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A NOVEL STRATEGY FOR THE SYNTHESIS OF CATENA COMPOUNDS VIA MACROCYCLIC CYCLOPENTADIENONE

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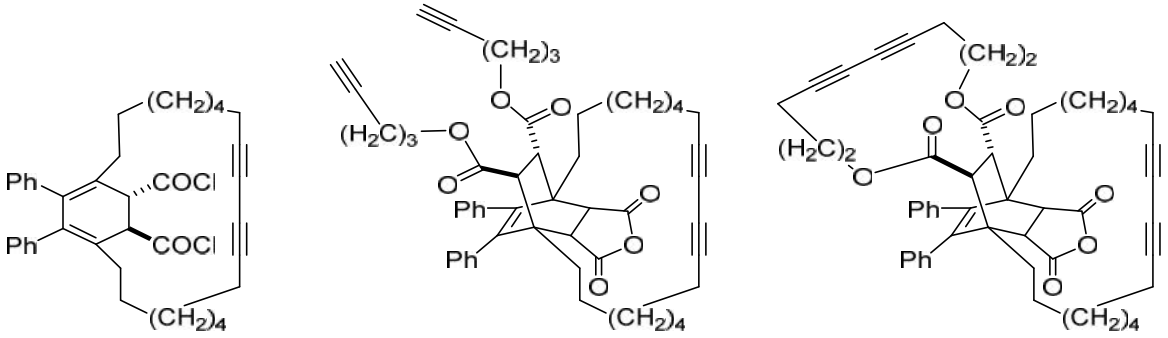
Abstract

Herein we report the Diels-Alder cycloaddition of macrocyclic- cyclopentadienone **1** and fumaryl chloride gives carbonyl bridged adduct **2**, followed by decarbonylation to provide product **3** which in turn is reacted with maleic anhydride to obtain the *trans* carbonyl chloride anhydride adduct **4**, attachment of the medium chain of acetylenic alcohol **5** to the adduct **4** produce compound **6**, followed by ring closure to form a precatenene **7.**

Key words: Synthesis, Carbonyl-bridged anhydride adduct, Macrocyclic-cyclohexa-1,3-diene, Acetylenic alcohol.

Graphical Abstract

Diels-Alder cycloaddition of macrocyclic cyclopentadienone to fumaryl chloride to give carbonyl bridged adduct, followed by decarbonylation to produce (I) which was reacted with maleic anhydride to give the trans carbonyl chloride anhydride adduct, attachment of the medium chain of acetylenic alcohol to the trans carbonyl chloride of head–bridged adduct to provide compound (II), followed by ring closure to form (III) in successful yield.



