Indian Journal of Chemistry
Vol. 59B, January 2020, pp. 75-84

Synthesis of cage heterocycles containing tetrahydrofuran and pyran ring system *via* Grignard addition and ring-closing metathesis

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Received 3 September 2019; accepted (revised) 16 December 2019

Several cage compounds containing tetrahydrofuran and pyran rings have been reported by using the Grignard addition and ring-closing metathesis as key steps. Cage hemiketal derivatives have been generated due to the proximity of two carbonyl groups in cage dione. These cage heterocycles have been derived from readily available starting materials such as 1,4-hydroquinone and dicyclopentadiene.

Keywords: Cage heterocycles, tetrahydrofuran ring system, Grignard addition, ring-closing metathesis (RCM), cage hydroxyethers, transannular cyclization

Symmetrical polycyclic cage compounds[1] are promising candidates as high energy or high density materials due to their rigid and compact architecture. They are useful precursors to natural and non-natural products synthesis and also act as potential bioactive molecules[2]. Synthesis of new cage frameworks has become a challenging task due to their strained architecture. Some of the oxa-cage compounds are useful substrates in understanding π-facial selectivity. They are also valuable synthons to design ligands for chelation of metal ions[3]. Moreover, these cage systems provide a unique opportunity to design unknown cage systems *via* rearrangement approach[4].

Several routes are available for synthesis of oxa-cage frameworks[5] through tandem cyclization[6], transannular cyclization[7], base promoted rearrangement[8], dehydration of diols[9], intramolecular alkene-oxirane photo-cycloaddition[10] and intramolecular etherification of the alkene bond with the involvement of organoselenium reagent[11]. Additionally, transannular cyclization plays a prominent role in the design of oxa-cage systems through hemiketal formation during the Grignard addition[12].

Selected oxa cage scaffolds **1**-**4**[13] are depicted in Figure 1, cage compound **1** can act as chiral ligand in asymmetric synthesis and whereas compound **2** show N-methyl-D-aspartate receptor (NMDAR) inhibitory activity, as well as **3** acts as metal ion complexing agent.

Recently, we have developed a new synthetic route to oxa-bridged trishomocubane derivative **4** *via* acid-promoted (Zn/AcOH and fuming HNO_3) rearrangement starting with the cage [4.4.2] propellane[14] and also established a new strategy to oxa-cage propellanes *via* ring-closing metathesis (RCM) as a key step[15]. Here, we report a new synthetic strategy towards intricate oxa-cages containing tetrahydrofuran and pyran ring system **5** using Grignard addition and RCM as key steps.

Results and Discussion

As part of our major programme aimed at the synthesis of interesting cage heterocycles using RCM protocol, here, we selected cage diones **9**, **10**, and **11** to design diverse oxa-cage compounds containing tetrahydrofuran and pyran ring systems. These diones **9**-**11** were prepared by known literature methods[16] using 1,4-benzoquinone **5** *via* a Diels–Alder (DA) reaction with dienes such as **6**, **7**, and **8** followed by intramolecular [2+2] photocycloaddition (Scheme I).

Having prepared the cage diones **10** and **11**, the parent dione **10** was subjected to Grignard addition sequence[17] with allylmagnesium bromide in dry THF at 0 °C for 1 h to deliver an inseparable mixture of the cage diol **12** along with the hemiketal **13**. This mixture **12** and **13** (70:30 conversion based on NMR) was further subjected to allylation with excess amount of allyl bromide/NaH in dry DMF to furnish the triallyl derivative **14** (58%) and diallyl derivative

