Pergamon

Tetrahedron Letters 39 (1998) 8313–8316

TETRAHEDRON LETTERS

Total Synthesis of (–)-Pironetin

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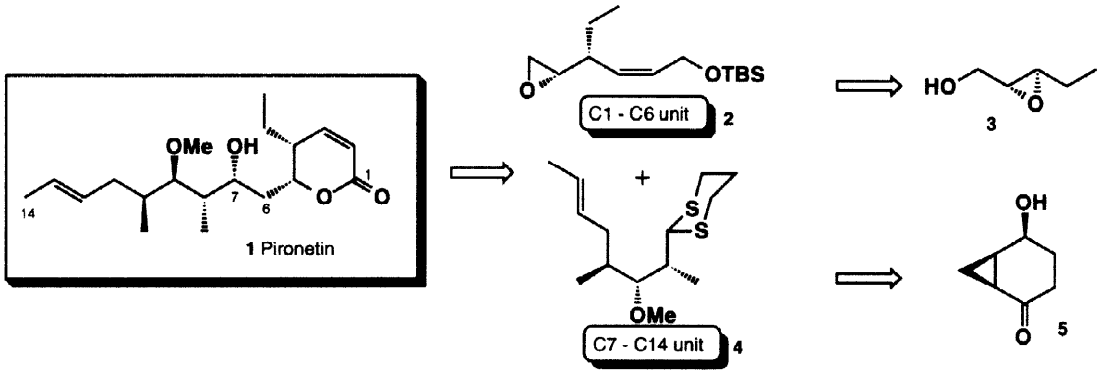
Received 4 July 1998; revised 1 September 1998; accepted 4 September 1998

Abstract: *The convergent total synthesis of (–)-pironetin using a chiral building block, (1S,5S,6R)-5-hydroxybicyclo[4.1.0]heptan-2-one* ***5*** *is described. Both the dithiane* ***4*** *and the epoxide* ***2*** *with proper substituents were employed as coupling partners to construct the whole carbon skeleton* ***15****, which was converted to pironetin* ***1*** *in a few steps.*

In 1993, two groups independently isolated a novel unsaturated δ-lactone derivative, pironetin **1** (PA-48153C), from the fermentation broths of *Streptomyces prunicolor* PA-48153 and *Streptomyces* sp. NK10958, respectively.[1] Yoshida *et al.* reported that **1** shows immunosuppressive activity on the responses of T and B lymphocytes to mitogens.[1a] Alternatively, its potent activity as a plant growth regulator, which might be applicable to produce dwarf plants, was also described by Kobayashi and coworkers.[1b,c] Several total syntheses[2] of **1** have been reported to date, but we show here a novel approach to **1** *via* a convergent route using our chiral building block, (*1S,5S,6R*)-5-hydroxybicyclo[4.1.0]heptan-2-one **5**, which is available in large quantity by simple operation,[3a,b] and we succeeded in total synthesis of natural products, sporogen-AO 1,[3b] other phytotoxins[3c] and dendryphiellin C[3d] using this compound. We dissected pironetin at C6-C7 and employed, as a key step, the coupling of epoxide **2** with the dithiane **4** which would be derived from **5** (Scheme 1).



