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A study on the intramolecular catalytic aldol cyclodehydration of 3,4-disubstituted 1,6-dialdehydes

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Abstract

The intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted 1,6-dialdehydes was investigated and it was found that the transformation is strongly dependent on the substrate structure. If the substituents are of carbonyl or acetonil protected diol type, the cyclopentene carbaldehydes are formed, while starting from acylated diols, an open chain unsaturated dialdehyde is generated. It was observed that the catalyst efficiency also depends on the substrate substituents and if the latter are of carbonyl or acyl protected diol type, both dibenzylammonium trifluoroacetate (Bn_2NH·TFA) and piperidine·AcOH are effective, while only the second one catalyses the transformation of acetonil protected diols. It was shown that a secondary amine catalyses the reaction itself even in the cases where the corresponding salt is not effective.

Keywords: Cyclopentene carbaldehydes; Muconaldehyde; Aldol; Cyclodehydration; Catalysis; 1,6-Dialdehydes; Ozonolysis; Ozonides

1. Introduction

Considerable effort has been devoted to the development of new methods for the construction of five-member rings, since cyclopentanoid compounds play a fundamental role in synthetic organic chemistry, both as intermediates and as targets, like prostaglandins, prostacyclins, rethrolones and many other natural products of biological importance. The aldol reaction is one of the most powerful methods for carbon–carbon bond formation [1–4], which in the case of the direct catalytic cross-aldol cyclisation of 1,6-dialdehydes leads to the formation of the cyclopentanoid unit, a key precursor in the synthesis of a broad range of biologically active products (Scheme 1).

Contrary to the aldol condensation of 1,7-dialdehydes, where the aldol product is the main one in the most part of the cases, the cross-aldol cyclisation of 1,6-dialdehydes leads in general to dehydration products, the corresponding cyclopentene carbaldehydes. Reported at first as a step in the Woodward's [5] classical steroid synthesis, this aldol cyclisation has been widely exploited. As piperidinium acetate (pip.AcOH) has been used as a catalyst by Woodward, this salt, as well as the similar pyrrolidinium acetate, have been applied not only in steroid synthesis [6,7], but in the preparation of alkaloids [8], prostanoids [9,10], sesquiterpenes [11], pentomycin antibiotics [12,13] and many others. For the preparation of the key tricyclic intermediate in the total synthesis of (±)-Gibberellic acid Corey et al. [14] have applied the same aldol condensation using dibenzylammonium trifluoroacetate (Bn_2NH·TFA) as a catalyst. The regioselectivity of the aldol product has been fully controlled and high yields have been facilitated in many cases, where piperidinium acetate was not effective [15–20].

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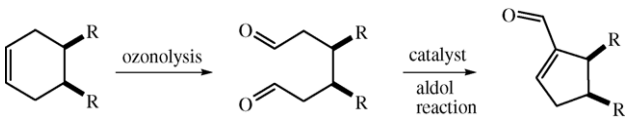


Scheme 1.

An investigation on the intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted 1,6-dialdehydes, readily obtained by olefin oxidation of a series of different *meso*-4,5-disubstituted cyclohexenes, is presented herein. The influence of substrate substituents both on products and on catalysts efficiency were studied and it was found that the reaction strongly depends on the substrate structure.

2. Experimental

All reagents were purchased from Aldrich and Fluka and were used without any further purification. The dichloromethane was dried over P_2O_5. MN Kieselgel 60 M was used for the column chromatography isolation of the starting materials and MN Kieselgel G/UV_{254} was applied for preparative TLC (PTLC) of the products. The ozonolyses were performed on Fischer Ozon Generator 500 M using dry (in-steam molecular sieve-silica gel blue tube) oxygen. The melting points were determined with an Electrothermal Mod. IA6304 in capillary tubes without corrections. The NMR spectra were recorded on a Bruker AMX 400 in deuterochloroform, the chemical shifts were quoted in ppm in δ-value against tetramethylsilane (TMS) as internal standard and the coupling constants were calculated in Hz. The IR spectra were recorded on a Unicam ATI Mattson Genesis Series FTIR as a film, obtained by evaporation of dichloromethane solutions on the NaCl plates and were quoted in cm^{-1}. The microanalyses were taken on CHNS Analyser Thermo Finnigan model Flash 1112 Series. High and low resolution mass spectra (EI, FAB+) and the X-ray analysis of the product **12** were carried out by mass spectrometry and crystallography services of the University of Santiago de Compostela, Spain.

2.1. Starting cyclohexene derivatives

2.1.1. Compound **11** [21]

To a boiling solution of **9** [22] (154 mg, 1 mmol) in aq. dioxane (5 ml) a solution of SeO_2 (55 mg, 0.5 mmol) in aq. dioxane (5 ml) was added drop wise under stirring and the mixture was refluxed for 7 h. After evaporation of the solvent in vacuo and column chromatography on silica gel using hexane–ethyl acetate 3:2 as a mobile phase, the hydroxy cyclohexene **11** was isolated as a colourless oil; R_f 0.42; 24% yield (40 mg); IR 738.6, 1057.2, 1213.3, 1265.6, 1281.9, 2340.7, 2360.0, 3447.0; ^{1}H NMR 1.374 (s, 3H, CH_3), 1.481 (s, 3H, CH_3), 2.178 (dm, 1H, J^2 16.8, J^3 2.5, 7.0, 1/2 of CH_2-6, *trans* to CH-1), 2.658 (dt, 1H, J^2 16.8, J^3 12.2, 6.0, 1/2 of CH_2-6, *cis* to CH-1), 2.971 (brs, 1H, OH), 4.019 (t, 1H, J_{12} 6.8, CH-2), 4.193 (dd, 1H, J_{23} 5.2, J_{34} 2.3, CH-3), 4.361 (m, 1H, J_{12} 6.8, J_{16}^{cis} 12.2, J_{16}^{trans} 4.9, CH-1), 5.782 (m, 1H, CH-5), 5.839 (dt, 1H, J_{34} 2.3, J_{45} 9.8, CH-4); ^{13}C NMR 24.95 (CH_3), 27.33 (CH_3), 28.54 (CH_2-6), 70.10 (CH-3), 71.71 (CH-1), 80.58 (CH-2), 108.36 (C_{quat}), 125.49 (CH-5), 130.48 (CH-4); MS (EI+) *m*/*z* 170 (M^+, 21), 155 (M–CH_3, 32), 112 (M–CH_3COCH_3, 41), 95 (M–CH_3COCH_3–OH, 64), 58 (CH_3COCH_3, 78), 43 (CH_3CO, 100).

