crude product was purified by flash chromatography through silica gel to afford **26** (45 mg, 55% yield).

5. Identification of Cyclization with ¹H NMR, ¹³C NMR, COSY, HMBC, HSQC

The product was identified structure by H¹ NMR, C¹³ NMR, COSY and HSQC. The assignments were shown below. After confirming the structure, the spectrum from HMBC showed that C5 was correlated to H2 (as shown below). This piece of evidence confirmed the cyclization.

¹H NMR



Note:

- 1) The assignment shown here only showed the core structure of the ring.
- 2) The assignment shown here were in the circumstance R=OMe. All the rest spectra shown later will follow the same assignment. The small peaks next to “3”, “4” and “6” were assigned from peaks where R= H.
- 3) The unassigned peaks with 4.3ppm were impurity with the structure shown below.

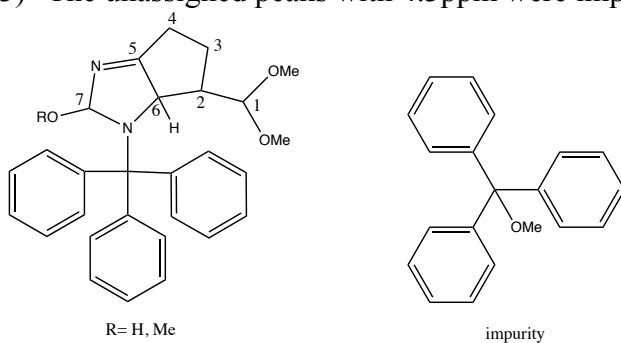


Figure 3 Cyclized Product Structure and Impurity

^{13}C NMR

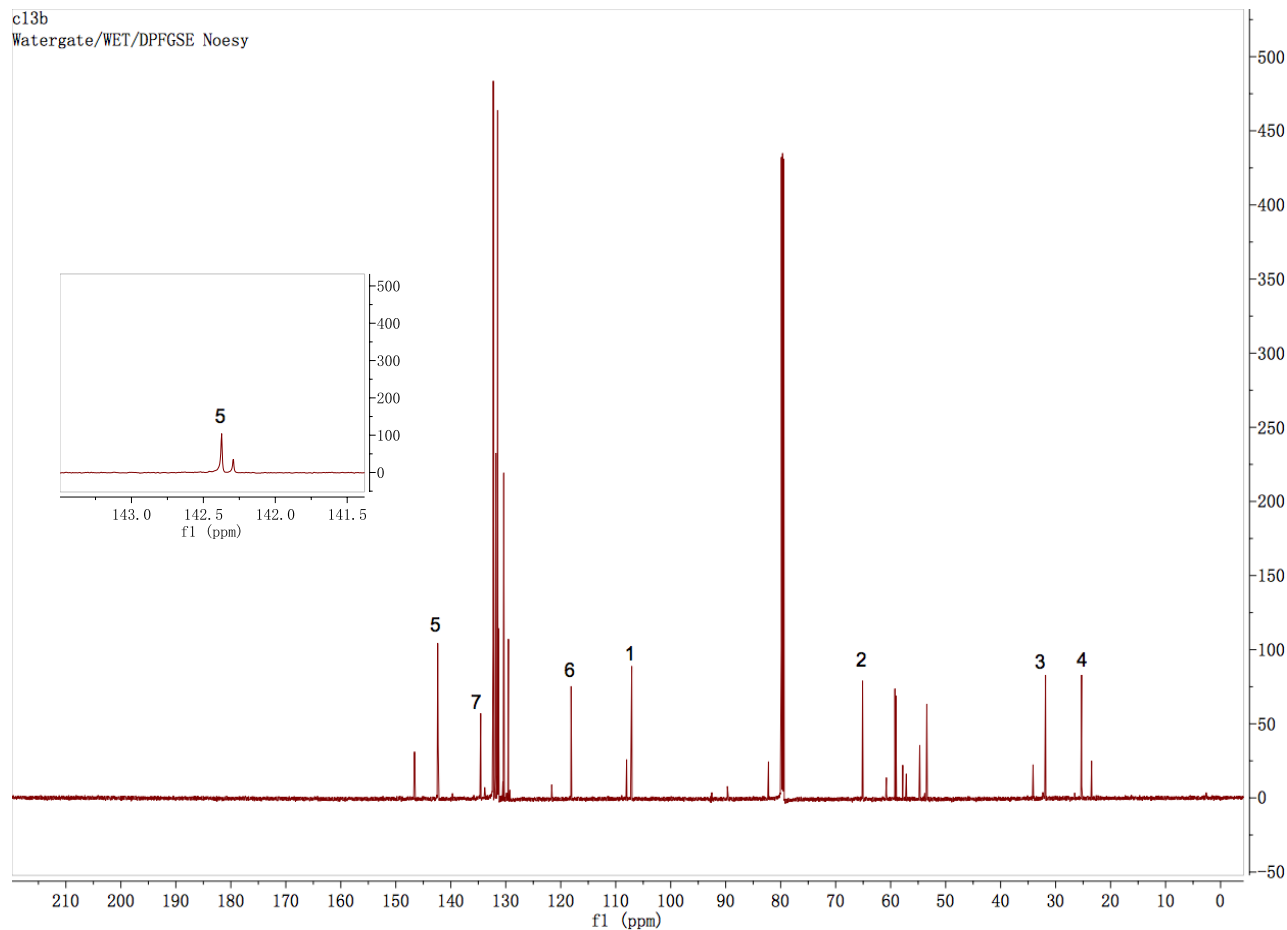


Figure 2 Cyclized Product ^{13}C NMR

Note:

- 1) The assignment shown here only showed the core structure of the ring.
- 2) The assignment shown here were in the circumstance $\text{R}=\text{OMe}$. The peaks between 50-60ppm and around 130ppm were from OMe and trityl group. The unassigned peaks were in the circumstance $\text{R}=\text{H}$.
- 3) The peak at 142ppm (buried under "5") and 108ppm were associated with impurity shown before.

