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Total Synthesis of the Immunosupressant (−)-Pironetin (PA48153C)

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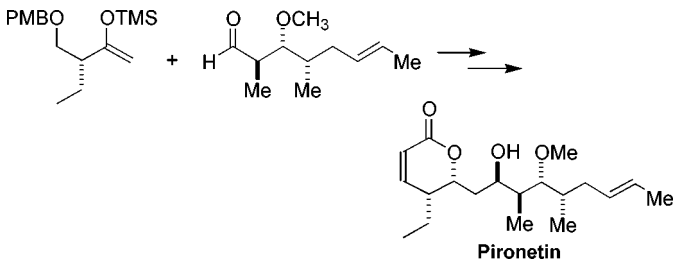
ABSTRACT



Total synthesis of the immunosuppresant pironetin has been achieved by a synthetic route in which the connections between starting materials and the desired structure are readily discerned. Key steps include a diastereoselective Lewis acid mediated crotylstannane aldehyde addition, a highly selective Lewis acid promoted Mukaiyama aldol reaction, an *anti*-selective SmI_2 reduction of a *β*-hydroxyketone, and finally a lactone annulation reaction.

Natural products possessing immunosuppressant activity have received a great deal of attention since the introduction of cyclosporin A (CsA)[1] and FK-506[2] for the treatment of autoimmune diseases, especially those associated with organ transplantation.[3] Recently Kawada and co-workers reported the isolation of **1** (PA-48153C)[4] from the fermentation broth of *Streptomyces prunicolor* PA-48153 and found it to possess potent immunosupressant activity similar to that exhibited by CsA (**2**) and FK-506 (**3**). Perhaps more interesting than its activity per se is its differing mode of action: PA-48153C was found to inhibit the responses of both T and B lymphocytes to mitogens, while CsA and FK-506 affect only T-cell activation.[5] Kobayashi and co-workers have also reported the isolation of a plant-growth regulator, given the name pironetin, from *Streptomyces* sp. NK10958 whose structure has proven to be identical with that of **1** (Figure 1).[6]

A major limitation of pironetin as a therapeutic agent is its high cytotoxicity; however, certain structurally modified derivatives of pironetin have recently shown promise.[5] Moreover, these relatively simple structures exhibit potency comparable to that shown by CsA. Another recent report in the patent literature suggests efficacy of certain formulations of such derivatives in assays against uterine and ovarian tumors, in addition to activity as inhibitors of tubulin polymerization and thus the cell cycle.[7]

The desire to synthesize derivatives in which activity might be dissociated from toxicity and the need to unambiguously

(1) For general reviews, see: (a) Borel, J. F. *Pharmacol. Rev.* **1990**, *41*, 259. (b) Schreiber, S. L. *Science* **1991**, *251*, 283. (c) Sigal, N. H.; Dumant, F. J. *Annu. Rev. Immunol.* **1992**, *10*, 519. (d) Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int., Ed. Engl.* **1992**, *31*, 384. (e) Armistead, D. M.; Harding, M. W. *Annu. Rep. Med. Chem.* **1993**, *28*, 207. (f) Schreiber, S. L.; Albers, M. W. Brown, E. J. *Acc. Chem. Res.* **1993**, *26*, 412.

(2) Peters, D. H.; Fitton, A.; Plosker, G. L.; Faulds, D. *Drugs* **1993**, *46*, 746.

(3) Thomson, A. W.; Starzl, T. E. *Immunol. Rev.* **1993**, *136*, 71.

(4) (a) Yoshida, T.; Koizumi, K.; Kawamura, Y.; Matsumoto, K.; Itazaki, H. Japanese Patent kokai 5-310726, 1993; (b) European Patent 60389 A1, 1993.

(5) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, *60*, 7567.

(6) (a) Kobayashi, S.; Tsochia, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, *47*, 697. (b) Kobayashi, S.; Tsochia, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, T. *J. Antibiot.* **1994**, *47*, 703.

