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SYNTHESIS OF SYN- AND ANTI-TRICYCLO [4.1.0.0^{2,4}] HEPTAN-5-ONES AND RELATED COMPOUNDS

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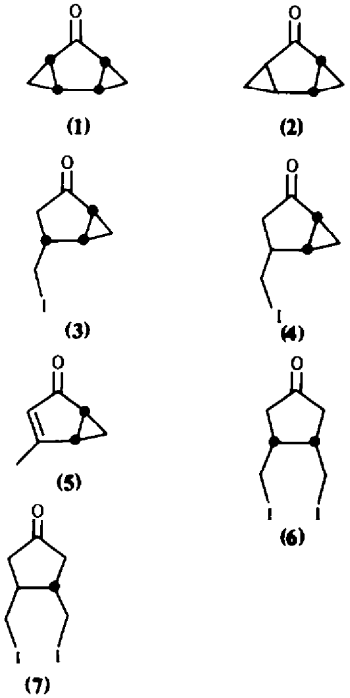
Abstract—A convenient entry to both title compounds **1**, and **2**, as well as to *cis*- and *trans*-4-iodomethyl-bicyclo [3.1.0]-hexan-2-ones **3** and **4** and to 4-methyl-bicyclo [3.1.0]-hex-3-en-2-one **5** involving base-promoted reactions of *cis*- and *trans*-3,4-diiodomethylcyclopentanones **6** and **7** is reported, and the behaviour of **6** and **7** towards different bases.

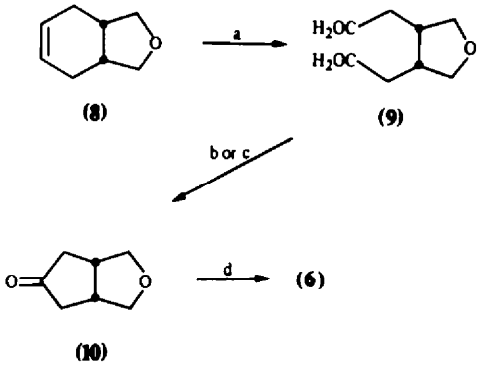
During the last years, the synthesis of stable mono- and bis-homo derivatives of the exceedingly unstable cyclopentadienones have been receiving considerable attention.[1,2] This class of compounds exhibits several interesting properties: (a) as precursors of a bis-homo antiaromatic cation, rising by solvolytic process and undergoing a series of coupled degenerate cyclopropylcarbinyl–cyclopropylcarbinyl[3] cationic rearrangements;[4] (b) as precursors of epimeric carbenes[5] undergoing a number of unusual σ-bond fragmentation processes such as the conversion of cyclopropylidene to allene or the cleavage of cyclopropylcarbene into ethylene and acetylene. The lack of a synthetic methodology for an unequivocal and practical route to **1-5** prompted us to develop new synthetic methods for their preparation starting from **6** and **7**.



Preparation of **6** *and* **7**

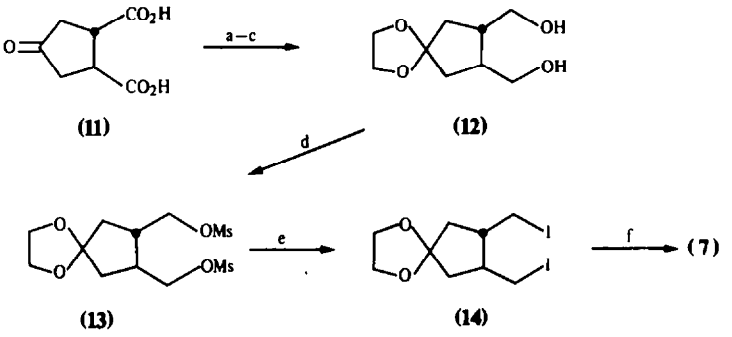
The pathway to **6** began with the ozonolysis of the known[6] cis-bicyclic unsaturated ether **8** at $-78°$ in 1:2 CH_2Cl_2–MeOH solution, followed by oxidative work-up with performic acid, to provide the crystalline dicarboxylic acid **9** in 90% yield. Its pyrolysis at atmospheric pressure in the presence of powdered iron and barium hydroxide afforded the bicyclic ketone **10** in 55% yield.

