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Synthetic Possibilities for Hemilabile Ligands: A Case Study of Decacyclo[10.8.1^{5,8}.0^{2,11}.0^{4,9}.0^{13,20}.0^{15,18}]-heneicosane-3,10,14,19-tetraone

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ABSTRACT

As proof of the synthetic possibilities for hemilabile ligands the chemistry of decacyclo[10.8.1^{5,8}.0^{2,11}.0^{4,9}.0^{13,20}.0^{15,18}]heneicosane-3,10,14,19-tetraone (5) was investigated. Reacting 5 with ethylene glycol under acid conditions gave the expected di-acetal protected ketone (6) as four possible isomers. Reduction of these isomers to produce the dialcohol ketal (7) was only possible with $LiAlH_4$, after $NaBH_4$, Luche's, and Meerwein-Ponndorf-Verley reduction methods were unsuccessful. Deprotection of 7 to the hydroxyl ketone (8) derivative was not possible under reflux with a 25% HCl solution. To evaluate the reactivity of 5, and investigate alternative synthetic routes to Grubbs pre-catalysis, 5 was treated with the reducing agents i) $NaBH_4$, ii) glacial AcOH, Zn and iii) 80% AcOH/H_2O/Zn mixture, which resulted in various reduction products. The AcOH/H_2O/Zn reduction resulted in various products and a further investigation into the mechanism is given within this report.

KEYWORDS

Pentacycloundecane, Grubbs pre-catalyst, Cyclo-addition, Hemilabile ligands

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INTRODUCTION

As part of a program that is concerned with the design and synthesis of novel Grubbs-type pre-catalysts, containing the hemilabile pyridinyl alcholato ligand for the metathesis of 1-alkene derivates, these ligands convey increased thermal stability of the pre-catalysts and decreased the extent of side reactions.[1-7] Incorporation of an alicyclic moiety in the hemilable ligands may further improve the thermal stability of these Grubbs-type pre-catalysts.[8] Filipescu[9] and Kusher[10] were able to synthesize the Diels-Alder adduct (**2**) from the cyclo-addition of cyclopentadiene and 1,4-naphthoquinone (**1**) by intramolecular photocyclization to produce the expected hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-dione (**3**, **Scheme 1**). Besides this compound's thermal stability,[11] and thus the potential to bestow additional stability to the Grubbs-type pre-catalysts, it can also undergo further Diels-Alder reactions.[12] Various researchers have shown that **3** can react exclusively either from the cyclobutane face or from the ketone face of the diene, depending on the nature of dienophiles (**Figure 1**).[12-16] In 1987 Coxon *et al.*[12] showed that due to the steric bulk of the *p*-benzoquinone, it reacts exclusively on the carbonyl face to produce the Diels-Alder adduct (**4**). If **4** is then irradiated with UV it undergoes a cyclization reaction to form the decacyclo-[10.8.1^{5,8}.0^{2,11}.0^{4,9}.0^{13,20}.0^{15,18}]heneicosane-3,10,14,19-tetraone (**5**, **Scheme 1**).[10, 17, 18]

It was envisaged that cage compound **5**, be used as a substrate for the synthesis of bidentate or monodentate hemilabile ligands for Grubbs-type pre-catalysts. However, before the hemilabile ligands are to be synthesized, an understanding of the chemistry and reactions of **5** is required. This paper will present the synthesis, characterization, and chemistry of derivatives of **5**.

EXPERIMENTAL

The quantum-chemical calculations were carried out by density functional theory (DFT) since it usually gives realistic geometries, relative energies, and vibrational frequencies for transition metal compounds. All calculations were performed with the DMol^3 DFT code as implemented in Accelrys Materials Studio® 4.2 using GGA/DNP/PW91 functional. The convergence criteria for these optimisations consisted of threshold values of 2 x 10^{-5} Ha, 0.004 Ha/Å and 0.005 Å for energy, gradient and displacement convergence, respectively, while a self-consistent field (SCF) density convergence threshold value of 1x10^{-5} Ha was specified. The electron density,

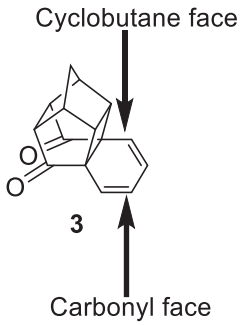
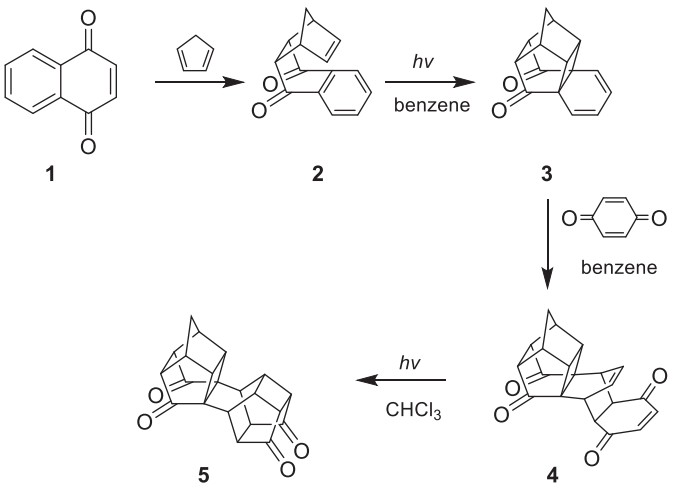


Figure 1: π-Facial selectivity of **3**.[12]



Scheme 1: The reaction scheme for the synthesis of **5**.

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frontier orbitals and Fukui-function was also calculated. Two computer systems were used for calculations, viz.

- HP Proliant CP4000 Linux Beowulf cluster, with 12 calculation nodes consisting of 4 HP DL145, 2 x 2.8 GHz AMD Opteron 64 CPU, 2 GB RAM, running Redhat Enterprise Linux 4
- HP Compaq dx2200 MT Intel® Core™2 Duo T7300 CPU @ 2.00 GHz, 3 GB RAM running Microsoft Windows XP Professional with service pack 2.

Experimental data were recorded using the following instruments: Infrared spectra (KBr discs) were recorded on a Bruker Tensor 27-IR spectrometer; EI mass spectra were obtained at 70 eV on a Micromass Autospec-TOF mass spectrometer and FAB mass spectra were obtained on a VG 70-70E magnetic sector analyser with matrix of nitrobenzyl alcohol (NBA). High-resolution MS spectra were obtained on a Bruker Micro-QTof II with an APCI source. NMR data were collected on a Varian Gemini-300 NMR spectrometer and a Bruker 600MHz Avance Ultrashield Plus. Melting points were determined using a Büchi Melting Point B-540 apparatus. Melting points are uncorrected.

