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Study Toward the Synthesis of Gweicurculactone

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Abstract

In this work significant progress towards the synthesis of sesquiterpene lactone (SL) which have been used to prepare Gweicurculactone using an *N*-heterocyclic carbene (NHC). Starting from the aldehyde compound **2** that convert to compound **4** through Wittig reaction follow by hydrogenation. Protection the phenol group using TBS-Cl to achieve compound **5**. The ester was converted to an aldehyde **6** using DIBAL-H. The Henry reaction was applied on compound **6** with nitromethane in present TMG as a catalyst to produce nitro alcohol compound **7**. Compound **8** was prepared after removing water molecule using Methane sulfonyl chloride in present of triethyl amine at -78 °C. Methylation on the nitroalkene **8** using Methyl lithium and cupper iodide at -78 °C obtain compound **9**. After deprotection of **9** with tetrabutylammonium fluoride at room temperature to afford compound **10**. The key tropon compound **11** framework which was made from intermolecular cyclization dearomatization through single electron transfer using potassium ferrocyanide.

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1. Introduction

Terpenoids are among the largest and most diverse group of natural compounds. They are most known for their function as plant metabolites and their role in terpene synthesis with its many derivatives. There are approximately more than sixty thousand known compounds, describe almost 400 diverse structural groups [1,2]. Sesquiterpene is one of these enormous types of terpenes, and a subdivision plentiful on earth. Sesquiterpene produces sizable quantities of multiple compounds with a possibility to be categorized as multi-product synthases [3]. Sesquiterpene lactones (SLs) display a plethora of biological effects including anticancer, antimicrobial, antioxidant, antiprotoxoal, antiviral and immunobiological activities [4]. Many guaianolides compounds were isolated from plants such as Zedoarondiol, pseudoneolinderane, Linderenone, and Grosheimin, See Figure 1.

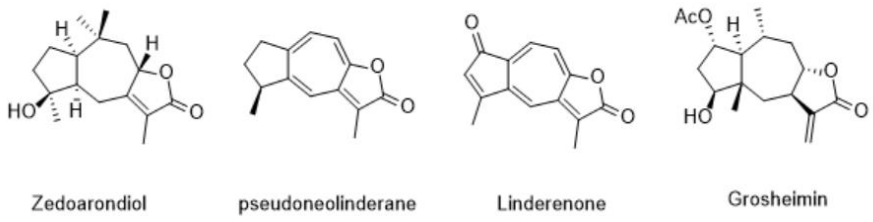


Figure 1. guaianolide compounds were isolated from plants

The growing interest in sesquiterpene lactones (SLs) as promising bioactive molecules is a closely linked to its continuous use of SL rich plant extracts in traditional medicine for the treatment of various ailments over the centuries. Various studies have reported the anti-inflammatory active potential of natural extracts containing SLs, especially research studies concerning different plant species from the Asteraceae family, which is characterized by having high degree of structural diversity of SLs [5].

Gweicurculactone **1** is a unique SL that contains three rings with a seven-membered ring central scaffold. It was first isolated from Curcuma kwangsiensis [6] in1988, before being isolated from other plants like *Curcuma zedoaria* [7] and *Curcuma aromatica* [8]. Several Curcuma species have been used as medicine [9] for their strong anti-inflammatory [10,11], anti-cancer [12], cytotoxic [13], and hepatoprotective [14] activities. Gweicurculactone (**1**) specifically has displayed strong antioxidant activity [15] and antiproliferative effect [16].

Zografos and his co-workers have successfully synthesized **1** through an anionic oxy-cope reaction followed by aerobic oxidation [17].

2. METHODOLOGY

2.1 SUPPLEMENTAL INFORMATION

All chemicals and solvents were used without further purification unless otherwise noted. Melting points were measured using a Stuart SMP20 melting point apparatus. NMR spectra were recorded on a Bruker AV-400 spectrometer (1H NMR at 400 MHz and ^{13}C NMR at 100 MHz). Proton chemical shifts were referenced virtual to residual $CDCl_3$ proton signals at δ 7.24 ppm or residual CD_3OD: δ 3.31 ppm. Carbon chemical shifts were referenced relative to $CDCl_3$ at δ 77.23 ppm CD_3OD: δ 49.10. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz), integration. Data for ^{13}C NMR are reported in chemical shift (ppm). Mass spectra were recorded on an Agilent 6230 TOF LC-MS instrument with an Agilent Zorbax SB-C18 analytical column.

2.2 Experimental

Compounds 3 and 4 were prepared according to reference [18].

