Revue Roumaine de Chimie, **2008**, *53*(3), 189–193

USEFUL INTERMEDIATES FOR FINE ORGANIC SYNTHESIS BY HYDROXYLATION OF 1,2,3,3a,4,6a-HEXAHYDRO-1,3-PENTALENEDIMETHANOL AND *BIS* OH-PROTECTED DERIVATIVES

Constantin I. TĂNASE,[a*] Florea G. COCU,[a] Constantin DRĂGHICI[b] and Miron T. CĂPROIU[b]

[a] National Institute for Chemical & Pharmaceutical Research and Development, 112 Vitan Av., 74373 Bucharest 3, ROUMANIA
[b]Center for Organic Chemistry "C. D. Nenitzescu", 202B Splaiul Independentei, Bucharest 060023, ROUMANIA

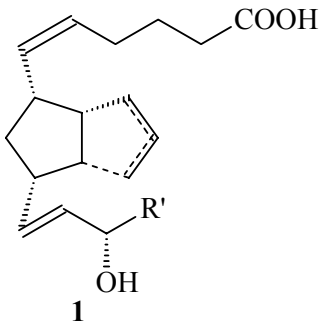
Received March 7, 2007

Synthesis of 4,6-*bis*-hydroxymethyl-octahydro-pentalene-1,2-diol was realized in high yield by direct $KMnO_4$ hydroxylation of 3-hydroxymethyl-1,2,3,3a,6,6a-hexahydro-pentalen-1-yl)-methanol. Two easier ways for isolation of tetrol from the reaction mixture were realized by hydroxylating first the *bis*-benzoyloxy- or *bis*-tetrahydropiranyl-derivatives of alkenediol and then the removing of the protecting groups. The compounds were investigated by elemental analysis, IR and ^{1}H-NMR spectra.

INTRODUCTION

Synthesis of new eicosanoid, isoprostane and carbacyclin analogues with useful therapeutical properties and of the adequate intermediates for their preparation is a continue demand for the scientists.

Our works in the field resulted in the synthesis of new carbacyclin type compounds with unconventional position of α-side chain and without a hydroxyl group on the pentalenofurane fragment (named by us "*pseudo*-carbacyclins"),[1,2] **1**.



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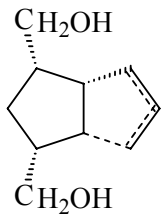
"Pseudocarbacyclins"



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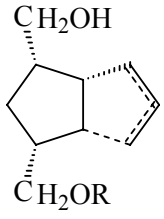

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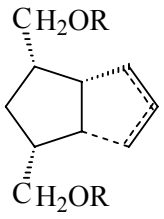

