Natural Product Synthesis

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Asymmetric Total Synthesis of the Immunosuppressant (−)-Pironetin**

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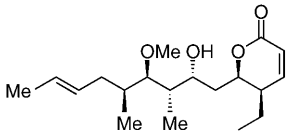
Independently isolated by Yoshida et al.[1] and Kobayashi and co-workers[2] from *Streptomyces sp.* NK-10958 and the fermentation broths of *Streptomyces prunicolor* PA-48153, (−)-Pironetin (**1**) was found to display plant-growth-regulatory[2a] as well as immunosuppressive activities[1a] similar to those exhibited by cyclosporin A (CsA) and FK-506.[3] More recently, (−)-pironetin has since been identified as a strong antitumor agent that influences the dynamics of the tubulin–microtubules system by inhibiting the polymerization of tubulin.[4] Interestingly, whereas other antitumor agents such as colchicin, vinblastin, rhizoxin, and epothilone B, bind to β-tubulin, (−)-pironetin was shown to bind to the α subunit of tubulin.[4e]



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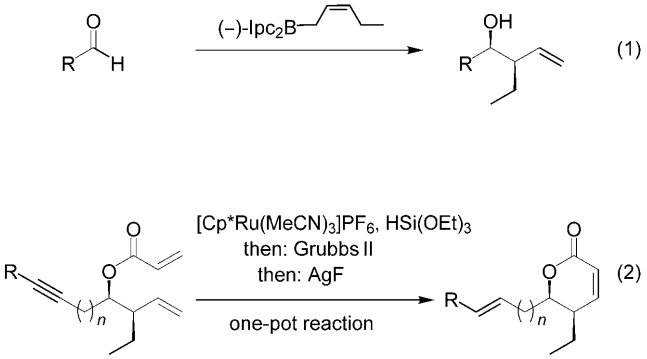
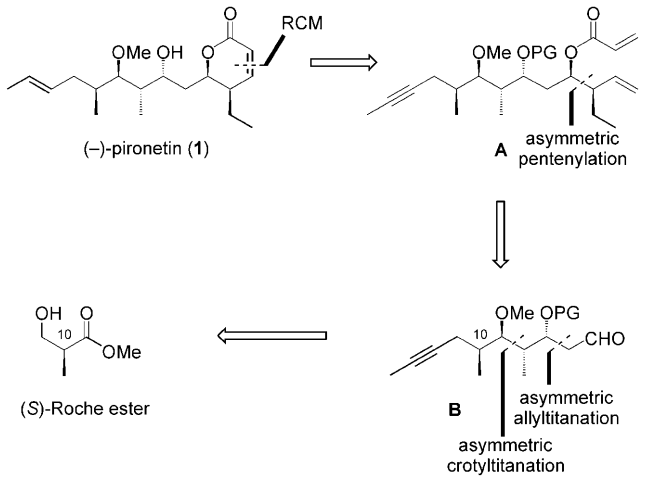
Owing to the very limited natural availability of (−)-pironetin, as well as its interesting mode of action and its unique structure, this natural product has been the focus of considerable synthetic interest, which has resulted in the development of several total syntheses.[5] Herein we report a highly stereoselective and straightforward synthesis of (−)-pironetin (**1**) for which we developed two novel and efficient synthetic methodologies: a stereoselective boron-mediated pentenylation reaction[6] [Scheme 1, Eq. (1)] and a one-pot hydrosilylation/ring-closing metathesis (RCM)/protodesilylation reaction [Scheme 1, Eq. (2)].

Our strategy for the synthesis of (−)-pironetin (**1**) is depicted in Scheme 2. Thus, we planned to introduce the δ-lactone moiety and reduce the triple bond stereoselectively by subjecting compound **A** to a RCM and a hydrosilylation/protodesilylation sequence. Compound **A** was in turn envisioned to arise from aldehyde **B** through a highly diastereo- and enantioselective Brown-type pentenylation reaction, which should establish the *syn* relationship between the substituents at C4 and C5. Finally, aldehyde **B** could be synthesized from the readily available (*S*)-Roche ester, whereby two stereoselective titanium-mediated reactions, a crotylation and an allylation, would control the configuration of the three stereogenic centers introduced at C7, C8, and C9.