2.2.1 Compound 5:

In a round bottom flask, (2.7 g ,13.0 mmol) of phenol (compound 4), (2.36 g, 15.73 mmol) of TBS-Cl and (2.14 g, 31.4 mmol) of imidazole in 20 mL of DMF, stirring the mixture for 12 hrs. at room temperature under nitrogen. (50 mL) of water was added and extracted with EtOAc, the EtOAc was removed under reduced pressure. The crude was purified to afford (3.94 g, 12.22 mmol, 94% yield) as a colorless semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 6.59 (dd, J = 8.2, 2.6 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.85 (dd, J = 9.0, 6.8 Hz, 2H), 2.56 – 2.48 (m, 2H), 2.24 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.96 (s, 9H), 0.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 153.9, 137.1, 131.4, 129.4, 121.8, 117.4, 77.4, 77.1, 76.7, 60.4, 35.0, 27.7, 25.7, 19.4, 18.2, 14.2, -4.4; HRMS (ESI), m/z calcd for $C_{18}H_{31}O_3Si^+$ [M-H]$^+$ 323.2042, found 323.2062.

2.2.2 Compound 6:

To a solution (3.15 g, 9.77 mmol) of ester (compound 5) in 50 mL of dry DCM the reaction was allowed to stir at -78 °C under argon before (11.7 mL, 11.7 mmol) 1 M DIBAL-H in heptane was added dropwise. After minutes, HCl was added to quench the reaction till the solution was clear, and evaporating the solvent to get the crude aldehyde that purified by column to obtain (2.28 g, 8.2 mmol, 86% yield) as a colorless oil. The ^{1}HMR and ^{13}CNMR are shown in Figures 2 and 3.

