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Total Synthesis of PF1163B

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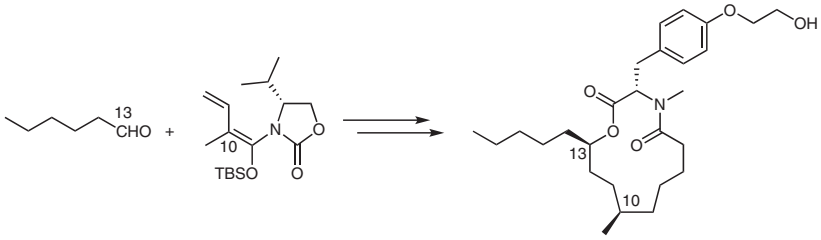

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Abstract A total synthesis of PF1163B has been achieved. The vinylogous Mukaiyama aldol reaction of ketene silyl *N*,*O*-acetal **6** (*ent*-**6**) mediated by excess $TiCl_4$ proceeded with saturated aldehydes to give adduct **10** in moderate yield with moderate stereoselectivity. The major isomer is the diastereomer that was provided by using one equivalent of $TiCl_4$. The Birch reduction of α,β-unsaturated imide **4**, possessing a less hindered side chain, gave **12** in good stereoselectivity by employing 2-isopropylbenzimidazole as a bulky proton source. After elongation of the carbon chain and connection with the amino acid part, we accomplished a total synthesis of PF1163B. These methods constitute a concise synthetic route to obtain polyketides as well as depsipeptides.

Key words PF1163B, total synthesis, vinylogous Mukaiyama aldol reaction, bulky proton source, depsipeptide, stereoswitching

PF1163B (Figure 1) was isolated as a potent antifungal antibiotic from a fermentation broth of *Penicilium* sp. by Sasaki and coworkers.[1] It has been discovered as a potent inhibitor of ergosterol synthesis and has an IC_{50} value of 34 ng/ml.[1] PF1163B is a depsipeptide possessing a polyketide chain with a methyl group and a hydroxy group in a separate position.[1] Despite its attractive biological activity and structure, only two precedent syntheses have been reported.[2,3] In a series of our synthetic studies of polyketides,[4] we have been interested in the structure and biological activities of PF1163B. Herein, we present our synthesis of PF1163B.

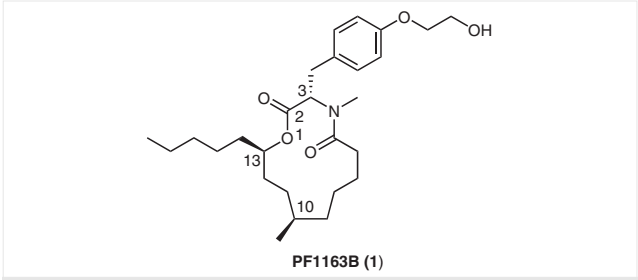
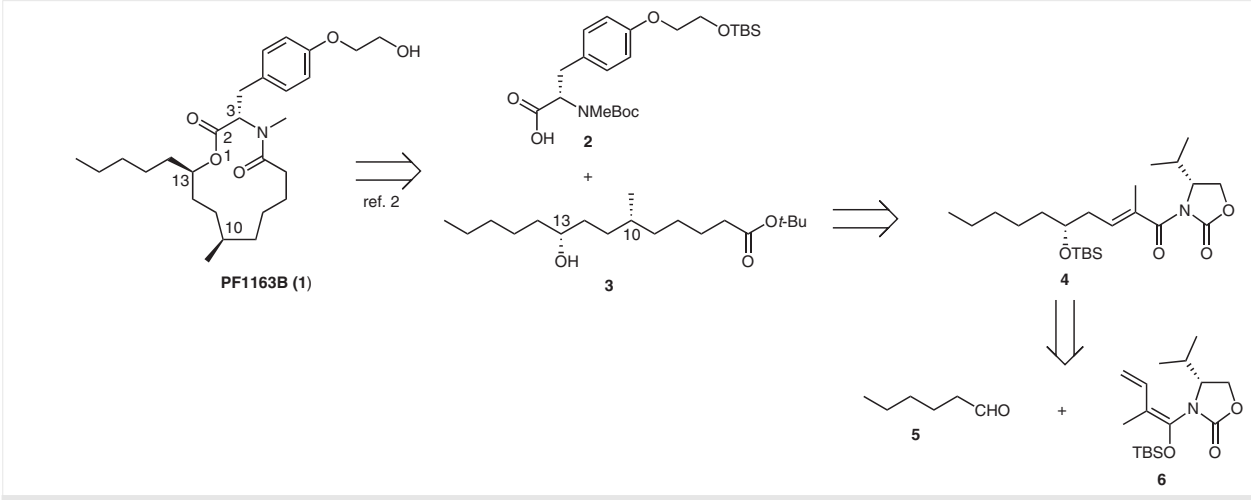


