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Total Synthesis of a Potent Immunosuppressant Pironetin

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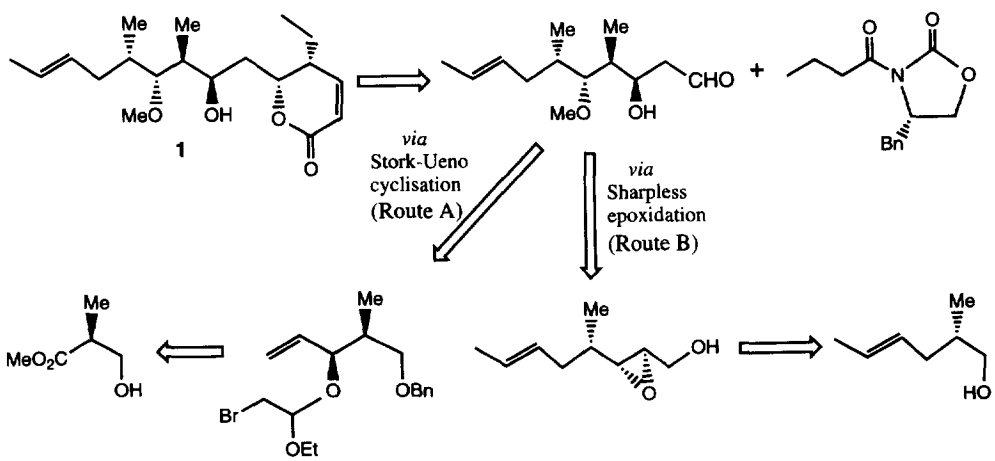
Abstract : Total synthesis of PA-48153C Pironetin - a potent immunosuppressant is described. Copyright © 1996 Elsevier Science Ltd

Two Japanese groups simultaneously reported[1] the isolation of Pironetin (PA-48153C) from the fermentation broths of *Streptomyces prunicolor* PA-48153 and *Streptomyces sp.* NK 10958. Pironetin (**1**) showed the plant growth regulator as well as immunosuppressive activity[2]. However, more importantly the mode of action of **1** which is different from those of established immunosuppressants cyclosporin A (CsA) and FK-506, makes pironetin an attractive target for studies. CsA and FK-506 both antagonise T cell activation[3] whereas **1** inhibits both T and B lymphocytes to mitogens. Due to severe renal toxicity of CsA and FK-506, there is a need to locate new immunosuppressants with different mechanism of action and pironetin (**1**) offers an ideal candidature. The basic limitation with Pironetin is its cytotoxicity and recent efforts to reduce toxicity by chemical modification[4] of parent structure was quite promising. In addition, being a simple structure compared to CsA and FK-506, such structural modifications are indeed feasible with **1**.

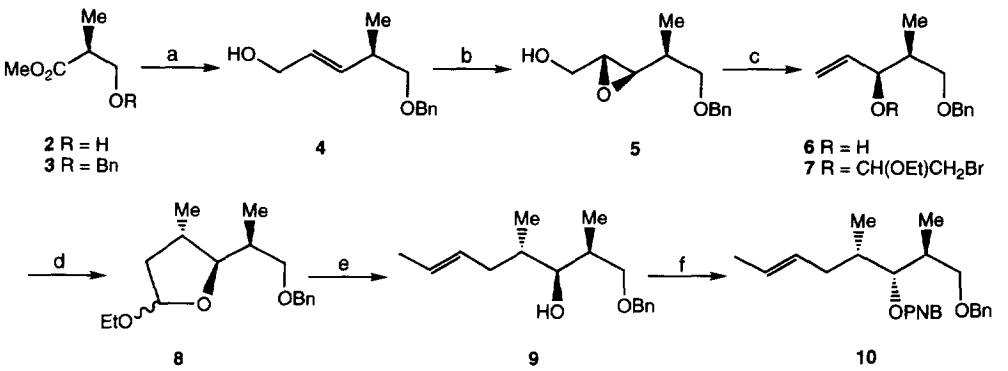
Since nothing was known about the absolute stereochemistry of pironetin, we embarked on its total synthesis[5], not only to provide its correct stereostructure but also to develop a synthetic strategy which could be adopted for the preparation of its analogues in order to conduct structure-activity relationship.