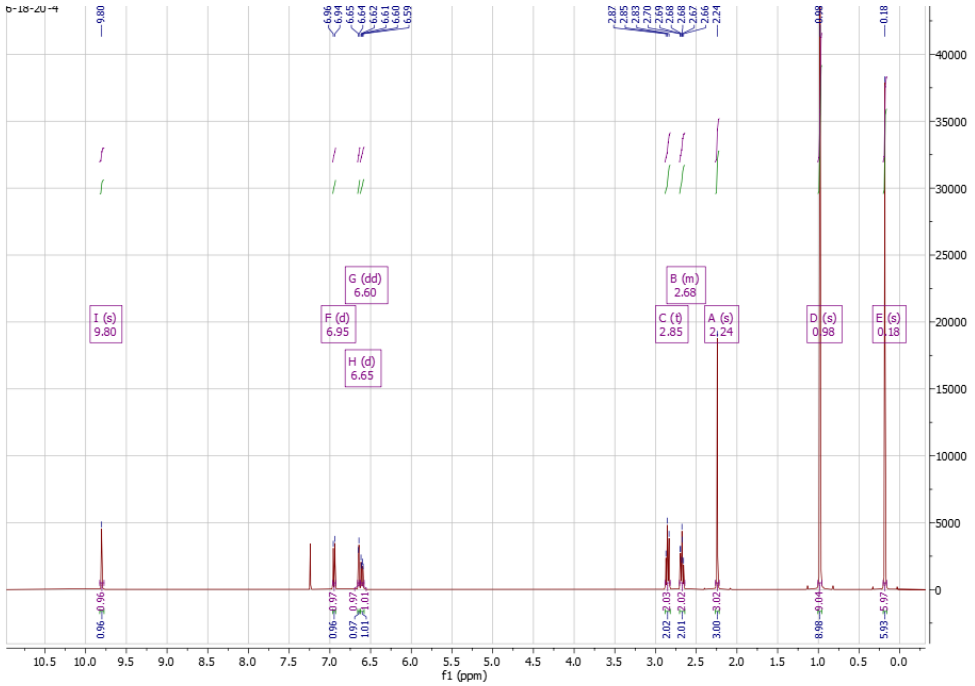


Figure 2. 1H NMR of compound 6

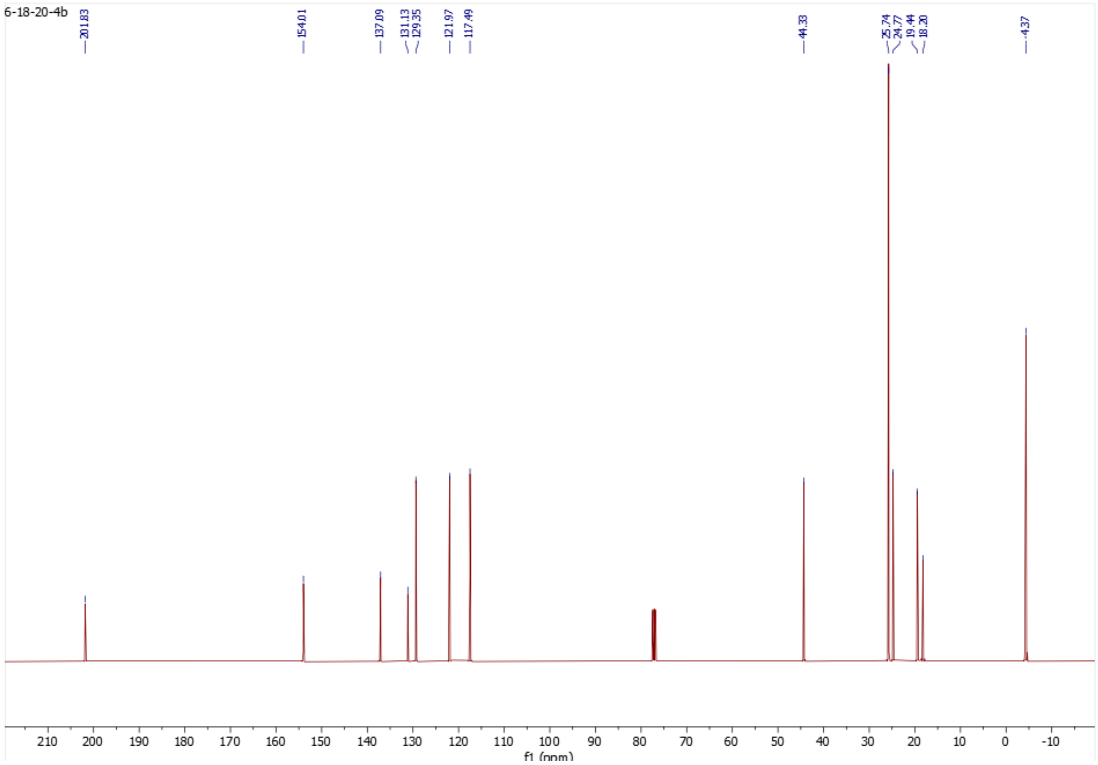


Figure 3. 13C NMR of compound 6

2.2.3 Compound 7:

A solution of aldehyde (compound 6) (2.6 g, 9.35 mmol), (4.16 mL, 74.8 mmol) of nitro methane and (0.12 mL, 0.93 mmol) of tetramethyl guanidine in (30 mL) of dry tetrahydrofuran was stirred for 12 hrs. at room temperature. Then (5 mL) of 0.1 M of HCl was added, then of 100 mL of ethyl acetate was added. Evaporating the solvent and the crude was purified by

column to obtain (2.57 g, 7.57 mmol, 81% yield) of **7** as a pale yellow oil: HRMS (ESI), m/z calcd for $C_{17}H_{30}NO_4Si^+$ $[M-H]^+$ 340.1944, found 340.1871. The ^{1}HMR and ^{13}CNMR are shown in Figures 4 and 5.

