TERREIN, AN OPTICALLY ACTIVE PROSTAGLANDIN SYNTHON OF FUNGAL ORIGIN. III.[1] CHEMICAL CONVERSION TO 1(S),4(R),7(R)-ACETOXY-5(S)-HYDROXY-2-OXABICYCLO[2.2.1] HEPTANE-3-ONE, A FLEXIBLE INTERMEDIATE FOR PROSTAGLANDIN SYNTHESIS.+

George W. Clark, III, Paul D. Hammesfahr, P. Bryan Hudson, Lester A. Mitscher,* Kunikatsu Shirahata, Jerzy Sulko, and Tarik Veysoglu

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas, 66045, U. S. A.

1(S),4(R),7(R)-Acetoxy-5(S)-hydroxy-2-oxabicyclo[2.2.1]heptane-3-one (2), a flexible intermediate for the synthesis of novel optically active prostaglandins, has been synthesized from the optically active and readily available mold metabolite, terrein (1). Some reactions of 2 are described.

The mold metabolite terrein (1) has proven to be a useful starting material for two previously published syntheses of monocyclic prostaglandins.[1,2] One of these syntheses[2] proved useful for analogues rather than for the natural prostaglandins (3) because, in a key intramolecular Michael reaction, an SN_2' elimination intervened resulting in the loss of the future C_{11}-OH group. In principle, one way to avoid this complication would be to pass through bicyclo intermediates where such eliminations are mechanistically forbidden (Bredt's rule). The value of the intermediate would be enhanced if the essential oxygen atoms were present at different oxidation levels and so differentially protected that each could be manipulated selectively. Thus, we designed a new route involving the heterocycle 2 as a key intermediate and report here its successful preparation and some of its properties--including an unanticipated O to O acyl migration reaction which lessens the utility of 2 itself for prostaglandin synthesis. Formula 2a emphasizes the relationship of 2 to 1 and 3.

Terrein (1) forms a C_5-monoacetate (4a) preferentially.[1] The isomeric C_4-monoacetate (4d) could be prepared selectively in 54% overall yield (98% based upon terrein consumed) in a three-step, one-pot sequence without purification of intermediates. Terrein was stirred in ether for 30 min at room temperature with 1.35 eq. of trifluoroacetic anhydride. The reaction mixture was

+ Dedicated to Professor Sumio Umezawa with congratulations on the occasion of his sixty-fifth birthday.

carefully evaporated under reduced pressure and excess acetic anhydride was added to the resulting yellow oil. After stirring at room temperature for 30 h., the reaction mixture was evaporated in vacuo, the oily residue stirred in THF/water (2:1) at room temp. for 45 min. to effect selective hydrolysis and evaporated before chromatography over Sephadex LH-20 (chf/PhH:1/1) to give 4d, mp 57-58°; ir (CCl_4) 1735 cm^{-1}; eims m/e 196 (M^+); pmr ($CDCl_3$) 2.15 δ (3H, s, $COCH_3$); anal., C, H, O; etc., and 45% of recovered terrein (presumably derived from the ditriflate ester). Monoacetate 4d, in contrast to 4a, is readily attacked by periodate. Reaction with dihydropyran catalyzed by tosic acid at room temperature for 30 min. in EtOH-free chloroform converts 4d to the thp-ether acetate (4e) in 99% yield; yellow oil; cims (NH_3) m/e 298 ($M{\cdot}NH_4^+$), 281 ($M{\cdot}H^+$); anal., C, H, O; etc.

