TERREIN, AN OPTICALLY ACTIVE PROSTAGLANDIN SYNTHON OF FUNGAL ORIGIN. I. CHEMICAL CONVERSION TO A COREY-TYPE LACTONE.+

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1(R), 5(R), 8(R)-Hydroxy-6-(3-oxo-trans-1-octenyl)-3-oxo-2-oxabicyclo[3.3.0]oct-6-ene (14), a flexible synthon suitable for the preparation of numerous natural and unnatural analogs of prostaglandin, has been synthesized from the optically active and readily available mold metabolite, terrein (1).

Terrein (1) is a well-known mold metabolite available in satisfactory quantities via fermentation of a variety of Aspergillus species.[1-4] It has been shown to possess the same absolute configuration at C_4 as do the prostaglandins at the corresponding C_{11}

+Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

position,[5] and has convenient functionality for chemical transformation into a wide variety of natural and artificial prostaglandins without requiring either chiral reagents or resolution steps. In this communication we report our experiences with one of these pathways.

Terrein was converted first to its viscous dibenzoyl ester (2)* in greater than 95% yield by warming at 60° for 24 hr. in a melt of benzoic acid and benzoic anhydride (15/5 equivalents) [ir (film) 1745 and 1600 cm^{-1}; UV λ_{max}^{EtOH} 274 nm (log ε = 4.37) and 232 nm (log ε = 4.47); pmr ($CDCl_3$) δ 1.88 (3H, d, J = 6 Hz, =CHC<u>H</u>$_3$), 5.02 (1H, d, J = 2.5 Hz, <u>H</u>COBz), 5.21 (1H, br.m., <u>H</u>COBz), 6.17 (1H, br.s., COC<u>H</u>= 6.40 (1H, d, J = 16 Hz, =C-C<u>H</u>=CHCH$_3$), 6.80 (1H, d.q., J = 16+6 Hz, =C-CH=C<u>H</u>CH$_3$), 7.50 (6H, m. <u>m</u> and <u>p</u> Ar<u>H</u>) and 8.18 (4H, m, <u>o</u>-Ar<u>H</u>)]. Selective hydroxylation[6] of the terminal conjugated double bond proceeded with high regioselectivity in 75% yield using OsO_4 (0.1 mole) and $Ba(ClO_3)_2$ (0.5 mole) in amine-free DMF/H_2O (9:1) at -15° to -20° for 24 hr. Resinous diastereomeric diols 4 showed ir (film) bands at 3400-3600 cm^{-1}; UV (EtOH) maximum at 232 nm (log ε = 4.64) and pmr ($CDCl_3$) peaks at δ1.22 (3H, d, J = 6 Hz, HOCHC<u>H</u>$_3$), 4.06 (1H, m, HOC<u>H</u>CH$_3$), 4.32 (1H, m, <u>H</u>COH) and 5.50 (1H, s, =C<u>H</u>), etc. Because 4 forms a highly insoluble Zn chelate, it was treated with 2,2-dimethoxy propane (1.1 eq.) and tosic acid (0.1 eq.) in dry THF to yield

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*All new compounds described gave satisfactory microanalyses and/or mass spectra and their spectral properties are in accord with the assigned structures.

oily acetonide 5 in 79% yield [pmr ($CDCl_3$) δ 1.36 (6H, s, $C(CH_3)_2$); no OH bands in the ir]. Reduction of 5 with $Zn(BH_4)_2$ in dry THF (6-8 hr.) produced a variable mixture of epimeric alcohols 6 and 8 (typically 3:2). [The coupling constant between H_1 and H_5 was smaller (3 Hz) for slower eluting acetonide 6 than for epimer 8 (6 Hz)].[7] Acetonide hydrolysis of mixed 6+8 (1N aq. HCl/THF for 12 hr. at room temperature) afforded triols 7 and 9 in 79% overall yield from acetonide 5. Chromatography over silica gel with ether gave the desired alcohol 7 as a resinous white powder [ir (film) 3150-3650 cm^{-1} and 1740 cm^{-1}; UV λ_{max}^{EtOH} 232 nm (log ε = 4.32)]. Oxidation of glycol 7 with $NaIO_4$ (1.10 eq.) in Et_2O/H_2O (3:1)[8] leads to the rapid formation of hydroxyaldehyde 10 in 96% yield [ir (film) 3150-3650, 1745 and 1710 cm^{-1}; UV λ_{max}^{EtOH} 230 nm (log ε = 4.43); pmr ($CDCl_3$) δ 7.00 (1H, s, =CH) and 9.92 (1H, s, CHO); chemical ionization mass spectrum (i-BuH)MH^+ = 353]. Completion of the carbon skeleton comprising the desired lower side chain went smoothly following a well-established method.[9,10] Condensation of aldehyde 10 with the Na salt of dimethyl-(2-oxoheptyl)-phosphonate (prepared in THF with NaH) leads to the desired hydroxy dieneone 11 as a colorless oil in 68% yield [ir (film) 3540, 1735 and 1690 cm^{-1}; UV λ_{max}^{EtOH} 274 nm (log ε = 4.37) and 231 nm (log ε = 4.48); chemical ionization mass spectrum (i-BuH)MH^+ = 449; pmr (CCl_4) δ 0.91 (3H, t, J = 5 Hz, CH_2CH_3), 1.06-1.70 (6H, br.m., R-$CH_2CH_2CH_2$-), 2.37 (2H, t, J = 6 Hz, $COCH_2CH_2$), 6.27 (1H, d, J = 16 Hz, $CH\overset{t}{=}CH$) and 7.18 (1H, d, J = 16 Hz, $CH\overset{t}{=}CH$).