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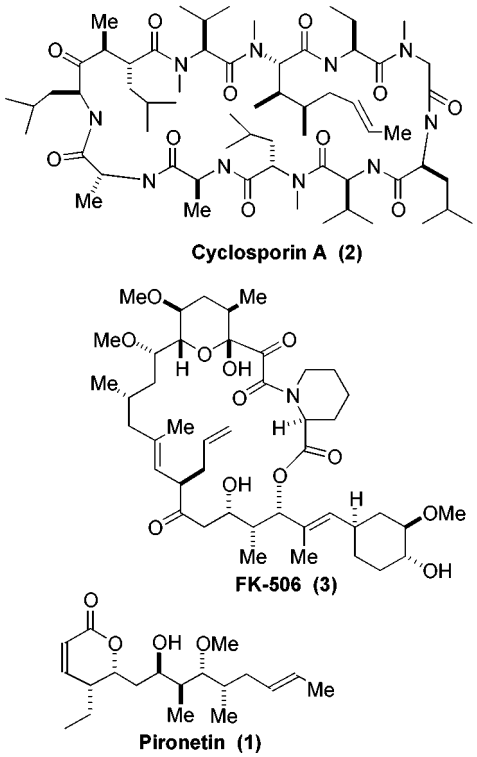


Figure 1. Pironetin, CsA, and FK506.

verify the absolute stereochemistry of **1** have prompted several investigations which have culminated in successful total syntheses. Kawada and co-workers reported the first synthesis of **1**, which utilized a carbohydrate approach to the 2-pyranone ring system.[8] Gurjar has disclosed two syntheses[9] in which the stereochemistry was set via combinations of epoxide ring openings and Evans aldol reactions. Kitahara and Chida have also reported syntheses in which nucleophilic additions to epoxides play prominent strategic roles.[10]

The route chosen for experimental investigation is outlined in Figure 2. We envisioned application of the lactone annulation procedure recently developed in our laboratories to install the lactone moiety by reaction of the lithium enolate of methyl acetate with β-acetoxy aldehyde **4**.[11] This material was in turn envisioned to arise by the Lewis acid promoted Mukaiyama aldol union of silyl enol ether **5** and aldehyde **6**. Aldehyde **6** should be accessible from β-benzyloxy aldehyde **7** by chain extension using procedures previously developed in our laboratories.[12]

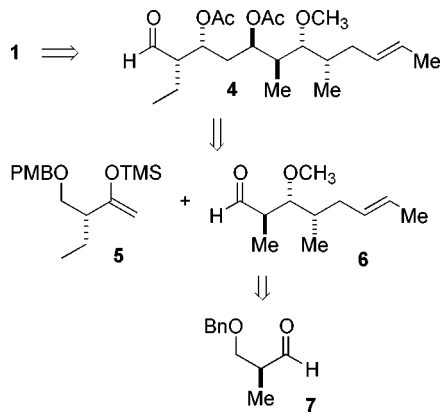


Figure 2. Antithetic analysis

The preparation of aldehyde **6** commenced with the chelation-controlled addition of (*Z*)-crotyltri-*n*-butylstannane to the β-benzyloxy aldehyde **7**, using $TiCl_4$ as previously described,[12] to give the desired *anti*,*syn* homoallylic alcohol **8** in 89% yield after purification by chromatography. After conversion of the free hydroxyl to the corresponding methyl ether **9** by reaction with KH/MeI (92% yield), a hydroboration−oxidation of the terminal olefin was employed to secure aldehyde **11** (92%). In this instance, direct oxidation of the organoborane formed from reaction of **9** with 9-BBN proved to be low yielding. Better results were obtained by isolation of the intermediate alcohol **10**, followed by oxidation using the method of Ley (TPAP/NMO).[13] Installation of the requisite *E* alkene was initiated by treatment of this aldehyde with $CBr_4/P(Ph)_3$ according to the Corey−Fuchs protocol[14] to afford the homologated dibromoalkene **12** in 68% yield for two steps from alcohol **10**. Reaction of this material with *n*-BuLi and quenching with methyl iodide furnished alkyne **13** (99%). Reduction of alkyne **12** with lithium/ammonia then effected conversion of the alkyne to the corresponding *E* alkene and also effected removal of the benzyl protecting group to give alcohol **14** (84%); aldehyde **6** was prepared from this material by Ley oxidation and used immediately in the subsequent Mukaiyama aldol reaction (Scheme 1).