Synthesis of 2:[10]

10 g (63.28 mmol) 1,4-naphthoquinone (**1**) was dissolved in 800 ml methanol, after which 10 g of activated carbon was added and stirred for 10 minutes on a hot plate. The solution was filtered to yield a yellow solution of 1,4-naphthoquinone. To this solution 2.5 g (6.86 mmol) cetyl trimethylammonium bromide (CTAB) was added, followed by the addition of 25 ml (297.28 mmol) freshly distilled cyclopentadiene. After 3 hours of stirring in the dark at room temperature, the solution was concentrated to a small volume and was poured into 500 ml water, upon which a white to light-peach coloured precipitate formed. The precipitate was filtered and washed with 10 ml cold water and 5 ml methanol under vacuum suction, successively. The crystals were dried to yield 12.03 g (53.69 mmol, 85 %) as a white powder. Melting point: 101 °C. **IR (KBr)**: ν_{max} 3443, 2992, 1680, 1589 and 1270 cm^{-1}. **MS (EI)**: M^+ *m/z* 224. **NMR**: data were identical to the authentic samples.

Synthesis of hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-dione (3):[10]

6 g (26.78 mmol) of the Diels-Alder adduct **2** was dissolved in 300 ml benzene and irradiated with a medium-pressure UV lamp for 2 hours in Pyrex vessels. After 2 hours the benzene was removed by reduced pressure which afforded an off-white solid, which was recrystallized from n-heptane to yield white-light yellow crystals (5.2 g, 23.21 mmol, 87%). Melting point: 109 °C. **IR (KBr)**: ν_{max} 3443, 2984, 1745, 1089 and 704 cm^{-1}. **MS (EI)**: M^+ *m/z* 224. **^{13}C-NMR [$CDCl_3$, 150 MHz]**: δ_C 210.33 (S, C=O), 124.67 (D, HC=CH), 119.73 (D, HC=CH), 54.538 (D), 51.57 (D), 50.10 (S), 44.16 (D), 38.91 (T, CH_2) ppm. **^{1}H NMR [$CDCl_3$, 600MHz]**: δ_H 5.96-5.90 (m, HC=CH), 5.38-5.31 (m, HC=CH), 3.31-3.0 (s), 2.98-2.93 (m), 2.77-2.76 (s), 1.98-1.93 (d) and 1.74-1.70 (d) ppm.

Synthesis of octacyclo[10.6.2.^{15,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,18}]hene-icosa-15,19-diene-3,10,14,17-tetraone (4):[12]

4.8 g (21.42 mmol) of **3** was dissolved in 350 ml benzene to which 2.32 g (21.48 mmol) para-benzoquinone was added and refluxed for 20 h after which a yellow solid precipitated. The solid was filtered and washed with 40 ml, 50% water/methanol solution to remove any unreacted reactants. The yellow crystals were dried to yield 6.79 g (20,45 mmol, 95 %) of **4**. Mp: 265°C, Lit. Mp: 265 – 267 °C. **IR (KBr)**: ν_{max} 2924, 1744, 1716, 1666, 1276 and 1062 cm^{-1}. **MS (EI)**: M^+ *m/z* 332, **HRMS (APCI):** m/z calc. for $C_{21}H_{16}O_4$ [M^+]: 332.1043, found: 332.1056. **^{13}C-NMR [$CDCl_3$, 75 MHz]**: δ_C 211.96 (S, C=O), 197.75 (S, C=O), 141.43 (D, HC=CH), 133.79 (D, HC=CH), 55.99 (D), 53.15 (S), 43.47 (D), 43.39 (D), 41.66 (D), 40.68 (T, CH_2), 34.28 (D) ppm. **^{1}H NMR [$CDCl_3$, 300MHz]**: δ_H 6.63 (s, HC=CH), 6.38-6.36 (m, HC=CH), 3.57-3.56 (s), 3.47-3.44 (m), 2.89-2.87 (t), 2.74-2.73 (d), 2.64-2.63 (d), 1.97-1.93 (d, CH_2), 1.84-1.80 (d, CH_2) ppm.

Synthesis of decacyclo[10.8.1^{5,8}.0^{2,11}.0^{4,9}.0^{13,20}.0^{15,18}]hene-icosane-3,10,14,19-tetraone (5):[17]

6 g (18.07 mmol) of **4** was dissolved in 600 ml chloroform and irradiated with a medium-pressure UV lamp for 3 hours in a Pyrex vessel. After 3 h a white solid precipitated which was filtered and washed with chloroform to remove any unreacted reagents (4.31 g, 12.98 mmol, 95 %). Mp: 371°C, Lit. Mp: >360°C. **IR (KBr)**: ν_{max} 2984, 1736, 1709, 1347, 1301, 1237, 1145 and 1095 cm^{-1}. **MS (EI)**: M^+ *m/z* 332, **HRMS (APCI):** m/z calc. for $C_{21}H_{16}O_4$ [M^+]: 332.1043, found: 332.1083. **^{13}C-NMR [$CDCl_3$, 75 MHz]**: δ_C 210.50 (S, C=O), 209.22 (S, C=O), 55.12 (D), 46.77 (S), 45.53 (D), 43.99 (D), 43.93 (D), 40.92 (D), 40.74 (T, CH_2), 33.12 (D), 31.81 (D) ppm. **^{1}H NMR [$CDCl_3$, 300MHz]**: δ_H 3.38-3.34 (m), 3.15-3.13 (m), 3.14-2.96 (m), 2.86-2.84 (s), 2.80-2.79 (s), 2.23-2.20 (m), 2.08-2.07 (d, CH_2), 1.96-1.92 (d, CH_2) ppm.