Completion of this pathway required introduction of a carbon chain at C_2 and elimination of the endocyclic double bond in such a way that the two side chains take up the trans spatial orientation of the prostaglandins. This proved unexpectedly difficult* but was finally achieved in good yield by the following sequence. Acylation of 11 with ethyl malonylchloride and triethylamine (1.2/1.1 eq.) in dry ether at room temperature gave rise cleanly to oily malonyl ester 12 in 71% yield [ir (film) 1735, 1690 sh, 1645 and 1620 cm^{-1}; $UV\lambda_{max}^{MeOH}$ 264 nm (log ε = 4.36) and 232 nm (log ε = 4.46); chemical ionization mass spectra (i-BuH) 441 (MH^+-benzoic acid); pmr ($CDCl_3$) δ 1.19 (t, J = 7 Hz, $CH_2\underline{CH_3}$), 4.19 (2H, J = 7 Hz, $\underline{CH_2}CH_3$), 3.34 (2H, s, $COCH_2CO_2Et$)]. The stereochemistry about the malonyl ester function was used to control both the regio and stereospecificity of the next step. Intramolecular Michael addition of the potassium salt of 12 was accomplished in good yield (68%) by careful adherence to experimental conditions. Treatment of 12 with t-BuOK (1.5 eq.) in THF/t-BuOH (9:1) at -78° for 1 hr. followed by warming to room temperature (3 hr.) was needed to produce 13 [ir (film) 1790, 1735, and 1690 sh cm^{-1}; $UV\lambda_{max}^{EtOH}$ 272 nm (log ε = 4.37) and 231 nm (log ε = 4.24); chemical ionization mass spectrum (i-BuH) 441 (MH^+)]. These properties and the pmr spectrum of 13 (illustrated below) showed that the desired cyclization had taken place; but, despite several attempts,

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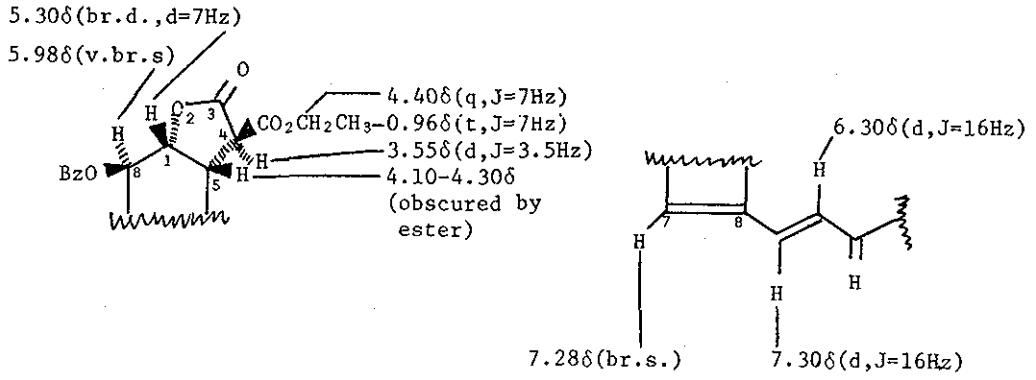
*Conjugate addition of organocopperlithium reagents failed to give the desired products because of an SN_2' elimination at C_{11} followed by virtually instantaneous further addition.

loss of the pro $C_{11}OH$ groups (presumably via an SN_2' mechanism) could not be prevented. The superfluous functionality of 13 was



removed via hydrolysis, decarboxylation and relactonization by treatment with 1N NaOH in $MeOH/H_2O$ (4:1) at pH 12-14 until the odor of methyl benzoate was no longer detected, followed by acidification (1N HCl), extraction (chf), drying and heating the oily residue in toluene at 100° ($-CO_2$) for 1 hr. to yield (60%) oily 1(R), 5(R), 8(R)-hydroxy-6-(3-oxo-trans-1-octenyl)-3-oxo-2-oxabicyclo[3.3.0]oct-6-ene (14) [ir (film) 3450, 1775 and 1680 cm^{-1}; $UV\lambda_{max}^{EtOH}$ 274 nm (log ε = 4.31); cd (MeOH), $[\theta]_{max}^{335}$ -1420; pmr ($CDCl_3$) δ2.20+2.52 (1H, d d, J = 18 + 4 Hz, $H_4\beta$), 2.81+3.10 (1H, d d, J = 18+10 Hz, $H_4\alpha$), 3.88 (1H, v.br.m., H_5), 5.01 (1H, d, J = 7 Hz, H_1) and 4.95 (1H, br.s., H_8), etc.]