1. Introduction

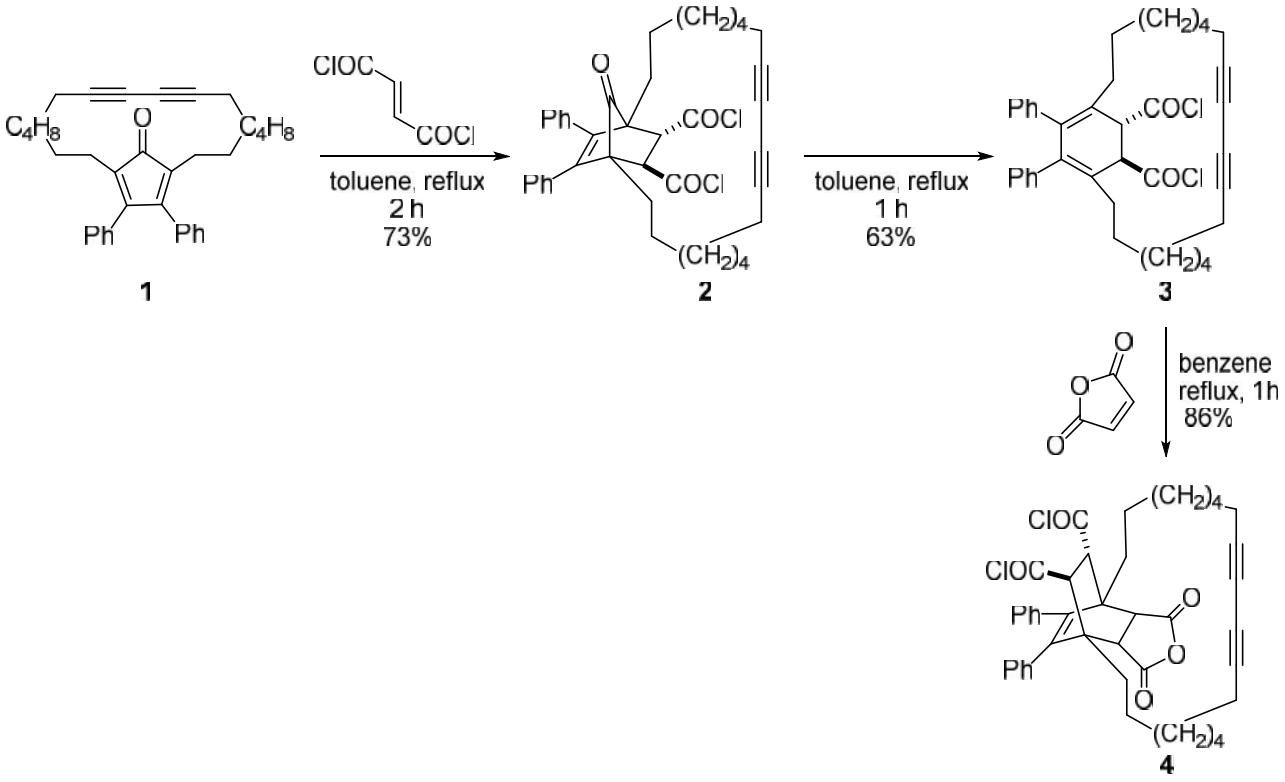
Recently the discovered catena pharmaceutical compounds, have the potential to become drugs to help fill the unmet medical need by attacking prain-anti-cancer mechanism of anglagenesis in a novel way[1]. In our research progress, we focus to synthesise a new required type of catena compounds such as compound 7. In a directed synthesis of catenanes, the two components are held by one or more auxiliary linkages, so that chain is held within a ring for the crucial cyclisation. Cleavage of the auxiliary linkages then gives a catenane. This principle was used for the first time by Schill and Lüttringhaus[2], A later development[3] used the concept of a template, on which the central portions of two chains were held at right-angles to each others while the ends of each were joined. In a new approach to the directed synthesis of catena compounds which was applied in our research work, and more recently, the

macrocyclic -cyclopentadienone **1** was synthesised[4,5,6] as initial target to catena compounds**,** and more recently some model experiments were carried out to prepare a different type of cyclopentadienone[7] in order to improve the yield of the required starting material.

The Diels-Alder cycloaddition of compound **1** with dimethyl fumarate, fumaronitryl, and fumaryl chloride was carried out, and the thermal decarbonylation[8] of the resulting carbonyl-bridged adducts was studied, the fumaryl chloride lost carbon monoxide of **2** to give the cyclohexa-1,3-diene **3** cleanly. Which was reacted with maleic anhydride to produce the anhydride adduct **4** with successfully yield, attachment of a medium chains of acetylenic alcohol[9] **5** to the double head bridged carbonyl chloride groups, to produce product **6**, then followed by ring-closure to give a precatenane adduct **7** which is analytically pure obtained.

