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, Yoshida1 and Kobayashi2 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 C₅-C₆, C₇-C₈ and C₁₀-C₁₁ units. For the introduction of these stereochemical centres, we have explored Evans asymmetric aldol, regiospecific reductive opening of C₄-branched tertiary epoxide and Grignard (nucleophilic substitution) reaction to complete the total synthesis of 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 °C6 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. NH₃⁷ and then the primary hydroxyl group was oxidized under Swern conditions to provide the aldehyde (5) in 85% yield. The Evans asymmetric aldol reaction⁸ employing (S)-4-benzyl-3-propionyl-2-oxazolidinone in the presence of Bu₂BOTf at -78 °C gave 6.

Scheme 2

Reagents - a) Ref. 5; b) (i) EtMgBr, cat. CuI, THF-Et₂O (1:5), -40 °C, 30 min; ii) NaIO₄, THF-H₂O (1:1), 1 h; iii) Me₂C(OEt)₂, MeCOMe, cat. H₂SO₄, 30 min; c) (i) Ca, liq.NH₃, -33 °C, 2 h; ii) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h; d) (S)-4-benzyl-3-propionyl-2-oxazolidinone, Bu₂BOTf, Pr₂NEt, CH₂Cl₂, -78 °C, 5 h; e) (i) TBS-OTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 10 min; ii) LiBH₄, MeOH, THF, 0 °C - room temperature, 4 h; f) (i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h, ii) Ph₃P=C(Me)CO₂Et, C₆H₅, room temperature, 6 h; g) DIBAL-H, CH₂Cl₂, -78 °C, 15 min; h) mCPBA, CH₂Cl₂, -20 °C, 4 h; i) NaBH₄, 2M BH₃·SMe₂, THF, 24 h; j) (i) Me₃CCOCl, Py, CH₂Cl₂, room temperature, 3 h; (ii) KH, MeOTf, THF, 0 °C, 1 h; (iii) Dibal-H, CH₂Cl₂, -78 °C, 10 min; k) (i) Ph₃P, CBr₄, CH₂Cl₂, room temperature, 10 h; ii) KCN, 18-Crown-6, MeCN, Δ, 3 h; (iii) Dibal-H, C₆H₅-Me, -78 °C, 1 h; l) Ph₃P+EtBr⁻, BuLi (2 eq), -78 °C → -30 °C, THF, tBuOH, KOtBu, -78 °C → 0 °C, 1 h; (m) (i) HCl-MeOH, 0 °C, 1 h; (ii) Me₃CCOCl, Py, CH₂Cl₂, room temperature, 1 h; (iii) TBS-OTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 15 min; iv) Dibal-H, CH₂Cl₂, -78 °C, 5 min; n) i) IBX, DMSO, room temperature, 30 min; ii) (CCl₃CH₂O)₂P(O)CH₂CO₂Et, 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\(_3\)P-C(Me)CO\(_2\)Et and DIBAL-H reduction at -78 °C gave the allylic alcohol (9) in 78% yield. Treatment of 9 with mCPBA in CH\(_2\)Cl\(_2\) at -20 °C cleanly produced the epoxide (10) in 96% yield as a single product. The predicted stereochemistry of 10 was \textit{anti}, based on several literature precedents of ours as well as others.\(^9\) Compound (10) was treated 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 \textit{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\(_3\)P=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-\(2H\)-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\(_3\)CH\(_2\)O)\(_2\)P(O)=CHCO\(_2\)Et at -40 °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 \{[\alpha]_D\} -1330 (CHCl\(_3\)), lit., -136.60 and -142.80 (CHCl\(_3\)) was comparable to the reported data of 1.

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REFERENCES AND FOOTNOTES


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


16. $^1$H Nmr (CDCl$_3$, 200 MHz) data of selected compounds: Compound (4) - $\delta$ 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) - $\delta$ 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) - $\delta$ 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) - $\delta$ 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) - $\delta$ 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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