Tetrahedron Letters,Vol.24,No.33,pp 3527-3530,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

PERHYDROPENTALENONE EQUIVALENT FROM COREY'S LACTONE

N. Mongelli, A. Andreoni, L. Zuliani and C.A. Gandolfi

Farmitalia C. Erba, Via C. Imbonati, 24 - 20159 Milano (Italy)

2-Oxa-bicyclo[3.3.0]octane-3,7-diones work as a δ-oxo-ß,γ-cyclopentenyl-acetic acid substrates when submitted to the Barco procedure in the synthesis of perhydropentalenones.

Perhydropentalenone derivative are key intermediates in the synthesis of carboprostacyclins[1]. Jones' reagent oxidation of (1S,5R,6S,7R)-7-hydroxy-6-triphenylmethoxymethyl-2-oxabicyclo[3.3.0] octane-3-one (IIIa, m.p. 106-8°; $[\alpha]_D$ =+4.1)[2], easily accessible by the nor-bornadiene route[3a,b], as shown in scheme 1[4], or by selective tritylation of the diol IIIb[5] gives an almost quantitative yield of the crystalline ketone IVa (m.p. 141-6°; $[\alpha]_D$ = -74, $[\alpha]_{365}$ = -365). Alkaline acetate (i.e., potassium) treatment transforms IVa into the α,ß-unsaturated ketone Va (oil; $[\alpha]_D$ = +112, $[\alpha]_{365}$ = +106); when stood at room temperature the latter crystallizes, giving IVa which, when reacted with carbonyldiimidazole (CDI) in dry THF (1.07 g:0.49 g:2.6 ml/IVa: CDI: THF), produces the imidazolide Vb. Obviously IVa in THF solution equilibrates in part to Va that reacting with CDI drives the reaction to completion.

This chemical behaviour strongly suggests that IVa may be an effective substrate in the synthesis of 2,5-perhydropentalenedione via δ-oxo-ß,γ-cyclopentenyl-acetic acid using the Barco procedure[6] thus formally achieving an oxa → methylene change on 2-oxa-bicyclo[3.3.0]octane-3,7-dione compounds. The clean and very simple one-pot conversion of IVa into VIa (oil; $[\alpha]_D$ = -30, $[\alpha]_{365}$ = -270) with an overall yield of 85% confirmed our working hypothesis.

Working under argon atmosphere at r.t., magnesium-monomalonic ethyl ester complex[7], 2 mol equiv. prepared by adding $HO_2CCH_2CO_2Et$ (1.3 g) to a suspension of commercial Mg ethoxide (0.57 g) in dry THF (4 ml) and stirring until complete dissolution, is added to a solution of the imidazolide Vb in dry THF (2.6×10^{-3} M in 2.6 ml). After 3 hours, the mixture is poured into water and a solution of the collected precipitate in EtOAc-EtOH (90 : 10) is warmed in the presence of potassium acetate (1.5 g) at 50-70°C to complete internal Michael addition of the intermediate ß-ketoester Va. The cyclopenten-4-yl-3-oxo-butanoic ethyl ester Vc is the major component of the crude precipitate together with the internal addition product (VIa) and the adducts of the reaction of the cyclopent-2-en-4-one moiety of Vc with imidazole, by-product of the lactone carbonyl activation of IVa by CDI.

The amounts of the 2'S- and 2'R-imidazolyl-cyclopentanones, VIIa, b, are closely related to the time course of the reaction. Starting from the 6-benzyloxymethyl-oxo-lactone, IVb, and after a very long reaction time (14 h) we obtained the imidazolide adduct VIIb (m.p. 94-96°, $[\alpha]_D$ = +67, $[\alpha]_{365}$ = +448) as a major component of the reaction mixture; this adduct is also rapidly converted by KOAc treatment to the corresponding perhydropentalenedione VIb (oil; $[\alpha]_D$ = -72.7). Since the imidazolide adducts are very polar, their formation, not described by Barco et al., might explain the reported 50% yield after internal Michael addition of the chromatographed pure cyclopentenyl-3-oxo-butanoic ethyl ester.

