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Enantioselective Total Synthesis of (-)-Pironetin:

Iterative Aldol Reactions of Thiazolidinethiones

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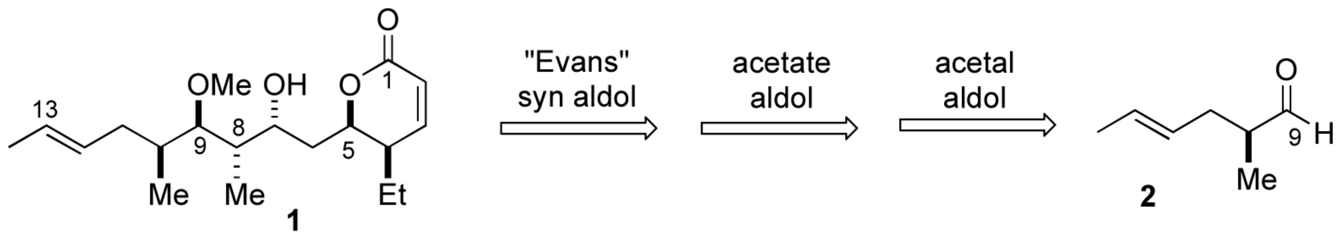
Abstract



The enantioselective total synthesis of pironetin has been achieved in 11 steps from known aldehyde 2. The synthesis relies on the formation of 5 out of 6 stereocenters through titanium mediated iterative aldol reactions. Key steps in this synthesis include an acetal aldol reaction to establish the stereochemistry at C8 and C9, an acetate aldol reaction, and “Evans” syn aldol reaction.

In 1994, the Kobayashi and Yoshida groups independently isolated the α,β-unsaturated lactone (-)-pironetin **1** from the fermentation broth of *Streptomyces prunicolor* PA-48153 and *Streptomyces sp*. NK 10958.[1] (-)-Pironetin, originally identified as a novel plant growth inhibitor with immunosupressant activity,[1b] was later shown to possess antiproliferative activity against several tumor cell lines.[2] Further investigation established that (-)-pironetin has a unique mode of action compared to other tubulin binding agents, in that it covalently binds to the α subunit of tubulin.[3]

(-)-Pironetin consists of an α,β-unsaturated δ lactone possessing a linear alkyl chain containing four contiguous stereogenic centers and a *trans*-olefin. To date, several other syntheses of (-)-pironetin and its derivatives have been reported.[4]

Most recently, Cossy reported an approach to (-)-pironetin utilizing enantioselecive crotylation and allylation methods,[4m] Enders and coworkers have disclosed a convergent total synthesis relying on RAMP/SAMP hydrazone methodology,[4l] and Nelson and coworkers have completed a total synthesis employing acyl halidealdehyde cyclocondensations to construct the polypropionate units present in pironetin.[4k]

We have previously demonstrated the ability to execute iterative propionate aldol reactions for the synthesis of complex polypropionates in the context of the completion of a formal synthesis of deoxyerythronolide B.[5] A key goal in our designed approach to (-)-pironetin was to take advantage of an iterative aldol sequence that would exploit not only the syn aldol variant, but also other variations of the titanium tetrachloride mediated aldol additions of *N*-acylthiazolidinethiones to aldehydes and acetals. The demonstration that different types of

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polyketide frameworks found in natural products could be accessible through this technology was seen as an important goal of the synthesis.

The use of chlorotitanium enolates of thiazolidinethione chiral auxiliaries allows access to either “Evans” syn and “non-Evans” syn aldol adducts in high diastereosectivity simply by changing the stoichiometry and nature of the amine base employed. This interesting tunability can be rationalized by a highly ordered transition state, in which the sulfur can either coordinate to the titanium metal center leading to “non-Evans” syn aldol adducts (Figure 1, A), or in the case when a strongly coordinating amine ligand is used, inhibit the thiocarbonyl from chelating to the metal center resulting in “Evans syn” aldol adducts (Figure 1, B).[6]

Access to β-hydroxyl carbonyl subunits such as **5**, has proven more challenging with regard to obtaining high levels of diastereoselectivity due to the lack of substitution at the α carbon of the enolate, however, we recently reported the use of the mesityl-substituted thiazoldinethione chiral auxiliary to access the β-hydroxyl carbonyl subunit in an efficient and highly diastereoselective reaction. The high diastereoselectivity is thought to arise from a highly ordered chair-like transition state (Figure 1, C), though a non-chelate boat-like transition state cannot be ruled out (Figure 1, D).[7]

