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Intramolecular Cyclopropene-Furan [2 + 4] Cycloaddition followed by a Cyclopropylcarbinyl Rearrangement to Synthesize the BCD Rings of Cortistatin A

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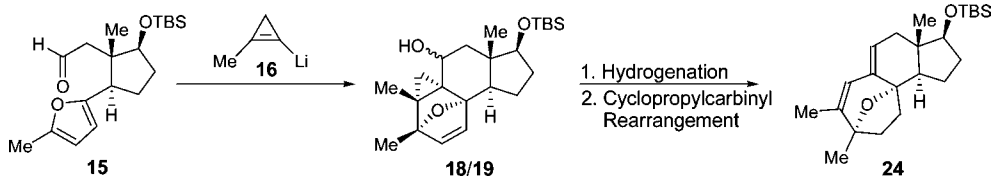
ABSTRACT



Synthesis of the BCD ring system of cortistatin A has been accomplished in 9 steps and 30% overall yield starting from commercially available 2-methylcyclopent-2-enone. Key transformations include the addition of cyclopropenyllithium 16 to aldehyde 15, an intramolecular cyclopropene-furan [2 + 4] cycloaddition leading to epimers 18/19, and a subsequent cyclopropylcarbinyl rearrangement to afford 24.

Cortistatin A (**1**, Figure 1) is one of several steroidal alkaloids isolated from a marine sponge *Corticium simplex*.[1] The cortistatins are members of a relatively small group of steroidal alkaloids known as the *Buxus* (boxwood) alkaloids.[2,3] Most interestingly, cortistatins A−D inhibited proliferation of human umbilical vein endothelial cells (HUVECs) with high selectivity. Of the four substances, cortistatin A (**1**) showed the strongest antiproliferative activity (IC_{50} = 1.8 nM) against HUVECs; the selectivity index was more than 3000-fold in comparison with normal fibroblasts and several tumor cell lines. Because tumor growth and metastasis are highly dependent on angiogenesis,[1] it follows that "specific inhibitors of angiogenesis are expected to be promising antitumor agents."[1,4]

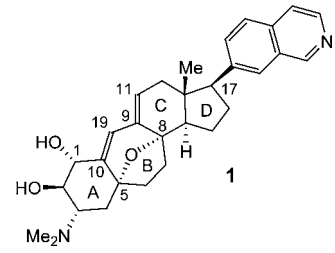


Figure 1. Cortistatin A (**1**).

These intriguing biological properties have elevated cortistatin A to be a topical target for both partial[5] and total

(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, S.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079. (c) 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. (d) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488.

(2) (a) Introduction to Alkaloids. A Biogenetic Approach. Cordell, G. A. *Buxus Alkaloids*; Wiley-Interscience: New York 1981; pp 907−910. (b) Ata, A.; Naz, S.; Choudhary, M. I.; Atta-ur-Rahman.; Sener, B.; Turkoz, S. *Z. Naturforsch, C: J. Biosci.* **2002**, *57*, 21–28.

(3) Uddin, B. Z.; Athar, A.; Hadi, M. M. *Steroids* **2006**, *71*, 1045–1051.

(4) Folkman, J.; Shing, Y. *J. Biol. Chem.* **1992**, *267*, 10931–10934.

(5) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

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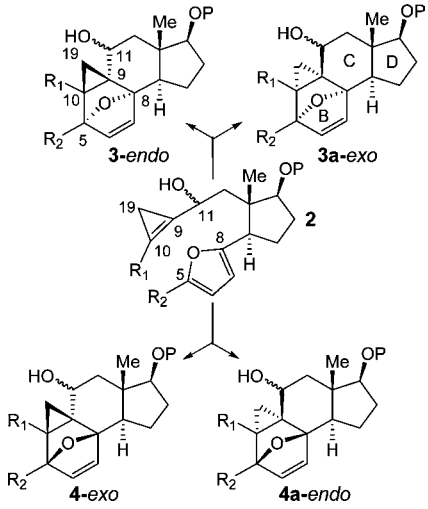
synthesis.[6] In order to examine its potential as an antitumor agent, several synthetic strategies have been published toward the synthesis of **1**.[7a−h] A number of studies regarding the preparation and biological activity of cortistatin analogues have also been reported.[7i−k]