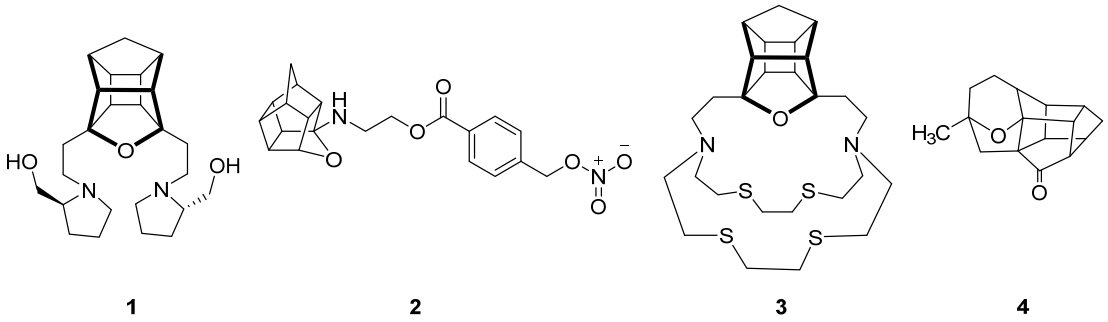
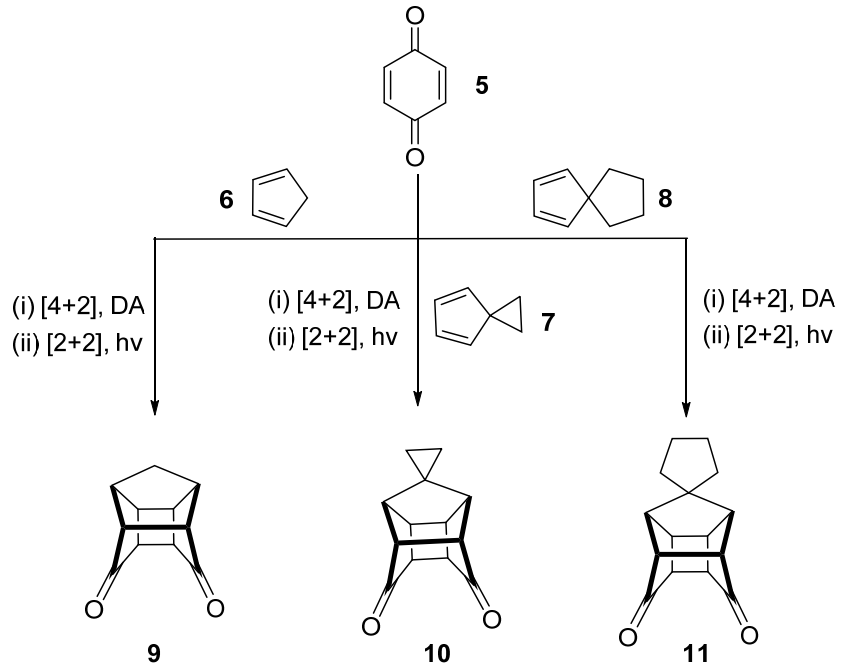
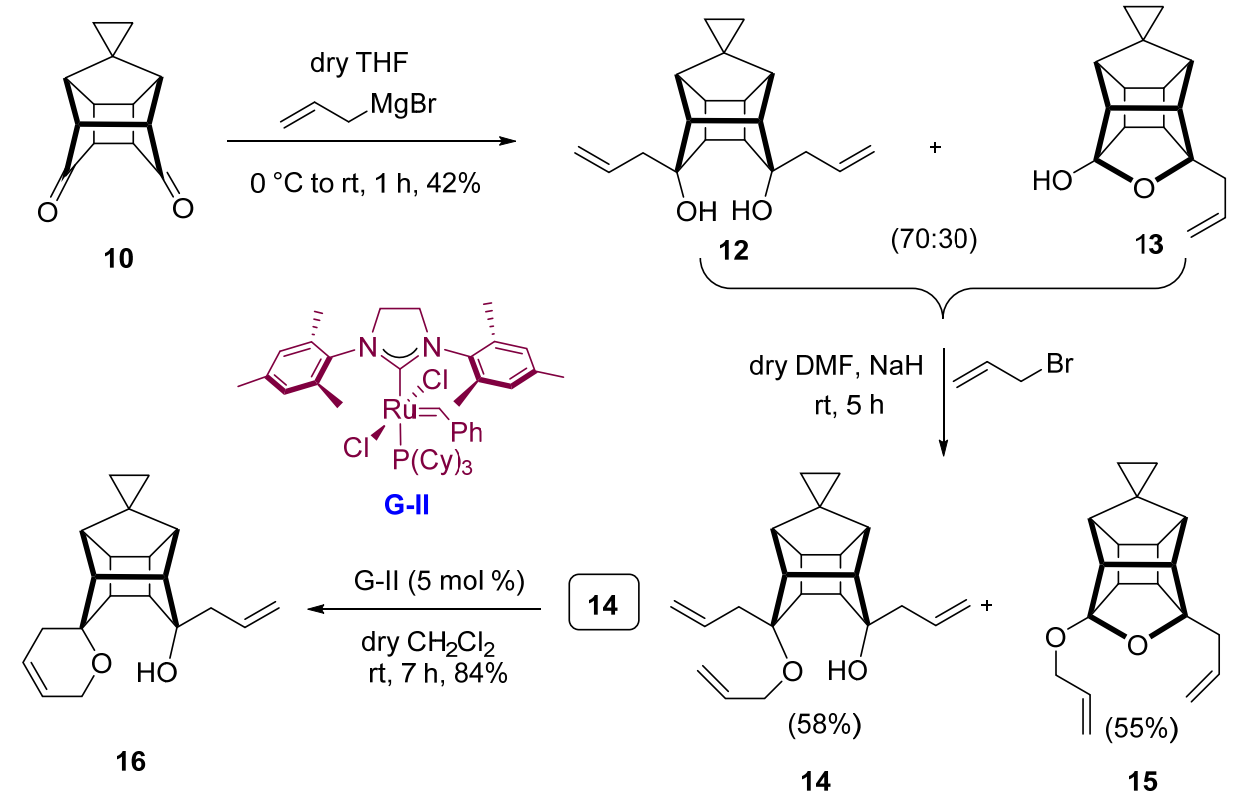