Direct access to the anti β-hydroxy aldol adducts is not currently possible using the chlorotitanium enolates. Several alternative approaches have been developed to access the β-hydroxy anti aldol adducts.[8] Evans and coworkers have developed an anti aldol reaction employing both oxazolidinones and thiazolidinethiones through the use of magnesium enolates.[8a,8b] Although aromatic aldehydes give highly diastereoselective aldol reactions in high yelds using this method, aliphatic aldehydes give significantly lower conversion. A viable alternative to this method is the acetal aldol, developed by Urpi and coworkers, allowing access to *anti* β-alkoxy-α-methyl aldol adducts.[9] The high diasteroselectivity associated with the acetal aldol is thought to arise through an open transition state, in which the oxacarbenium ion is attacked from the less hindered face of the chelated Z enolate, in an antiperiplanar arrangement (Figure 1, E).[9]

The Urpi anti acetal aldol seemed ideally suited to access the the anti subunit at C8-9 of pironetin since a methoxy group, rather than a free hydroxyl group, resides at C9.[9] Our strategy to access pironetin thus relies on the formation of 5 out of the 6 stereocenters through titanium tetrachloride mediated iterative aldol reactions[5] utilizing the thiazolidinethione chiral auxiliary to execute an anti propionate acetal aldol, an acetate aldol and a syn propionate aldol. Our retrosynthetic analysis is outlined in Scheme 1. We envisioned formation of the Z-enoate of **1** through a modified Horner-Emmons reaction[10] with aldehyde **8**. Aldehyde **8** could be synthesized via an “Evans” syn aldol reaction with aldehyde **10** and thiazoldidinethione **9**. Aldehyde **10** could be accessed via a highly diastereoselective acetate aldol reaction between mesityl-substituted thiazolidinethione **11** and aldehyde **12**. Aldehyde **12** would result from a highly diastereoselective acetal aldol reaction between a chiral dimethylacetal **14** and propionate **13**. The stereocenter at C-10 would be set using an asymmetric alkylation, originally developed by Evans.[11]

The synthesis commenced with treatment of known aldehyde **2**[12] with MeOH and *p*-TsOH to provide acetal **14**. An acetal aldol reaction with the resultant dimethyl acetal **14** and propionate **13** according to the conditions described byUrpi,[9] provided the methylated aldol adduct **15** in a 64% yield with 98:2 dr. The reaction was optimized by employing an excess of the enolate (2 equiv), and using $SnCl_4$, as opposed to $BF_3{}^{-}OEt_2$, as the Lewis acid. The stereochemical outcome is further reinforced by the presence of the alpha stereocenter of the acetal resulting in Felkin control.[9b]

Reductive cleavage[12] of the chiral auxiliary afforded aldehyde **12**, which was subjected to an acetate aldol reaction[7] with thiazolidinethione **11** to afford alcohol **16** in 88% yield and 95:5 dr. An excess of the enolate (1.5 equiv.) was necessary to achieve complete conversion of the aldehyde to the aldol adduct. Protection of alcohol **16** as its triethylsilyl ether delivered the thiazolidinethione **17**. Reductive removal of the auxiliary with diisobutylaluminum hydride furnished aldehyde **10**. Aldehyde **10** was then subjected to "Evans" syn aldol reaction conditions[6] employing an excess of the enolate of thione **9**, affording aldol adduct **18** in >20:1 *dr* and a 65% yield. Silylation of the resulting alcohol provided triethylsilyl ether **19**, which was then exposed to diisobutylaluminum hydride to effect reductive cleavage of the chiral auxiliary affording aldehyde **8**. Thus, three iterative aldol reactions (8 steps overall) allowed the incorporation of 5 of the stereocenters of pironetin affording aldehyde **8**.

Aldehyde **8** was treated with excess phosphonate **20**, to effect a modified Horner-Emmons reaction to access α,β-unsaturated ester **21** as a 10:1 mixture of *E/Z*-isomers. Exposure of **21** to PPTS in 10:1 CH_2Cl_2/MeOH provided only the unprotected diol, however, upon heating ester **21** with PPTS in 10:1 benzene/MeOH, both protecting groups were removed and lactonization was induced to furnish (-)-pironetin **1** in 63% yield. Synthetic **1** was identical in all aspects to the natural product.

