A Molybdenum-Catalysed Electrocyclisation-Cycloaddition Sequence: Synthesis and Structure of a Pentacyclic Unsaturated Ketone

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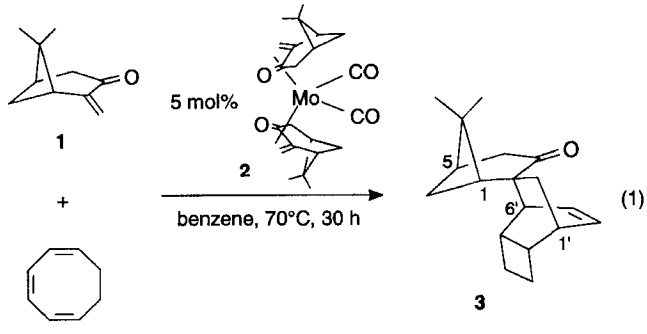
The pentacyclic unsaturated ketone **3** is obtained as the sole product by the reaction of pinocarvone (**1**) with cyclooctatriene in the presence of catalytic amounts of dicarbonylbis(η^4-pinocarvone)molybdenum (**2**). Compound **3** formally resulting from a [4 + 2] cycloaddition reaction of bicyclo[4.2.0]octa-2,4-diene with the alkene fragment of pinocarvone was characterised by means of spectroscopy (^{1}H, ^{13}C NMR, IR, MS) as well as by X-ray crystal structure analysis. A mechanism is proposed involving rigid molybdenum complexes as intermediates in order to explain the stereospecificity of the reaction.

Tandem reactions, i.e. sequences where a primary occurring reaction almost enforces a secondary reaction, have become increasingly popular[1]. Combinations of Michael and aldol reactions[2], e.g. in the Robinson annulation, are early examples of such reactions. Tandem sequences involving cycloaddition steps are frequently used in organic synthesis. For example, Diels-Alder reactions can be triggered by various other reactions which produce highly reactive diene moieties such as eliminations[3a], redox reactions[3b], or photoenolisation steps[3c]. Combinations of cycloadditions and other pericyclic, e.g. electrocyclic reactions, have extensively been employed in anthracyclinone and steroid synthesis, using the "benzocyclobutene→*o*-quinodimethane isomerisation/-Diels-Alder reaction" cascade[4].

We recently discovered a new type of molybdenum-catalysed cycloaddition reaction that has already been shown to be preparatively useful for the synthesis of [6 + 2] cycloadducts from α,β-unsaturated ketones and cyclopolyenes[5]. Dicarbonylbis(η^4-1-oxa-1,3-diene)molybdenum complexes[6] have been found to be the most efficient catalysts. In the following we report on the unexpected result of a reaction employing cyclooctatriene as cycloaddition partner.

Compared to the reaction of pinocarvone **1** with cycloheptatriene, which already proceeds efficiently at room temperature[5], the reaction with cyclooctatriene required elevated temperatures of about 70 °C and longer reaction times of about 30 h. 5 mol-% of dicarbonylbis[η^4-(*R*)-(+)-pinocarvone]molybdenum (**2**) was employed as catalyst. Under these conditions, cycloocta-1,3,6-triene is smoothly isomerised by the molybdenum catalyst to yield the totally conjugated 1,3,5-triene. Both triene isomers could thus be employed in the reaction. The reaction could be performed even more conveniently by using directly the mixture of isomers (ratio about 2:3) as obtained from the metalation of 1,5-cyclooctadiene with *n*-butyllithium in the presence of tmeda and subsequent hydrolysis[7].

