



## Synthetic study of fomitelic acids: construction of the AB ring moiety

Makoto Yamaoka, Yuichi Fukatsu, Atsuo Nakazaki, Susumu Kobayashi \*

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI), 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

### ARTICLE INFO

#### Article history:

Received 17 March 2009

Revised 6 April 2009

Accepted 9 April 2009

Available online 14 April 2009

#### Keywords:

Titanium(III)-mediated radical cascade cyclization

Epoxy polyene

Vinylogous Mukaiyama aldol reaction

Triterpenoid

### ABSTRACT

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

© 2009 Elsevier Ltd. All rights reserved.

Fomitelic acids, originally isolated by Sakaguchi et al.<sup>1</sup> from the mycelium of a basidiomycete, *Fomitella fraxinea*, are potent inhibitors of calf DNA polymerase  $\alpha$ , rat DNA polymerase  $\beta$ , and human DNA topoisomerases I and II (Fig. 1).<sup>2</sup> In recent years, these DNA-dependent enzymes have been recognized as important targets for cancer chemotherapy. Structurally, fomitelic 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 fomitelic acids potential lead compounds for anti-cancer agents.<sup>3</sup> With these considerations in mind, we embarked on the total synthesis of fomitelic acids. Here, we wish to report the stereocontrolled construction of the fully functionalized 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 epoxy polyene. The tricyclic skeleton 6, or its equivalent, could be formed either by cationic or by radical cascade cyclization of epoxy polyene 7. However, there are very few examples of the cyclization of an epoxy polyene possessing an oxygenated carbon at C1 (i.e., 7).<sup>4</sup> Recently, titanium(III)-mediated radical cascade cyclization of epoxy polyenes has attracted a great deal of attention.<sup>5</sup> Indeed, this reaction has been used in the synthesis of several natural products<sup>6</sup> 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)<sup>7</sup> of 10, and the latter could be obtained by a vinylogous Mukaiyama aldol reaction (VMAR)<sup>8,9</sup> 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.<sup>10</sup> Initial attempts using standard conditions, previously established in our laboratory (TiCl<sub>4</sub>, 0.1 M in CH<sub>2</sub>Cl<sub>2</sub>, –50 °C), afforded an aldol adduct 13<sup>11</sup> 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),

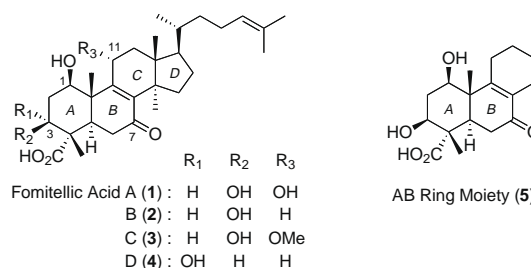
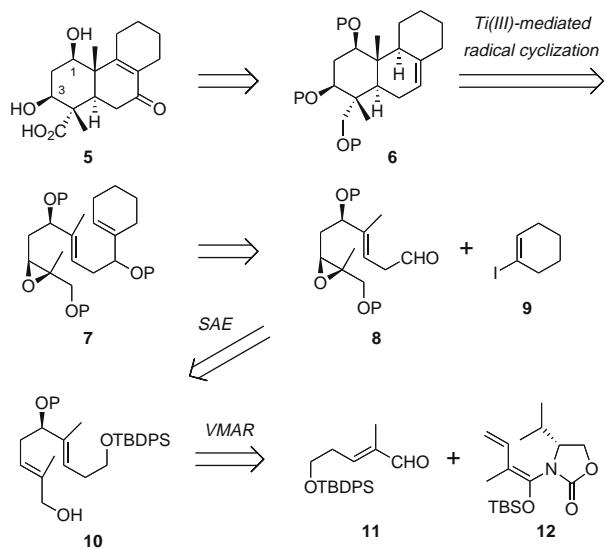