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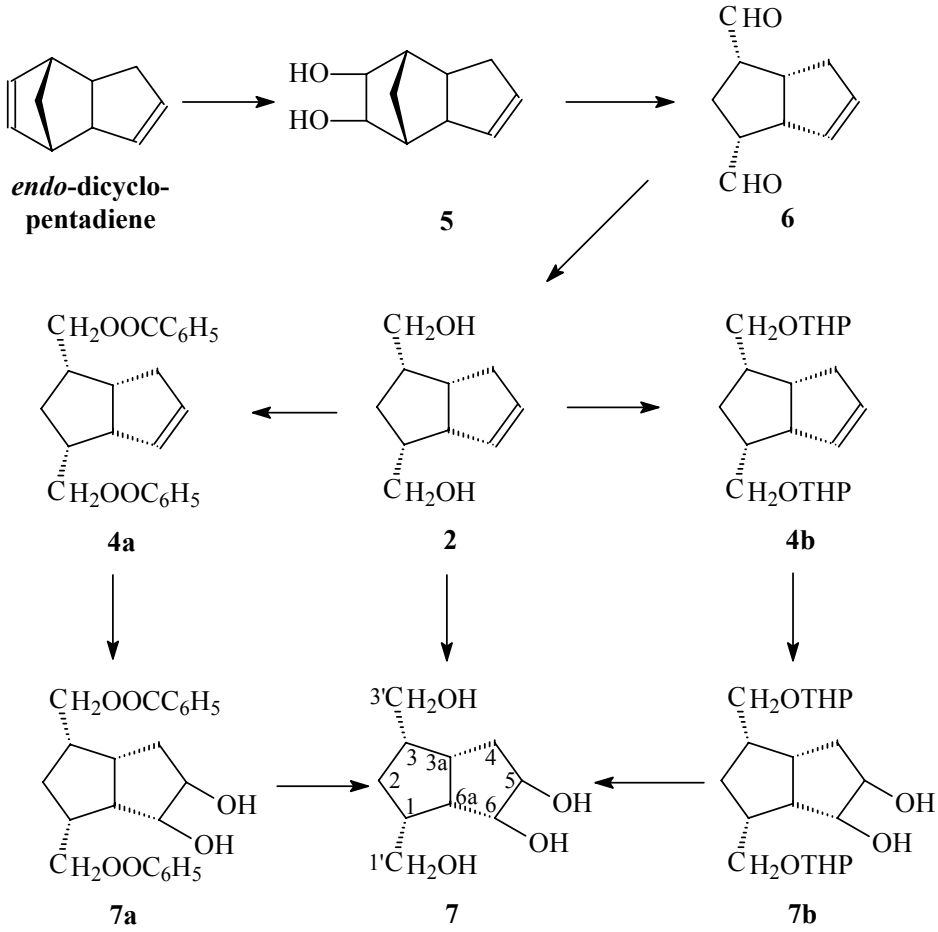
Their synthesis was realised using the exocyclic hydroxymethyl groups of compound **2**, to link the α- and ω-side chains. In a separate paper we presented the synthesis of the compound **2** from *endo*-dicyclopentadiene[3] in three steps and *mono*- and *bis*-protection of its hydroxymethyl groups to **3** and **4**, with ester, ether and TBDMS groups.

In this paper we present the hydroxylation of the double bond of compound **2** to the tetrole **7** (Scheme 1). Other two alternatives for obtaining the same tetrole **7**, starting from the *bis*-benzoate derivative **4a** and *bis*-tetrahydropyran(2-yl-oxy)-derivative **4b** are also presented.

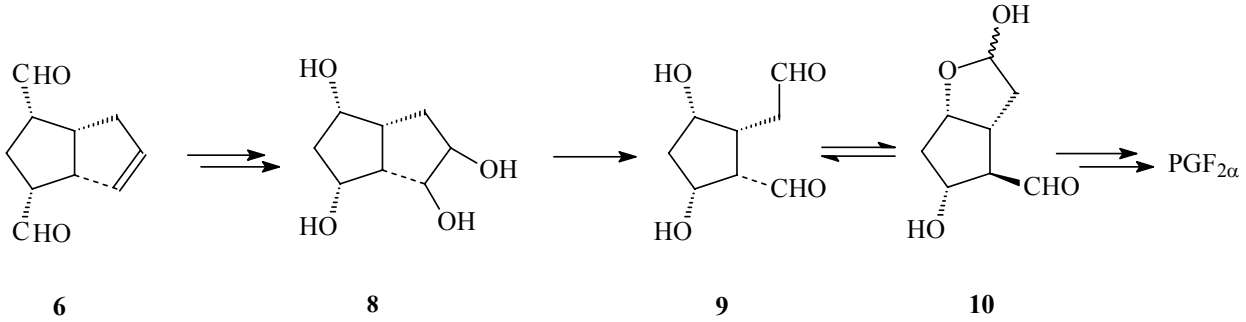
* Corresponding author: cvtanase@gmail.com



Scheme 1 – Synthesis of tetroles **7, 7a** and **7b**.