Alternatively **10** was obtained in 50% yield by cyclization of **9** in refluxing acetic anhydride in the presence of sodium acetate. The ether ring of **10** was then cleaved by treatment with 67% hydroiodic acid and red phosphorus to produce the di-iodomethyl derivative **6** in 54% yield (Scheme 1).



Reagent: (a) O_3, $-78°C$; HCO_2H–H_2O_2; (b) $Ba(OH)_2$, Fe; (c) Ac_2O, heat; (d) HI 67%

The route to **7** employed a reported three steps sequence to transform the known[7] trans-cyclopentanone-3,4-dicarboxylic acid **11** to the dihydroxymethyl derivative **12**, then converted to the corresponding dimesylate **13** under standard conditions. The latter was subjected to exchange with sodium iodide in refluxing acetone to give the ketalized di-iodomethyl cyclopentanone **14**, easily transformed to **7** by acid treatment, in 63% overall yield from **11**.



Reagent (a) MeOH, H^+; (b) $(CH_2OH)_2$, p-Ts-OH; (c) $LiAlH_4$i (d) $MeSO_2Cl$, TEA; (e) NaI, Me_2CO; fH^+

Having both *cis*- and *trans*-3,4-di-iodomethylcyclopentanone **6** and **7**, we studied their chemical behaviour towards bases and devised conditions suitable for their easy transformation into several mono- and bis-homo derivatives of cyclopentadienones. Such an improved approach was featured both by the lack of tedious chromatographic separations[2] or by the extremely mild and selective experimental conditions, which are particularly essential in the case of the rather unstable bis-homo derivatives.

RESULTS AND DISCUSSION

The action of different bases on **6** and **7** resulted in the pattern of reactivity summarized in Table 1. Taking into account the reactions carried out in the presence of bases such as $KHCO_3$ and K_2CO_3, **6** and **7** seem to behave similarly. However **7** does undergo easier proton abstraction compared to **6** followed by intramolecular substitution, as demonstrated by the formation of considerable quantities of **2** already in the presence of $KHCO_3$.

This small but significant difference encouraged us to investigate the behaviour of **6** and **7** towards a more hindered base which should possibly stress effects due to the different stereochemistry of both **6** and **7** (the starting points) as well as of the corresponding **3** and **4** (the final points). Thus treatment of **7** with DBU in benzene gave rise exclusively to the tricyclic compound **2**, while **6** produced a mixture of **1** and **5** or exclusively **5**, depending on the temperature.

Table 1

Starting materials	Experimental conditions	Reaction time (min.)	Products*
(6)	$KHCO_3$/EtOH ass. reflux	150	(5)
(7)	" " " "	150	(4)(50%)+(2)(50%)
(6)	K_2CO_3/EtOH ass. reflux	240	(1)
(7)	" " " "	240	(2)
(6)	DBU/Benzene 0°C	30	(1)(50%)+(5)(50%)
(7)	" " "	30	(2)
(6)	DBU/Benzene reflux	300	(5)
(7)	" " "	300	(2)
(3)	K_2CO_3/EtOH ass. reflux	120	(1)
(3)	DBU/Benzene reflux	210	(5)
(4)	K_2CO_3/EtOH ass. reflux	120	(2)
(4)	DBU/Benzene reflux	210	(2)

* The yields are always quantitative.

The different reaction courses may be accounted for the different stereochemistry of the bicyclic systems **3** and **4** which may cause competition between proton abstraction and elimination reaction. The last important point concerns the yields, which are always practically quantitative: it follows that the selected experimental conditions above reported feature a superior route for the preparation of compounds **1–5**.