Figure 1 — Representative examples of oxa-cage systems

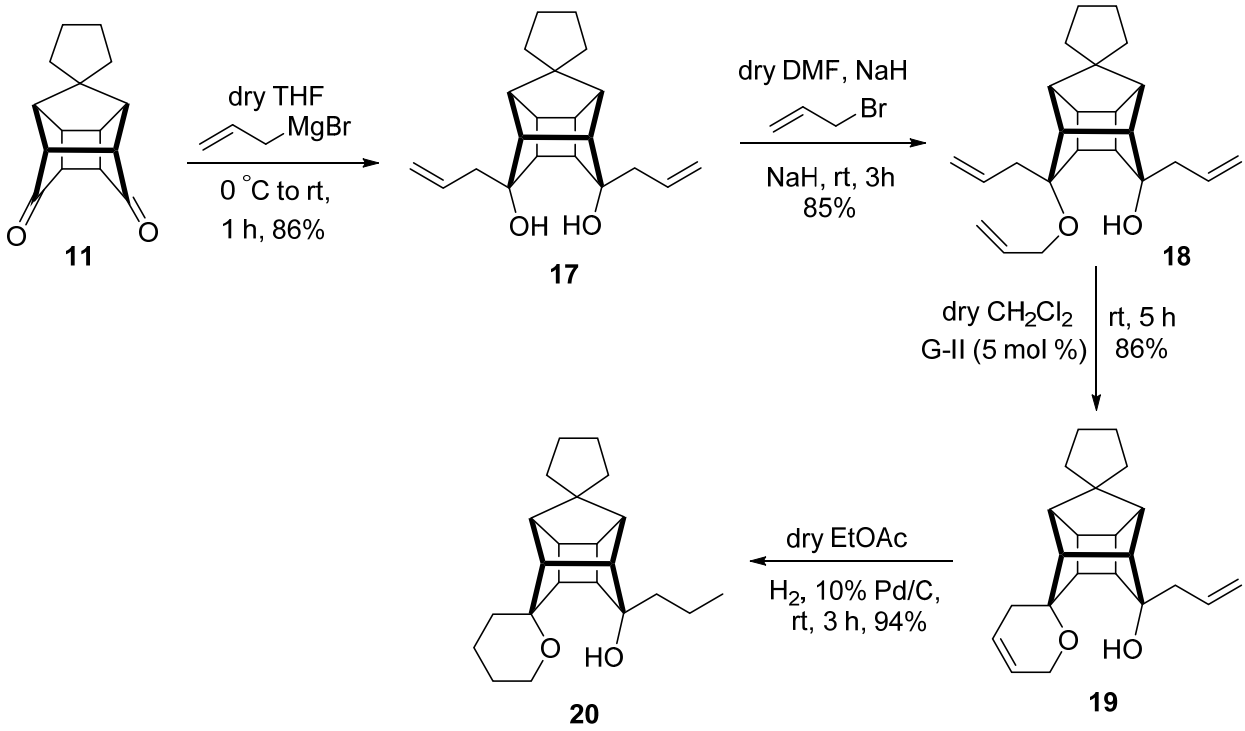


Scheme I — Synthesis of cage diones **9**, **10**, and **11**

(hemiketal) **15** (55%). Later on, RCM[18] of triallyl derivative **14** in the presence of Grubbs second generation (G-II, 5 mol%) catalyst in dry DCM at RT for 7 h gave the cage pyran **16** in 84% yield (Scheme II). The structure of the RCM product **16** was supported by spectral data and further supported by HRMS. Along similar lines, this strategy has been extended to other cage system **11** bearing spiro cyclopentane ring. In this regard, the dione **11** was treated with allylmagnesium bromide (6 equiv.) in dry THF at RT for 1 h to deliver the expected cage diol **17** (86%). Next, the diol **17** was subjected to *O*-allylation by reaction with allyl bromide (8 equiv) in dry DMF to produce the triallyl derivative **18** which on treatment with G-II catalyst (5 mol%) in dry DCM gave the ring-closure product **19** in 86% yield. Finally, hydrogenation of the RCM product **19** in the presence 10% Pd-C in hydrogen atmosphere in dry EtOAc yield the saturated cage pyran **20** in excellent yield (Scheme III). The structures of the compounds **17**, **18**, **19**, and **20** were determined by spectroscopic data. Later, the other oxa-cage compound containing tetrahydrofuran ring system was prepared *via* vinyl Grignard addition. To this end, the cage diones **9** and **10** were treated with vinyl Grignard reagent (6 equiv.) in dry THF to yield the hemiketals **21** and **24** in good yields. The generation of hemiketal during the Grignard addition was due to the proximity of the carbonyl groups in the dione system[19]. The hemiketals produced such as **21** and **24** were further derivitized by *O*-allylation in the presence of NaH and allyl bromide in dry DMF to deliver the cage ethers **22** (76%) and **25** (80%) respectively. Afterwards, hydrogenation of ethers **22** and **25** with the aid of



Scheme II — Synthesis of cage heterocycle **16** bearing pyran ring system



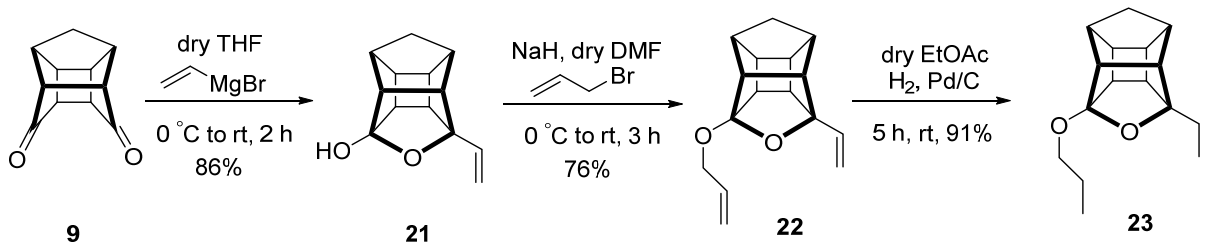
Scheme III — Synthesis of caged ether **20** containing pyran ring system

10% Pd-C in hydrogen atmosphere generated the alkyl cage derivatives **23** and **26** in an excellent yield (Scheme IV and Scheme V). Similarly, the dione **11** bearing spiro cyclopentane ring was treated with vinyl magnesium bromide (6 equiv.) in dry THF at RT to generate the hemiketal **27** (67%) along with the cage diol **28** (20%). Later on, the *O*-allylation of the hemiketal **27** in the presence of NaH with allyl bromide in dry DMF at RT for 3 h produced the ether derivative **29** in 75% yield. Finally, the unsaturated compound **29** was subjected to hydrogenation in the presence H_2/Pd-C to afford the cage alkyl ether **30** in good yield (Scheme VI). The structures of these compounds **27**, **28**, **29**, and **30** were fully supported by spectroscopic data (IR, ^{1}H, ^{13}C, ^{13}C-APT, and HRMS data). The structure of the compound **27** unambiguously confirmed by its single crystal X-ray diffraction studies (Figure 2)[20].