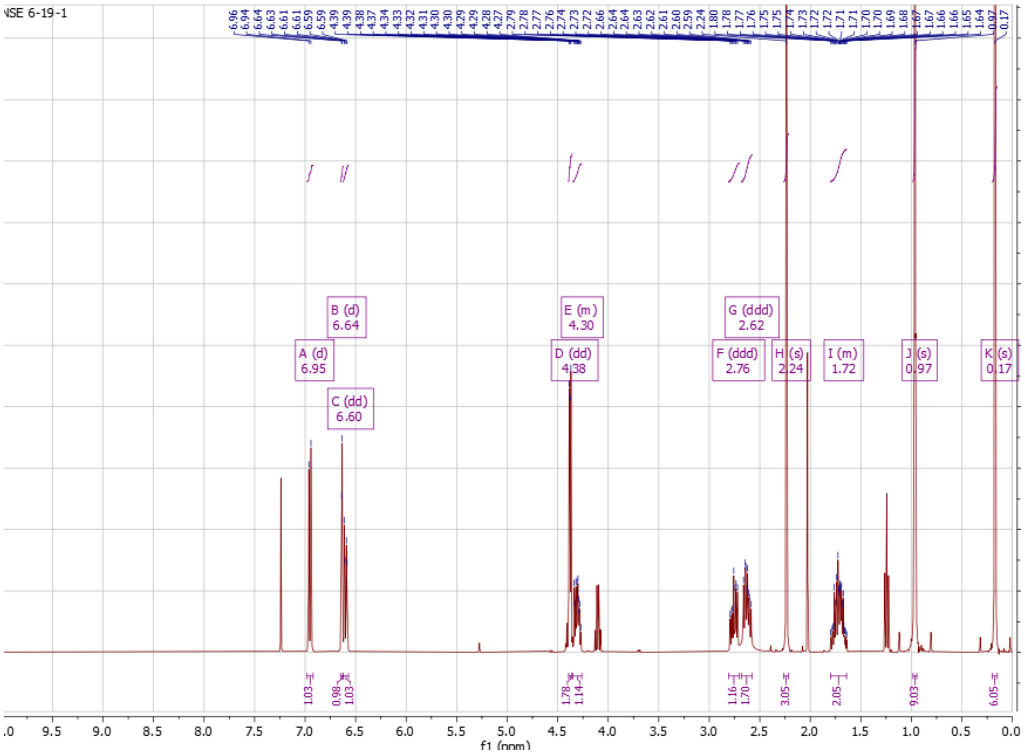


Figure 4. 1H NMR of compound 7

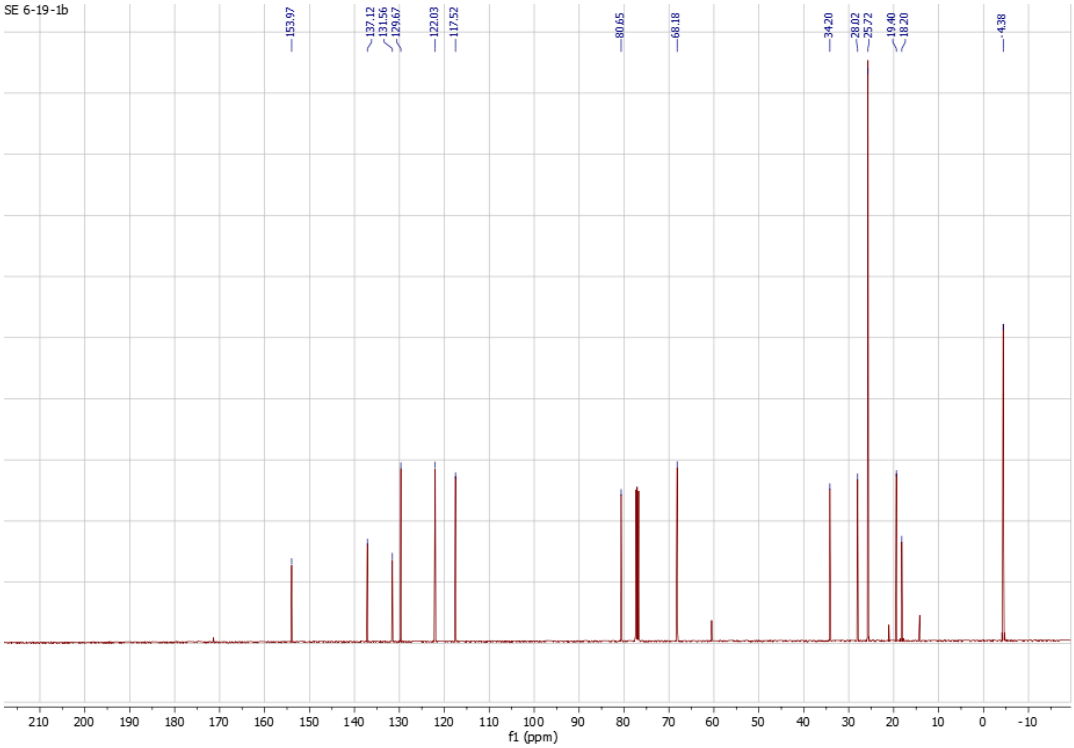


Figure 5. 13C NMR of compound 7

2.2.4 Compound 8:

To a solution of **7** (2.4 g, 7.07 mmol, 1.0 eq.) in (40 mL) of dichloromethane at -25 °C, (715 µL, 9.2 mmol, 1.3 eq.) of methane sulfonyl chloride was added to the reaction mixture and stirred for 10 minutes. Then (2.4 mL, 16.7 mmol, 2.4 eq.) of triethylamine was added to the reaction and the stirring continuously for 1 hr. Diluting with DCM and neutralized with 5% $NaHCO_3$. Solvent was removed under vacuum and the crude was purified to produce yellow oil (1.90 g, 5.94 mmol, 84% yield) as a pale yellow solid M.P. 63-64 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 13.4, 7.4 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.66 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.2, 2.6 Hz, 1H), 2.73 (dd, J = 8.6, 6.6 Hz, 2H), 2.49 (qd, J = 7.6, 1.4 Hz, 2H), 2.23 (s, 3H), 0.98 (s, 10H), 0.18 (s, 7H), HRMS (ESI), m/z calcd. for $C_{17}H_{28}NO_3Si^+$ [M-H] $^+$ 322.1838, found 322.1771.