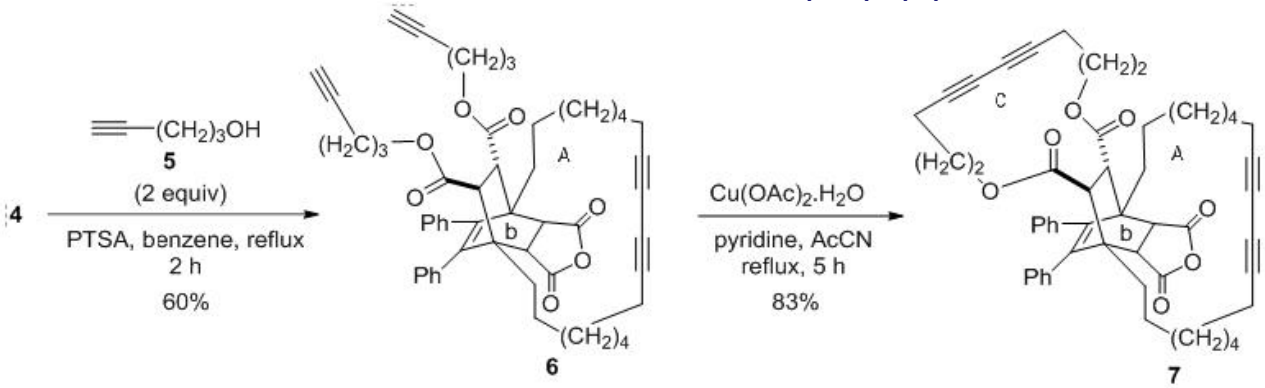
2. Results and Discussion

We sought to develop a good procedure for the synthesis of catena compounds, the macrocyclic cyclopentadienone **1** was reacted with fumaryl chloride, which is a highly reactive dienophile, in which was apparently satisfactory to give the carbonyl bridged **2**, the structure of the product being confirmed as **2** by its IR spectrum, which showed absorption at υ_{max} 1786 (bridged-CO) and 1765 cm^{-1} (COCl). The thermal decarbonylation of **2** produce the required product **3** as yellow oil in high yield. The IR spectrum exhibited absorption at υ_{max} 1762 cm^{-1} (COCl). The mass spectrum showed a peak at m/z 571 corresponding to the loss of carbon monoxide from the molecular ion (M^+ m/z 599), and another fragment ion at m/z 535,5 corresponding to the loss of carbonyl chloride from the molecular ion. The spectral evidence was thus consistent with the illustrated structure **3**. The cyclohexa-1,3-diene **3** with trans-carbonyl chloride was reacted with maleic anhydride in refluxing toluene to give the adduct **4**, which was chromotographed to obtain an orange oil with a successfully yield. The spectral evidence was consisted with expected structure.



Scheme 1. Synthesis of structure **4** from macrocyclic cyclopentadienone **1**

Thus the IR spectrum showed absorption at υ_{max} 1865, 1784 (anhydride CO), and 1790 Cm^{-1} (double head-bridged COCl), and the mass spectrometry indicated that. MS m/z 697 M^+, 599 (M^+ - maleic anhydride, base peak). two medium chains were attached to **4** as ester exchange[8] with the known[10] acetylenic alcohol **5** to give a bridged -adduct with trans chains of carboxylate acetylene **6** in (60% yield), attention then turned to



A = ring a
b = ring b
c = ring c

Scheme 2. Synthesis of precatenene **7**

the cyclization of the head-bridged chains of dicarboxylate acetylene **6** to produce **7.**[10,11,12] In the classical Eglinton- Galbraith procedure,[5,6] copper(II)acetate in pyridine is used to effect intramolecular oxidative coupling of a medium chain of diacetylene at high dilution in the presence of a cosolvent, e.g. (ether), in our case acetonitrile was used as cosolvent, and a special high- dilution conditions were found to be an necessary for a reaction which was carried out with only about (0.30 g) of dicarboxylate acetylene adduct **6**. Slow addition of a solution of **6** to a refluxing solution of the catalyst gave the macrocyclic adduct **7** as a yellow orange oil in 83% yield **,** the spectral properties of **7** were consistent with expected spectral data for structure **7,** which indicated that cyclization had occurred as required, the IR spectrum exhibited absorption at υ_{max} 1740 and 1728 sh cm^{-1} ester CO, but there was no indication of the presence of ≡CH, the mass spectrum contained a peak at MS m/z 790 (M; base peak), showing the loss of two hydrogen atoms from compound **6** (M^+ m/z 792).

4. Conclusion

In view of the results of these model reactions, it is clear that a completely new approach will be necessary for the successful use of the Diels-Alder cycloaddition and its retrogression in the synthesis of catena compounds. In our proposal work In a new approach to the directed synthesis of other catena compounds it was proposed to prepare a new type of catenanes by using the concept of a template, on which the central portions of two chains were held at right –angles to each other while the ends of each were joined, thus the 1,10-phenanthrolinoic acid derivative formed a Nickel complex, which reacted with 1,14-diiodo-3,6,9,12-tetraoxatetradecane at high dilution in the presence of caesium carbonate to give the metallocatenane a 'catenate'. This strategy, of subunits must contain suitable coordination sites.

3. Experimental

Unless otherwise stated, the following conditions apply. Thin layer chromotography (TLC), using silica plates, was the tool following up the reaction mixture during and after each process, the plates being examined under U V light at 254 or 336 nm. Column chromotography was carried out on either silica gel (60-120 mesh) or Merck kieselgel (60 H). Infrared (IR) spectra were recorded on a Perkin – Elmer 1420 spectrophotometer. Mass spectra (MS) were recorded on an AET MS9 Instrument updated with VG ZAB components. Nuclear magnetic resonance (NMR) spectra were recorded on a Jeol G×400 and 270 instrument using (TMS) as the internal standard.

