ORGANIC LETTERS

2007
Vol. 9, No. 5
849−852

# Total Synthesis of Khafrefungin Using Highly Stereoselective Vinylogous Mukaiyama Aldol Reaction

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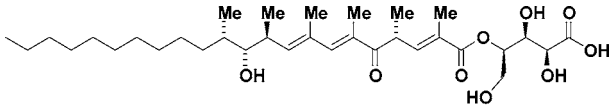
**Received December 14, 2006**

## ABSTRACT

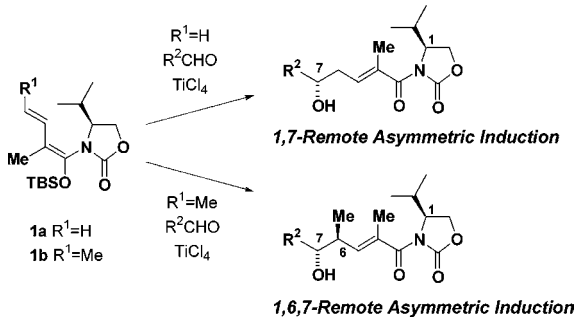


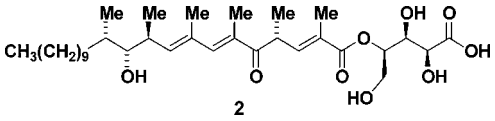

Khafrefungin

**A convergent total synthesis of khafrefungin was accomplished on the basis of (1) the highly stereoselective $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction using vinylketene silyl *N,O*-acetal and (2) *syn*-selective aldol reaction of enal 5a and ethyl ketone 6 followed by *anti*-dehydration under Mitsunobu conditions.**

We recently reported a highly stereoselective vinylogous Mukaiyama aldol reaction of vinylketene silyl *N*,*O*-acetal **1**, which also provides a unique and remarkable entry to a remote asymmetric induction (Scheme 1).[1,2] From a synthetic point of view, this method can directly afford the $\delta$-hydroxy-$\alpha$,$\gamma$-dimethyl-$\alpha$,$\beta$-unsaturated carbonyl unit that is seen in polyketide natural products.[3] In order to demonstrate the usefulness of our methodology, we investigated the total synthesis of khafrefungin (**2**) (Figure 1). In the polyketide moiety of khafrefungin, we can recognize two sets of the vinylogous Mukaiyama aldol adducts.

**Scheme 1.** Remote Asymmetric Induction




2

**Figure 1.** Structure of khafrefungin (**2**).

Khafrefungin (**2**) is an antifungal agent isolated from the fermentation culture MF6020 by a Merck group in 1997.[4] It has been shown to inhibit inositol phosphorylceramide (IPC)

(1) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

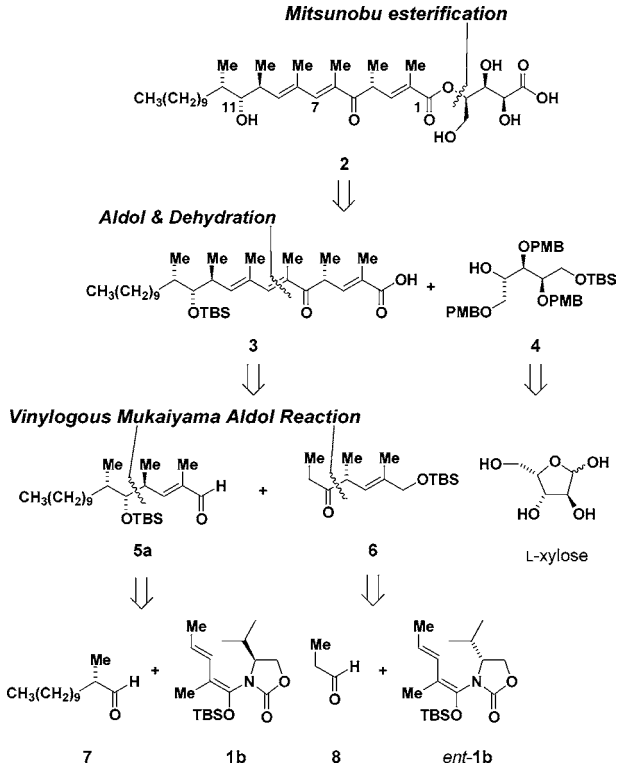
(2) For general reviews, including vinylogous aldol reaction of silyl dienol ethers to aldehyde, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. (c) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43.

