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Synthesis of Pentacycloundecane (PCUD) Based Spiro-Pyrano-Cage Framework via Ring-Closing Metathesis

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Abstract: Here, we demonstrate a short synthetic route to pyrano cage systems containing pentacycloundecane units by employing ring-closing metathesis (RCM) as a key step. These cage systems were constructed starting with readily available starting materials by adopting atomic economic processes such as cycloadditions (Diels-Alder reaction and [2+2] cycloaddition), Grignard addition, and olefin metathesis. The key building block, such as hexacyclic cage dione, was prepared from 1,4-naphthoquinone derivative and freshly cracked 1,3-cyclopentadiene. Some of these heterocyclic motifs are useful in biological chemistry and valuable as key synthons for high-energy-density materials.

Keywords: heterocycles; cage framework; RCM; cycloadditions; oxidation; hydrogenation

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1. Introduction

Heterocycles have attracted interest from the scientific community because of their biological activities against various diseases [1]. They are considered promising candidates that are available from natural sources, show applications in medicinal chemistry and pharmaceutics, play a prominent role in the synthesis of agrochemicals, and act as key synthons for the design of pharmacophores in modern drug chemistry [2]. Amongst the known heterocyclic compounds, cage-containing heterocyclic scaffolds are found in applications of bioorganic chemistry, material science, and supramolecular chemistry [3–5]. Cage polycycles bearing heteroatoms in their molecular architecture act as ligands and are also suitable for chelation with metal ions [6]. These are also considered core frameworks for energetic and photonic/electronic materials [7]. Furthermore, functionalized hetero cages exhibit medicinal properties and act as valuable candidates for pharmaceutical applications [8,9]. Additionally, some of the cage scaffolds (**1**–**6**) depicted in Figure 1 were constructed by employing novel synthetic approaches. These heterocyclic cages are used as chiral ligands (**1**) [10] and supramolecules (**2**–**3**) [11,12], and some of those (**4**–**6**) display interesting activities against tuberculosis, anti-Parkinson activity, and neurodegenerative diseases [13–15].

In view of the literature reports and valuable applications of cage polycycles, we are actively involved in developing new methods and simple synthetic strategies for cage frameworks. During the last two decades, we have demonstrated various new synthetic routes to diverse and functionalized cage molecules by employing cycloaddition and olefin metathesis protocols as key steps [16]. Several reports are available for the synthesis of oxa-cage molecules in the literature [17]. Some of these strategies to create hetero-cages rely on tandem cyclization, transannular cyclization, base-promoted rearrangement, dehydration of diols, intramolecular, and alkene-oxirane photocycloaddition [17]. As part of our ongoing research focused on designing intricate molecules based on metathesis, here we conceived a ring-closing metathesis (RCM) approach to construct functionalized hetero-cage systems [18–20]. In this regard, we identified cage dione **13** [21,22] as a useful starting material for the design of a target compound such as **17**.

