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THE FORMATION OF SPIRO-BRIDGED DIMERS OF CYCLO-OCTANE–1,2–DICARBONYL COMPOUNDS *VIA* DOMINO ALDOL–CYCLOALKYLATION[#]

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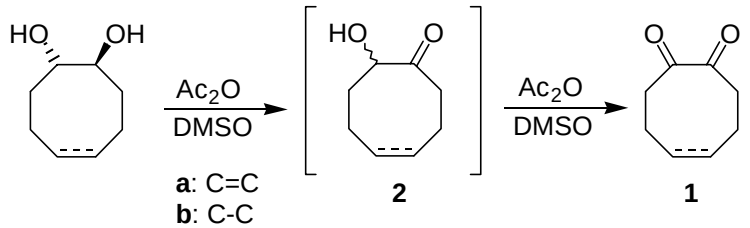
Abstract - Starting from the corresponding 8-membered cyclic 1,2-diones, *spiro*-bridged cyclic dimers were prepared in moderate to good yields *via* barium oxide/ hydroxide mediated coupling, followed by *in situ* methylation with dimethyl sulfate.

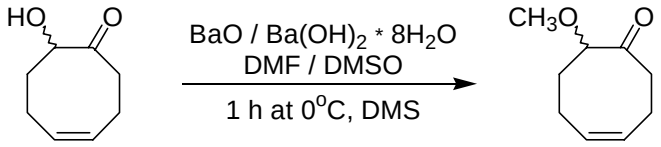
During our ongoing studies regarding new compounds for absolute asymmetric synthesis,[1] we became interested in the synthesis and chemistry of 8-membered cyclic α-diones. A standard approach to these target compounds is oxidation with activated DMSO,[2] and prolonged reaction of the corresponding vicinal diols with acetic anhydride/DMSO gave the desired cyclic 1,2-diones (**1**) in moderate yields of 30-35% (Scheme 1).[5]



Scheme 1

Two main factors limited the efficiency of the oxidation: (1) incomplete oxidation led to the isolation of larger amounts of the primary oxidation products – α-hydroxy ketones (**2**) – as identified for **2a** by comparison with independently synthesized specimen,[6] and (2) the desired diones tend to dimerize in the presence of base.[7] Although the later process is limited to 8-membered cyclic 1,2-diones,[7] we turned our

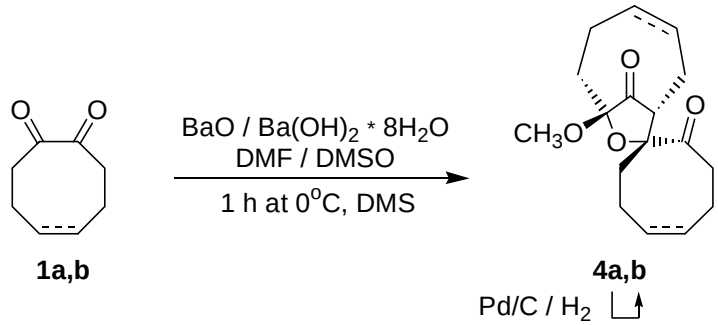
attention to an efficient access to these unique *spiro*-bridged tricyclic substrates. Since the dimeric compounds are known to be thermally unstable,[7b] a simple pathway to stable derivatives was additionally desirable. A suitable procedure was found in the barium oxide/hydroxide-mediated coupling and *in situ* methylation with dimethyl sulfate (DMS), which is known in the literature as a mild and efficient method for the methylation of α-hydroxy ketones.[8] Indeed, when *e.g.* **2a** was subjected to this procedure, the corresponding methoxy compound **3** was readily obtained in a good yield of 77% (Scheme 2).



2a **3**

Scheme 2

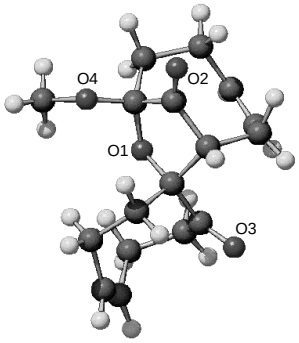
With the α-diketones (**1**) as starting materials, the desired *spiro*-bridged dimers (**4**) were obtained in good and moderate yields of 79% (**4a**) and 53% (**4b**), respectively (Scheme 3). To prove the formation of identical diastereoisomers, **4b** was independently synthesized *via* hydrogenation of **4a** in 94% yield.[9] VT NMR analysis unambiguously revealed the identity of both compounds (**4b**).

