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Total Synthesis of (−)-Pironetin†

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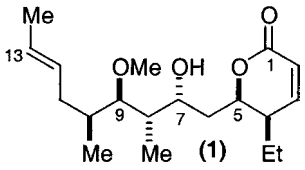
ABSTRACT



Pironetin

The asymmetric total synthesis of pironetin, a compound that shows plant growth regulatory activity, immunosuppressive as well as a remarkable antitumoral activity, is described. The approach involves the use of three very efficient Evans oxazolidinone-mediated *syn*-aldol condensations, a high-yielding coupling between lithium acetylide ethylenediamine complex and a tosylate followed by methylation, and selective reduction to establish the C12–C13 (*E*) double bond.

Pironetin[1] or PA-48153C[2] (**1**) is an unsaturated δ-lactone derivative, which was isolated independently by two research groups from *Streptomyces sp.* NK10958 and from the fermentation broths of *Streptomyces prunicolor* PA-48153, respectively. This very interesting compound possesses plant growth regulatory and immunosuppressive activities. Recently, the biological effects of **1** and its derivatives on cell cycle progression and antitumor activities were reported.[3] More importantly, the mode of action of **1** is different from those established for the immunosuppressants cyclosporin A (CsA) and FK506 that inhibit T cell activation.[4] Pironetin showed suppressive effects on the responses of T and B lymphocytes to mitogens.

The structure of pironetin has been suggested mainly by spectral methods, the relative stereochemistry has been determined by X-ray analysis, and the absolute configuration has been confirmed by total synthesis.[5,6] In a recent paper, Osada et al. showed that the α,β-unsaturated lactone, the chirality at the C7-position bearing a hydroxyl group, and the terminal portion of the alkyl chain are important for microtubule inhibitory activity of pironetins.[3,6h] To provide material for more extensive biological evaluation, and to develop a synthetic strategy useful for the preparation of promising new derivatives of pironetin, we have undertaken its total synthesis.

The illustrated structural examination of **1** revealed that all syn stereocenters are present in pairs represented by C4−C5, C7−C8, and C9−C10 units (Scheme 1).[7] For introduction of these stereochemical centers, we explored three Evans

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† This paper is dedicated to Prof. Albert Kascheres on the occasion of his 60th birthday and also to the Brazilian Chemical Society (SBQ).

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(7) The numbering of **1** follows that suggested in ref 1b.

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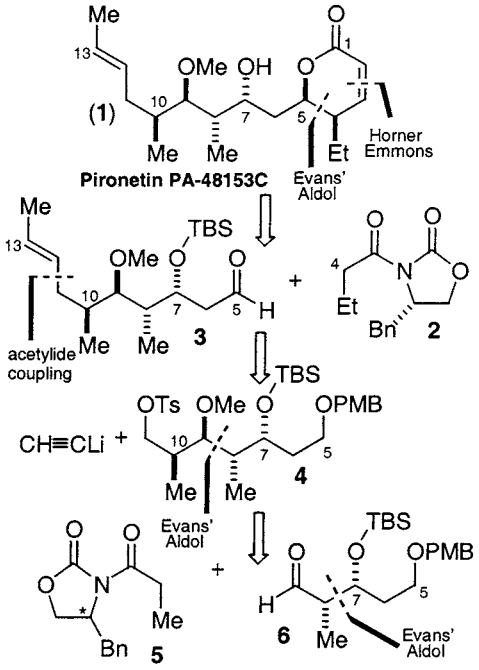
Scheme 1