RESULTS AND DISCUSSION

An earlier approach for $F_{2\alpha}$ prostaglandin synthesis[4,5] started from dialdehyde **6** following a strategy to replace the aldehyde groups with hydroxyl ones, in the same configuration (this being the correct stereochemistry in the prostaglandins) and then to hydroxylate the double bond (OsO_4 cat., $KClO_4$), in order to result tetrole 7 (Scheme 2). The diol was then oxidativelly cleaved to dialdehyde **9**, which is intramolecular cyclised to lactol-aldehyde **10**, the remaining aldehyde being used in the Horner-Emmons reaction to introduce the ω-side chain of natural prostaglandins. In alcaline conditions (K_2CO_3 used as base), the aldehyde, linked to the cyclopentane ring, due to the steric hindrance of vicinal groups, was partially epimerised to the correct β-configuration requested for construction of ω-side chain.



Scheme 2 – $PGF_{2\alpha}$ synthesis from dialdehyde **6**.

For obtaining eicosanoid and isoprostan analogues, we wanted to synthesize tetrole **7**, with *cis*- stereochemistry of the cyclopentenic dihydroxy groups, by $KMnO_4$ *cis*-hydroxylation of the double bond of compound **2** in slightly alcaline conditions generated by buffering the KOH formed in the reaction with $MgSO_4$. The resulted tetrole **7** (obtained in 72% yield) is very soluble in water and difficult to isolate from the aqueous reaction mixture. To overcome this difficulty, the alkenediol **2** was benzoylated to compound **4a**, as we presented in another paper,[3] obtained as a pale-yellow oil, and then hydroxylated in the same reaction conditions to the *cis*-diol intermediate **7a**. Compound **7a**, easier to separate from the aqueous reaction mixture, was purified by flash chromatography on silicagel and crystallization from acetone, giving pure compound in 70% yield. Finally the benzoate groups were hydrolyzed with Dowex 50x8 acid exchange resin, methanol evaporated, methyl benzoate extracted with petroleum ether and tetrole **7** crystallized (methanol-benzene) in >90% yield.

In the reactions described above it is the solubility of the tetrole in water which decrease the yield in the first reaction and the hydrolysis of the benzoate group in the second one.

We used then the bis-[tetrahydropyran-(2-yl-oxy)] protected compound **4b**, obtained from diole **2** as mentioned in our paper,[3] for hydroxylation of the double bond in the same conditions, taking into account that THP groups are stable in the slightly alcaline reaction conditions and the hydroxylated compound **7b** is even easier to separate from the aqueous reaction mixture. The crude *cis*-diol **7b** was used without purification in the acid hydrolysis of the THP protecting groups (MeOH, TsOH), the catalyst removed by passing the solution on a column with MP7080 anion exchane resin (OH form) and finally the product crystallised from methanol-benzene resulted in 71.9% yield. Using Dowex 50x8 as acid catalyst, the work-up was easier and the yield was similar.

A full characterization of the structure of the compounds **7a** and **7** was realized by ^1H and ^{13}C-NMR spectroscopy. For compound **7a**, ^1H and ^{13}C-NMR spectra in $CDCl_3$ were difficult to be resolved due to the hydroxyl couplings with vicinal protons. Adding TFA, this couplings were eliminated and a better atribution of the protons were realized. Even in these conditions, due to small differences in chemical shifts and cross-coupling constants, it was difficult to precisely give the multiplicity and coupling constants for some protons. By doing the proton and ^{13}C- NMR spectra for both compounds in the same solvent, DMSO-d_6 (ading THF, a reduced mutiplicity of protons was also obtained), and also COSY(H,C) spectra, the attribution of the signals to the protons and carbon atoms of the molecules were precisely done.

EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. The progress of the reaction was monitored by TLC on Merck silica gel 60 or $60F_{254}$ plates (Merck) eluted with the solvent system: (I). benzene: ethyl acetate: hexane (5:3:2), (II). ethyl acetate: hexane: acetic acid (5:1:0.1) (v: v: v). IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer. ^1H-NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) and UNITY 400 PLUS (400 MHz for ^1H, 100 MHz for ^{13}C), chemical shifts are given in ppm relative to TMS (δ =0 for 1H and ^{13}C) as internal standard. To simplify the proton spectra, due to overlaping of broad OH groups' signals, triflouroacetic acid (TFA) was added; so, the signals of OH and their coupling with neighbour protons were eliminated. The numbering of the compounds is presented in Scheme 1.