Synthesis of oxa-ketal (6):[19, 20]

5 g (15.6 mmol) of **5**, 1.9 g (1.7 ml, 30.63 mmol) ethylene glycol and 0.3 g (1.74 mmol) *p*-toluenesulfonic acid (PTSA) was added in a conical flask equipped with a magnetic stirrer and a Dean-Stark apparatus and refluxed in 300 ml toluene for 12 h. After this time, the toluene was removed under reduced pressure and a brown solid precipitated. The solid was washed with cold water and 10 ml cold methanol, to remove the unreacted ethylene glycol and PTSA, which liberated light brown-white crystals. The crystals were dried to yield 5.66 g (13.47 mmol, 89 %) of **6**. Mp: 253 °C. **IR (KBr)**: ν_{max} 2970, 1743, 1332, 1111 and 942 cm^{-1}. **MS (EI)**: M^+ *m/z* 420, **HRMS (APCI):** m/z calc. for $C_{25}H_{25}O_6$ [M^++H]: 421.1646, found: 421.1653. **^{13}C-NMR [$CDCl_3$, 150 MHz]**: δ_C 214.04 (S, C=O), 213.94 (S, C=O), 213.41(S, C=O), 212.96 (S, C=O), 113.55 (S, O-C-O), 113.31 (S, O-C-O), 113.04 (S, O-C-O), 112.94 (S, O-C-O), 65.81 (T, O-CH_2), 65.65 (T, O-CH_2), 65.43 (T, O-CH_2), 65.31 (T, O-CH_2), 65.26 (T, O-CH_2), 65.24 (T, O-CH_2), 64.56 (T, O-CH_2), 64.27 (T, O-CH_2), 54.23 (D), 54.11 (D), 51.18 (D), 46.84 (S), 46.74 (S), 44.49 (D), 44.44 (D), 44.19 (D), 43.86 (D), 43.41 (D), 43.36 (D), 42.88 (D), 42.64 (D), 42.55 (D), 42.45 (D), 42.38 (D), 42.20 (D), 41.86 (D), 39.03 (T, CH_2 of bridge), 38.98 (D), 38.19 (D), 35.59 (D), 35.24 (D), 32.79 (D), 32.04 (D), 31.47 (D), 31.10 (D), 30.33 (D) ppm.

Synthesis of the hydroxyl-ketal (7):

Method 1:

2 g of the diketal (**6**) was dissolved in 100 ml ethanol. The solution was cooled to 0 °C by means of an ice bath. 1.5 g sodium borohydride (NaBH4) was added in small amounts so that the temperature did not rise above 5 °C. After addition, the reaction was stirred for 2 h in the ice bath, after which it was quenched with the addition of a solution of 50 ml water and 5 ml HCl. The resulting mixture was subjected to rotary evaporation to remove the excess ethanol. Subsequently, the solution was extracted three times with 50 ml CH_2Cl_2. The combined organic layers were washed with a small amount of water and successively with brine. The organic layer was dried with $MgSO_4$ and filtered, after which the solvent was removed by rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (**6**) as the only compound present.

Method 2 (Luche reaction):[21, 22]

2 g of the diketal (**6**) was dissolved in a 0.4 M solution of $CeCl_3{\cdot}7H_2O$ in ethanol. The solution was cooled to 0 °C in an ice bath. 1.5 g sodium borohydride (NaB14) was added in small amounts so that the temperature did not rise above 5 °C. After addition, the reaction was stirred for 2 h in the ice bath, after which it was quenched with the addition of a solution of 50 ml water and 5 ml HCl. The resulting

mixture was subjected to rotary evaporation to remove the excess ethanol. Subsequently, the solution was extracted three times with 50 ml CH_2Cl_2. The combined organic layers were washed with a small amount of water and successively with brine. The organic layer was dried with $MgSO_4$ and filtered, after which the solvent was removed by rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (**6**) as the only compound present.

Method 3 (Meerwein-Ponndorf-Verley reduction):[23]

3 g of **6** and 5 g of isopropanol was added to 100 ml toluene to which 0.3 g $Al(O^iPr)_3$ was added. The reaction mixture was refluxed at 60 °C for 96 h. The solution was cooled and extracted with 3x75 ml CH_2Cl_2 and the combined organic layers were washed with 100 ml water. The organic layer was dried with $MgSO_4$ and concentrated by means of rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (**6**) as the only compound present.

Method 4:[20, 24]

1.2 g (31.62 mmol) $LiAlH_4$ was added over a period of 30 minutes to a stirred solution of 4 g (9.52 mmol) of **7** in 100 ml dry THF. After addition, the solution was refluxed for 30 minutes and left to cool to room temperature. 200 ml H_2O was added to decompose the reaction mixture. This solution was extracted with 3 × 50 ml dichloromethane, washed with water, dried over $MgSO_4$ and the solution was condensed *in vacuo*. The brown oil that formed was dissolved in 2 ml dichloromethane and added to 20 ml petroleum ether. The milky solution was poured into a clean beaker and left to evaporate to yield 3.8 g (8.96 mmol, 94%) of **7** as a white powder. Mp: 223°C. **IR (KBr)**: ν_{max} 3427, 2966, 2890, 1468, 1454, 1320, 1282, 1269, 1150, 1102, 1068, 1027, 1003, 956 and 581 cm^{-1}. **MS (EI)**: M^+ *m/z* 424, **HRMS (APCI):** m/z calc. for $C_{25}H_{29}O_6$ $[M^+H]$: 425.1959, found: 425.1987. **^{13}C-NMR [$CDCl_3$, 150 MHz]**: δ_C 115.70 (S, O-C-O), 115.69 (S, O-C-O), 115.12 (S, O-C-O), 115.07 (S, O-C-O), 75.67 (D), 73.79 (D), 65.76 (T, O-CH_2-R), 65.60 (T, O-CH_2-R), 65.08(T, O-CH_2-R), 64.94 (T, O-CH_2-R), 64.06 (T, O-CH_2-R), 63.86 (T, O-CH_2-R), 62.34 (T, O-CH_2-R), 62.08(T, O-CH_2-R), 47.70 (D), 47.63 (D), 47.46 (D), 47.29 (D), 44.58 (S), 43.89 (S), 43.71 (S), 43.63 (D), 43.47 (D), 43.16 (S), 41.89 (D), 41.83 (D), 41.26 (D), 41.07 (D), 40.96 (D), 40.57 (D), 40.37 (D), 39.80 (D), 39.61 (D), 39.31 (D), 38.25 (D), 38.22 (D), 38.00 (D), 36.93 (D), 35.57 (D), 35.49 (D), 34.89 (T, CH_2 Bridge), 34.87 (T, CH_2 Bridge), 34.74 (D), 34.62 (D), 32.70 (D), 31.38 (D) ppm. **^{1}H NMR [$CDCl_3$, 600MHz]**: δ_H 6.13-6.00 (dd, OH); 5.07-5.01 (dd, OH).

Synthesis of hydroxy-ketone (8):[25]

1 g (2.36 mmol) of **7** was added to a stirring solution of a 24% HBr solution. This was refluxed for 12 hours after which the hot solution was poured over ice water. The solution was extracted with 3 × 50 ml CH_2Cl_2, washed with water, and dried over $MgSO_4$. The CH_2Cl_2 was concentrated on a rotary evaporator to yield a small amount of clear oil. The oil was dissolved in 1 ml CH_2Cl_2 and poured into 20 ml petroleum ether. A white solid precipitated and was filtered off to yield 116 mg (0.35 mmol, 14%) of **8**. **IR (KBr)**: ν_{max} 3423, 2964, 2867, 1720, 1333, 1304, 1276, 1150, 1131, 1076, 1056, 1004 and 923 cm^{-1}. **MS (EI)**: M^+ *m/z* 336, **HRMS (APCI):** m/z calc. for $C_{21}H_{20}O_4$ $[M^+H]$: 336, found: 336. **NMR** data were inconclusive in the identification of the product, due to solubility problems.