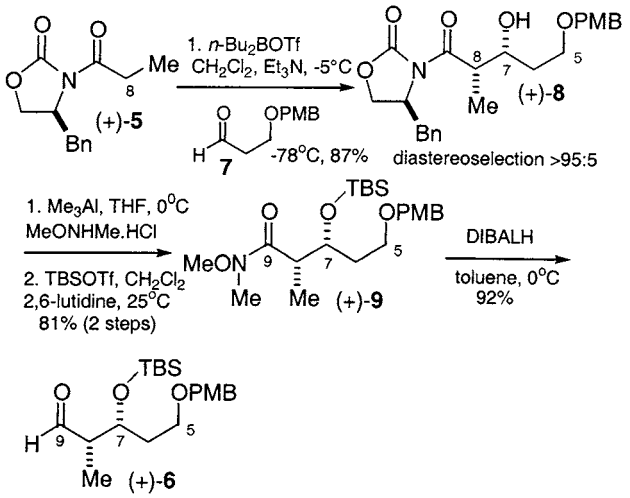


asymmetric aldol reactions. By employing an aldol addition of oxazolidinone **2** to aldehyde **3**, we planned to establish the stereocenters at C4 and C5. Aldehyde **3** may be further dissected in a straightforward manner to give tosylate **4**, bearing 4 stereogenic centers. The C12−C13 (*E*) double bond segment in **3** was viewed as arising from coupling between lithium acetylide ethylenediamine complex and tosylate **4**, followed by methylation and selective reduction. Of the available options for the synthesis of **4**, we speculate that the desired C8−C10 *anti*-methyl bearing stereocenters might be established through a boron enolate mediated aldol reaction using *N*-propionyloxazolidinone **5** with aldehyde **6**, with *anti*-Felkin addition, followed by methylation of the newly formed OH-function.

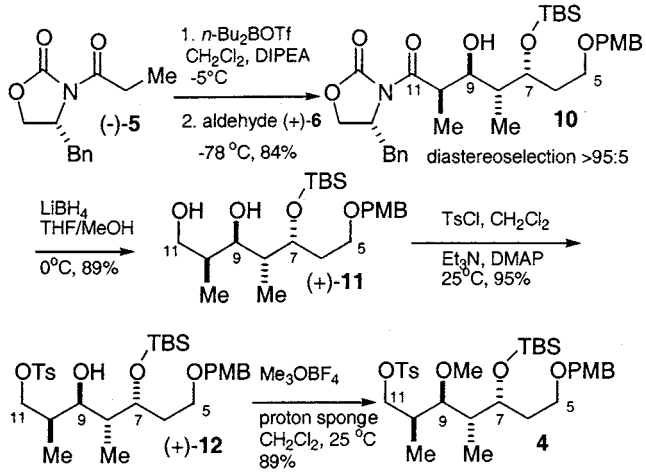
Synthesis of aldehyde **6** began with the known (*S*)-acyloxazolidinone (+)-**5**, which was most conveniently prepared by acylation of the correponding (−)-(*S*)-oxazolidinone (Scheme 2).[8]

Asymmetric aldol addition of the boron enolate derived from oxazolidinone (+)-**5** with aldehyde **7** gave aldol adduct (+)-**8** in 87% isolated yield and with excellent diastereoselectivity (>95:5) (Scheme 2).[9,10] Exchange of the oxazolidinone auxiliary in the *syn*-aldol (+)-**8** with *N*,*O*-dimethylhydroxylamine generated the Weinreb amide, purification of which was done by isolation of the recyclable oxazolidinone chiral auxiliary (92%) by efficient crystallization of this oxazolidinone from the reaction mixture.[11] Protection of the OH-function as its TBS ether gave Weinreb amide (+)-**9** in 81% yield (over two steps, transamidation and TBS protection). This amide was smoothly reduced to aldehyde (+)-**6** in 92% yield on treatment with diisobutylaluminum hydride in toluene at 0 °C (Scheme 2). The aldehyde (+)-**6**, without purification, was treated with the boron enolate generated from (*R*)-oxazolidinone (−)-**5** to give the corresponding aldol adduct **10**, which possesses the *syn*−*anti*−*syn* stereochemistry concerning the four contiguous stereocenters, in 84% isolated yield and >95:5 diastereoselectivity (Scheme 3).[9] This result illustrates that the chiral auxiliary

Scheme 2



Scheme 3



is effective in controlling the stereoselectivity of the reaction, even overriding the facial bias of chiral aldehyde (+)-**6** for Felkin addition. Reductive removal of the oxazolidinone

