Tetrahedron Letters 50 (2009) 3277–3279

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient and stereoselective installation of isoquinoline: formal total synthesis of cortistatin A

Shuji Yamashita [a,*], Kazuki Kitajima [a], Kentaro Iso [a], Masahiro Hirama [a,b,*]

[a] Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan
[b] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

ARTICLE INFO

Article history:
Received 6 January 2009
Revised 3 February 2009
Accepted 6 February 2009
Available online 10 February 2009

Keywords:
Marine natural product
Cortistatin A
Isoquinoline
Total synthesis

ABSTRACT

The highly stereoselective attachment of isoquinoline onto the steroidal framework of cortistatin A has been achieved. Our strategy features a Ce-mediated nucleophilic addition of an isoquinoline unit to the sterically congested ketone followed by formation of the phenyl thiocarbamate, and subsequent stereoselective radical reduction. The new method results in a formal total synthesis of cortistatin A.

Cortistatins have been isolated from the marine sponge *Corticium simplex* by Kobayashi and co-workers[1] Cortistatin A (**1**, Fig. 1), the most potent congener, exhibits extremely strong cytotoxicity against human umbilical vein endothelial cells (HUVECs: IC_{50} = 1.8 nM). Owing to its unique inhibition activity of angiogenesis and unusual steroidal structure, **1** has currently become one of the most challenging targets in total synthesis.[2,3] Among the 11 isolated congeners, cortistatin A (**1**)–D (**4**), J (**5**), K (**6**), and L (**7**) that possess an isoquinoline unit exhibit highly selective inhibition of proliferation of HUVECs against other normal or tumor cell lines. SAR studies of cortistatins and simple analogs have revealed that the isoquinoline moiety is essential for their potent anti-angiogenesis activities.[4] Although installation methods of the isoquinoline motif have been reported in recent total syntheses of **1**, there appears to be room for improvement.[2,3g] We report here a new, secure method to install isoquinoline to the steroidal framework resulting in a formal total synthesis of **1**.

First, we examined the nucleophilic addition of isoquinoline to ketone (**8**) prepared from androsterone (Table 1).[5] When **8** was treated with 7-lithioisoquinoline, which was prepared from the corresponding iodide **9a**[6] in THF/HMPA at −78 °C, a trace amount of coupling product **10a** was isolated (entry 1). An organocerium reagent, which was expected to be a superior nucleophile,[7] gave **10a** in an even lower yield (entry 2). In both cases, 1-butylisoquinoline **11a** was obtained as a byproduct, which likely arose from the addition of *n*-BuLi to the C1-position of isoquinoline followed by rapid elimination of LiH.[8] To decelerate this undesired reaction, 1-chloroisoquinoline derivatives were employed (entries 3–5).[9] Treatment of **8** with a mixture of **9b**,[10] *i*-PrMgCl, and $CeCl_3$ at −78 to 0 °C gave the desired adduct **10b** in 40% yield (entry 3). The best yield of **10b** was achieved by treatment with a mixture of 5 equiv of lithiated **9b** and 10 equiv of $CeCl_3$ in THF at −78 °C (92%, entry 4). Surprisingly, **10b** was obtained as a 1.8:1 diastereomeric mixture. The minor product was determined to be an α-OH isomer by an NOE experiment.

We next focused on the deoxygenation of the newly formed tertiary alcohol. Without separation of the diastereomers, alcohol **10b** was treated with excess amounts of KH, CS_2, and MeI, but instead of the formation of xanthate **13a**, **10b** decomposed (Table 2, entry 1). Attempted formation of the thiocarbonate using phenyl thionochloroformate resulted in no reaction (entry 2), and treatment with a thiophosgene/MeOH combination caused β-elimination of the alcohol to give **14** in 50% yield (entry 3). After careful screening of reagents and conditions, we found that treatment of **10b** with KH and phenyl isothiocyanate in THF at room temperature afforded the corresponding thiocarbamate **13d** in 70% yield (entry 4).[11] Under these conditions, both C17-diastereomers of **10b** were transformed to the corresponding thiocarbamates without byproduct formation. Finally, radical reduction of **13d** using AIBN and *n*-Bu_3SnH afforded **15** as the sole product in 81% yield. It is noteworthy that the simultaneous removal of the thiocarbamate and chloride substituents of the isoquinoline ring was achieved in a single operation.

