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ENONE TRANSPOSITION IN PROSTAGLANDINS - A USEFUL SEQUENCE FOR THE SYNTHESIS OF 13-HYDROXYPROSTANOIC ACID ANALOGS

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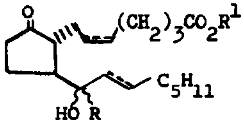
In a program directed toward the synthesis of potential gastric antisecretory agents, we undertook the synthesis of 13-hydroxyprostanoic acid analogs of the type represented by formula I.



I

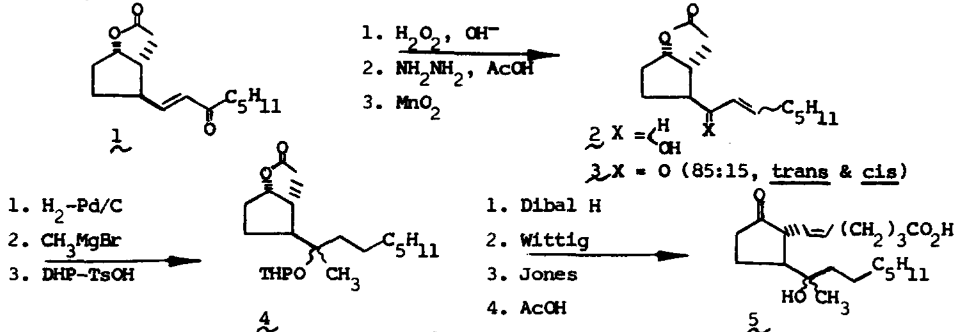
We anticipated, based on the reported results obtained with methylated 15-hydroxyprostanoic acid analogs,[1] that enzymatic degradation could also be inhibited in I resulting in potent and long acting derivatives.

Herein we wish to report a potentially general synthetic entry into compounds of the type I based on an enone transposition sequence utilizing the Wharton rearrangement.[2] We have applied this transformation to enone lactone **1** because of the large supply available to us, but it should be applicable to other prostanoic intermediates and derivatives as well.

Enone **1**, prepared from 1,3-cyclohexadiene in 5 steps as described by Corey and Ravindranathan,[3] was converted to the corresponding α,β-epoxy ketone by treatment of a methanol solution of **1** containing 3 eq. of 30% hydrogen peroxide at 0° with 0.5 eq. of 6N sodium hydroxide.[4] Without purification, the crude epoxy ketone was subjected to the Wharton rearrangement[2] by treatment of a solution of the epoxy ketone in methanol containing a catalytic amount of acetic acid (0°) with *ca*. 2 eq. of 85% hydrazine hydrate to afford **2**. Crude **2** was then converted, using activated manganese dioxide in chloroform, to an 85:15 mixture of *trans*- and *cis*- enones, **3**, which could be readily purified and separated (42% overall yield from **1**).[5,6]

A 13-hydroxyprostanoic acid of particular interest to us was **5**. This was obtained by sequential treatment of the above mixture of enones with hydrogen - Pd/C in ethyl acetate (single ketone by TLC), methyl magnesium bromide in ether, and dihydropyran-tosyl acid in methylene chloride to afford in over 80% yield **4**, which was elaborated as shown using now standard methodology.[7,8]

Analog **5** showed only mild activity upon subcutaneous administration in the pylorus-ligated rat.[9]



References

1. For example, see A. Robert, B. Nylander, and S. Andersson, *Life Sci.*, **14**, 533 (1974); J. Bagli, T. Bogri, and S. Sehgal, *Tetrahedron Lett.*, 3329 (1973); D. Carter, S. Karim, D. Bhana, and P. Ganesan, *Brit. J. Surg.*, **60**, 828 (1973); E. W. Yankee and G. L. Bundy, *J. Amer. Chem. Soc.*, **94**, 3651 (1972); and references cited.
2. P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); P. S. Wharton, *ibid.*, **26**, 4781 (1961).
3. E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971); E. J. Corey and B. B. Snider, *J. Org. Chem.*, **39**, 256 (1974).
4. H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **79**, 1488 (1957).
5. The *trans*-allylic alcohol **2** was more rapidly oxidized than the *cis*-allylic alcohol and consequently nearly pure *trans*-enone **3** could be obtained from the mixture of alcohols by utilizing a shorter reaction period and/or less MnO_2. Alternatively, a separation could be effected on silica gel.
6. The *trans*-enone **3** displayed the following properties: $R_f(SiO_2)$ 0.60 using 10% EtOAc in CH_2Cl_2; IR (neat) 1775 (lactone), 1690, 1665, 1655 (sh), and 1625 (conj. ketone), 1170, and 985 cm^{-1} (*trans*-olefin), NMR ($CDCl_3$)δ 6.92 (1 H, d of t, J=16, 7 Hz, COCH=<u>CH</u>), 6.10 (1 H, d, J=16 Hz, CO<u>CH</u>=CH) and 5.05 ppm (1 H, br.s., OCO<u>CH</u>); UVλmax (CH_3OH) 227 nm (ϵ13,100); mass spectrum 250 (M^+). The *cis*-enone **3** (R_f 0.74) displayed properties in accord with the structural assignment.
7. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).
8. Compound **5** purified by conversion to the methyl ester [CH_2N_2, ether; separable C-13 epimers, R_f (SiO_2) 0.35 (minor) and 0.32 (major) using 20% EtOAc in ØH] followed by hydrolysis (K_2CO_3, H_2O, CH_3OH), displayed the following properties: R_f (SiO_2) 0.29 using 50% EtOAc in ØH with 1 drop AcOH/10 ml; IR (neat) 3450 (OH), 3015 (vinyl H), 1740-1700 (carbonyls), and 710 cm^{-1} (*cis*-olefin); NMR ($CDCl_3$)δ 6.25 (2H, OH's), 5.40 (2H, br. m. CH=CH), 1.20 (major) and 1.15 (minor) (CH_3~C~OH), and 0.90 ppm (3H, t, J=6Hz, CH_2CH_3); mass spectrum (2 TMS) 481 $(M-CH_3)^+$, 397 $(M-C_7H_{15})^+$.
9. We thank Dr. J. Liu and Mr. G. Connelly, Jr., for the large scale preparation of **1**, Mr. W. Groves and Ms. L. Sofranko for the pharmacological testing, and Mr. G. Roberts for the mass spectra.