Tetrahedron Letters,Vol.29,No.43,pp 5521-5524,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CARBOCYCLES FROM CARBOHYDRATES: A SIMPLE ROUTE TO AN ENANTIOMERICALLY PURE PROSTAGLANDIN INTERMEDIATE

Pascale Bélanger and Petpiboon Prasit *

Merck Frosst Centre for Therapeutic Research
P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8.

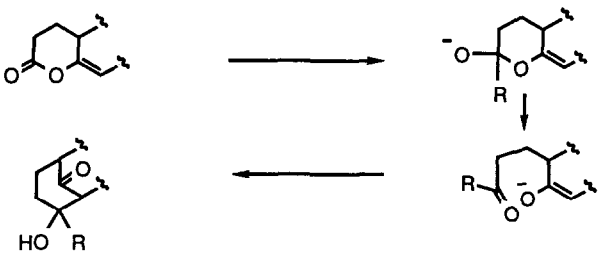
Abstract: The enone **7** , the key intermediate in the three component coupling approach to prostaglandins, has been prepared efficiently from commercially available **D**-ribonic acid γ-lactone by an intramolecular aldol condensation .

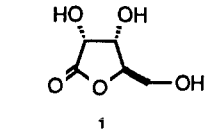
Recent successes in the field of prostaglandin synthesis by Noyori[1] and Johnson[2] using three component coupling approaches have greatly facilitated the preparation of these biologically important molecules. These approaches involved the conjugate addition of the ω-side chain to cyclopentenone derivatives, followed by trapping of the resultant enolate with an alkyl halide containing the complete α-side chain. The success of the approach relies on the availability of the enantiomerically pure starting materials. Herein, we outline a convenient synthesis of the enone **7**, from the readily available **D**-ribonic acid γ-lactone **1** which was pivotal in Johnson's synthesis of PGE_2.

The reaction of nucleophiles with exocyclic γ–enollactones to give cyclohexane derivatives has been well documented.[3] The reaction proceeds by the initial attack of nucleophiles at the carbonyl center, followed by ring-opening which unravels an enolate at one terminus and a carbonyl at the other. Intramolecular aldol condensation then affords β-hydroxycyclohexanone (Scheme1). In contrast, the analogous reaction to produce five-membered rings are scarce.[4] In view of the potential utility of such a transformation and the large number of biologically important cyclopentane-containing natural products, this strategy was investigated as a method to prepare enantiomerically pure cyclopentanes.

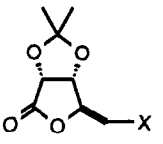
The enollactone **4** was prepared in enantiomerically pure form from **D**-ribonic acid γ-lactone **1** in 4 steps in an overall yield of 67%. Treatment of the known tosylate **2** [5] with NaI in

Scheme 1

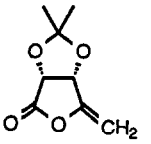




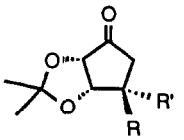
1
Ribonic acid γ-lactone



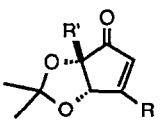
2: X = OTs
3: X = I



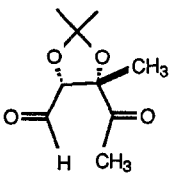
4



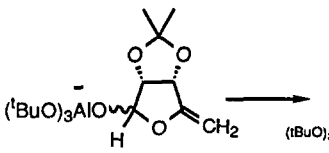
5: R = OH, R' = H
6: R = Ph, R' = OH



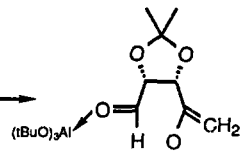
7: R' = H, R = H
8: R' = H, R = Ph
9: R' = Me, R = H



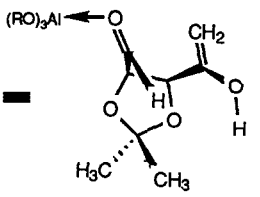
10



11



12



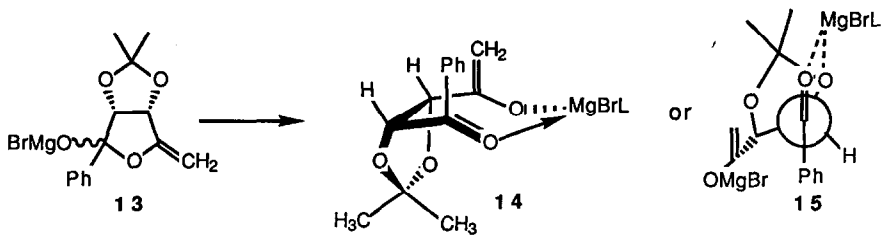
refluxing acetone afforded the iodide **3** in quantitative yield { mp. 95-97°C, $[\alpha]_D$ -30° (*c* 1.5, $CHCl_3$)}. Dehydroiodination of the iodide **3** was effected by treatment with DBU in benzene at room temperature and the enollactone **4** was isolated as an oil in a 78% yield after Kugelrohr distillation,{$[\alpha]_D$+ 55° (*c* 2, $CHCl_3$)}.

