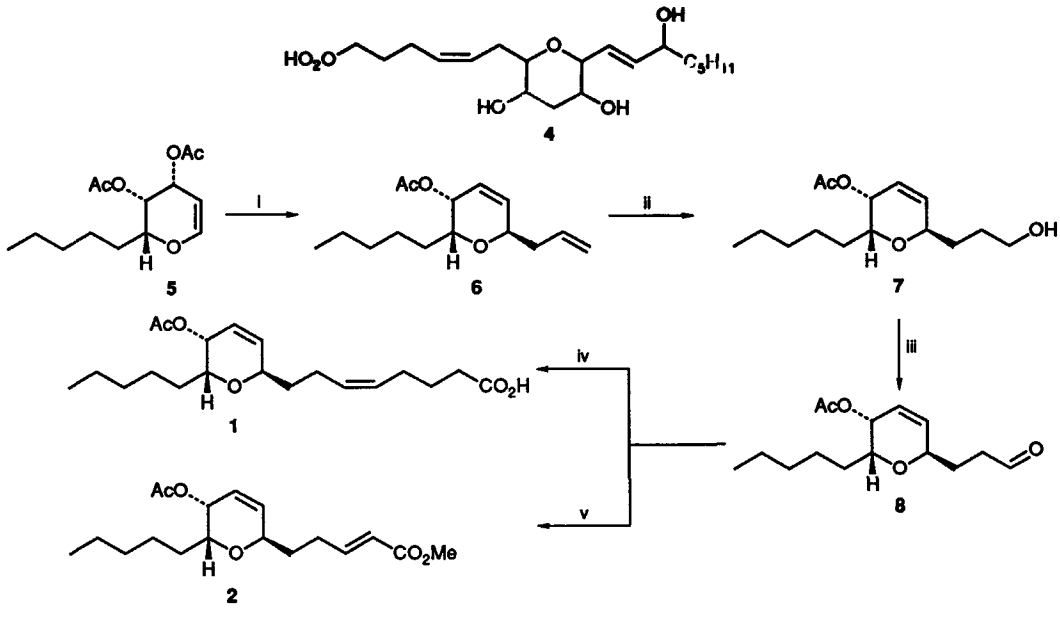
Mendeleev Commun., 1991, 1(2), 52–53

Synthesis of Unsaturated Polyhydroxycarboxylic Acids as Structural Analogues of an Arachidonic Acid Metabolite

Aleksander G. Tolstikov, Oleg F. Prokopenko, Leonard M. Khalilov, Leonid V. Spirikhin, Arnold A. Berg, Vilina R. Sultanmuratova and Genrikh A. Tolstikov*

Institute of Chemistry, Bashkirian Research Centre, Ural Department of the Academy of Sciences of the USSR, SU-450054 Ufa, USSR

(5*Z*,10*Z*,9*R*,12*R*,13*R*)-12-Acetoxy-9,13-epoxyoctadeca-5,10-dienoic acid **1**,
(2*E*,7*Z*,6*R*,9*R*,10*R*)-9-acetoxy-6,10-epoxypentadeca-2,7-dienoic acid methyl ester **12** and
(5*Z*,10*Z*,9*R*,12*R*,13*R*,14*R*)-12,14-diacetoxy-9,13-epoxyicosa-5,10-dienoic acid **3** have been synthesized, starting from modified glycals **5** and **12α** prepared from 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose.



Scheme 1 *Reagents and conditions*: i, allyltrimethylsilane, $BF_3 \cdot Et_2O$, CH_2Cl_2, −50→0 °C, 1.5 h; ii, 9-borabicyclo[3.3.1]nonane (BBN), tetrahydrofuran (THF), 0 °C, 1 h; NaOAc–H_2O_2, 0 °C, 2 h; iii, pyridinium chlorochromate (PCC), CH_2Cl_2, 25 °C, 2 h; iv, $Br^-Ph_3+P^+CH_2CH_2CH_2CH_2CO_2H$, Me_6Si_2NNa, C_6H_6, 20 °C, 4 h; v, $Ph_3P{=}CH{-}CO_2Me$, THF, 65 °C, 0.5 h

Since a report on the isolation of the arachidonic acid metabolite **4**,[1] no data on the biological activity of such compounds have appeared in the literature. This paper describes the synthesis of the structural analogues **1–3** of the acid **4** and gives a brief summary of their bioassays. The reaction of glycal acetates with allyltrimethylsilane[2] was employed as the key transformation in all the synthetic experiments.

