Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8151-8152, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01769-7

Convenient Chemical Resolution of a Bicyclic Hydroxylactone of Synthetic Interest

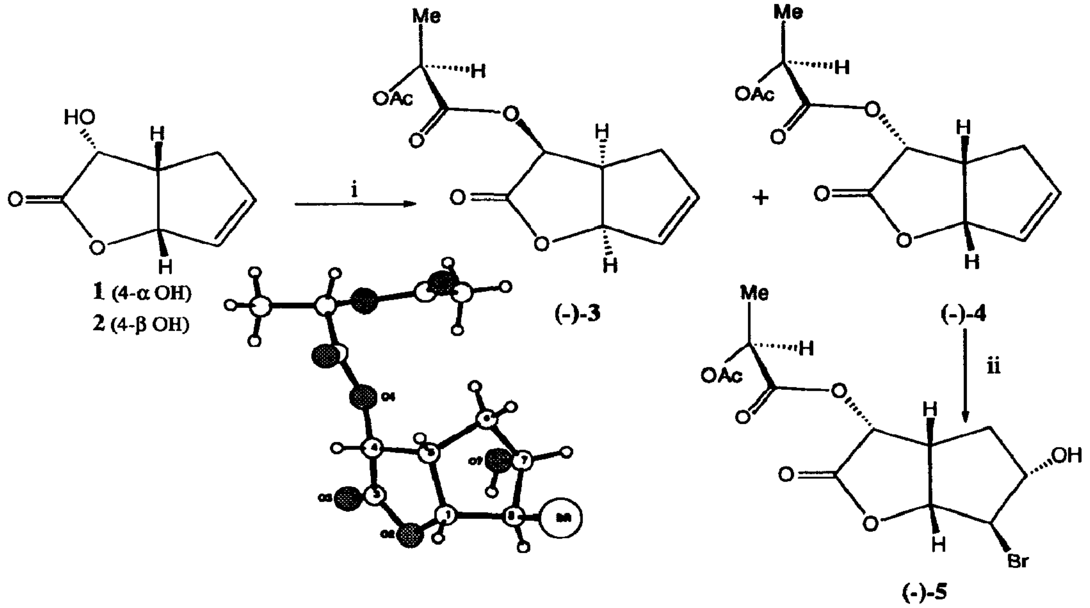
Fabienne Burlina, Pascale Clivio, Jean-Louis Fourrey*, Claude Riche and Martial Thomas

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France.

Key words: chemical resolution, configuration, cyclopentene, lactone synthon.

Abstract: The readily available bicyclic lactone **1** was resolved by treatment with (S)-O-acetyllactyl chloride to give a separable pair of diastereoisomers (-)-**3** and (-)-**4** the respective configuration of which was deduced from X-ray crystallography performed on the bromo derivative (-)-**5**.

4-Hydroxy-2-oxabicyclo [3.3.0] oct-7-en-3-one **1** can be obtained in moderate yield, together with its 4β epimer **2**, by means of a cycloaddition reaction between the readily available glyoxylic acid and cyclopentadiene[1,2].



1 (4-α OH)
2 (4-β OH)
(-)-**3**
(-)-**4**
(-)-**5**

i: (S)-O-acetyllactyl chloride, pyridine, 0°C, 3h (91%); ii: NBA, 50% aq. acetone, r.t., overnight, (72%)

In their systematic study of this useful reaction Lubineau *et al.*[1] have established the crucial role of water and the importance of low pH conditions for improving both the lactone overall yield and the ratio **1**/**2**. Finally, lactone **1** can be easily isolated pure by crystallization (from ether) in multigram quantities, making this compound an attractive multipurpose synthon as already illustrated in a few representative syntheses[2-4]. It is of interest to note that lactone **1** could be resolved by an enzyme-catalysed process. Thus, in the presence of *P. fluorescens* lipase (pfl)[3a] **1** was partially acetylated (40-60% conversion) and the products of this reaction were isolated. A reaction sequence was proposed for the conversion of the 4-acetyl derivative of (-)-**1** into the anti-HIV agent (-)-carbovir allowing its configuration assignment[3a].

Recently, in this laboratory, we have needed large amounts of lactone **1** in both its (+) and (-) form. We were pleased to find that simple treatment of lactone (+/-)-**1** by (*S*)-O-acetyllactyl chloride[5] in pyridine gave a mixture of diastereomers (-)-**3** and (-)-**4** which were easily separated in that order by silica gel column chromatography using a gradient of ethyl acetate in heptane[6]. Both compounds (-)-**3** and (-)-**4** were fully characterized by their analytical and spectral data[7]. The determination of the absolute configuration of (-)-**4** was established by X-ray analysis of the cristalline derivative (-)-**5**. The latter 8-bromo-7-hydroxylactone (-)-**5**, which cristallized in ether, was obtained in 72% yield after treatment of (-)-**4** by *N*-bromoacetamide (NBA) in 50% aqueous acetone[8, 9].