We were particularly interested in the possibility of assembling the BCD rings of **1** by an intramolecular cyclopropene-furan [2 + 4] cycloaddition (Scheme 1). In

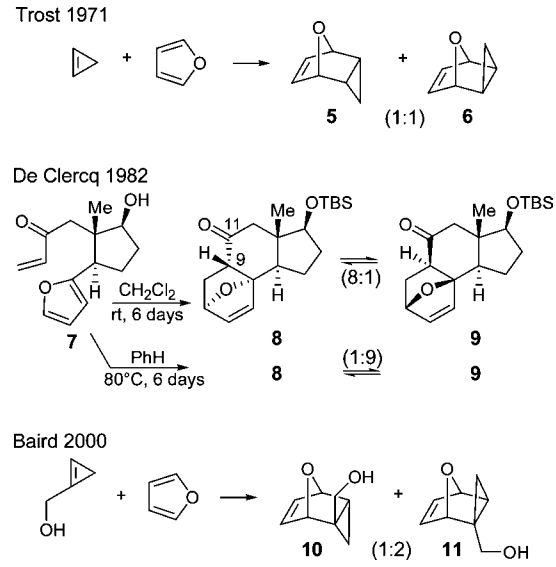
Scheme 1. Cyclopropene-Furan Cyclization



principle, the cycloaddition of **2** can give rise to four adducts (ignoring the possible C-11 epimers), which are **3/3a** and **4/4a**. Clearly, only the adducts **3** and **3a** have the correct stereochemistry at the crucial 5,8-oxido bridge.[8] The substituents R_1 and R_2 in **2** will comprise the necessary structural features to construct the A ring of cortistatin A.

The literature that is pertinent to this problem is outlined in Scheme 2. Trost trapped cyclopropene with furan (rt) and obtained the *endo* and *exo* adducts **5** and **6**, respectively, in a 1:1 ratio.[9] Similarly, Baird trapped 1-cyclopropene carbinol with furan (rt) to give **10** and **11** (1:2).[10] It appears that the usual *endo* kinetic preference is eroded by the extremely

Scheme 2. Pertinent Prior Literature in Chronological Order



exothermic relief of cyclopropenyl ring strain in the transition state leading to the Diels−Alder adducts.

Importantly, De Clercq showed that **7** was converted into **8** and **9** (rt) in a ratio of 8:1, the desired α-5,8-oxido adduct being the major product.[11] Both isomers were designated as *exo* adducts because the C9−C11 bond is *cis* to the smaller bridge. The same reaction conducted at 80 °C gave **8** and **9** in a ratio of 1:9. Taking **8** and **9** separately at 80 °C resulted in the same 1:9 mixture, thus establishing the reversibility of the process. The other two diastereoisomers (designated as *endo*) were not observed, and it was concluded that they were too strained to be formed. In view of this work, it was anticipated that the *exo* adducts **3a** and **4**, Scheme 1, would be observed as the major and minor cycloaddition products, respectively, en route to the BCD ring system of **1**.

To examine the crucial issue of the furan facial selectivity in the intramolecular cyclopropene-furan [2 + 4] cycload-

(6) (a) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313. (b) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

(7) (a) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653. (b) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415. (c) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934. (d) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612. (e) Kurti, L.; Czako, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247–5450. (f) Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277–3279. (g) Dai, M.; Danishefsky, S. J. *Heterocycles* **2008**, *77*, 157. (h) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662–664. (i) Shi, J.; Shigehisa, H.; Guerrero, C.; Shenvi, R.; Li, C.-C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331. (j) Czako, B.; Kurti, L.; Mammoto, A.; Ingber, D. E.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 9014–9019. (k) 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*, 10587–10597.

