New cyclic acetals related to Ambergris and their olfactory evaluation

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Hemisyntheses of cyclic acetals (**11–18**) were performed using (–)-polygodial and (+)-confertifolin as chiral starting materials. The acetals obtained were evaluated for their odoriferous properties.

Keywords: hemisyntheses, drimane sesquiterpenes, cyclic acetals, Ambergris, odoriferous properties

Cyclic acetals with 1,3-dioxane rings, such as Magnolan® (**1**) are very important odorants in the composition of perfumes.[1] Some of these acetals possess odoriferous properties related to Ambergris, in particular **2**,[1] **3**[2,3] and its higher homologue **4** (Fig. 1).[4]

In relation with our research on odorant heterocycles, we have previously reported the partial syntheses of Ambrox®[5,6] and Ambraoxide.[7,8]

Here we report the preparation and olfactory evaluation of eight chiral cyclic acetals (**11**–**18**), structurally related to **3** and **4**.

The diol and triol precursors of the cyclic acetals, were prepared previously from natural (–)-polygodial and (+)-confertifolin.[9-11] (Fig. 2).

Acetals were prepared by treatment of the corresponding alcohols with *para*-formaldehyde and *p*-toluenesulfonic acid in anhydrous THF at room temperature.

Acetalisation of triol **5** gave two products: **11** (32%) and **12** (50%). Oxidation of the latter with PCC, gave the corresponding aldehyde. The ^{1}H NMR of the oxidised product showed a doublet at 9.92 ppm (J = 2.1 Hz). When acetal **15** was treated with PCC only the starting material was recovered. Oxidation of **17** gave aldehyde **18**, the ^{1}H NMR for **18** shows a singlet at 9.36 ppm.

The new compounds (**11**–**18**) were evaluated by qualified perfumers (Givaudan, Schweiz AG). The results are summarised in Table 1.

With the exception of **15** and the odourless **12**, all compounds exhibited a weak woody note. Odourless **12** differs from the rest of the cyclic acetals because the 1,3 dioxane ring is fused to C-7 and C-8. In the other heterocycles the dioxane ring is fused to C-8 and C-9, and these exhibit some odour. Only compound **16** possessed an ambery odour. It is structurally similar to **3** and **4**. The rest of the cyclic acetals which were prepared, contained either double bonds or hydroxyl groups, making an important difference with the structure of **3** or **4**. Comparison of **16** with the previously described seven member acetal **4**, suggests that the stereochemistry and the methylene acetal position could be of importance in the note intensity. The absence of a methyl group at C-8 as in **4**, and the presence in **16** of a methylene instead, could also be an important structural feature.

In conclusion this work is a contribution to structure-odoriferous properties relationship in this series.

Experimental

Melting points were determined on a Stuart-Scientific SMP3 apparatus and are uncorrected. Optical rotations were obtained for $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter, and the concentrations are expressed in g/100 ml. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-200 spectrometer. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale) in $CDCl_3$ solutions and coupling constants (J) are expressed in Hz. Carbon multiplicity was established by a DEPT pulse sequence. IR spectra were recorded as KBr disks in a Bruker FT-IR Vector-22 and frequencies are in cm^{-1}. Elemental analyses were obtained on a Fisons-Carlo-Erba FA-1108 Autmost microanalyser.

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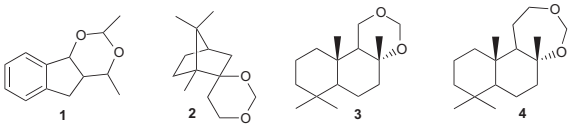

Fig. 1 Cyclic acetals **1–4**.

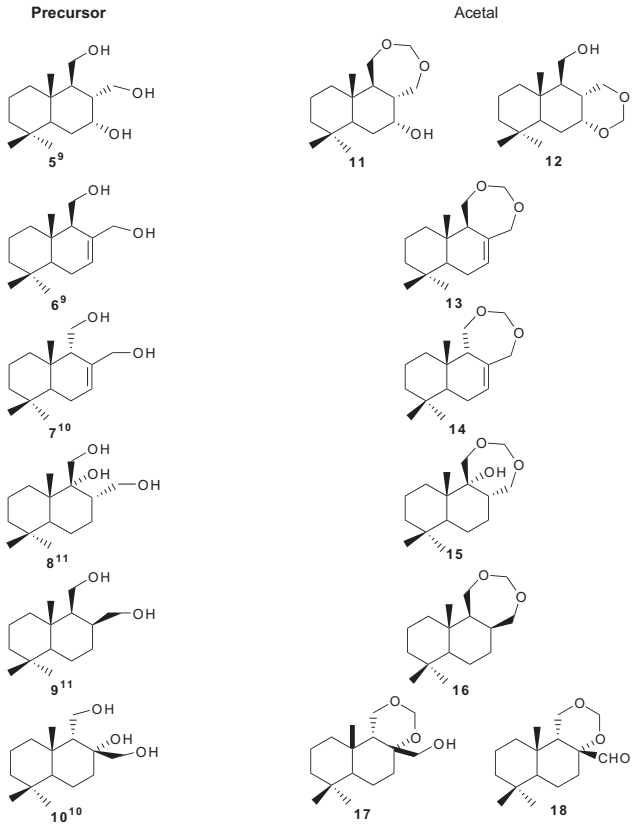

Fig. 2 Compounds **5**, **6**, **7** an **10** from (–)-polygodial; **8** and **9** from (+)-confertifolin.