The preparation of the methyl ketone required for the aldol coupling proved somewhat more difficult than originally envisioned, since it was found that a PMB protecting group for the β-oxygen function was necessary[15] to preclude adventitious acetate migration prior to the installation of the lactone moiety (vide infra). Although the corresponding benzyl ether was easily synthesized, it proved more trouble-

(7) Yasui, K.; Tamura, Y.; Nakatani, T.; Horibe, I.; Kawada, K.; Koizumi, K.; Suzuki, R.; Ohtani, M. *J. Antibiot.* **1996**, *49*, 173.

(8) (a) Gurjar, M. K.; Henri, J. T. Jr.; Bose, D. S.; Rau, A. V. R. *Tetrahedron Lett.* **1996**, *37*, 6615. (b) Gurjar, M. K.; Chakrabarti, A.; Rao, A. V. R. *Heterocycles* **1997**, *45*, 7.

(9) Watanabe, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **1998**, *39*, 8313.

(10) Chida, N.; Yoshinaga, M.; Tobe, T.; Ogawa, S. *Chem. Commun.* **1997**, 1043.

(11) Keck, G. E.; Li, X.-Y.; Knutson, C. E. *Org. Lett*, **1999**, *1*, 411.

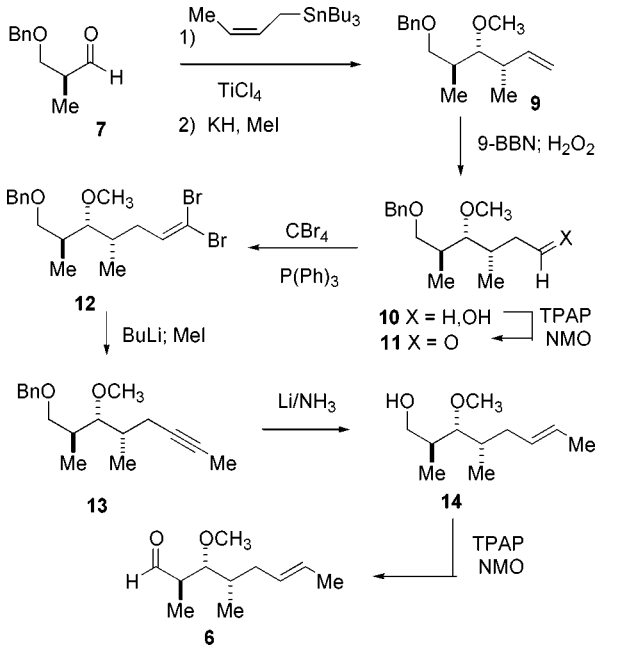
(12) (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.

(13) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

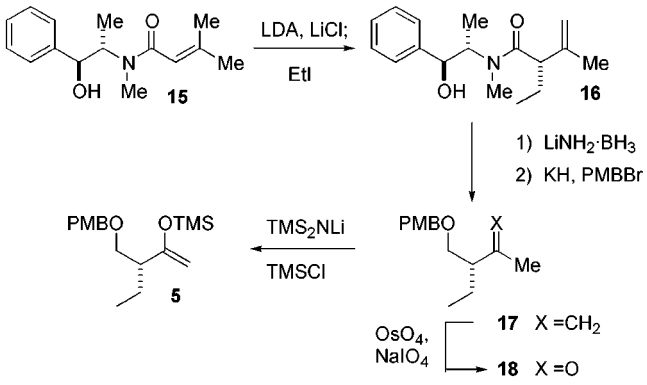
(15) It was straightforward to prepare the corresponding benzyl ether by using the Evans oxazolidinone alkylation procedure with chloromethylbenzyl ether as the alkylating agent, and the derived β-benzyloxy methyl ketone intermediate was used sucessfully in condensation with aldehyde **6**. However, all attempts to remove the benzyl ether at the stage of intermediate **21** were either compromised by olefin reduction or by acetate migration. Also, it proved impractical to prepare the *p*-methoxybenzyl ether **18** using the simple sequence employed to prepare the corresponding benzyl ether.