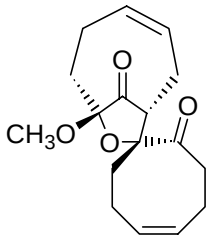


1a,b **4a,b**

Scheme 3

Crystallization from *n*-hexane gave suitable crystals of **4a** for X-Ray crystallographic analysis, which allowed us to determine the unknown stereochemistry of the tricyclic dimer (Figure 1).[10] The structure of **4a** is remarkable with respect to the conformations of the two cyclooctenone rings. The cyclooctenone ring, which is part of the bridging *spiro* moiety is unusually distorted, whereas the second cyclooctenone ring is relaxed in a *half-chair* conformation (an intermediate of a *chair*-to-*boat* inversion).[11] The central *spiro* ring exists in an envelope conformation with the *spiro*-carbon at the apex.

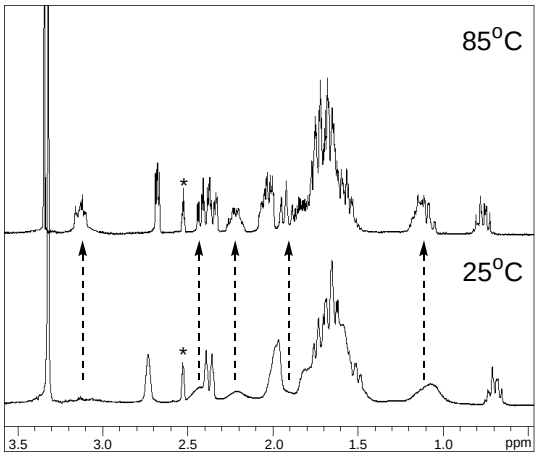


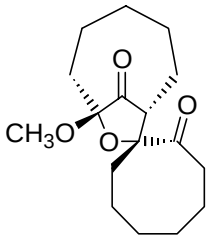


4a

Figure 1. Structure of **4a** in the crystal.

The conformations of **4a** and **b** were further analyzed by means of VT ^{1}H-NMR measurements in DMSO-d_6. Compound (**4a**) showed almost no changes in chemical shifts within the broad temperature range of 25°C to 125°C (not shown) implying that the structure of the molecule is particularly rigid. In contrast, the VT ^{1}H-NMR studies on **4b** revealed its flexible structure (Figure 2). Whereas only broad signals were recorded at 25°C, the resolution of the signals improved steadily with raising the temperature to 85°C.



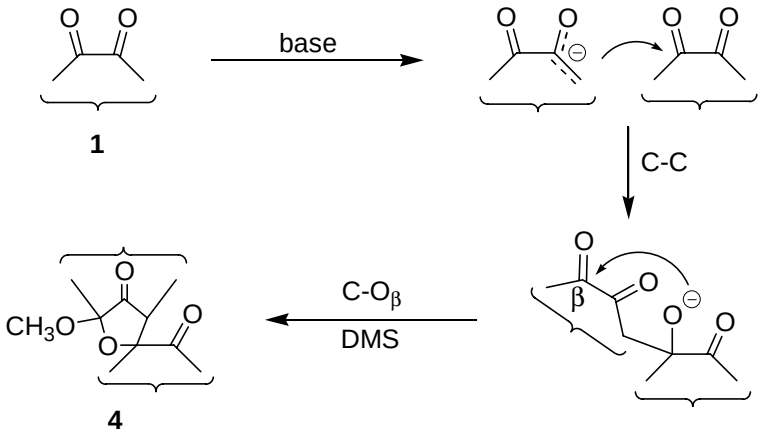


4b

Figure 2 VT ^{1}H-NMR (400 MHz, DMSO-d_6) measurements for **4b**.