The synthesis of (−)-pironetin (**1**) began with the tosylation of commercially available (*S*)-Roche ester, followed by the reduction of the ester moiety to the corresponding aldehyde **2** with diisobutylalumninum hydride (DIBAL-H; Scheme 3). The aldehyde **2** was then subjected to a diastereo- and enantioselective crotylation using the complex (*R*,*R*)-[Ti]-



Scheme 1. Stereoselective boron-mediated pentenylation [Eq. (1)], and one-pot hydrosilylation/RCM/protodesilylation [Eq. (2)]. Cp* = pentamethylcyclopentadienyl, Grubbs II = Grubbs second-generation catalyst, Ipc = isopinocampheyl.



Scheme 2. Retrosynthetic analysis of (−)-pironetin. PG = protecting group.

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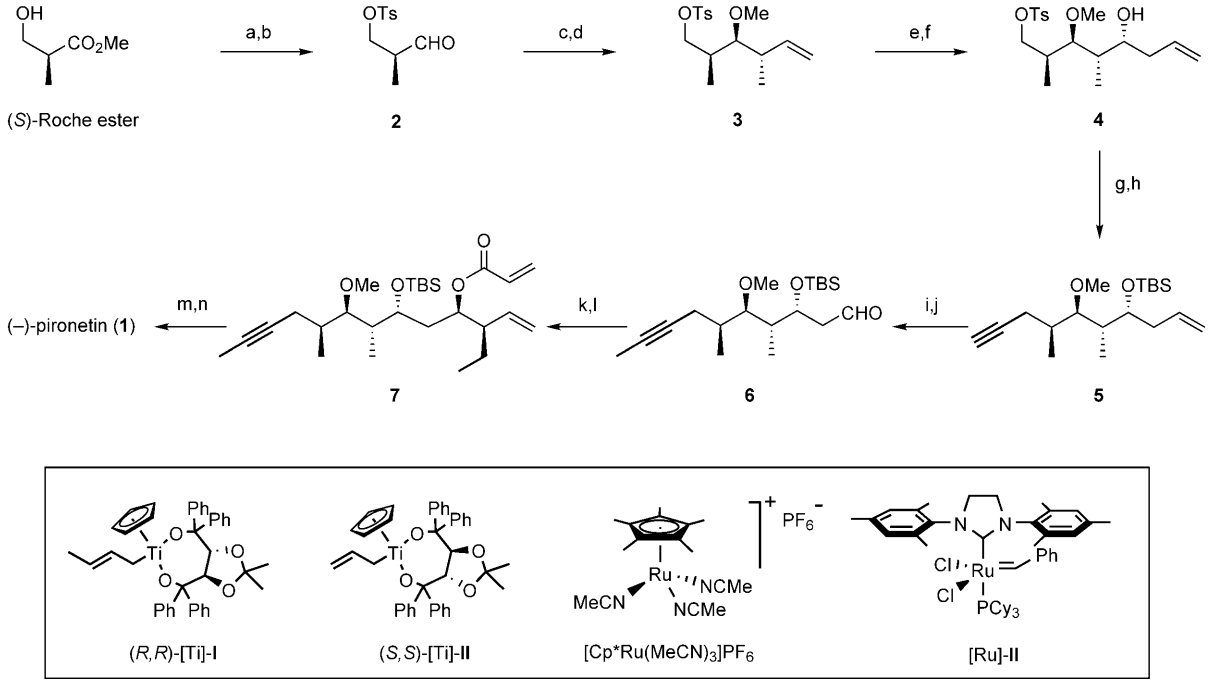
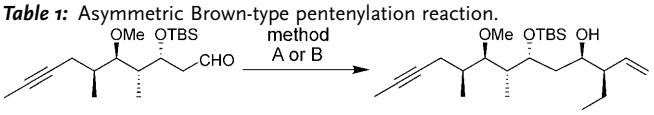