EXPERIMENTAL

Reaction courses and product mixtures were routinely monitored by TLC on precoated silica gel 60 F_{254} plates (Merck). IR spectra were measured on a Perkin Elmer 237 spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WP 80 spectrometer and peak positions are given in ppm downfield from tetramethylsilane as an internal standard. All drying operations were performed over anhydrous Na_2SO_4.

cis-Tetrahydrofuran-3,4-diacetic acid **9**

A solution of **8**[6] (10 g, 81 mmol) in a 2:1 mixture (200 ml) of CH_3OH and CH_2Cl_2 was placed in a standard ozonolysis vessel. The reaction mixture was cooled in an acetone–dry ice bath to about −70°, while ozonized oxygen was passed through until all the product has reacted (monitored by TLC). Nitrogen was next bubbled through the solution to displace any free ozone and the solvent was removed at reduced pressure. The residue, dissolved in a mixture of formic acid 99% (70 ml) and 36% hydrogen peroxide (10 ml), was heated at 50° for 8 h. Evaporation of solvents in vacuo gave **9** (13.6 g, 90%) as a white solid: m.p. 138–140° (MeOH); IR (Nujol) 1710 cm^{-1}. Calc for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.91; H, 6.49%.

cis-3-Oxabicyclo [3.3.0] *octan-7-one* **10**

Method A. Compound **9** (6.2 g, 33 mmol), Ba $(OH)_2 \cdot 8H_2O$ (0.95 g), and iron powder (6.5 g) were thoroughly mixed in a round-bottom flask and heated with an open flame. The ketone **10** was separated from the codistilled water, dried and distilled to yield 2.3 g (55%) of a yellow-colored oil: b.p. 105–110° (15 mm Hg); IR (film) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00–2.75 (m, 4H), 3.00 (m, 2H), 3.62 (dd, 2H, J = 9 Hz, J = 4 Hz), 4.00 (dd, 2H, J = 9 Hz, J = 7 Hz). Calc for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.88; H, 7.81%.

Method B. A stirred solution of **9** (4 g, 21 mmol) in Ac_2O (50 ml) was refluxed for 2.5 h; after addition of NaOAc (5 g) the reflux was continued for 2.5 h. The mixture was concentrated *in vacuo* and the residue treated cautiously with 10 ml MeOH (exothermic reaction) and filtered. The filtrate was concentrated to a semi-solid mass, water (20 ml) was added and the mixture made basic with $KHCO_3$. Ether extraction of the basic aqueous solution and elimination of the solvent *in vacuo* left **10** (1.34 g, 50%).

cis-3,4-Diiodomethylcyclopentanone **(6)**

A solution of **10** (2 g, 16 mmol) in AcOH (35 ml) was heated at 130–135° in the presence of HI 67% (35 ml) and red phosphorus (4 g) for 3 h. After removal of red phosphorus by filtration, the filtrate was extracted with $CHCl_3$ (3 × 25 ml) and the extracts were washed throughly with saturated $NaHCO_3$ solution, then with saturated brine. After drying, the solvent was evaporated in vacuo to leave **6** (3,12 g, 54%) as a solid which was recrystallized from Et_2O: m.p. 92–93°; IR (Nujol) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 4H), 2.80 (m, 2H), 3.2 (m, 4H). Calc for $C_7H_{10}OI_2$: C, 22.95; H, 2.73. Found: C, 22.99; H, 2.88%.

trans-7,8-Bismesyloxymethyl-1,4-dioxaspiro [4.4] *nonane* **13**

To a cooled solution (−20°) of the known diol[1] **12** (4 g, 21 mmol) in CH_2Cl_2 (80 ml), containing 13.6 ml (97 mmol) of triethylamine, 4.8 ml (61 mmol) of mesyl chloride were added dropwise. After complete disappearance of the starting material, the reaction mixture was diluted with CH_2Cl_2 and washed twice with water and brine. Evaporation of the dried organic phase at reduced pressure gave a residue which, after standing, solidified. Crystallization from MeOH afforded **13** (6.6 g, 90%): 77–78°; IR ($CHCl_3$) 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.6–2.5 (m, 6H), 3 (s, 6H), 3.9 (s, 4H), 4.2 (d, 4H, J = 6 Hz). Calc for $C_{11}H_{20}O_8S_2$: C, 38.37; H, 5.81. Found: C, 38.30; H, 5.72%.

trans-7,8-Diiodomethyl-1,4-dioxaspiro [4.4] *nonane* **14**

Sodium iodide (6.5 g, 43.5 mmol) was added to a solution of **13** (5 g, 14.5 mmol) in freshly distilled acetone (100 ml) and the mixture refluxed for 12 h. The solution was then filtered and the solvent evaporated to reduced pressure. The residue, which on standing solidified, was crystallized from n-hexane affording **14** (5 g, 84%): p.f. 47–48°; ^{1}H NMR ($CDCl_3$): δ 1.6–2.4 (m, 6H), 3.1–3.6 (m, 4H), 3.9 (s, 4H). Calc for $C_9H_{14}O_2I_2$: C, 26.47; H, 3.43. Found: C, 26.61; H, 3.30%.

