A STEREOCONTROLLED SYNTHESIS OF PIRONETIN

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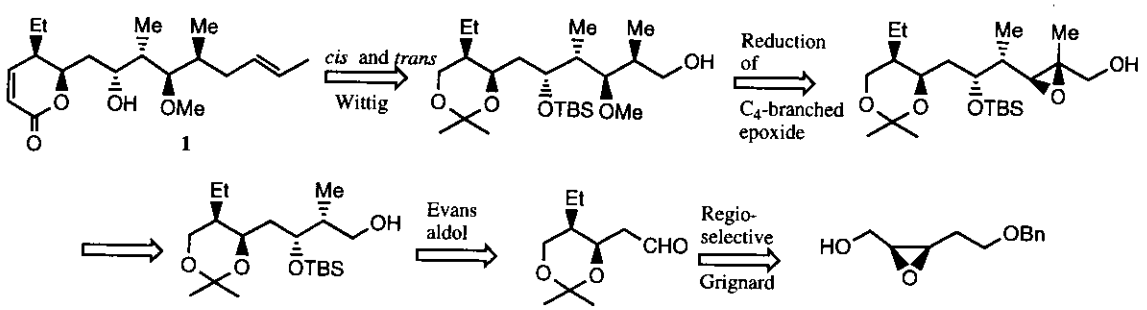
Abstract - The total synthesis of potent immunosuppressive agent - pironetin (PA-48153c) was achieved using highly stereocontrolled reactions.

In 1993, Yoshida[1] and Kobayashi[2] and their coworkers independently isolated pironetin (PA-48153c) (**1**) from the fermentation broths of *Streptomyces prunicolor* PA-48153 and *Streptomyces sp.* NK 10958 respectively. The natural product (**1**) showed a wide range of biological properties such as immunosuppressive, antitumour, and antifungal activities. A number of immunosuppressants have been developed some of which are in clinical use such as cyclosporin A (CsA) and FK-506.[3] Because of their weak and adverse effects, there is a desire to develop new immunosuppressive agents having different mode of action than those observed for CsA and FK-506. The natural product (**1**) fulfils this criteria. Structural modifications of **1** by synthesis to reduce its toxicity are being actively pursued.[4]

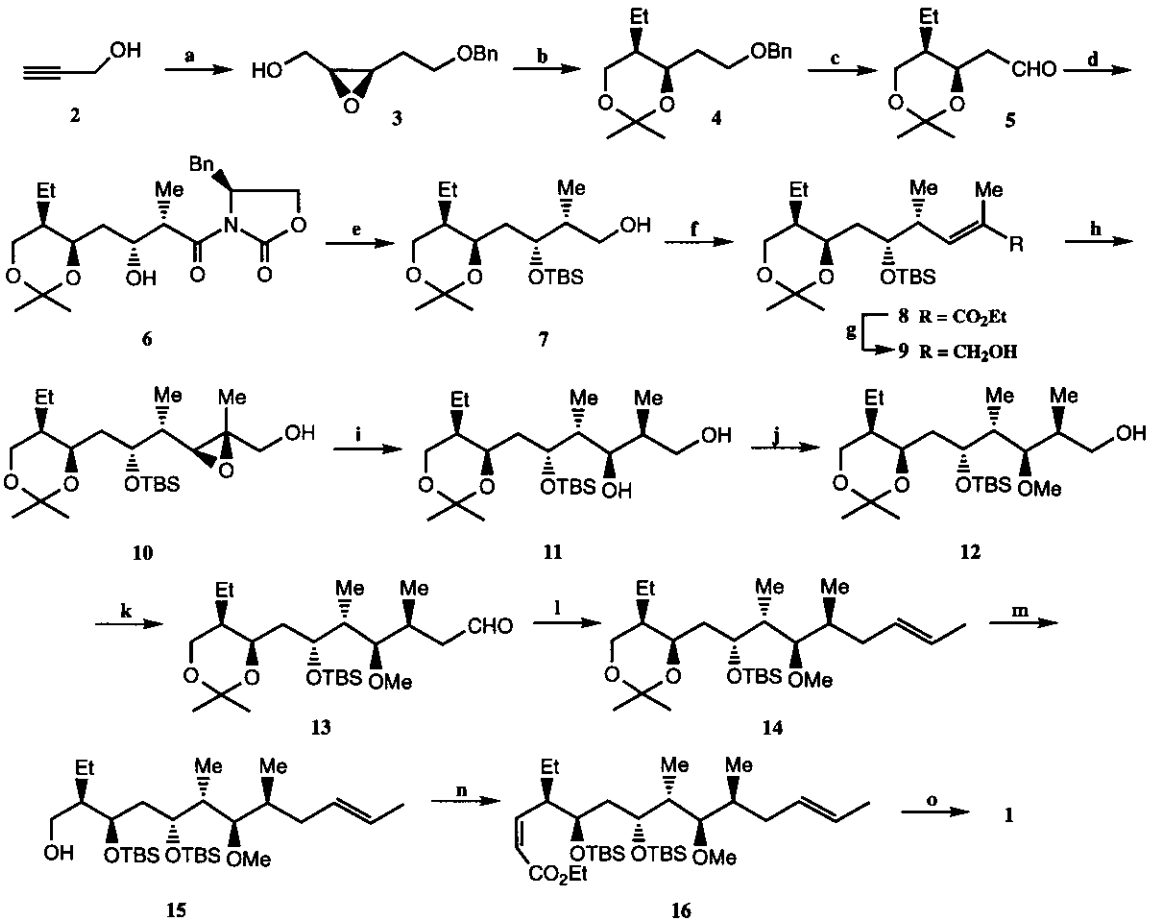
Structural examination of **1** revealed that all *syn* stereochemistries are present in pairs represented by C_5-C_6, C_7-C_8 and C_{10}-C_{11} units. For the introduction of these stereochemical centres, we have explored Evans asymmetric aldol, regiospecific reductive opening of C_4-branched tertiary epoxide and Grignard (nucleophilic substitution) reaction to complete the total synthesis of **1** (Scheme 1).