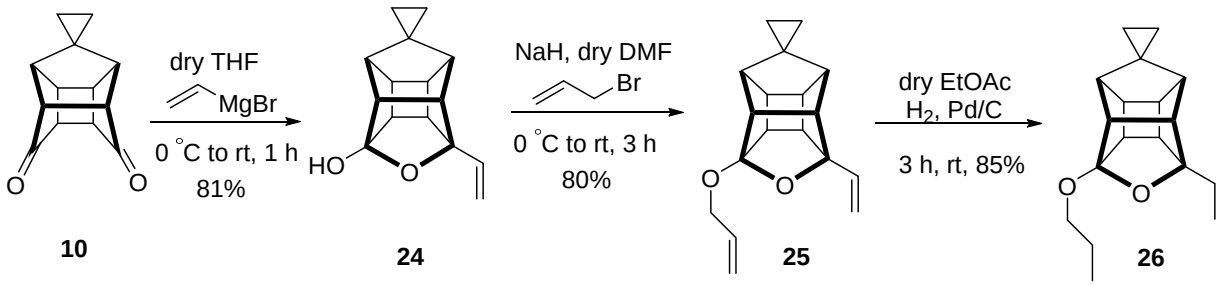
Experimental Section

Required chemicals, reagents, and solvents were purchased from the commercial suppliers and used as such without any further purification. Analytical TLC was performed on (10 × 5) glass plates coated with Acme's silica gel (GF-254) containing 13% calcium sulfate as a binder. Reactions were monitored by TLC using a suitable solvent system and visualization was done under UV light, exposure to iodine vapour and by dipping into a solution of $KMnO_4$. Air and moisture sensitive reactions were carried out in oven-dried glassware under nitrogen atmosphere using syringe-septum techniques. Acme's silica gel (100-200 mesh size) was used for column chromatography. Anhydrous dichloromethane (DCM), dimethylformamide (DMF), benzene, and toluene was distilled from P_2O_5 or CaH_2. Ethyl acetate (EtOAc) was dried over powdered K_2CO_3. Dry THF was distilled over sodium wire and benzophenone prior to use.

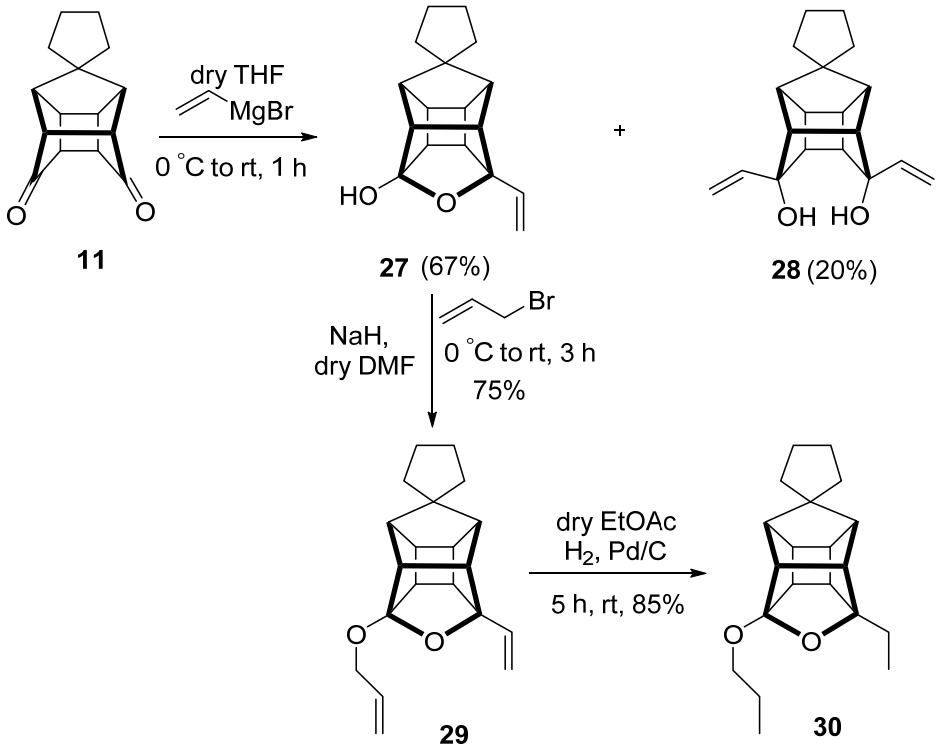
Infrared spectra (IR) were recorded on a Nicolet Impact-400 FTIR spectrometer. ^{1}H NMR (400 and 500 MHz), ^{13}C NMR, ^{13}C-APT NMR, DEPT 135 NMR (100.6 and 125.7 MHz) spectra were recorded on Bruker spectrometer and samples were prepared in $CDCl_3$ solvent. The chemical shifts are reported in parts per million (ppm) on delta scale with TMS as an internal standard and values for the coupling constants (*J*) are given in Hz. The multiplicities abbreviations are reported as s, d, t, q, ABq, dd, dt, td, and m for s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet and multiplet respectively. High-resolution mass spectra (HRMS) were recorded in positive ion electrospray ionization (ESI/Q-TOF) mode. All melting points were recorded on Veego VMP-CMP melting point apparatus and are uncorrected. Single crystal X-ray data were collected on diffractometer (Rigaku Saturn 724+) equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) and structure was solved by direct methods Shelxl-97 and refined by full-matrix least-squares against F^2 using Shelxl-97 software. Spiro dienes such as spiro



Scheme IV — Synthesis of oxa-cage **23** containing tetrahydrofuran ring system



Scheme V — Synthesis of oxa-cage **26** containing tetrahydrofuran ring system



Scheme VI — Synthesis of oxa-cage **30** containing tetrahydrofuran ring system

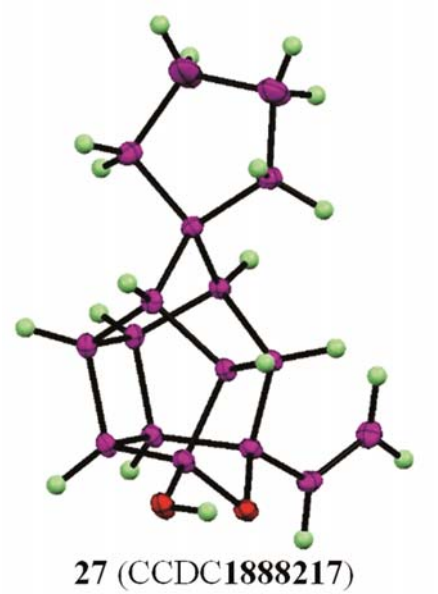


Figure 2 — X-ray crystal structure of compound **27**

[2.4]hepta-4,6-diene **7** and spiro [4.4]nona-1,3-diene **8** were prepared according to literature methods[16].