Next, the side chain was prepared for subsequent cleavage by $OsO_4/KClO_3$ oxidation in Me_2CO[3] at room temperature for 7 h. After work-up, the yellow oil (5a) was reacted with $(CH_3)_2C(OCH_3)_2$ and tosic acid overnight at room temperature in ether[7] to give acetonide 5b in 36% yield as a yellow oil: ir (neat) 2980 cm^{-1}, 2995, 1730, 1630, 1455, 1430, 1375, 1350, 1320, 1220, 1120, 1070, 1030, 960, 900, 860 and 810; pmr ($CDCl_3$) 1.35 δ (d, 3H, J=5Hz), 1.43 (s, 6H), 1.76 (br., 6H), 2.10 (s, 3H), 3.6 (br. m, 2H), 4.2 (m, 3H), 5.0 (br. m, 1H), 5.95 (br. m, 1H) and 6.30 (br. m., 1H); eims m/e 339 ($M-CH_3$), 255 ($M-CH_3-OH$), 195 ($M-CH_3$-HOAc-dhp), 84; cims (NH_3) m/e 372 ($M{\cdot}NH_4^+$), 355 ($M{\cdot}H^+$), etc.; λ_{max}^{MeOH} 227 nm (log ε 4.08); etc. Subsequently, it was found that conversion of alcohol 4d to its isopropylidenedioxy analogue (61% yield) followed by thp ether formation (to give 5b in 100% yield) was much more efficient. Use of a molar equivalent of OsO_4 and an H_2S work-up gave even better yields but poisoned the catalyst in the subsequent hydrogenation stage and had to be given up. Because of incomplete steric control in the hydroxylation step, all intermediates from 5a to 6c are necessarily mixtures of diastereoisomers.

It was next necessary to saturate the remaining olefinic linkage in such a way that the side-chain would become β. The normal expectation would be that the 1-OH and 4-OAc groups which flank the double bond, both being α, would lead to β-side adsorption to the catalyst surface and β-attachment of hydrogen. However, it was reasoned that a free α-OH and use of a nonpolar solvent would alter the adorption face because of hydrogen bonding to the catalyst (7).[8] Accordingly, 5b was dissolved in ether and reduced with $Zn(BH_4)_2$ (1 molar equivalent)[9] to give alcohol 5c in ∿85% yield; ir (neat) 3440 cm^{-1}, 2980, 2915, 2860, 1735, 1440, 1430, 1360, 1305, 1220, 1155, 1100, 1050, 1010, 950, 880, 845 and 790; pmr (CCl_4) δ1.15 (d, 3H, J=5Hz), 1.30 (s, 6H), 1.60 (br. s., 6H), 2.05 (s, 3H), 3.2-3.6 (m, 3H, 1 exch.), 3.8 (m, 3H), 4.3 (d, 1H, J=4), 4.75 (br. s., 1H), 5.55 (d, 1H, J=4) and 5.74 (s, 1H); λ_{max}^{MeOH} 227 nm (log ε 3.16); cims (NH_3) m/e 374 ($M{\cdot}NH_4^+$), 339 ($M{\cdot}H^+$), 339 ($M{\cdot}H^+$-HOH), etc. Reaction times longer than 15 min. resulted in progressive loss of the OAc group. Next, hydrogenation over prereduced platinum oxide catalyst in anhydrous EtOAc took place in 2.5 h. and gave 96% of 6a; ir 1730 cm^{-1}; λ_{max}^{MeOH} end abs.; pmr ($CDCl_3$) 1.24 δ (d, 3H, J=5), 1.35 (s, 6H),

1.57 (br. s, 6H), 2.00 and 2.05 (s, 3H), 1.7-2.5 (m, 3H), 3.2-4.0 (br. m, 7H, 1 exch.), 4.60 (m, 1H) and 4.76 (br. s, 1H); cims (NH_3) m/e 376 ($M{\cdot}NH_4^+$), 359 ($M{\cdot}H^+$); etc. Deblocking to the tetrol (6b) was accomplished in 91% yield by stirring in MeOH containing 0.2% of conc. HCl at room temp. for 5 h. and then at 0° overnight; ir (neat) 1720 cm^{-1}; pmr (CD_3OD) 1.14 δ (d, 3H, J=5Hz), 2.07 (s) and 1.18-2.3 (6H), 3.73 (m, 4H), 4.98 (m, 1H); cims (NH_3) m/e 252 ($M{\cdot}NH_4^+$), 235 ($M{\cdot}H^+$); etc.