Scheme 1

The (2S,3R)-epoxy-alcohol (**3**) was prepared from propargyl alcohol (**2**) in six high yielding steps.[5] Subsequent Grignard reaction of **3** using EtMgBr in the presence of CuI at -40 ^{0}C[6] followed by periodate oxidation and isopropylidation provided **4** in 70% yield. At this stage, the benzyl group was cleaved

quantitatively by hydrogenolysis using Ca/liq. NH_3[7] and then the primary hydroxyl group was oxidized under Swern conditions to provide the aldehyde (**5**) in 85% yield. The Evans asymmetric aldol reaction[8] employing (S)-4-benzyl-3-propionyl-2-oxazolidinone in the presence of Bu_2BOTf at -78 °C gave **6**.



Scheme 2

Reagents - a) Ref. 5; b) (i) EtMgBr, cat. CuI, THF-Et_2O (1:5), -40 °C, 30 min; ii) $NaIO_4$, THF-H_2O (1:1), 1 h; iii) $Me_2C(OMe)_2$, MeCOMe, cat. H_2SO_4, 30 min; c) (i) Ca, liq.NH_3, -33 °C, 2 h; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; d) (S)-4-benzyl-3-propionyl-2-oxazolidinone, Bu_2BOTf, $^iPr_2NEt$, CH_2Cl_2, -78 °C, 5 h; e) (i) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min; ii) $LiBH_4$, MeOH, THF, 0 °C - room temperature, 4 h; f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h, ii) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, room temperature, 6 h; g) DIBAL-H, CH_2Cl_2, -78 °C, 15 min; h) mCPBA, CH_2Cl_2, -20 °C, 4 h; i) $NaBH_4$, 2M BH_3:SMe_2, THF, 24 h; j) (i) Me_3CCOCl, Py, CH_2Cl_2, room temperature, 3 h; (ii) KH, MeOTf, THF, 0 °C, 1 h; (iii) DIBAL-H, CH_2Cl_2, -78 °C, 10 min; k) (i) Ph_3P, CBr_4, CH_2Cl_2, room temperature, 10 h; ii) KCN, 18-Crown-6, MeCN, Δ, 3 h; (iii) DIBAL-H, C_6H_5-Me, -78 °C, 1 h; l) $Ph_3P^+EtBr^-$, BuLi (2 eq), -78 °C → -30 °C, THF, ^tBuOH, KO^tBu, -78 °C → 0 °C, 1 h; (m) (i) HCl-MeOH, 0 °C, 1 h; (ii) Me_3CCOCl, Py, CH_2Cl_2, room temperature, 1 h; (iii) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min; iv) DIBAL-H, CH_2Cl_2, -78 °C, 5 min; n) i) IBX, DMSO, room temperature, 30 min; ii) $(CCl_3CH_2O)_2P(O)CH_2CO_2Et$, NaH, DMF, -40 °C, 6 h; o) 1% HCl-EtOH, room temperature, 12 h.