In summary, the enantioselective total synthesis of (-)-pironetin has been completed in 11 steps from previously prepared aldehyde **2** with an overall yield of 12.5%. In addition, the versatility of chlorotitanium mediated asymmetric aldol reactions was demonstrated through a sequence of steps to rapidly construct pironetin in a highly stereoselective fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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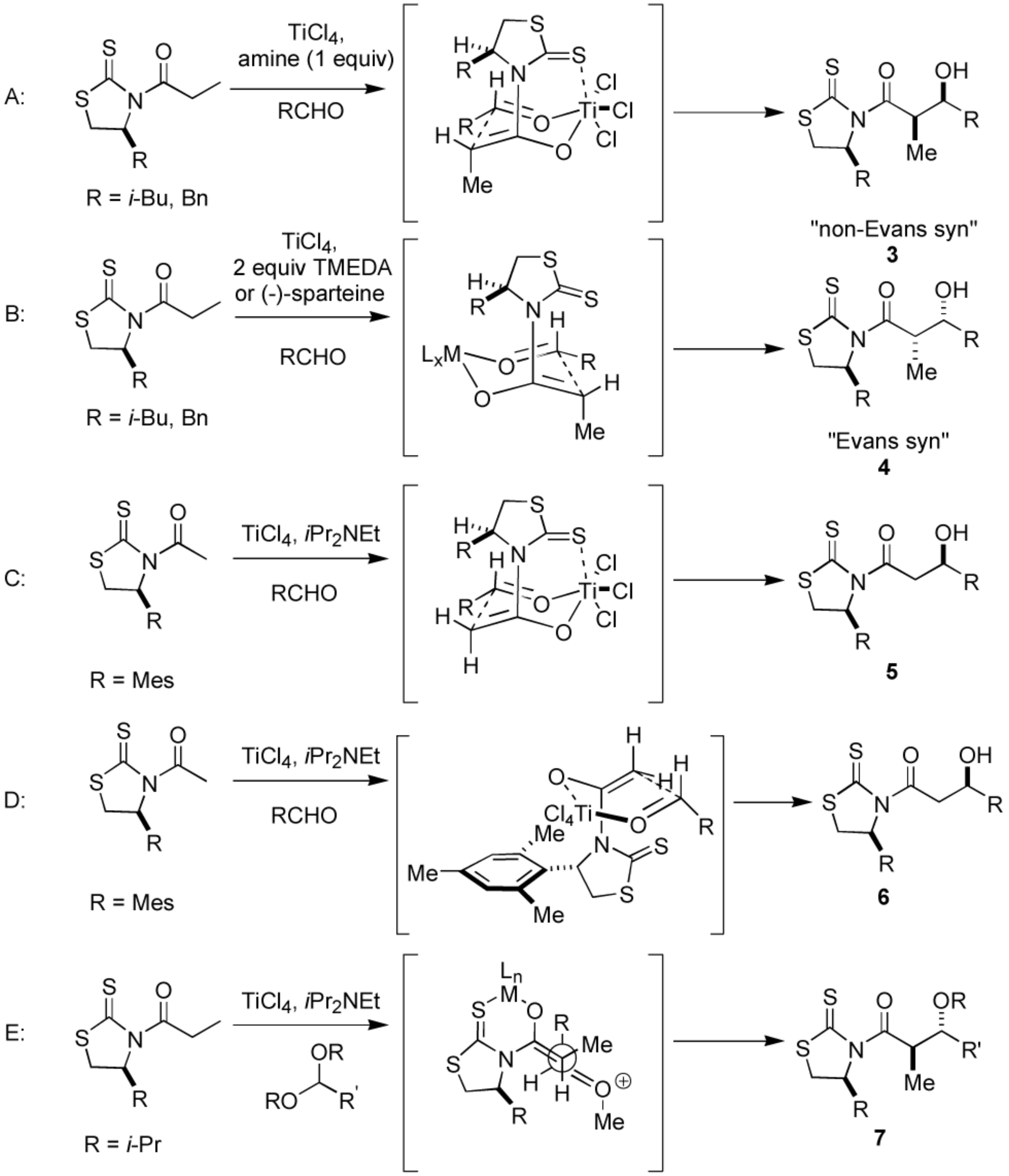
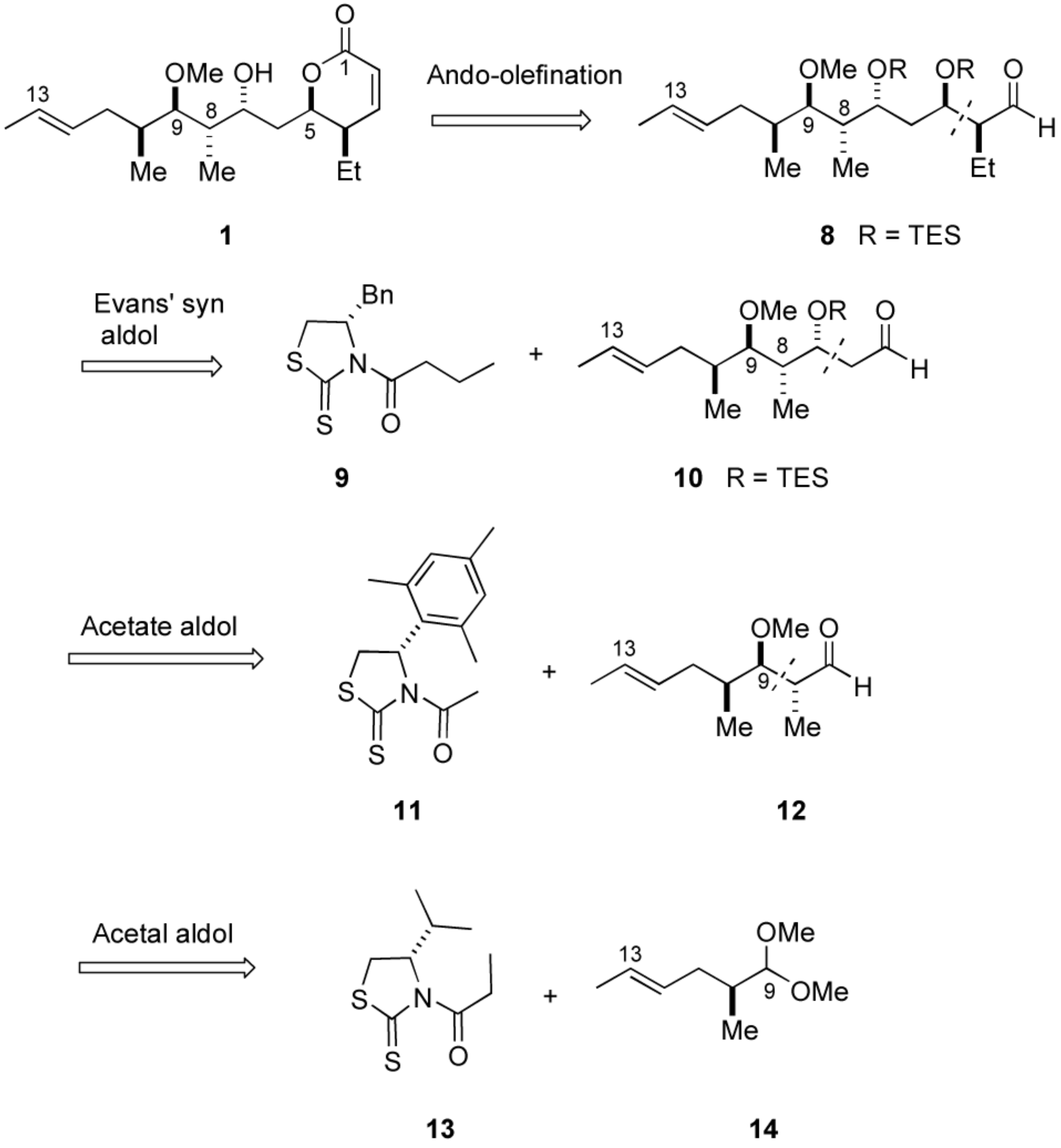
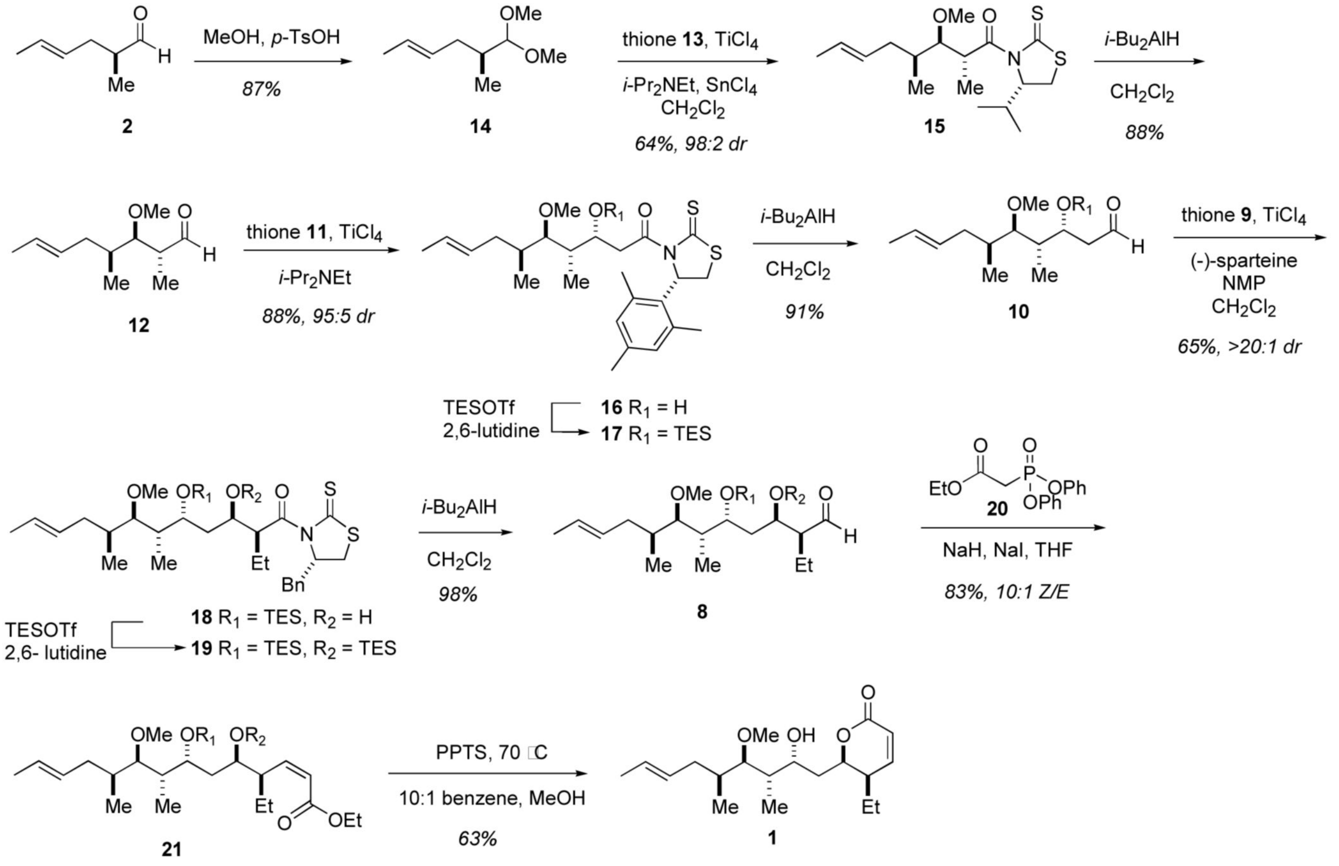