Reaction of 5 with Zn/AcOH/H_2O:[26]

20 g (305.90 mmol) Zinc was activated with a small amount of hydrochloric acid (HCl), after which the Zn was washed with acetone and subsequently with water. The activated Zn was added to a stirred solution of 100 ml 80 % acetic acid/H_2O (AcOH) and 1 g (3.01 mmol) of **5**. This solution was refluxed for 5 h, after which it was subjected to rotary evaporation until only a small amount of acetic acid was left and a white solid precipitated. This solid was filtered off and water was added to the mother liquor after which **30** precipitated (96 mg). The remaining filtrate was dissolved in water and extracted with 3 × 50 ml CH_2Cl_2. The combined organic layers were washed with water and dried over $MgSO_4$. The CH_2Cl_2 was concentrated on a rotary evaporator to yield **33** and **35** (558 mg) as a white solid. **30:** Mp: 281°C, **IR (KBr)**: ν_{max} 3400, 2961, 2874, 1741, 1355, 1296, 1226, 1196, 1134, 1071, 1013, 951, 908, 864, 643 and 499 cm^{-1}. **MS (FAB)**: $[M]^+$ *m/z* 352. **^{13}C-NMR [DMSO, 150 MHz]**: δ_C 215.13 (S, C=O), 109.54 (S, O-C-O), 108.10 (S, O-C-O), 84.12 (S), 55.32 (D), 49.85 (D), 49.71 (D), 49.66 (D), 49.52 (D), 47.89 (D), 47.72 (D), 47.63 (S), 45.44 (D), 44.76 (D), 43.58 (D), 38.92 (D), 38.57 (D), 37.96 (D), 37.05 (D), 36.75 (D), 31.72 (D) ppm. **^{1}H NMR [DMSO, 300MHz]**: δ_H 6.55 (s), 5.12 (s), 3.35 (s), 2.54-1.46 (a series of multiples), 1.48-1.46 (d, CH_2 – Bridge), 1.38-1.36 (d, CH_2 – Bridge) ppm. **31 and 32:** Mp: 278°C **IR (KBr)**: ν_{max} 3307, 2969, 1740, 1332, 1273, 1228, 1156, 1066, 1013, 913, 850, 709 and 540 cm^{-1}. **MS (FAB)**: $[M\text{-}H_2O+H]^+$ *m/z* 337. **^{13}C-NMR [DMSO, 150 MHz]**: δ_C 215.10 (S, C=O), 215.04 (S, C=O), 116.06 (S, O-C-O), 114.69 (S, O-C-O), 84.25 (S), 84.20 (S), 77.71 (D), 76.36 (D), 55.31 (S), 55.25 (S), 49.88 (D), 49.86 (D), 49.70 (D), 49.66 (D), 48.11 (D), 47.93 (D), 47.91 (D), 47.78 (D), 47.70 (D), 47.66 (D), 45.50 (D), 45.42 (D), 45.25 (D), 45.08 (D), 44.74 (D), 44.70 (D), 42.77 (D), 41.45 (D), 40.73 (D), 40.04 (D), 38.74 (D), 38.67 (D), 38.56 (D), 38.53 (D), 38.03 (D), 37.53 (D), 37.48 (D), 37.03 (T, CH2 – Bridge), 37.01 (T, CH2 – Bridge), 35.52 (D), 32.54 (D), 30.33 (D) ppm. **^{1}H NMR [DMSO, 300MHz]**: δ_H 6.66 (s), 5.22 (s), 4.35-4.33 (t), 4.26-4.24 (t), 3.33 (s), 2.72 -2.71 (t), 2.67-2.66 (t), 2.61-2.56 (m), 2.52-2.40 (series of multiples), 2.36-2.34 (d), 2.26-2.22 (m), 2.14-1.88 (series of multiples), 1.75-1.72 (m), 1.48-1.46 (d, CH_2-Bridge), 1.38-1.36 (d, CH_2-Bridge) ppm.

Synthesis of the transannulated hydrate (25):

1g of **5** was added to a stirred solution of glacial acidic acid and zinc. After 24h of reflux, a white solid precipitated. The solution was cooled, filtered, and dried to yield 1.01 g of **25** as the exclusive product (96%). **IR (KBr)**: ν_{max} 3412, 2984, 1736, 1709, 1348, 1302, 1237, 1201, 1146, 1096, 911 and 575 cm^{-1}. **MS (FAB)**: $[M+H]^+$: *m/z* 351. **^{13}C-NMR [DMSO, 150 MHz]**: δ_C 213.48 (S, C=O), 110.37 (S, O-C-O), 54.84 (D), 48.74 (S) 46.65 (D), 44.92 (D), 43.43 (D), 40.55 (T, CH_2 – Bridge) 40.25 (D), 34.67 (D), 31.91 (D) ppm. **^{1}H NMR [DMSO, 600MHz]**: δ_H 6.82, 3.34, 2.93, 2.88, 2.74, 2.63, 2.49, 2.39, 2.20, 1.95, 1.92(d, 11.07 Hz), 1.80 (d, 10.84 Hz) ppm.

RESULTS AND DISCUSSION

It was found that for compounds **2**-**5b**, all analytical data were in accordance with authentic samples. For **5**, the melting point was higher than that published by Pandey *et al.*,[17] however it was in the same order (374–375 °C) as that published by Tolstikov *et al.*[18] The melting point of 371 °C was confirmed with thermogravimetric analysis (TGA). The discrepancy in melting points between the two authors could be ascribed to the limitation of the older apparatus used by Pandey. The mono addition of ethylene glycol to pentacycloundecane compounds was introduced by Eaton *et al.*[19] in 1976. According to Eaton the steric bulk of the cage compound together with the introduction of the first acetal group hinders the introduction of a second acetal group on the adjacent carbonyl. Although this reaction is chemoselective it is not regioselective, resulting in the formation of four different isomers (**Figure 2**). It can be observed from **Figure 2** that **6a** and **6c** as well as **6b** and **6d** will result in only two isomers detected by NMR analysis. The ^{13}C-NMR of **5** indicates that there are only two carbonyls present and only eleven signals are registered instead of the twenty-one carbons present, which designate that the adjacent carbonyls are equivalent. Thus any one of the carbonyls on each side can therefore form an acetal, but the formation of a second acetal on the same side is prevented, due to steric hindrance, as indicated by Eaton *et al.*[19]

