Tetrahedron Letters Vol. 21, pp 3667 - 3668 0040-4039/80/0915-3667$02.00/0

A MICROMETHOD FOR THE DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY AT C-15 OF PROSTANOIDS AND RELATED COMPOUNDS

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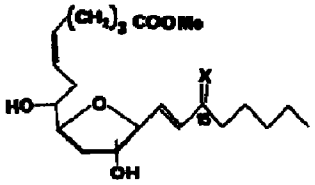
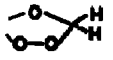
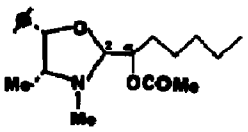
Reductive ozonolysis of Δ^{13}-15-acetoxy prostanoids, followed by reaction of the resulting 2-acetoxyheptanal with l-ephedrine, gives oxazolidines whose R_f values on t.l.c. are characteristic of the chirality of the acetoxy group, thus permitting the determination of the absolute stereochemistry at a 5 µg level.

We were confronted with the problem of determining the chirality at C-15 of alcohols 2 and 3[1], which were obtained by reduction of ketone 1 with di-isobornyloxyaluminum isopropoxide[2] in relatively small quantities, thus making the usual method[3] inappropriate.



1, X = O
2, X = H, OH (R at C-15)
3, X = H, OH (S at C-15)

4, X = CH_2
5, X = O
6, X = 



7a, (2R, αR)
b, (2R, αS)
c, (2S, αR)
d, (2S, αS)

This problem was resolved in the following manner. 3-Acetoxy-1-octene 4 was ozonolyzed and the ozonide reduced with dimethylsulfide for 18 hr at 20°C (shorter reduction time gave substantial amounts of ozonide 6). Treatment of D,L-2-acetoxyheptanal 5 thus obtained with l-ephedrine in CH_2Cl_2 at RT[4] gave two major (7a[5], R_f = 0.44 and 7b[6], R_f = 0.33 in petroleum ether - EtOAc 5:1) and two very minor (7c[7], R_f = 0.23 and 7d[8], R_f = 0.18) oxazolidines which were cleanly separable by t.l.c.[9] 7a and 7c equilibrated upon standing or contact with silica gel, showing that they were isomers at C-2(7) position of the ring. 7b and 7d had a similar relation. The configuration of the four isomers was based on analogy with known oxazolidines[4b]; n.m.r. data confirm this assignment.

Mild acid hydrolysis of 7b gave 2S-acetoxyheptanal as proven by its oxidative conversion with pyridinium dichromate in DMF at RT[10] to 2S-acetoxyheptanoic acid, and hydrolysis of the latter to 2S-hydroxyheptanoic acid, $[\alpha]_D^{23}$ = +5.5° (lit[3] + 6.0, +6.9).

In order to test the method, triacetoxy $PGF_{2\beta}$ methyl ester (1 mg) was ozonolyzed in dry CH_2Cl_2 at -78° for 5 min, reduced with dimethylsulfide at 20° for 18 hr, and after evaporation of the solvent, reacted with l-ephedrine in dry CH_2Cl_2 at 20° for 30 min. The ^1H n.m.r. spectrum (200 MHz) and R_f value of the oxazolidine derivative obtained from triacetoxy $PGF_{2\beta}$ methyl ester were identical to those of 7b obtained above, showing that, as expected, the 2-acetoxyheptanal isolated had the S-configuration.

Similarly, the more polar alcohol 3 was shown to have the 15-S configuration. The sequence could be easily carried out on a 50 µg sample of 3 without taking special precautions. At a 5 µg-level, some special care is needed to have unambiguous results, although 1 µg amounts of pure 7 can easily be detected by t.l.c.