Figure 1.

Proposed transition states to access (A) “non-Evans” syn aldol adducts, (B) “Evans” syn aldol adducts, (C) & (D) β-hydroxy aldol adducts, and (E) anti β-alkoxy-α-methyl aldol adducts.


1
Ando-olefination
8 R = TES
Evans' syn aldol
9
10 R = TES
Acetate aldol
11
12
Acetal aldol
13
14
OMe
OH
OR
Me
Et
Bn
13
9
8
5
1

Scheme 1.


2
MeOH, p-TsOH
87%
14
thione 13, TiCl4
i-Pr2NEt, SnCl4
CH2Cl2
64%, 98:2 dr
15
i-Bu2AlH
CH2Cl2
88%
12
thione 11, TiCl4
i-Pr2NEt
88%, 95:5 dr
i-Bu2AlH
CH2Cl2
91%
10
thione 9, TiCl4
(-)-sparteine
NMP
CH2Cl2
65%, >20:1 dr
TESOTf
2,6-lutidine
16 R1 = H
17 R1 = TES
i-Bu2AlH
CH2Cl2
98%
8
20
NaH, NaI, THF
83%, 10:1 Z/E
TESOTf
2,6- lutidine
18 R1 = TES, R2 = H
19 R1 = TES, R2 = TES
21
PPTS, 70 □C
10:1 benzene, MeOH
63%
1

Scheme 2.