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REGIOSPECIFIC PRINS REACTION, A NEW WAY TO PROSTANOIDS

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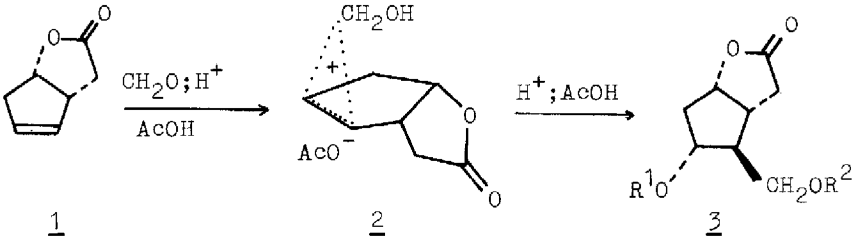
Bicyclic lactones corresponding to formula 3 are of key importance in the Corey synthesis[1] of natural prostaglandins and their analogues. This communication reports a short and simple conversion of the readily available[2,4] cis-(-)-oxabicyclo[3.3.0]oct-2-en-7-one(1) into 3a - d *via* regio- and stereospecific addition of formaldehyde on the olefinic double bond under conditions of the Prins-reaction[3]. Since asymmetric synthesis of lactone 1 has been reported by American authors[4], this conversion opens a new way without resolution of optically active prostanoids.



a, $R^1 = R^2 = Ac$

b, $R^1 = H; R^2 = Ac$

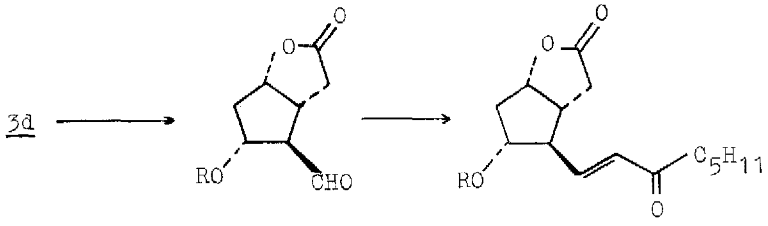
c, $R^1 = Ac; R^2 = H$

d, $R^1 = R^2 = H$

The reaction of 1 with excess paraformaldehyde monomerized *in situ* with sulfuric acid in glacial acetic acid took place at 60-80° affording 3a in 75-85%

yield together with small amounts of monoacetates 3b and c. Chromatography on silica gel or acetylation of the crude product gave pure 3a, $[\alpha]_D$ - 57,6° (*c* 0.9, $CHCl_3$), R_f: 0.53 (EtOAc). Methanolysis (1 eq NaOMe) led to the known lactone diol[5] 3d, mp 117,5-118.5°, $[\alpha]_D$ - 43.4° (*c* 1.46, MeOH). Both products were identical with authentic samples[6] in every respect[7]. No other regio— or stereoisomeric product could be detected in the reaction mixture. Preferential opening of the alleged three-center carbonium ion 2 at the sterically less hindered position indicated seems to account for both regio- and stereospecificity[3,8].

A plausible way to join the line of the brilliant Corey synthesis[1] requires blocking of the *sec*-hydroxyl group of 3d prior to oxidation to 4. Selective deacetylation of the *prim*-alkyl acetate moiety by solvolytic procedure (either alkoxide or proton catalysed) seems to be inevitably frustrated by the facile migration of the unsolvolysed acetyl group. Model experiments with 3c (Ac = p-Ph-PhCO) in dry DME with NaH revealed the occurrence of both intra- and intermolecular acyl migration[9]. Similarly, acetylation or benzoylation were found to proceed with fair selectivity, even trichloroacetylation[5] in pyridine or pyridine-dichloromethane at 0° led to detectable amount of 3c (Ac = Cl_3C-CO) in our hands. Completely selective blocking of the *prim*-OH of 3d was achieved however with either trimethylsilyldiethylamine (1 eq, MeCN, 0°, 15 min) or trityl chloride (1:1 eq, pyridine, 25°, 2 days), affording 3 R^1 = H, R^2 = $SiMe_3$, 82%, mp 48.5 — 49.5°, $[\alpha]_D$ - 27° (MeCN) and R^1 = H R^2 = CPh_3, 92%, mp 114-115°, $[\alpha]_D$ - 16.7° (MeOH), respectively. Acylation (Ac_2O, PhCOCl, p-Ph-PhCOCl) and



4 5

subsequent removal of the prim-blocking group could be carried out in the same pot[10] with more than 80% yield in each case. Protected diols 3c thus obtained were identical with authentic samples.

A more promising route from 3d towards prostanoids was realized by selective oxidation to 4 (R = H) with thioanisole-chlorine[11] or more conveniently with the Pfitzner-Moffatt reagent[12].

In order to avoid isolation of the extremely labile[13] hydroxyaldehyde 4 the reaction mixture was immediately treated with 2-oxo-heptylidenetriphenylphosphorane to give 5 [R = H, oil[7,14], R_f: 0.37 (EtOAc-hexane, 2:1)] in 67% overall yield. The product was identified by p-phenylbenzoylation to the known[1] bicyclic enone 5 (R = p-Ph-PhCO) and comparison with authentic sample.

References and notes

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6. Authentic samples were prepared from Corey's iodolactone[1] by the following sequence: i, AcCl-Py; ii, Bu_3SnH; iii, Ac_2O-$BF_3.Et_2O$ (→ 3a); iv, NaOMe-MeOH (→ 3d).

7. Satisfactory infrared, nuclear magnetic resonance, and combustion data were obtained for all compounds using chromatographically homogeneous samples.

8. Specific formation of only one isomer seems to be characteristic for **1** or analogous bicyclic olefins in electrophilic addition reactions, cf. K.C. Murdock and R.B.Angier, *J.Am.Chem.Soc.*, **84**, 3758 (1962); J.C.Gilbert, T.Luo and R.E.Davis, *Tetrahedron Lett.*, 2545 (1975); Z.Grudzinski and S.M.R.Roberts, *J.Chem.Soc.Perkin Transaction 1.*, 1767 (1975).

9. In the first period (*ca.* 50 min) of the reaction only **3b** and **3c** could be detected by TLC (silica gel, EtOAc, R_f: 0.61 and 0.34, resp.) with increasing **b** : **c** ratio. After 1 hr all four compounds appeared as spaciously separated spots (R_f, **a**: 0.78, **d**: 0.10).

10. Isolation of doubly protected derivative **3** (R^1 = p-Ph-PhCO, R^2 = CPh_3) was performed for characterization, mp 182-184°, $[\alpha]_D$ - 65° (*c* 1.04, $CHCl_3$).

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