Scheme 3. Total synthesis of (−)-pironetin: a) TsCl (1.2 equiv), DIPEA (1.2 equiv), DMAP (0.05 equiv), CH_2Cl_2, 0 °C→RT, 2 h; b) DIBAL-H in toluene (1.2 equiv), toluene, −78 °C, 2 h; c) (*R*,*R*)-[Ti]-**I** (1.5 equiv), Et_2O, −78 °C, 12 h, 60% (3 steps); d) MeOTf (7 equiv), 2,6-di-*tert*-butylpyridine (8 equiv), $CHCl_3$, 65 °C, 12 h, 90%; e) O_3, then PPh_3 (1.5 equiv), CH_2Cl_2, −78 °C; f) (*S*,*S*)-[Ti]-**II** (1.3 equiv), Et_2O, 12 h, −78 °C, 56% (2 steps); g) TBSOTf (1.3 equiv), 2,6-lutidine (1.6 equiv), CH_2Cl_2, 0 °C, 2 h; h) HC≡CLi·EDA (5 equiv), DMSO, RT, 12 h, 80% (2 steps); i) *n*BuLi (1.2 equiv), MeI (3 equiv), THF, −78 °C; j) OsO_4 (0.05 equiv), NMO (1.5 equiv), acetone/H_2O, then $NaIO_4$ (1.5 equiv), THF/pH 7 buffer, 82% (2 steps); k) *cis*-2-pentene (6 equiv), *n*BuLi (2 equiv), *t*BuOK (2 equiv), (−)-Ipc_2BOMe (2.5 equiv), $BF_3{\cdot}Et_2O$ (2.5 equiv), THF/Et_2O, −78 °C, 12 h; l) acryloyl chloride (1.5 equiv), DIPEA (3 equiv), 0 °C→RT, 1 h, 65% (2 steps); m) $HSi(OEt)_3$ (1.2 equiv), CH_2Cl_2, 0 °C, then $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), 0 °C→RT, then Grubbs second-generation catalyst (5 mol%), 40 °C, then AgF (2.4 equiv), MeOH/H_2O/THF, RT; n) aqueous HF, CH_3CN/THF, 0 °C→RT, 64% (2 steps). Cy = cyclohexyl, DIPEA = diisopropylethylamine, DMAP = 4-dimethylaminopyridine, EDA = ethylenediamine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

I to generate the desired homoallylic alcohol (d.r. > 95:5, 60% yield over three steps), which was subsequently methylated with methyl triflate in the presence of 2,6-di-*tert*-butylpyridine in $CHCl_3$ at reflux.[7] This methylation procedure was chosen to avoid basic conditions, which would lead to the formation of the undesired oxetane. The resulting ether **3** was treated with ozone followed by PPh_3 to generate the corresponding aldehyde, which was treated immediately with the complex (*S*,*S*)-[Ti]-**II** to afford the homoallylic alcohol **4** in good yield and with excellent diastereoselectivity (d.r. > 95:5, 50% yield over three steps).