2.1.2. Compound **15**

To a solution of **14** [23,24] (114 mg, 1 mmol) in CH_2Cl_2 (20 ml), Et_3N (0.35 ml, 2.5 mmol) and then $(COCl)_2$ (0.15 ml, 1.75 mmol) were added at −78 °C under argon atmosphere. After 1 h stirring at 0 °C, the solution was washed with brine, dried over $MgSO_4$ and evaporated to dryness in vacuo to give the oxalate **15** as a colourless solid, which was characterised without purification; quantitative conversion; m.p. 135–136 °C; IR 669.4, 704.7, 738.0, 1193.5, 1265.7, 1319.5, 1781.3, 2307.2, 2360.3, 3054.9; ^{1}H NMR 2.506 (m, 4H, CH_2-3 and CH_2-6), 5.328 (m, 2H, CH-1 and CH-2), 5.633 (s, 2H, CH-4 and CH-5); ^{13}C NMR 28.03 (CH_2-3 and CH_2-6), 71.70 (CH-1 and CH-2), 123.07 (CH-4 and CH-5), 156.58 (C=O); MS (EI+) *m*/*z* 169 (M^+, 31), 153 (M–O, 100), 141 (M–CO, 15), 96 (M–OCOCO, 68), 80 (M–OCOCOO, 100); HRMS (FAB+) *m*/*z* Calc. for $C_8H_9O_4$ 169.050084, Found 169.049955.

2.1.3. Compound **18**

To a solution of **14** [23,24] (570 mg, 5 mmol) in dry toluene (10 ml), pyridine (1.0 ml, 7.5 mmol) and phosgene (2.5 ml, 5 mmol) in a form of 20% solution in toluene, were added under argon atmosphere. After 2 h stirring at room temperature the solution was washed with brine, with 5% aq. HCl and again with brine, was dried over $MgSO_4$ and evaporated to dryness in vacuo to give the carbonate **18** as a colourless solid, which was characterised without purification; quantitative conversion; m.p. 44–45 °C; IR 1061.4, 1179.3, 1212.2, 1373.3, 1797.3, 2969.8, 3061.6; ^{1}H NMR 2.202 (brd, 2H, *J* 6.4, 1/2 of CH_2-3 and CH_2-6), 2.565 (brd, 2H, *J* 6.0, 1/2 of CH_2-3 and CH_2-6), 4.988 (s, 2H, CH-1 and CH-2), 5.922 (d, 2H, *J* 2.4, CH-4 and CH-5); ^{13}C NMR 26.94 (CH_2-3 and CH_2-6), 74.61 (CH-1 and CH-2), 125.58 (CH-4 and CH-5), 154.95 (C=O); MS (EI) *m*/*z* 140 (M, 27), 112 (M–CO, 11), 96 (M–CO_2, 38), 68 (M–CO_2–CO,100); HRMS (EI+) *m*/*z* Calc. for $C_7H_8O_3$ 140.047344, Found 140.047418.

2.2. Ozonolysis and subsequent catalytic aldol reaction of cyclohexene derivatives

2.2.1. General procedure

Through a solution of an alkene (1 mmol) in dry dichloromethane (5 ml, 10 ml in the case of **15**) a steam of ozone in oxygen was bubbled at −78 °C until the solution turned blue. The system was purged with argon until the colour disappeared and dimethylsulphide (4 mmol, 0.3 ml)

was then added. The solution was kept at room temperature for 2 h and a catalyst (0.2 mmol, 20%), dibenzylammonium trifluoroacetate or piperidinium acetate, was added. After 18–20 h at room temperature the solvent was removed in vacuo and the crude reaction mixture was purified by preparative thin layer chromatography (PTLC) on silica gel using hexane–ethyl acetate as a mobile phase. The products were eluted from the silica gel by ethyl acetate.

2.2.2. Substrate **2**

The substrate **2** [25] was ozonised to give the corresponding 1,6-dialdehyde **3**; ^{1}H NMR 2.656 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 2.821 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 3.317 (m, 2H, CH-3 and CH-4), 4.547 (s, 2H, CH_2–Ph), 7.19–7.50 (m, Ph), 9.601 (s, 2H, CHO-1 and CHO-6); ^{13}C NMR 37.06 (CH-3 and CH-4), 40.78 (CH_2-2 and CH_2-5), 42.52 (CH_2–Ph), 127.70 (CH, Ph), 127.82 (CH, Ph), 128.30 (CH, Ph), 128.35 (CH, Ph), 128.53 (CH, Ph), 135.44 (C_{quat}, *i*-Ph), 173.26 (C=O), 178.03 (C=O), 199.71 (CHO-1 and CHO-6). The aldol reaction was carried out with both catalysts Bn_2NH·TFA and pip.AcOH and the product was characterised as a 2,4-dinitrophenylhydrazone (DNPH). Thus, the crude reaction mixture was added to a solution of 2,4-dinitrophenylhydrazine (200 mg) and conc. H_2SO_4 (0.5 ml) in abs. methanol (3 ml). The precipitate was filtered and then purified by PTLC (ethyl acetate–hexane 1:1) to afford the DNPH of **4** (X = DNPH) as orange crystals, R_f 0.42; 91% yield (396 mg) using Bn_2NH·TFA and 82% (357 mg) with pip.AcOH; m.p. 171–173 °C; IR 705.8, 740.5, 896.0, 1265.3, 1422.1, 1618.0, 1708.2, 2305.3, 2986.8, 3054.3; ^{1}H NMR (DMSO) 2.756 (dd, 1H, *J* 2.7, 19.8, 1/2 of CH_2-6), 3.012 (dd, 1H, *J* 11.0, 19.8, 1/2 of CH_2-6), 3.720 (m, 1H, CH-6a), 4.362 (d, 1H, *J* 8.0, CH-3a), 4.552 (s, 2H, CH_2–Ph), 6.395 (s, 1H, CH-5), 7.18–7.32 (m, 5H, Ph), 8.194 (d, 1H, *J* 9.6, CH-5′, Ar–DNPH), 8.366 (dd, 1H, *J* 2.0, 9.6, CH-6′, Ar–DNPH), 8.468 (s, 1H, CH-3′, Ar–DNPH), 8.838 (d, 1H, *J* 2.5, CH=N), 11.549 (s, 1H, NH); ^{13}C NMR (DMSO) 35.57 (CH_2-6), 41.56 (CH_2–Ph), 43.31 (CH-6a), 51.58 (CH-3a), 114.78 (C_{quat}, Ar), 117.42 (CH, Ar), 123.00 (CH=N), 127.36 (CH, Ar), 127.57 (CH, Ar), 128.71 (CH, Ar), 129.80 (CH, Ar), 136.37 (C_{quat}, Ar), 136.47 (C_{quat}, Ar), 137.38 (C_{quat}, Ar), 140.26 (CH-5), 144.83 (C-4), 145.13 (CH, Ar), 175.57 (CO-3), 179.39 (CO-1); Anal. Calc. for $C_{21}H_{17}N_5O_6$C 57.93, H 3.94, N 16.09; Found C 58.11, H 4.41. The aldol condensation of dialdehyde **3** (0.5 mmol) was performed in $CDCl_3$ (0.5 ml), using dibenzylammonium trifluoroacetate (0.1 mmol) as a catalyst inside a tube and was followed by NMR spectra. The signals for aromatic nuclei as well as for the substrate substituents have their usual values and thus are not given. The resonances for the intermediate disappeared completely after 17 h. *Intermediate aldol product*: ^{1}H NMR 1.810 (ddd, 1H, *J* 3.2, 10.1, 14.1, 1/2 of CH_2-6), 2.199 (brd, 1H, *J* 14.1, 1/2 of CH_2-6), 3.217 (brt, 1H, *J* 9.0, CH-6a), 3.431 (brs, 1H, CH-4), 3.648 (brd, 1H, *J* 7.6, CH-3a), 4.58 (CH-5, overlapped with benzylic resonances), 9.660 (s, 1H, CHO); COSY cross peaks 1.810/3.217, 1.810/4.58, 3.217/3.648; 1D TOCSY uninterrupted connection between 1.810, 2.199, 3.217, 3.431, 3.648, 4.58; ^{13}C NMR 32.78 (CH_2-6), 39.51 (CH-6a), 43.66 (CH-3a), 63.72 (CH-4), 72.01 (CH-5), 199.95 (CHO); HMQC cross peaks 1.810/32.78, 2.199/32.78, 3.217/39.51, 3.431/63.72, 3.648/43.66, 4.58/72.01, 9.660/199.95; HMBC cross peaks 1.810/39.51, 3.217/32.78, 3.217/43.66, 3.431/43.66, 3.431/72.01, 3.648/39.51, 3.648/63.72, 3.648/72.01, 4.58/32.78, 4.58/63.72, 4.58/199.95, 9.660/63.72, 9.660/43.66, 9.660/72.01; *dehydration product* **4** (X=O): ^{1}H NMR 3.004 (m, 2H, CH_2-6), 3.562 (dt, 1H, *J* 4.4, 9.7, CH-6a), 4.216 (d, 1H, *J* 6.8, CH-3a), 6.857 (d, 1H, *J* 1.6, CH-5), 9.768 (s, 1H, CHO); COSY cross peaks 3.004/3.562, 3.004/6.857, 3.562/4.216; 1D TOCSY uninterrupted connection between 3.004, 3.562, 4.216, 6.857; ^{13}C NMR 35.98 (CH_2), 43.16 (CH-6a), 50.00 (CH-3a), 141.95 (C_{quat}-4), 151.84 (CH-5), 175.03 (C=O), 178.29 (C=O), 187.49 (CHO); HMQC cross peaks 3.004/35.98, 3.562/43.16, 4.216/50.00, 6.857/151.84, 9.768/187.49; HMBC cross peaks 3.004/43.16, 3.004/151.84, 3.004/141.95, 3.562/35.98, 3.562/50.00, 3.562/178.29, 4.216/43.16, 4.216/141.95, 4.216/151.91, 4.216/175.03, 6.857/35.98, 6.857/141.95, 6.857/187.49, 9.768/141.95, 9.768/151.84.

