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Concise Synthesis of the Oxapentacyclic Core of Cortistatin A

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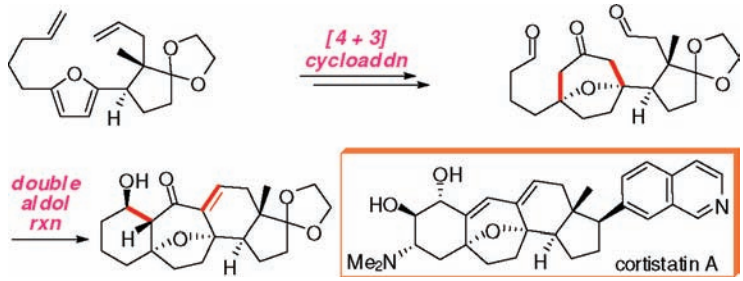
ABSTRACT



A concise synthetic approach for constructing the oxapentacyclic framework of cortistatin A is described. The synthesis features a furan−oxyallyl [4 + 3] cycloaddition and double-intramolecular aldol reactions. In addition, an interesting core structure was obtained in 11 steps from furan by using our method.

Cortistatins, containing a common unprecedented [6.7.6.5] oxapentacyclic [or termed as 9-(10,19)-*abeo*-androstane] skeleton, were isolated from the marine sponge *Corticium simplex* by Kobayashi and co-workers and were found to possess potent antiangiogenic and antiproliferative activities against human umbilical vein endothelial cells (HUVECs).[1] Among these natural substances, cortistatin A (**1**, Figure 1a) demonstrated the strongest antiproliferative activity (IC_{50} = 1.8 nM) against HUVECs. It also had a selectivity index that was 3000 times different from that of normal fibroblasts and various tumor cell lines. The unique structural characteristics and remarkable pharmacological profiles of cortistatins have spurred synthetic chemists to develop efficacious and practical synthetic routes to them for further biological investigations.[2] Until now, elegant semi-, total, and formal syntheses of **1** have been accomplished by the teams of Baran,[3] Nicolaou,[4] Shair,[5] Hirama,[6] Sarpong,[7] and Myers,[8] respectively, and synthetic studies toward the construction

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(1) (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485. (d) 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.

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(3) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241 (semi-synthesis).

(4) (a) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310 (total synthesis). (b) Nicolaou, K. C.; Peng, X.-S.; Sun, Y.-P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, *131*, 10587 (total synthesis).

(5) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864 (total synthesis).

(6) Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2008**, *49*, 6613 (formal synthesis).

(7) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron* **2010**, *66*, 4696 (formal synthesis).

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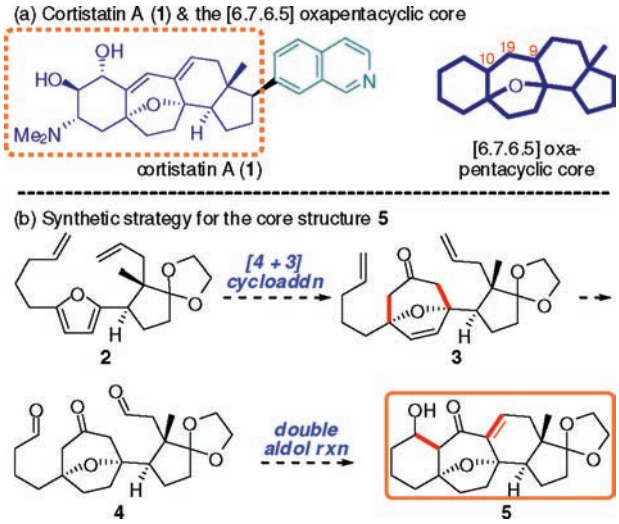