(21*R**,22*R**)-25-oxo-23,24-diphenyltricyclo [18.2.2.1[1,20]]pentacos-23-ene-9,11-diyne-21,22-dicarbonyl dichloride (2)

A mixture of the macrocyclic cyclopentadienone **1** (1.5g) and fumaryl chloride (0.48g) in dry toluene (25 mL) was heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue was chromotographed on silica gel. Elution with ethyl acetate- light petroleum (1:6) then gave the adduct **2** as a deep orange oil in good yield (1.10g, 73%).

IR (KBr): ũ = 1786 (bridged CO), and 1765 cm^{-1} (COCl).

^{1}H NMR (400 MH_Z, $CDCl_3$) : δ = 7,6 – 7,2 (m, 10H, Ar-2x ph), 3.53 and 3.35 (s, 2H, H-21 and H-22), for the macrocyclic (a), 2.66 – 2.20 [m, 8H, 2x H-2, 2x H-19, 2.30 (t, 4H, *J* = 7.5 Hz)], 2x H- 8 and 2x H-13, 1.60 – 1.22 (m, 20 H) ppm; MS: *m/z* (%) = 627 (M^+, base peak), 599 (M^+ - CO), and 472 (M^+ - 2 COCl); Anal. Calcd. for $C_{39}H_{40}O_3Cl_2$; C, 74.63; H, 6.42; O, 3.37; Cl, 11.29 Found: C, 74.39; H, 6.28; O,7.30; Cl, 10.98.

(21*R,22*R**)-23,24-diphenylbicyclo[18.2.2] tetracosa-1(23),20(24)-diene-9,11-diyne-21,22-dicarbonyl dichloride (3)**

The carbonyl bridged compound **2** (5.50g) was heated in tetralin (10 mL) under reflux for 1h. The solution was cooled and then treated with light petroleum (bp.30–40°C), (30 mL) and the crude product was chromatographed using ethyl acetate and light petroleum (b.p. 30- 40°C), (1:3) as eluent**,** yielded (3.50 g, 63%).

IR (KBr, cm^{-1}) 1762 (COCl) ; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 7.6 – 6.8 (m, 10H, Ar-H), 3.60 (s, 2H, H-21 and H-22), for the macrocyclic ring (a), 2.66 – 2.20 [m, 8H, 2x H-2, 2x H-19, 2.30 (t, 4H, *J* = 7.5 Hz)], 2x H- 8 and 2x H-13, 1.85 –2.1(m, 20 H) ppm.MS: *m/z* (%) = 599 (M^+, base peak), and 535.5 (M^+- COCl); Anal. Calcd. for $C_{38}H_{40}O_2Cl_2$: C, 76.11; H, 6.72; O, 5.33; Cl, 11.82 Found: C, 75.90; H, 6.30; O, 4.89; Cl, 11.50.

(24*S,25*S**)-1,3-dioxo-26,27-diphenyl-12,13,14,15-tetradehydro1,3,3a,5,6,7,8,9,10,11,16,17,18,19,20, 21,22,23a-octadecahydro-4,23-ethano-4,23-ethenocyclodocosa[*c*]furan-24,25-dicarbonyl dichloride (4)**

A mixture of dicarbonyl chloride adduct (**3**) (1.00g) and maleic anhydride (0.6g) was dissolved in dry benzene (10 mL) then the mixture was heated at reflux for 1h. The solvent was removed under pressure, and the adduct **4** was obtained as a residue which was chromatoghraphed on silica gel, using light petroleum (b.p. 60- 80°C)-ethyl acetate (3:1) as eluent, yielded (0.12g, 86%).