Scheme 1. Preparation of Aldehyde **6**



some to obtain the PMB ether. This was ultimately accomplished using the asymmetric alkylation protocol developed by Meyers.[16] Unsaturated amide **15** was formed by acylation of the chiral auxiliary (1*S*,2*S*)-(+)-psuedodphedrine with β,β-dimethylacryloyl chloride. Asymmetric alkylation of **15** with ethyl iodide gave **16** (93%), which was reduced using lithium amidoborane as described by Meyers to give the primary alcohol. Protection of the hydroxyl as the PMB ether gave **17**, and oxidative cleavage of the olefin then gave the requisite ketone **18** (52% overall from **16**). Conversion of **18** to the trimethylsilyl enol ether **5** was accomplished in the normal way using LiHMDS and TMSCl (Scheme 2).

Scheme 2. Preparation of Enol Ether **5**



With the necessary components for the Mukaiyama aldol in hand, we were now in a position to couple these fragments.

(16) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

A considerable body of evidence was available to suggest that the desired stereochemical outcome should be highly preferred in this case.[17] The diastereoselectivity associated with nucleophilic additions to aldehydes possessing both α and β stereocenters has been termed "merged 1,2 and 1,3 asymmetric induction".[17] In these Lewis acid promoted reactions, the effects due to the stereocenters at the α and β carbons can be reinforcing or opposing; only for the case in which the directing effects of both centers operate in the same direction is a very high level of diastereoselectivity expected.

That this reinforcing scenario applies in the present circumstance is most easily seen by inspection of Figure 3.

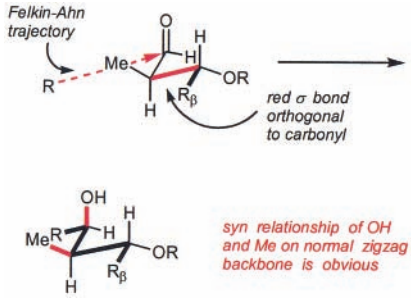


Figure 3. A convenient description of "merged 1,2 and 1,3 asymmetric induction".

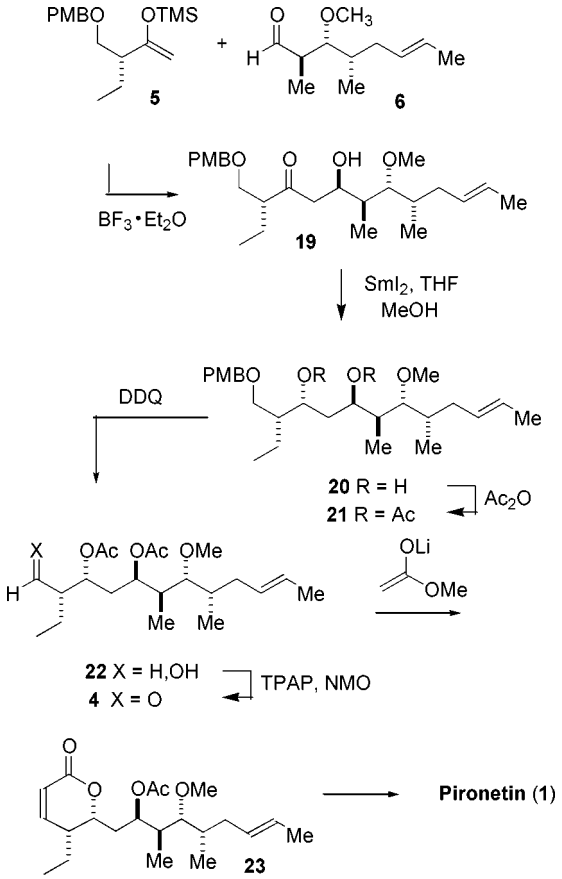
In this attempted depiction of the preferred transition state for the nucleophilic addition, the three-carbon backbone of the β-alkoxy aldehyde, and the associated substituents, is drawn as if it were $^1/_2$ of a chair cyclohexane, using the normal conventions for structural drawing of chair cyclohexane. Orientation of the aldehyde carbonyl with oxygen "up" as shown leads to the preferred Felkin−Ahn[18] transition state arrangement with the largest α substituent perpendicular to the carbonyl group. In can be seen that in this preferred Felkin arrangement the α-Me group is placed in the "equatorial" position. The preferred trajectory of attack, at approximately the tetrahedral angle, as indicated by the dashed arrow, is also seen to be "equatorial". At the β position, the preferred arrangement of substituents which minimizes steric interactions and dipole−dipole repulsions can be seen to be that which places the large carbon substituent "equatorial" and H "axial".[19]