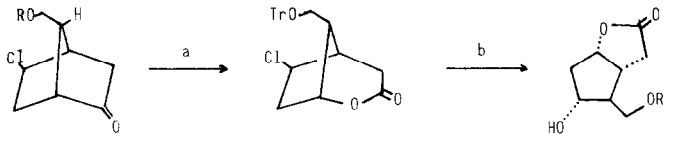
Selective, stereospecific reduction of the keto group at C-5 of the 1-carbethoxy-perhydropentalene-2,5-diones is obtained, for example, by treatment of VIa (1.42 g) with lithium triterbutoxy aluminum hydride (1.02 g) in dry THF (15 ml) at 0-5°C for 30 minutes followed by the usual work-up (aqueous 30% NaH_2PO_4/AcOEt). In agreement with Skuballa[8], the ß-ketoester moiety is preserved and VIIIa (oil; $[\alpha]_D$ = +40, $[\alpha]_{365}$ = +81) is submitted to deethoxycarbonylation in DMSO with NaCl[9] to give the crystalline tritylketoalcohol, IXa (m.p. 94-96°; $[\alpha]_D$ = +29, $[\alpha]_{365}$ = +63). Esterification with benzoylchloride in CH_2Cl_2-pyridine yields the benzoate, IXb, (m.p. 103-5°; $[\alpha]_D$ = -52, $[\alpha]_{365}$ = -205) whose detritylation gives the 4-hydroxymethyl-benzoate IXc, (oil; $[\alpha]_D$ = -28.9, $[\alpha]_{365}$ = -183) uncrystallizable in contrast to the p-nitrobenzoate IXd (m.p. 102-3°; $[\alpha]_D$ = -41) and the p-phenylbenzoate, IXe, (m.p. 79-82°; $[\alpha]_D$ = -47, $[\alpha]_{365}$ = -277).

A complicated mixture of substances was obtained using 1,5-diazabicyclo[4.3.0]non-5-ene as catalyst for the internal Michael addition and $NaBH_4$ for selective reduction of the isolated keto group.

An alternative route was treatment of the Michael adduct VIb with acetic anhydride in pyridine for 10 hours at r.t. to give the enolacetate Xa (oil; $[\alpha]_D$ = -1.7) followed by $NaBH_4$ reduction in CH_2Cl_2 - EtOH at -20°C; the resulting alcohol, XI, (oil; $[\alpha]_D$ = +53, $[\alpha]_{365}$ = +154) was deethoxycarbonylated in acidic medium to give the (1aR, 4aS, 4S, 5R)-4-benzoyloxymethyl-5-hydroxy-perhydropentalene-2-one, IXf, (oil, $[\alpha]_D$ = +16).

Acknowledgements: The authors are indebted to Mr. F. Casabuona for synthesis of IIIa via norbornadiene route and to W. Fava and A. Pizzamiglio for the large-scale development of the method. They are grateful to Drs. E. Pella, M. Di Somma and S. De Munari for analytical determinations.