General procedure for allyl Grignard addition to cage diones 10 and 11

To a commercially available allylmagnesium bromide solution in dry THF was added the spiro cage diones **10** and **11** (250 mg, 1.25 mmol for **10** or 300 mg, 1.31 mmol for **11**) in dry THF by drop-wise addition under nitrogen at 0 °C. The resulting reaction mixture was stirred at RT for 1 h. After the reaction was complete by TLC monitoring, the reaction mixture was quenched with saturated aq. NH_4Cl solution and the resulting aqueous layer was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed by reduced pressure and the crude compound obtained was purified by silica gel column chromatography (8 to 10% EtOAc/petroleum ether as an eluent) to afford the pure **12**, **13** (inseparable mixtures of two compounds), and **17** as colourless solids.

Compound 12 and **13 (mixture of cage diol and hemiketal**):

White solid. Yield 279 mg (42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95-5.86 (m, 1H), 5.81-5.73 (m, 2H), 5.13-5.04 (m, 5H), 4.53 (brs, 1H), 2.94-2.90 (m, 2H), 2.82-2.73 (m, 6H), 2.69-2.60 (m, 3H), 2.52-2.50 (m, 4H), 2.40 (s, 1H), 2.15-2.11 (m, 1H), 2.06-2.02 (m, 1H), 1.98-1.96 (m, 1H), 1.77-1.69 (m, 3H), 0.52-046 (m, 4H), 0.36-0.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.8, 133.7, 118.3, 118.2, 117.9, 91.4, 77.3, 58.1, 57.9, 51.5, 50.5, 50.26, 50.21, 48.2, 48.1, 44.0, 43.2, 42.4, 42.1, 40.4, 39.8, 37.8, 30.4, 5.37,

5.30, 5.1, 4.7; HRMS (ESI): (for compound **12**) *m/z* Calcd for $C_{19}H_{24}NaO_2$ $[M+Na]^+$: 307.1669. Found: 307.1660; HRMS (ESI): (for compound **13**) *m/z* Calcd for $C_{16}H_{18}NaO_2$ $[M+Na]^+$: 265.1199. Found: 265.1191.

Cage diol 17: Colorless solid. m.p.98-100°C. Yield 356 mg (86%). IR (neat): 3184, 2966, 2865, 2364, 1639, 1457, 1282, 1159, 1077, 1042, 999, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.95-5.87 (m, 2H), 5.13-5.05 (m, 4H), 4.62 (brs, 2H), 2.64 (t, *J* = 2.1 Hz, 2H), 2.47 (s, 2H), 2.30 (s, 2H), 2.16-2.12 (m, 2H), 2.07-2.03 (m, 2H), 1.95 (s, 2H), 1.60-1.51 (m, 6H), 1.22 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.9, 118.1, 77.5, 56.0, 52.8, 49.4, 44.1, 42.6, 40.1, 32.6, 30.0, 25.9, 25.7; HRMS (ESI): *m/z* Calcd for $C_{21}H_{28}NaO_2$ $[M+Na]^+$: 335.1982. Found: 335.1982.

General procedure for vinyl Grignard addition to cage diones 9, **10**, **and 11**

To a commercially available vinylmagnesium bromide solution (6 eqviv., 1.0 M in THF) in dry THF was added to the spiro cage diones **9**, **10**, and **11** (200 mg, 1.14 mmol for **9** or 300 mg, 1.50 mmol for **10** or 400 mg, 1.75 mmol for **11**) in dry THF by drop-wise addition under nitrogen at 0 °C. The resulting reaction mixture was stirred at RT for 1-2 h. After completion the reaction (by TLC monitoring), the reaction mixture was quenched with saturated aq. NH_4Cl solution and the resulting aqueous layer was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed by reduced pressure and the crude compound obtained was purified by silica gel column chromatography (10 to 20% EtOAc/petroleum ether as an eluent) to afford the pure **21** and **28** as colourless liquids where **24** and **27** obtained as colourless solids.

Hemiketal 21: Colorless liquid. Yield 198 mg (86%). IR (neat): 3341, 2967, 2865, 1424, 1346, 1294, 1273, 1216, 1149, 1133, 1079, 1010, 909, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.13 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.21 (d, *J* = 1.5 Hz, 1H), 5.13 (d, *J* = 1.5 Hz, 1H), 2.78-2.71 (m, 3H), 2.68-2.61 (m, 4H), 2.50-2.49 (m, 1H), 1.88 (d, *J* = 10.0 Hz, 1H), 1.54 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.3, 114.6, 91.3, 58.9, 57.1, 49.1, 47.3, 45.3, 43.8, 43.2, 42.0, 41.9, 30.4; HRMS (ESI): *m/z* Calcd for $C_{13}H_{14}NaO_2$ $[M+Na]^+$: 225.0886. Found: 225.0882.

Hemiketal 24: Colourless solid. m.p.128-130°C. Yield 280 mg (81%). IR (neat): 3311, 2979, 1421, 1347, 1274, 1265, 1219, 1149, 1081, 1013, 984, 914, 871, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.14-6.07 (m, 1H), 5.20-5.09 (m, 2H), 2.95-2.64 (m, 6H), 1.98 (t, *J* = 4.8 Hz, 1H), 1.84 (t, *J* = 4.8 Hz, 1H), 0.53-0.46 (m, 2H), 0.37-0.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 114.6, 91.2, 58.8, 56.9, 51.5, 50.0, 49.4, 47.6, 42.2, 42.0, 39.5, 5.3, 5.1; HRMS (ESI): *m/z* Calcd for $C_{15}H_{16}NaO_2$ $[M+Na]^+$: 251.1043. Found: 251.1040.

Hemiketal 27: Colourless solid. m.p.116-118°C. Yield 302 mg (67%). IR (neat): 3356, 3055, 2953, 2860, 1643, 1455, 1423, 1346, 1265, 1221, 1182, 1132, 1081, 1013, 990, 957 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.14-6.07 (m, 1H), 5.21-5.10 (m, 2H), 2.85-2.62 (m, 6H), 2.24 (t, *J* = 4.8 Hz, 1H), 2.09 (t, *J* = 4.4 Hz, 1H), 1.51-1. 50 (m, 6H), 1.34-1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 114.5, 91.1, 68.1, 58.6, 56.7, 53.4, 51.7, 48.8, 47.1, 42.1, 41.8, 33.2, 31.0, 25.6, 25.4; HRMS (ESI): *m/z* Calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$: 283.1669. Found: 283.1674.

