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Synthetic study of fomitellic acids: construction of the AB ring moiety

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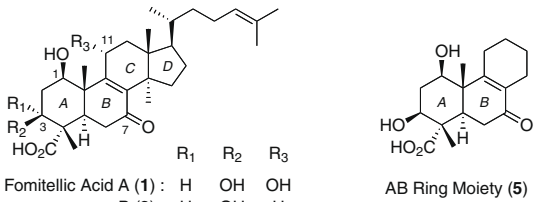
ABSTRACT

Stereocontrolled synthesis of a fully functionalized AB ring moiety of fomitellic acids was accomplished. The tricyclic skeleton was stereoselectively constructed by means of titanium(III)-mediated radical cascade cyclization of epoxypolyene. The stereochemistry at C1 and C3 was controlled by a vinylogous Mukaiyama aldol reaction and a Sharpless asymmetric epoxidation, respectively.

Fomitellic acids, originally isolated by Sakaguchi et al.[1] from the mycelium of a basidiomycete, *Fomitella fraxinea*, are potent inhibitors of calf DNA polymerase α, rat DNA polymerase β, and human DNA topoisomerases I and II (Fig. 1).[2] In recent years, these DNA-dependent enzymes have been recognized as important targets for cancer chemotherapy. Structurally, fomitellic acids belong to the triterpenoid family of compounds, which are characterized by a highly oxygenated steroidal AB ring moiety. The array of hydrophilic groups in the AB ring along with a hydrophobic CD ring and side chain moiety makes fomitellic acids potential lead compounds for anti-cancer agents.[3] With these considerations in mind, we embarked on the total synthesis of fomitellic acids. Here, we wish to report the stereocontrolled construction of the fully fuctionalized AB ring moiety (**5**).

Retrosynthetic analysis of the AB ring moiety (**5**) is depicted in Scheme 1. We simplified our target to the tricyclic compound **6** containing six stereogenic centers. There are several efficient methodologies for constructing an AB trans-decaline ring system. However, in view of the hydroxy group at C3, we favored a cascade cyclization of an epoxypolyene. The tricyclic skeleton **6**, or its equivalent, could be formed either by cationic or by radical cascade cyclization of epoxypolyene **7**. However, there are very few examples of the cyclization of an epoxypolyene possessing an oxygenated carbon at C1 (i.e., **7**).[4] Recently, titanium(III)-mediated radical cascade cyclization of epoxypolyenes has attracted a great deal of attention.[5] Indeed, this reaction has been used in the synthesis of several natural products[6] due to its high degree of selectivity and mild reaction conditions. Thus, we intended to apply this methodology to the transformation of **7** to **6**. The cyclization precursor **7** was divided into two fragments, the aldehyde part **8** and the vinyl iodide part **9**. We planned to couple these two parts by 1,2-addition of the vinyl lithium species derived from **9** to the aldehyde **8**. The aldehyde **8** could be stereoselectively prepared using a Sharpless asymmetric epoxidation (SAE)[7] of **10**, and the latter could be obtained by a vinylogous Mukaiyama aldol reaction (VMAR)[8,9] of vinylketene silyl *N*,*O*-acetal **12** with enal **11**.

At the outset, we examined the vinylogous Mukaiyama aldol reaction between the vinylketene silyl *N*,*O*-acetal **12** and the enal **11** (Scheme 2). The enal **11** was readily prepared in five steps from 1,3-propanediol.[10] Initial attempts using standard conditions, previously established in our laboratory ($TiCl_4$, 0.1 M in CH_2Cl_2, −50 °C), afforded an aldol adduct **13**[11] in low yield (43%). During a survey of reaction conditions, a marked increase in yield was observed by using toluene as solvent in high concentration (0.5 M),



	R_1	R_2	R_3
Fomitellic Acid A (**1**) :	H	OH	OH
B (**2**) :	H	OH	H
C (**3**) :	H	OH	OMe
D (**4**) :	OH	H	H

AB Ring Moiety (**5**)

Figure 1. Structures of fomitellic acids.