COSY

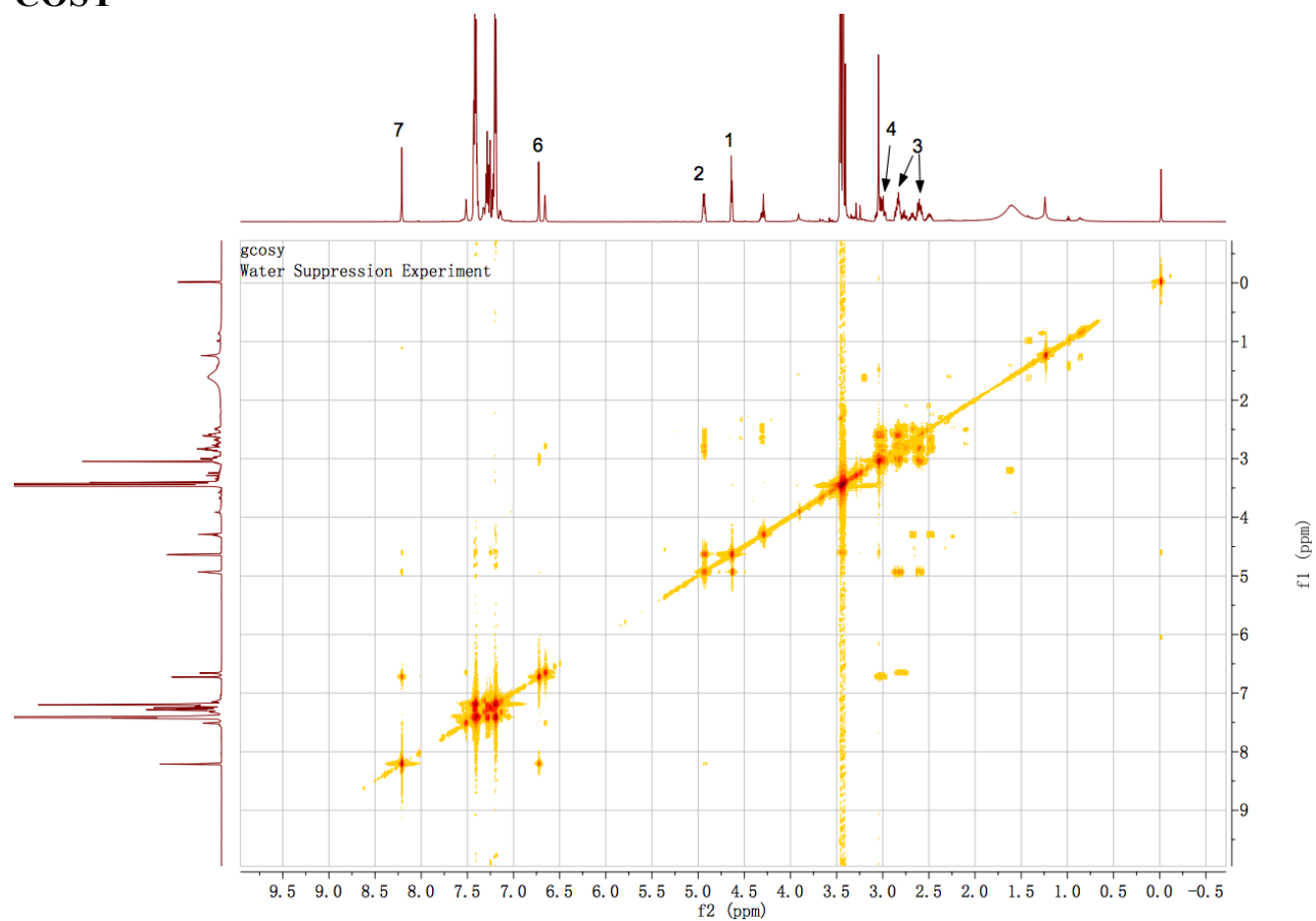


Figure 5 Cyclized Product COSY

HSQC

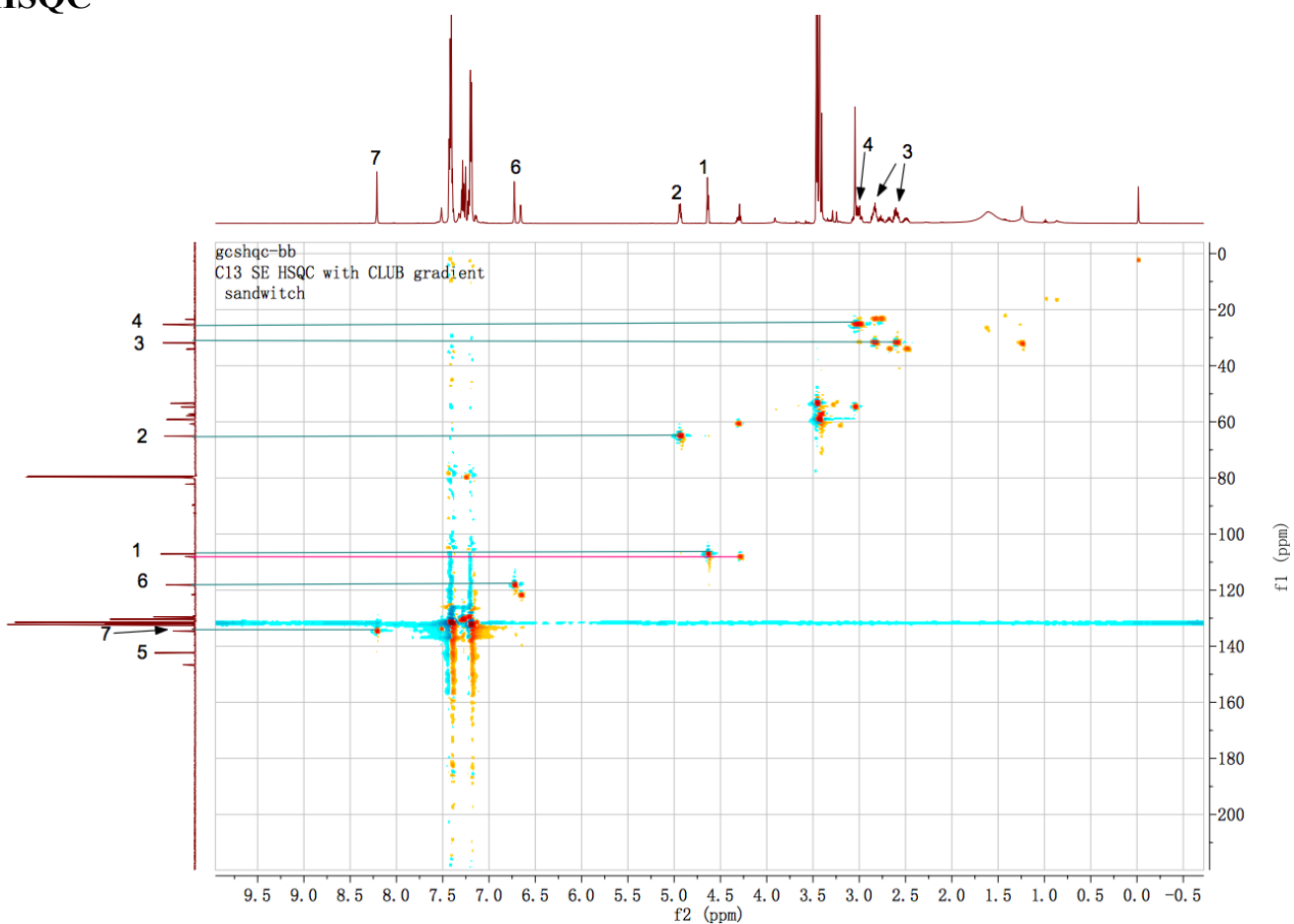


Figure 6 Cyclized Product HSQC

Note:

- 1) The assignment shown here only showed the core structure of the ring.
- 2) The correlation between C and H were shown in green line.
- 3) The correlation from methoxy group C-H in impurity was shown in pink line.