2.2.3. Substrate **1**

The substrate **1** [26] was ozonised to give the corresponding 1,6-dialdehyde; ^{1}H NMR 2.593 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 2.873 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 3.655 (m, 2H, CH-3 and CH-4), 9.761 (s, 2H, CHO-1 and CHO-6; ^{13}C NMR 37.30 (CH-3 and CH-4), 40.92 (CH_2-2 and CH_2-5), 176.72 (C=O), 199.14 (CHO-1 and CHO-6). The aldol reaction was carried out with Bn_2NH·TFA and pip.AcOH, to form **5**, detected in both reaction mixtures by NMR. As the product was highly unstable in the course of the purification, as well as in the conditions of the derivatisation as DNPH, its further characterisation was not performed; ^{1}H NMR 2.223 (m, 1H, 1/2 of CH_2-6), 2.427 (m, 1H, 1/2 of CH_2-6), 3.417 (m, 1H, CH-6a), 3.905 (d, 1H, *J* 9.2, CH-3a), 6.968 (s, 1H, CH-5), 9.582 (s, 1H, CHO); COSY cross peaks 2.223/3.417, 2.223/6.968, 2.427/3.417, 3.417/3.905; ^{13}C NMR 35.96 (CH_2-6), 46.36 (CH-6a), 47.71 (CH-3a), 145.64 (C-4), 155.56 (CH-5), 175.60 (C=O), 176.90 (C=O), 187.83 (CHO).

2.2.4. Substrate **6**

The substrate **6** [27] was ozonised to give the corresponding 1,6-dialdehyde as a major product [28]; ^{1}H NMR 2.559 (dd, 2H, J^2 18.5, J^3 3.8, 1/2 of CH_2-2 and CH_2-5), 3.006 (dd, 2H, J^2 18.5, J^3 8.7, 1/2 of CH_2-2 and CH_2-5), 3.397 (m, 2H, CH-3 and CH-4), 3.709 (s, 6H, CH_3), 9.753 (s, 2H, CHO-1 and CHO-6); ^{13}C NMR 39.65 (CH-3 and CH-4), 42.34 (CH_2-2 and CH_2-5), 52.25 (CH_3), 172.35 (C=O), 198.98 (CHO-1 and CHO-6); and an "ozonide"; ^{1}H NMR (the integrals are given in comparison with that of the first signal, which is chosen as a reference one) 1.609 (m, 1H, 1/2 of CH_2), 2.096 (m,

1H, 1/2 of CH_2), 3.195 (m, 1H, CH), 3.58 (s, CH_3, overlapped with dialdehyde CH_3), 5.121 (m, 1H, CH); COSY cross peaks 1.609/3.195, 2.096/5.121, 1.609/3.195, 2.096/5.121; ^{13}C NMR 31.13 (CH_2), 42.03 (CH), 52.15 (CH_3), 102.28 (CH); HMQC cross peaks 1.609/31.13, 2.096/31.13, 3.195/42.03, 3.58/52.15, 5.121/102.28. *Caution*: An explosion occurred when the dialdehyde of **6** (35 mmol scale) was attempted to distil under vacuum (90 °C, 0.01 mmHg).