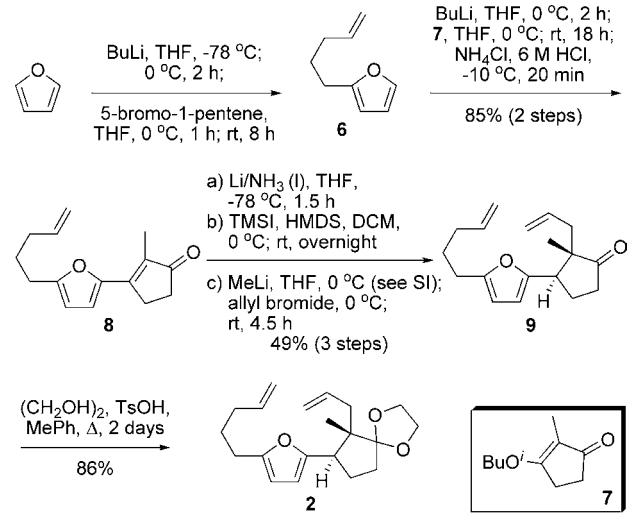
Figure 1. Structural features of cortistatin A and synthetic strategy for core structure **5**.

of **1** have been conducted by a number of research groups.[9] Moreover, certain novel cortistatin analogues have been synthesized and their biological activities evaluated.[4b,10]

Furan-involving [4 + 2] cycloaddition was utilized in the core construction studies by both Yang[9i] and Magnus.[9j] We envisaged that a core structure of cortistatin A (**1**) such as **5** (Figure 1b) may be rapidly assembled via a furan−oxyallyl [4 + 3] cycloaddition[9d] (**2** → **3**) and double-intramolecular aldol reactions (**4** → **5**).

As outlined in Scheme 1, furan was alkylated to afford the known intermediate **6**,[11] which was lithiated at C-5 and reacted with ketone **7**[12] followed by hydrolysis to give enone **8** in 85% yield over two steps. Stereoselective reductive α-allylation[13] of the cyclopentenone moiety in **8** led effectively to ketone **9** with a quaternary carbon center (49%) via a three-step sequence consisting of (i) Birch reduction (Li/NH_3 (l), THF, −78 °C), (ii) thermodynamic enol silyl ether formation (TMSI, HMDS, DCM, 0 °C to rt), and (iii)

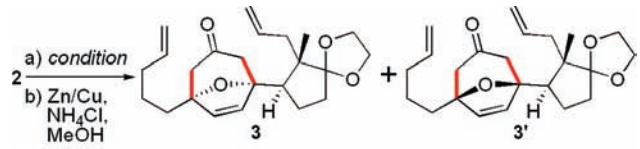
Scheme 1. Synthesis of Furan Derivative **2**



regiospecific enolate generation and subsequent alkylation (MeLi, THF, 0 °C; allyl bromide, THF, rt). Treatment of **9** with ethylene glycol in the presence of TsOH in toluene at reflux furnished acetal **2** in 86% yield.

With 2,5-disubstituted furan derivative **2** in hand, the [4 + 3] cycloaddition[14] was extensively investigated under a series of conditions (Scheme 2). Although the cycloaddition

Scheme 2. Intermolecular [4 + 3] Cycloaddition of **2**



entry	condition	result
1	TBA(2.5 equiv), Et_2Zn (2 equiv), MePh, 2 d	**3** (12%) + **3'** (15%)
2	TCA (1.5 equiv), TEA (3 equiv), TFE, 4 d	most of **2** unreacted
3	TCA (1.5 equiv), TEA (3 equiv), HFIP	**3** 43% + **3'** (53%)
4	TCA (3 equiv), TEA (4 equiv), HFIP	**3** (42%) + **3'**: (45%)
5	TCA (5 equiv), TEA (10 equiv), HFIP	**3** (46%) + **3'** (47%)

reaction (under improved Föhlisch's conditions[15]) seemed to generate slightly less of the desired cycloadduct **3** than the other isomer **3′** after reductive dehalogenation, the combined yield of both stereoisomers reached as high as 96% (entry 3). The highest yield of **3** (46%) was obtained when

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(12) Funk, R. L.; Vollhardt, K. P. C. *Synthesis* **1980**, 118.

(13) Van Royen, L. A.; Mijngheer, R.; De Clercp, P. J. *Bull. Soc. Chim. Belges.* **1984**, *93*, 1019.