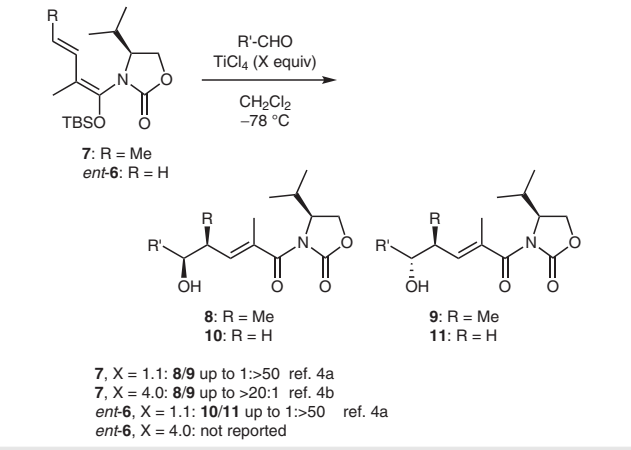
Figure 1 Structure of PF1163B



Scheme 1 Synthetic plan of PF1163B

Our synthetic plan of PF1163B is disclosed in Scheme 1. The macrolide was divided into known segments **2** and **3**.[2] Polyketide segment **3** would be synthesized from α,β-unsaturated imide **4** by stereoselective reduction and carbon elongation. α,β-Unsaturated imide **4** might be constructed by a vinylogous Mukaiyama aldol reaction.

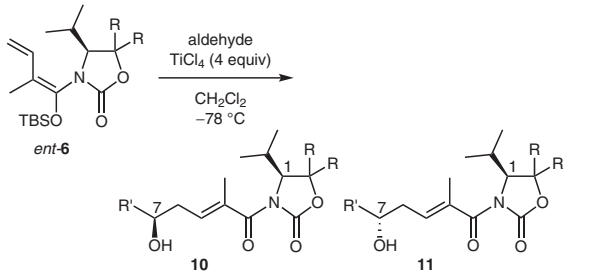
Our previous works on vinylogous Mukaiyama aldol reactions have been developed to proceed in a stereoselective manner (Scheme 2).[4] Treatment of *E*,*E*-vinylketene silyl *N*,*O*-acetal **7** with aldehyde in the presence of 1.1 equivalents of $TiCl_4$ gave *anti* adduct **9** in high stereoselectivity, whereas employment of an excess amount (4.0 equivalents) of $TiCl_4$ afforded *syn* adduct **8** as a predominant product.[4] Therefore, a stereo-switching synthesis of polypropionates became possible by employing the same chiral synthon and the same Lewis acid. Additionally, the reaction of vinylketene silyl *N*,*O*-acetal *ent*-**6**, the terminal methyl group-missing substrate, in the presence of 1.1 equivalents of $TiCl_4$ also proceeded to yield **11** in a stereoselective manner.[4] However, no report has described the reaction of *ent*-**6** with an excess amount of $TiCl_4$. And our desired reaction is the one providing **10**, the diastereomer of **11**. Therefore, we first explored the conditions using vinylketene silyl *N*,*O*-acetal *ent*-**6** with an excess amount of $TiCl_4$ to develop a new stereo-switching reaction.