References

1) Lubineau, A.; Augé, J.; Lubin, N. *Tetrahedron Lett.* **1991**, *32*, 7529-7530.

2) Grieco, P. A.; Henry, K. J.; Nunes, J. J.; Matt , J. E. Jr. *J. Chem. Soc., Chem. Commun.* **1992**, 368-370.

3) (a) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Palmer, C. F.; Roberts, S. M. *J. Chem. Soc, Perkin Trans. 1* **1993**, 313-314. (b) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Roberts, S. M. *Tetrahedron Lett.* **1993**, *34*, 3785-3786.

4) Toyota, A.; Katagiri, N.; Kaneko, C. *Heterocycles* **1994**, *38*, 27-30.

5) Mosandl, A.; Gessner, M.; Günther, C.; Deger, W.; Singer, G. *J. High Resolut. Chromatogr. Chromatogr. Commun.* **1987**, *10*, 67-70.

6) 25g of (+/-)-**1** was treated with 1.1 eq. (*S*)-O-acetyllactyl chloride to give 41.4g of a mixture of (-)-**3** and (-)-**4**. Chromatography (Chromagel SDS 60 ACC (230-400 mesh)) of 14g of this mixture provided 5.5g of (-)-**3**, 0.9g of (-)-**3** + (-)-**4** and 5.26g of (-)-**4**. Lactone **1** can be regenerated by simple treatment in THF containing 10% 1N aq. NaOH.

7) (-)-**3** oil; $[\alpha]_D$ -21 (c=1, $CHCl_3$); i. r. 1786, 1763, 1744 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 6.24 (H-8); 5.95 (H-7); 5.62 (H-4); 5.40 (H-1); 5.06 (H-2'); 3.39 (H-5); 2.55 (H-6); 2.15 (H-6); 1.55 (Me); ^{13}C nmr ($CDCl_3$, δ ppm): 171.7; 170.6; 170.2; 140.5; 127.9; 86.6; 70.3; 68.5; 39.2; 31.5; 20.6; 16.8.

   (-)-**4** m.p. 60-61°C; $[\alpha]_D$ -30 (c=2, $CHCl_3$); i. r. 1789, 1763, 1745 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 6.23 (H-8); 5.96 (H-7); 5.64 (H-4); 5.39 (H-1); 5.22 (H-2'); 3.39 (H-6); 2.43 (H-6); 2.15 (H-6); 1.55 (Me); ^{13}C nmr ($CDCl_3$, δ ppm): 171.2; 170.2; 169.8; 140.2; 128.1; 86.3; 70.5; 68.4; 39.3; 31.4; 20.6; 17.

8) (-)-**5** m.p. 98-100°C; $[\alpha]_D$ -6 (c=0.9, $CHCl_3$), ^1H nmr ($CDCl_3$, δ ppm): 5.51 (H-4); 5.29 (H-2'); 5.17 (H-1); 4.46 (H-7); 4.3 (H-8); 3.57 (H-5); 2.35 (H-6); 2.12 (Me); 1.94 (H-6); ^{13}C nmr ($CDCl_3$, δ ppm): 171.5; 170.8; 169.7; 87.7; 78.6; 69.9; 68.7; 54.7; 38.5; 31.2; 20.6; 16.9.

9) Crystal data . $C_{12}H_{15}O_7Br$, M_W = 351.15, crystal size: 0.02x0.04x0.46mm, orthorhombic, space group P $2_12_12_1$, Z = 4, a = 7.474 (3), b = 8.979 (4), c = 21.179 (9) Å, V = 1421 (1) $Å^3$, d_c = 1.64g cm^{-3}, F(000) = 712, λ (Cu Kα) = 1.5418 Å, μ = 4.23 mm^{-1}; 1664 measured intensities, 1556 unique.

   Intensity data were measured on a Nonius CAD-4 diffractometer using graphite monochromated Cu Kα radiation and the (θ-2θ) scan technique up to $\theta = 60°$. 891 intensities with $I > 3.0\,\sigma(I)$ were considered as observed and kept in refinement calculations, s(I) being derived from counting statistics.The structure was solved by direct methods using *SHELXS86* and refined by full matrix least-squares with *SHELX76*, minimizing the function $\Sigma w(Fo-|Fc|)^2$ The hydrogen atoms were introduced in theoretical position except HO7 which was located in difference Fourier map and not refined. They were assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.067 and R_w = 0.089 (with $R_w = \{\Sigma w(Fo-|Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.008\, Fo^2]$. No residual was higher than 0.8 e $Å^{-3}$ in the final difference map. The absolute configuration, known from (S)-O-acetyllactyl chloride, was established by comparison of the pertinent Bijvoet pairs. In the crystal, an intermolecular hydrogen bond is observed between the hydroxyl O7-H of one molecule and the oxygen atom O3 of the neighbouring one (distances O7...O3 = 2.89(2), HO7...O3 = 2.13 Å, angle O7-H...O3 = 144°). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

(*Received in France* 22 *August* 1994; *accepted* 5 *September* 1994)