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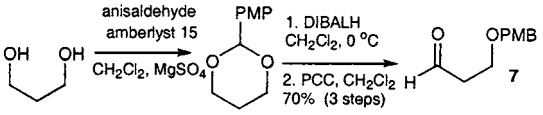
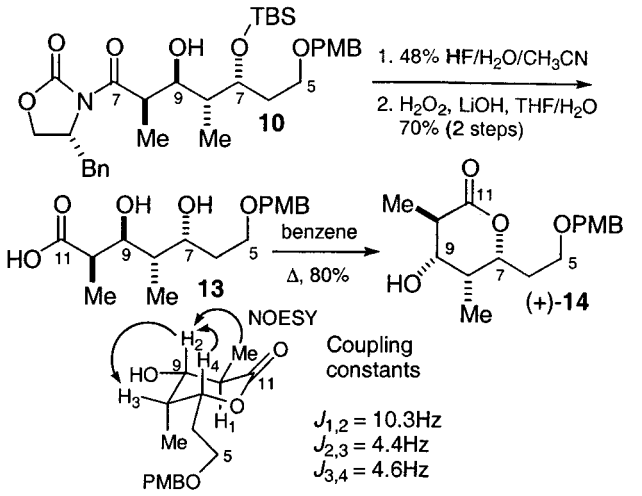
(10) Aldehyde **7** was prepared from 1,3-propanediol:



auxiliary in the crude aldol adduct **10** was accomplished with $LiBH_4$ in THF/MeOH at 0 °C.[12] This protocol provided 1,3-diol (+)-**11** in 89% yield (Scheme 3). Recovery of the oxazolidinone auxiliary in this reaction is nearly quantitative.

Selective tosylation of the primary OH-function led to compound (+)-**12** in 95% yield. Methylation with Me_3OBF_4 in the presence of a proton sponge at room temperature proceeded smoothly, producing the desired product **4** in 89% isolated yield (Scheme 3).[13] Transformation of the aldol adduct **10** to the corresponding lactone (+)-**14** enabled the relative stereochemistry of both aldol bond constructions to be confirmed (Scheme 4). Treatment of aldol **10** with HF/

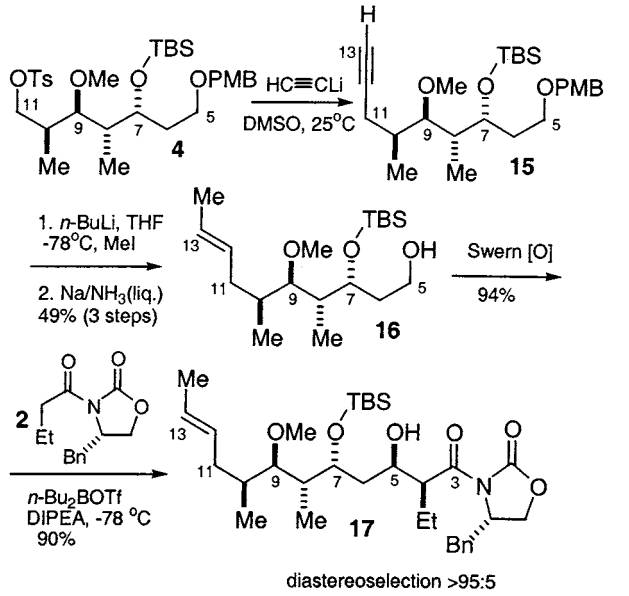
Scheme 4



H_2O/CH_3CN to remove the TBS protecting group followed by oxidative cleavage of the oxazolidinone auxiliary with $H_2O_2/LiOH$[14] gave an intermediate carboxylic acid (**13,** 70% yield, two steps), which was dehydrated in refluxing benzene to give lactone (+)-**14** in 80% isolated yield. The observed relative stereochemistry was proved by analysis of the coupling constants in the ^1H NMR spectrum as well as by NOESY experiments. The illustrated NOESY interactions on the lactone established the *anti* relationship between the newly formed hydroxyl and methyl bearing stereocenter in the *anti*-Felkin adduct **10**. The large vicinal coupling constant between H1−H2 (10.3 Hz), together with the small observed values between H2−H3 (4.4 Hz) and H3−H4 (4.6 Hz), unambiguously established the proposed *syn*−*anti*−*syn* relative stereochemistry of aldol adduct **10** (Scheme 4).