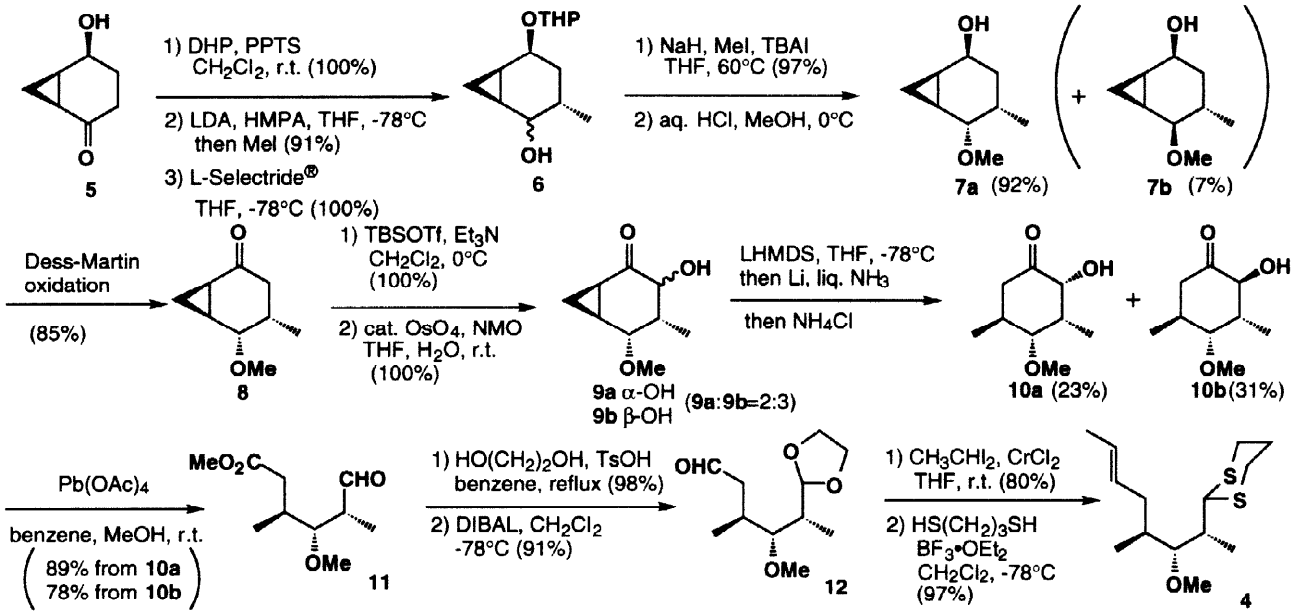
Scheme 1: Synthetic plan

Preparation of the C7-C14 unit (Scheme 2)**:** Stereoselective methylation of the THP ether of **5** (no observation of the β-methyl isomer), followed by selective reduction with L-Selectride® gave an inseparable mixture of four diastereomers **6**. After etherification, removal of the THP group afforded separable isomers **7a**[4] and **7b**[4] in a ratio of 13 to 1, thereby showing the high selectivity of the hydride reduction. The desired major isomer **7a** was oxidized by the Dess-Martin procedure[5] to give ketone **8**.[4]

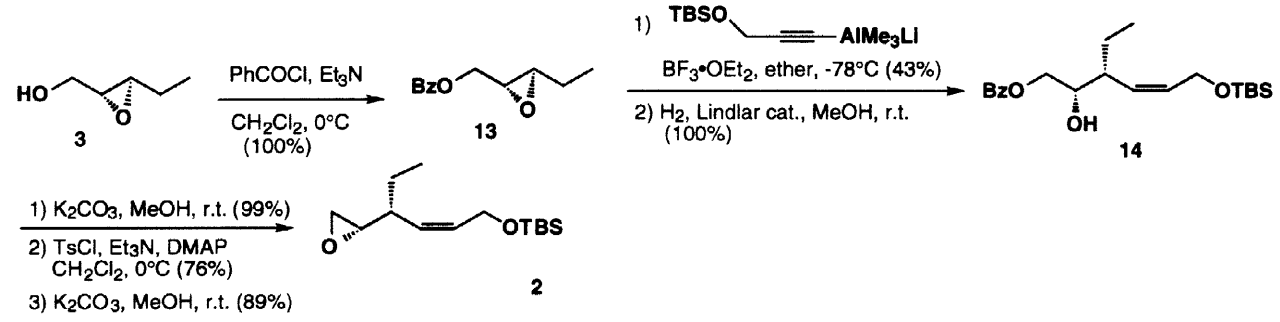
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01860-7