Since only one diastereoisomer was formed, a chelating effect by the barium cation is postulated.[12] This assumption was tested for dione (**1a**) by comparing several group-I and group-II metal hydroxides, *i.e.* LiOH, NaOH, KOH, CsOH, $Mg(OH)_2$ and $Ba(OH)_2$. Among these bases, solely CsOH and the mixture of $BaO/Ba(OH)_2$ gave good results and **4a** was found as major compound in yields higher 60%. KOH readily gave a mixture of 3 dimeric products in a total amount of 69% (including 24% of **4a**). All other metal hydroxides showed only low reactivity and gave mainly sluggish mixtures of C- and O-methylated monomers. These findings clearly indicate that the size of the metal cation controls the diastereoselective formation of **4**,[12] whereas the basicity controls the entire equilibrium of the reaction. Key step in the mechanistic scenario (Scheme 4)[7b] is the formation of the conjugated monoenolates of **1**, which undergo a

domino sequence of *intermolecular* Aldol-reaction and *intramolecular* cycloalkylation.[13] The later ring-closure step proceeds regioselectively at the β-carbonyl group (β with respect to the direct C-C bond). Subsequent methylation with DMS affords the stable *spiro* dimers (**4**).



Scheme 4

EXPERIMENTAL

Melting points were measured on a Mettler Toledo FP62 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL EX400 spectrometer (400 MHz and 100 MHz, respectively) using the solvent residual peak as internal standard. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. MS spectra were recorded on a JEOL JMS-DX303 spectrometer. IR spectra were recorded on a JASCO FT/IR-230 or Perkin Elmer 1600 Series FT/IR spectrometer, UV/VIS spectra on a Shimadzu UV-3101PC spectrophotometer using *n*-hexane (Kanto Chemical, for spectroscopy) as solvent. Solvents and reagents were commercially available and were used without further purification. Compounds (**1a**,**b**)[5] and (**2a**)[6] were prepared *via* literature procedures. In case of compounds (**1**) prolonged reaction times (3-5 days) were necessary to reach total conversion.

8-Methoxy-4-cyclooctenone (3)

To a solution of 2 g (14.3 mmol) of **2a** in a mixture of 30 mL of DMSO and 30 mL of DMF were added 8.7 g (57 mmol) of barium oxide and 4.5 g (14.3 mmol) of barium hydroxide octahydrate at 0°C. After stirring for 1 h,[14] 20 mL (215 mmol) of dimethyl sulfate were added dropwise at 0°C. After stirring overnight and warming up to rt, 25 mL of concentrated aqueous ammonia solution were added dropwise. The reaction mixture was acidified with 4 N hydrochloric acid, poured into 150 mL of water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (twice) and brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by column chromatography (SiO_2, *n*-hexane/ethyl acetate 9:1) gave 1.7 g (11.0 mmol, 77%) of **3** as a colorless oil. The original protocol[8] used large excess amounts of the reagents, which were not necessary in our case. ^{1}H NMR ($CDCl_3$): δ 1.58 (ddd, *J* = 12.2, 12.2, 2.7 Hz, 1 H), 1.90 (ddd, *J* = 12.2, 13.4, 6.4 Hz, 1 H), 1.90 (m, 1 H), 2.09 (m, 1 H),

2.32 (ddd, *J* = 12.6, 12.4, 5.2 Hz, 1 H), 2.52 (m, 1 H), 2.95 (ddd, *J* = 12.6, 4.8, 4.8 Hz, 1 H), 3.06 (m, 1 H), 3.39 (s, 3 H, OCH_3), 3.76 (dd, *J* = 6.4, 2.7 Hz, 1 H), 5.66 (m, 2 H, H_{olef}). ^{13}C NMR ($CDCl_3$): δ 20.2 (CH_2), 21.1 (CH_2), 29.3 (CH_2), 44.4 (CH_2), 57.5 (OCH_3), 86.4 (CH), 130.7 (2 C, CH_{olef}), 215.0 (CO). MS (EI, 70 eV): *m/z* (%) 154 (M^+, 75), 126 (38), 122 (7), 110 (100), 97 (92), 94 (41), 79 (90), 68 (89), 58 (63), 41 (33). IR (film) ν (cm^{-1}): 2935 (br, s), 1709 (C=O, s), 1462 (m), 1203 (m), 1107 (s), 887 (w), 737 (m). UV/VIS (*n*-hexane) λ_{max} (ε): 297 nm (14.9). Anal. Calcd for $C_9H_{14}O_2$: C 70.10, H 9.15. Found: C 70.02, H 9.24.