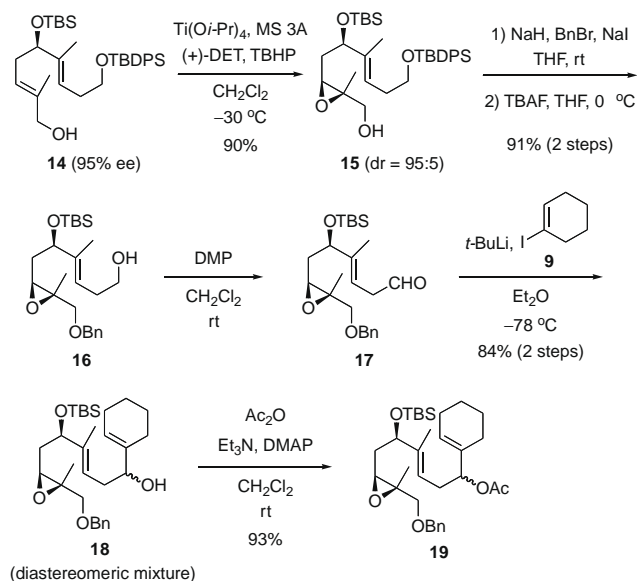
Figure 1. Structures of fomitelic acids.

\* Corresponding author. Tel./fax: +81 4 7121 3671.

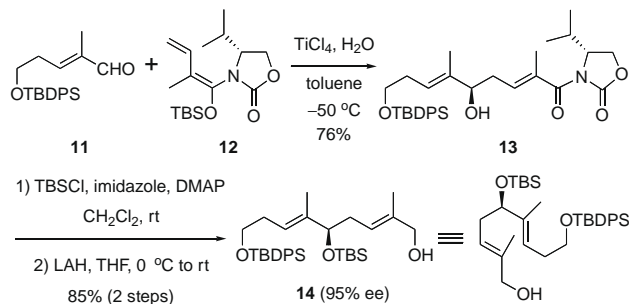
E-mail address: [kobayash@rs.noda.tus.ac.jp](mailto:kobayash@rs.noda.tus.ac.jp) (S. Kobayashi).



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



Scheme 3. Preparation of epoxy polyene 19.

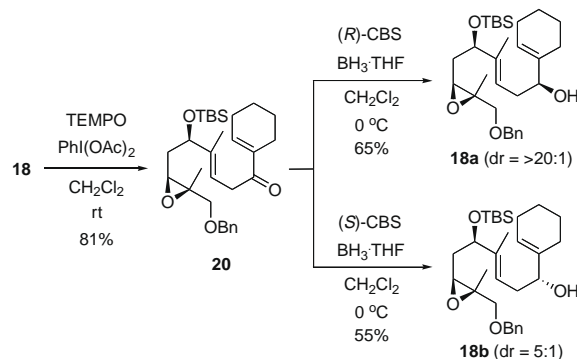


Scheme 2. Vinylogous Mukaiyama aldol reaction.

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.<sup>12</sup> After protection of the secondary hydroxyl group in 13 as the TBS ether, the chiral auxiliary was removed with LiAlH<sub>4</sub> to give allylic alcohol 14 in 85% yield with 95% ee.<sup>13</sup>

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).<sup>14</sup> 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<sup>15</sup> provided a key intermediate 17 in good yield. The vinyl iodide 9<sup>16</sup> was treated with *t*-BuLi in Et<sub>2</sub>O 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<sup>11</sup> 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<sup>17</sup> (Scheme 4).

With epoxy polyene 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<sub>2</sub>TiCl<sub>2</sub>,<sup>18</sup> which was prepared from Cp<sub>2</sub>TiCl<sub>2</sub> and Zn, in THF at room temperature

Scheme 4. Selective preparation of 18a and 18b.<sup>14</sup>

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).<sup>19</sup> 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

Reaction scheme for Table 1: 19 (diastereomeric mixture) reacts with Cp<sub>2</sub>TiCl<sub>2</sub> in a solvent to form 21. 19a is the 7S isomer and 19b is the 7R isomer.