The homoallylic alcohol **4** was protected as a *tert*-butyldimethylsilyl ether before the propyne group was introduced in two steps through displacement of the tosylate group with lithium acetylide in dimethyl sulfoxide (DMSO)[8] and subsequent treatment of the terminal alkyne with *n*BuLi followed by methyl iodide. Selective oxidative cleavage of the double bond with OsO_4, *N*-methylmorpholine *N*-oxide (NMO), and $NaIO_4$ gave aldehyde **6** (66% yield over two steps), which was subjected to a highly stereoselective boron-mediated pentenylation reaction inspired Brown's asymmetric crotylation protocol[9] (Table 1, entry 2). Thus, aldehyde **6** was treated with the preformed *Z*-configured boron complex resulting from the reaction between (−)-methoxydiisopinocampheylborane ((−)-Ipc_2BOMe), *cis*-2-pentene, and the Schlosser base. The corresponding homoallylic alcohol was isolated in good yield and with an exclusively *syn* relationship between the two substituents at C4 and C5. Acylation with acryloyl chloride then afforded the key intermediate **7** in 65% yield (over two steps). It is noteworthy that all our attempts to use the conditions reported by Roush et al.[10] also led to the desired homoallylic alcohol, however, the observed selectivity was rather poor (Table 1, entry 1).

Table 1: Asymmetric Brown-type pentenylation reaction.



6 **8**

Entry	Method[a]	*syn*/*anti*[b]	d.r.[b]	Yield [%][c]
1	A	> 95:5	1.8:1	62
2	B	> 95:5	21:1	68

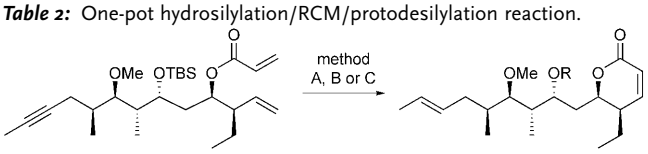
[a] Method A: *cis*-2-pentene, *t*BuOK, *n*BuLi, THF, −78 °C→−65 °C, then $iPrO_3B$, then 1 M HCl, (*R*,*R*)-diisopropyl tartrate, then **6**, toluene, −78 °C. Method B: *cis*-2-pentene, *t*BuOK, *n*BuLi, THF, −78 °C, then (−)-Ipc_2BOMe, $BF_3{\cdot}Et_2O$, **6**, THF, −78 °C. [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield of the isolated product.

This 12-step sequence set the stage for our final one-pot hydrosilylation/RCM/protodesilylation reaction, which was

developed after multiple attempts at the RCM of substrate **7** had failed as a result of the presence of the alkyne moiety (Table 2, entry 1). To circumvent the problem, we decided to switch the order of our synthetic sequence and performed the ruthenium-catalyzed hydrosilylation reaction prior to the RCM step. Thus, dienyne **7** was first hydrosilylated under the conditions developed by Trost and Ball[11] with $HSi(OEt)_3$ in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), and subjected subsequently to RCM with the second-generation Grubbs catalyst ([Ru]-**II**; 5 mol%) to afford the corresponding δ-lactone. The δ-lactone was then treated with AgF to remove the two silyl groups (Table 2, entry 2). However, although these conditions enabled the construction of both the α,β-unsaturated δ-lactone moiety and the substituted alkene with the *E* configuration in a one-pot process, final deprotection of the alcohol at C7 with aqueous HF was necessary to generate the natural product. Thus, **1** was isolated in 64% yield over two steps (Table 2, entry 3). The spectroscopic and physical data of **1** were in accordance with those reported for the natural product ($[\alpha]_D^{20} = -133.6$ ($c = 3.5$, $CDCl_3$); lit. $[\alpha]_D^{20} = -137.5$ ($c = 3.4 \times 10^{-3}$, $CDCl_3$)).[1,2,5]

In conclusion, we have described a short and highly stereoselective synthesis of (−)-pironetin (**1**), which was obtained in 14 steps and 8.2% overall yield from the commercially available (*S*)-Roche ester. The stereogenic centers at C4 and C5 were generated in the desired configuration by use of a stereoselective boron-mediated pentenylation, whereas those at C7, C8, and C9 resulted from stereoselective titanium-mediated crotylation and allylation reactions. Finally, the α,β-unsaturated δ-lactone and the *E* alkene were formed in a single step through a one-pot hydrosilylation/RCM/protodesilylation sequence. This synthesis of (−)-pironetin is the shortest reported to date. Furthermore, as the configuration of all stereogenic centers can be controlled readily through the selection of the appropriate chiral auxiliary, and as diversity in the olefinic side chain can be introduced by simple alkylation of the terminal alkyne, this approach allows straightforward access to any of the various stereoisomers and a wide array of structural analogues.