Cage diol 28: Colourless liquid. Yield 103 mg (20%). IR (neat): 3355, 2953, 2867, 1348, 1265, 1222, 917, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.87-5.81 (m, 2H), 5.16 (d, *J* = 1.5 Hz, 2H), 5.13 (d, *J* = 1.0 Hz, 2H) 2.75 (d, *J* = 5 Hz, 2H), 2.65 (d, *J* = 4.0 Hz, 2H), 2.38 (s, 2H), 1.97-1. 96 (m, 2H), 1.57-1.49 (m, 6H), 1.20 (t, *J* = 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 113.0, 76.9, 56.4, 53.0, 51.3, 41.2, 40.5, 32.5, 29.9, 25.8, 25.6; HRMS (ESI): *m/z* Calcd for $C_{19}H_{24}NaO_2$ $[M+Na]^+$: 307.1669. Found: 307.1669.

General procedure for synthesis of compounds 14, **15**, **18**, **22**, **25**, **and 29** ***via*** **allylation**

The diols and hemiketals **12**, **13**, **17**, **21, 24**, and **27** (0.39-0.96 mol, 1 equiv.) were added to a suspension of sodium hydride (7.69-1.56 mol, 10 to 4 equiv) in dry DMF (5 mL) under nitrogen. The reaction mixture was allowed to stir for 15 min at RT. Afterwards, allyl bromide (1.56-7.69 mol, 4 to 10 equiv) was added and the reaction mixture was stirred for 3-5 h. At the end of the reaction (TLC analysis) the crude material was quenched with saturated aq. NH_4Cl and the resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting

crude residue was subjected to silica gel column chromatography using 1-3% EtOAc/petroleum ether as an eluent to obtained pure compounds **14**, **15**, **18**, **22**, **25**, and **29** as colourless liquids.

14: Colorless liquid; started with a mixture of compounds **12** and **13** (279 mg). Yield 127 mg (58%). IR (neat): 3341, 3075, 3007, 2955, 2865, 1639, 1441, 1338, 1299, 1158, 1077, 1046, 998, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.03-5.95 (m, 1H), 5.93-5.77 (m, 2H), 5.30 (ABq, *J* = 17.2, 1.4 Hz, 1H), 5.16 (ABq, *J* = 10.4, 1.2 Hz, 1H), 5.08-4.96 (m, 4H), 4.08 (dd, *J* = 11.7, 5.6 Hz, 1H), 4.00 (dd, *J* = 11.7, 5.4 Hz, 1H), 2.72-2.67 (m, 3H), 2.59-2.57 (m, 1H), 2.45-2.41 (m, 1H), 2.37-2.29 (m, 2H), 2.16 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.04 (dd, *J* = 15.4, 7.8 Hz, 1H), 1.94 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.69-1.67 (m, 2H), 0.54-0.48 (m, 2H), 0.37-0.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 133.4, 133.2, 117.8, 117.4, 116.4, 83.6, 65.6, 50.8, 50.5, 50.2, 48.4, 43.7, 43.6, 40.8, 40.5, 40.2, 37.8, 30.3, 5.2, 4.8; HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}KO_2$ $[M+K]^+$: 363.1721. Found: 363.1720.

15: Colorless liquid. Starting with mixture of compounds **12** and **13** (279 mg). Yield 53 mg (55%). IR (neat): 3060, 2977, 2935, 1642, 1423, 1349, 1322, 1266, 1215, 1130, 1024, 950, 919, 877 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.98 (m, 1H), 5.82-5.74 (m, 1H), 5.28 (ABq, *J* = 3.3, 1.6 Hz, 1H), 5.16-5.03 (m, 3H), 4.24-4.16 (m, 2H), 2.96-2.92 (m, 1H), 2.90-2.85 (m, 1H), 2.80-2.74 (m, 3H), 2.64-2.60 (m, 1H), 2.53 (dd, *J* = 7.1, 1.2 Hz, 2H), 1.89 (t, *J* = 4.7, 1H), 1.76 (t, *J* = 4.8 Hz, 1H), 0.50-0.46 (m, 2H), 0.35-0.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 134.1, 121.3, 117.6, 116.7, 90.7, 67.1, 57.9, 55.1, 51.5, 50.2, 47.9, 45.0, 42.0, 39.8, 37.9, 5.3, 5.1; HRMS (ESI): *m/z* Calcd for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512. Found: 305.1510.

18: Colorless liquid. Starting with compound **17** (300 mg, 0.96 mmol). Yield 287 mg (85%). IR (neat): 3443, 2950, 1447, 1275, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H), 6.02-5.94 (m, 1H), 5.92-5.77 (m, 2H), 5.28 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.09-4.98 (m, 4H), 4.08-3.96 (m, 2H), 2.65 (d, *J* = 3.9 Hz, 3H), 2.49-2.47 (m, 1H), 2.41-2.37 (m, 1H), 2.34-2.25 (m, 2H), 2.16 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.06 (dd, *J* = 15.3, 7.7 Hz, 1H), 1.98-1.93 (m, 3H), 1.61-1.49 (m, 6H), 1.28-1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 133.4, 133.2, 117.7, 117.4, 116.3, 83.8, 65.5, 55.8, 53.1, 52.4, 49.7, 47.6, 43.8, 43.1, 40.2, 39.9, 37.9, 32.6, 30.0, 25.9, 25.7; HRMS (ESI): *m/z* Calcd for $C_{24}H_{32}NaO_2$ $[M+Na]^+$: 375.2995. Found: 375.2995.