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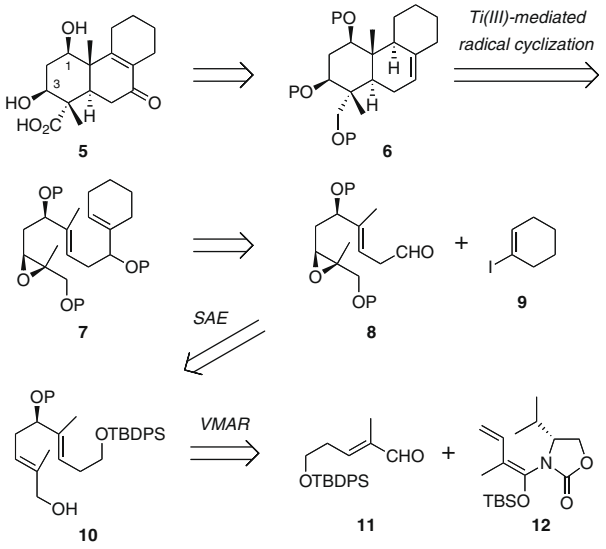
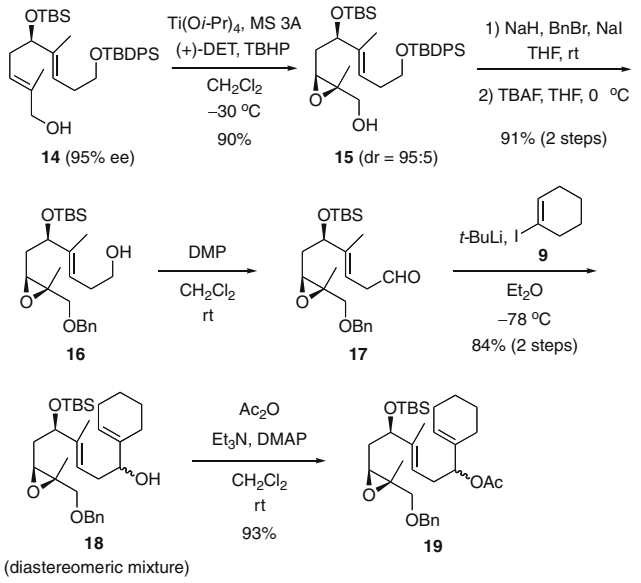
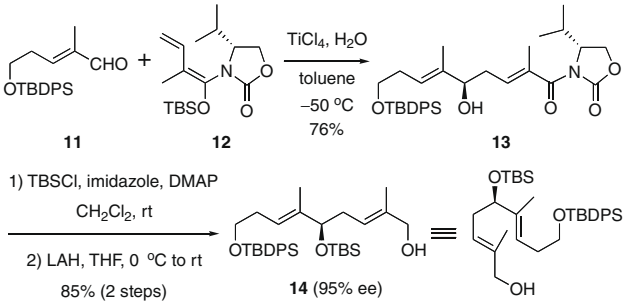


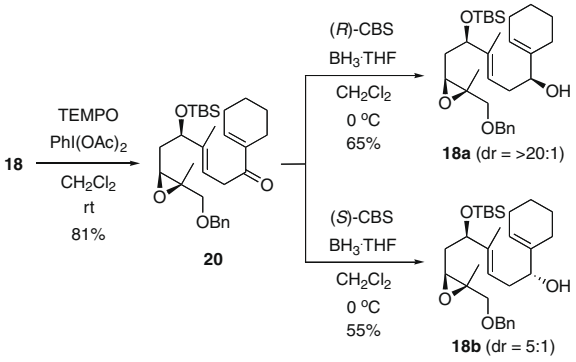
Scheme 1. Synthetic strategy for the AB ring moiety (**5**).



Scheme 3. Preparation of epoxypolyene **19**.



Scheme 2. Vinylogous Mukaiyama aldol reaction.



