Synthesis of Functionalized Cyclopentenecarboxaldehydes

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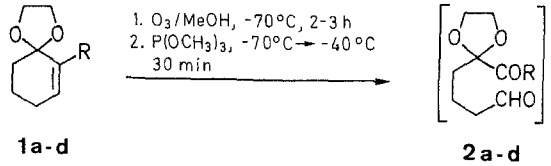
Ozonolysis of the ethylene acetals of 2-substituted 2-cyclohexenones followed by cyclization of the intermediate 1,6-dicarbonyl compounds affords 6-substituted 7-formyl-1,4-dioxaspiro[4,4]non-6-enes in modest yields. The same procedure applied to protected 2-substituted 2-cyclohexenols gives 2-substituted 3-formyl-2-cyclopentenyl 2-methoxyethoxymethyl ethers in satisfactory yields.

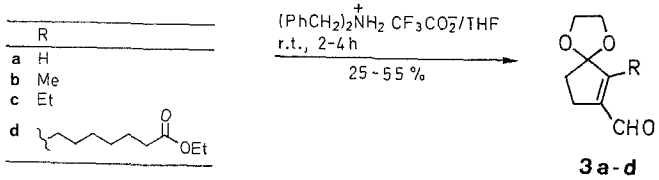
Cyclopentanoid compounds play a fundamental role in synthetic organic chemistry, both as intermediates and as targets. Stimulated by the biological importance of cyclopentanoid natural products (*e.g.*, prostaglandin, prostacyclin, rethrolones), considerable effort has been devoted to the development of new methods for the construction of five-membered rings.[1]

During our studies on the total synthesis of the ophiobolane skeleton,[2] we prepared in one step 7-formyl-1,4-dioxaspiro [4.4]non-6-ene (**3a**); this result prompted us to further investigate this ring-contraction reaction.

We here report the synthesis of functionalized cyclopentenes and make a comparison with literature data. Our first approach was based on the ozonolysis of 6-substituted 1,4-dioxaspiro[4.5]dec-6-enes **1** to give the intermediate 1,6-dicarbonyl compounds **2** which, in turn, were immediately cyclized to 6-substituted 7-formyl-1,4-dioxaspiro[4.4]non-6-enes **3** without isolation and purification.



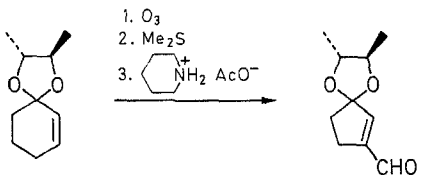
1a-d **2a-d**



3a-d

The ozonolyses were carried out in participating solvents (methanol or ethanol)[3] at −70 °C; in the reduction step, trimethyl phosphite was used at low temperatures. The use of other solvents or reducing agents (like triphenylphosphine, dimethyl sulfide) led to poorer yields or to complex reaction mixtures whose components were not clearly detectable. The best catalyst for the cyclization of compounds **2** was found to be dibenzylammonium trifluoroacetate;[4] the method of Woodward et al.[5] (piperidinium acetate) gave lower yields in all cases. As shown in Table 1, 6-substituted 7-formyl-1,4-dioxaspiro[4.4]non-6-enes **3** were obtained in modest overall yields, except for **3b** (55%).

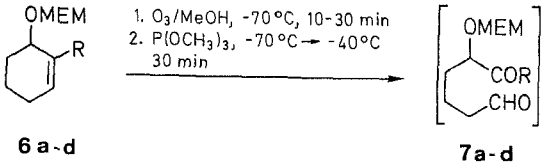
It has been reported[6] that the masked 3-oxocyclopentenecarboxyaldehyde **5** can be readily obtained by a similar procedure in 90% overall yield. We tried to follow the described procedure with the same starting material **4** but we never succeeded in obtaining more than 30% yield of compound **5**.



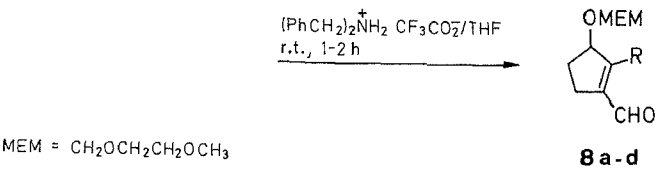
4 **5**

In view of the instability of the aldehydes **3a** and **5**, (oxidation and hydrolytic agents possibly being responsible for loss of product), we carried out a quantitative GLC analysis of the reaction mixtures, using naphthalene as the internal standard; however, the yields were never higher than those reported here. Despite these modest yields, the present method looks promising for the synthesis of 6-substituted 7-formyl-1,4-dioxaspiro[4.4]-non-6-enes, owing to simplicity and low-cost starting materials. The acetal protection of the ketonic carbonyl group allows the differentiation of its reactivity from that of the aldehydic carbonyl group, thus providing chemoselectivity for subsequent transformations. Compound **3d** represents a useful prostanoid synthon, *viz* for the synthesis of 11-desoxyprostaglandins.