The cycloaddition reactions could be performed in different solvents, e.g. benzene, cyclohexane, or THF, to yield the identical product without significant influence on the rate of the reaction. In all cases, a dark red-brown solution was finally obtained. The molybdenum complexes were oxidatively destroyed by diluting the reaction mixture with diethyl ether and stirring the solution under normal atmosphere conditions for 12 h. After filtration of the resulting brown suspension through a pad of silica, a colourless filtrate was obtained. Evaporation of the solvents and a small amount of unreacted cyclooctatriene in vacuo yielded colourless crystals of analytically pure **3**. As shown by the NMR spectra, only one compound is formed under these conditions, being a C_1-symmetrical ketone of the molecular formula $C_{18}H_{24}O$. Whereas ^{1}H- and ^{13}C-NMR spectra indicate the presence of one carbon-carbon double bond, the IR spectrum proves this double bond to be isolated from the carbonyl group ($\tilde{\nu}_{C=O}$ = 1704 cm^{-1}). It is already obvious from these data that no [6 + 2] cycloaddition has occurred as observed with cycloheptatriene[5]. Instead, a monounsaturated ketone is formed whose identity can most easily be explained in terms of a [4 + 2] cycloaddition involving the bicyclic valence tautomer of cyclooctatriene, i.e. bicyclo[4.2.0]octa-2,4-diene.



Although a complete assignment of the proton-NMR resonances of **3** could be achieved by two-dimensional techniques, it was not possible to unambiguously clarify which of the possible diastereomers was formed. In addition to the four isomers arising from different approaches of the C_8 fragment to the alkene moiety (Structures **A** to **D**), each of these could still differ with respect to the type of fusion of the four-membered ring (*syn*/*anti*).

In order to determine which of these eight isomers had been formed, an X-ray diffraction analysis of **3** was performed. The result graphically represented in Figure 1 confirms the product structure **A** which is remarkable in several respects. Firstly and most

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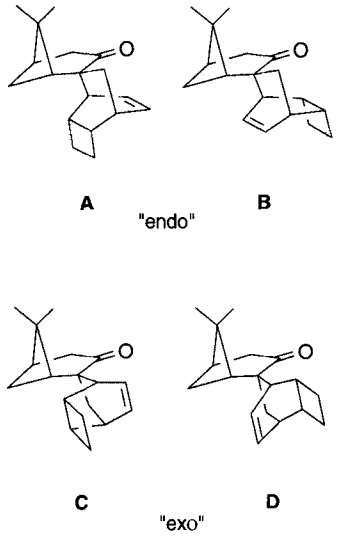
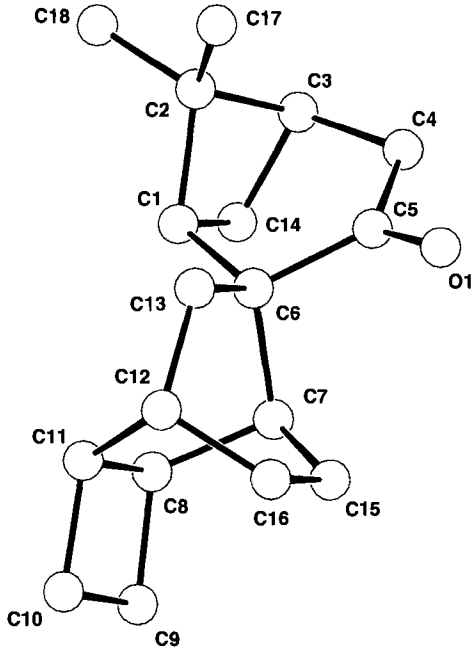


importantly, the hypothesis of an addition involving the bicyclo-[4.2.0]octadiene moiety was confirmed. Secondly, although not positioned in conjugation, the carbonyl group and the alkene moiety in **3** are in the spatial vicinity of each other, which will turn out to be important in our mechanistic rationale for the product selectivity (vide infra). Finally, the alkene fragment of pinocarvone was approached by the C_8 reactant from the *endo* rather than the *exo* face of the pinocarvone[8]. This is in contrast to what was observed for the products of the [6 + 2] cycloaddition reactions with cycloheptatriene.