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

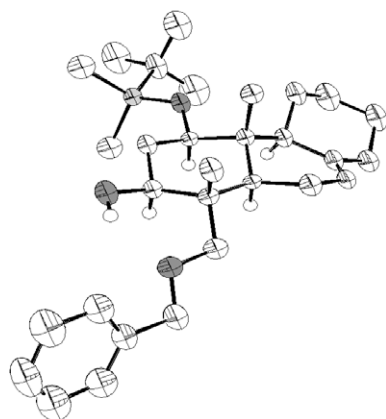
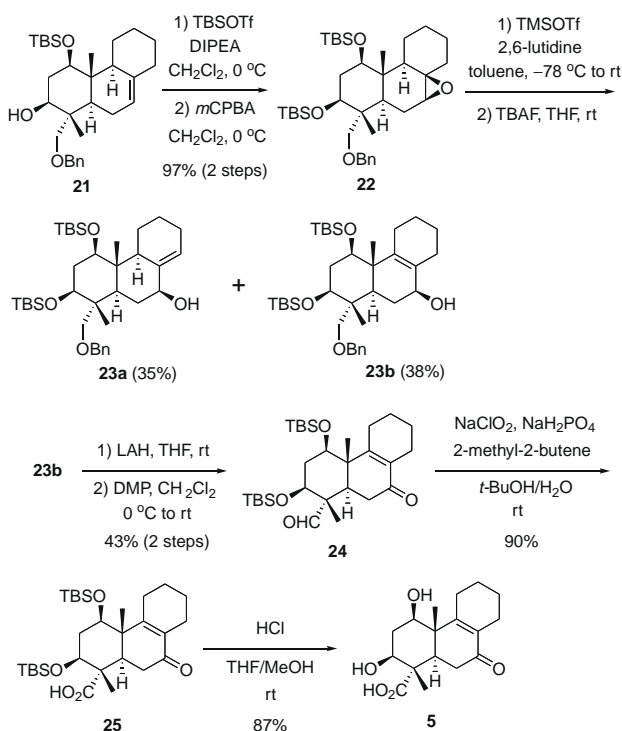


Figure 2. ORTEP drawing of cyclization product **21**.

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).<sup>20</sup> 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,<sup>21</sup> followed by removal of the TMS group of the resulting allyl silyl ethers with TBAF afforded allylic alcohols **23a**<sup>11</sup> 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 fomitelic 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<sub>4</sub>, 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<sub>2</sub>. 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 fomitelic 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 fomitelic 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 fomitelic acid **B** (**2**) are in progress.

## Acknowledgments

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. We thank Professor Kazuo Miyamura and Dr. Kazuaki Tomono (Department of Chemistry, Faculty of Science, Tokyo University of Science) for the X-ray analysis.

## 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

- Tanaka, N.; Kitamura, A.; Mizushima, Y.; Sugawara, F.; Sakaguchi, K. *J. Nat. Prod.* **1998**, *61*, 193–197.
- (a) Mizushima, 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) Mizushima, Y.; Iida, A.; Ohta, K.; Sugawara, F.; Sakaguchi, K. *Biochem. J.* **2000**, *350*, 757–763; (c) Obara, Y.; Nakahata, N.; Mizushima, Y.; Sugawara, F.; Sakaguchi, K.; Ohizumi, Y. *Life Sci.* **2000**, *67*, 1659–1665.
- (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.
- (a) Petterson, L.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 789–800; (b) Petterson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753–2756.
- (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.; Tejjón, 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.; Bazzi, B.; Oller-López, J. L.; 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.; Piester, F. *Top. Curr. Chem.* **2007**, *279*, 25–52.
- (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) Campaña, A. G.; Bazzi, B.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *Adv. Synth. Catal.* **2008**, *350*, 571–576.
- Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
- 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 <sup>1</sup>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<sub>2</sub>TiCl-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](http://www.ccdc.cam.ac.uk/data_request/cif).
21. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738–2739.