The elimination of the benzoyloxy group was unfortunate; nevertheless, the versatility of Corey-type lactone 14 for the preparation of numerous novel prostaglandins, particularly in the PG-C series,[11] is apparent. In one of the many potential paths, heterocycle 14 was reduced in 78% yield to the 1:1 epimeric pair of

alcohols 15 and 16 with $Zn(BH_4)_2$ in dry THF (5 eq., 3 hr.,); this was converted (90% yield) to the di-thp-ether lactone and then reduced with diisobutylaluminum hydride (95+% yield) to the lactol, and the latter condensed with the ylid of 5-bromopentanoic acid (67% yield). The ylid had to be prepared by a variation of the Corey-Wittig procedure[9,10] in which a dry DMSO solution of the triphenylphosphonium salt of 5-bromopentanoic acid is titrated to a pale yellow-orange endpoint with t-BuOK in THF, and the ylid is then generated by addition of a second equivalent of base to produce a bright red solution. Details of the preparation of 17 and its biological properties will appear in a full paper as will alternate means of preparing analogs of 11 (by SeO_2 oxidation[12] (30% yield) of terrein diacetate 3 (99% yield from 1 using Ac_2O/NaOAc) followed by reaction of the resulting aldehyde 18 with amyl magnesium bromide at -78° (52% yield of 19) and our experiences in converting terrein to a variety of other prostaglandin synthons.

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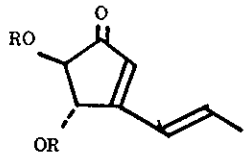
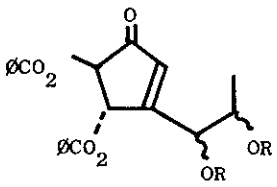
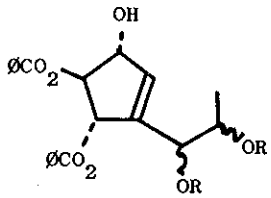


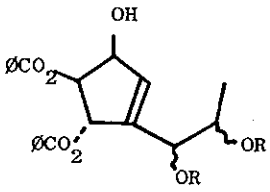
1. R = H
2. R = COØ
3. R = COMe



4. R = H
5. R = Me Me

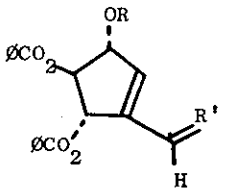


6. R = Me Me
7. R = H

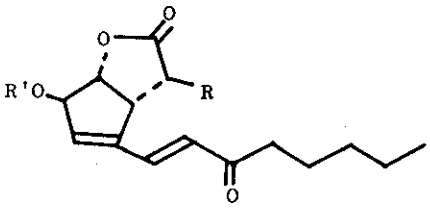


8. R = Me Me

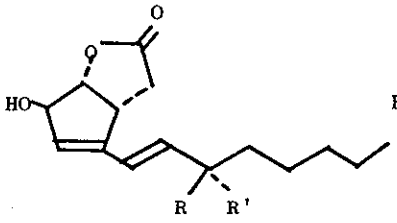
9. R = H



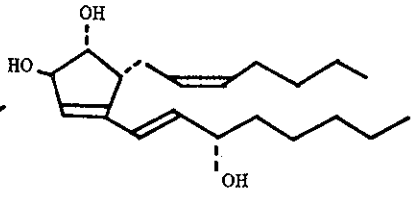
10. R = H, R' = O
11. R = H, R' = CHCO$(CH_2)_4$Me
12. R = $COCH_2CO_2Et$, R' = CHCO$(CH_2)_4$Me



13. R = CO_2Et, R'=ØCO
14. R = R' = H



15. R = H, R' = OH
16. R = OH, R' = H



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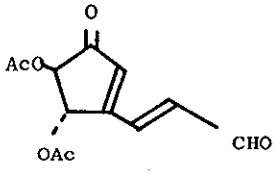

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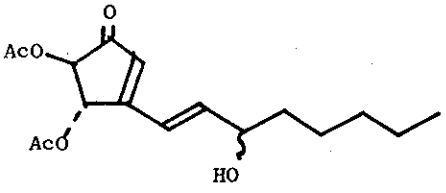

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