In order to prepare the desired compounds **1** and **2**, modified glycal **5**[3] was treated with allyltrimethylsilane (1.4 mol equiv.) in the presence of boron trifluoride–diethyl ether (1.1 mol equiv.) in CH_2Cl_2 at −50 °C. The reaction proceeds stereospecifically to yield 75% of C-1-allylglycoside **6**, in contrast with the reported reaction of tri-*O*-acetyl-D-glucal with allyltrimethylsilane, which gave a mixture of epimeric C-1-glycosides[4] under otherwise equivalent conditions. The glycoside **6** was hydroborated to give the primary alcohol **7**. Oxidation of **7** resulted in a 70% yield of aldehyde **8**. Finally, condensation of **8** with 4-carboxybutylidenetriphenylphosphorane gave the acid **1** in 21% yield. The reaction of the aldehyde **8** with methoxycarbonylmethylenetriphenylphosphorane gave the methyl ester **2** in 45% yield.

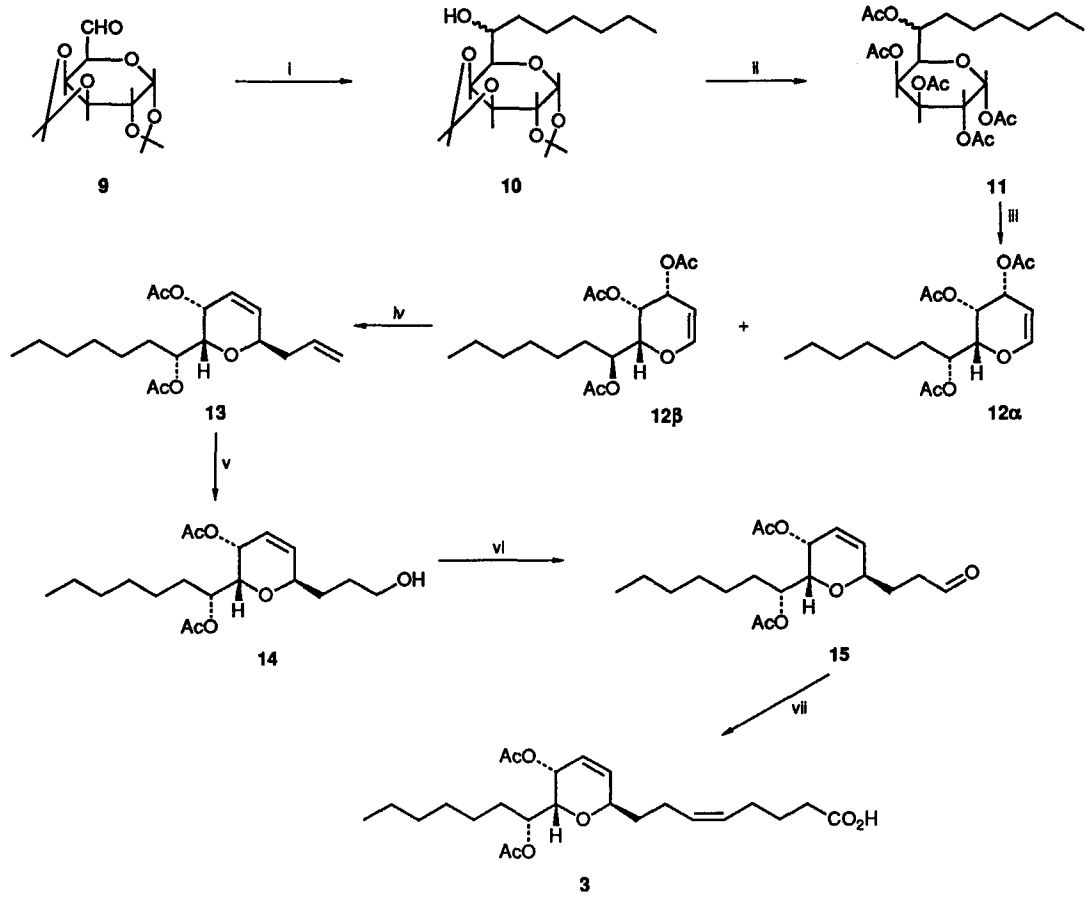
Scheme 2 shows the preparation of the glycal **12α** from the known aldehyde **9**.[5] The glycal **12α** was used as the starting compound in a synthesis of the acid **3**. The coupling of **9** with hexylmagnesium bromide gave a mixture of diastereoisomeric alcohols, which was further converted into a mixture of the diastereoisomeric glycals **12α** and **12β** in a 2:1 ratio. The major isomer **12α**† was used in subsequent transformations. Thus, the reaction of **12α** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether at room temperature was highly stereoselective, resulting in a 70% yield of the C-1-glycoside **13**. Hydroboration of **13** followed by oxidation of the resulting alcohol **14** with the Collins reagent immobilized on silica gel gave aldehyde **15** in 70% yield. Reaction of **15** with 4-carboxybutylidenetriphenylphosphorane gave a 40% yield of the acid **3**. Compounds **1** and **3** were found to be highly effective as antiinflammatory agents in mice. Detailed results of their bioassays will be reported elsewhere.