Figure 1. Molecular structure of **3**. Selected bond distances [Å] and angles [°]: O1–C5 1.225(5), C15–C16 1.290(6), C1–C6 1.550(4), C5–C6 1.542(5), C6–C7 1.571(4), C6–C13 1.555(5); C6–C5–O1 120.1(4), C5–C6–C1 107.1(3), C5–C6–C7 107.2(3), C5–C6–C13 112.6(3), C1–C6–C13 111.0(3) (Numbering scheme differs from that according to IUPAC rules as used in eq. 1)



The above findings allow us to draw some conclusions as to the mechanism of the addition reaction. The unusual *endo* selectivity in this reaction may be attributed to the fact that primarily both reactants are coordinated to the same metal centre (Scheme 1). If both the pinocarvone molecules initially coordinated in **2** remain coordinated during the reaction, a hapticity change from η^4 to η^2 or η^1 has to occur for at least one of them in order to allow the coordination of the hydrocarbon reactant. An intramolecular addition reaction could then proceed much more rapidly than any intermolecular reaction involving the monocyclic triene. This concept of the prereduction of entropy was already employed successfully to enhance the rate of Diels-Alder reactions[9]. A valence isomerisation of the cyclooctatriene is obviously favoured in the coordination sphere of molybdenum. It might even instantaneously occur during coordination. Brookhart and co-workers already reported in detail[10] on the possibility of stabilising one or the other valence isomer of cyclooctatriene when preparing their tricarbonyliron complexes, depending on complexation conditions. Our own investigations employing tricarbonylmolybdenum fragments have so far only led to complexes of the monocyclic isomer. However, one might argue that the properties of the molybdenum centre are markedly dependent on the nature of the attached ligands, which must include at least one oxadiene ligand in the course of the catalytic reaction, whereas the tricarbonylmolybdenum fragment might exhibit a different behaviour. Unfortunately, all attempts to isolate molybdenum or tungsten complexes bearing both oxadiene and hydrocarbon ligands as model compounds have failed so far in our hands.

The preference for the spatial vicinity of the π fragments in **3** leads to the assumption that in the course of the reaction both these fragments are coordinated to the same metal centre. For example, the formation of an η^3-allyl/carbonyl lone pair complex after initial carbon-carbon bond formation can be envisioned as shown in Scheme 1. Such a conformationally rigid intermediate would preorganise the organic ligand for the final carbon-carbon bond formation and thus explain the second type of diastereoselection that is similarily found in [6 + 2][5] and [4 + 2] cycloadditions. After this intramolecular alkylation of the metal enolate, a labile alkene or ketone molybdenum complex could then transfer the metal fragment to new substrate molecules, thus closing the catalytic cycle.

In summary, the highly effective tandem reaction we have described presumably consists of two independent reactions, i.e. electrocyclisation and addition step, both being catalysed by the molybdenum centre. An extension of such sequences by the introduction of other triggering steps such as metal-catalysed sigmatropic rearrangements or even simple coordination of a reactant, thus making use of a previous reduction of entropy, is currently under investigation.