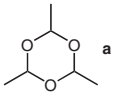
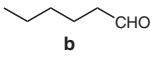
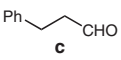
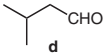
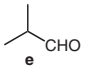
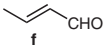
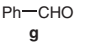


Scheme 2 Previous works on the vinylogous Mukaiyama aldol reaction with vinylketene silyl *N*,*O*-acetals **7** and *ent*-**6**

The vinylogous Mukaiyama aldol reaction of *ent*-**6** with an excess amount of $TiCl_4$ is disclosed in Table 1. The best results to obtain **10** were achieved with use of four equivalents of $TiCl_4$. The reaction with paraldehyde (**a**) gave adducts in low stereoselectivity (entry 1). However, hexanal (**b**) gave δ-hydroxyimide **10**, the diastereomer of known **11**, by using one equivalent of $TiCl_4$, in moderate stereoselectivity (entry 2). In the case of the reaction employing 5',5'-dimethyl derivative of *ent*-**6** as a chiral building block (entry 3), the reaction gave adducts **10** and **11** in low yield without stereoselectivity (entry 3). The reaction with *ent*-**6** and 3-

Table 1 Vinylogous Mukaiyama Aldol Reaction by Using *ent*-**6** with an Excess Amount of $TiCl_4$



Entry	R	Aldehyde	Yield (%)	dr[a]
1	H	 **a**	64	1.6:1
2	H	 **b**	53	4.1:1
3	Me	**b**	12	1:1
4	H	 **c**	55	3.1:1
5	H	 **d**	56	4.2:1
6	H	 **e**	50	3.4:1
7	H	 **f**	0	–
8	H	 **g**	0	–

[a] Determined by 400 MHz ^{1}H NMR spectroscopy.

phenylpropanal (**c**) gave **10** in moderate yield with moderate stereoselectivity (entry 4). Branched aldehydes including β-branched aldehyde (isovaleraldehyde, **d**) and α-branched aldehyde (isobutyraldehyde, **e**) also gave adducts in comparable yields and stereoselectivities (entries 5 and 6). However, unfortunately, the reactions with unsaturated aldehydes including crotonaldehyde (**f**) and benzaldehyde (**g**) gave no adducts (entries 7 and 8) and underwent decomposition to afford the corresponding α,β-unsaturated imide. Therefore, the vinylogous Mukaiyama aldol reaction with vinylketene silyl *N*,*O*-acetal *ent*-**6** in the presence of an excess amount of $TiCl_4$ was found to proceed with saturated aldehydes to give adduct **10** in moderate yield with moderate stereoselectivity.

On the basis of these results, we started the synthesis of the propionate segment of PF1163B (Scheme 3). The reaction of **6** with hexanal **5** in the presence of four equivalents of $TiCl_4$ proceeded as shown in Table 1 to give in 54% yield an inseparable 4:1 mixture of *ent*-**10b** and *ent*-**11b**. The ad-

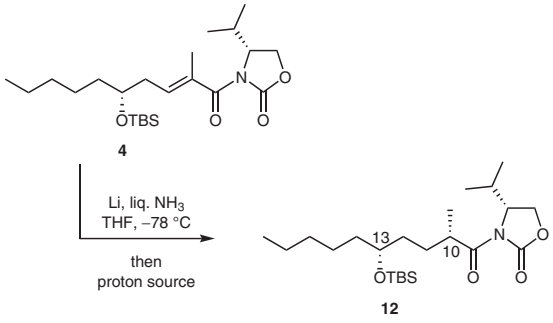
ducts were converted into the corresponding TBS ethers, which were separated by column chromatography. The next reduction of the α,β-unsaturated imide **4** led to the C10 stereogenic center. In our total synthesis of mycocerosic acid, we found that 2-methylbenzimidazole worked as a bulky proton source to protonate the intermediate enolate in the Birch reduction of an α,β-unsaturated imide containing Evans chiral auxiliary in a stereoselective manner.[5] Therefore, we examined the protonation with 2-alkylated benzimidazoles (Table 2).[6,7]