Though oxidation of **8** to ketol **9** with Davis' reagent[6] or *m*-CPBA *via* the silyl enol ether resulted in low yield, treatment of the silyl enol ether of **8** with osmium tetroxide gave **9** in quantitative yield as an inseparable mixture (α:β=2:3). Reduction of the cyclopropylketone moiety *via* lithium alkoxide of **9** under Birch conditions afforded a separable mixture of **10a** and **10b** in moderate yields. The ketol moiety of **10a** and **10b** was oxidatively cleaved with lead tetraacetate in benzene-methanol to give the single aldo-ester **11**. Acetalization of **11** followed by reduction of the ester group with DIBAL gave aldehyde **12**. Introduction of the C2-unit *via* Takai's protocol[7] as *E*-olefin followed by thioacetalization of ethylene acetal afforded dithiane **4** having the C7-C14 unit of pironetin (overall 14 steps, 21.4% from **5**).

Preparation of the C1-C6 unit (Scheme 3): The known epoxy alcohol **3** (93% e. e.)[8a] prepared by Sharpless' asymmetric epoxidation[8b] was benzoylated to give **13**. Regioselective epoxide opening of **13** using acetylenic alanate,[9] followed by hydrogenation over Lindlar catalyst gave *Z*-homoallylalcohol **14**. Methanolysis of benzoate, tosylation of the primary hydroxl group and the following epoxide formation afforded C1-C6 unit **2** (overall 6 steps, 28.8% from **3**).



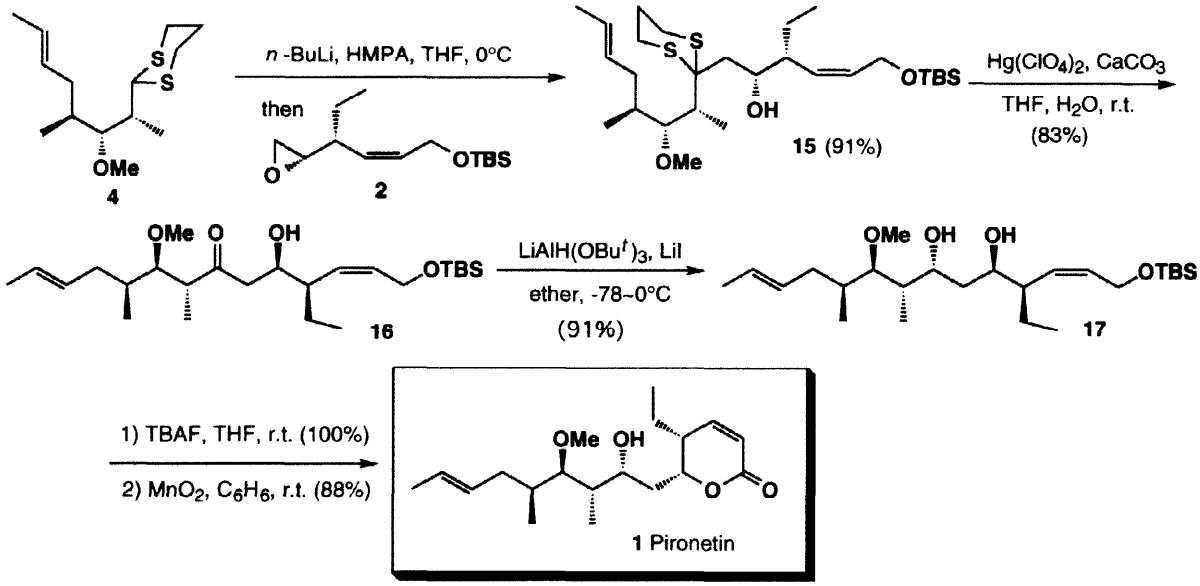
Scheme 2: Preparation of C7-C14 unit



Scheme 3: Preparation of C1-C6 unit

Coupling and synthesis of pironetin (Scheme 4): Coupling reaction of two units, the dithiane **4** and the epoxide **2**, successfully gave the product with the whole skeleton **15** in high yield. The key feature of this reaction is that anion formation and treatment of **4** with *n*-BuLi at 0 ° C for a short period of time (5 minutes) are requisite conditions. The reaction under usual conditions, for example, *t*-BuLi at lower temperature (-78 ° C), gave no products. Mercuric ion assisted hydrolysis of the thioacetal **15** gave ketol **16**. Selective reduction of β-hydroxyketone **16** by Mori's method[10] afforded *anti*-diol **17** predominantly (91:9).[11] Finally, desilylation and oxidation with manganese dioxide afforded pironetin **1**. The ^{1}H and ^{13}C NMR and IR spectra, optical rotation,[12] melting point[13] were identical with reported data.