In order to increase the yields in the formation of functionalized cyclopentenecarboxaldehydes, we applied the described method to 2-alkyl-2-cyclohexenols where the hydroxy function is protected by a 2-methoxyethoxymethyl group (MEM ethers).



6a-d **7a-d**



MEM = $CH_2OCH_2CH_2OCH_3$

8a-d

It is worthy of note that the ozonolyses of compounds **6** are complete within 10–30 min.

As shown in Table 1, 2-substituted 3-(2-methoxyethoxymethoxy)cyclopentene-1-carboxaldehydes **8** were obtained in better yields, except for **8a**.

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Table 1. Compounds **2a–d** and **8a–d** Prepared

Product[a]	Yields (%)	Molecular Formula[b]	MS (70 eV) (*m/z*)	IR (CCl_4) ν (cm^{-1})	UV (MeOH) λ (nm) (ε)	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	30	$C_8H_{10}O_3$ (154.2)	154 (M^+), 125, 81	2890, 1695	226 (8000)	2.20 (m, 2H); 2.53 (m, 2H); 3.98 (m, 4H); 6.58 (m, 1H); 9.82 (s, 1H)
3b	55	$C_9H_{12}O_3$ (168.2)	168 (M^+), 139, 125, 86	2860, 1685	238 (11000)	2.05 (m, 2H); 2.15 (t, 3H, J = 2); 2.46 (m, 2H); 4.02 (m, 4H); 10.06 (s, 1H)
3c	25	$C_{10}H_{14}O_3$ (182.2)	182 (M^+), 153, 86	2860, 1685	239 (10500)	1.20 (t, 3H, J = 7.3); 1.95 (m, 2H); 2.30–2.60 (m, 4H); 4.00 (m, 4H); 10.03 (s, 1H)
3d	35	$C_{17}H_{26}O_5$ (310.4)	310 (M^+), 265, 263, 229, 160, 86, 84	2880, 1740, 1685	242 (10000)	1.24 (t, 3H, J = 8.0); 1.84–2.00 (m, 4H); 2.30 (t, 2H, J = 7.8); 2.40–2.58 (m, 4H); 4.02 (m, 4H); 4.10 (q, 2H, J = 8.0); 10.08 (s, 1H)
8a	30	$C_{10}H_{16}O_4$ (200.2)	200 (M^+), 171, 170, 125, 124, 111, 110, 96, 94	2890, 2810, 2710, 1695	229 (7500)	1.90–2.40 (m, 4H); 3.35 (s, 3H); 3.40–3.80 (m, 4H); 4.60–4.90 (m, 3H); 7.25 (m, 1H); 10.03 (s, 1H)
8b	55	$C_{11}H_{18}O_4$ (214.2)	214 (M^+), 185, 139, 138, 125, 124, 110, 108, 89	2890, 2815, 2715, 1680	247 (11000)	1.85–2.60 (m, 7H); 3.37 (s, 3H); 3.45–3.85 (m, 4H); 3.65–5.00 (m, 3H); 9.80 (s, 1H)
8c	55	$C_{12}H_{20}O_4$ (228.2)	228 (M^+), 213, 199, 153, 152, 139, 138, 124, 122	2890, 2815, 2715, 1680	247 (12500)	1.10 (t, 3H, J = 7.0); 1.50–2.80 (m, 6H); 3.33 (s, 3H); 3.40–3.80 (m, 4H); 4.80 (m, 3H); 10.01 (s, 1H)
8d	60	$C_{19}H_{32}O_6$ (356.5)	356 (M^+), 238, 193, 192, 150, 134, 123, 109, 89	2890, 2810, 2710, 1738, 1680	249 (11000)	1.80 (t, 3H, J = 7.1); 1.20–2.80 (m, 16H); 3.35 (s, 3H); 3.40–3.80 (m, 4H); 4.05 (q, 2H, J = 7.1); 4.75 (m, 2H); 5.05 (m, 1H); 9.98 (s, 1H)

[a] Except for compound **3a** (bp 52–55°C/0.04 Torr), all other compounds are viscous oils.