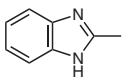
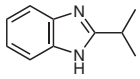
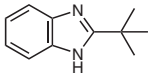
When NH_4Cl was employed as a proton source, no stereoselectivity was observed (Table 2, entry 1). 2-Methylbenzimidazole, reported as an excellent proton source in the total synthesis of mycocerosic acid, gave the reduced products in 64% as a 4.4:1 mixture with the desired isomer **12** as a major isomer (entry 2). 2-Isopropylbenzimidazole gave **12** in comparable yield with 6:1 ratio (entry 3). More bulky 2-*tert*-butylbenzimidazole afforded **12** in moderate yield with low stereoselectivity (entry 4). Therefore, we employed 2-isopropylbenzimidazole as the best proton source in the Birch reduction of **4**.[7]

Synthesis of the polyketide segment **3** and completion of the total synthesis is described in Scheme 4. DIBAL reduction of **4** directly gave aldehyde **13**, which was subjected to Horner–Wadsworth–Emmons reaction[8] with **14** gave α,β,γ,δ-unsaturated ester **15**. Hydrogenation of unsaturated ester **15** gave saturated ester **16**, which was subjected to desilylation to give polyketide segment **3**. Spectral data of **3** were identical to those of reported **3**.[2] Thus, configurations of C10 and C13 positions were confirmed. Polyketide **3** was coupled with tyrosine derivative **2**[9] by Yamaguchi esterification to give ester **17**. Following known procedure,[2] removal of the *tert*-butyl groups and the TBS group was followed by intramolecular cyclization to provide PF1163B (**1**).[10]

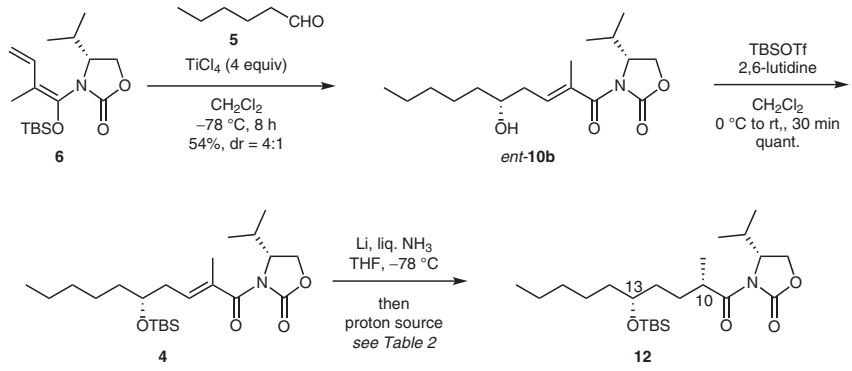
In conclusion, we have achieved a total synthesis of PF1163B. Stereogenic centers in the polyketide moiety were constructed by the vinylogous Mukaiyama aldol reaction of ketene silyl *N*,*O*-acetal **6** mediated by excess $TiCl_4$ and the Birch reduction proceeded with 2-isopropylbenzimidazole as the proton source. Therefore, the separate stereogenic centers in PF1163B were constructed with one chiral synthon, the vinylketene silyl *N*,*O*-acetal containing the Evans chiral auxiliary. This is a short strategy to prepare medium-size compounds. After elongation of the carbon chain and connection with the amino acid part, we accomplished a total synthesis of PF1163B (10 steps from **6**, 5.5% overall yield). These methods give a concise synthetic route to obtain polyketides as well as depsipeptides.