After examining several different attempts to couple C12 vinyl cuprates and C11 tosylates, bromides, and iodides, we turned our attention to the use of a coupling approach employing lithium acetylide ethylenediamine complex with tosylate **4**. We were gratified to see that this modification proved successful (Scheme 5). The optimal conditions

Scheme 5



involved treatment of tosylate **4** with 5 equiv of lithium acetylide in DMSO at room temperature to give the acetylene **15**.[15] Treatment of **15** with *n*-BuLi and quenching with methyl iodide gave the corresponding alkyne.[16]

Reduction of the alkyne proceeded smoothly providing control for the *E*-geometry of the C12−C13 double bond with concomitant removal of the PMB group at C5, giving primary alcohol **16** in 49% yield for the three-step sequence from **4**.[17] Swern oxidation of **16** under the standard conditions gave the desired aldehyde in 94% yield (Scheme 5).[18] A final Evans-type asymmetric aldol reaction between the unpurified aldehyde and the boron enolate derived from **2**[8] proceeded with high diastereoselectivity (>95:5) to give adduct **17** in 90% yield. At this juncture, all the stereocenters in the target had been installed, leaving only final refunctionalizations to complete the synthesis. The final steps of the synthesis are summarized in Scheme 6. Protection of the secondary alcohol functionality at C5 in **17** as its TBS ether followed by reductive removal of the chiral auxiliary with $LiBH_4$ in THF/MeOH at 0 °C produced primary alcohol **18** in 87% overall yield, along with almost quantitative recovery of the chiral auxiliary.[12] TPAP oxidation of **18** gave an intermediate aldehyde that was directly submitted to a Horner−Wadsworth−Emmons homologation with the requisite stabilized reagent **19** under Ando's conditions to give the corresponding α,β-unsaturated ester **20** (*Z*:*E* >95:5) in 84% yield (two steps).[19,20]

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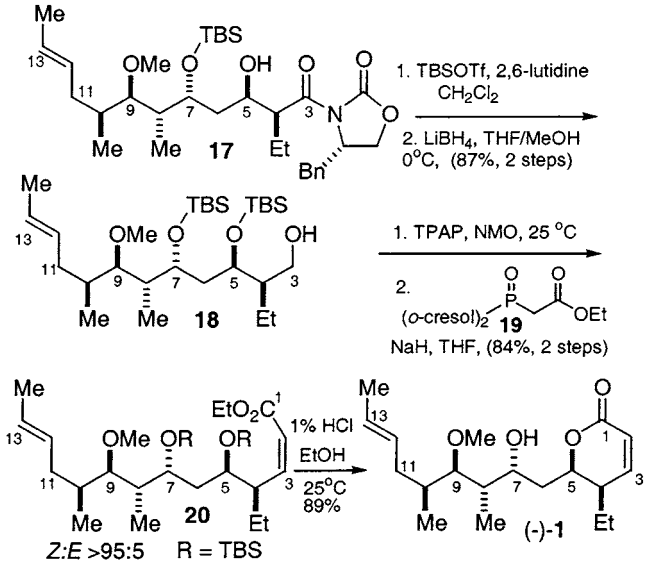
Scheme 6



All that remained was to carry out the necessary lactonization. Treatment of ester **20** with 1% HCl/EtOH at room temperature occurred with efficient removal of both TBS protecting groups positioned at C5 and C7, followed by lactonization to give (−)-pironetin **1** in 89% isolated yield, after purification by silica gel column chromatography.[1,2,21] The spectroscopic and physical data [^{1}H and ^{13}C NMR, IR, $[\alpha]^{20}_D$, R_f] were identical in all respects with the published data.[1−3,6] The synthesis required 18 steps from (+)-**5** (longest linear sequence), produced the desired product in 11% overall yield, being amenable to a gram scale-up, and compares well with other published routes,[5,6] being one of the shortest approaches.

We described here an asymmetric total synthesis of pironetin. Notable features of this approach include three high-yielding *syn* aldol reactions to set up the six stereogenic centers, a very efficient coupling between a tosylate and lithium acetylide, followed by methylation and reduction to establish the *(E)* double bond at C12−C13, and a diastereoselective Horner−Wadsworth−Emmons reaction under Ando's conditions. The route to (−)-pironetin described here might easily afford access to additional analogues with potential relevance to biological studies. The results will be described in a full account of this work.[21]

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Supporting Information Available: Spectral data for key intermediates and spectroscopic data for natural and synthetic pironetin (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL027211O

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(21) New compounds and the additional isolated intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.