* Corresponding authors. Tel./fax: +81 22 795 6566 (M.H.).
E-mail addresses: s-yamashita@mail.tains.tohoku.ac.jp (S. Yamashita), hirama@mail.tains.tohoku.ac.jp (M. Hirama).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.038

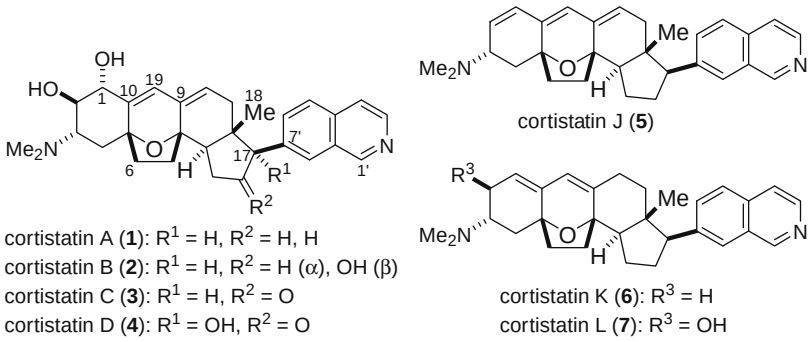
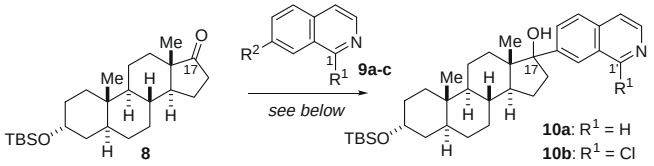


Figure 1. Structures of cortistatins.

Table 1
Nucleophilic addition of isoquinoline moiety



Entry	R^1	R^2	Conditions	Results
1	H	I (**9a**)	*n*-BuLi, HMPA, THF, −78 °C	**10a**:Trace, **11a**:5%
2	H	I	*n*-BuLi, $CeCl_3$, THF, −78 °C	**10a**:Trace, **11a**:Trace
3	Cl	I (**9b**)	*i*-PrMgBr, $CeCl_3$, THF, −78 to 0 °C	**10b**:40%, **12**:38%
4	Cl	I	*n*-BuLi, $CeCl_3$, THF, −78 °C	**10b**:92% (dr = 1.8:1)
5	Cl	Br (**9c**)	*n*-BuLi, $CeCl_3$, THF, −78 °C	**10b**:68% (dr = 1.7:1)

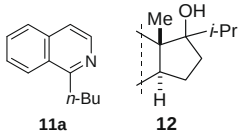
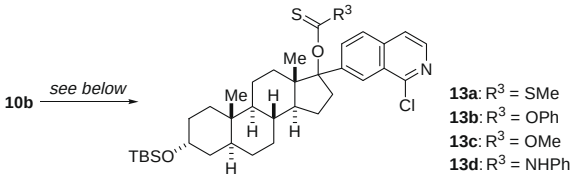
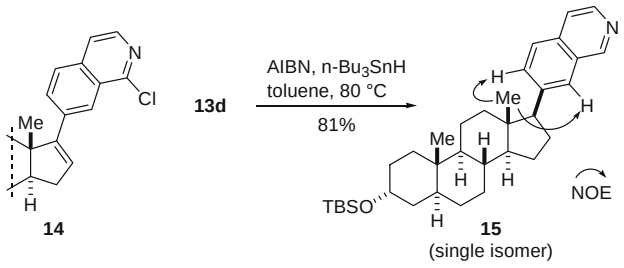


Table 2
Formation of thiocarbamate and radical reduction



Entry	Conditions	Results
1	KH, CS_2; MeI	Decomposed
2	DMAP, PhOC(S)Cl, CH_3CN, reflux	No reaction
3	KH, $CSCl_2$, THF, rt; MeOH	**14**:50%
4	KH, PhNCS, THF, rt	**13d**:70%[a]
5	NaH, PhNCS, THF, rt	**13d**:30%[a]

[a] **13d** was obtained as a mixture of diastereomeric and atrop-isomers.



Having successfully established the new installation method, we then applied it to the cortistatin framework (Scheme 1). The ketone **18** was synthesized from dienone **16**[3a] according to the Nicolaou–Chen protocol.[2b] Treatment of **18** with the organocerium reagent generated from **9b**, *n*-BuLi, and $CeCl_3$ gave the desired adduct **19** in quantitative yield. In this case, the resultant alcohol **19** was a single isomer, which was produced through the α-face attack of isoquinoline. Formation of the phenyl thiocarbamate from **19** provided **20** as a 4:1 mixture of atrop-isomers. Finally, one-pot removal of the thiocarbamate and chloride substituents of **20** furnished the isoquinoline diene **21** as a single stereoisomer in 73% overall yield from ketone **18**. A formal total synthesis of **1** was achieved by acid hydrolysis of **21** to give dienone **22** (71% yield), whose proton and carbon NMR spectra are identical with those of Nicolaou-Chen's intermediate.[2b]