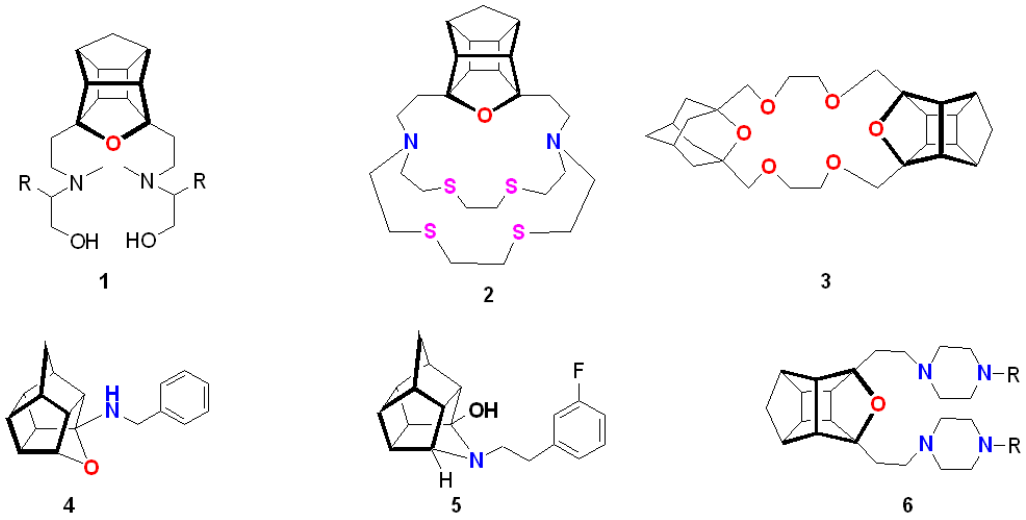
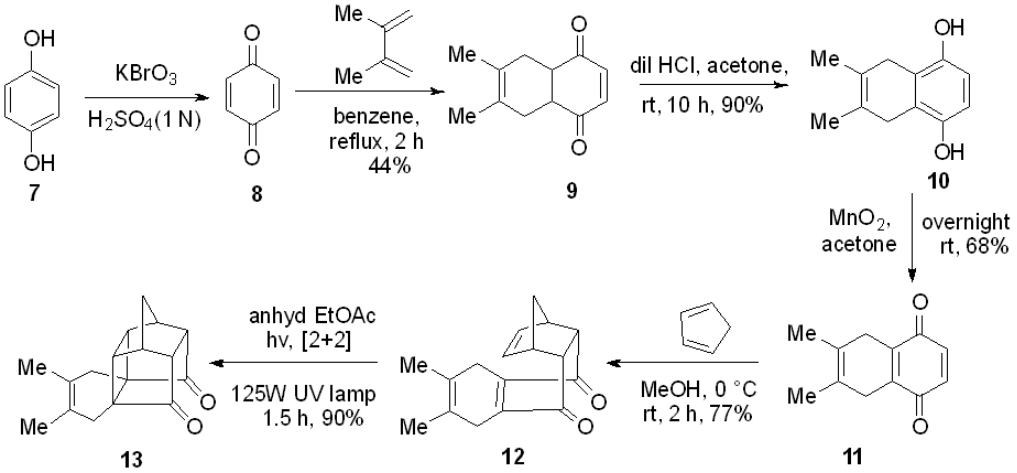


Figure 1. Examples of hetero-cages **1**–**6** useful in various fields.

2. Results and Discussion

Our journey towards the synthesis of the hexacyclic dione **13** [21,22] began with the preparation of the DA precursor, such as the dihydronaphthalene-1,4-dione **11,** from inexpensive and commercially available hydroquinone **7** (Scheme 1). In this context, the [4+2] cycloaddition of 1,4-benzoquinone **8** prepared from the hydroquinone **7** was treated with 2,3-dimethyl 1,3-butadiene under reflux conditions in anhydrous benzene to give the cycloadduct **9**. Aromatization of cycloadduct **9** in the presence of dil. HCl at room temperature furnished the diol **10**.

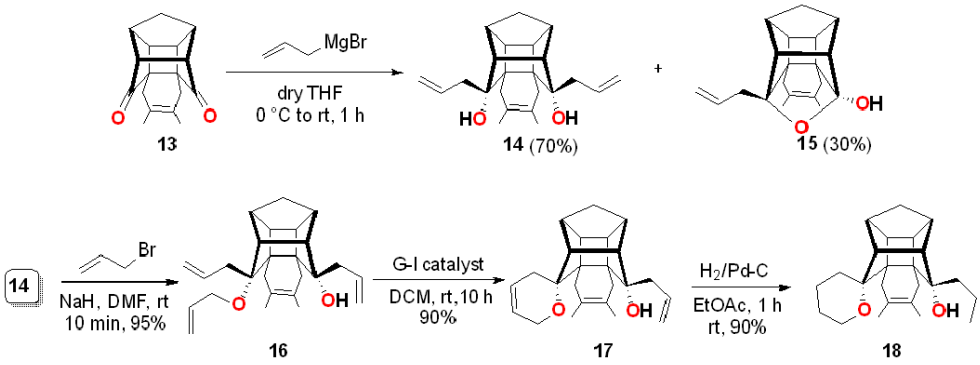


Scheme 1. Synthesis of hexacyclic cage system **13**.