2.2.5 Compound 9:

A suspension of CuI (1.77 g, 9.34 mmol, 2.1 eq.) in ether (15 mL) was gradually added to a (11.7 mL, 18.7 mmol, 4.2 eq.) solution of (1.6 M) MeLi at 0 °C and stirred at same temperature for an hour. In different round bottom flask, (1.5 gm, 4.67 mmol, 1.0 eq.) of **8** in dry ether (20 mL) cooled to -78°C, then the solution of dimethyl cupper lithium was gradually added with stirring for 1 hr. the mixture was stirred overnight at room temperature. The flask was put in an ice water bath, then NH_4Cl was added, the ether layer was separated and evaporated, then the crude was purified to obtain (1.17 g, 3.46 mmol, 74% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 6.60 (dd, J = 8.0, 2.8 Hz, 1H), 4.34 (dd, J = 11.6, 6.4 Hz, 1H), 4.22 (dd, J = 11.6, 7.8 Hz, 1H), 2.61 (ddd, J = 13.8, 10.8, 5.5 Hz, 1H), 2.51 (ddd, J = 13.8, 10.6, 5.8 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.23 (s, 3H), 1.61 (ddt, J = 13.4, 11.0, 5.6 Hz, 1H), 1.47 (dddd, J = 13.4, 10.6, 7.9, 5.6 Hz, 1H), 1.09 (d, J = 6.8 Hz, 3H), 0.97 (s, 10H), 0.18 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 136.9, 132.2, 129.5, 121.9, 117.4, 81.5, 77.4, 77.1, 76.8, 34.5, 32.8, 29.6, 25.7, 19.4, 18.2, 17.2, -4.4;), HRMS (ESI), m/z calcd for $C_{18}H_{32}NO_3Si^+$ [M-H] $^+$ 338.2151, found 338.3348.

2.2.6 Compound 10:

To a solution of (1.15 g, 3.41 mmol) of compound **9** dissolved in (10 mL) of dry tetrahydrofuran, was added a solution (3.4 mL, 3.4 mmol) of 1M tetra butyl ammonium fluoride in THF. The stirring continued at room temperature for 20 minutes. It was then diluted with water. Ethyl acetate was added to extract the crude which was purified to afford (693 mg, 3.1 mmol, (91% yield) of **10** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 11.8 Hz, 1H), 6.93 (dd, J = 17.1, 5.1 Hz, 2H), 3.20 – 3.08 (m, 1H), 2.97 – 2.82 (m, 1H), 2.82 – 2.71 (m, 1H), 2.20 (d, J = 7.9 Hz, 3H), 2.19 – 2.12 (m, 1H), 1.55 (ddt, J = 12.7, 8.8, 6.3 Hz, 1H), 1.20 (d, J = 7.0 Hz, 3H). HRMS (ESI), m/z calcd for $C_{12}H_{18}NO_3^+$ [M-H] $^+$ 224.1287, found 224.1240. The ^{1}HMR and ^{13}CNMR are shown in Figures 6 and 7.