(a) The aldol reaction was carried out with $Bn_2NH{\cdot}TFA$, to afford after PTLC (ethyl acetate–hexane 2:3) **7** as a colourless oil; R_f 0.31; 78% yield (165 mg); IR 706.2, 742.1, 896.2, 1209.0, 1265.1, 1422.2, 1437.7, 1624.9, 1685.5, 1740.6, 2304.9, 2987.0, 3054.7; ^{1}H NMR 2.823 (m, 1H, 1/2 of CH_2-5), 3.173 (m, 1H, 1/2 of CH_2-5), 3.461 (m, 1H, CH-1), 3.598 (s, 3H, CH_3), 3.632 (s, 3H, CH_3), 4.011 (d, 1H, *J* 8.5, CH-2), 6.996 (s, 1H, CH-4), 9.642 (s, 1H, CHO); ^{13}C NMR 35.53 (CH_2-5), 46.37 (CH-1), 49.16 (CH-2), 52.13 (CH_3), 52.24 (CH_3), 144.10 (C-3), 152.85 (CH-4), 171.61 (C=O), 171.97 (C=O), 187.69 (CHO); MS (EI+) *m/z* 212 (M^+, 19), 197 (M–CH_3, 17), 181 (M–OCH_3, 23), 154 (M^+–$COOCH_3$, 87), 136 (M–$COOCH_3$–CH_3, 100); HRMS (EI+) *m/z* Calc. for $C_{10}H_{12}O_5$ 212.068474, Found 212.067953.

(b) Performing the reaction with pip.AcOH, the carbaldehyde **7** was isolated; 64% yield (136 mg); R_f 0.31; as well as **8** as a colourless oil; R_f 0.14; 31% yield (66 mg); IR 705.2, 738.8, 874.6, 896.2, 1071.8, 1121.0, 1210.9, 1265.5, 1422.4, 1437.9, 1608.4, 1743.2, 2304.5, 2955.0, 2986.6, 3054.7, 3456.4; ^{1}H NMR 2.007 (ddd, 1H, *J* 2.0, 8.1, 13.7, 1/2 of CH_2-6), 2.122 (dd, 1H, *J* 11.7, 13.7, 1/2 of CH_2-6), 2.821 (m, 1H, CH-1), 3.210 (d, 1H, *J* 4.8, CH-2), 3.694 (s, 3H, CH_3-1′), 3.751 (s, 3H, CH_3-2′), 4. 635 (d, 1H, *J* 2.0, CH-3), 5.379 (s, 1H, CH-4), 5.813 (s, 1H, CH-5); COSY cross peaks 2.007/2.821, 2.007/5.813, 2.122/2.821, 2.122/5.813, 2.821/3.210, 3.210/4.635; 4.635/5.379, 5.379/5.813; ^{13}C NMR 29.95 (CH_2-6), 34.68 (CH-1), 43.10 (CH-2), 52.11 (CH_3-1′), 52.41 (CH_3-2′), 80.60 (CH-3), 95.81 (CH-4), 102.83 (CH-5), 170.60 (C=O-2′), 173.02 (C=O-1′); HMQC cross peaks 2.007/29.95, 2.122/29.95, 2.821/34.68, 3.210/43.10, 3.694/52.11, 3.751/52.41, 4.635/80.60, 5.379/95.81, 5.813/102.83; HMBC cross peaks 2.007/34.68, 2.007/102.83, 2.122/34.68, 2.122/102.83, 2.821/29.95, 2.821/43.10, 2.821/173.02, 3.210/34.68, 3.210/80.60, 3.210/170.60, 3.694/173.02, 3.751/170.60, 4.635/43.10, 4.635/95.81, 5.379/80.60, 5.379/102.83, 5.813/29.95, 5.813/95.81; MS (FAB+) *m/z* 215 (M^+, 18), 199 (M–CH_3, 37), 197 (M–OH, 24), 183 (M–OCH_3, 31), 154 (M–$COOCH_3$, 100), 137 (M–$COOCH_3$–H_2O, 96); HRMS (FAB+) *m/z* Calc. for $C_{10}H_{15}O_5$ 215.091949, Found 215.091858.

2.2.5. Substrate *9*

The substrate **9** [22] was ozonised to give the corresponding 1,6-dialdehyde as a major product; ^{1}H NMR 1.270 (s, 3H, CH_3), 1.361 (s, 3H, CH_3), 2.423 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 2.609 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 4.564 (m, 2H, CH-3 and CH-4), 9.711 (s, 2H, CHO-1 and CHO-6); ^{13}C NMR 25.54 (CH_3), 27.88 (CH_3), 44.18 (CH_2-2 and CH_2-5), 72.31 (CH-3 and CH-4), 108.59 (C_{quat}), 199.63 (CHO-1 and CHO-6); and an "ozonide"; ^{1}H NMR (the integrals are given in comparison with that of the first signal, which is chosen as a reference one) 1.642 (m, 2H, CH_2), 4.248 (m, 1H, CH), 5.319 (m, 1H, CH); COSY cross peaks 1.642/4.564, 1.642/5.319;^{13}C NMR 32.07 (CH_2), 72.91 (CH), 102.03 (CH); HMQC cross peaks 1.642/32.07, 4.248/72.91, 5.319/102.03. The aldol reaction was carried out with pip.AcOH.

(a) Performing the reaction in dry dichloromethane, as it is described in the general procedure, **10** [13] was isolated after PTLC (ethyl acetate–hexane 2:3) as a colourless syrup, which crystallised on storage in an ice box; R_f 0.40; 62% yield (104 mg); m.p. 40–41 °C (literature [13] 41–42 °C); ^{1}H NMR 1.372 (s, 3H, CH_3), 1.401 (s, 3H, CH_3), 2.807 (m, 2H, CH_2-6), 4.873 (dt, 1H, J_{56} 2.2, J_{66a} 5.2, J_{3a6a} 7.3, CH-6a), 5.317 (d, 1H, *J* 7.3, CH-3a), 6.872 (d, 1H, *J* 2.2, CH-5), 9.838 (s, 1H, CHO); ^{13}C NMR 24.94 (CH_3), 26.99 (CH_3), 39.08 (CH_2-6), 77.80 (CH-6a), 81.37 (CH-3a), 110.80 (C_{quat}), 112.80 (C_{quat}), 151.05 (CH-5), 188.76 (CHO).