Table 1 Olfactory evaluation of acetals **11**–**18**

Acetal	Description
11	Extremely weak, but also slightly woody
12	Odourless
13	Almost odourless, a slight woody note
14	Weak, but a slightly woody note is present
15	Shows a green, fruity and acidic smell
16	Smell woody, a bit ambery
17	Weak, woody
18	Acidic, woody odour

Table 2 ^{13}C NMR ($CDCl_3$ data, 50.3 MHz)

	Compound							
Carbon	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	39.1	39.0	39.2	36.1	31.7	40.3	35.8	35.8
2	18.7	18.7	18.7	18.6	18.7	18.9	20.3	19.8
3	41.9	41.9	42.0	42.7	41.5	42.1	42.3	42.1
4	32.8	32.8	32.9	33.0	33.2	33.1	33.4	32.4
5	45.7	46.8	49.7	42.7	45.6	54.1	46.3	46.5
6	27.9	27.9	23.7	24.3	21.2	18.3	18.5	18.2
7	75.7	75.8	125.6	126.0	23.7	28.0	26.2	47.0
8	36.0	36.0	135.9	136.4	43.3	38.1	77.4	78.0
9	46.8	48.4	55.2	55.7	75.2	52.8	48.3	47.0
10	37.2	37.3	35.2	35.7	40.5	37.5	37.4	37.7
11	66.8	61.1	66.8	71.5	67.2	67.4	64.7	64.0
12	69.0	69.3	73.6	73.9	68.1	73.1	69.4	197.9
13	14.6	14.8	21.8	21.5	16.0	16.2	21.8	21.9
14	21.5	21.5	21.7	22.1	21.9	21.9	23.5	22.6
15	33.1	33.1	33.2	33.0	33.5	33.6	33.3	33.4
OCO	94.4	94.5	96.7	93.7	93.5	96.2	86.5	86.9

For analytical TLC, Merck silica gel 60 in 0.26 mm layer was used. Chromatographic separations were carried out by conventional column chromatography on Merck silica gel 60 (230–400 mesh) using hexane–EtOAc gradients of increasing polarity.

All reactions were carried out under a N_2 atmosphere. All organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure, below 65°C.

General procedure for the preparation of acetals

To a solution of diol or triol (1.2 mmol) in tetrahydrofuran (20 ml), paraformaldehyde (2 mmol) and *p*-toluensulfonic acid (0.6 mmol) was added while stirring at room temperature. After 48 h, the reaction mixture was filtered through silica gel. The filtrate was poured into water (50 ml), neutralised with sodium hydrogencarbonate and extracted with dichloromethane (2 × 25 ml). The organic extract was washed with water, dried and concentrated. The crude products were purified by column chromatography.

Acetals **11** *and* **12**: Acetalisation of triol **5** (300 mg (1.17 mmol)), yielded two products. The less polar compound was identified as **11** (100 mg, 32%) as a white solid, m.p. 160–161°C (from hexane–ethyl ether); $[\alpha]_D^{27}$+8.55 (c, 2.34); IR 3540, 2947, 1093, 1034; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.09 (d, 1H, *J* = 5.9 Hz, OCHO); 4.77 (d, 1H, *J* = 5.9 Hz, OCHO); 4.21 (d, 1H, *J* = 11.6 Hz, H-12); 3.95 (m, 1H, H-7); 3.73-3.51 (m, 2H, H-11); 3.66 (d, 1H, *J* = 11.6 Hz, H-12); 0.88 (s, 3H, 10 Me); 0.86 (s, 3H, 4α Me); 0.81 (s, 3H, 4β Me); (Found: C, 72.0; H, 10.6%. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%). The more polar compound was identified as **12** (160 mg, 51%) as a white solid, m.p. 116–117°C (from hexane); $[\alpha]_D^{22}$-5.0 (c, 2.01); IR 3449, 2990, 1117, 1014; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.10 (d, 1H, *J* = 6.0 Hz, OCHO); 4.79 (d, 1H, *J* = 6.0 Hz, OCHO); 4.37 (d, 1H, *J* = 11.7 Hz, H-12); 3.96 (m, 1H, H-7); 3.91 (m, 1H, H-11); 3.76–3.62 (m, 2H, H-11+H-12); 1.93–1.06 (m, 12H); 0.87 (s, 3H, 10 Me); 0.81 (s, 6H, 4α Me+4β Me); (Found: C, 71.35; H, 10.7%. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%).