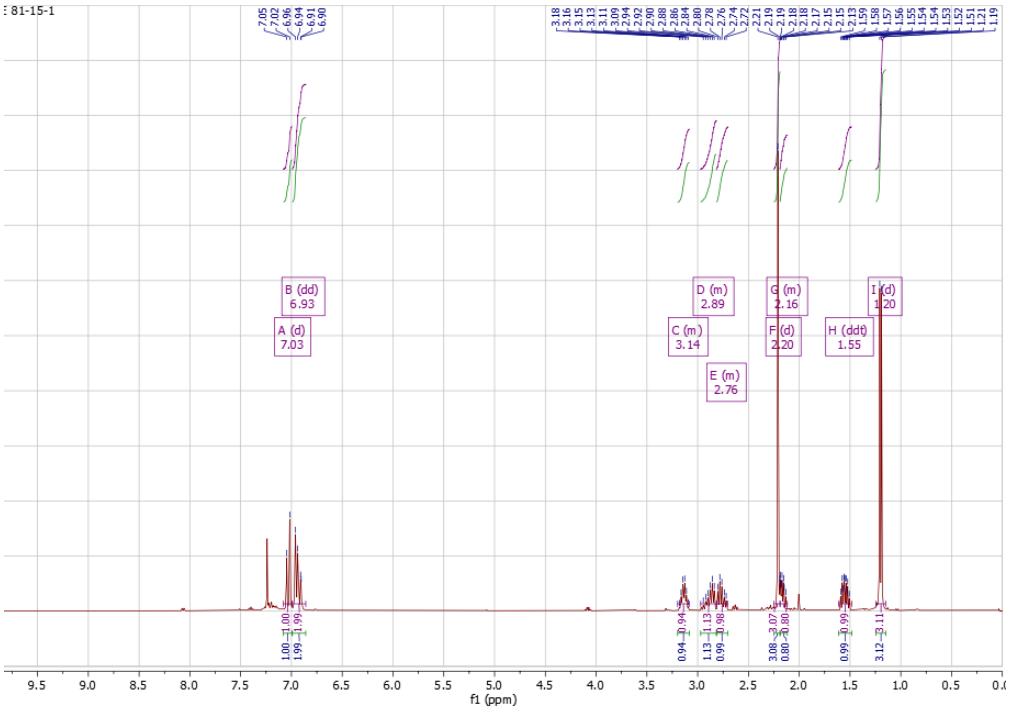


Figure 6. 1H NMR of compound 10

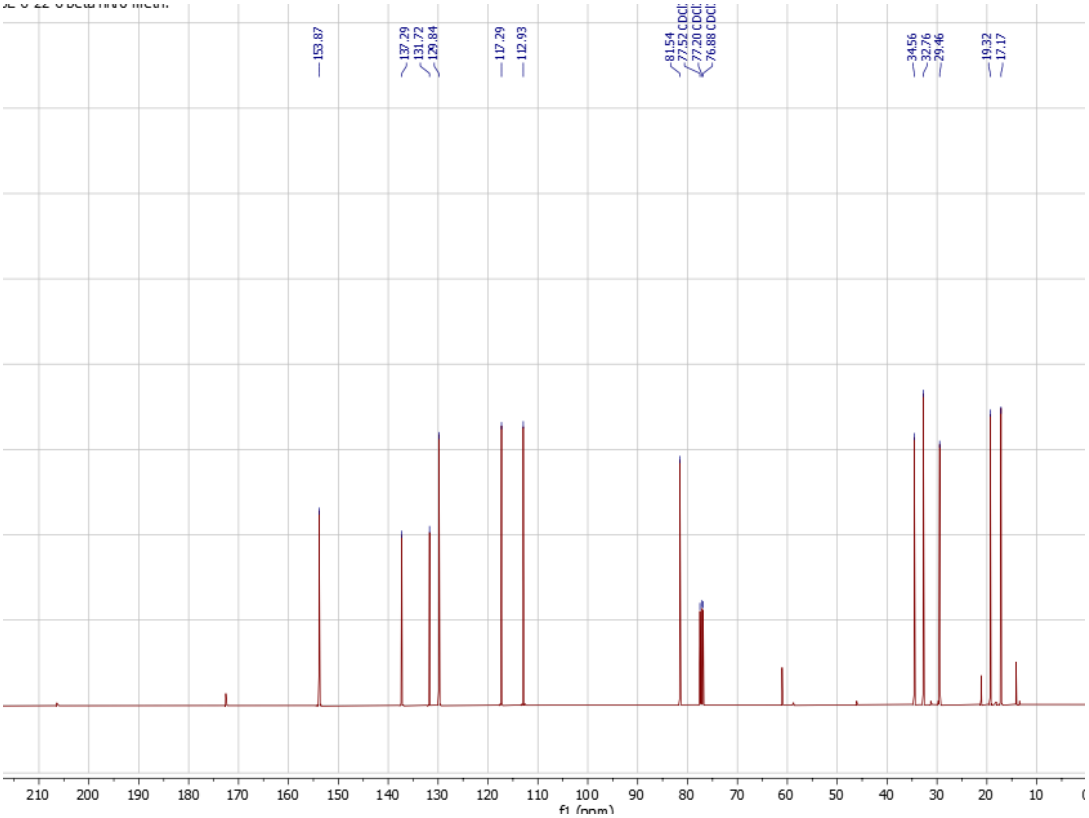


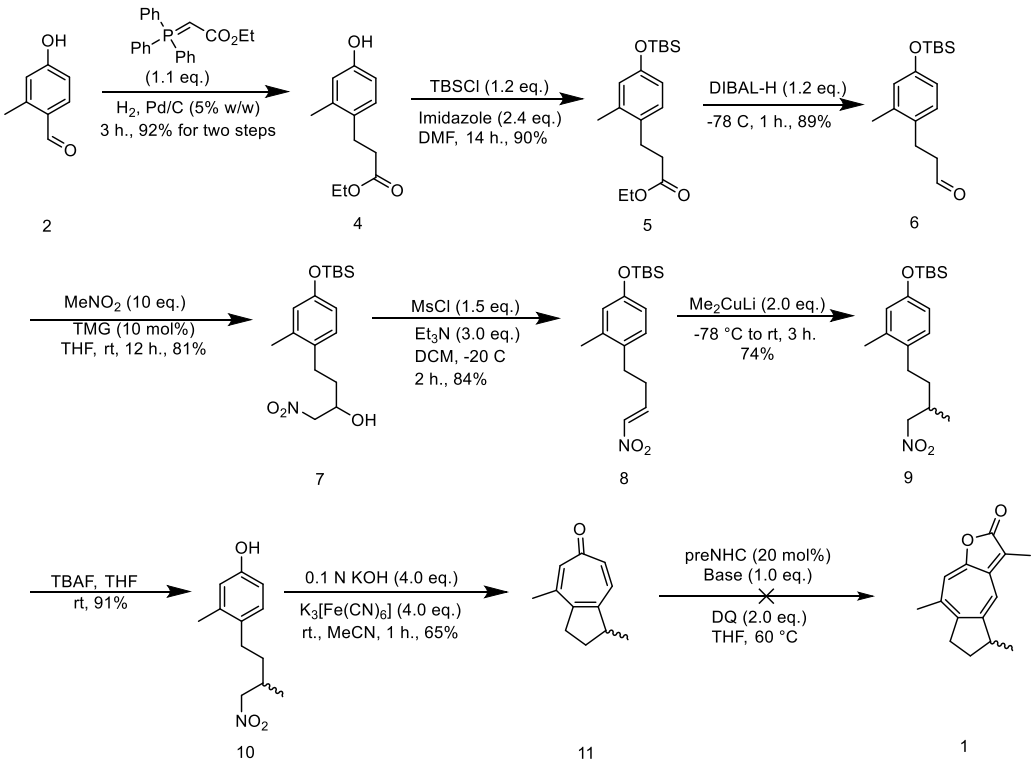
Figure 7. 13C NMR of compound 10

2.2.7 Compound 11:

At room temperature a solution (140 mg, 0.63 mmol) of **10** in (2 mL) of acetonitrile, (826 mg, 2.5 mmol) of $K_3[Fe(CN)_6]$ was added following (25.1 mL, 25.1 mmol) of 0.1 N KOH. Stirring the reaction for 1 hr. then (1M HCl) was added to make the mixture at pH of 3. Next, DCM was added to extract the product, the DCM layer was evaporated. The residue was purified to obtain (71 mg, 0.4 mmol, 65% yield) as white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 11.8 Hz, 1H), 6.99 – 6.96 (m, 1H), 6.96 – 6.91 (m, 1H), 3.15 (q, J = 7.2 Hz, 1H), 2.95 – 2.84 (m, 1H), 2.83 – 2.71 (m, 1H), 2.22 (d, J = 1.2 Hz, 3H), 2.21 – 2.13 (m, 1H), 1.56 (ddt, J = 12.6, 8.8, 6.2 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 150.9, 148.6, 146.6, 140.5, 139.5, 134.3, 44.4, 35.1, 30.5, 25.7, 20.2;), HRMS (ESI), m/z calcd for $C_{12}H_{15}O^+$ $[M-H]^+$ 175.1123, found 175.1087.