(b) Carrying the reaction in wet dichloromethane three products were isolated after PTLC (ethyl acetate–hexane 2:3) as follows: the same carbaldehyde **10**, R_f 0.40; 42% yield (71 mg); cyclohexenone **12** as colourless crystals, R_f 0.31; 12% yield (22 mg); m.p. 164–165 °C with decomp.; IR 1113.1, 1222.9, 1260.0, 1272.1, 1363.2, 1711.9, 2870.8, 2928.6, 2977.6, 3683.1; ^{1}H NMR 1.589 (s, 3H, CH_3), 1.691 (s, 3H, CH_3), 1.987 (m, 1H, 1/2 of CH_2-5), 2.425 (m, 1H, 1/2 of CH_2-6), 2.473 (m, 1H, 1/2 of CH_2-5), 2.643 (m, 1H, 1/2 of CH_2-6), 4.986 (dd, 1H, J_{cis} 4.8, J_{trans} 10.8, CH-4); ^{13}C NMR 24.17 (CH_3), 26.68 (CH_3), 28.41 (CH_2-5), 32.04 (CH_2-6), 74.88 (CH-4), 117.47 (C_{quat}, $C(CH_3)_2$), 125.36 (C-2), 151.14 (C-3), 192.26 (C-1); MS (EI) *m/z* 184 (M^+, 31), 126 (M–CH_3COCH_3, 100), 98 (M–CH_3COCH_3–CO, 26), 58 (CH_3COCH_3, 53); HRMS (EI+) *m/z* Calc. for $C_9H_{12}O_4$ 184.073559, Found 184.073233; The 3D structure of the product based on X-ray data is shown in Fig. 1 [29]; and *cis*-**13** as a colourless oil; R_f 0.15; 8% yield (15 mg); IR 705.2, 741.5, 896.0, 1265.3, 1421.7, 1640.8, 1710.2, 2987.0, 3054.5, 3424.2; ^{1}H NMR 1.422 (s, 6H, CH_3), 4.763 (brd, 1H, *J* 5.5, CH-6), 4.880 (t, 1H, *J* 5.6, CH-6a), 5.264 (d, 1H, *J* 5.5, CH-3a), 6.814 (s, 1H, CH-5), 9.868 (s, 1H, CHO); ^{13}C NMR 25.82 (CH_3), 27.09 (CH_3), 73.13 (CH-6), 77.28 (CH-6a), 79.84 (CH-3a), 109.88 (C_{quat}), 112.91 (C_{quat}), 189.36 (CHO); MS (FAB+) *m/z* 185 (M^+, 3), 167 (M–OH, 16), 154 (M^+–CHO, 31), 137 (M^+–CHO–OH, 24), 109 (M–OH–CH_3COCH_3, 6, 58 (CH_3COCH_3, 100). To confirm the structure of the product **13**, it was reduced by $LiAlH_4$ in dry ether to the

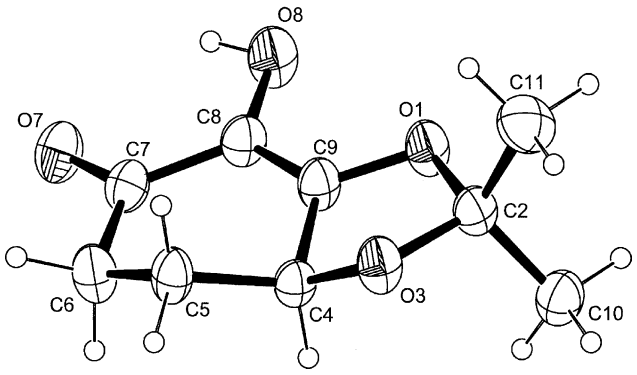


Fig. 1. 3D Structure of hydroxy cyclohexenone (**12**) based on X-ray data.

corresponding known diol [30], isolated as a colourless oil; ^{1}H NMR 1.407 (s, 3H, CH_3), 1.452 (s, 3H, CH_3), 4.333 (q, 2H, J^2 14.4, CH_2–OH), 4.578 (dd, 1H, *J* 1.6, 5.5, CH-4), 4.793 (t, 1H, *J* 5.5, CH-3a), 4.997 (d, 1H, *J* 5.5, CH-6a), 5.750 (s, 1H, CH-5); ^{13}C NMR 26.39 (CH_3), 27.50 (CH_3), 59.71 (CH_2–OH), 73.19 (CH-4), 77.79 (CH-3a), 83.17 (CH-6a), 107.47 (C_{quat}), 110.19 (C_{quat}), 130.18 (CH-5).

2.2.6. Substrate *11*

The substrate **11** [21] was ozonised to give an "ozonide"; ^{1}H NMR 1.295 (s, 3H, CH_3), 1.501 (s, 3H, CH_3), ca. 2.0 (CH_2, overlapped with the DMS signal), 4.191 (d, 1H, *J* 5.6, CH), 4.246 (t, 1H, *J* 6.0, 6.8, CH), 4.323 (t, 1H, *J* 6.4, CH), 5.561 (s, 1H, CH), 5.656 (s, 1H, CH); ^{13}C NMR 24.26 (CH_3), 25.72 (CH_3), 33.20 (CH_2), 68.84 (CH), 69.54 (CH), 78.98 (CH), 94.20 (CH), 99.97 (CH), 108.52 (C_{quat}); HMQC cross peaks 1.295/24.26, 1.501/25.72, ca. 2.0/33.20, 4.191/78.98, 4.246/69.54, 4.323/68.84, 5.561/94.20, 5.656/99.97; HMBC cross peaks 1.295/108.52, 1.501/108.52, ca. 2.0/69.54, 4.191/68.84, 4.191/94.20, 4.246/33.20, 4.323/78.98, 5.561/78.98, 5.561/99.97, 5.656/94.20. The aldol reaction was performed using pip.AcOH, while no reaction occurred by Bn_2NH·TFA, and after PTLC the same cyclohexenone **12** was isolated in 78% yield (144 mg), which physical and spectral properties were identical with those of the product, described in part (b) of Section 2.2.5.

2.2.7. Substrate *16*

The substrate **16** [31] was ozonised to give the corresponding 1,6-dialdehyde; ^{1}H NMR 2.054 (s, 6H, CH_3), 2.717 (m, 4H, CH_2-2 and CH_2-5), 5.517 (m, 2H, CH-3 and CH-4), 9.714 (s, 2H, CHO-1 and CHO-6); COSY cross peaks 2.717/5.517, 2.717/9.714; ^{13}C NMR 20.70 (CH_3), 43.84 (CH_2-2 and CH_2-5), 68.41 (CH-3 and CH-4), 169.91 (C=O), 197.65 (CHO-1 and CHO-6); HMBC cross peaks 2.054/169.91, 2.717/68.41, 2.717/197.65, 5.517/43.84, 9.714/43.84. The aldol reaction was carried out with Bn_2NH·TFA and pip.AcOH and after PTLC (ethyl acetate–hexane 2:3) the *E*,*E*-muconaldehyde **17** [32–38] was isolated as pale yellow crystals; R_f 0.53; 53% (58 mg) using Bn_2NH·TFA and 54% (60 mg) with pip.AcOH, m.p. 120 °C (literature 121 °C [32,34–38], 117 °C [33]), IR 990.2, 1090.0, 1092.7, 1586.2, 1682.4, 2740.4, 2825.1; ^{1}H NMR 6.530 (m, 2H, *J* 3.2, 7.7, 11.7, CH-2 and CH-5), 7.296 (dd, 2H, *J* 3.2, 11.7, CH-3 and CH-4), 9.733 (d, 2H, *J* 7.7, CH-1 and CH-6); ^{13}C NMR 137.91 (CH-2 and CH-5), 146.28 (CH-3 and CH-4), 192.37 (CH-1 and CH-6).