1. Synthesis of 4,6-Bis-(benzoyloxymethyl)-octahydro-pentalene-1,2-diol, 7a

24 g (63.76 mmoles) Compound **4a** were solved in 500 mL ethanol, the solution cooled to -18ºC and then a solution of 13.3 g (82.6 mmoles) 98%$KMnO_4$ and 20.36 g (82.6 mmoles) $MgSO_4.7H_2O$ in 250 mL water was added in 3h under vigorous stirring and maintaining the reaction temperature under -10ºC. The stirring was continued 1 h on the cooling bath, then 16 h at r.t., monitoring the reaction by TLC (I, R_{f4a}=0.88, R_{f7a}=0.24). MnO_2 resulted was filtered, washed with 70 ml ethanol, the solution concentrated to remove ethanol, the aqueous concentrate extracted with dichloromethane (3x300 ml), the unified extracts washed with 150 ml water, dried ($MgSO_4$) and concentrated. 25g Crude product resulted which was purified by pressure chromatography (eluent: benzene, then solvent system: benzene-ethyl acetate-hexane, 5:3:2). A pure cristallyzed fraction of 18.3 g (70%) was obtained which was recrystallized from acetone, giving a first crop of 15.7 g (60.2%) at pure **7a**, with m.p. 134-136ºC, which was characterized by: elemental analysis, calctd for $C_{24}H_{26}O_6$: th.(%): C: 70.24, H: 6.36, found (%): C: 70.11, H: 6.28; FT-IR(solid in ATR, cm^{-1}): 3467i; 3061w; 2937w; 2877m; 1694vi; 1581w; 1451m; 1392w; 1322m; 1279vi; 1175m; 1117m; 1093m; 1017m; 960m; 856m; 805w; 715vi; 633vw; 531w. ^1H-NMR($CDCl_3$, δ ppm, *J* Hz): **8.05÷8.02**(m, 4H, H-arom, H-*ortho*); 7.60÷7.54(m, 2H, H-arom, H-*para*); **7.48÷7.42**(m, 4H, H-arom, H-*meta*); **4.57**(dd, 1H, H-1'A, syst. AB, 7.8, 11.3); **4.52**(dd, 1H, H-1'B, syst. AB, 6.7, 11.3); **4.41**(dd, 1H, H-3'A, syst. AB, 6.9, 11.0); **4.25**(dd, 1H, H-3'B, syst. AB, 8.5, 11.0); **4.16**(m, 1H, H-5); **3.98**(m, 1H, H-6); **3.14**(qv, 1H, H-3a, 9.2); **2.66**(q, 1H, H-6a, 8.2); **2.60÷2.38**(m, 4H, H-1, H-3, HO-5, HO-6); **1.96÷1.87**(m, 2H, H-2A, H-4A); **1.46**(ddd, 1H, H-4B, syst. AB., 3.7, 10.0, 13.8); **1.16**(q, 1H, syst. AB, H-2B, 12.5). ^1H-NMR($CDCl_3$ + tfa, δ ppm, *J* Hz): **8.03÷8.01**(m, 4H, H-arom, H-*ortho*); **7.64÷7.60**(m, 2H, H-arom, H-*para*); **7.50÷7.46**(m, 4H, H-arom, H-*meta*); **4.66**(dd, 1H,