10.1021/ol0630191 CCC: $37.00 
**Published on Web 02/09/2007**

synthase, which catalyzes the fungal specific step in *Saccharomyces cerevisiae* and pathogenic fungi such as *Cryptococcus neoformans* and *Candida albicans* in picomolar and nanomolar concentrations and causes ceramide accumulation.[5] Distinct from other sphingolipid inhibitors such as viridiofungin A, myriocin, and australifungin, khafrefungin does not impair sphingolipid synthesis in mammals. A convergent total synthesis of khafrefungin and its derivatives has been achieved by Kobayashi and co-workers on the basis of their excellent catalytic and enantioselective aldol reaction.[6]

Our retrosynthetic analysis of khafrefungin (**2**) is outlined in Scheme 2. Khafrefungin was divided into two fragments,

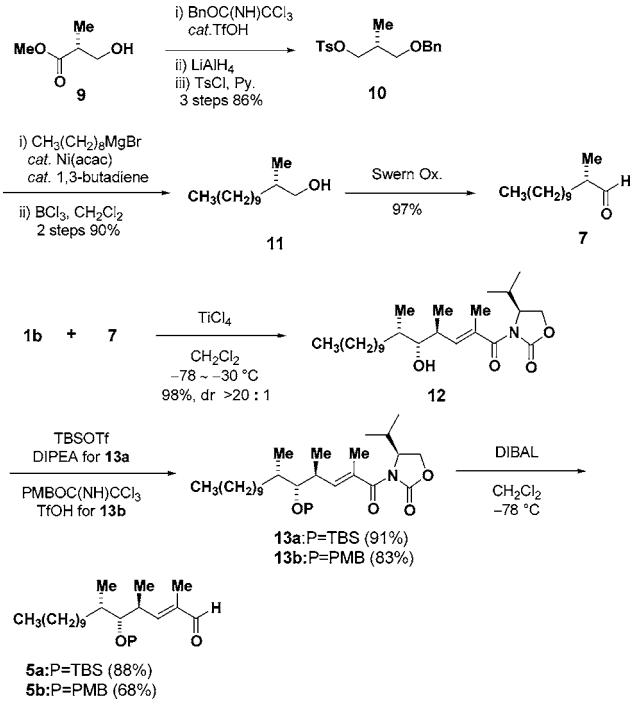
**Scheme 2.** Retrosynthetic Analysis




the polyketide acid part **3** and the aldonic acid part **4**. We planned to couple these parts by Mitsunobu esterification. Alcohol **4** (aldonic acid part) could be prepared from L-xylose. Polyketide acid **3** could be assembled via the aldol condensation of enal **5a** and ethyl ketone **6** and dehydration. We envisioned that both enal **5a** and ethyl ketone **6** could be stereoselectively prepared by the vinylogous Mukaiyama aldol reaction. According to the above retrosynthetic analysis, enal **5a** could be accessed from chiral aldehyde **7** and the vinylketene silyl *N*,*O*-acetal **1b** and ethyl ketone **6** from propionaldehyde (**8**) and *ent*-**1b**, respectively.

The synthesis of enal **5a** (Scheme 3) commenced with the

**Scheme 3.** Synthesis of C7−C22 Fragment




protection of commercially available methyl (*R*)-*β*-hydroxyisobutyrate (**9**) as a benzyl ether. The benzyl ether was then subjected to a reduction using lithium aluminum hydride and tosylation of the resulting alcohol. The Ni-catalyzed cross-coupling reaction of tosylate **10** with a Grignard reagent using Kambe's protocol[7] provided the benzyl ether in excellent yield, and the benzyl group was cleanly removed by exposure to boron trichloride to obtain chiral alcohol **11**. The primary alcohol **11** was oxidized to give aldehyde **7** using the standard Swern conditions.[8] According to the established protocol, the vinylogous Mukaiyama aldol reaction of chiral aldehyde **7** with the vinylketene silyl *N*,*O*-acetal **1b** using $TiCl_4$, which proceeded in the matched manifold, afforded the correspond-

(3) For synthetic application of this methodology, see: (a) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333. (b) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 5415. (c) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677. (d) Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 6183.

(4) Mandala, S. M.; Thornton, R. A.; Rosenbach, M.; Milligan, J.; Garcia-Calvo, M.; Bull, H. G.; Kurtz, M. B. *J. Biol. Chem.* **1997**, *272*, 32709.

(5) Reviews: (a) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532. See also: (b) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311*, 335−348. (c) Dickson, R. C. *Annu. Rev. Biochem.* **1998**, *67*, 27. (d) Other IPC inhibitors: Nagiec, M. M.; Nagiec, E. E.; Baltisberger, J. A.; Wells, G. B.; Lester, R. L.; Dickson, R. C. *J. Biol. Chem.* **1997**, *272*, 9809. (e) Mandala, R. A.; Thornton, R. A.; Milligan, J.; Rosenbach, M.; Garcia-Calvo, M.; Bull, H. G.; Harris, G.; Abruzzo, G. K.; Flattery, A. M.; Gill, C. J.; Bartizal, K.; Dreikorn, S.; Kurtz, M. B. *J. Biol. Chem.* **1998**, *273*, 14942.