2.2.8. Substrate *15*

The substrate **15** was ozonised to give the corresponding 1,6-dialdehyde; ^{1}H NMR 2.473 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 2.769 (m, 2H, 1/2 of CH_2-2 and CH_2-5), 4.924 (t, 2H, *J* 6.0, CH-3 and CH-4), 9.713 (s, 2H, CHO-1 and CHO-6); COSY cross peaks 2.473/2.769, 2.473/4.924, 2.769/4.924, 2.473/9.713, 2.769/9.713. Performing the aldol reaction the same product, muconaldehyde **17**, was isolated using both catalysts, 59% yield (65 mg) with Bn_2NH·TFA and 62% yield (68 mg) with pip.AcOH.

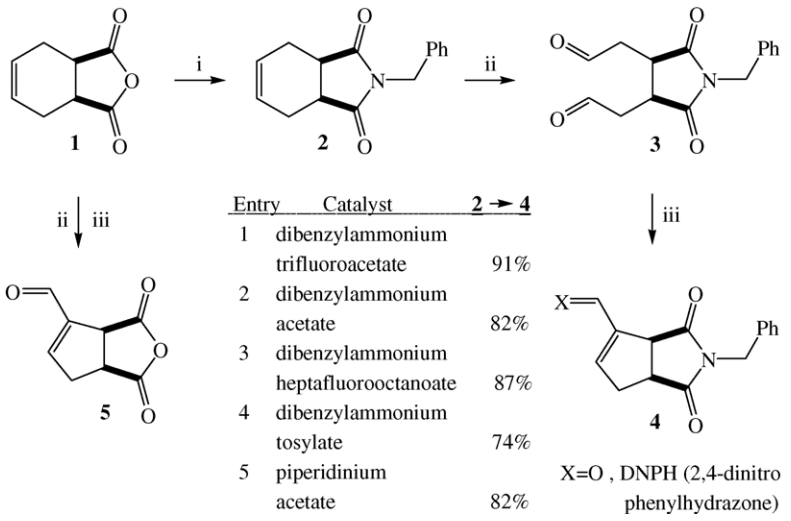
3. Results and discussion

The ozonolysis of cyclohexene derivatives to 1,6-dialdehydes, which are unstable as a norm at room temperature, was carried out under standard conditions using dimethyl sulphide (DMS) as reduction agent [39,40]. The dialdehydes were then treated with catalytic amount of dibenzylammonium trifluoroacetate (Bn_2NH·TFA) or piperidinium acetate (pip.AcOH) to afford the corresponding cyclopentene carbaldehydes.

As a first series, cyclohexenes with carbonyl type substituents were studied. The formation of the target cyclopentene carbaldehydes was observed both with Bn_2NH·TFA and pip.AcOH, but the substrates tested showed different patterns of behaviour in respect to the catalysts used. The amide **2**, prepared in a simple one-step procedure from anhydride **1** [41–43], was first investigated. It was found that the aldol product **4** was formed readily at room temperature, while no aldolysation occurred in the absence of a catalyst (Scheme 2).

In the case of aldol cyclisation of the 1,6-dialdehyde **3**, it was found that both catalysts are effective (entries 1 and 5), leading to cyclopentene carbaldehyde **4** in high yield, isolated as a stable 2,4-dinitrophenylhydrazone derivative. The same results, obtained by other dibenzylammonium salts (entries 2–4), showed that the anion does not influence the reaction yield significantly in this case.

The Bn_2NH·TFA catalysed cyclodehydration of dialdehyde **3** was performed in a NMR tube in an attempt to ascertain if the reaction goes via an enamine mechanism, like the one proposed by List and co-workers [44] for aldol condensation of 1,7-dialdehydes to the corresponding hydroxy cyclohexane aldehydes. No enamine resonances were detected but the spectra showed the presence of a compound which signals disappeared completely after 17 h. These signals are consistent with the aldol product before dehydration, hydroxy cyclopentane aldehydes, the corresponding



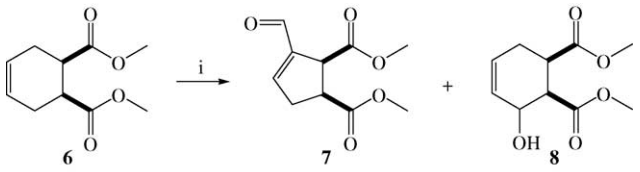
Entry	Catalyst	2 → 4
1	dibenzylammonium trifluoroacetate	91%
2	dibenzylammonium acetate	82%
3	dibenzylammonium heptafluorooctanoate	87%
4	dibenzylammonium tosylate	74%
5	piperidinium acetate	82%

Scheme 2. (i) $PhCH_2NH_2$, EtOH, 170 °C, 2 h, pressure (closed metal reactor); (ii) O_3, dry CH_2Cl_2, −78 °C, DMS; (iii) catalyst (0.2 eq.), r.t., 20–22 h.

five-membered ring analogue of the products of the condensation, investigated by List and co-workers [44]. This result could be an indication that the dehydration is the rate determining step of the transformation described herein and that if the reaction goes via an enamine mechanism, the latter intermediate is not enough long-lived to be detected in a NMR time scale.

In the case of *meso*-anhydride **1**, the carbaldehyde **5** was detected as the major product by ^{1}H NMR of the crude reaction mixtures of the transformation catalysed both by Bn_2NH·TFA and pip.AcOH. Besides product **5** and a small amount of the unreacted dialdehyde, no other products were observed. Both reaction mixtures showed almost the same pictures on the NMR scale, which could be an indication that both catalysts are also equally effective in respect to the anhydride **1**. However, because the product **5** was not enough stable to be purified, as well as to be converted into DNPH derivative, its formation was not investigated in detail.