H-3'A, syst. AB, 8.2, 11.0); **4.51÷4.46**(m, 2H, H-1'A, H-1'B, syst. AB); **4.36**(m, 1H, H-5); **4.27**(dd, 1H, H-3'B, 8.6, 11.0); **4.15**(dd, 1H, H-6, 3.3, 8.9); **3.17**(qv, 1H, H-3a, 8.9); **2.75**(q, 1H, H-6a, 8.9); **2.59**(m, 1H, H-1); **2.50**(m, 1H, H-3); **2.02÷1.96**(m, 2H, H-2A, H-4A); **1.56**(ddd, 1H, H-4B, syst. AB., 3.3, 10.0, 14.0); **1.21**(q, 1H, H-2B, 12.5). ^{1}H-NMR(dmso, δ ppm, *J* Hz): **7.99÷7.94**(m, 4H, H-arom, H-*ortho*); **7.63÷7.60**(m, 2H, H-arom, H-*para*); **7.54÷7.48**(m, 4H, H-arom, H-*meta*); **4.54**(dd, 1H, syst. AB, H-1'A, 5.9, 11.0); **4.43**(bs, 1H, HO); **4.30÷4.28**(m, 2H, syst. AB, H-3'A, H-3'B); **4.20**(dd, 1H, syst. AB, H-1'B, 8.9, 11.0); **3.84**(m, 1H, H-5); **3.69**(dd, 1H, H-6, 3.5, 8.6); **3.40**(bs, 1H, OH**); 2.86**(qv, 1H, H-3a, 9.0); **2.47**(q, 1H, H-6a, 9.0); **2.39÷2.24**(m, 2H, H-1, H-3); **1.82**(dt, 1H, syst. AB, H-2A, 12.5, 5.8); **1.53**(dd, 1H, syst. AB, H-4A, 9.3, 13.1); **1.38**(m, 1H, syst. AB, H-4B); **1.20**(q, 1H, syst. AB, H-2B, 12.5). ^{1}H-NMR(dmso + tfa, δ ppm, *J* Hz): **7.98÷7.93**(m, 4H, H-arom, H-*ortho*); **7.60÷7.56**(m, 2H, H-arom, H-*para*); **7.60÷7.46**(m, 4H, H-arom, H-*meta*); **4.53**(m, 1H, syst. AB, H-1'A); **4.29÷4.27**(m, 2H, H-1'B, H-3'A); **4.19**(m, 1H, H-3'B); **3.85**(m, 1H, H-5); **3.69**(m, 1H, H-6); **2.87**(qv, 1H, H-3a, 8.7); **2.49**(q, 1H, H-6a, 8.7); **2.39÷2.23**(m, 2H, H-1, H-3); **1.80**(dt, 1H, syst. AB, H-2A, 11.5, 5.4); **1.54**(dd, 1H, syst. AB, H-4A, 7.6, 13.3); **1.37**(m, 1H, syst. AB, H-4B); **1.17**(q, 1H, syst. AB, H-2B, 11.5). ^{13}C-NMR(dmso, δ ppm): **166.16**(COO); **165.95**(COO); **133.59**(C-*p*); **133.45**(C-*p*); **130.41**(Cq); **130.18**(Cq); **129.52**(C-*o*); **129.40**(C-*o*); **129.10**(C-*m*); **128.99**(C-*m*); **75.07**(C-6); **74.96**(C*-6); **74.20**(C-5); **74.10**(C*-5); **66.00**(C-1'); **65.61**(C-3'); **48.69**(C-6a); **41.03**(C-3a); **40.46**(C-1); **40.30**(C-3); **31.11**(C-2); **30.96**(C-4). ^{13}C-NMR(dmso+tfa, δ ppm): **166.17**(COO); **165.95**(COO); **133.41**(C-*p*); **133.29**(C-*p*); **130.49**(Cq); **130.27**(Cq); **129.49**(C-*o*); **129.38**(C-*o*); **128.94**(C-*m*); **128.84**(C-*m*); **75.09**(C-6); **74.23**(C-5); **65.95**(C-1'); **65.54**(C-3'); **48.75**(C-6a); 41.06(C-3a); **40.46**(C-1); **40.32**(C-3); **31.90**(C-2); **30.94**(C-4).

2. Synthesis of 4,6-Bis-(hydroxymethyl)-octahydro-pentalene-1,2-diol, 7

7.11 g (13.32 mmoles) 4,6-Bis-(benzoyloxymethyl)-octahydro-pentalene-1,2-diol, **7a** were hydrolized by transesterification in 200 ml 0.05M MeONa (r.t., 48 h), monitoring the reaction by TLC (II, R_{f7a}=0.78, R_{f7}~0.05). Na^+ ion was retained on Dowex 50x8 (H^+ form), filtered, washed with methanol, filtrate concentrated and crude product extracted with benzene to remove methyl benzoate and product cristallyzed from benzene-methanol. Pure 3.16 g (90%) tetrole **7** resulted, m.p. 166-167ºC. (The mixt m.p. of this compound with that of the tetrole obtained by direct hydroxylation of diole **2** was 164.5-166ºC).