Cyclooctendione-dimer (4a)

Following the above procedure 2 g (14.4 mmol) of cyclooct-5-ene-1,2-dione (**1a**) gave, after crystallization from *n*-hexane at -30°C, 1.6 g (5.6 mmol, 79%) of **4a** as colorless prisms. mp: 123-125°C. ^1H NMR ($CDCl_3$): δ 1.54 (dd, *J* = 13.2, 13.2 Hz, 1 H), 1.74 (m, 2 H), 1.91 (m, 2 H), 2.04 (m, 2 H), 2.19 (m, 2 H), 2.34 (ddd, *J* = 12.6, 12.6, 5.6 Hz, 1 H), 2.50 (ddd, *J* = 14.8, 8.4, 8.4 Hz, 1 H), 2.65 (m, 1 H), 2.74 (dd, *J* = 8.0, 2.4 Hz, 1 H), 3.22 (m, 1 H), 3.39 (m, 1 H), 3.51 (s, 3 H, OCH_3), 5.48 (m, 1 H, H_{olef}), 5.68 (m, 2 H, H_{olef}), 5.78 (m, 1 H, H_{olef}). ^{13}C NMR ($CDCl_3$): δ 20.6 (CH_2), 21.3 (CH_2), 23.2 (CH_2), 25.3 (CH_2), 27.9 (CH_2), 38.8 (CH_2), 45.2 (CH_2), 50.3 (OCH_3), 59.3 (CH), 90.8 (Cq), 104.9 (Cq), 128.2 (CH_{olef}), 130.3 (CH_{olef}), 130.8 (CH_{olef}), 133.6 (CH_{olef}), 212.2 (CO), 212.9 (CO). MS (EI, 70 eV): *m/z* (%) 290 (M^+, 25), 262 (26), 230 (18), 188 (19), 161 (100), 135 (23), 91 (30), 67 (25), 41 (18). IR (KBr disc) ν (cm^{-1}): 2951 (br, s), 1770 (C=O, s), 1705 (C=O, s), 1462 (w), 1196 (w), 1118 (m), 1068 (s), 941 (m), 741 (m). UV/VIS (*n*-hexane) λ_{max} (ε): 291 nm (37.1). Anal. Calcd for $C_{17}H_{22}O_4$: C 70.32, H 7.64. Found: C 70.10, H 7.76.

Cyclooctandione-dimer (4b)

Following the above procedure 1.6 g (11.4 mmol) of cyclooctane-1,2-dione (**1b**) gave, after crystallization from *n*-hexane at -30°C, 889 mg (3.0 mmol, 53%) of **4b** as a colorless solid. Alternatively, **4b** was prepared from **4a** *via* hydrogenation: 229 mg (0.79 mmol) of **4a** were dissolved in 50 mL of methanol. 50 mg of 10% Pd/C were carefully added under nitrogen, and the reaction mixture was stirred under positive hydrogen pressure for 48 h. The reaction mixture was filtrated over Celite, and the remaining solid material was washed with 50 mL of MeOH. Evaporation of the solvent gave 218 mg (0.74 mmol, 94%) of **4b** as a colorless solid. mp: 93-99°C. ^1H NMR (85°C, DMSO-d_6): δ 0.78 (m, 1 H), 1.12 (m, 2 H), 1.50-1.90 (br m, 12 H), 1.92 (m, 1 H), 2.04 (m, 2 H), 2.22 (m, 1 H), 2.37 (m, 2 H), 2.68 (dd, *J* = 7.8, 2.6 Hz, 1 H), 3.10 (m, 1 H), 3.34 (s, 3 H, OCH_3). ^{13}C NMR (85°C, DMSO-d_6): δ 21.3 (CH_2), 24.4 (CH_2), 24.9 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 38.5 (CH_2), 41.9 (CH_2), 49.0 (OCH_3), 53.5 (CH), 89.3 (Cq), 101.9 (Cq), 213.8 (CO), 215.4 (CO). MS (EI, 70 eV): *m/z* (%) 294 (M^+, 23), 266 (28), 234 (12), 206 (9). IR (KBr disc) ν (cm^{-1}): 2928 (br, s), 1763 (C=O, s), 1698 (C=O, s), 1454 (s), 1141 (s), 1064 (br, s), 943 (m), 758 (w). Anal. Calcd for $C_{17}H_{26}O_4$: C 69.36, H 8.90. Found: C 69.61, H 8.74.