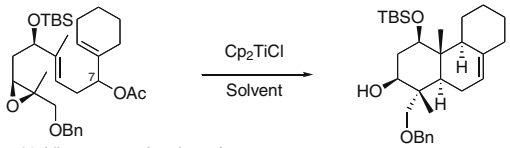
Scheme 4. Selective preparation of **18a** and **18b**.[14]

although the reaction was slow and not particularly reproducible. However, by adding a catalytic amount of water (10 mol %) the reaction proceeded quite efficiently in a reproducible manner without any decrease in yield.[12] After protection of the secondary hydroxyl group in **13** as the TBS ether, the chiral auxiliary was removed with $LiAlH_4$ to give allylic alcohol **14** in 85% yield with 95% ee.[13]

Scheme 3 shows the preparation of the cyclization precursor **19** from **14**. Sharpless asymmetric epoxidation of **14** using the catalyst derived from (+)-diethyl tartrate afforded **15** in 91% yield (dr = 95:5).[14] Protection of the primary alcohol in **15** as the benzyl ether, followed by selective removal of the TBDPS group by treatment with TBAF at 0 °C afforded homoallylic alcohol **16** in 91% yield for the two steps. Oxidation of the resulting alcohol **16** using Dess–Martin periodinane[15] provided a key intermediate **17** in good yield. The vinyl iodide **9**[16] was treated with *t*-BuLi in Et_2O at −78 °C, and the resulting vinyl lithium was then reacted with the aldehyde **17** giving a 1:1 diastereomeric mixture of **18** in 84% yield (inseparable by silica gel column chromatography). Subsequent acetylation of the secondary alcohol in **18** provided the cyclization precursor **19** (1:1 diastereomeric mixture). Each isomer, **18a**[11] and **18b**, could be obtained by sequential oxidation of **18** with TEMPO and asymmetric reduction of the resulting ketone **20** with a chiral borane reagent[17] (Scheme 4).

With epoxypolyene **19** in hand, we then examined the titanium(III)-mediated radical cascade cyclization of **19**. Treatment of **19** (diastereomeric mixture) with 3 equiv of Cp_2TiCl,[18] which was prepared from Cp_2TiCl_2 and Zn, in THF at room temperature afforded the desired tricyclic product **21** in 29% yield as a single isomer, along with mixture of monocyclic and acyclic products. The reaction was also carried out by changing the solvent and reaction temperature as shown in Table 1. The desired **21** was best obtained in 47% yield at elevated temperature (entry 2).[19] In addition, the diastereomeric compounds **19a** and **19b** were separately subjected to the same reaction to afford **21** in 43% and 45% yields, respectively (entries 5 and 6). These results revealed that the configuration of the acetoxy group at C7 position does not influence

Table 1
Titanium(III)-mediated radical cascade cyclization



Entry	Substrate	Solvent	Temperature (°C)	Yield (%)
1	**19**	THF	rt	29
2	**19**	THF	60	47
3	**19**	Benzene:THF = 2:1	60	45
4	**19**	Toluene:THF = 2:1	80	41
5	**19a**	Benzene:THF = 2:1	60	43
6	**19b**	Benzene:THF = 2:1	60	45

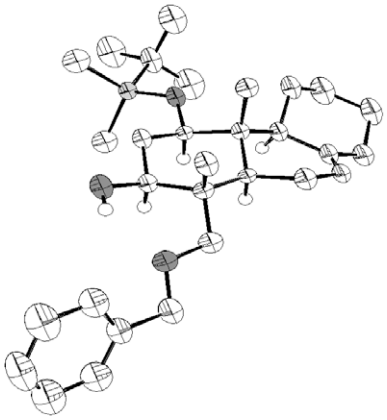
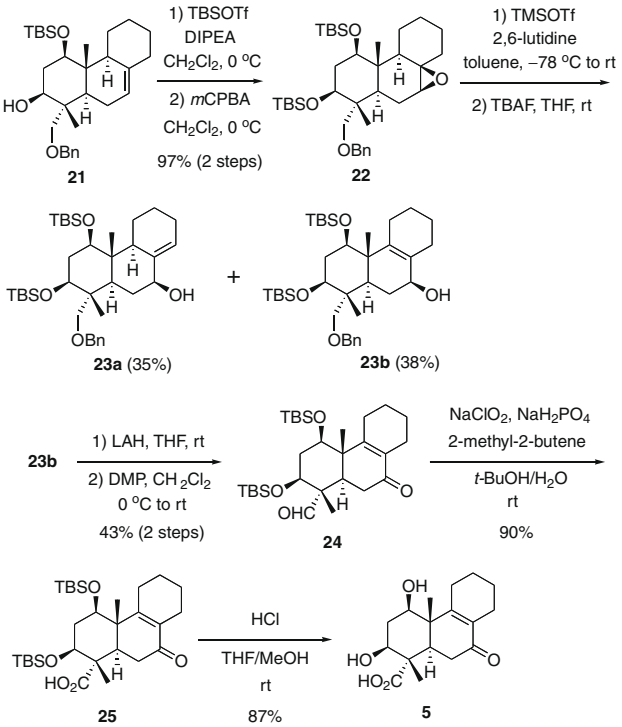