The desired bicyclo[2.2.1] stage was reached through side-chain cleavage. Treatment of 6b with 1.5 molar equivalents of $NaIO_4$ in distilled water at room temp. produced a distinct odor of acetaldehyde and an 88% yield of aldehyde 6c as a clear resinous solid; ir (mull) 3440 cm^{-1}, 2940, 2880, 2750, 1730, 1710, 1660, 1630, 1450, 1365, 1230 and 1025; pmr ($(CD_3)_2CO$) 1.2 δ (m, 2H), 2.00 (ca. 4H and Me_2CO), 2.9 (m, 1H, $J_{4,5}$=7Hz, $J_{4,3}$=9.5Hz, $J_{4,CHO}$=2Hz), 3.8 (m, 4H), 5.0 (m, 1H, $J_{3,4}$=9.5Hz), 9.72 (d, 1H, $J_{CHO,4}$=2Hz); cims m/e 206 ($M{\cdot}NH_4^+$), 1.89 ($M{\cdot}H^+$), 146, 128; etc. This reaction serves to confirm the stereochemistry of the $Zn(BH_4)_2$ reduction for the epimeric alcohol would have suffered periodate cleavage of the cyclopentane ring in addition to the side-chain.

Treatment of aldehyde 6c with anh. MeOH-HCl produced a mixture which could not be clearly separated by various column techniques or by preparative tlc. The electron impact ms showed peaks at m/e 188, 234, and 202 corresponding to the molecular ions of the starting aldehyde (6c), its dimethylacetal, and 8, respectively. PMR ($CDCl_3$) peaks at 1.40 δ (ca. 2H, m), 1.8 (ca. 1H, br. m), 2.0 (ca. 3H, br. s), 2.4 (ca. 6H, m), 4.3 (ca. 1H, br. m), 5.2 (ca. 2H, br. m) and 9.0 (br. s) were recorded. In this spectrum the bands were judged to be very broad; especially the untypically broad peak at 2.0δ. This suggested a possible migration of the acetyl group which would lead to two more diastereomers of the bicyclo system and result in the spectral broadness observed. Oxidation of aldehyde 6c to the corresponding acid followed by lactonization would simplify the isomer situation. Accordingly, the acid (6d) was obtained by oxidizing aldehyde 6c with $KMnO_4$ in water at pH 7.8 at room temperature for 1 h.; ir 3700-2700 cm^{-1} and positive bromocresol green spray reaction.

The homogeneous acid readily lactonized on refluxing for 1 h. in anh. THF[11] and was characterized in this form. The same result could be achieved more conveniently by Lemieux-Von Rudloff oxidation[10] of tetrol 6b at pH 7.6 with addition of extra $KMnO_4$ when the acetaldehyde odor was pronounced. Repeated evaporative distillation of benzene from the reaction residue gave a mixture of two lactones with the pmr revealing two distinct methyl signals at 2.10 and 2.07δ (85% yield). Separation by preparative tlc gave the desired lactone (2) and its isomer (9) which had similar ir and pmr spectra but which differed in their mass spectra. Under electron impact both showed molecule ions at m/e 186 and base peaks at m/e 43 but differed distinctly in the high mass region because of peaks arising from thermodynamically more favorable fragmentations involving facile eliminations from the non-bridgehead positions. Thus, 2 had major peaks at m/e 168 (M^+-H_2O),

124 (M^+-H_2O and CO_2) and 81 (M^+-H_2O and CO_2 and MeCO) while 9 had major peaks at m/e 126 (M^+-HOAc) and 82 (M^+-HOAc and CO_2). Upon acetylation (Ac_2O/NaOAc), both lactones gave an identical diacetate (identical tlc, ir and eims). On the other hand, pyridinium chlorochromate oxidation[12] of the lactone mixture produced two separable ketolactones.

These findings support the occurrence of an O to O acyl migration via ortho acetate 12. Thus, while we have successfully prepared heterocycles 2 and 10 in which the various functionalities are present differentially protected so that great flexibility is present for completion of the synthesis of a wide variety of optically active prostaglandins with retention of all desired oxygen atoms, the isomerism occurring at a very late stage in the synthesis requires tedious separation and diminishes the yield. The overall success achieved in controlling stereo and regiospecificity and the comparative efficiency of the basic route lead us now to explore slight modifications whereby potential migration of the blocking group is prevented rather than to carry the synthesis forward from 2. The results will be reported in due course.