Table 2: One-pot hydrosilylation/RCM/protodesilylation reaction.



7

R = TBS: **9**
R = H: (−)-pironetin (**1**)

Entry	Method[a]	Product	Yield [%][b]
1	A	–	–
2	B	**9**	78
3	C	**1**	64

[a] Method A: Grubbs second-generation catalyst (5 mol%), 40°C, then $HSi(OEt)_3$ (1.2 equiv), CH_2Cl_2, 0°C, then $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), 0°C→RT, then AgF (2.4 equiv), MeOH/H_2O/THF, RT. Method B: $HSi(OEt)_3$ (1.2 equiv), CH_2Cl_2, 0°C, then $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), 0°C→RT, then Grubbs second-generation catalyst (5 mol%), 40°C, then AgF (2.4 equiv), MeOH/H_2O/THF, RT. Method C: $HSi(OEt)_3$ (1.2 equiv), CH_2Cl_2, 0°C, then $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), 0°C→RT, then Grubbs second-generation catalyst (5 mol%), 40°C, then AgF (2.4 equiv), MeOH/H_2O/THF, RT, then aqueous HF, CH_3CN/THF, 0°C→RT. [b] Yield of the isolated product.

Experimental Section

Pentenylation of **6**: *n*BuLi (2 equiv) was added dropwise to a stirred suspension of *t*BuOK (2 equiv) and *cis*-2-pentene (6 equiv) in THF at −78°C. The reaction mixture was then stirred for 5 min at −50°C. The resulting orange solution was cooled to −78°C, and a solution of (−)-methoxydiisopinocampheylborane in Et_2O (0.5 M; 2.5 equiv) was added dropwise. The reaction mixture was stirred for 30 min at −78°C, and then boron trifluoride diethyl etherate (2.5 equiv) was added, followed by **6** (1 equiv). The reaction mixture was stirred for a further 5 h at the same temperature, treated with a 3 M solution of NaOH and H_2O_2, and heated at reflux for 1 h. The mixture was then extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel afforded the desired homoallylic alcohol.

Hydrosilylation/RCM/protodesilylation of **7**: Triethoxysilane (1.2 equiv) was added to a solution of **7** (1 equiv) in CH_2Cl_2 (0.1 M solution) at 0°C, followed by $[Cp^*Ru(MeCN)_3]PF_6$ (0.01 equiv). The mixture was allowed to warm to room temperature and was stirred until no starting material remained. The second-generation Grubbs catalyst was then added (0.05 equiv), and the reaction mixture was stirred at 40°C until complete conversion was observed. The reaction mixture was allowed to cool to room temperature, and then AgF (2.4 equiv) was added, followed by MeOH (0.01 M), H_2O (0.01 M), and THF (0.1 M). Stirring was continued in the dark until consumption of the silylated intermediate was complete. The reaction mixture was then filtered through Celite, extracted with CH_2Cl_2, and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel afforded the lactone product.

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[1] a) T. Yoshida, K. Koizumi, Y. Kawamura, K. Matsumoto, H. Itazaki, Japan Patent Kokai 5-310726, **1993**; b) T. Yoshida, K. Koizumi, Y. Kawamura, K. Matsumoto, H. Itazaki, European Patent 560389A1, **1993**; c) K. Yasui, Y. Tamura, T. Nakatani, K. Kawada, M. Ohtani, *J. Org. Chem.* **1995**, *60*, 7567–7574.