(8) The designation of *exo* and *endo* for **3/3a/4/4a** is based on the stereochemical relationship between the 5,8-oxido bridge and the C-19 methylene bridge.

(9) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126–1136.

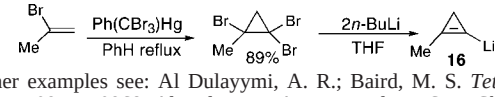
(10) Al Dulayymi, A. R.; Al Dulayymi, J. R.; Baird, M. S. *Tetrahedron* **2000**, *56*, 1115–1125.

(11) (a) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Bull Soc. Chim. Belg.* **1984**, *93*, 1019–1036. (b) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1982**, *23*, 3283–3286. (c) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron* **1985**, *41*, 4667–4680.

(12) Dujardin, G.; Poirier, J.-M. *Bull. Soc. Chim. Fr.* **1994**, *131*, 900–909.

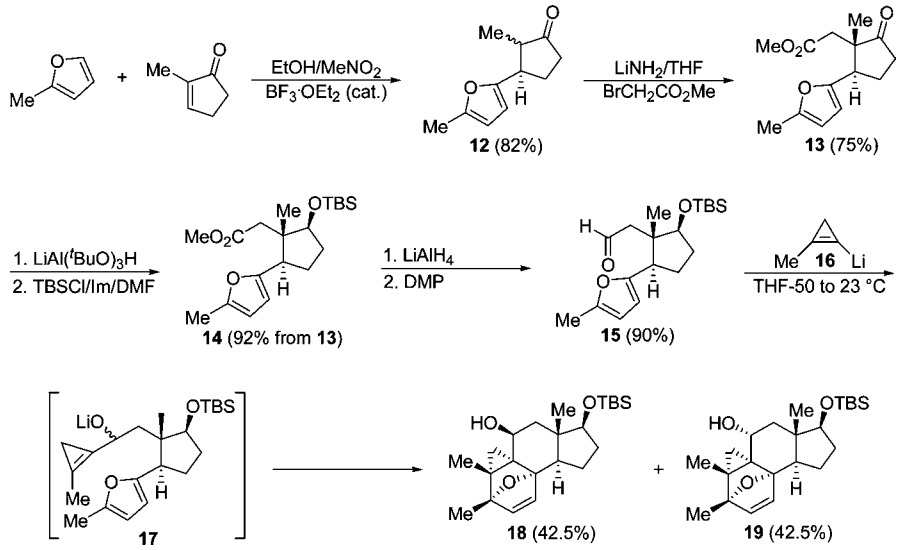
(13) The use of NaH gave none of **13**, and KH gave just a trace. $LiNH_2$ is frequently vastly superior in generating the thermodynamically more stable enolate anion and for regiospecific alkylation of enolates made from treatment of trimethylsilyl enol ethers with $LiNH_2/NH_3$. (a) Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156–2160. (b) Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron* **1981**, *37*, 4515–4519.

(14) The cyclopropenyl lithium reagent **16** is made as shown below. Al Dulayymi, A. R.; Baird, M. S. *Tetrahedron* **1996**, *52*, 10955–10968. For a review on the $Ph(Chal_3)Hg$ (Seyferth reagents) see: Seyferth, D. *Acc. Chem. Res.* **1972**, *5*, 65–74.



For other examples see: Al Dulayymi, A. R.; Baird, M. S. *Tetrahedron* **1996**, *52*, 10955–10968. Al Dulayymi, A. R.; Baird, M. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1547–1558.