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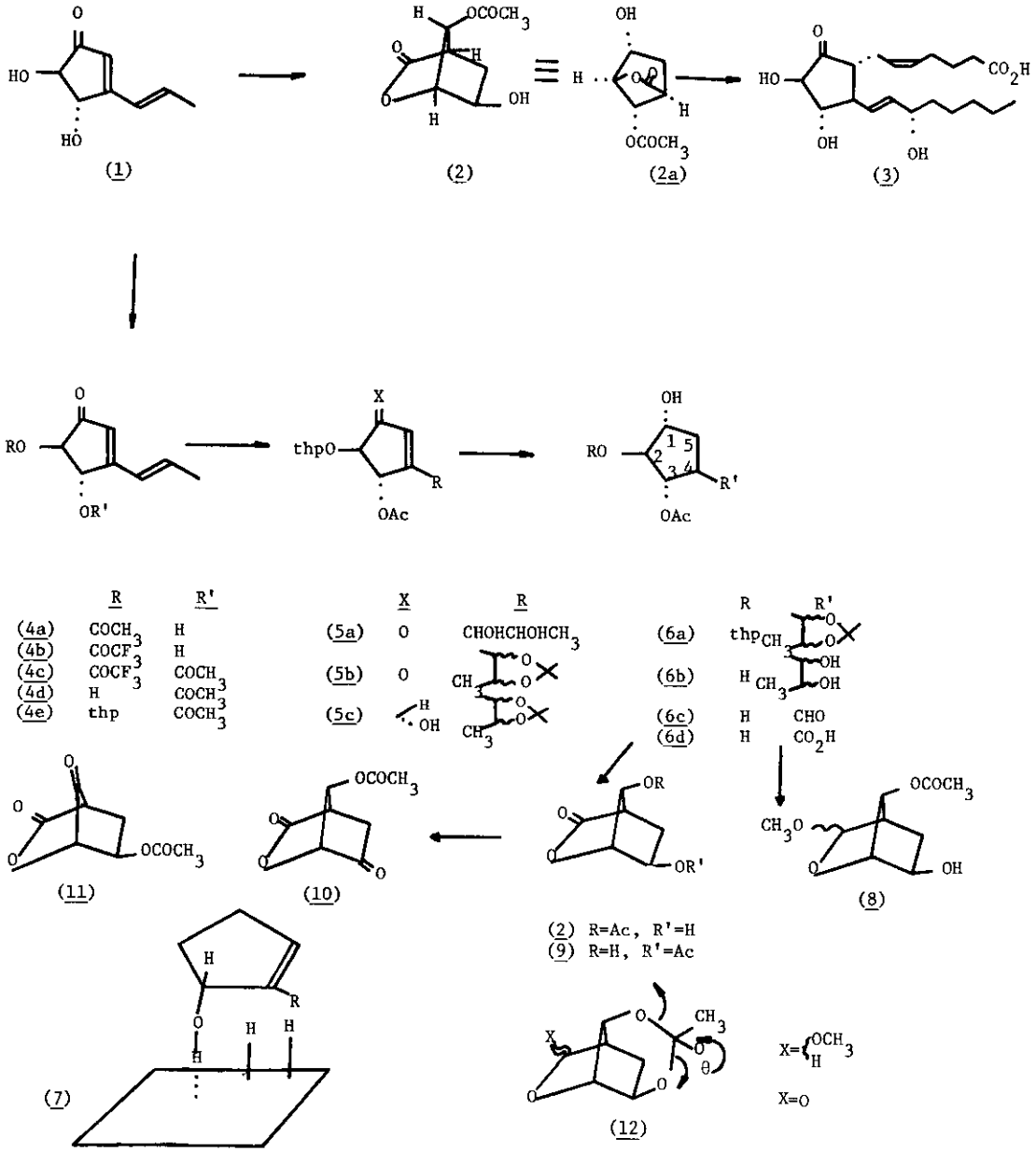

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