3. Results and discussion

The retrosynthesis strategy to prepare **1** was kick-started through a Witting reaction of p- hydroxy benzaldehyde **2** with (Carbethoxymethylene)triphenylphosphorane and give **3**. (**Scheme1**) The ^{1}HNMR spectrum showed two alkene protons and the ethyl group of the ester. Directly after this, hydrogenation of **3** using hydrogen gas with palladium over carbon produced **4.** The ^{1}HNMRspectrum showed the appearance of signals related to the two methylene groups at 2.81-2.88 ppm and 2.53 ppm and the proton of ethyl group at 4.13 ppm and 2.22 ppm. The OH group was protected by TBS-Cl in the presence of imidazole to yield **5**. The ^{1}HNMR spectrum showed two new peaks at 0.96 ppm and 0.17 ppm related to isobutyl and two methyl protons of the TBS group respectively. The ester **5** was reduced to an aldehyde **6** with DIBAL-H at -78 °C, then treated with nitro methane in the presence of catalytic amount of trimethyl guanidine (TMG) to give β-nitro alcohol **7**. The ^{1}HNMR showed multiple signals of CH_2 protons that attached to NO_2 at 4.36-4.40 ppm beside another signal at 4.35-.4.27 related to the CH group attached to an alcohol. The best way for dehydration of **7** was using mesyl chloride with triethyl amine at -78 °C to produce nitro alkene **8**, the 1HNMR showed disappeared of hydroxy pick. The methylation of **8** via a Core-House reaction using MeLi and CuBr gave **9** as a racemic product in 74% yield. The ^{1}HNMR showed disappearance of the alkene protons and the appearance of a signal at 1.09 ppm corresponding to a methyl group. The deprotection of the TBS group was done using TBAF to give **10** in 91% yield. The ^{1}HNMR shows disappearance of two picks of TBS group as it showed in figure 5 and 6.



Scheme 1: synthesis diagram of Gweicurculactone

The next phase of the synthesis used the Kende [19] protocol to prepare the tropon **11** scaffold which features a seven-member ring fused to a five-member ring. The ^{1}HNMR showed disappearance of the methylene group which was bonded to the NO_2 group and the ^{13}CNMR showed the carbon peak representative of the tropon carbonyl. Fortunately, a single isomer from this reaction was isolated [20] which resulted from the steric effects between the methyl groups on the phenyl ring and the methyl group on the aliphatic chain. Ye's group developed a method using the N-heterocyclic carbene as a catalyst via [8+2] oxidative annulation of tropone with aldehydes [21] to prepare cycloheptatriene-fused furanone. Compound **11** in hand; using the same method but unfortunately it was unsuccessful, then the procedure was by using different bases such as potassium carbonate and potassium tri butoxide, and organic bases like DBU, DABCO, TMG. Furthermore, then different solvents were screened like DMF, 1,4-dioxane and acetonitrile but still were unsuccessful in achieving the target compound. The hypothesis that the five-member ring, which is fused with tropon ring, may impact the conjugation of the tropon system, making common cyclization ineffectual.

4. Conclusions

In summary, significant progress had been made towards the synthesis of Gweicurculactone **1** by reaching the tropon precursor from propionaldehyde using NHC.

5. Acknowledgment.

The author is grateful to Dr. David Richardson for NMR assistance and the University of Mosul.

6. Declarations

6.1 Ethics approval and consent to participate

Not applicable.

6.2 Consent for publication

Not applicable.

6.3 Availability of Data and Materials

Data will be provided upon receiving a valid request.

6.4 Conflicts of interest
The authors declare that there is no conflict of interest

6.5 Funding
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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دراسة عن التحضير الشامل لكويكورلاكتون

نمير سعدالله عزة

قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة الموصل، الموصل، العراق

الخلاصة

في هذا العمل، تم تخليق لاكتون السيسكويتربين (**SL**). وقد سعينا إلى تحضير غويكركولاكتون باستخدام كاربين حلقي غير متجانس نيتروجيني (**NHC**). بدأنا من مركب الألدهيد 2 الذي تحول إلى المركب 4 من خلال تفاعل ويتيج، ثم هدرجته، ثم حمينا مجموعة الفينول باستخدام **TBS-Cl** للحصول على المركب 5. حُوّل الإستر إلى ألدهيد 6 باستخدام **DIBAL-H**. طُبِّق تفاعل هنري على المركب 6 باستخدام نيتروميثان بوجود **TMG** كمحفز لإنتاج مركب كحول النيترو 7. حُضِّر المركب 8 بعد إزالة جزيء ماء باستخدام كلوريد ميثان سلفونيل بوجود ثلاثي إيثيل أمين عند درجة حرارة -78 درجة مئوية. يتم الحصول على المركب 9 عن طريق مثيلة النيتروألكين 8 باستخدام ميثيل الليثيوم ويوديد النحاس عند درجة حرارة -78 درجة مئوية. بعد إزالة مجموعة الحماية من المركب 9 باستخدام فلوريد رباعي بوتيل الأمونيوم عند درجة حرارة الغرفة، نحصل على المركب 10. أما هيكل مركب التروبون الرئيسي 11، فقد تم تكوينه من خلال عملية التدوير بين الجزيئات وإزالة العطرية من خلال نقل إلكترون واحد باستخدام فيروسيانيد البوتاسيوم.