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REFERENCES AND NOTES

Dedicated to Prof. Sang-Chul Shim on the occasion of his 66th birthday.

1. B. L. Feringa and R. A. van Delden, *Angew. Chem., Int. Ed.*, 1999, **38**, 3418.
2. For a review, see: A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165. However, most of the applied literature procedures were found irreproducible[3] or not suitable for large scale synthesis,[4] respectively.
3. From α-bromo ketones using KI/DMSO: D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, 1975, **40**, 1990.
4. a) From vicinal diols using TFAA/DMSO: C. M. Amon, M. G. Banwell, and G. L. Gravatt, *J. Org. Chem.*, 1987, **52**, 4851; b) from cycloalkenes using $KMnO_4/CuSO_4/Cu(OAc)_2$: S. Baskaran, J. Das, and S. Chandrasekaran, *J. Org. Chem.*, 1989, **54**, 5182.
5. a) P. Yates, E. G. Lewars, and P. H. McCabe, *Can. J. Chem.*, 1972, **50**, 1548; b) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, 1967, **89**, 2416.
6. Prepared *via* epoxide opening in 43% yield: a) R. J. Anderson and C. A. Henrick, *J. Am. Chem. Soc.*, 1975, **97**, 4327; b) M. A. Khuddus and D. Swern, *J. Am. Chem. Soc.*, 1973, **95**, 8393.
7. a) K. Kawada, R. S. Gross, and D. S. Watt, *Synth. Commun.*, 1989, **19**, 777. For contradictory results, see [4a]; b) D. V. Rao, F. A. Stuber, and H. Ulrich, *J. Org. Chem.*, 1979, **44**, 456.
8. a) T. W. Greene, and P. G. M. Wuts, 'Protective Groups in Organic Synthesis', Wiley, New York, 1991; b) J. T. A. Reuvers and A. de Groot, *J. Org. Chem.*, 1986, **51**, 4594; c) R. Kuhn, H. Egge, R. Brossmer, A. Gauhe, P. Klesse, W. Lochinger, E. Röhm, H. Trischmann, and D. Tschampel, *Angew. Chem.*, 1960, **72**, 805.
9. T. A. Robbins, V. Van Toan, J. W. Givens III, and D. A. Lightner, *J. Am. Chem. Soc.*, 1992, **114**, 10799.
10. Crystal data for **4a**: $C_{17}H_{22}O_4$; M = 290.36; from *n*-hexane; tetragonal, space-group $P\,4_12_12$; a = 9.1731(8), c = 37.300(2) Å; V = 3138.6(6) Å^3; Z = 8; d_{calc} = 1.229 g/cm^3; unique reflections: 2194; reflections $I > 2\sigma(I)$: 1699; $R1$, R_w: 0.039, 0.052. The crystallographic data has been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-167827. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

11. a) H. Tsuneishi, Y. Inoue, T. Hakushi, and A. Tai, *J. Chem. Soc., Perkin Trans. 2*, 1993, 457; b) N. L. Allinger, and J. T. Sprague, *J. Am. Chem. Soc.*, 1972, **94**, 5734.
12. a) T.-Y. Luh, *Synlett*, 1996, 201; b) A. Loupy and B. Tchoubar, 'Salt Effects in Organic and Organometallic Chemistry', VCH, Weinheim, 1992.
13. For other domino reactions, see: a) T. Lavoisier-Gallo, E. Charonnet, J.-M. Pons, M. Rajzman, R. Faure, and J. Rodriguez, *Chem. Eur. J.*, 2001, **7**, 1056; b) P. Langer and V. Köhler, *Org. Lett.*, 2000, **2**, 1597.
14. Stirring for 1 h was essential for the success of the dimerization. Otherwise, the methylated monoenolates of **1** became the major products, see: M. S. Gibson, *J. Chem. Soc.*, 1962, 681.