trans-3,4-Diiodomethylcyclopentanone **7**

A solution of ketal **14** (5 g, 12 mmol) in a mixture of MeOH (100 ml) and water (5 ml) containing g 2 of Amberlite H–15, was stirred for 6 h at 40°. The reaction mixture was filtered, most of the solvent concentrated in vacuo and the residue poured in water (20 ml). Extraction with ether (3 × 20 ml), followed by evaporation of the dried extracts gave **7** as a colorless oil (4 g, 90%). IR (film) 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.9–2.9 (m, 6H), 3.2–3.6 (m, 4H). Calc for $C_7H_{10}OI_2$: C, 22.95; H, 2.73. Found: C, 23.14; H, 2.57%.

syn-Tricyclo[4.1.0.0.^{2,4}]*heptan-5-one* **(1)**

A solution of **6** (3 g, 8.2 mmol) in absolute EtOH (40 ml) containing K_2CO_3 (5.8 g, 41.4 mmol), was refluxed for 4 h. The reaction mixture was evaporated in vacuo at room temperature and the residual product was diluted with water and extracted with $CHCl_3$ (3 × 25 ml). The dried organic phase was then concentrated to dryness to yield **1** as an oily residue, which was purified by filtration through Florisil (Et_2O eluent). Spectroscopic properties are identical with those previously reported by Dolbier *et al.*[2] Calc for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.73; H, 7.49%.

anti-Tricyclo [4.1.0.0^{2,4}] *heptan-5-one* **2**

By analogy to the procedure for the preparation of **1**, **7** gave **2** as a solid m.p. 41–42°. Spectroscopic properties are identical with those previously reported by Dolbier *et al.*[2]. Calc for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.43%.

cis-4-Iodomethylbicyclo [3.1.0] *hexan-2-one* **3**

A solution of **6** (3g, 8.2 mmol) in absolute EtOH (40 ml) containing $KHCO_3$ (4.2 g, 41.2 mmol), was refluxed for 2.5 h. The reaction mixture was evaporated *in vacuo* at room temperature and the residual products were diluted with water and extracted with $CHCl_3$ (3 × 20 ml). The dried organic phase was then concentrated to dryness to yield quantitatively **3** as an oily residue which was purified by filtration through Florisil (Et_2O eluent). IR (film) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.9–1.35 (m, 2H), 1.62–2.5 (m, 4H), 2.6–3 (m, 1H), 3–3.3 (m, 2H). Calc for C_7H_9OI: C, 35.59; H, 3.81. Found: C, 35.27; H, 3.69%.

trans-4-Iodomethyl bicyclo [3.1.0] *hexan-2-one* **4**

By analogy to the procedure for the preparation of **3** **7** gave quantitatively a 1:1 mixture if **4** and **2** separated by flash chromatography over silica gel (Et_2O-cyclohexane 1:1). IR (film) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.86–1.04 (m, 1H), 1.08–1.46 (m, 2H), 1.66–2.8 (m, 4H), 3.26 (d, 2H, J = 7). Calc for C_7H_9OI: C, 35.59; H 3.81. Found: C, 35.43; H, 3.71%.

4-Methylbicyclo [3.1.0] *hex-3-en-2-one* **5**

A solution of **6** (3 g, 8.2 mmol) and DBU (4.5 ml) in benzene (45 ml) was heated was heated under reflux for 5 h. The cooled mixture was washed with water, then with diluted H_2SO_4 (10%). After drying, the solvent was evaporated *in vacuo* at room temperature to leave **5** as a yellow-colored oil, which was purified by filtration through Florisil (Et_2O eluent). IR (film) 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1–1.4 (m, 1H), 1.42–1.6 (m, 1H), 2.1 (d, 3H, J = 1 Hz), 2–2.45 (m, 2H), 5.35 (q, 1H, J = 1 Hz). Calc for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.64; H, 7.50%. With the same procedure **7**, **3** and **4** afforded respectively **2**, **5** and **2**.

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