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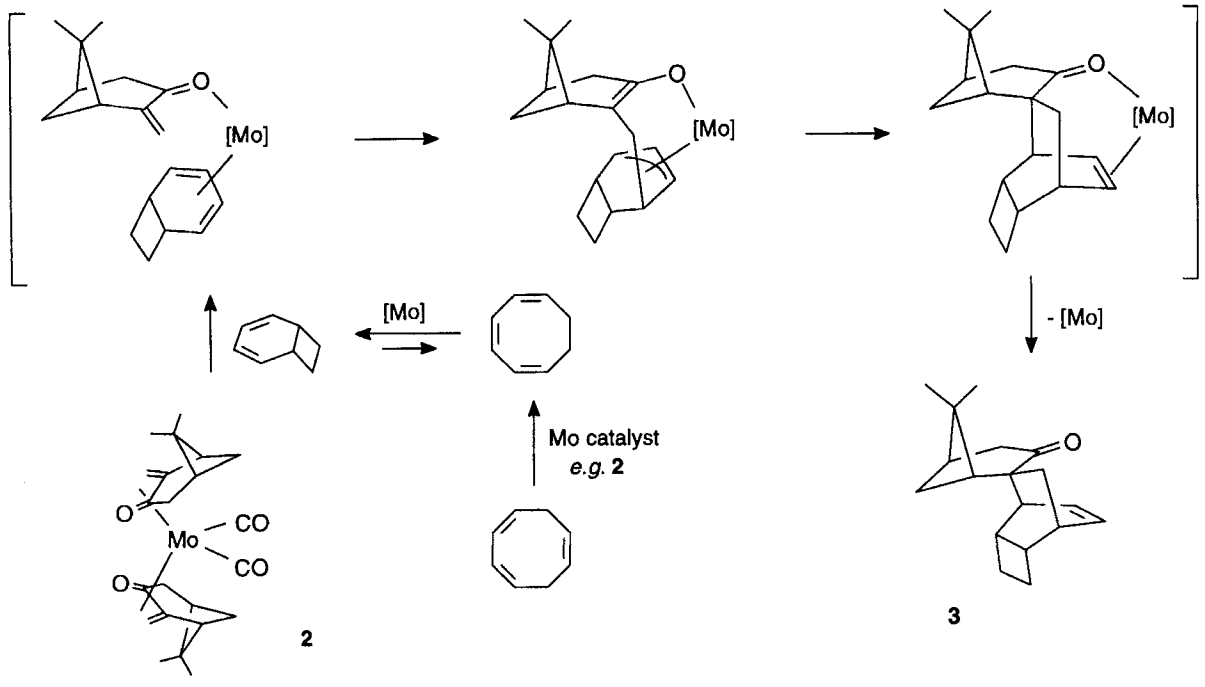
Experimental

All manipulations of organometallic compounds were carried out under purified, dry argon by employing standard Schlenk technique. Solvents were dried by using $Na[AlEt_4]$ as drying agent, subsequently distilled and saturated with argon. – Melting points: Capillary tubes sealed under argon, uncorrected. – (*R*)-(+)-Pinocarvone (**1**) was obtained from α-pinene by epoxidation, epoxide cleavage and oxidation of the resulting *trans*-pinocarveol[11]. Cyclooctatriene (isomeric mixture) was prepared as described[7]. Pure cycloocta-1,3,5-triene was obtained by subsequent isomerisation of that mixture by using 3 mol-% of (η^6-benzene)tricarbonylmolybdenum at 80 °C. – IR: Nicolet 7199 FT-IR. – MS: Varian 311A.

Scheme 1. Proposed mechanism for the diastereospecific, catalytic formation of **3**



– ^{1}H, ^{13}C NMR: Bruker AC 200, AMX 400. Standards: $SiMe_4$ (^{1}H), solvent signal (^{13}C). Multiplicities of ^{13}C-NMR signals are given in parentheses as obtained from DEPT experiments. – Elementary analysis: Dornis & Kolbe, Microanalytical Laboratory, Mülheim an der Ruhr.