HMBC

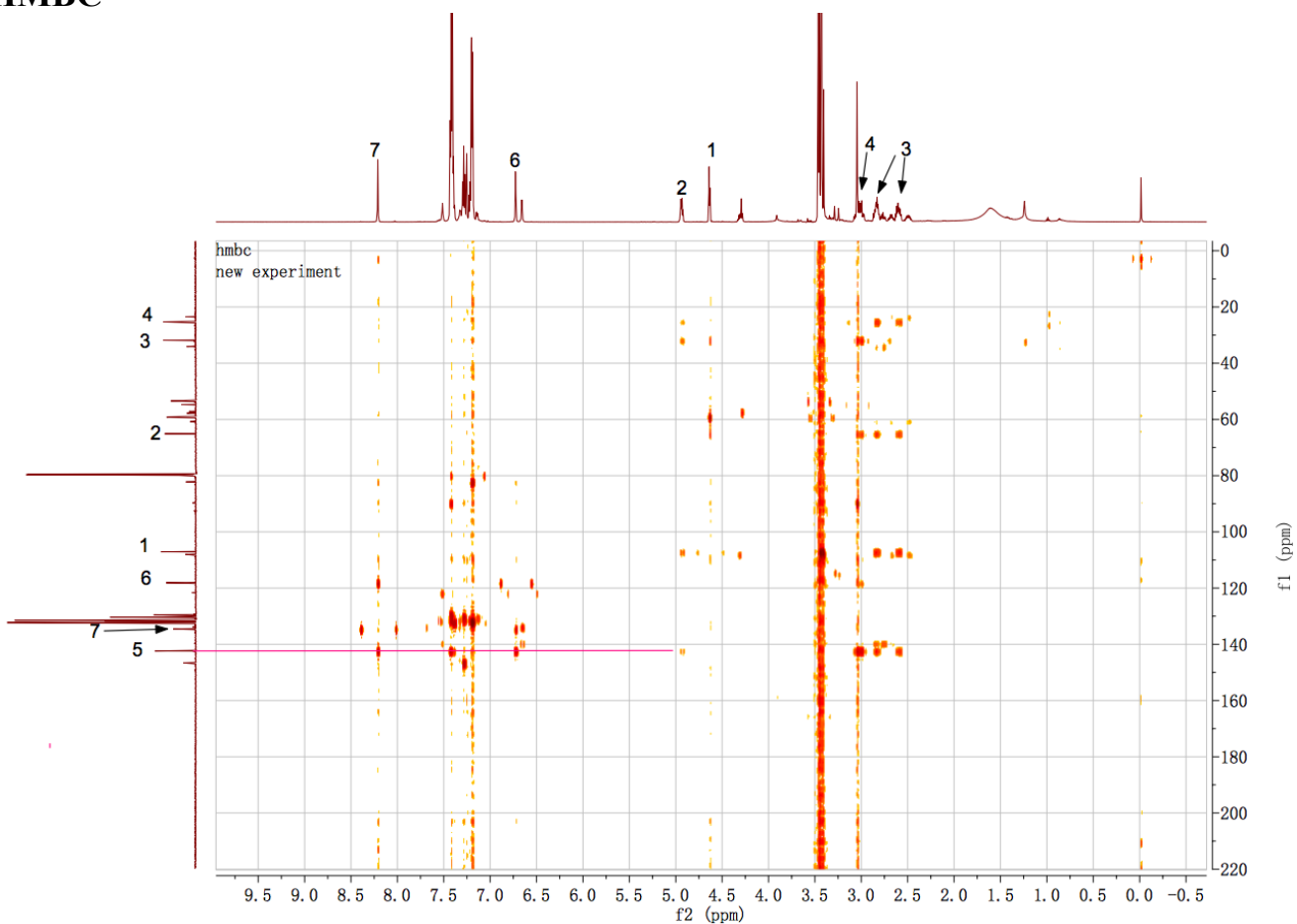
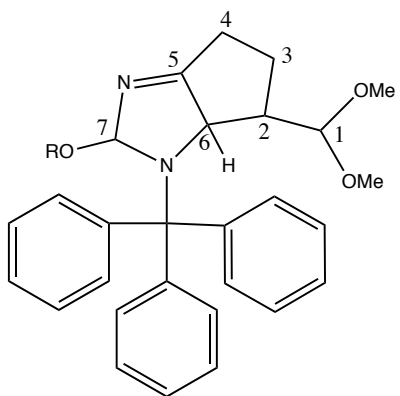


Figure 7 Cyclized Product HMBC

Note:

- 1) The assignment shown here only showed the core structure of the ring.
- 2) The correlation between C5 and H2, H6, H7 was shown in pink line. This long distance correlation confirmed the cyclization.



R= H, Me

Figure 8 Cyclized Product Assignment