Figure 2. ORTEP drawing of cyclization product **21**.

the cyclization. We also attempted the cyclization of epoxypolyene possessing a silyloxy (TBSO) group instead of an acetoxy group to result in the formation of a complex mixture of products.

The stereochemistry of **21** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 2).[20] The cyclization product **21** was found to possess the desired stereochemistry and to be formed via a trans-fused chair/chair-like transition state.

Transformation of **21** to the AB ring moiety (**5**) is illustrated in Scheme 5. Protection of the secondary alcohol in **21** as the TBS ether and subsequent epoxidation with *m*CPBA provided epoxide **22** in 97% yield for the two steps as an almost single isomer. Treatment of **22** with TMSOTf and 2,6-lutidine,[21] followed by removal of the TMS group of the resulting allyl silyl ethers with TBAF afforded allylic alcohols **23a**[11] and **23b** in 35% and 38% yield, respectively (separable by silica gel column chromatography). No regioselectivity was observed in this model reaction, although no attempt was made to improve the selectivity. For total synthesis of fomitellic acids, epoxide opening should proceed in the desired fashion due



Scheme 5. Synthesis of the AB ring moiety (**5**).

to the quaternary nature of the adjacent carbon. Deprotection of the benzyl group in **23b** with $LiAlH_4$, followed by oxidation of the resulting diol with Dess–Martin periodinane provided ketoaldehyde **24** in 43% yield for two steps. The ketoaldehyde **24** was then oxidized to carboxylic acid **25** with $NaClO_2$. Finally, deprotection of two TBS ethers with concentrated HCl completed the synthesis of the AB ring moiety (**5**).

In summary, we have demonstrated the synthesis of the fully functionalized AB ring moiety of fomitellic acids. The stereoselective construction of the tricyclic core was achieved by titanium(III)-mediated radical cascade cyclization of epoxypolyene, and the stereochemistry at C1 and C3 was controlled by vinylogous Mukaiyama aldol reaction and Sharpless asymmetric epoxidation, respectively. The present strategy would be applicable to the total synthesis of fomitellic acids using a suitable vinyl iodide part instead of vinyl iodide **9**. Preparation of the vinyl iodide part and further studies toward the total synthesis of fomitellic acid B (**2**) are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.039.