Subsequent oxidation of the hydroquinone **10** in the presence of MnO_2 gave the quinone derivative **11** (Scheme 1) [15]. Having prepared the DA precursor **11**, cage dione **13** was prepared via [4+2] cycloaddition and intramolecular [2+2] photocycloaddition. In this context, cycloaddition of the quinone **11** was accomplished by reacting with a freshly cracked 1,3-cyclopentadiene at 0 °C, delivering the desired cycloadduct **12** and furthering the DA adduct **12** and undergoing [2+2] photocycloaddition through UV irradiation with a 125 W-homemade lamp, producing the hexacyclic cage dione **13** (Scheme 1). The structure of cage dione **13** was confirmed by ^{1}H NMR and ^{13}C NMR data.

In view of our interest in designing new polycyclic systems containing heteroatoms via metathesis and other protocols [23–29], we intended to synthesize our target compound **17**. In this regard, the cage dione **13** was treated with the commercially available allyl magne-

sium bromide in dry ether to deliver the diallyl cage diol **14** along with another hemiketal derivative **15** by transannular cyclization. Next, the cage diol **14,** on allylation with the NaH in the presence of allyl bromide in dry DMF, gave the triallyl cage compound **16** (Scheme 2). Subsequent ring-closing metathesis of triallyl compound **16** with the G-I catalyst under rt conditions produced the cage derivative **17**. Finally, hydrogenation of the compound **17** with hydrogen in the presence of 10% palladium on activated charcoal in dry EtOAc gave the saturated cage system **18** with a 90% yield (Scheme 2). The structures of cage heterocycles **17** and **18** were fully characterized on the basis of ^{1}H NMR, ^{13}C NMR, and DEPT-135 NMR spectroscopic data and finally supported by the mass spectra HRMS values.



Scheme 2. Synthesis of spiro-pyrano-cage framework **17**.

The ^{1}H NMR spectrum of the cage spiro-pyran derivative **17** displayed the presence of one singlet (-OH proton) at δ 6.96 (1H), which indicates the proton of alcohol, one doublet at δ 5.66 (1H), and three multiplets at δ 5.06 (2H), δ 5.80 (1H), and δ 6.01 (1H), which represents the olefinic proton of allylic carbon and the spiro-pyran ring. In addition, the ^{13}C NMR spectrum of **17** shows the four characteristic peaks (olefinic carbon) at δ 135.1, 123.9, 123.8, and 116.2 ppm of allyl carbon, and the spiro-pyran ring system represents the –CH and –CH_2 carbon (Figure 2). In the ^{1}H NMR spectrum of compound **18**, the one singlet (-OH proton) at δ 6.96 (1H) indicates the proton of alcohol, and the multiplet at δ 0.91 (4H) represents two –CH_2 carbons adjacent to the quaternary carbon of -OH. In addition, the ^{13}C NMR spectrum of compound **18** also shows two peaks at δ 81.6 and 76.8 that represent the quaternary carbon and at δ 65.1 that represent the -CH_2 carbon adjacent to the oxygen in the spiro-pyrane ring. In the spectra of cage spiro-pyran derivative **18,** it shows the two olefinic peaks of the cyclohexane ring, and the other peaks of the allyl carbon and spiro-pyran rings are missing, which shows the reduction of double bonds. So, we clearly identified cage spiro-pyran derivative **17** and hydrogenated spiro-pyrane product **18** based on chemical shift values (^{1}H and ^{13}C). The NMR spectra of all of these are provided in the Supplementary Materials.

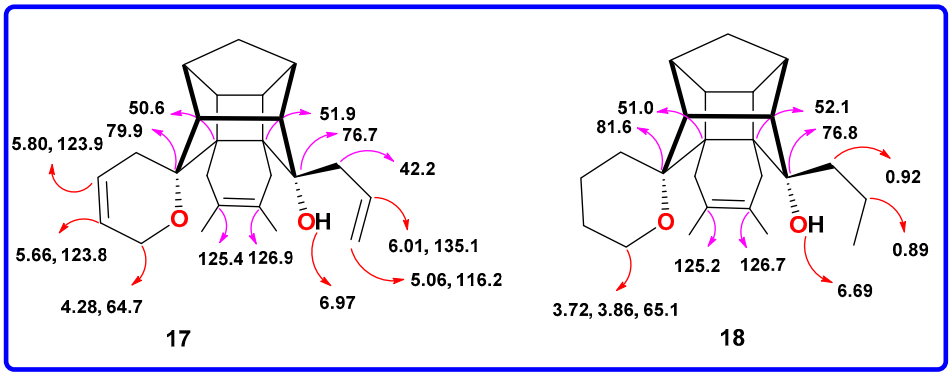


Figure 2. Comparison of NMR (^{1}H and ^{13}C) value(s) of targets **17** and **18**.