Acetal **13**: Acetalisation of diol **6** (300 mg; 1.26 mmol) afforded compound **13** (230 mg, 73%) as a colourless oil; $[\alpha]_D^{26}$ +27.86 (c, 6.46); IR 2923, 1036; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.67 (m, 1H, H-7); 4.81 (d, 1H, *J* = 5.1 Hz, OCHO); 4.70 (d, 1H, *J* = 5.1 Hz, OCHO); 4.24 (d, 1H, *J* = 13.2 Hz, H-12); 4.10 (d, 1H, *J* = 13.2 Hz, H-12); 3.97 (dd, 1H, *J* = 4.1, 11.7 Hz, H-11); 3.65 (dd, 1H, *J* = 9.6, 11.7 Hz, H-11); 2.21–2.01 (m, 3H, H-6+H-9); 0.89 (s, 3H, 10 Me); 0.86 (s, 3H, 4α Me); 0.82 (s, 3H, 4β Me).

Acetal **14**: Acetalisation of diol **7** (250 mg; 1.05 mmol) gave compound **14**, as a white solid, m.p. 59–60°C (from hexane); $[\alpha]_D^{26}$–150.2 (c, 2.13); IR 2990, 1110; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.72 (m, 1H, H-7); 4.90 (d, 1H, *J* = 7.1 Hz, OCHO); 4.66 (d, 1H, *J* = 7.1 Hz,OCHO); 4.19 (s, 2H, H-12); 4.12 (m, 1H, H-11); 3.38 (m, 1H, H-11); 0.93 (s, 3H, 10 Me); 0.90 (s, 3H, 4α Me); 0.88(s, 3H, 4β Me); (Found C, 77.3; H, 10.7%. $C_{16}H_{26}O_2$ requires C, 76.8; H, 10.5%).

Acetal **15**: Compound **15** (230 mg, 71%) was obtained from triol **8** (310 mg, 1.21 mmol) as a white solid, m.p. 52–53°C (from hexane); $[\alpha]_D^{22}$ –29.6 (c, 2.03); IR 3490, 2944, 1123; ^1H NMR δ 4.74 and 4.69 (AB system, 2H, J_{AB} = 4.2 Hz, OCH_2O); 3.65 (s, 2H, H-11); 3.41 (dd, 1H, *J* = 3.9, 12.1 Hz, H-12); 3.30 (dd, 1H, *J* = 10.1, 12.1 Hz, H-12); 2.81 (s, 1H, OH); 0.85 (s, 3H, 10 Me); 0.81 (s, 3H, 4 αMe); 0.76 (s, 3H, 4β Me); (Found C, 71.3; H, 10.7%. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%).

Acetal **16**: Using the same general procedure, diol **9 (**120 mg (0.5 mmol)), afforded compound **16** (87 mg, 69%) as a white solid, m.p. 67–69 °C (from ethyl ether); $[\alpha]_D^{20}$ –13.40 (c, 5.2); IR 2920, 1074, 1027; ^1H NMR δ 4.79 (AB system, 2H, J_{AB} = 5.5 Hz, OCH_2O); 3.65 (m, 4H, H-11+H-12); 1.11 (s, 3H, 10 Me); 0.85 (s, 6H, 4αMe+4βMe); (Found C, 76.3; H, 11.0%. $C_{16}H_{28}O_2$ requires C, 76.1: H, 11.2%).

Acetal **17**: Triol **7** (400 mg (1.56 mmol)), gave acetal **17** (310 mg (74%)) as a white solid, m.p. 45–46°C (from hexane-ethyl ether); $[\alpha]_D^{26}$+8.6 (c, 2.3); IR 3445, 2990, 1068; ^1H NMR δ 4.86 (d, 1H, *J* = 6.5 Hz, OCHO); 4.79 (d, 1H, *J* = 6.5 Hz, OCHO); 4.18–3.99 (m, 1H, H-11); 3.81–3.59 (m, 3H, H-11+2H-12); 2.3 (broad s, 1H, OH); 1.11 (s, 3H, 10 Me); 0.88 (s, 3H,4αMe); 0.78 (s, 3H, 4βMe); (Found C, 72.0; H, 10.4%. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%).

Acetal **18**: To a stirred mixture of PCC (300 mg, 1.38 mmol) and CH_2Cl_2 (10 ml), a solution of acetal **17** (200 mg, 0.75 mmol) in 5 ml of CH_2Cl_2 was added at room temperature for 4 h. The reaction mixture was filtered and concentrated in a vacuum. Column chromatography of the residue afforded aldehyde 18 as white solid (170 mg, 86%) m.p. 78–80°C (from hexane); $[\alpha]_D^{25}$+25.2 (c, 3.7); IR 2996, 1731, 1006; ^1H NMR δ 9.36 (s, 1H, CHO); 4.86 (s, 2H, OCH_2O); 4.18 (dd, 1H, *J* = 5.4, 11.5 Hz, H-11); 3.78 (dd, 1H, J = 11.0, 11.5 Hz, H-11); 0.89 (s, 6H, 10 Me+4α Me); 0.75 (s, 3H, 4β Me); (Found C, 71.8; H, 10.0%. $C_{16}H_{26}O_3$ requires C, 72.1; H, 10.0%).

The ^{13}C chemical shifts for all the acetals prepared are summarised in Table 2.

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