(6) (a) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372. (b) Kobayashi, S.; Mori, K.; Wakabayashi, T.; Yasuda, S.; Hanada, K. *J. Org. Chem.* **2001**, *66*, 5580. (c) Nakamura, M.; Mori, Y.; Okuyama, k.; Tanikawa, K.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Org. Biomol. Chem.* **2003**, *1*, 3362.

(7) (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *5*, 663.

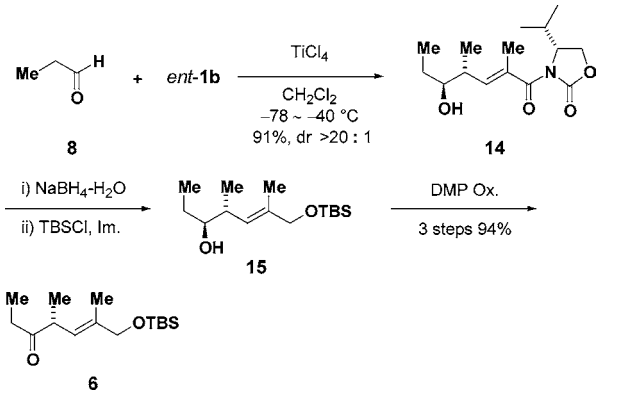
(8) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

ing C(10)−C(11) *anti*-aldol adduct **12** in 98% yield with >20:1 diastereoselectivity.

The secondary hydroxyl group of the aldol adduct **12** was protected as the *tert*-butyldimethylsilyl (TBS) ether by the reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and diisopropylethylamine (DIPEA). The *p*-methoxybenzyl (PMB) ether **13b** was provided by reaction with PMB trichloroacetimidate and a catalytic amount of trifluoromethanesulfonic acid.[9] Reductive removal of the chiral auxiliary in **13a** and **13b** using DIBAL produced the aldehyde **5a** and **5b**, respectively. The stereochemistry of **5b** (thus **12**) was confirmed by comparison of the spectral data with those reported by Kobayashi.[6a]

The C(1)−C(6) ethyl ketone **6** was synthesized starting from propionaldehyde (**8**) as summarized in Scheme 4. The

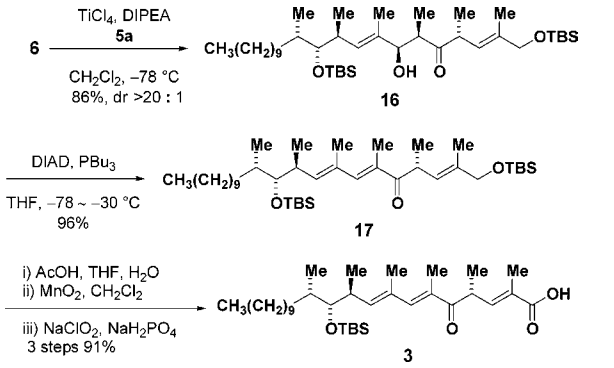
**Scheme 4.** Synthesis of C1−C6 Fragment




vinylogous Mukaiyama aldol reaction of propionaldehyde with the vinylketene silyl *N*,*O*-acetal *ent*-**1b** using $TiCl_4$ afforded the corresponding *anti*-aldol adduct **14** in 91% yield with high diastereomeric ratio (>20:1 dr). Reductive removal of the chiral auxiliary, followed by the protection of the resulting primary alcohol as a TBS ether, and Dess-Martin oxidation of the secondary alcohol provided ethyl ketone **6**.[10]