[b] Satisfactory microanalyses obtained: C ±0.10, H ±0.07.

Table 2. Compounds **1b–d** and **6a–d** Prepared

Product[a]	Yields (%)	Molecular Formula[b]	MS (70 eV) *m/z*	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
1b	80	$C_9H_{14}O_2$ (154.2)	154 (M^+), 126, 99,82	1.70–1.80 (m, 7H); 2.02 (m, 2H); 4.02 (s, 4H); 5.70 (m, 1H)
1c	82	$C_{10}H_{16}O_2$ (168.2)	168 (M^+), 140, 125, 99, 86	1.03 (t, 3H, J = 7.5); 1.72 (m, 4H); 2.05 (m, 4H); 3.98 (s, 4H); 5.68 (m, 1H)
1d[c]	80	$C_{17}H_{28}O_4$ (296.4)	296 (M^+), 267, 252, 124, 99	1.22 (t, 3H, J = 7.5); 1.97 (m, 4H); 2.25 (t, 2H, J = 7.5); 3.96 (s, 3H); 4.9 (q, 2H, J = 7.5)
6a	95	[d]	186 (M^+), 171, 156, 143, 111, 110, 97, 89, 82	1.40–2.10 (m, 6H); 3.40 (s, 3H); 3.45–3.80 (m, 4H); 4.10 (m, 1H); 4.75 (s, 2H); 5.78 (m, 2H)
6b	97	[d]	200 (M^+), 170, 124, 111, 95	1.40–2.20 (m, 6H); 1.80 (m, 3H); 3.45 (s, 3H); 3.50–3.90 (m, 4H); 4.03 (m, 1H); 4.72–5.00 (2d, 2H, AB system, J = 6.7); 5.68 (m, 1H)
6c	95	[d]	214 (M^+), 184, 138, 125, 109, 108, 93, 89	1.01 (t, 3H, J = 7.3); 1.40–2.20 (m, 8H); 3.38 (s, 3H); 3.45–3.82 (m, 4H); 3.97 (m, 1H); 4.67–4.92 (2d, 2H, AB system, J = 7.2); 5.60 (m, 1H)
6d[c]	95	[d]	342 (M^+), 312, 267, 266, 253, 236, 207, 148, 137, 121, 107, 101, 89	1.20 (t, 3H, J = 7.2); 1.30–2.40 (m, 18H); 3.40 (s, 3H); 3.45–3.85 (m, 4H); 3.96 (m, 1H); 4.10 (q, 2H, J = 7.2); 4.65–4.92 (2d, 2H, AB system, J = 7.5); 5.60 (m, 1H)

[a] All products are viscous oils.

[b] Satisfactory microanalyses obtained: C ±0.10, H ±0.07.

[c] IR (CCl_4): ν = 1740 cm^{-1}.

[d] No element analysis performed.

Compounds **6** were obtained by $NaBH_4$ reduction of the corresponding α,β-unsaturated ketones and reaction with 2-methoxyethoxymethyl chloride, according to the literature method.[7] Taking into account that these two steps give almost quantitative yields, the sequence, i.e., ozonolysis of compounds **6** and cyclization of the intermediate dicarbonyl compounds **7**, represents a convenient method for the synthesis of 3-hydroxycyclopentene-1-carboxaldehydes. Compound **8d** has a structural features of a prostanoid synthon; its application in that field is under investigation.

Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin-Elmer 240 instrument. Mass spectra were obtained with a Varian MAT-112 spectrometer (direct inlet). IR spectra were recorded with a Perkin Elmer 457 spectrophotometer and UV spectra with a Perkin Elmer UV-VIS 552. ^{1}H-NMR spectra were measured with a Bruker WP 80 (80 MHz) instrument.

Flash chromatography was carried out with Merck Kieselgel 60 (0.040–0.063 mm, 230–400 mesh ASTM) and analytical TLC on Merck Kieselgel 60 F_{254}. Light petroleum refers to the fraction of bp 40–60°C. Solvent evaporation under reduced pressure refers to the use of a Büchi rotary film evaporator operating at 15 Torr. Boiling points refer to bulb-to-bulb distillation using a Büchi GRK-50 apparatus.