22: Colorless liquid. Starting with compound **21** (150 mg, 0.74 mmol). Yield 137 mg (76%). IR (neat): 3055, 2957, 1430, 1344, 1324, 1265, 1215, 1132, 972, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.19-6.12 (m, 1H), 5.99-5.89 (m, 1H), 5.30-5.18 (m, 2H), 5.15-5.10 (m, 2H), 4.24-4.15 (m, 2H), 2.79- 2.62 (m, 6H), 2.57 (t, *J* = 3.7 Hz, 1H), 2.48 (t, *J* = 4.8 Hz), 1.88 (d, *J* = 10.5 Hz, 1H), 1.53 (dt, *J* = 10.5, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 134.8, 121.6, 116.6, 114.5, 91.2, 67.1, 58.7, 54.6, 48.9, 45.2, 44.4, 43.6, 43.4, 42.1, 41.7; HRMS (ESI): *m/z* Calcd for $C_{16}H_{18}KO_2$ $[M+K]^+$: 281.0938. Found: 281.0938.

25: Colorless liquid. Starting with compound **24** (150 mg, 0.65 mmol). Yield 139 mg (80%). IR (neat): 2965, 2878, 1462, 1357, 1298, 1274, 1152, 1130, 1030, 962, 935, 911, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.16-6.09 (m, 1H), 5.94-5.85 (m, 1H), 5.26-5.06 (m, 4H), 4.22- 4.12 (m, 2H), 2.95- 2.68 (m, 6H), 1.88 (t, *J* = 4.7 Hz, 1H), 1.81 (t, *J* = 4.7 Hz, 1H), 0.50-0.43 (m, 2H), 0.35-0.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 134.7, 121.4, 116.4, 114.4, 91.0, 66.9, 58.5, 54.4, 51.3, 49.7, 49.2, 44.7, 42.2, 41.8, 39.7, 5.2, 5.0; HRMS (ESI): *m/z* Calcd for $C_{18}H_{20}NaO_2$ $[M+Na]^+$: 291.1356. Found: 291.1356.

29: Colorless liquid. Starting with compound **27** (100 mg, 0.39 mmol). Yield 87 mg (75%). IR (neat): 3064, 2945, 1652, 1264, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.19-6.13 (m, 1H), 5.98-5.90 (m, 1H), 5.30-5.10 (m, 4H), 4.24- 4.15 (m, 2H), 2.89- 2.69 (m, 6H), 2.18 (t, *J* = 4.6 Hz, 1H), 2.09 (t, *J* = 4.6 Hz, 1H), 1.57-1.49 (m, 6H), 1.35-1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 134.8, 121.5, 116.6, 114.5, 91.1, 68.4, 67.1, 58.4, 54.4, 53.2, 51.5, 48.7, 44.1, 42.1, 41.7, 33.2, 31.0, 25.6, 25.3; HRMS (ESI): *m/z* Calcd for $C_{20}H_{24}NaO_2$ $[M+Na]^+$: 319.1669. Found: 319.1668.

General procedure for synthesis of compounds 16 and 19 *via* RCM protocol

To a stirred solution of RCM precursors such as tri-allyl derivatives **14** and **18** (0.30-0.71 mmol, 1 equiv.) in dry DCM (15 mL) were degassed with nitrogen for 15 min and then added G-II catalyst (5 mol%). Afterwards, the reaction mixture was allowed to stir at RT for 5-7 h. After completion of the reaction monitored by TLC, the solvent was removed under vacuo and the crude mixture was subjected to column

chromatography (silica gel, 100 mesh, 8-10% EtOAc/PE as an eluent) to give the cyclized products **16** and **19** as colorless liquids.

16: Colorless liquid. Prepared from compound **14** (100 mg, 0.30 mmol). Yield 77 mg (84%). IR (neat): 3352, 3074, 2955, 2864, 1639, 1440, 1341, 1300, 1193, 1158, 1076, 1046, 997, 910, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 6.06-5.88 (m, 1H), 5.70 (s, 2H), 5.07-4.99 (m, 2H), 4.17 (s, 2H), 2.80-2.73 (m, 4H), 2.48-2.41 (m, 4H), 2.19-2.11 (m, 2H), 1.99-1.94 (m, 2H), 0.57-0.50 (m, 2H), 0.39-0.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 124.1, 123.9, 116.6, 79.5, 63.9, 51.6, 51.2, 50.7, 50.3, 50.0, 44.0, 43.7, 43.5, 42.8, 40.8, 40.0, 38.4, 34.0, 30.5, 5.2, 4.8; HRMS (ESI): *m/z* Calcd for $C_{20}H_{24}NaO_2$ $[M+Na]^+$: 319.1669. Found: 319.1667.

19: Colorless liquid. Prepared from compound **18** (250 mg, 0.71 mmol). Yield 195 mg (86%). IR (neat): 3319, 3041, 2954, 2857, 1638, 1441, 1391, 1344, 1266, 1182, 1156, 1072, 1047, 1004, 909, 866, 812 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 1H), 6.01-5.90 (m, 1H), 5.67 (s, 2H), 5.05-4.98 (m, 2H), 4.13 (s, 2H), 2.73-2.60 (m, 3H), 2.41-2.29 (m, 3H), 2.16-2.04 (m, 2H), 1.98-1.93 (m, 3H), 1.77-1.72 (m, 1H), 1.59-1.48 (m, 6H), 1.24-1.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 124.0, 123.9, 116.5, 79.6, 63.8, 56.0, 52.4, 52.2, 50.4, 49.9, 43.8, 42.9, 40.4, 39.7, 37.7, 34.1, 32.5, 30.0, 25.8, 25.6; HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}NaO_2$ $[M+Na]^+$: 347.1982. Found: 347.1982.

General procedure for the synthesis of 20, **23**, **26**, **and 30** ***via*** **catalytic hydrogenation**

10 mol% Pd/C was added to a stirred solution of allyl derivatives such as **19**, **22, 25,** and **29** (0.33-0.46 mmol, 1 equiv.) in dry EtOAc (10 mL). Then the resulting reaction mixture was allowed to stir at RT for 3-5 h under hydrogen (1 atm). After completion of the reaction (TLC analysis), the reaction mixture was filtered through Celite pad and washed with EtOAc (10 mL). The combined washings and the filtrate was evaporated under vacuum and the resulting crude material was subjected to silica gel column chromatography using 1-5% EtOAc/PE as an eluent to yield the pure hydrogenated products **20** as white solid and **23, 26,** and **30** as colourless liquids.