Scheme 1



Ia R = H
b R = -C(C$_6$H$_5$)$_3$ Tr = trityl

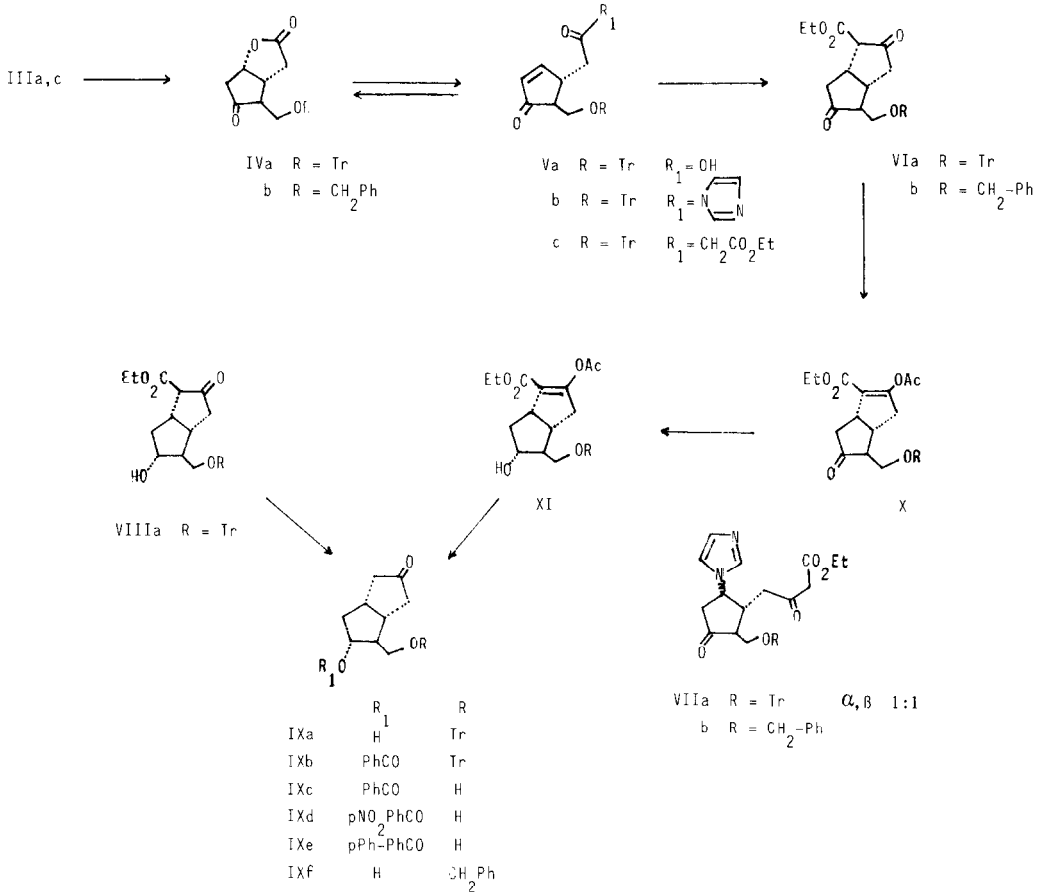
II

IIIa R = trityl
b R = H
c R = CH$_2$-Ph

a) monoperphthalic acid

b) H$_2$O$_2$, THF, H$_2$O, NaOH

Scheme 2



IVa R = Tr
b R = CH$_2$Ph

Va R = Tr R$_1$ = OH
b R = Tr R$_1$ = imidazolyl
c R = Tr R$_1$ = CH$_2$CO$_2$Et

VIa R = Tr
b R = CH$_2$-Ph

VIIIa R = Tr

XI

X

VIIa R = Tr α,β 1:1
b R = CH$_2$-Ph

	R$_1$	R
IXa	H	Tr
IXb	PhCO	Tr
IXc	PhCO	H
IXd	pNO$_2$PhCO	H
IXe	pPh-PhCO	H
IXf	H	CH$_2$Ph

References and footnotes

(1) W. Bartmann, G. Beck, Ang. Chemie. Int. Edition, (21), 10, 751 (1982) and references cited therein.

(2) All the rotatory powers are measured in $CHCl_3$ (1% c). The m.p. are uncorrected. The elemental analyses of the new compounds are in good agreement with the calculated value.

(3) a. J.S. Bindra, A. Grodski, T.K. Schaaf, E.J. Corey, J. Am. Chem. Soc., 95, 7522 (1973);
b. R. Peel, J.K. Sutherland, J. Chem. Soc., Chem. Commun., 151 (1974).

(4) C. Erba U.K. Pat. 1.533.207 (7.3.1979); U.K. Pat. 1.533.208 (7.3.1979).

(5) I. Tömösközi, L. Gruber, G. Kovács, I. Székely and V. Simonidez, Tetrahedron Lett., 4369 (1976).

(6) A. Barco, S. Benetti, G.P. Pollini, P.G. Baraldi and C.A. Gandolfi, J. Org. Chem., 45 4776 (1980).

(7) D.W. Brooks, L.D.L. Lu, S. Masamume, Angew. Chem. Inst., Ed. Engl., 18, 72 (1979).

(8) W. Skuballa and H. Vorbrüggen, Angew. Chem. Int., Ed. Engl., 20, 1046 (1981).

(9) A.P. Krapcho, Synthesis, 822 and 893 (1982) and references cited therein.

(Received in UK 8 June 1983)