References and spectroscopic data

1. G. Just, C. Luthe and H. Oh, Tet. Lett., 1001 (1980).
2. J. Hutton, Syn. Comm., 9(6), 483 (1979).
3. D.H. Nugteren, D.A. Van Dorp, S. Bergström, M. Hamburg and B. Samuelsson, Nature, 212 38 (1966).
4. a) R. Kelly and V. VanRheenen, Tet. Lett., 1709 (1973).
   b) L. Neelakantan, J. Org. Chem., 36 2256 (1971).
5. 7a δ: 0.65 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 0.77 ∿ 1.97 (m, 11H, $4CH_2$, CH_3), 2.17 (s, 3H, $COCH_3$), 2.33 (s, 3H, $N\text{-}CH_3$), 2.83 (dq, 1H, J = 7,8 Hz, $N\text{-}C\underline{H}CH_3$), 3.85 (d, 1H, J = 2 Hz, $N\text{-}C\underline{H}OCH$), 5.00 (d, 1H, J = 8 Hz, $C_6H_5C\underline{H}OCH$), 5.18 (m, 1H, $C\underline{H}OAc$), 7.14 ∿ 7.60 (m, 5H, C_6H_5) ppm. I.r.: 1740 ($OCOCH_3$) cm^{-1}. M.s.: m/e 176 (M^+-$C_5H_{11}CHOCOCH_3$), 148, 91.
6. 7b δ: 0.68 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 0.91 (m, 3H, CH_3), 1.17 ∿ 2.03 (m, 8H, $4CH_2$), 2.13 (s, 3H, $COCH_3$), 2.41 (s, 3H, $N\text{-}CH_3$), 2.89 (dq, 1H, J = 7, 8Hz, $N\text{-}C\underline{H}CH_3$), 4.04 (d, 1H, J = 3.5 Hz, $N\text{-}C\underline{H}OCH$), 5.03 (d, 1H, J = 8 Hz, $C_6H_5C\underline{H}OCH$), 5.14 (m, 1H, $C\underline{H}OAc$), 7.33 (s, 5H, C_6H_5) ppm. I.r.: 1735 ($OCOCH_3$) cm^{-1}. M.s.: m/e 176, 148, 91.
7. 7c δ: 0.61 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 0.73 ∿ 2.03 (m, 11H, $4CH_2$, CH_3), 2.13 (s, 3H, $COCH_3$), 2.47 (s, 3H, $N\text{-}CH_3$), 3.55 (dq, 1H, J = 5,7 Hz, $N\text{-}C\underline{H}CH_3$), 4.45 (d, 1H, J = 3 Hz, $N\text{-}C\underline{H}OCH$), 5.03 (m, 1H, $C\underline{H}OAc$), 5.27 (d, 1H, J = 5 Hz, $C_6H_5C\underline{H}OCH$), 7.34 (s, 5H, C_6H_5) ppm. I.r.: 1740 ($OCOCH_3$) cm^{-1}. M.s.: m/e 176, 148, 91.
8. 7d δ: 0.60 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 0.72 ∿ 2.00 (m, 1H, $4CH_2$, CH_3), 2.12 (s, 3H, $COCH_3$), 2.41 (s, 3H, $N\text{-}CH_3$), 3.55 (dq, 1H, J = 6,7 Hz, $N\text{-}C\underline{H}CH_3$), 4.36 (d, 1H, J = 2 Hz, $N\text{-}C\underline{H}OCH$), 5.10 (m, 1H, $C\underline{H}OAc$), 5.25 (d, 1H, J = 6 Hz, $C_6H_5C\underline{H}OCH$), 7.30 (s, 5H, C_6H_5) ppm. I.r.: 1740 ($OCOCH_3$) cm^{-1}. M.s.: m/e 176, 148, 91.
9. Visualized by dipping into a solution of 2.5 g ammonium molybdate and 1 g ceric sulfate in 10 ml c-H_2SO_4/90 ml H_2O and heating on a hot-plate.
10. E.J. Corey and G. Schmidt, Tet. Lett., 399 (1979).

(Received in USA 19 May 1980)