[2] a) S. Kobayashi, K. Tsuchiya, T. Harada, M. Nishide, T. Kurokawa, T. Nakagawa, N. Shimada, K. Kobayashi, *J. Antibiot.* **1994**, *47*, 697–702; b) S. Kobayashi, K. Tsuchiya, T. Harada, M. Nishide, T. Kurokawa, T. Nakagawa, N. Shimada, T. Iitaka, *J. Antibiot.* **1994**, *47*, 703–707.

[3] Whereas CsA and FK-506 only antagonize T-cell activation, (−)-pironetin has a suppressive effect on the responses of both T and B lymphocytes to mitogens.

[4] a) K. Yasui, Y. Tamura, T. Nakatani, I. Horibe, K. Kawada, K. Koizumi, R. Suzuki, M. Ohtani, *J. Antibiot.* **1996**, *49*, 173–180; b) M. Kondoh, T. Usui, S. Kobayashi, K. Tsuchiya, K. Nishikawa, T. Nishikiori, T. Mayumi, H. Osada, *Cancer Lett.* **1998**, *126*, 29–32; c) M. Kondoh, T. Usui, T. Nishikiori, T. Mayumi, H. Osada, *Biochem. J.* **1999**, *340*, 411–416; d) H. Watanabe, H. Watanabe, T. Usui, M. Kondoh, H. Osada, T. Kitahara, *J. Antibiot.* **2000**, *53*,

540 – 545; e) T. Usui, H. Watanabe, H. Nakayama, Y. Tada, N. Kanoh, M. Kondoh, T. Asao, K. Takio, H. Watanabe, K. Nishikawa, T. Kitahara, *Chem. Biol.* **2004**, *11*, 799 – 806.

[5] a) K. Yasui, Y. Tamura, T. Nakatani, K. Kawada, M. Ohtani, *J. Org. Chem.* **1995**, *60*, 7567 – 7574; b) M. K. Gurjar, J. T. Henri, Jr., D. S. Bose, A. V. R. Rau, *Tetrahedron Lett.* **1996**, *37*, 6615 – 6618; c) M. K. Gurjar, A. Chakrabarti, A. V. R. Rao, *Heterocycles* **1997**, *45*, 7 – 10; d) N. Chida, M. Yoshinaga, T. Tobe, S. Ogawa, *Chem. Commun.* **1997**, 1043 – 1044; e) H. Watanabe, H. Watanabe, T. Kitahara, *Tetrahedron Lett.* **1998**, *39*, 8313 – 8316; f) T. Kitahara, H. Watanabe, *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 884 – 895; g) H. Watanabe, H. Watanabe, M. Bando, M. Kido, T. Kitahara, *Tetrahedron* **1999**, *55*, 9755 – 9776; h) H. Watanabe, H. Watanabe, T. Usui, M. Kondoh, H. Osada, T. Kitahara, *J. Antibiot.* **2000**, *53*, 540 – 545; i) G. E. Keck, C. E. Knutson, S. A. Wiles, *Org. Lett.* **2001**, *3*, 707 – 710; j) X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438 – 7439; k) D. Enders, S. Dhulut, D. Steinbusch, A. Herrbach, *Chem. Eur. J.* **2007**, *13*, 3942 – 3949.

[6] Hatakeyama et al. have very recently used a similar procedure in their synthesis of phoslactomycin B, see: S. Shibahara, M. Fujino, Y. Tashiro, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2008**, *10*, 2139 – 2142.

[7] D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *Tetrahedron Lett.* **1994**, *35*, 7171 – 7172.

[8] a) K. Toshima, T. Jyojima, N. Miyamoto, M. Katohno, M. Nakata, S. Matsumura, *J. Org. Chem.* **2001**, *66*, 1708 – 1715; b) S. Mouné, G. Niel, M. Busquet, I. Eggleston, P. Jouin, *J. Org. Chem.* **1997**, *62*, 3332 – 3339; c) N. Smith, O. F. Beumel, *Synthesis* **1974**, 441 – 442.

[9] H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 293 – 294.

[10] W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339 – 6348.

[11] B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2001**, *123*, 12726 – 12727.