Contradictory to **5**, the ^{13}C-NMR of **6** shows almost double the number of peaks, 44 versus the expected 50 carbons for the expected

isomers. The discrepancy in the number of peaks is due to some carbons having the same chemical shift (being degenerate) in both structures, for example, the DEPT shows only one CH_2 bridge carbon and only two quaternary carbons, while there are two CH_2 bridge carbons and four quaternary carbons respectively.[27] Furthermore, the ^{13}C-NMR of **6** shows four different carbonyl groups at δ_C 214.04, 213.94, 213.41 and 212.96 ppm. **Figure 3** illustrates the numeric numbering of **6a** and **6b** used in **Table 1**, which shows the calculated C-C-O bond angles (Accelrys Materials Studio® 4.2 using GGA/DNP/PW91 functional). From this table, it was observed that although the angles do not differ significantly, this could be responsible for the slight chemical shift in the ^{13}C-NMR. The distance between the oxygen of the acetal transannular to the carbonyl oxygen was also measured.

The carbonyl oxygen (on C10) and the acetal oxygen (on C3) distances are 3.26 Å and 3.23 Å for **6a** and **6b**, respectively, while the carbonyl oxygen (on C19) and the acetal oxygen (on C14) distance are 3.17 Å and 3.15 Å, respectively. The bond angles together with the slight difference in interatomic distances cause a minor change in the electronic environment around the carbonyls which causes the carbon atoms of **6a** to be deshielded and shifted downfield, while the carbon atoms of **6b** are more shielded and shifted upfield. This is commonly known as magnetic anisotropic systems and refers to the electron distribution of molecules with high electron density. This change in electron density affects the applied magnetic field on the different carbons and causes the observed chemical shift to change.[28] This effect can be seen especially for the bridge CH_2, where the two protons are split into two very distinct doublets in the ^{1}H-NMR. Normally the carbonyl peak of C10 is downfield of the carbonyl peak of C19, which means that the chemical shift at δ_C 214.04 ppm, can be assigned to C10 in **6a**, 213.94 ppm can be assigned to C10 in **6b**, likewise, 213.41 ppm can be assigned to C19 in **6a**, and 212.96 ppm can be assigned to C19 in **6b**.

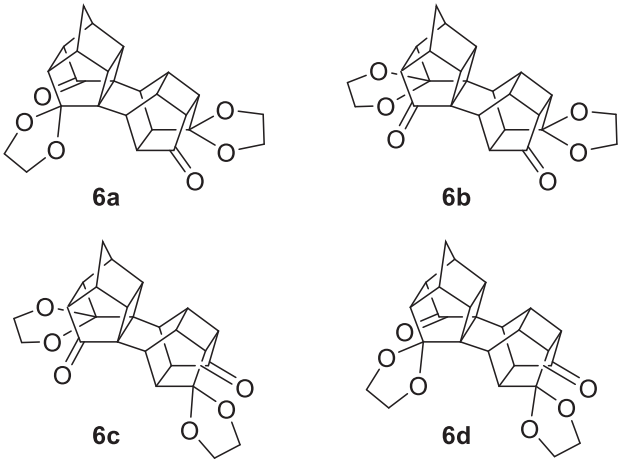


Figure 2: The four possible isomers that can form during the addition of ethylene glycol to **5**.

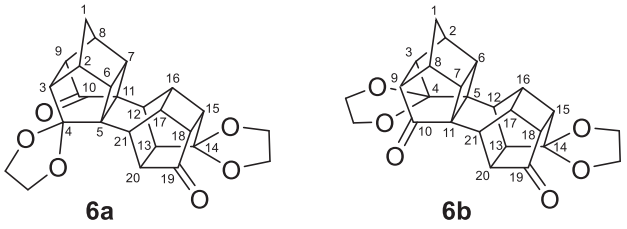


Figure 3: 6a and 6b showing the numeric numbering.

Table 1: Calculated bond angles of the carbonyl groups.

Selected bond angle	6a	6b
C9-C10-O	127.53	127.59
C11-C10-O	127.65	127.67
C20-C19-O	127.23	127.59
C18-C19-O	127.71	127.57

Since two distinguishable isomers are forming during the addition of ethylene glycol to **5** and conventional separation techniques, such as column chromatography, are unable to separate/purify these cage compounds, all the following products will have two or more isomers. Thus, for simplicity, the numeric value alone will imply all the isomers of a specific compound, while the alphabetical letter together with the numeric value will imply the specific isomer.

For the reduction of **6** to **7** the first method employed was the reduction of a carbonyl with $NaBH_4$ (**Scheme 2**). Since the carbonyls of **6** are sterically blocked on one side by the acetal group, only *exo* hydride attack can occur, producing only the *endo* product. However, this method was unable to reduce the carbonyls of **6** and only the starting compound could be extracted in high yields.

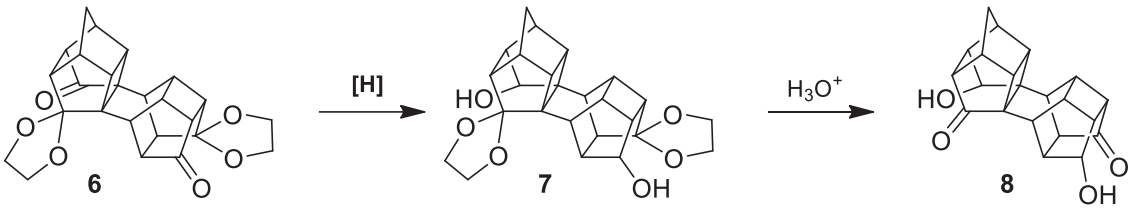
Since $NaBH_4$ alone were incapable of reducing the carbonyl groups of **6**, the Luche[21, 22] reaction was attempted. The Luche reaction is a selective reduction method for the reduction of enones or ketones in the presence of aldehydes. The activity of the Luche reaction can be explained by the Hard and Soft Acid and Base (HSAB) theory. Carbonyl groups require hard nucleophiles for the addition of a nucleophile to the carbonyl. The hardness of the borohydride is increased by replacing the hydride groups with alkoxide groups. This reaction is catalysed by cerium salts by increasing the electrophilicity of the carbonyl groups.[22] Thus, a stronger reducing agent is produced and the cerium facilitates the reduction by binding to the oxygen, thereby weakening the carbonyl bond and making it more susceptible to reduction. Even with the ketone being more susceptible to reduction no reaction took place.