References and notes

1. Tanaka, N.; Kitamura, A.; Mizushina, Y.; Sugawara, F.; Sakaguchi, K. *J. Nat. Prod.* **1998**, *61*, 193–197.
2. (a) Mizushina, Y.; Tanaka, N.; Kitamura, A.; Tamai, K.; Ikeda, M.; Takemura, M.; Sugawara, F.; Arai, T.; Matsukage, A.; Yoshida, S.; Sakaguchi, K. *Biochem. J.* **1998**, *330*, 1325–1332; (b) Mizushina, Y.; Iida, A.; Ohta, K.; Sugawara, F.; Sakaguchi, K. *Biochem. J.* **2000**, *350*, 757–763; (c) Obara, Y.; Nakahata, N.; Mizushina, Y.; Sugawara, F.; Sakaguchi, K.; Ohizumi, Y. *Life Sci.* **2000**, *67*, 1659–1665.
3. (a) Sakaguchi, K.; Sugawara, F. *Curr. Top. Med. Chem.* **2003**, *3*, 1–33; (b) Sakaguchi, K.; Sugawara, F. *Curr. Drug Ther.* **2008**, *3*, 44–53.
4. (a) Pettersson, L.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 789–800; (b) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753–2756.
5. (a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074–4078; (b) Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M. M.; Loayza, I.; Sánchez, E. M.; Arteaga, J. F. *Tetrahedron* **2006**, *62*, 5215–5222; (c) Fernández-Mateos, A.; Teijón, P. H.; Clemente, R. R.; González, R. R.; González, F. S. *Synlett* **2007**, 2718–2722; For reviews see: (d) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627–1641; (e) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem.* **2006**, *3*, 23–35; (f) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63–91; (g) Gansäuer, A.; Justicia, J.; Fan, C.-A.; Worgull, D.; Piestert, F. *Top. Curr. Chem.* **2007**, *279*, 25–52.
6. (a) Yamada, H.; Hasegawa, T.; Tanaka, H.; Takahashi, T. *Synlett* **2001**, 1935–1937; (b) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *Tetrahedron Lett.* **2004**, *45*, 4293–4296; (c) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Ha, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778–1788; (d) Justicia, J.; Oller-López, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911–14921; (e) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301–2304; (f) Justicia, J.; Oltra, J. E.; Barrero, A. F.; Guadaño, A.; González-Coloma, A.; Cuerva, J. M. *Eur. J. Org. Chem.* **2005**, 712–718; (g) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.* **2005**, *70*, 8265–8272; (h) Gansäuer, A.; Justicia, J.; Rosales, A.; Worgull, D.; Rinker, B.; Cuerva, J. M.; Oltra, J. E. *Eur. J. Org. Chem.* **2006**, 4115–4127; (i) Gansäuer, A.; Rosales, A.; Justicia, J. *Synlett* **2006**, 927–929; (j) Gansäuer, A.; Worgull, D.; Justicia, J. *Synthesis* **2006**, 2151–2154; (k) Justicia, J.; Campaña, A. G.; Bazdi, B.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *Adv. Synth. Catal.* **2008**, *350*, 571–576.
7. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
8. Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.

9. For synthesis of natural products, see: (a) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333–337; (b) Nakamura, T.; Shirokawa, S.-i.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679; (c) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 5415–5418; (d) Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 6183–6186; (e) Xin Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387; (f) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900; (g) Shirokawa, S.-i.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849–852; (h) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644; (i) Schmauder, A.; Müller, S.; Maier, M. E. *Tetrahedron* **2008**, *64*, 6263–6269; (j) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Chem. Asian J.* **2008**, *3*, 1415–1421; (k) Lipshutz, B. H.; Amorelli, B. *J. Am. Chem. Soc.* **2009**, *131*, 1396–1397; For reviews, see: (l) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707–4729; (m) Tatsuta, K.; Hosokawa, S. *Chem. Rec.* **2006**, *6*, 217–233; (n) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1–18.
10. See the Supplementary data.
11. The stereochemistry was determined by the modified Mosher's method: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
12. The specific role of water in the vinylogous Mukaiyama aldol reaction remains unclear. We are currently investigating the role of water in this reaction as well as exploring the possible applications of this phenomenon.
13. Enantiomeric excess (ee) was determined by HPLC with CHIRALCEL OD-H column (2-propanol/hexane = 1:400, flow rate 1.0 ml/min, detection at 254 nm, 30 °C).
14. Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis.
15. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
16. Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147–162.
17. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
18. For pioneer works on Cp_2TiCl-mediated epoxide openings see: (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc* **1988**, *110*, 8561–8562; (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997; For reviews see: (c) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788; (d) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465–475; (e) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556–5573.
19. Takahashi et al. reported that a non-polar solvent and heating are essential for the titanium(III)-mediated radical cascade cyclization (see Ref. 6a).
20. CCDC 721347 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
21. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738–2739.