Treatment of the enollactone **4** with 1 equivalent of $LiAlH(O^tBu)_3$ in THF at 0°C and warming to room temperature over 1h followed by quenching the reaction with aqueous NH_4Cl gave cleanly a single epimer of the cyclopentanone **5** { mp. 83-85°C, $[\alpha]_D$ +237° (*c* 1, $CHCl_3$)}. The coupling constant $J_{3,4}$ was zero, indicating the *anti* relationship between the newly formed hydroxyl group and the isopropylidene ring. Dehydration of compound **5** was effected using MsCl and pyridine in dichloromethane. In this manner, the prostaglandin intermediate **7** was obtained in a 74% yield over two steps from the enollactone **4** as white needles after recrystallization from ethyl acetate/hexane {mp. 69-70°C, $[\alpha]_D$ +71° (*c* 1, $CHCl_3$) or $[\alpha]_D$ +68° (*c* 1, MeOH) ; lit.,[2,6] $[\alpha]_D$ +71.8° (*c* 0.91, $CHCl_3$), no mp. was reported; lit.,[7] $[\alpha]_D$ -33° (*c* 0.91, MeOH), no mp. was reported}.

Several comments regarding the mechanism of the cyclization are appropriate. Upon running this reaction in THF-d_8 in the NMR probe, it was found that the hydride rapidly added to the carbonyl to form a surprisingly stable aluminate complex **11** which unraveled to expose the reactive termini on the addition of aqueous NH_4Cl. It appears that the cyclization step requires an acidic medium since acetic acid can also be used although partial concomittant dehydration occured, whereas, water, aq. NH_4OAc or aq. sodium potassium tartrate gave complex mixtures with little or none of the expected product **5** or the enone **7**. This suggested that the second step of the reaction was the protonation of the ring oxygen followed by ring-opening to give the enol **12**. Inspection of molecular models suggests that **12** is the least energetic transition state which leads to the observed product **5** . It is interesting to note that Moffat and coworkers[8] have found that compound **10** could not be induced to undergo intramolecular aldol condensation except when distilled in the presence of Al_2O_3 where the enone **9** was obtained.

The enollactone **4** also reacted with carbon nucleophiles. For example, treatment of **4** with 1 equivalent of PhMgBr in THF (-78°C / 0.5h) gave a single hydroxycyclopentanone **6** after workup. N.O.E. experiments indicated that the newly formed stereocenter at C-4 had the hydroxyl group *syn* to the isopropylidene ring as indicated by the enhancements of H_3 and H_4 protons upon irradiating the ortho protons of the phenyl ring. This stereochemical outcome of the reaction could be rationalized through a seven-membered ring transition state **14** although a chelation control model **15** which is usually operative when organometallics are allowed to react with α- or β-oxygenated carbonyl compounds[9] could not be ruled out. The added rigidity of the intramolecular mode of cyclization undoubtedly enhanced the selectivity. Dehydration of compound **6** using MsCl and

pyridine in dichloromethane gave the enone **8** in 40% yield over the two steps {mp. 120-121°C, $[\alpha]_D$ -12° (*c* 0.5, $CHCl_3$)}.



In summary, enantiomerically pure cyclopentane derivatives could be readily prepared from carbohydrate derived enollactones which could serve as building blocks in the synthesis of natural products including prostaglandins.

We thank Dr. Michael Bernstein for performing N.O.E. experiments, Dr Marc Labelle for mechanistic discussions and NSERC of Canada for an undergraduate summer fellowship (PB).

References

1. Suzuki, M.; Yanakisawa, A.; Noyori, R., *J. Am. Chem. Soc.*, **1985**, 3348.
2. Johnson, C.R.; Penning, T.D., *J. Am. Chem. Soc.*, **1986**, 5655.
3. Referred to as the Fujimoto-Belleau Reaction, for a review see: Weill-Raynal, J., *Synthesis*, **1969**, 49.
4. For examples: Dauben, W.G.; Boswell, G.A.; Templeton, W.H., *J. Am. Chem. Soc.*, **1961**, 5006; Colvin, E.W.; Malchenko, S., Raphael; R.A., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1989; Welch, S.C.; Walters, R.L., *J. Org. Chem.*,**1974**, 2665.
5. Hough, L.; Jones, J.K.N.; Mitchell, D.L., *Can. J. Chem.*, **1963**,1898.
6. Hudlicky, T.; Barbieri, G.; Luna, H.; Kwart, I.D., Abstract of Papers, 193rd National Meeting, American Chemical Society, Denver, Colorado, April **1987**, ORGN 28.
7. Bestmann, H. J.; Moenius T., *Angew. Chem. Int. Ed. Engl.*, **1986**, 994.
8. Verheyden, J.P.H.; Richardson, A.C.; Bhatt, R.S.; Grant, B.D.; Fitch, W.L.; Moffatt, J.G., *Pure and Appl. Chem.*,**1978**, 1363
9. Cram, D.J.; Kopecky, K.R., *J. Am. Chem. Soc.*, **1959**, 2748; Cherest, M.; Felkin, H.; Prudent, N., *Tetrahedron Lett.*, **1968**, 2199; Reetz, M.T., *Angew. Chem. Int.Ed. Engl.*, **1984**,556.

(Received in USA 2 August 1988)