As a last option, $LiAlH_4$ was used as a reducing agent.[20, 24] It was possible to reduce **6** to **7**, with relative ease and high yields (94%). This reaction was initially conducted with $LiAlH_4$ dissolved in THF and the ketone being added portion-wise, over a period of 2 hours. It was argued that since the ketone is resistant to reduction this setup will result in a higher concentration of H^- (hydride) at any given time compared to the concentration of the ketone. The resulting product was an orange-brown oil that we were unable to crystalize, however, the IR showed a distinctive OH stretching band at 3427 cm^{-1} and the disappearance of the carbonyl peak at 1743 cm^{-1}, however, the resultant reaction mixture was highly contaminated, and we were unable to purify this any further. The reaction was therefore repeated in the same manner as before, except that $LiAlH_4$ was added slowly to the stirred ketone (**6**) in THF over a period of 2 hours which resulted in **7** as an off-white powder. ^{13}C NMR confirmed the disappearance of the carbonyl peaks. As with **6**, the number of signals attributed to the different inseparable isomers made full elucidation problematic, however, the HRMS indicated that the calculated and measured *m/z* were in accordance to compound **7** (calc. for $C_{25}H_{29}O_6$ [M^++H]: 425.1959, found: 425.1987).

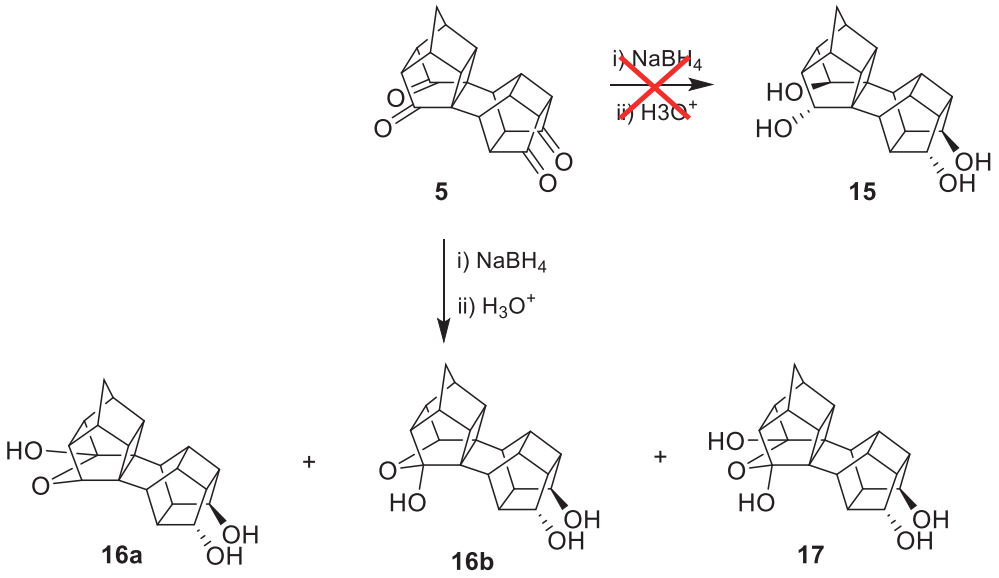
As with **6**, there are two distinguishable compounds giving rise to eight different CH_2-O-R carbon peaks between δ_C 65 and 62 ppm. The DEPT indicate two CH_2 bridge peaks that were degenerate in **6**. In comparison to **6**, **7** has four different quaternary carbons, indicating that the isomer effect is more prominent in **6** than in **7**. This can be explained by taking into consideration that the hydroxyl group is spatially larger than the ketone group, which has an increased electronic effect on the C3, C10, C14 and C19 of the two isomers.

The logical next step would then be the removal of the protecting acetal group of **7** to produce the hydroxyl ketone **8**. For the pentacyclo-undecane system, this can normally be accomplished by stirring the ketol **7** in a 10% HCl solution for 2 hours under reflux. For **7** this procedure was inadequate to remove the acetal group. Even when the solution was refluxed for 6 days in a 25% HCl solution no reaction took place.

To test the reactivity of the 4 carbonyl groups of **5**, it was subjected to reduction with $NaBH_4$. The expected product was a tetraol, **15** (**Scheme 3**), but the triol **16a** and **16b**, as the major products with **17** as a minor product were obtained.



Scheme 2: Reduction of **6** to **7** with reducing agents [RA]: a) $NaBH_4$, b) $NaBH_4$, $CeCl_3$, c) ^iPrOH, $Al(O^iPr)_3$, d) $LiAlH_4$, THF



Scheme 3: Reduction of **5**.

Molecular modelling indicates that the LUMO of **5** (**Figure 4**) is concentrated on the CH_2-bridge side of the molecule and thus it is expected to be reduced first. It has been reported by Mehta *et al.*[29] that for the pentacycloundecane system, the hemiacetal **18** is only observed in equilibrium with the ketol **19** (**Scheme 4**). It should be noted that the two carbonyl groups are equivalent and the reaction occurs without regiospecificity, although it was pointed out by Sasaki *et al.*[30] that **18** did not cyclise to **19**, even at 270 °C. Whether or not this cyclization occurs, it is evident from the ^{13}C-NMR that only **16a** and **16b** are present, with **17** as the minor product, in this case.

Although physical evidence such as δ_C at 78.80 and 78.65 ppm are indications of a transannular ether-bearing carbon with hydrogen (instead of the normal hydroxyl group attached to this carbon). DEPT135 indicates that there are five quaternary carbons at δ_c 44.99, 44.51, 44.28, 43.90 and 43.80 ppm, four originating from **16a**, **16b** and one for **17** (since **17** is symmetrical). From the reaction in **Scheme 3**, it seems that all four ketones are active towards reduction. However, due to the steric hindrance around the ketones in **6**, conveyed by the steric bulk of the acetal groups, they may be resistant to reduction.

In 1981 Mehta *et al.*[26] showed that **20** can be directly synthesized from **3** with the use of zinc and acetic acid. It was argued that this reaction will allow the direct synthesis of **21**, a hydroxyl ketone with the correct functionality, akin to **8** (**Scheme 5**).