In conclusion, we have succeeded in total synthesis of (−)-pironetin *via* a convergent route in overall 12.9% yield through 19 steps from **5**. Also, our chiral building block **5** was proved to be extremely versatile for natural products synthesis. Further study on the synthesis of related analogs is in progress and these results, including biological data, will be reported in due course.



Scheme 4: Completion of pironetin synthesis

Acknowledgements: We gratefully thank Dr. Masaru Kido and Mr. Masahiko Bando of Otsuka Pharmaceutical Co., Ltd., for X-ray analysis of **20a**, Dr. Shinichi Kobayashi of Nippon Kayaku Co., Ltd., for the ^{1}H and ^{13}C NMR and IR spectra of natural pironetin. This work was supported in part by a Grant-in Aid from the Ministry of Education, Science, Sports and Culture of Japan.

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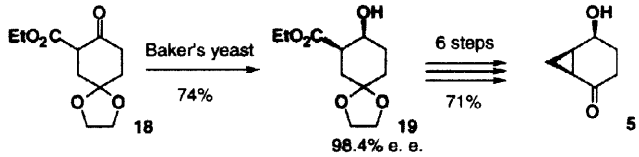
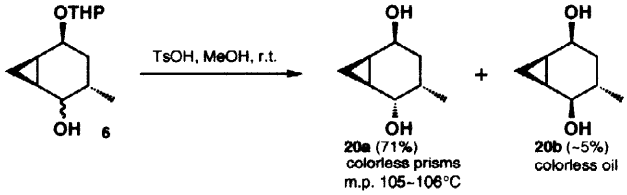
Preparation of **5** is as follows.



4) The stereochemistry of **7a**, **7b**, and **8** could not be determined by NMR spectroscopy, but was confirmed by X-ray analysis of crystalline diol **20a**.



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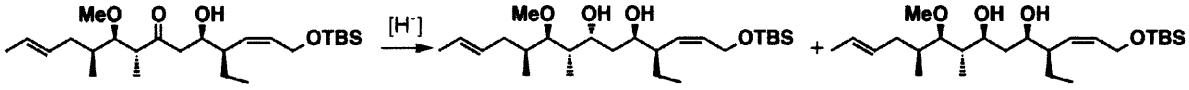
11) Other reduction conditions and results are as follows.



16 17 17'

Entry	Reagent	Solvent	Temp(°C)	17(*anti*):17'(*syn*)	Yield(%)	Reference
1	$NaBH(OAc)_3$	AcOH, CH_3CN	0	49 : 51	77	14
2	$Me_4NBH(OAc)_3$	AcOH, CH_3CN	-20	64 : 36	94	15
3	$Me_4NBH(OAc)_3$	Acetone	-78	59 : 41	86	15
4	L-Selectride®	THF	-78	62 : 38	90	
5	$LiAlH_4$, LiI	Ether	-78	30 : 70	92	16
6	$LiAlH(OBu^t)_3$, LiI	Ether	-78	91 : 9	100	10
7	Isobutyraldehyde, SmI_2	THF	-10	-	No reaction	17

12) $[\alpha]_D^{25}$= −150.0° (*c* 0.52, $CHCl_3$). lit. $[\alpha]_D^{27}$= −143.7° (*c* 0.5, $CHCl_3$),[1a] $[\alpha]_D^{20}$= −136.6° (*c* 1.0, $CHCl_3$).[1b]

13) mp 77~78 °C, lit. 78~79 °C.

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17) Intramolecular Tishchenko reduction, see: Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.