The ethylene acetals of 2-cyclohexenone,[8] 2-methyl-2-cyclohexenone,[9] 2-ethyl-2-cyclohexenone,[9,10] and 2-(6-ethoxycarbonylhexyl)-2-cyclohexenone[11] were prepared as previously described. 2-Cyclohexenol and 2-methyl-2-cyclohexenol are commercially available. 2-Ethyl-2-cyclohexenol[12] and ethyl 6-hydroxycyclohexene-1-heptanoate were prepared by $NaBH_4$ reduction of the corresponding cyclohexenones in presence of cerium(III) chloride.[13]

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Ethyl 6-Hydroxycyclohexene-1-heptanoate; yield: 95%; oil.

IR (CCl_4): ν = 3615, 1740 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.25 (t, 3H, J = 7.5 Hz); 1.45–2.45 (m, 18H); 4.10 (q, 2H, J = 7.5 Hz); 4.05 (m, 1H); 5.52 (m, 1H).

6-Substituted 1,4-Dioxaspiro[4.5]dec-6-enes (1); General Procedure:

To a solution of the appropriate cyclohexenone (40 mmol) in benzene (80 mL), ethylene glycol (5.8 mL, 104 mmol) and fumaric acid (0.42 g, 3.6 mmol) are added.[14] The mixture is refluxed with azeotropical removal of H_2O. After 24 h (96 h for the preparation of **1d**), the mixture is cooled to room temperature and neutralized with 5% $NaHCO_3$ solution (15 mL). The layers are separated. The aqueous layer is extracted with Et_2O (2 × 80 mL). The combined extracts are washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). Filtration and evaporation under reduced pressure affords the crude product **1** which is purified by flash chromatography (light petroleum/EtOAc 8.5:1.5).

6-Substituted 7-Formyl-1,4-dioxaspiro[4.4]non-6-enes 3; General Procedure:

Compounds **1a–d** (20 mmol) are dissolved in dry MeOH (60 mL). The solution is cooled to −70°C and treated with a 4% oxygen/ozone stream till complete disappearance of the starting material (2–3 h; TLC, light petroleum/EtOAc 7:3). A nitrogen stream is then bubbled through the solution and $P(OMe)_3$ (3.97 g, 32 mmol) is added at −70°C. After 30 min at −40°C, the solvent is evaporated under reduced pressure; the residue is dissolved in dry THF (10 mL) containing the preformed dibenzylammonium trifluoroacetate (from 0.77 mL of dibenzylamine and 0.31 mL of trifluoroacetic acid, 4 mmol). The mixture is stirred at room temperature, under argon for 2–4 h (TLC, light petroleum/EtOAc 8:2), then purified by flash chromatography (light petroleum/EtOAc 8:2) without any previous manipulation.

2-Substituted 6-(2-Methoxyethoxymethoxy)cyclohexenes 6; General Procedure:[7]

A solution of the 2-cyclohexenol (20 mmol) in anhydrous CH_2Cl_2 (50 mL) is stirred with 2-methoxyethoxymethyl chloride (3.4 mL, 30 mmol) in the presence of i-Pr_2NEt (5.2 mL, 30 mmol) at room temperature for 3 h. The mixture is then diluted with H_2O (30 mL), the layers are separated, and the aqueous phase is extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts are dried (Na_2SO_4) and evaporated under reduced pressure. The crude compounds **6** thus obtained are pure enough for the next step (TLC light petroleum/EtOAc 8.5:1.5).

2-Substituted 3-(2-Methoxyethoxymethoxy)cyclohexene-1-carboxaldehydes 8; General Procedure:

The ozonolyses of compounds **6a–d** (20 mmol) in dry MeOH (60 mL) are carried out as described for compounds **1a–d** (reaction times: 10 min for **6a**, 15–30 min for **6b–d**; TLC: light petroleum/EtOAc 8:2). Trimethyl phosphite (3.97 g, 32 mmol) is added at −70°C and after 30 min at −40°C, the solvent is evaporated and the residue is cyclized using dibenzylammonium trifluoroacetate (from 0.77 mL of dibenzylamine and 0.31 mL of trifluoroacetic acid, 4 mmol) in dry THF (10 mL). After 1–2 h at room temperature (TLC light petroleum/EtOAc), the mixture is diluted with H_2O (40 mL) and extracted with Et_2O (5 × 25 mL). The combined organic extracts are washed with water H_2O (2 × 40 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude products **8** are purified by flash chromatography (light petroleum/EtOAc 8.5:1.5).

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