20: Colorless solid. Prepared from compound **19** (150 mg, 0.46 mmol). Yield 143 mg (94%). IR (neat): 3310, 2955, 2871, 1451, 1277, 1169, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 1.1 Hz, 1H), 3.80-3.77 (m, 1H), 3.66-3.60 (m, 1H), 2.81-2.77 (m, 1H), 2.60 (s, 2H), 2.46-2.43 (m, 1H), 2.38-2.34 (m, 1H), 2.32-2.29 (m, 1H), 1.92-1.87 (m, 2H), 1.70 (s, 1H), 1.65-1.49 (m, 11H), 1.44-1.34 (m, 2H),1.32-1.19 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 81.3, 76.8, 65.0, 55.9, 52.5, 52.3, 49.6, 48.9. 43.6, 41.9, 40.4, 39.6, 38.1, 33.5, 32.6, 30.1, 25.9, 25.7, 25.4, 20.0, 15.9, 15.0; HRMS (ESI): *m/z* Calcd for $C_{22}H_{32}NaO_2$ $[M+Na]^+$: 351.2295. Found: 351.2299.

23: Colorless liquid. Prepared from compound **22** (100 mg, 0.41 mmol). Yield 93 mg (91%). IR (neat): 2966, 2932, 2867, 1461, 1361, 1330, 1300, 1269, 1208, 1151, 1130, 1029, 961, 936, 912, 863 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.60-3.53 (m, 2H), 2.73-2.64 (m, 3H), 2.60-2.48 (m, 4H), 2.39 (t, *J* = 4.7 Hz 1H), 1.83 (d, *J* = 10.4 Hz, 1H), 1.79-1.73 (m, 2H), 1.60 (td, *J* = 14.5, 7.3 Hz, 2H), 1.49 (d, *J* = 10.3 Hz, 1H), 0.89 (dt, *J* = 9.4, 7.5 Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ 121.1, 92.0, 67.6, 57.6, 54.8, 47.1, 45.3, 44.4, 43.6. 43.4, 42.0, 41.7, 26.0, 23.4, 10.5, 9.4; HRMS (ESI): *m/z* Calcd for $C_{16}H_{22}NaO_2$ $[M+Na]^+$: 269.1512. Found: 269.1510.

26: Colorless liquid. Prepared from compound **25** (100 mg, 0.37 mmol). Yield 87 mg (85%). IR (neat): 3064, 2969, 2877, 1463, 1361, 1330, 1288, 1266, 1220, 1144, 1127, 1081, 1029, 941, 920, 878 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.59-3.53 (m, 2H), 2.93-2.82 (m, 2H), 2.77-2.67 (m, 3H), 2.58-2.54 (m, 1H), 1.85 (q, *J* = 4.9 Hz, 1H), 1.81-1.71 (m, 3H), 1.58 (dt, *J* = 14.4, 7.3 Hz, 2H), 0.88 (dt, *J* = 7.4, 5.3 Hz, 6H), 0.49-0.43 (m, 2H), 0.33-0.26 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 121.1, 92.0, 67.6, 57.6, 54.8, 51.6, 49.8, 47.5, 44.9, 42.3, 42.0. 39.8, 26.0, 23.4, 10.5, 9.3, 5.2, 5.0; HRMS (ESI): *m/z* Calcd for $C_{18}H_{24}NaO_2$ $[M+Na]^+$: 295.1669. Found: 295.1669.

30: Colorless liquid. Prepared from compound **29** (100 mg, 0.33 mmol). Yield 85 mg (85%). IR (neat): 3068, 2968, 2878, 1462, 1356, 1331, 1286, 1269, 1215, 1141, 1128, 1082, 1028, 988, 940, 921, 878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.57-3.56 (m, 2H), 2.82-2.51 (m, 6H), 2.10 (t, *J* = 4.7 Hz, 1H), 1.98 (t, *J* = 4.7 Hz, 1H), 1.79-1.71 (m, 2H), 1.62-1.47 (m, 8H), 1.33-1.25 (m, 2H), 0.89 (q, *J* = 7.0 Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ 121.0, 92.0, 68.2, 67.5, 57.3, 54.6, 53.4, 51.5, 46.9, 44.1, 42.0, 41.8, 33.2. 31.0, 26.0, 25.6, 25.3, 23.4, 10.5, 9.4; HRMS (ESI): *m/z* Calcd for $C_{20}H_{28}NaO_2$ $[M+Na]^+$: 323.1982. Found: 323.1984.

Conclusions

In conclusion, we have successfully synthesized various cage oxygenated compounds containing tetrahydrofuran and pyran ring system. In this sequence, we used Grignard addition and RCM as key steps. These oxa-cages were generated from cheap and readily available starting materials such as 1,4-hydroquinone and dicyclopentadiene. Transannular cyclization provided an easy access to oxa-cage derivatives *via* hemiketal generation during Grignard addition.

Supplementary Information

The supporting information is available free of charge on the journal website. Characterization data of ^{1}H, ^{13}C, ^{13}C-APT, DEPT-135 NMR spectra of all new products (PDF) and X-ray refinement data for **27** (ORTEP diagrams) are available in supplementary information (SI) file.

Acknowledgements

The authors greatly appreciate the Defence Research and Development Organisation (DRDO, Grant NO. ARDB/01/1041849/M/1) and Department of Science and Technology (DST, Grant NO. SR/S2/JCB-33/2010) New Delhi, India for financial support. The authors gratefully acknowledge Praj Industries for providing the Pramod Chaudhari Chair Professorship (Green Chemistry). The authors also acknowledge Mr. Darshan S Mhatre and Ms. Saima A for their help in collecting X-ray data and structure refinement. SRC thanks University Grants Commission (UGC), New Delhi for the Senior Research Fellowship (SRF).

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20 CCDC-1888217 (for **27**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif. For ORTEPs of product **27**, please see the supplementary information (SI) file.