In contrast to substrates **1** and **2**, the *meso*-diacetate **6** showed different patterns of behaviour in respect to the two catalysts investigated (Scheme 3). Carbaldehyde **7** was formed, using both catalysts, but while in the case of the transformation catalysed by Bn_2NH·TFA it was the only product



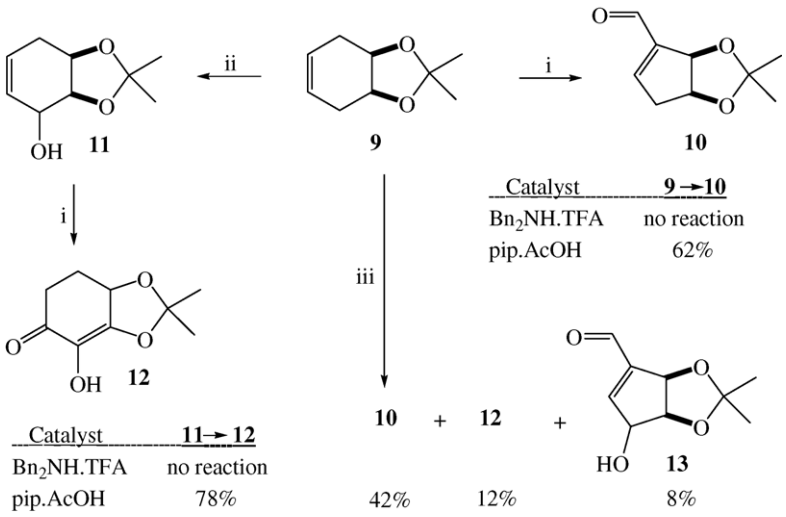
Entry	Catalyst	Product
1	dibenzylammonium trifluoroacetate	**7**, 78%
2	piperidinium acetate	**7**, 64%; **8**, 31%
3	dibenzylamine	**7**, 63%
4	piperidine	**7**, 59%

Scheme 3. (i) O_3, dry CH_2Cl_2, −78 °C, DMS; catalyst (0.2 eq.), r.t., 20–22 h.

in good yield (entry 1), when pip.AcOH was used, the corresponding hydroxy alkene **8** was also isolated (entry 2).

Compound **8** seems to be the result of an allylic oxidation of **6**, but the same product formation was not detected when Bn_2NH·TFA was used. Also, no starting alkene was observed in the NMR spectra of the crude reaction mixture after ozonolysis. The same result was obtained by using in vacuo over-dried catalyst, which is moderately hygroscopic. Additionally, the dibenzylamine and piperidine effectiveness as catalysts was verified. It was found that both secondary amines catalysed the reaction, leading only to the formation of the main carbaldehyde **7**, although in moderate yields (entries 3 and 4). This observation is in contrast to the main assumption in the literature that this aldol condensation needs a salt consisted of a secondary amine and a carboxylic acid as a catalyst. However, it is in agreement with the results of Bryce and Gardiner [17] where a fused azaspirocyclic skeleton has been constructed as a single product by passing 1,6-dialdehyde down a column of basic alumina. The NMR data of the ozonolysis mixture after DMS treatment correlate with the corresponding dialdehyde as a main product in parallel with a substance, having a CH group with a proton resonance at 5.121 ppm and a carbon one at 102.28 ppm. These signals are consistent with an ozonide, as it is known [45] that the latter can be recognised by the signals of the CH in the ozonide rings, which appear in the range of 5.03–5.30 ppm in the proton spectra and 93.82–114.04 ppm in the carbon. The isolation of the allylic alcohol **8** is quite intriguing, because the results suggest that instead of expected formation by allylic oxidation of olefin **6**, this is obtained from the ozonide and only in the presence of piridinium acetate as catalyst. Perhaps the presence of some acetic acid resulted of salt dissociation in dichloromethane have some rule in this transformation, but with the information available no reasonable explanation can be suggested at the moment.

In an attempt to distil the dialdehyde of **6**, according to the literature data [28], an exothermic reaction was observed,



Scheme 4. (i) O_3, dry CH_2Cl_2, −78 °C, DMS; catalyst (0.2 eq.), r.t., 20–22 h; (ii) SeO_2 (0.5 eq.), aq. dioxane, reflux, 7 h; (iii) O_3, wet CH_2Cl_2, −78 °C, DMS; catalyst (0.2 eq.), r.t., 20–22 h.

resulting in an explosion in a relatively big scale (35 mmol) at 0.01 mmHg and 90 °C. The aldehyde **7** was isolated from the distillate, which is an indication that the reaction occurs as a thermal one at these conditions, while at room temperature it was very slow and no product formation was detected even after 48 h in the absence of a catalyst.

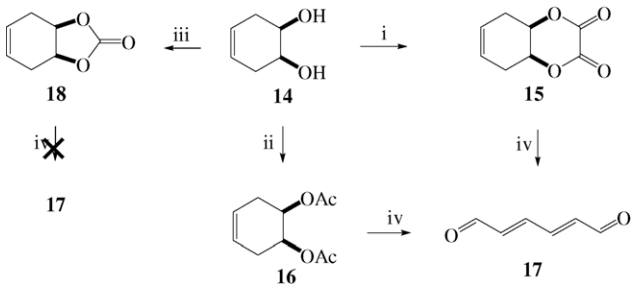
As a second series, differently protected *meso*-cyclohexene diols were investigated. These substrates allow a direct synthesis of a cyclopentanoid unit, which is an important carbocyclic nucleoside.

The acetonide **9**, prepared according to a known procedure [22], based on a partial oxidation of 1,4-cyclohexadiene and subsequent protection of the diol, was first studied. It was found that while pip.AcOH catalysed the aldol cyclodehydration of the dialdehyde, giving the target carbaldehyde **10** in a moderate yield, $Bn_2NH{\cdot}TFA$ was not effective as a catalyst and only unreacted dialdehyde was detected (Scheme 4).

Based on the observed efficiency of the amines as catalysts in the generation of **7** (Scheme 3), the basic component of the non-effective catalyst, dibenzylamine, was tested. It was found that it converts the dialdehyde of **9** into the corresponding carbaldehyde **10**, but in relatively low yield (23%), with the impurities of unpolar side products. Carrying out the reaction in wet dichloromethane instead of dry one, in parallel with the main aldehyde **10**, a side product, the hydroxy cyclohexenone **12**, was isolated, as well as traces of the corresponding hydroxy cyclopentene carbaldehyde **13** (Scheme 4). As the formation of a product like **12** was highly unexpected in these conditions, its structure was confirmed by X-ray analysis, as it is shown in Fig. 1 [29].

Being a precursor of an even more functionalised cyclopentanoid unit, the aldehyde **13** appears as an ideal target. Alkene **11**, prepared by allylic oxidation of **9**, was tested in the transformation (Scheme 4). When pip.AcOH was used, instead of the expected hydroxylated cyclopentene carbaldehyde **13**, the same hydroxy cyclohexenone **12** formation was observed as the only reaction product in a good yield. Like in the case of **9**, $Bn_2NH{\cdot}TFA$ was not effective as a catalyst (Scheme 4). The NMR data of the product after ozonolysis correlate with an ozonide with two non-equivalent CH groups in the ozonide ring giving signals at 5.56 and 5.66 ppm and at 94.20 and 99.97 ppm in the proton and carbon spectra, respectively [45]. As this was the only product after the reductive work-up, it should mean that the "ozonide" in this case is quite stable. This is in contrast with its chromatographic behaviour, as well as with the stability of the "ozonides", obtained from the other investigated alkenes, where the corresponding dialdehydes were formed as a single or main product. To verify this suggestion the spectra of the ozonolysis product without DMS work-up were recorded and the same resonances were observed. This is an indication that the hydroxyl group stabilises the "ozonide" in respect to the reductive reagent and only pip.AcOH promotes the formation of the product **12**. The same intermediate product was not detected by NMR inside the mixture after ozonolysis of **9**, both in dry and in wet dichloromethane. Even after 24 h of reductive work-up, the presence of another substrate was observed, in parallel with the dialdehyde, which resonances correlated again with an ozonide. The fact that the reaction mixtures after ozonolysis of **9** in dry and in wet solvent show the same NMR spectra and as **12** was generated only in the presence of water, it could be suggested that the latter does not participate significantly in the time of ozonolysis, but in the catalytic step of the transformation, leading to the formation of **12**.