We initiated the synthesis of **1** by route A in which the Stork-Ueno radical cyclisation[6] formed the basic premise of our strategy. The free OH group of methyl (S)-3-hydroxy-2-methylpropionate (**2**) was protected (BnO-C(=NH)-CCl_3, TfOH (cat.), CH_2Cl_2, RT) as benzyl ether derivative **3** (95%) (Scheme 1). Conversion of **3** into the corresponding allylic alcohol (**4**) was a high yielding three step synthetic sequence involving i)

partial reduction with DIBAL-H (C_6H_6, -78⁰), ii) Wittig olefination ($Ph_3P{=}CHCO_2Et$, C_6H_6, RT) and iii) DIBAL-H reduction (CH_2Cl_2, -20⁰-RT). Sharpless asymmetric epoxidation[7] (TBHP, TTIP, CH_2Cl_2, -20⁰) of **4** using (-)DIPT as a chiral auxiliary provided the epoxy alcohol (**5**) (80%) with 95% ee (HPLC analysis). A one pot conversion of **5** into the optically pure allylic alcohol (**6**)[8] was conveniently effected at room temperature by reacting with Cp_2TiCl_2-$ZnCl_2$-Zn in THF[9]. The ^{1}H-NMR spectrum of **6** was consistent with the structure.

Scheme 1



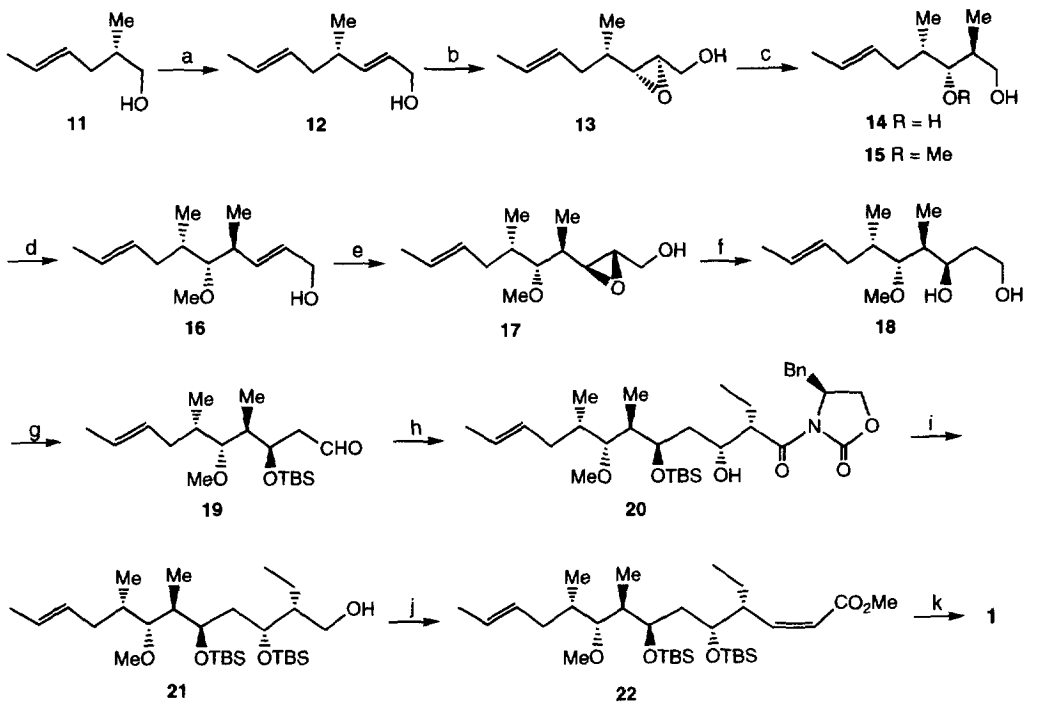
a) (i) $BnOC(=NH)CCl_3$, TfOH (Cat.), CH_2Cl_2, RT, 15 h; (ii) DIBAL-H, C_6H_6, -78⁰, 30 min., (iii) $Ph_3P{=}CHCO_2Et$, C_6H_6, RT, 3 h; (iv) DIBAL-H, CH_2Cl_2, -20⁰-RT, 30 min; (b) TBHP, TTIP, (-)DIPT, CH_2Cl_2, -20⁰, 20 h; (c) (i) $(Cp)_2TiCl_2$, $ZnCl_2$, Zn, THF, RT, 1.5 h; (ii) $EtOCH{=}CH_2$, NBS, CH_2Cl_2, 0⁰, 3 h; (d) Bu_3SnH, AIBN, $C_6H_5CH_3$, Δ , 12 h; (e) (i) 80% AcOH, 100⁰, 1 h; (ii) $Ph_3P^+CH_2$-CH_3Br^-, n-BuLi (2 eq.), t-BuOH, KtOBU, -78⁰, 1 h; (f) Ph_3P, DEAD, p-NO_2, C_6H_4COOH, THF, RT.

Treatment of **6** with ethyl vinyl ether-NBS in CH_2Cl_2 at 0⁰ for 3 h gave the bromoacetal derivative **7** (82%) which was subjected to radical cyclisation under dilute condition (5% solution) using Bu_3SnH-AIBN in refluxing toluene to afford the cyclised product **8** in 70% yield[10]. The cleavage of the ethyl acetal group of **8** was conducted in the presence of 80% acetic acid on boiling water bath followed by olefination with $Ph_3P{=}CHCH_3$ under Schlosser's conditions (n-BuLi, BuOH, t-BuOK, THF, -78⁰) to afford **9** (35%) whose E-geometry was assigned based on literature precedents[11,6c]. The next concern was the epimerisation at C_3 (**10**) for which the Mitsunobu reaction (DEAD, TPP, THF, p-NO_2-C_6H_4COOH, RT) was employed. However, the reaction was far from satisfactory in our hands, most of the starting material remained unreacted. Since Wittig and Mitsunobu reactions of route A were not satisfactory to complete the total synthesis of **1**, we felt the need to develop an alternate route which is described below.

Earlier we reported[12] the synthesis of both the isomers of (E)-2-methylhexen-1-ol which was amenable to large scale preparation. The (2S,4E)-isomer (**11**) was successively oxidised[13] [o-iodoxybenzoic acid (IBX), DMSO, RT], olefinated ($Ph_3P{=}CH$-CO_2Et, C_6H_6, RT), and reduced (DIBAL-H, CH_2Cl_2, -20⁰) to afford the allylic alcohol (**12**) (60% overall yield) (Scheme 2). The Sharpless epoxidation using (-)-DIPT gave the epoxide derivative **13** [$\alpha]_D$ +31.0 (c 1.5, $CHCl_3$), lit.[14] value for the (-)enantiomer [$\alpha]_D$ -34.0 (c 1.3, CH_2Cl_2)]. Subsequently **13** was treated with Me_2CuLi in ether at -78⁰ to give **14** (20:1) whose primary

hydroxyl group was first protected (TBS-Cl, Imidazole, CH_2Cl_2, RT) as TBS-ether followed by methylation (KH, MeI, Et_2O, RT) and deprotection (Bu_4NF, THF, RT) to obtain **15** (80% overall yield). Conversion of **15** into **16** was carried out essentially by the same sequence reported above for compound **12**. The Sharpless epoxidation of **16** with (+)-DIPT as a chiral auxiliary gave **17** (80%) with good diastereoselectivity (92%).

Scheme 2



(a) (i) IBX, DMSO, RT, 30 min., (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, RT, 3 h; (iii) DIBAL-H, CH_2Cl_2, -20°, 30 min., (b) TBHP, TTIP, (-)DIPT, CH_2Cl_2, -20°, 20 h, (c) (i) Me_2LiCu, EtOEt, -78°, 8 h, (II) TBS-Cl, Imid, CH_2Cl_2, RT, 3 h; (iii) KH, MeI, EtOEt, RT, 30 min, (iv) Bu_4NF, THF, RT, 2 h; (d) (i) IBX, DMSO, RT, 30 min; (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, RT, 3 h; (iii) DIBAL-H, CH_2Cl_2, -20°, 45 min; (e) TBHP, TTIP, (+)DIPT, CH_2Cl_2, -20°, 18 h; (f) Red-Al, THF, 0°, 4 h; (g) (i) Piv.Cl, Py, CH_2Cl_2,RT, 1h; (ii) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0°, 5 min., (iii) DIBAL-H, CH_2Cl_2, -20°, 20 min., (iv) IBX, DMSO, RT, 30 min; (h)(S)-N-butanoyloxazolidinone, Bu_2BOTf, CH_2Cl_2, -78°, 6 h; (i) (i) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0°, 10 min., (ii) $LiBH_4$, MeOH-THF, 0°-RT, 4h, (j) (i) IBX-DMSO, RT, 30 min; (ii) $(CCl_3CH_2O)_2P{=}CHCO_2Me$, NaH, DMF, -40°, 6 h; (k) 1% HCl, EtOH, RT, 12 h.

The regioselective reduction (THF, 0°) of **17** with Red-Al gave 1,3-diol (**18**) (77%) as an exclusive product. By involving protection-deprotection sequence followed by oxidation, **18** was converted into the aldehyde **19** without any difficulty. The Evans aldol condensation[15] of **19** with (S)-N-butanoyloxazolidinone in the presence of dibutylborontriflate at -78° for 6 h gave **20** with high diastereoselectivity as confirmed by the high resolution ^1H NMR spectrum of the condensed product. At this juncture the free OH group of **20** was protected (TBS-triflate, 2,6-lutidine, CH_2Cl_2, 0°) and then reduced ($LiBH_4$, MeOH (1 eq.),THF, 0°-RT) to give **21** (59% yield)[16]. Oxidation (IBX, DMSO, RT) of **21** followed by cis-olefination with modified Horner-Wadsworth-Emmons reaction[17] [$(CCl_3CH_2O)_2P{=}CHCO_2Me$, NaH, DMF, -40°] gave **22** as a sole product,

whose structure was proven by the ^{1}H-NMR spectrum (δ_{H-3} 6.10, J_{H-2} 5.81, $J_{H2,H3}$ 11.0 Hz). Finally compound **22** was treated with 1% HCl in EtOH at room temperature for 12 h to give pironetin (**1**) whose m.p., ^{1}H-NMR spectrum and optical rotation [[α]$_D$ -133^0, ($CHCl_3$), lit.[2,5] -136.6^0 and -142.8^0 ($CHCl_3$)] were identical with the authentic data.

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10. Compound **8** - ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (d, 3H, J=6.4 Hz), 1.01 (d, 3H, J=6.4 Hz), 1.14 (t, 3H), 1.15-2.4 (m, 4H), 3.25-3.80 (m, 5H), 4.48 (ABq, 2H), 4.90 (d, 1H, J=4.4 Hz), 7.28 (s, 5H).
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16. Compound **21** - [α]$_D$ -40^0 (c 1.0, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 12 H), 0.75 (d, 3H, J=7.0 Hz), 0.80 (d, 3H, J=7.0 Hz), 0.89 (s, 18 H), 0.98 (t, 3H, J=7.2 Hz), 1.45-2.25 (m, 9H), 1.66 (d, 3H, J=5.5 Hz), 3.14 (brd, 1H), 3.44 (s, 3H), 3.59 (m, 2H), 3.96 (m, 2H), 5.39 (m, 2H).
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