(17) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

(18) Ahn, T. N.; Eisentein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(19) One arrives at the correct predictions using this model simply by using sterically based *A* values for conformational preferences in cyclohexanes to predict the preferred arrangements of substituents at the α and β carbons. However, dipole−dipole repulsions are also easily evaluated by inspection. For example, it is easily seen that interchanging H and R_β will give a 1,3-diaxial interaction between R_β and the aldehyde oxygen, while interchanging H and the O substituent will give both a diaxial steric interaction and also maximum dipole−dipole repulsion between the two C−O bonds. Although there might be some ambiguity about which of these alternative arrangements would be favored, it is a certainty that both would be considerably higher in energy than the preferred arrangement depicted.

Scheme 3. Completion of the Route to Pironetin



Thus, the product structure arising from nucleophilic addition is already drawn with the carbon backbone in the normal extended zigzag arrangement and no cumbersome manipulations are needed to ascertain the stereochemical relationships in the product. This model is of course consistent with both previous experimental results and the model set forth by Evans;[17] however, we find the use of the conventions delineated above to be exceptionally convenient.

In the event, reaction of **5** with **6** using $BF_3 \cdot Et_2O$ as Lewis acid proceeded in accord with expectation to yield **19** as essentially a single diastereomer (86% yield, diastereomeric products not detected). It was now necessary to reduce the β-hydroxy ketone to the *anti*-1,3-diol, a transformation which has proven difficult in this system.[9] However, application of the recently described[20] samarium diiode reduction protocol afforded the desired **20** in good chemical yield (91%) and with reasonable diastereoselectivity (4.6:1).[21] Acetylation of the diol (Ac_2O, NEt_3; 97%), followed by removal of the PMB protecting group, gave the desired primary alcohol (**22**) in 92% yield. Key to the overall success of this route is the finding that this deprotection can be accomplished with no detectable 1,3-migration of the secondary acetate to the primary hydroxyl, a process which precludes the use of many other common protecting groups. Ley oxidation then furnished the aldehyde **4**, now properly functionalized to effect incorporation of the lactone ring in a single step using the lactone annulation process.[11] Lactone annulation was effected by reaction of this material with the lithium enolate of methyl acetate (initially at −78 °C for 15 min with warming to 0 °C and reaction at that temperaure for 30 min) and afforded, after quenching and normal extractive workup, the desired lactone **23** in 74% yield. Finally, removal of the acetate by acid-catalyzed methanolysis (MeOH, 3 N HCl, 65 °C, 8 h) gave (−)-pironetin in 86% yield (Scheme 3).[22]

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Supporting Information Available: Experimental procedures and spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172.

(21) A similar level of stereoselectivity was obtained using tetramethylammonium triacetoxyborohydride reduction. In contrast, both reductions were completely stereoselective for the *anti* diol when conducted on the corresponding benzyl compound (**19** with PMB replaced by benzyl).

(22) The spectral and analytical data for **1** were in excellent agreement with that previously reported for the natural material and that from previous synthetic efforts.