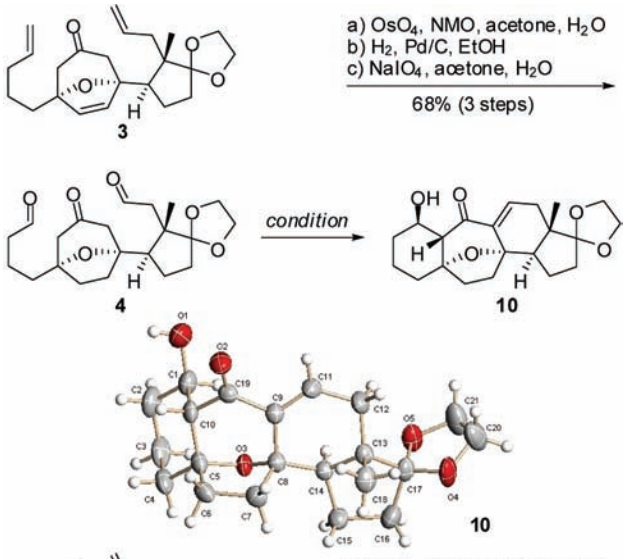
(14) For reviews on oxyallyl [4 + 3] cycladditions, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (d) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934. For recent examples, see: (e) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243, and references cited therein. (f) See also ref 11.

(15) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Hendle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem.* **1999**, *64*, 3398, and references cited therein.

2 was treated with 1,1,3-trichloroacetone (5 equiv) and triethylamine (10 equiv) in 1,1,1,3,3,3-hexafluoro-2-propanol (entry 5).

Both **3** and **3′** were further converted into more advanced intermediates with an attractive [6.7.6.5] tetracarbocyclic framework (Scheme 3). Upon terminal alkene dihydroxylation, internal alkene hydrogenation, and vicinal diol cleavage,[16] ketodialdehyde **4** was formed from triene **3** in 68% overall yield. Condensation parameters such as the substrate concentration, the base, the solvent, and the reaction time were carefully scrutinized for the double-aldol reaction (see the table at the bottom of Scheme 3). The best yield (82%) for tetracarbocycle **10** was obtained when **4** (0.02 M) was exposed to K_2CO_3 (5 equiv) in MeOH for 30 min (entry 5). In this case, the double dehydration product (dienone **11**, $\Delta^{1,10,9,11}$) was not observed, which turned out to be a superior result since hydroxy enone **10** may be a better substrate for further structural manipulations than dienone **11**. The structure of **10** was unambiguously confirmed by X-ray crystallographic analysis. Analogously, triene **3′** was transformed into ketodialdehyde **4′** in three steps, while the overall yield was slightly higher (71%) compared to that of **4**. Double aldol reaction of **4′** in the presence of K_2CO_3 in MeOH for 2 days resulted in double cyclization to furnish **10′** (48%) as a single isomer, although the relative configuration for the newly formed stereogenic centers in **10′** remains uncertain at this stage.[17]

Scheme 3. Synthesis of Core Structures **10** and **10′**



entry	condition (**4** → **10**)	result
1	**4** (0.02 M), L-proline, MeCN, 3 d	NR
2	**4** (0.02 M), K_2CO_3 (5 equiv), dioxane, 3 d	NR
3	**4** (0.05 M), K_2CO_3 (5 equiv), MeOH, 2 h	**10** (62%) + **11** (10%)
4	**4** (0.05 M), K_2CO_3 (5 equiv), MeOH, 0.5 h	**10** (71%) + **11** (6%)
5	**4** (0.02 M), K_2CO_3 (5 equiv), MeOH, 0.5 h	**10** (82%)

Compound **11** is a dienone ($\Delta^{1,10,9,11}$) derived from **10** via dehydration.

In summary, we have described a short synthetic approach for constructing the oxapentacyclic framework of cortistatin A featuring a furan−oxyallyl [4 + 3] cycloaddition[9d] and double-intramolecular aldol reactions. Core structure **10**, as well as isomeric **10′**, was obtained in 10 steps from the known furan derivative **6** or in 11 steps from furan. The current strategy has the full potential to lead to a total synthesis due to the proper arrangement of the desired functionalities in our target molecule that are amenable for further elaborations.

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Supporting Information Available: Experimental procedures and analytical data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The structure of **10′** can presumably be represented by: