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Cyclopropanation and epoxidation of tricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one☆

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ABSTRACT

Cyclopropanation of tricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one using dimethylsulfoxonium ylide gave a highly strained annulated cyclopropane in 68% yield with complete *exo*-face selectivity. Nucleophilic epoxidation gave a strained epoxide in 68% yield, again completely *exo*-face selective. Surprisingly, using methanol as the co-solvent in this epoxidation yielded a disubstituted tricyclodecenone in 85% yield instead of the epoxide. This result can be explained by a Payne-type rearrangement of the initially formed epoxide.

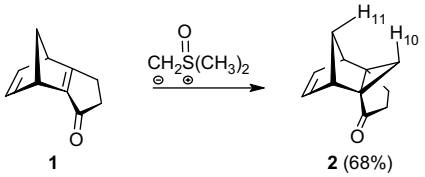
1. Introduction

Tricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one **1** is an intriguing tricyclic structure containing a highly strained and therefore reactive C_2–C_6 enone double bond as a result of the geometrical constrains imposed by the tricyclic skeleton, which hampers optimal sp^2 hybridization at the C_2 and C_6 bridgehead positions.[1] In the preceding paper,[2] we discussed the facial selectivity in the nucleophilic addition of series of different nucleophiles including alkoxides and dialkyllithiumcuprates. These reactions lead to addition products, which are thermodynamically considerably more stable than the starting enone as considerable strain energy is released. An interesting question is whether tricyclodecadienone **1** could be enforced to undergo a three-ring annulation by nucleophilic addition, by epoxidation or cyclopropanation. Such an annulation would lead to an increase in total ring strain as compared with the starting enone.

2. Results and discussion

Cyclopropanation of **1** applying dimethylsulfoxonium ylide afforded tetracyclic ketone **2** in a satisfactory yield of 67% and with complete *exo*-facial stereoselectivity (Scheme 1).

The structure of **2** was unambiguously determined using 2D NOESY NMR techniques, which showed a strong and indisputable NOE contact between H_{10} and H_{11}. Epoxidation of **1** under standard conditions using hydrogen peroxide (30% aq) in dichloromethane

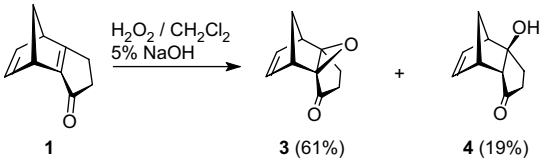


1 **2** (68%)

Scheme 1.

in the presence of 5% sodium hydroxide gave a single epoxide **3** in 61% yield (Scheme 2). 6-Hydroxytricyclodecenone **4** was obtained as a byproduct in 19% yield. The *exo*-position of the epoxide function was resolved by 2D NOESY NMR techniques showing an NOE contact between the H_{5n} and H_8 protons in the norbornene moiety. The formation of the mono-alcohol **4** is readily explained by attack of water or the hydroxide anion to the enone system. Normally, such an addition is reversible and eventually complete conversion of the enone to the epoxide is attained. However, due to the intrinsic strain of enone **1**, elimination of water from **4** is an unfavorable process.

When methanol was used as co-solvent during the epoxidation reaction of **1** a new product was isolated in 85% yield in addition to the expected epoxide **3**, which was now obtained only in a low yield of 8%. This new product, which appeared to be disubstituted tricyclodecadienone **5**, is only obtained when methanol and



1 **3** (61%) **4** (19%)

Scheme 2.

☆ Preliminary account (without experimental part): Mao, X. S.; Volkers, A. A.; Klunder, A. J. H.; Zwanenburg, B., *Chinese Chem. Lett.*, **2001**, *12*, 585; published without permission of the senior author (B.Z.).

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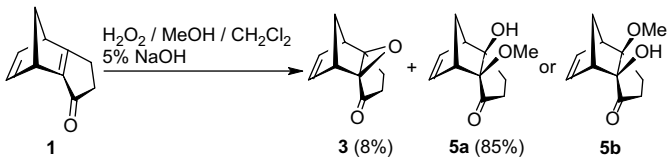
hydrogen peroxide are both present. In the absence of hydrogen peroxide, with methanol and base only, 6-methoxytricyclodecadienone **6**, being the methanol addition product,[1] was formed. The new product **5** contains an OH and OMe group added to the central double bond (Scheme 3). The structure of **5** was eventually established unequivocally to be **5a** on the basis of spectroscopic evidence and an FVT experiment (vide infra).



Scheme 3.

Extensive analysis of the spectroscopic features of the methoxy alcohol **5**, including 2D NOESY NMR experiments, indicate that the structure of this material may be **5a** rather than **5b**. At this point prudence is in order as the analysis of the spectroscopic data did not allow a fully unambiguous interpretation. Usually, H_{5n} and H_8 show a clear NOE contact on the basis of which the chemical shifts of the norbornene hydrogens were assigned (Fig. 1). In the present case however, the chemical shifts of H_{10} and H_{5n} are the same. Since H_{10} always has an NOE interaction with H_8, it is somewhat uncertain whether H_{5n} has an NOE interaction with H_8. The cross peak in the 2D NOESY data is larger between H_{10} and H_8 as compared with H_{10} and H_9, indicating an additional NOE contact between H_8 and H_{5n}. Because of this observation the other hydrogens in the norbornene system were assigned and an NOE contact was found between H_1 and the hydrogens of the methoxy group. Therefore, the structure of the new product is most likely **5a**.

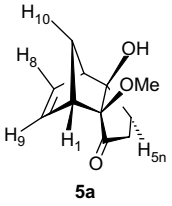
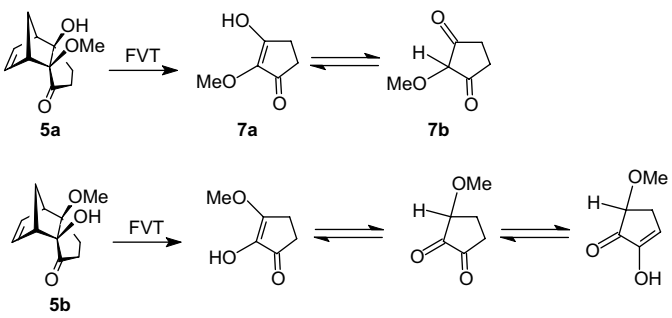


Figure 1.

Unequivocal support for structure **5a** was obtained from FVT experiments. Cycloreversion of this new product **5** led to a cyclopentanoid in 83% yield with the expected mass and a typical ^1H NMR proton spectrum, showing only two peaks and an extremely broad signal for an acidic proton. This high symmetry is only conceivable for cyclopentanoid product **7**, which can exist in two tautomeric forms, which rapidly equilibrate (Scheme 4). For the

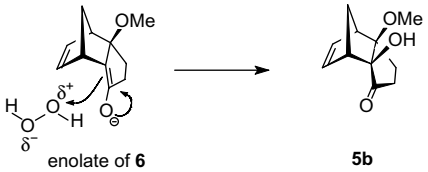


Scheme 4.

cycloreversion product of **5b** all tautomers are different and none of them has a plane or axis of symmetry.

Furthermore, by repeating the synthesis reported by Hesse and Mix[3] 3-hydroxy-2-methoxy-cyclopent-2-enone (**7a**) was prepared and its analytical data are in agreement with those of product **7**, obtained by cycloreversion of **5a**.

The mode of formation of product **5** is also a matter of concern. Remarkably, the unobserved formation of isomer **5b** would be easily explainable as follows. Reaction of the enolate of **6**, derived from a straightforward Michael addition of methoxide to the central enone group, with hydrogen peroxide should lead to product **5b** (Scheme 5).



Scheme 5.

In contrast, the formation of product **5a** is much more difficult to rationalize. The initially formed epoxide **3** is proposed to undergo a nucleophilic addition at the carbonyl group, either by hydroxide or methoxide. Intermediate **8** can then undergo an intramolecular epoxide opening by analogy with the Payne rearrangement[4] (Scheme 6). The thus obtained epoxide **9** can now be readily ring-opened by a methoxide ion to give the desired product **5a**. Such a Payne-type rearrangement was reported earlier for a tricyclodecadienone epoxide and support for the mechanistic sequence shown in Scheme 6 is obtained from these reported observations.[5]

An independent experiment in which epoxy ketone **3** was treated with methoxide ion in methanol yielded indeed the disubstituted tricyclodecenone **5a** confirming the mechanism in Scheme 6.

In this paper we showed that Michael additions to the central 2,6-olefinic bond of tricycle[5.2.1.$0^{2,6}$]deca-2(6),8-dien-3-one (**1**) using appropriate nucleophiles and solvents allow a three-ring annulation to form cyclopropane **2** and epoxide **3** in relatively good yields. The geometrical constrains of these compounds are nicely illustrated by the observed solvent dependency in the epoxidation of **1**. Finally, as already indicated in Scheme 4, epoxide **3** offers good perspectives for the synthesis of oxygenated cyclopentenoids using the FVT-methodology.

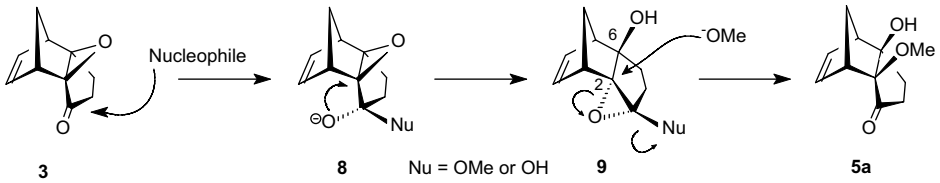
3. Experimental section

3.1. General

General experimental details have been described previously.[6]

3.2. *endo*-Tetracyclo[4.3.1.$1^{2,5}$.$0^{1,6}$]undec-3-en-7-one 2

A mixture of trimethylsulfoxonium iodide (0.198 g, 0.9 mmol) and sodium hydride (0.036 g, 60%, 0.9 mmol) in dry DMSO (2 mL) under argon atmosphere was stirred for 30 min. A solution of tricyclodecadienone **1** (110 g, 0.75 mmol) in dry THF (2 mL) was added to the mixture in one portion and the mixture was stirred for 1 h. The reaction was quenched with water (20 mL) and extracted with diisopropyl ether (3×100 mL). The organic layers were combined, washed with water, brine, and dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel (EtOAc/hexane=1:6) and tetracycloundecenone **2** (0.080 g) was obtained as a colorless oil in 67% yield.



Scheme 6.

Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (dd, $^3J_{4,3}$=5.6 Hz, $^3J_{4,5}$=2.8 Hz, 1H, H_4), 6.44 (dd, $^3J_{3,4}$=5.6 Hz, $^3J_{3,2}$=2.8 Hz, 1H, H_3), 3.00 (m, 1H, H_5), 2.92 (d, $^3J_{2,3}$=2.8 Hz, 1H, H_2), 2.54 (m, $^3J_{8x,8n}$=17.6 Hz, $^3J_{8x,9x}$=8.8 Hz, 1H, H_{8x}), 2.39 (d, $^2J_{10a,10s}$=8.0 Hz, 1H, H_{10a}), 2.15 (dd, $^3J_{8n,8x}$=17.6 Hz, $^3J_{8n,9n}$=9.6 Hz, 1H, H_{8n}), 1.96 (dd, $^3J_{9x,9n}$=12.7 Hz, $^3J_{9x,8x}$=8.8 Hz, 1H, H_{9x}), 1.78 (m, 1H, H_{9n}), 1.70 (d, $^2J_{10s,10a}$=8.0 Hz, 1H, H_{10s}), 1.35 (d, $^2J_{11s,11a}$=9.8 Hz, 1H, H_{11a}), 1.35 (d, $^2J_{11a,11s}$=9.8 Hz, 1H, H_{11s}). ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 214.3 (quat.), 142.7, 140.7 (*tert*), 49.4, 46.1 (quat.), 45.1, 40.0 (*sec*), 43.8, 40.1 (*tert*), 28.5, 23.5 (*sec*). IR ($CDCl_3$): δ 2980 (C–H), 2940 (C–H), 2872 (C–H), 1718 (C=O) cm^{-1}. GC–MS (EI): *m*/*e* (%) 161 (11, M^++1), 160 (6, M^+), 117 (100). HRMS (EI): *m*/*e* 160.0888 [calcd for $C_{11}H_{12}O$ (M^+) 160.0888].

3.3. 10-Oxa-*endo*-tetracyclo[4.3.1.1^{2,5}.0^{1,6}]undec-3-en-7-one 3

Hydrogen peroxide (0.680 g, 35% aq, 7 mmol) was added to a solution of tricyclodecadienone **1** (0.101 g, 0.7 mmol) in dichloromethane (10 mL) at 0–5 °C, followed by the addition of NaOH aq (0.900 g, 5%, 1.1 mmol). After stirring overnight at room temperature, the reaction was complete (GC). Then satd NH_4Cl aq (10 mL) was added and the mixture was extracted with dichloromethane (2×100 mL). The organic layers were combined and dried over $MgSO_4$. After evaporating the solvent in vacuo, the crude product (0.115 g) was purified by preparative TLC on silica gel (EtOAc/hexane=1:2). Epoxide **3** (0.070 g) was obtained as a colorless oil in 61% yield. Byproduct **4** (0.022 g) was obtained as a white amorphous solid in 19% yield.

Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (m, 2H, H_3 and H_4), 3.06 (m, 1H, H_5), 3.03 (m, 1H, H_2), 2.76 (m, 1H, H_{8x}), 2.28 (m, 2H, H_{8n} and H_{9x}), 2.03 (d, $^2J_{11a,11s}$=8.0 Hz, 1H, H_{11a}), 1.88 (m, 1H, H_{9n}), 1.68 (d, $^2J_{11s,11a}$=8.0 Hz, 1H, H_{11s}). ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 208.1 (quat.), 141.7 (2×) (*tert*), 79.5, 73.2 (quat.), 44.6, 40.0 (*tert*), 46.9, 39.4, 21.3 (*sec*). IR ($CDCl_3$): δ 2999 (C–H), 2962 (C–H), 1743 (C=O) cm^{-1}. GC–MS (EI): *m*/*e* (%) 163 (9, M^++1), 162 (9, M^+), 134 (M^+−CO), 91 (100), 65 (26, $C_5H_5^+$). HRMS (EI): *m*/*e* 162.0681 [calcd for $C_{10}H_{10}O_2$ (M^+) 162.0680].

Compound **4**: (0.086 g, 65%) was obtained as a white amorphous solid. A pure sample was obtained by recrystallization from diisopropyl ether, mp 73–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (m, 2H, H_9, H_8), 3.21 (m, 1H, H_1), 2.85 (m, 1H, H_7), 2.64 (d, $^3J_{2,1}$=4.5 Hz, 1H, H_2), 2.52 (m, 1H, H_{4x}), 2.06 (m, 4H, H_{4n}, H_{5x}, H_{5n}, H_{10s}), 1.96 (br s, 1H, O*H*), 1.80 (d, $^2J_{10s,10a}$=8.0 Hz, 1H, H_{10a}). ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 204.6 (quat.), 137.7, 134.8 (*tert*), 87.5 (quat.), 63.5, 54.9, 45.8 (*tert*), 50.9, 42.4, 33.7 (*sec*). IR ($CDCl_3$): δ 3580 (O–H), 2960 (C–H), 2938 (C–H), 1735 (C=O), 1248 (C–O) cm^{-1}. GC–MS (EI): *m*/*e* (%) 163 (<1, M^+−H), 99 (100, M^+−C_5H_5), 66 (38, $C_5H_6^+$). HRMS (EI): *m*/*e* 164.0835 [calcd for $C_{10}H_{12}O_2$ (M^+) 164.0837].

3.4. 2-Methoxy-6-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one 5a

Hydrogen peroxide (60 mg 35%, 0.6 mmol) was added to a solution of **1** (0.088 g, 0.6 mmol) in dichloromethane/methanol (10 mL, 1:1) at room temperature, followed by the addition of KOH aq (0.680 g, 5%, 0.6 mmol). After 30 min, the reaction was complete (GC). Then satd NH_4Cl aq (10 mL) was added and the mixture was extracted with dichloromethane (2×100 mL). The organic layers were combined and dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the crude product (120 mg) was purified by preparative TLC on silica gel (EtOAc/hexane=1:2). Disubstituted tricyclodecenone **5a** (0.099 g) was obtained as a white solid in 85% yield and recrystallized from *iso*-propyl alcohol. Byproduct epoxide **3** (0.009 g) was obtained as a colorless oil in 9% yield.

Compound **5a**: mp: 62–63 °C (white crystals). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (dd, $^3J_{8,9}$=5.7 Hz, $^3J_{8,7}$=2.8 Hz, 1H, H_8 or H_9), 5.95 (dd, $^3J_{9,8}$=5.7 Hz, $^3J_{9,1}$=2.8 Hz, 1H, H_9 or H_8), 3.76 (s, 1H, O*H*), 3.57 (s, 3H, CH_3), 3.11 (br, 1H, H_7 or H_1), 2.83 (br, 1H, H_7 or H_1), 2.64 (m, 1H, H_{4x}), 2.12 (d, $^2J_{10s,10a}$=8.0 Hz, 1H, H_{10s}), 2.06 (m, 2H, H_{4n}, H_{5x}), 1.85 (m, 1H, H_{5n}), 1.84 (d, $^2J_{10s,10a}$=8.0 Hz, 1H, H_{10a}). ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 215.2 (quat.), 137.4, 134.7 (*tert*), 86.7, 83.4 (quat.), 53.6 (prim.), 52.7, 43.9 (*sec*), 48.6, 40.1, 32.8 (*tert*). IR ($CDCl_3$): δ 3446 (O–H), 2999 (C–H), 2959 (C–H), 1720 (C=O), 1135 (C–O) cm^{-1}. GC–MS (EI): *m*/*e* (%) 194 (1, M^+), 177 (2, M^+−OH), 129 (74, M^+−C_5H_5), 128 (100, M^+−C_5H_5-1), 66 (20, $C_5H_5^+$+1). HRMS (EI): *m*/*e* 194.0941 [calcd for $C_{11}H_{14}O_3$ (M^+) 194.0943].

3.5. 6-Methoxy-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one 6

To a solution of tricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one **1** (0.059 g, 0.4 mmol) in methanol (2 mL) was added dropwise 2.5 N NaOH aq (0.2 mL) solution at 0–5 °C (ice–water) under a nitrogen atmosphere. The reaction mixture was stirred for 15 min and then quenched with aqueous ammonium chloride (10 mL) and the aqueous phase extracted with ether (3×50 mL). The combined organic phase was washed with water (3×), dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. After purification by preparative TLC on silica gel (EtOAc/hexane=1:2) product **6** (0.070 g) was obtained as a colorless oil in 99% yield. The spectral data were in agreement with the literature.[7]

3.6. 3-Hydroxy-2-methoxy-cyclopent-2-enone 7

3.6.1. Method A

Flash vacuum thermolysis (pressure: 0.05 mBar, sublimation oven: 110 °C, FVT oven: 500 °C, collection cooler: −80 °C) of **5a** (9 mg 0.046 mmol), followed by purification by preparative TLC on silica gel (EtOAc/hexane=1:1) provided product **7** (0.005 g, 85% yield) as a slightly yellow colored solid, which was recrystallized from *iso*-propyl alcohol.

3.6.2. Method B

Cyclopentenoid **7** was synthesized according to a procedure by Hesse and Mix[3] and analyzed. The analytical data are in agreement with those of the FVT product **7** via method A.

Compound **7**: mp: 134–135 °C. ^{1}H NMR (100 MHz, $CDCl_3$): δ 6.58 (br, 1H, O*H*), 3.83 (3H, OCH_3), 2.49 (s, 4H, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75–4.25 (v br, 1H, O*H*), 3.86 (3H, OCH_3), 2.47 (s, 4H, CH_2). ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 186.0 (2×) (quat.), 135.4 (*tert*), 59.0 (prim.), 27.1 (2×) (*sec*). IR ($CDCl_3$): δ 3506 (O–H), 2940 (C–H), 2959 (C–H), 1745 (weak, C═O), 1703 (weak, C═O), 1593 (strong, C═C),1116 (C–O) cm^{-1}. GC–MS (EI): *m*/*e* (%)129 (40, M^++1), 128 (90, M^+), 110 (5, M^+−18), 71 (14, M^+−57), 57 (100, C_3H_4O+1), 128 (100, M^+−C_5H_5-1), 66 (20, $C_5H_5^+$+1).

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