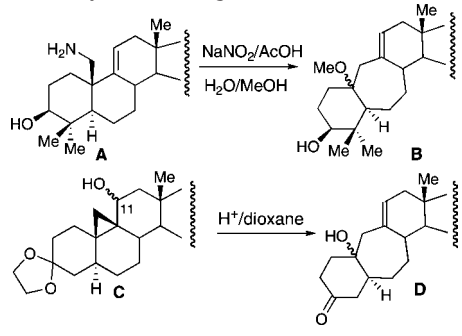
Scheme 3. Cyclopropene-Furan [2 + 4] Cycloaddition



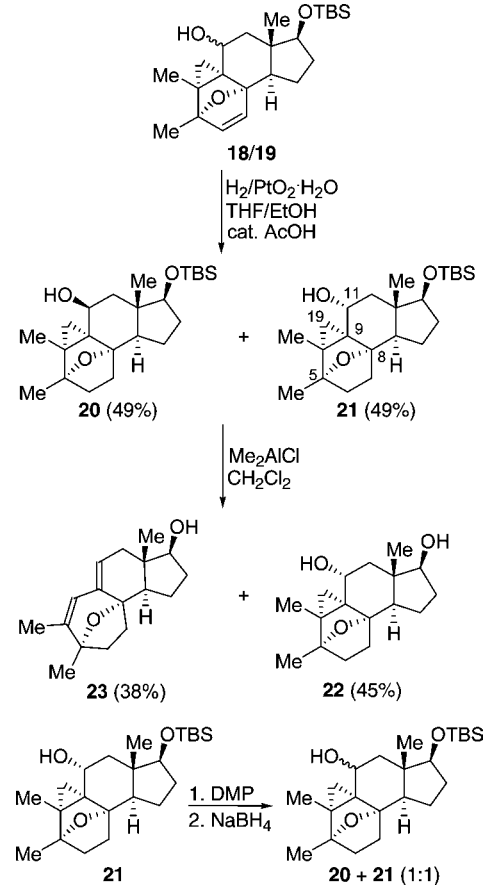
dition reaction, we have conducted a model study (Scheme 3). Treatment of 2-methylcyclopent-2-enone with 2-methylfuran in the presence of $BF_3{\cdot}OEt_2$(cat.)/EtOH (1 equiv)/$MeNO_2$ gave **12** (82%).[12] Alkylation of **12** using $BrCH_2CO_2Me$/$LiNH_2$/THF gave **13** (75%) as a single stereoisomer.[13] Selective reduction of **13**, followed by protection of the C17-OH as its TBS ether, gave **14**. Reduction and oxidation of **14** provided the aldehyde **15**. Addition of the cyclopropenyl lithium reagent **16**[14] to **15** at −50 °C, followed by warming to 23 °C, resulted in the formation of two separable compounds **18** (42.5%) and **19** (42.5%). The intermediate addition adduct **17** could be detected (after protonation) by TLC. The stereochemical assignments of **18** and **19** followed from the transformations described in Scheme 4.

The key step in the last part of this work involves a cyclopropylcarbinol rearrangement. This is precedented by Barton's work on the synthesis of cycloartenol, where the amine **A** (see structures in ref,15a 15b) was treated with $NaNO_2$/AcOH in aqueous MeOH to give **B**.[15a] Furthermore, Kupchan's work on 9β,19-cyclo steroids demonstrated that both C11 epimers of **C** were converted into **D** on treatment with H_2SO_4 in dioxane.[15b] It is reasonable to speculate that in the biosynthesis of the cortistatins a cyclopropylcarbinol rearrangement of a 11-hydroxy-9,10-cyclopropyl steroid might be responsible for the BC-ring diene. It should be noted

(15) (a) Barton, D. H. R.; Kumari, D.; Welzel, P.; Danks, L. J.; McGhie, J. F. *J. Chem. Soc. C* **1969**, 332–336. (b) Kupchan, S. M.; Findlay, J. W. A.; Hackett, P.; Kennedy, R. M. *J. Org. Chem.* **1972**, *37*, 2523–2532.