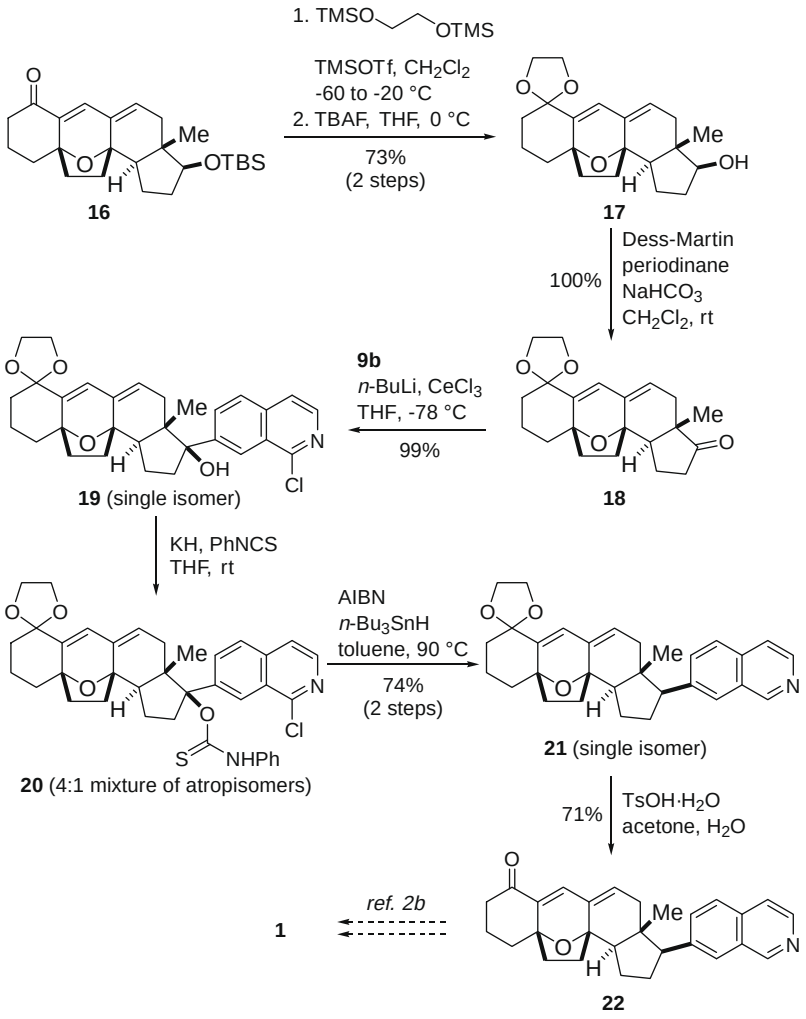
In conclusion, we have developed a highly convenient and stereocontrolled isoquinoline installation methodology to the pentacyclic framework of cortistatins. This method requires only three synthetic steps to attach the isoquinoline moiety, including (1) Ce-mediated nucleophilic addition to a sterically congested ketone, (2) formation of phenyl thiocarbamate from the tertiary alcohol, and (3) stereoselective radical reduction. We believe that the methodology developed here will accelerate not only the total synthesis and SAR studies of cortistatins, but also the development of new angiogenesis inhibitors.

Acknowledgments

This work was supported financially by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology in Japan, and by Suntory institute for bioorganic research (SUNBOR).

Supplementary data

Experimental section and ^{1}H NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.038.



Scheme 1. Formal total synthesis of cortistatin A.

References and notes

1. (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149; (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079; (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488.
2. (a) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243; (b) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313; (c) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.
3. Synthetic studies on cortistatins: (a) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415; (b) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653; (c) Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157–161; (d) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934; (e) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612; (f) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613–6616; (g) Kotoku, N.; Sumii, Y.; Hayashi, T.; Kobayashi, M. *Tetrahedron Lett.* **2008**, *49*, 7078–7081; (h) Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247–5250; Review, see: (i) Nising, C. F.; Bräse, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 9389–9391.
4. SAR studies of cortistatins: (a) Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem.* **2007**, *15*, 6758–6762; SAR study of simple analogs: (b) Sato, Y.; Kamiyama, H.; Usui, T.; Saito, T.; Osada, H.; Kuwahara, S.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2992–2997.
5. Maltais, R.; Mercier, C.; Labrie, F.; Poirier, D. *Mol. Diversity* **2005**, *9*, 67–79.
6. 7-iodoisoquinoline **9a** was synthesized from 7-trimethylstannyl isoquinoline.
7. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
8. (a) Abramovitch, R. A.; Poulton, G. A. *Chem. Commun.* **1967**, 274–275; (b) Fraenkel, G.; Copper, J. C. *Tetrahedron Lett.* **1968**, *9*, 1825–1830.
9. A selected reference on the effect of chlorine, see: Dietrich-Buchecker, C.; Colasson, B.; Jouvenot, D.; Sauvage, J.-P. *Chem. Eur. J.* **2005**, *11*, 4374–4386.
10. Compound **9b** was synthesized from 7-bromo-1-chloroisoquinoline **9c**.
11. Oba, M.; Nishiyama, K. *Tetrahedron* **1994**, *50*, 10193–10200.