3. Materials and Methods

3.1. General Information

Allylmagnisium bromide, dicyclopentadiene, hydroquinone, and other essential reagents, chemicals, and solvents are used as such, obtained from commercial suppliers, without any further purifications. The reaction progress was monitored by thin-layer chromatographic technique (TLC; Type-A, B, or C) using appropriate mobile phase (EtOAc/petroleum ether), and observation was conducted by UV, iodine exposure, and immersion in $KMnO_4$ solution. In all cases, column purification was performed with 100–200 mesh silica gel with a suitable solvent system. All IR samples were recorded with DCM and chloroform as solvents on the Nicolet Impact-400 FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C and DEPT 135) have been recorded on 400 and 500 MHz spectrometers (Bruker), with $CDCl_3$ solvent and chemical shifts (δ ppm) reported to be relative to an internal standard such as TMS. The *J* values (coupling constants) are given in Hz. Mass spectra (HRMS) have been recorded in positive ion electrospray ionization (ESI, Q-TOF) mode. Compounds **11** and **13** were synthesized via the literature methods [21,22], and the spectral data are consistent with the reported values.

3.2. Synthesis and Characterization

3.2.1. Synthesis of Cage Diol **14** via Grignard Addition

To a solution of cage dione 13 (200 mg, 0.78 mmol) in dry THF (10 mL), commercially available allylmagnesium bromide (1.0 M in THF, 6 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred at rt for 1 h. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with saturated aq. NH_4Cl solution (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (100–200 silica gel) using 5–10% EtOAc–petroleum ether as an eluent to afford compound **15** (for data, see the supplementary material). Further elution of column chromatography afforded the desired compound **14**. Off white solid; Yield: 186 mg (70%); M.P. 177–179 °C; IR (Neat) 3227, 2932, 2203, 2118, 1608, 1442, 1264, 1092, 919, 802 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 10.5 Hz, 1H), 1.44 (d, *J* = 10.5 Hz, 1H), 1.73–1.68 (m, 8H), 1.85 (s, 2H), 2.02–1.97 (m, 2H), 2.26–2.19 (m, 8H), 5.12–5.07 (m, 4H), 5.35 (bs, 1H), 5.99–5.90 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 126.0, 117.6, 77.9, 51.2, 48.7, 43.1, 43.0, 42.0, 34.5, 32.6, 20.3 ppm; HRMS (ESI, Q-TOF): *m/z* calcd for $C_{23}H_{31}O_2[M + H]^+$: 339.2319 found 339.2318.

3.2.2. Synthesis of Cage Triallyl Derivative **16**

To a suspension of sodium hydride (3 equiv.) in dry DMF (10 mL), the compound **14** (100 mg, 0.29 mmol) was added, and the reaction mixture was stirred for 10 min at rt. Allyl bromide (6 equiv.) was then added, and stirring was continued for 10 min at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with saturated aq. NH_4Cl (5 mL), and the aqueous layer was then extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (100–200 silica gel) using 1–3% EtOAc–petroleum ether as eluent to afford the desired compounds **16**. Colorless liquid; Yield: 106 mg (95%); IR (Neat) 3338, 3073, 2929, 2861, 1732, 1638, 1439, 1280, 1161, 1069,1050, 993, 914, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, *J* = 10.5 Hz, 1H), 1.45 (d, *J* = 10.5 Hz, 1H), 1.73 (s, 6H), 1.85–1.82 (m, 3H), 2.21–2.15 (m, 2H), 2.38–2.32 (m, 6H), 2.54 (dd, *J* = 15.9, 5.8 Hz, 1H), 4.05 (dd, *J* = 11.6, 5.5 Hz, 1H), 4.15 (dd, *J* = 11.7, 5.3 Hz, 1H), 5.28–5.02 (m, 8H), 5.86–5.79 (m, 2H), 6.05–5.91 (m, 2H), 6.61 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 134.3, 133.3, 127.0, 125.4, 117.2, 116.9, 116.0, 83.3, 77.1, 66.1, 52.4, 51.7, 49.4, 48.2, 43.6, 43.5, 42.7, 42.1, 39.02, 34.6, 34.1, 32.4, 20.29, 20.25 ppm; HRMS (ESI, Q-TOF): *m/z* calcd for $C_{26}H_{35}O_2[M + H]^+$: 379.2632 found 379.2630.