6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,7'-tricyclo[4.2.2.0^{2,5}]-dec-9-en]-3-one (**3**): 1.17 g (11 mmol) of a mixture of cycloocta-1,3,5- and -1,3,6-triene[10] (molar ratio 3:2) was added to a solution of 55 mg (0.25 mmol) of dicarbonylbis[η^4-(*R*)-(+)-pinocarvone]-molybdenum in 5 ml of dry benzene. 750 mg (5.0 mmol) of (*R*)-(+)-pinocarvone[11] was added, and the resulting clear yellow-brown mixture was heated to 70°C and stirred at that temp. for 30 h. The brown reaction mixture was diluted with 10 ml of diethyl ether and vigorously stirred under normal atmosphere conditions for 12 h in order to oxidatively destroy soluble molybdenum compounds. The brown suspension was then filtered through a pad of silica (length 3 cm, diameter 2.5 cm). The clear pale yellow filtrate was concentrated in vacuo to yield a semisolid residue. A small excess of cyclooctatrienes was removed under high vacuum (10 Pa), the crystalline material was then recrystallised from *n*-pentane to yield clear, colourless crystals of **3**. Yield: 1.18 g (84%, based on total amount of oxadiene, i.e. free + metal-coordinated pinocarvone), m.p. 108–110°C (pentane). – IR (KBr): $\tilde{\nu}$ = 3041 w cm^{-1} (HC=), 2982 m, 2970 m, 2922 s (CH), 1704 s (C=O), 1462 w, 1385 w, 1370 w, 1161 w, 1044 m, 735 m. – ^{1}H NMR ($CDCl_3$, 400.136 MHz): δ = 6.56 (t, *J* = 6.8 Hz, 1H, 10'-H), 6.15 (t, *J* = 7 Hz, 1H, 9'-H), 2.66 (dd, *J* = 6.8, 4.0 Hz, 1H, 6'-H), 2.59 (m, 1H, 5'-H), 2.55 (dd, *J* = 6.0, 3.5 Hz, 1H, 1'-H), 2.49 (m, 2H, 4-H_a, 4-H_b), 2.36 (m, 1H, 7-H_a), 2.25 (sept, 1H, 2'-H), 2.02 (oct, 1H, 5-H), 1.95 (m, 1H, 7-H_b), 1.93 (t, *J* = 6.5 Hz, 1H, 3'-H_a), 1.86 (dd, *J* = 12.3, 3.0 Hz, 1H, 8'-H), 1.80 (m, 1H, 4'-H_a), 1.49 (d, *J* = 10.8 Hz, 1H, 1-H), 1.47 (m, 1H, 4'-H_b), 1.35 (m, 1H, 3'-H_b), 1.29 (s, 3H, CH_3), 0.94 (dd, *J* = 12.3, 2.8 Hz, 1H, 8'-H_b), 0.74 (s, 3H, CH_3). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 215.61 (s, C=O), 134.04 (d, =CH), 131.34 (d, =CH), 54.41 (s, spiro-C), 50.87 (d), 44.58 (t), 40.02 (t), 39.60 (s, CMe_2), 38.73 (d), 38.64 (d), 36.25 (d), 35.75 (d), 32.79 (d), 28.95 (t), 27.40 (q), 22.80 (t), 22.50 (q), 21.69 (t). – MS (EI, 70 eV), *m/z* (%): 256 (20) [M^+], 213 (11), 106 (28) [$C_8H_{10}^+$], 91 (26) [$C_7H_7^+$], 78 (100), 41 (13). – $C_{18}H_{24}O$ (256.2): calcd. C 84.32, H 9.44; found C 84.28, H 9.50. – Mol. mass 256.18257, calcd. for $C_{18}H_{24}O$: 256.18272 (high-resolution MS).

X-Ray Analysis of **3**[12]: Clear, colourless single crystals were obtained from a concentrated solution in pentane by slowly cooling to –30°C; formula $C_{18}H_{24}O$, molar mass 256.4 g mol^{-1}, crystal size 0.11 × 0.31 × 0.18 mm, *a* = 6.882(1), *b* = 12.133(1), *c* = 17.233(2) Å, α = β = γ = 90.0°, *V* = 1438.9 Å^3, *T* = 293 K, d_{calc} = 1.18 g cm^{-3}, μ = 5.07 cm^{-1}, *Z* = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), Enraf-Nonius CAD4 diffractometer, λ = 1.54178 Å, $[\sin\Theta/\lambda]_{max}$ 0.63 Å^{-1}, ω-2Θ scans, index ranges $-9 \leq h \leq 9$, $k \leq 16$, $l \leq 22$, reflections collected 3416 ($\pm h$, $+k$, $+l$), independent reflections 2916, observed reflections 2181 [$I > 2\sigma(I)$], 173 refined parameters, no absorption correction. Structure solution: direct methods, structure refinement: full matrix least-squares on F, H-atoms calculated and not included into least squares refinement, R = 0.066, R_w = 0.070 [$w = 1/\sigma^2(F_o)$], max. residual electron density 0.22 eÅ^{-3}.

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[12] Additional details of the crystal structure determination may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-58993, the names of the authors, and the journal citation.

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