Initially, the reaction was carried out with the use of 99.9% acetic acid. However, ^{13}C-NMR elucidation indicated a symmetrical product with the presence of only one carbonyl as well as a hydrate (O-C-O) group at δ_C 213.47 and 110.37 ppm, respectively, which correlates to the NMR data of **25**. **Scheme 6** shows a possible reaction mechanism for the hydrate **25** formation as well as the formation of the hydroxyl ketone (**30**). It was posited that for the reaction to occur a hydrate must first form and thus there is insufficient water to solvate the acetic acid to release a proton that initiates the hydroxyl ketone formation (**30**). For this reason, the reaction stops at **25**. This is like the reduction of **5** with $NaBH_4$ (**Scheme 3**), of which **25** is a minor product that is reduced to **17** during the reaction. ^{13}C-NMR of **25** showed only one carbonyl group, indicating that the transannular

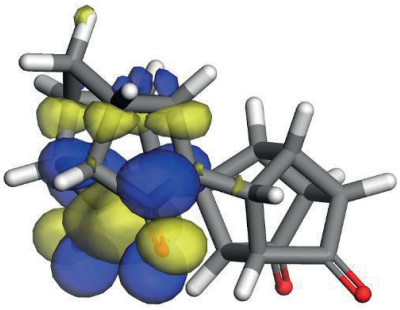
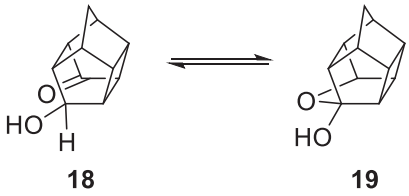
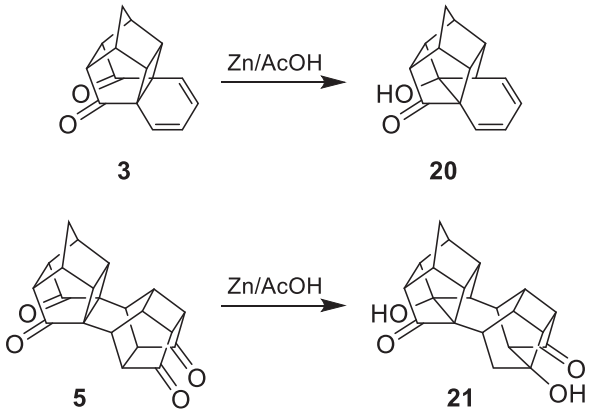


Figure 4: The LUMO of **5**.



Scheme 4: Transannular reaction of **18**.



Scheme 5: Synthesis of the hydroxyl ketones **20** and **21**.

hydrate formation is chemoselective and consequently forms only one symmetrical product (an interesting observation from the ^{1}H-NMR of this compound is the number of singlet peaks). This can be ascribed to the fact that within some cage compounds, 1, 2 and 3 bond coupling can be observed which results in extremely small coupling constants (*J*) which consequently results in the multiplet (that should have formed) being displayed as singlets.[28] Furthermore, it depicts that when the first hydrate forms on one side, the reaction stops, and the addition of a second hydrate does not occur. It also sheds some light on the mechanism of the reaction, i.e., non-concerted manner.

Galin *et al.*[31] showed that it is possible to hydrate **5** to form **31** by reacting **5** in an aqueous acetone solution for three days (**Figure 5**). The findings of Galin are supportive of the proposed hydration mechanism as shown in **Scheme 6**.

Repeating the reaction with an 80% acetic acid solution for 5 hours, the ^{13}C-NMR showed a mixture of products which included three hydroxyl-bearing carbons at δ_C 84.12, 84.25 and 84.20 ppm, which is consistent with a tertiary alcohol.[28] The ^{13}C-NMR also shows three different carbonyl groups at δ_C 215.13, 215.10 and 215.04 ppm. The spectrum also indicated that there still was a hydrate present together with two geminal alcohol groups. These products were separated by means of their differences in solubility. ^{13}C-NMR of the product removed by filtration and washed with water (**30**), indicated only one carbonyl peak at δ_C 215.13 as well as the presence of a hydrate (O-C-O) at δ_C 109.5 ppm.

The ^{13}C-NMR of the other fraction isolated (**33** and **35**), signifying that there were 42 resonance signals of which there were two carbonyl peaks at δ_C 215.1 and 215.04, two O-C-O peaks at δ_C 116.06 and 114.69, two different tertiary hydroxyl bearing carbon atoms at δ_C 84.25 and 84.20, two secondary hydroxyl bearing carbon atoms at δ_C 77.71 and 76.36, as well as two quaternary carbons at δ_C 55.31 and 55.25 ppm. This indicated that there were two isomers of which the degenerate peaks were split due to the isomer effect. Furthermore, the product contained a geminal alcohol together with an additional hydroxyl group. **Scheme 7** shows the possible reaction mechanism for the formation of **33** and **35**.

From these results it seemed that the formation of **25** is chemoselective and that only one hydrate is formed during the reduction of **5** with Zn/AcOH, resulting in only one side forming a hydroxyl ketone.

When the Zn/AcOH reduction reaction of **5** was carried out for 24 hours, instead of the original 5 hours with 80% AcOH, **33** and **35** are produced exclusively, confirming that **30** is a precursor for these compounds. It seems that the Zn/AcOH reduction of **5** does not form the double transannular hydroxy ketone **21**, but rather the reaction proceeds through the formation of **25** and subsequent reduction of **25** to form **30**, which reacts further with zinc in acetic acid to produce **33** and **35**.

Although these are interesting results as to the derivatization of **5** showing the possibilities, it would be advantageous to be able to synthesize the Schiff-base (**40**) or the pyridinyl alcholato (**38**) derivatives of **5** (**Figure 6**). For these can act as ligands for the Grubbs catalysts. Attempts to derivatise **6** to **38** via **36** or **37** by means of the Huang-Minlon reaction were unsuccessful. Similarly, were the attempts to react **6** with hydroxyl amine to produce **39** unsuccessful. In all these cases only the starting material **6** was recovered.

CONCLUSION

In the process of developing novel hemilabile ligands, it was important to understand the chemical and physical properties of the tetraone **5**. It seems that **5** shows similar chemistry as **3** when reacted with ethylene glycol to produce the corresponding acetal isomers

