Tetrahedron Letters No. 50, pp 4481 - 4482, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF PROSTANOIC ACID

A Hamon, B Lecoume, A Olivier, W R Pilgrim *
ORGANON R D S à r l Eragny-sur-Epte, 60590 SERIFONTAINE

(Received in UK 1 September 1975, accepted for publication 3 November 1975)

Prostanoic acid (3) which serves as the basis for the numbering system of the prostaglandins[1] is not a compound known to occur in nature, but has been prepared as a racemic mixture (although the synthesis has not appeared in the literature) and found to possess interesting biological properties[2] As well, its carnitine ester has been used in a study of mitochrondrial oxidation of fatty acids[3] and a preparation of 7- thiaprostanoic acid has recently been published[4]. We present herein a short, simple synthesis of racemic (3) by a method that has also allowed the obtention of the individual antipodes and assignment of their absolute configurations

Reaction of 1-formylcyclopentene[5] (0 15 mole) with excess lithium di-n-octylcuprate[6] prepared from 1-octyl lithium (0 8 mole) and cuprous iodide[7] (0 45 equiv) in dilute ether solution (2 5 l total volume) at -78°C under an argon atmosphere yielded a mixture of cis- and trans-2-n-octylcyclopentanecarboxaldehyde (1) in a ratio of 1 3 The mixture of cis- and trans (1), (aldehyde protons at δ 9 78, d, J = 4 Hz and δ 9 60, d, J = 3 Hz) evolves towards a single isomer (aldehyde proton δ 9 60) on treatment with a variety of bases, including sodium hydride in ether, sodium methoxide in methanol, basic alumina, or simply by chromatography on florisil Thus trans-2-n-octyl-1-cyclopentanecarboxaldehyde was obtained in 88 % yield, based on 1-formylcyclopentene, after florisil chromatography

Fig 1

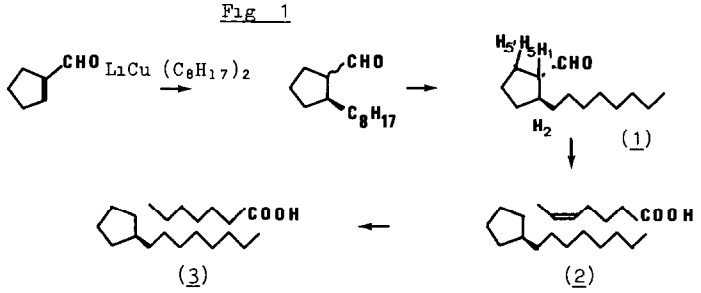
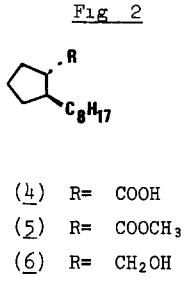


Fig 2



That the base-catalysed isomerisation does indeed lead to the expected trans aldehyde was confirmed by n m r experiment using the shift reagent Eu $(fod)_3$[9] with increasing amounts of Eu $(fod)_3$, H_1 moves rapidly downfield ($J_{1,2}= J_{1,5}= J_{1,5'} = 8Hz$, $J_{1,CHO}= 3,5$ Hz) followed by a multiplet integrating for two protons and then a slower moving multiplet corresponding to one proton.

* Present address I C I PHARMA, Z I S E BP 401, 51064 REIMS CEDEX

Thus, although the coupling constants do not allow an assignment of stereochemistry, the ratio of the areas of the displaced peaks (from low to high field) of 1 2 1 (H_1 H_2+H_5' H_5) is only consistent with the structure of the trans isomer , this ratio for the cis isomer would be 1 1 2 (H_1 H_5 H_5'+H_2) and this holds for both planar and puckered cyclopentane rings

Wittig reaction of trans-(1) with the ylide (1 2 equiv) derived from 5-triphenylphosphonio-valeric acid bromide and dimethylsulfinylcarbanion in dimethylsulfoxide gave the acid (2) in 54 % yield after purification on silica gel Hydrogenation using 10 % palladium on charcoal as catalyst furnished racemic prostanoic acid (3), homogeneous by g l c and t l c The high resolution mass spectrum of (3) and of its p-toluamide (m p 85 5-86 5°C) are in complete agreement with the structure

For preparation of the individual antipodes of prostanoic acid, trans-2-n-octylcyclopentane carboxaldehyde (1) was oxidized with acidic potassium permanganate to acid (4), m p 38.5-42°C (yield 70 %) which was resolved as its salts with (+)- and (-)- ephedrine, formed in diethyl ether and recrystallized to constant rotation from di-iso-propyl ether , use of (+)- ephedrine leads to (+)-trans-2-n-octylcyclopentane carboxylic acid Optical rotations ($[\alpha]_D^{20}$, C = 1, CH_3OH) measured (2) + 2 2°, (2') - 2 8°, (3) - 40 9°, (3')+ 43 0°, (4) -45 6°, (4') + 48 8°, (5) - 49 8°, (5') + 51 4°, (6) - 48 7°, (6') + 51 3°, where primed numbers refer to the mirror images of the structures in figures 1 and 2 The absolute configuration of (4) was determined by means of the modified Horeau method due to BROCKMANN and RISCH[11] using (+)- or (-)-α-phenethylamine with an excess of racemic (4) Each of these experiments indicated that (-)-trans-2-n-octyl-cyclopentanecarboxylic acid has the absolute configuration drawn for compound (4), i e 2-S, 6-S Each antipode of the resolved acid was converted to its methyl ester (5 or its mirror image 5') with diazomethane Although (5) could be reduced directly to trans-(1) with di-iso-butylaluminium-hydride, the longer sequence through alcohol (6) via aluminiumhydride reduction followed by oxidation with silver carbonate on celite[12] gave the pure aldehyde in higher overall yield (52 %) Each antipode (4) was taken through the above outlined synthetic sequence, (-)-(4) yielding (-)-prostanoic acid which thus has the absolute configuration described by structure (3)

REFERENCES AND NOTES

1) S BERGSTROM and B SAMUELSSON, editors, "Nobel Symposium 2 Prostaglandins", Almqvist and Wiksell, Stockjolm, p 22 (1967).
2) J FRIED, M M MEHRA and B J GAEDE in "Advance Abstracts International conference on Prostaglandins Vienna 1972" Friedr Vieweg & Sohn, Braunschweig, p 18 (1972)
3) M JOHNSON, P DAVISON, P C HOLLAND and P W. RAMWELL, Lipids, 7, 752 (1972)
4) J FRIED, M M MEHRA and Y Y CHAN, J Amer Chem Soc , 96, 6759 (1974)
5) J B BROWN, H B HENBEST and E R H JONES, J Chem Soc , 3634 (1950)
6) The general procedure used was that of G M WHITESIDES, W F FISCHER, J S FILIPPO, R W BASHE and H O HOUSE, J Amer Chem Soc , 91, 4871 (1969)
7) Purchased from PROLABO and used as received
8) All compounds have been characterised by n m r and i r spectra Compounds (2), (3) and (4) have been additionally characterised by high resolution mass spectra
9) R E RONDEAU and R E SIEVERS, J Amer Chem Soc , 93, 1522 (1971)
10) E J COREY, N M WEINSHENKER, T K SCHAAF and W HUBER, J Amer Chem Soc , 91, 5675 (1969)
11) H BROCKMANN and N RISCH, Angew Chem Int Ed , 13, 664 (1974)
12) M FETIZON and M GOLFIER, C R Acad Sci , Paris, ser C, 267, 900 (1968)