3.2.3. Synthesis of Compound Cage Spiro-Pyran **17** via RCM Protocol

To a stirred solution of compounds **16**, such as RCM precursor (50 mg, 0.13 mmol, 1 equiv.) in dry DCM (15 mL), which was degassed with nitrogen for 10 min, was added Grubbs catalyst (G-I, 10 mol%). Then the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (reaction progress was monitored by TLC), the solvent was removed under reduced pressure, and the crude reaction mixture was purified by silica gel column chromatography using 5% EtOAc/petroleum ether as an eluent to give 17. Colorless liquid; Yield: 42 mg (90%); IR (Neat): 3435, 2335, 1647, 1266, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, *J* = 10.5 Hz, 1H), 1.45 (d, *J* = 10.5 Hz, 1H), 1.77–1.72 (m, 6H), 1.93–1.83 (m, 4H), 2.33–2.21 (m, 8H), 2.46–2.44 (m, 1H), 4.28 (s, 2H), 5.07–5.05 (m, 2H), 5.66 (d, *J* = 10.5 Hz, 1H), 5.82–5.79 (m, 1H), 6.04–5.99 (m, 2H), 6.96 (d, *J* = 2.1 Hz, 1H),; ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 126.9, 125.4, 123.9, 123.8, 116.2, 79.9, 64.7, 51.9, 50.6, 49.4, 47.2, 43.7, 43.38, 43.30, 42.8, 42.2, 34.5, 34.4, 32.6, 30.9, 20.3, 20.2 ppm; HRMS (ESI) calcd for $C_{24}H_{31}O_2[M + H]^+$: 351.2319 found 351.2319.

3.2.4. Hydrogenation of Cage Spiro-Pyran **17**

To a stirred solution of compound **17** (50 mg, 0.11 mmol, 1 equiv) in dry EtOAc (5 mL), 10 mol% Pd/C was added. Then the resulting reaction mixture was stirred at room temperature for 1 h under a hydrogen atmosphere (1 atm). After the completion of the reaction by the TLC evident, the reaction mixture was filtered through a Celite pad and washed with ethyl acetate (10 mL). The combined washings and filtrate were evaporated under vacuo and the resulting crude residue was purified by silica gel column chromatography using 3% EtOAc/petroleum ether as an eluent to afford hydrogenated product 18. Colorless liquid; Yield: 36 mg (90%); IR (neat, cm^{-1}): υ_{max} = 3304, 2995, 2869, 1453, 1265, 1159, 1071, 1035; ^{1}H NMR (500 MHz, CDCl3): δ 0.92–0.89 (m, 4H), 1.66–1.03 (m, 16H), 1.73 (s, 6H), 1.83–1.79 (m, 1H), 2.26–2.18 (m, 4H), 2.80–2.78 (m, 1H), 3.86–3.72 (m, 2H), 6.96 (bs, 1H) ppm; ^{13}C NMR (125.7 MHz, CDCl3): δ 126.7, 125.2, 81.6, 76.8, 65.1, 52.1, 51.0, 48.8, 43.9, 43.4, 43.2, 42.8, 42.4, 39.8, 34.6, 33.2, 32.6, 32.5, 30.7, 25.5, 20.3, 18.6, 15.6, 15.0 ppm; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{24}H_{35}O_2$ $[M + H]^+$: 355.2632, found: 355.2628.

4. Conclusions

In summary, we successfully synthesized pyrano-cage compounds **17** and **18** containing a PCUD skeleton via RCM. We utilized cycloaddition reactions, Grignard addition, and olefin metathesis as key steps. The target compound synthesis was accomplished using readily available materials such as a 1,4-naphthoquinone derivative and dicyclopentadiene. These heterocyclic scaffolds may have applications in other areas.

Supplementary Materials: The following supporting information can be downloaded online. ^{1}H, ^{13}C, and DEPT NMR spectra of all new compounds.

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