Cyclohexenediols with other protecting groups were also investigated in this transformation, such as the cyclic oxalate **15**, diacetoxy derivative **16** and cyclic carbonate **18**. It was found that the type of the products depends also on the substrate substituents. Thus, performing the reaction with oxalate **15**, as well as with diester **16**, instead of the expected five membered carbocyclic product with 1,2-unsaturated formyl function, *E*,*E*-2,4-hexadienedial (**17**)



Entry	Catalyst	15→17	16→17
1	Bn_2NH.TFA	59%	53%
2	pip.AcOH	62%	54%
3	piperidine	55%	51%
4	AcOH	no reaction	no reaction
5	no catalyst	no reaction	no reaction

Scheme 5. (i) ClCOCOCl (1.75 eq.), Et_3N (2.5 eq.), CH_2Cl_2, 0 °C, 1 h; (ii) AcCl (4 eq.), Et_3N (4 eq.), CH_2Cl_2, r.t., 6 h; (iii) ClCOCl (1 eq.), toluene, r.t., 2 h; (iv) O_3, dry CH_2Cl_2, −78 °C, DMS; catalyst (0.2 eq.), r.t., 20–22 h.

formation was observed, catalysed by Bn_2NH·TFA and pip.AcOH (Scheme 5). The latter were equally effective in both cases, giving **17** in almost the same extend (entries 1 and 2).

The dialdehyde **17**, so-called muconaldehyde, is a well-known compound. Unsaturated dialdehydes and their epoxides are toxic products involved in aerosol formation and in the chemistry of photochemical smog as a result of tropospheric oxidation of benzene and methylated benzenes. Muconaldehyde is the major product in the oxidation of benzene and benzene oxide/oxepin as well. It is a widely investigated product [32–38,46] not only because of its multiform toxicity but also as a reactive six-carbon diene dialdehyde.

E,*E*-Muconaldehyde **17** was the only reaction product when cyclic oxalate **15** was used as a starting material. However, polymer formation was observed during the ozonolysis, most probably as a result of the low stability of the oxalate in the experimental conditions. This resulted in a relatively low reaction yield, in spite of the clean chromatogram of the crude reaction mixture. As the polymerisation depends on the concentration as a norm, the pip.AcOH catalysed experiments were performed in more diluted solutions of **15**, resulting in a considerable increase of the reaction yield, 62% in 0.1 M solution versus 38% in 0.2 M. In the case of diacetate **16** no polymerisation was observed but some impurities were detected by TLC and NMR, excluding the expected cyclopentene carbaldehyde, as no olefinic resonance was detected, and the reaction yield was in the same scale (Scheme 5). No muconaldehyde formation was observed without catalyst even after 24 h at room temperature in both cases (entry 5). The NMR spectra of the crude reaction mixtures correlate with the corresponding 1,6-dialdehydes, which shows that muconaldehyde formation occurs in the catalytic step from the corresponding dialdehyde. Additionally, the participation of the two catalyst components was investigated for the pip.AcOH-catalysed reaction. It was found that piperidine (entry 3) originated the product in a similar extend as the acetate (entry 2), while the acetic acid was not effective and no muconaldehyde resonances were observed (entry 4). The latter shows that piperidine is the efficient component of the catalyst, while the acetic acid does not influence significantly the transformation. The *E*,*E*-configuration of the product has to be a result of an isomerisation, which occurs under the experimental conditions, like it has been observed in many other cases [37,46,47].

Starting from the cyclic carbonate **18**, almost quantitative polymerisation was observed even in diluted solutions. Inside of the complex NMR spectra, aldehyde resonances could be recognised at 9.77 and 9.81 ppm after the ozonolysis and the catalytic step, respectively, but no muconaldehyde signals (Scheme 5), which are in areas free of other signals. As the product was highly unstable on chromatography and could not be purified to obtain explicit data for its structure, further investigations were not performed. Thus, no substantial conclusions could be drawn, except that no muconaldehyde generation occurs in this case. It has been found [48,49] that cyclic oxalates undergo a decarbonylation to the corresponding carbonates. As the muconaldehyde was the only product formed from the oxalate **15**, and as no muconaldehyde was detected from the carbonate **18**, it could be an indication that the oxalate does not undergo similar decarbonylation in the time of the ozonolysis as well as in the catalytic step of the reaction.

During this study the unexpected muconaldehyde formation was observed from the cyclic oxalate **15** and diacetate **16**, while carbaldehydes were formed from the rest of the substrates. This could be due to a preferential elimination in the first case as it is well known that acylated alcohols are good leaving groups, followed by an isomerisation, while the aldol condensation is the favoured process in the second group of substrates.

4. Conclusion

The intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted 1,6-dialdehydes was investigated and it was found that the type and the yield of the products strongly depend on the substrate substituents. It was shown that starting from compounds having carbonyl (**1**, **2** and **6**) or acetonil protected diol **9** type substituents, the corresponding carbaldehyde is the only or the main product. On the other hand, acylated diols (**15** and **16**) lead to an open chain conjugated dialdehyde, 2,4-hexadienedial, which most probably is due to a preferential elimination in this case. In the transformation provided with the open chain diester **6**, a side product formation was observed when piperidinium acetate was used, the hydroxyalkene **8**, which should be generated in the catalytic step. It was shown that the catalyst efficiency also depends on the substrate substituents. If the latter are of carbonyl (**1**, **2** and **6**) or acylated diol (**15** and **16**) type, both dibenzylammonium trifluoroacetate and piperidinium

acetate are effective, while starting from acetonil protected diols (**9** and **11**) the second one is the only efficient catalyst. It was observed that if a free hydroxyl group exists in the cyclohexene ring **11**, a hydroxy cyclohexenone **12** was formed as the only reaction product from an "ozonide", which is quite stable in this case in respect to the reductive work-up. Additionally, it was shown that a secondary amine catalyses the transformation itself, leading to the same products formation, even in the cases where the corresponding ammonium salt is not effective as a catalyst. Another study reported by us on the asymmetric catalytic aldol cyclodehydration transformation on substrates **2** and **9** demonstrated that the reaction behaviour is extremely dependent of the organocatalyst and substrate structures [50].

Acknowledgements

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