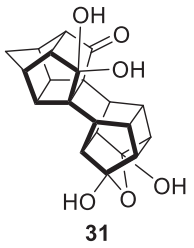
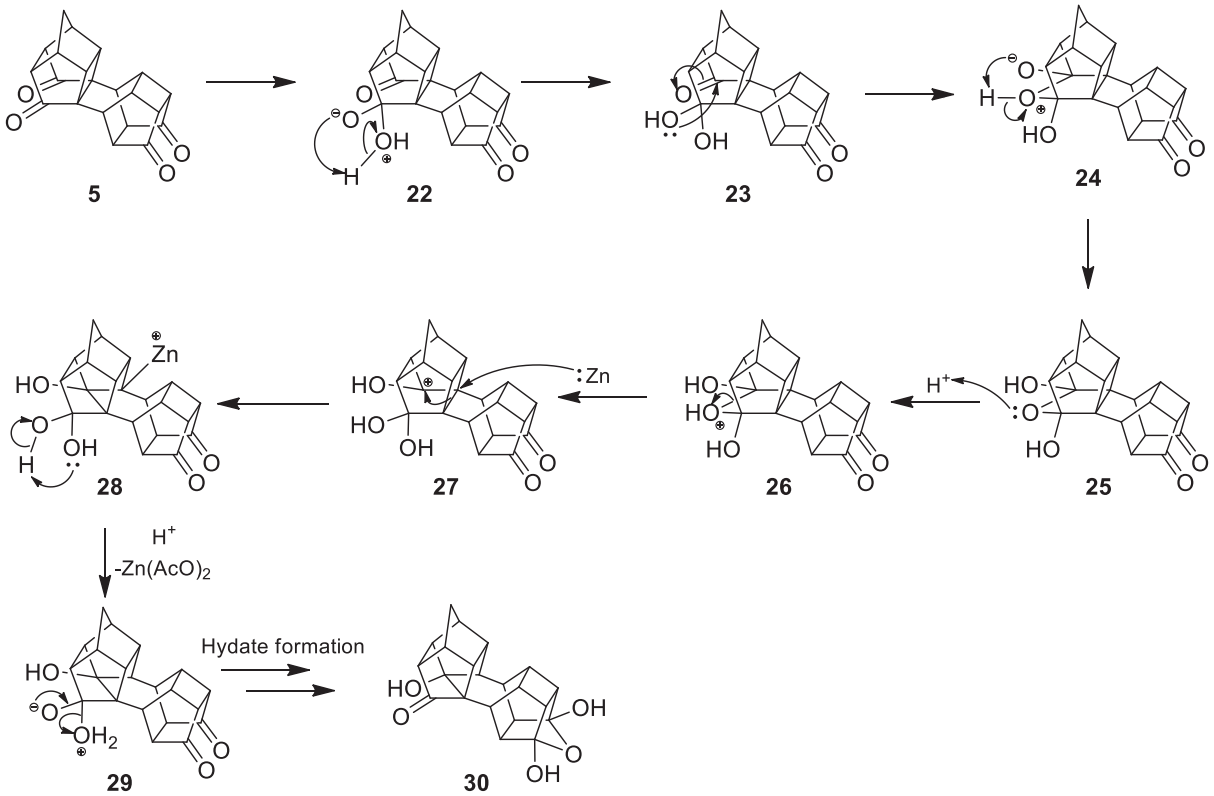
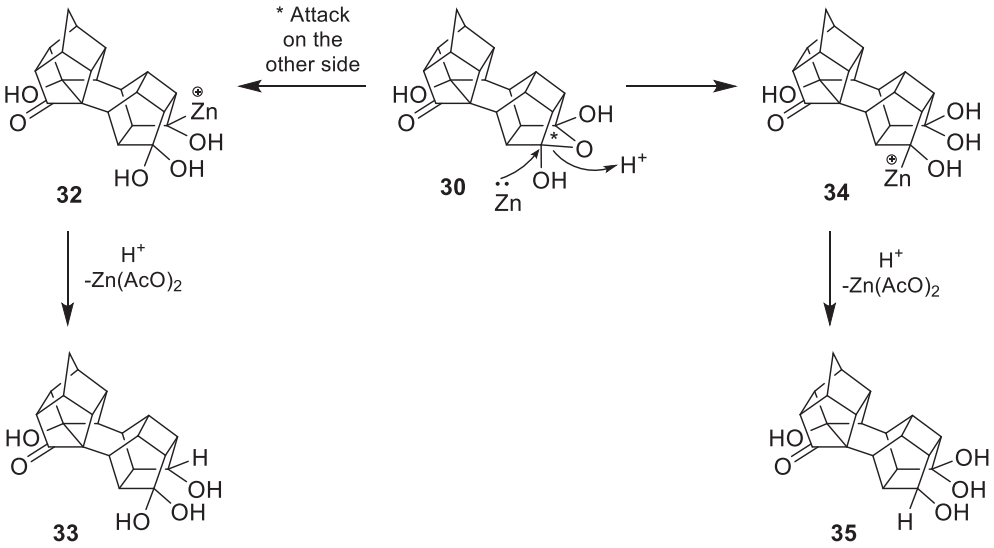


Figure 5: Hydrate of **5**.



Scheme 6: Possible reaction mechanism of the hydrate (**25**) and hydroxyl ketone (**30**) formation.



Scheme 7: Reaction mechanism for the formation of **33** and **35**.

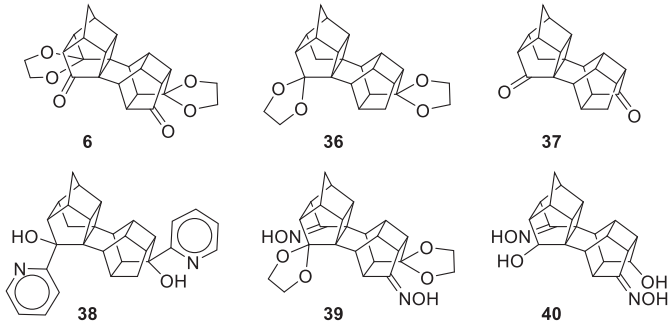


Figure 6: Envisioned pyridinyl alcholato (**38**) and Schiff-base (**39**, **40**) derivatives of **6**.

6a to **6d**. Paradoxically, the isomers of **6** did not react with, Luche's or Meerwein-Ponndorf-Verley's reagents to give the corresponding hydroxyl acetal derivative **7**, as it would have with **3**. It seems that stronger reducing agents were to be used to convert **6** to **7**. From the results obtained with the zinc/acetic acid reduction, it became clear that the chemistry of **5** is different from that of **3**. With two active reducing sites present, the ketones on the CH_2-bridge side were the first to undergo chemoselective hydration through a transannular mechanism. Following the formation of **25** it is further hydrated to form **30** and ultimately to **33** and **35**. This is not surprising, since the transannular distance between the carbonyl groups is shorter on the CH_2-bridge and the pi-orbitals show an overlap with molecular modelling. What is interesting though is that the extent of hydration can be controlled. Therefore, the chemistry which applies to **3** is not always applicable to that of **5**. This was seen with the deprotection of the ketone groups in **7**. It was also found that some of these compounds became less soluble and ultimately further reactions were not possible. This presents a problem with the synthesis of the possible ligands **38**-**40**. With the knowledge gained from this investigation, it should be possible to devise a synthetic strategy to synthesise these ligands.

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SUPPLEMENTARY MATERIAL

Supplementary information for this article is provided in the online supplement.

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