IR (KBr): ũ = 1865, 1884 (anhydride CO) and 1790 cm^{-1} (double head bridged- COCl)
^{1}H NMR (400 MHz, ($CDCl_3$): δ = 7.6- 6.85 (m, 10H, Ar-H), 3.78 (s, 2H, H-4 and H-23), 4.10- 3.65 (s, 2H, H-24 and H-25), 2.5 -2.2 [m, 8H, 2x H-2, 2x H-19, 2.30 (t, 4H, *J* = 7.5)], 2 x H- 8 , 2 x H-13, 1.60 – 1.20 (m, 20 H) ppm, for macrocyclic ring (a)

.MS: *m/z* (%) = 697(M^+, base peak), 599 (M^+-maleic anhydride); Anal. Calcd. for $C_{42}H_{42}O_5Cl_2$: C, 72.30; H, 6.06; O, 11.46; Cl, 10.16 Found: C, 71.98; H, 6.01; O, 11.39; Cl, 9.80.

dipent-4-yn-1-yl(24*S,25*S**)-1,3-dioxo-26,27-diphenyl-12,13,14,15-tetradehydro-1,3,3a,5,6,7,8, 9,10,11,16,17,18,19,20,21,22,23a-octadecahydro-4,23-ethano-4,23-ethenocyclodocosa[*c*]furan-24,25-dicarboxylate (6)**

The dicarbonyl chloride anhydride adduct **4** (0.50g) was reacted with (0.134g) of acetylenic alcohol and (50mg) of p-toluene sulphonic acid, the mixture was dissolved in dry benzene (15 mL) and heated slowly to 140°C for 2h, the solvent was removed and the residue was chromatographed on silica (Merck 60H), using light petroleum (b.p.30-40°C) and ethyl acetate (3:1) as eluent yields (0.30g, 60%).

IR (KBr): ũ = 3315(≡CH), 2120(C≡C), (1864, 1882 (anhydride CO) and 1793 cm^{-1} (carbonyl bridged CO).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.6-6.80 (m, 10H, Ar-H), 3.20 (s, 2H, H-4 and H-23), 2.50-2.20 [m, 4H, 2xH-2 and 2xH-19, 2.60 (t, J = 7.5, 4H, (2xH-8 and 2xH-13)], 1.50-1.20 (m, 20H, 2x $(CH_2)_5$, for macrocyclic ring (**a**), 3.90- 3.65(s, 2H, H-24 and H-24, for the two methine protons of the double head bridged adduct), 1.60(t, J = 2.5 Hz, 2xH-5 inside–chain and 2.10-1.90[(m,12H), ,2x$(CH_2)_3$)ppm)] for the acetylenic chain of the double head bridged diester.

MS: *m/z* (%) = 792 (M,$^+$base peak), 694 (M^+ - maleic anhydride); Anal. Calcd. for $C_{52}H_{56}O_7$: C, 78.75; H, 7.11; O, 14.12 Found: C, 78.65; H, 6.86; O, 13.95.
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(4a*S,18a*S**)-20,21-diphenyl-10,11,12,13-tetradehydro-3a,4a,7,8,9,14,15,16,18a,19a-decahydro-4,19-etheno-4,19-nonadeca[8,10] ynofuro[3,4-*q*][2,13]benzodioxacyclohexadecine-1,3,5,18-tetrone (7)**

Copper (II) acetate monohydride (0.6 g) was dissolved in pyridine (12 mL) and acetonitrile (20 mL) was added to the stirred and refluxed solution during 5h, a solution of the adduct product **6** (0.30 g) in acetonitrile (7 mL), heating was then discontinued, but the mixture was stirred for overnight. Most of the acetonitryl was removed under reduced pressure, water (5 mL) was added and the product was collected in light petroleum (b.p.30-40°C). The extract was washed with 2 % aqueous sulfuric acid, dried ($MgSO_4$), and evaporated to give a precatenane **7** as an yellow orange oil, yielded (0.25g, 83%).

IR (KBr): ũ = 1740 and 1728 sh cm^{-1} ester CO; 2122, (C≡C), 1865 and 1774 cm^{-1} (anhydride CO).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 –6.97[m, 10H, Ar-H), 3.21(s, 2H, H-4 and H-19, for the anhydride adduct for ring (**b**)), 2.50- 2.20[m, 4H, 2xH-2 and 2xH-

19, 2.60(t, J = 7.5 Hz, 4H), 2xH-8 and 2xH-13], 1.50-1.20[m, 20H, $2x(CH_2)_5$], (for a macrocyclic ring **a**), 3.40- 3.25(s, 2H, for the double head bridged adduct), and 2.18-1.95(m, 12H, $2x(CH_2)_3$) ppm, for the macrocyclic ring(**c**).

MS: *m/z* (%) 790 (M^+, base peak); Anal. Calcd. for $C_{52}H_{54}O_7$: C, 78.95; H, 6.88; O, 14.15 Found: C, 78.76; H, 6.65; O, 13.76.

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