Table 2 Protonation in the Birch Reduction of α,β-Unsaturated Imide **4**

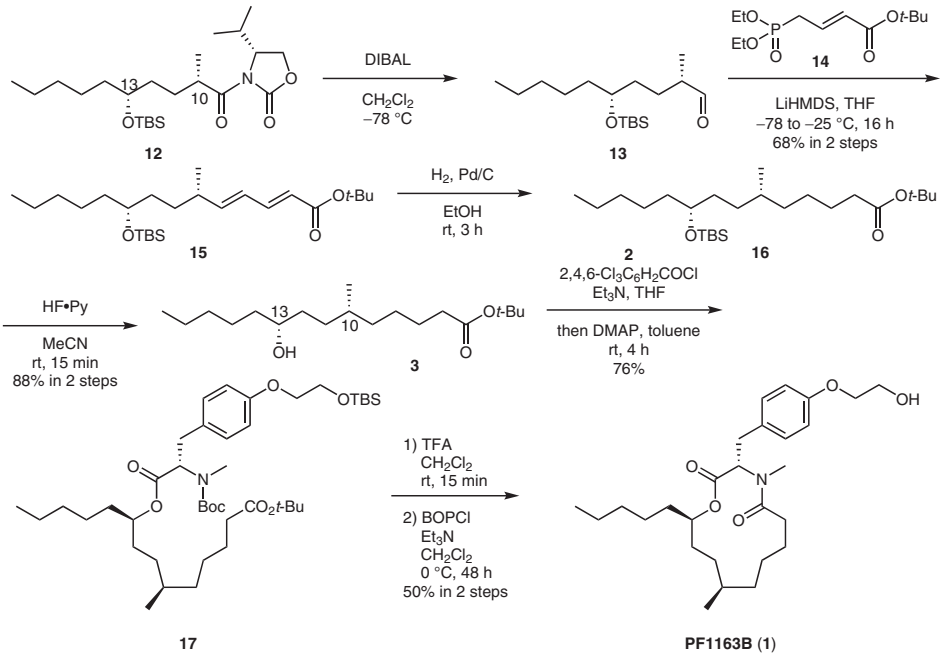


Entry	Proton source	Yield of **12** (%)[a]	dr[b]
1	NH_4Cl	41	1:1
2		64	4.4:1
3		65	6:1
4		57	2:1

[a] Isolated yield.
[b] Ratio of isolated compounds.



Scheme 3 Construction of stereogenic centers C10 and C13



Scheme 4 Completion of total synthesis of PF1163B (**1**)

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610694.

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(9) For synthesis of **2**: See Supporting Information.
(10) **Synthesis of PF1163B (1) from Acyclic 17**
To a solution of compound **17** (85.9 mg, 0.114 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added TFA (1.0 mL, 98%). The reaction mixture was stirred for 35 min at rt and then concentrated. The residue was then taken up in CH_2Cl_2 (64.0 mL) and cooled to 0 °C. Et_3N (0.19 mL, 1.368 mmol) was added dropwise, followed by the addition of BOP-Cl (174.1 mg, 0.684 mmol). The reaction mixture was stirred at 0 °C for 48 h. Then, it was concentrated and $NaHCO_3$ aq. (2.0 mL) was added. The aqueous layer was extracted two times with $CHCl_3$ (4.0 mL × 2) and the combined organic layers were concentrated, dried with Na_2SO_4, and purified by silica gel chromatography (*n*-hexane/EtOAc = 5:1) to give PF1163B (**1**) (27.0 mg, 0.058 mmoles, 50% over 2 steps) as a colorless oil. R_f = 0.48 (*n*-hexane/EtOAc = 1:1). $[\alpha]_D^{23}$ = –109.6 (*c* 0.49, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.05 (2 H, m), 6.88–6.79 (2 H, m), 5.84–5.75 (0.6 H, m), 4.94–4.78 (1 H, m), 4.60–4.54 (0.27 H, m), 4.09–4.01 (2 H, m), 3.99–3.91 (2 H, m), 3.60–3.14 (4 H, m), 3.04–2.90 (3 H, m), 2.84–2.61 (2 H, m), 2.47–1.96 (4 H, m), 1.54–1.03 (16 H, m), 0.92–0.79 (6 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.1, 170.2, 157.2, 130.2, 129.7, 129.1, 114.9, 114.4, 75.3, 69.1, 69.0, 61.5, 55.4, 35.1, 35.0, 34.0, 33.7, 33.6, 33.5, 31.7, 31.6, 29.4, 29.3, 28.7, 26.5, 25.0, 20.5, 14.0. HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{27}H_{43}O_5NNa$: 484.3033; found: 484.3033. IR (KBr): 3400, 2950, 2929, 1731, 1632, 1512, 1248, 1220, 1078, 772 cm^{-1}.