In conclusion, the structural analogues **1–3**‡ of the arachidonic acid metabolite **4** can be considered as biologically active substances showing potentially useful properties.

Received in USSR, 29th January 1991
Received in UK, 14th March 1991; Com. 1/00463H

† The (*R*)-configuration of the new chiral centre in **12α** was deduced from ^1H NMR data (300 MHz) and molecular mechanics calculations. This work will be reported elsewhere. The individual is omer **12α** was isolated by HPLC on a Du Pont 8800 instrument equipped with an R-401 refractometer, column, 250 × 21.2 mm i.d. (Zorbak-S11); eluent hexane–ethyl acetate (85:15).

‡ ^1H and ^{13}C NMR data and elemental analyses confirm the structures of the new compounds synthesized. Compound **1**: $[\alpha]_D^{20}$ −149.6° (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, 18-H_3, *J* 6.5 Hz), 2.1 (s, 3H, Ac), 2.35 (t, 2H, 2-H_2, *J* 7.5 Hz), 3.74 (ddd, 1H, 13-H, $J_{13,12}$ 2.4, $J_{13,14}$ 3.9, $J_{13,14}$ 8.7 Hz), 4.22 (dddd, 1H, 9-H, $J_{9,8}$ 5, $J_{9,8}$ 9.6, $J_{9,10}$ 2.9, $J_{9,11}$ 1.8 Hz), 4.98 (dd, 1H, 12-H, $J_{12,13}$ 2.4, $J_{12,11}$ 4.9 Hz), 5.39 (ddd, 1H, 6-H, $J_{6,5}$ 10.2, $J_{6,7}$ 5, $J_{6,7}$ 6 Hz), 5.42 (ddd, 1H, 5-H, $J_{5,6}$ 10.2, $J_{5,4}$ 5, $J_{5,4}$ 6 Hz), 5.93 (ddd, 1H, 11-H, $J_{11,10}$ 10.2, $J_{11,12}$ 4.8, $J_{11,9}$ 1.8 Hz), 6.00 (dd, 1H, 10-H, $J_{10,11}$ 10.2, $J_{10,9}$ 2.9 Hz); for **2**: $[\alpha]_D^{20}$ −208.1° (*c* 0.21, $CHCl_3$); for **3**: $[\alpha]_D^{20}$ −126.9° (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, 20-H_3, *J* 6.6 Hz), 2.35 (t, 2H, 2-H_2, *J* 4.2 Hz), 5.15 (ddd, 1H, 14-H, $J_{14,13}$ 9.3, $J_{14,15}$ 8.1, $J_{14,15}$ 3.9 Hz), 5.42 (dt, 1H, 6-H, $J_{6,5}$ 9.1, $J_{6,7}$ 3.4 Hz), 5.47 (dt, 1H, 5-H, $J_{5,6}$ 9.1, $J_{5,4}$ 3.3 Hz), 6.05 (dd, 1H, 10-H, $J_{10,9}$ 2.9, $J_{10,11}$ 10.1 Hz).



Scheme 2 *Reagents and conditions*: i, $C_6H_{13}MgBr$, THF, 0→25 °C, 2 h; ii, 50% AcOH, 100 °C, 2 h; Ac_2O, pyridine, 25 °C, 8 h; iii, HBr, AcOH, 16 °C, 2 h; Zn, AcOH, 0 °C, 3 h; iv, allyltrimethylsilane, $BF_3 \cdot Et_2O$, CH_2Cl_2, − 50→0 °C, 2 h; v, BBN, THF, 0 °C, 2 h; NaOAc–H_2O_2, 0 °C, 2 h; vi, $CrO_3 \cdot 2$ pyridine–SiO_2, CH_2Cl_2, 10 °C, 2 h; $Br^-Ph_3P^+CH_2CH_2CH_2CH_2CO_2H$, Me_6Si_2NNa, C_6H_6, 20 °C, 3 h

References

1 C. Pace-Asciak, *Biochemistry*, 1971, **20**, 3664; C. Pace-Asciak, *Chem. Commun.*, 1970, 1235; A. S. Bild, S. A. Bhat, C. S. Ramandoss and B. Axelrod, *J. Biol. Chem.*, 1978, **1**, 21.

2 S. Danishefsky and J. F. Kerwin, *J. Org. Chem.*, 1982, **47**, 3803.

3 A. G. Tolstikov, O. F. Prokopenko, L. M. Khalilov, L. V. Spirikhin and G. A. Tolstikov, *Mendeleev Commun.*, 1991, 51

4 Y. Inkawa, M. Isobe and T. Goto, *Tetrahedron*, 1987, **43**, 4749; K. C. Nicolaou, M. E. Duggan and C.-K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 6666.

5 G. B. Howard, J. D. A. Lance, W. A. Szalek and T. K. N. Jones, *Can. J. Chem.*, 1969, **47**, 75.