The diastereomeric purity (95%) of **6** was determined by ^{1}H nmr spectral studies. The free hydroxyl in **6** was silylated with TBS-OTf and consequently reduced with $LiBH_4$ to afford **7** (45% overall yield from **5**). Oxidation followed by Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$ and DIBAL-H reduction at -78 ^{0}C gave the allylic alcohol (**9**) in 78% yield. Treatment of **9** with mCPBA in CH_2Cl_2 at -20 ^{0}C cleanly produced the epoxide (**10**) in 96% yield as a single product. The predicted stereochemistry of **10** was *anti*, based on several literature precedents of ours as well as others.[9] Compound (**10**) was treated[10] with $NaBH_4$ and BH_3:SMe_2 in THF at room temperature to afford **11** in 81% yield. The C_4-branching in **10** effected regiospecific and stereospecific reduction of epoxide to occur at C-2 giving rise to *syn* derivative (**11**).[11] Compound (**11**) was converted into (**12**) by pivaloylation, methylation and depivaloylation in 81% yield. The structure of **12** was supported by ^{1}H nmr and mass spectral analysis (Scheme 2).

At this stage, introduction of *E*-propenyl group was considered. The transformation of **12** into **13** a three step sequence was a straightforward exercise in 71% yield which was followed by Wittig reaction with $Ph_3P{=}CHMe$ under Schlosser's conditions[12] to give (*E*)-product (**14**) in 56% yield, the structure of which was confirmed by chemical means.[13] Our next concern was to elaborate the 5,6-dihydro-2*H*-pyran-2-one system. Accordingly, **14** was converted into **15** in 92% yield by protection-deprotection sequence followed by oxidation of primary hydroxyl with IBX-DMSO system[14] and modified Wittig reaction[15] with $(CCl_3CH_2O)_2P(O){=}CHCO_2Et$ at -40 ^{0}C in DMF to give **16** in 78% yield whose structure was proved by characteristic coupling constants of olefinic protons (J=11.0 Hz). Finally, treatment of **16** with 1% HCl in EtOH cleaved both the TBS-groups followed by concomitant lactonisation to give PA 48153c (pironetin) in 90% yield whose ^{1}H nmr spectrum,[16] mp and {[α]$_D$ -133^0 ($CHCl_3$), lit., -136.6^0 and -142.8^0 ($CHCl_3$)} was comparable to the reported data of **1.**

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REFERENCES AND FOOTNOTES

1. a) T. Yoshida, K. Koizumi, K. Matsumoto, and H. Itazaki, *Japan Patent Kokai,* 1993, 5-310726. b) T. Yoshida, K. Koizumi, K. Matsumoto, and H. Itazaki, *European Patent,* 1993, 560389A1 (Chem. Abstr., 1993, **119**, 269 169s).
2. a) S. Kobayashi, K. Tsuchiya, T. Harada, M. Nishide, T. Kurokawa, T. Nakagawa, and N. Shimada, *J. Antibiot.*, 1994, **47**, 697. b) S. Kobayashi, K. Tsuchiya, T. Kurokawa, T. Nakagawa, N. Shimada, and T. Iitaka, *J. Antibiot.*, 1994, **47**, 703.
3. S.L. Schreiber, M.W. Albers, and E.J. Brown, *Acc. Chem. Res.*, 1993, **26**, 412.
4. For the synthesis of **1** and its analogues - a) K. Yasui, Y. Tamura, T. Nakatani, K. Kawada, and M. Ohtani, *J. Org. Chem.*, 1995, **60**, 7567. b) K. Yasui, Y. Tamura, T. Nakatani, I. Horibe, K. Kawada, K. Koizumi, R. Suzuki, and M. Ohtani, *J. Antibiot.*, 1993, **49**, 173. c) M.K. Gurjar, J.T. Henri, D.S. Bose, and A.V. Rama Rao, *Tetrahedron Lett.*, 1996, **37**, 6615.
5. Y. Hirai, M. Chintani, T. Yamazaki, and T. Momose, *Chem. Lett.*, 1989, 1449.
6. M.A. Tius and A.H. Fauq, *J. Org. Chem.*, 1983, **48**, 4131.

7. J. R. Hwu, V. Chua, J.E. Schroeder, R.E. Barrans, Jr., K.P. Khoudary, N. Wang, and J.M. Wetzel, *J. Org. Chem.*, 1986, **51**, 4731.

8. a) D.A. Evans, S.J. Miller, M.D. Ennis, and P.L. Ornstein, *J. Org. Chem.*, 1992, **57**, 1067. b) D.A. Evans, D.L. Rieger, M.T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, 1991, **113**, 1047.