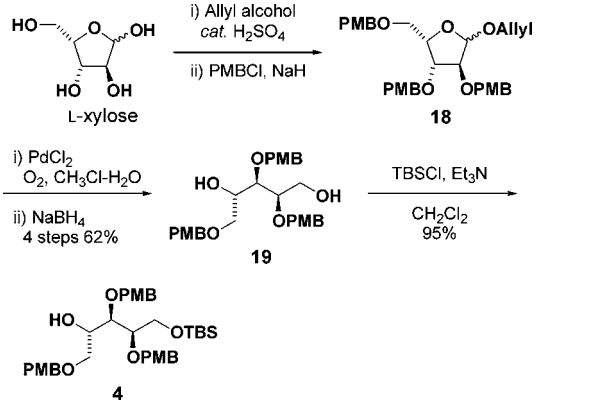
Aldol condensation of ethyl ketone **6** and enal **5a** was accomplished by using $TiCl_4$ and DIPEA in $CH_2Cl_2$ at −78 °C to afford *syn*-aldol adduct **16** in 86% yield (Scheme 5).[11] We then attempted an *anti*-dehydration of **16**. However, most of the typical *anti*-dehydration methods (MsCl/DMAP/Py, MsCl/$Et_3N$/$CH_2Cl_2$, TFAA/2,6-lutidine/$CH_2Cl_2$ followed by HCl/acetone, and $SOCl_2$/Py/$CH_2Cl_2$) were unsuccessful. In contrast, the desired dienone **17** was obtained in 96% yield under Mitsunobu conditions (DIAD and tributylphosphine in THF at −30 °C).[12] Dienone **17** was converted to acid **3** in 91% yield for the three steps by selective cleavage of the primary TBS ether followed by $MnO_2$ oxidation and $NaClO_2$ oxidation.[13]

**Scheme 5.** Fragment Assembly Aldol Reaction




The aldonic acid part **4** was prepared from L-xylose (Scheme 6). Thus, the allyl glycosidation of L-xylose was

**Scheme 6.** Synthesis of Aldonic Acid Part

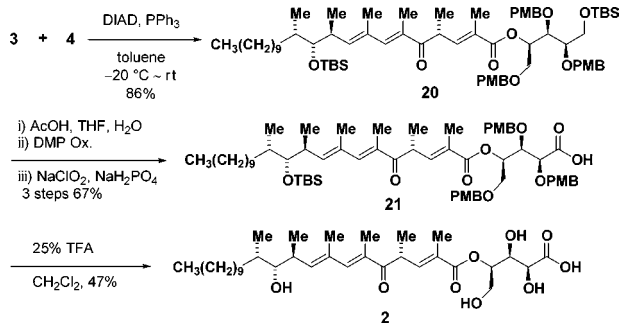



carried out by treatment with allyl alcohol, and the remaining hydroxyl groups were protected with the PMB group. Deprotection of the allyl group was successfully performed with $PdCl_2$ in $CHCl_3$/$H_2O$ under an $O_2$ atmosphere to give the hemiacetal, which on subsequent reduction with sodium borohydride in MeOH provided the diol in 62% yield for the four steps.[14] The resulting diol was protected selectively as its TBS ether to give secondary alcohol **4**.

With both segments in hand, we next carried out an esterification of the secondary alcohol **4** with the unsaturated acid **3** under Mitsunobu conditions to afford the desired ester **20** in 86% yield (Scheme 7). The primary TBS ether was selectively deprotected with AcOH/THF/$H_2O$, and the resultant primary alcohol was oxidized to a carboxylic acid **21** by a two-step sequence [(i) Dess−Martin oxidation; (ii) $NaClO_2$ oxidation]. Finally, deprotection of the secondary TBS ether and three PMB ethers with 25% TFA/$CH_2Cl_2$ completed the total synthesis of khafrefungin (**2**). The spectroscopic data

(9) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(11) Evans, D. A.; Rieger, J. C.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(12) Mitsunobu, O. *Synthesis* **1981**, 1.
(13) Bal, B. S.; Chiders, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(14) (a) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929. (b) Mereyala, H. B.; Lingannagura, S. R. *Tetrahedron* **1997**, *53*, 17501.

**Scheme 7.** Completion of the Total Synthesis




([1]H NMR, [13]C NMR, IR, HRMS, optical rotaiton) were in all respects identical to the data reported by Kobayashi and co-workers.[6a]

In summary, we were able to achieve a convergent synthesis of khafrefungin. Key transformations in the sequence included (i) construction of the C(1)−C(5) and C(7)−C(11) $\delta$-hydroxy-$\alpha$,$\gamma$-dimethyl-$\alpha$,$\beta$-unsaturated carbonyl unit using the vinylogous Mukaiyama aldol reaction and (ii) *syn*-selective aldol condensation and *anti*-dehydration under Mitsunobu conditions.

**Acknowledgment.** We thank Prof. Shu Kobayashi (The University of Tokyo) for helpful suggestions. We thank Kaneka Corp. for providing methyl (*R*)-$\beta$-hydroxyisobutyrate. This research was supported in part by a Grant-in-Aid for Scientific Research (B) (KAKENHI No.18390010) from the Japan Society for the Promotion of Science.

**Supporting Information Available:** Experimental details and spectroscopic data for compounds **2**−**4**, **5a**, **6**, **12**, **14**, **17**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0630191