3. Direct synthesis of tetrole 7 by hydroxylation of alkenediol 2

9.8 g (58.3 mmoles) Alkene-diol **2** were hydroxylated in the same conditions as **7a** with 12 g (76 mmoles) 98% $KMnO_4$ and 18.8 g (76 mmoles) $MgSO_4.7H_2O$, monitoring the reaction by TLC (II, R_{f2}=0.78, R_{f7}~0.05). MnO_2 resulted was filtered, washed with 300 ml ethanol, 300 ml water, filtrates concentrated, residue coevaporated with benzene, extracted with boiling acetone (3x200 ml), boiling methanol (3x200 ml) and unified extracts concentrated. The concentrate was solved in water, the salts removed on two columns of Dowex 50x8 and MP 7080, water distilled under reduced pressure, coevaporated with benzene, resulting 12.6 g. From benzene-methanol crystallyzed 5.39 g (45.7%) in the first crop, of pure tetrole **7**, m.p. 165-167ºC, which was characterized by: elemental analysis, calctd. for $C_{10}H_{18}O_4$: -th. (%): C:59,40; H:8,95; found (%): C:59,30; H:8,82; FT-IR(solid in ATR, cm^{-1}): 3345vi; 3265vi; 2977w; 2934m; 2881m; 1451m; 1402w; 1339m; 1265w; 1237w; 1208w; 1174w; 1086m; 1047w; 1017i; 991m; 952w;840w; 800w; 735w; 614m; 510w; 470w. ^{1}H-NMR(dmso, δ ppm, *J* Hz): **4.43**(d, 1H, HO-5 or HO-6, 5.1); **4.30÷4.24**(m, 2H, HO-1', HO-3'); **4.17**(bs, 1H, HO-5 or HO-6); **3.78**(m, 1H, H-5); **3.62÷3.58**(m, 2H, H-6, H-1'A); **3.44÷3.42**(m, 2H, H-1'B, H-3'A); **3.33**(m, 1H, H-3'B); **2.68**(q, 1H, H-3a, 9.0); **2.31**(q, 1H, H-6a, 8.6); **1.99**(m, 1H, H-1); **1.88**(m, 1H, H-3); **1.60**(dt, 1H, syst. AB, H-2A, 11.9, 5.1); **1.48**(dd, 1H, syst. AB, H-4A, 10.3, 13.4); **1.25**(ddd, 1H, H-4B, 3.4, 9.7, 13.4); **0.74**(q, 1H, syst. AB, H-2B, 12.4). By deuteration or by adding TFA, the OH signals dissapeared and NMR spectrum became simplier. ^{1}H-NMR(dmso+tfa, δ ppm, *J* Hz): **3.79**(m, 1H, H-5); **3.63÷3.57**(m, 2H, H-6, H-1'A); **3.43**(m, 1H, H-3'B); **3.36÷3.30**(m, 2H, H-1'B, H-3'A); **2.70**(q, 1H, H-3a, 9.0); **2.32**(q, 1H, H-6a, 8.4); **2.00**(spt, 1H, H-1, 6.0); **1.89**(spt, 1H, H-3, 6.4); **1.59**(dt, 1H, syst. AB, H-2A, 12.1, 6.0); **1.48**(dd, 1H, syst. AB, H-4A, 10.1, 13.2); **1.25**(ddd, 1H, H-4B, 3.4, 9.0, 13.2); **0.74**(q, 1H, syst. AB, H-2B, 12.1). ^{13}C-NMR(dmso, δ ppm): **74.53**(C-6); **73.84**(C-5); **62.22**(C-1'); **61.73**(C-3'); **48.59**(C-1a); **44.09**(C-1 or C-3); **43.61**(C-3 or C-1); **40.58**(C-3a); **31.08**(C-2); **30.66**(C-4). ^{13}C-NMR(dmso+tfa, δ ppm): **74.76**(C-6); **74.08**(C-5); **62.43**(C-1'); **61.93**(C-3'); **48.85**(C-1a); **44.30**(C-1 or C-3); **43.79**(C-3 or C-1); **40.82**(C-3a); **31.21**(C-2); **30.85**(C-4).

By concentrating the mother liquors, 5.5 g of impure tetrole resulted, which was purified by pressure chromatography, obtaining 3.1 g (26.3%) tetrole **7** (Total yield 72.0%).

4. Synthesis of 4,6-Bis-[tetrahydropiran(2-yl-oxy)methyl]-octahydro-pentalene-1,2-diol, 7b.

13.39 g (39.8 mmoles) Compound **7b** dissolved in 320 ml ethanol were hydroxylated as in ex. 1., with a solution of 8.5 g (53 mmoles) 98%$KMnO_4$ and 13.06 g (53 mmoles) $MgSO_4.7H_2O$ in 160 mL water, monitoring the reaction by TLC (I, R_{f4b}=0.57, R_{f7b}=0.04). MnO_2 resulted was washed with 350 ml boiling water, filtrate concentrated to remove ethanol, aqueous phase extracted with dichloromethane (2x300 ml), unified extracts dried (Na_2SO_4), filtered and concentrated to dryness, resulting 12.65 g crude product **7b** as oil, which was used as so in next step for hydrolysis of THP groups.

5. Synthesis of 4,6-Bis-(hydroxymethyl)-octahydro-pentalene-1,2-diol, 7 from 7b

12.65 g Crude product **7b** were dissolved in 200 ml methanol, 300 mg TsOH were added, the solution remained at r.t. over night and then warmed for 2 hrs at 40ºC, monitoring the reaction by TLC (II, R_{f7b}=0.37, R_{f7}=0.04). The catalyst was retained on MP7080 anion exchange resin column, column washed with methanol-water and methanol distilled under reduced pressure. The aqueous phase was extracted with benzene (2x50 ml), benzene extracts washed with 50 ml water, unified aqueous phases concentrated to dryness, coevaporated with benzene and the concentrate crystallized from benzene-methanol, resulting 5.73 g (71.9%) pure tetrol **7** from **4b**.

Replacing TsOH with sulfonic exchange resign Dowex 50x8 (H form) in the hydrolysis of THP groups, the result was similar.

CONCLUSIONS

Tetrole **7** was obtained in good yield by direct hydroxylation of alkene-diol **2**, with laborious separation from the reaction mixture due to its high solubility in water. The same tetrole was also obtained in good yield by realising first hydroxylation of bis-(benzoyloxy)- or bis-[tetrahydropyran(2-yl)oxy]- derivatives **4a**, respectively **4b**, of alkenediol **2** and then removing the protecting groups.

The structures of the tetrole **7** and tetrole dibenzoate **7a** were fully confirmed by IR and ^{1}H-, ^{13}C- and COSY(H,C)-NMR spectra.

REFERENCES

1. C. I. Tănase, F. G. Cocu, M. T. Căproiu and C. Drăghici, *Rev. Chim., (English Edition)*, **2001**, *2*, 11.
2. C. I. Tănase, F. G. Cocu, M. T. Căproiu and C. Drăghici, *RO-patent-116896*, **2001**.
3. C. I. Tănase, F. G. Cocu, M. T. Căproiu and C. Drăghici, *Rev. Roum. Chim.,* **2008**, *53*, 195-202.
4. D. Brewster, M. Myers, J. Ormerod, M. E. Spinner, S. Turner and A.C.B. Smith, *J.Chem.Soc., Chem. Commun.,* **1972**, 1235.
5. D. Brewster, M. Myers, J. Ormerod, P. Otter, A. C. B. Smith, M. E. Spinner and S. Turner, *J.Chem.Soc.,Perkin Trans. I*, **1973**, 2796.