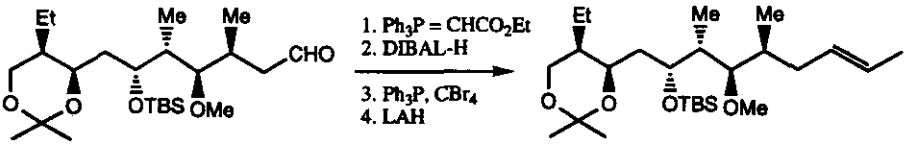
9. a) A.V. Rama Rao, M.K. Gurjar, N.B. Rao, and A. Bhandari, *Tetrahedron Lett.*, 1993, **34**, 7081, b) M.R. Johnson and Y. Kishi, *Tetetrahedron. Lett.*, 1979, **19**, 4347. c) M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, *J. Org. Chem.*, 1984, **49**, 3517.

10. H.C. Brown and N.M. Yoon, *J. Am. Chem. Soc.*, 1968, **90**, 2686.

11. a) H. Honda, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, 1984, **25**, 3857. b) M.K. Gurjar, A.S. Mainkar, and P. Srinivas, *Tetrahedron Lett.*, 1995, **36**, 5967. c) T. Katsuki and V.S. Martin, *Organic Reactions*, in press.

12. a) M. Schlosser and K.F. Christmann, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 689. b). M. Schlosser and K.F. Christmann, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 126. c) A.V. Rama Rao, M.K. Gurjar, and D.S. Bose, *J. Org. Chem.*, 1991, **56**, 1320.

13. The same product (**14**) was also obtained from **13** as follows:



13 **14**

14. M. Frigeno and M. Santagostino, *Tetrahedron Lett.*, 1994, **35**, 8019.

15. M.A. Reddy, R.J. Gopal, and V.J. Rao, *Indian J. Chem.*, 1996, **35B**, 312.

16. ^{1}H Nmr ($CDCl_3$, 200 MHz) data of selected compounds : Compound (**4**) - δ 0.86 (t, 3H, J=7.4 Hz), 1.24, 1.33 (2s, 6H), 1.5-1.8 (m, 3H), 3.42 (m, 2H), 3.68 (dd, 1H, J=1.0, 12.0 Hz), 3.85 (dd, 1H, J=2.4, 12.0 Hz), 4.08 (m, 1H), 4.40 (ABq, 2H, J=14.0, 22.0 Hz), 7.20 (s, 5H), Compound (**7**) - δ 0.06, 0.07 (2s, 6H), 0.74 (d, 3H, J=7.0 Hz), 0.87 (s, 9H), 0.93 (t, 3H, J=7.0 Hz), 1.39, 1.49 (2s, 6H), 1.55-1.75 (m, 2H), 1.91 (m, 1H), 3.45 (dd, 1H, J=4.4, 10.0 Hz), 3.60 (dd, 1H, J=8.0, 10.0 Hz), 3.74 (dd, 1H, J=1.0, 12.0 Hz), 3.80 (m, 1H), 3.88 (dd, 1H, J=2.0, 12.0 Hz), 3.98 (m, 1H), Compound (**12**) - δ 0.06 (s, 6H), 0.69 (d, 3H, J=6.7 Hz), 0.78 (d, 3H, J=6.7 Hz), 0.91 (t, 3H, J=6.5 Hz), 1.24, 1.35 (2s, 6H), 1.3-1.9 (m, 7H), 3.26 (dd, 1H, J=2.0, 8.9 Hz), 3.37 (s, 3H), 3.53 (d, 1H, J=6.6 Hz), 3.68 (br d, 1H, J=12.4 Hz), 3.84 (m, 2H), 3.97 (m, 1H), Compound (**15**) - δ 0.08 (s, 12H), 0.75 (d, 3H, J=7.0 Hz), 0.80 (d, 3H, J=7.0 Hz), 0.89 (s, 18H), 0.98 (t, 3H, J=7.2 Hz), 1.45-2.25 (m, 9H), 1.66 (d, 3H, J=5.5 Hz), 3.14 (br d, 1H), 3.44 (s, 3H), 3.59 (m, 2H), 3.96 (m, 2H), 5.39 (m, 2H), Compound (**1**) - δ 0.95-1.0 (m, 9H), 1.5-1.85 (m, 7H), 1.67 (d, J=6.0 Hz, 3H), 2.10 (m, 1H), 2.30 (m, 1H), 2.98 (dd, J=6.3, 4.3 Hz, 1H), 3.47 (s, 3H), 4.20 (br d, 1H), 4.74 (m, 1H), 5.38 (m, 2H), 6.03 (d, J=11.0 Hz, 1H), 7.01 (dd, J=9.3, 6.0 Hz, 1H).

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