Scheme 4. Lewis Acid Mediated Cyclopropylcarbinyl Rearrangement



that the BC-ring diene in **1** has been observed in other *Buxus* alkaloids[16] but not the 5,8-oxido functionality.

Hydrogenation of a 1:1 mixture of **18** and **19** over Adam's catalyst gave an inseparable mixture of **20** and **21** in 98% yield, Scheme 4. Treatment of a mixture of **20** and **21** in CH_2Cl_2 with excess Me_2AlCl at −20 °C and warming the solution to 23 °C resulted in the conversion of the C11 axial β-epimer **20** into the ring BC-diene **23** (38%), desilylated at C17. The unreactive equatorial C11 α-epimer **21** (under these reaction conditions) was desilylated at C17 to give **22** (45%), which was found to possess the desired 5,8-α-oxido bridge by X-ray crystallography (Figure 2).

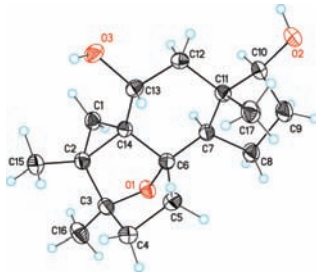
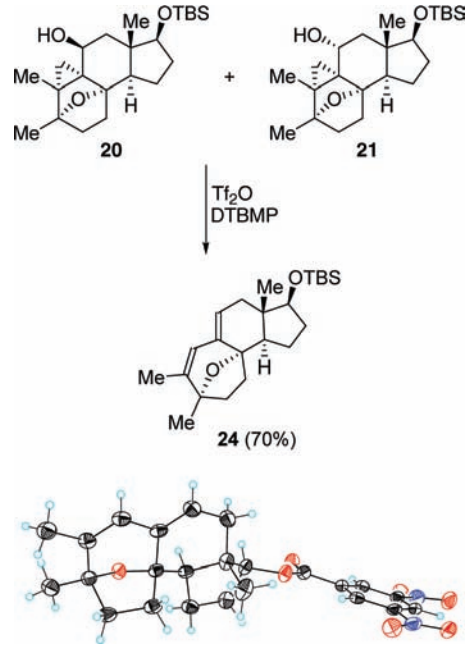


Figure 2. ORTEP of **22**. Displacement ellipsoids are scaled to the 50% probability level.

The stereochemical relationship between **20** and **21**, with respect to the 5,8-oxido bridge, was ascertained when a 1:1 mixture of **20** and **21** was exposed to an equimolar amount of Me_2AlCl, under the same reaction conditions as before. Compound **20** was consumed in the formation of the diene **24** (C17 silyl group in tact), and **21** was recovered. Oxidation of **21** to the cyclopropyl ketone (see Supporting Information) followed by reduction with $NaBH_4$/EtOH, Scheme 4, gave **20** and **21** (1:1). It follows from these results that the stereochemical relationship between **20** and **21** is that they are epimers at C11. Furthermore, **18**−**21** have the same 5α,8α-oxido bridge and 9α,10α-cyclopropane stereochemistry, which corresponds to **3a**-*exo* in Scheme 1.

To ionize the C11 hydroxyl group in the equatorial epimer **21**, the mixture of **20** and **21** was treated with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH_2Cl_2 at 0 °C and then warmed to 23 °C to give **24** (70%), Scheme 5. The

Scheme 5. Cyclopropylcarbinyl Rearrangement ORTEP of C17 3,5-Dinitrobenzoate Derivative of **24**[a]



[a] Displacement ellipsoids are scaled to the 50% probability level.

structure of **24**, as its C17 3,5-dinitrobenzoate derivative, was confirmed by X-ray crystallography.

This sequence of reactions from the two commercial starting materials to **24** is 9 steps and provides 30% overall yield. Efforts are currently underway toward the total synthesis of **1**, using the strategy described herein.

Acknowledgment. The Welch Chair (F-0018) is thanked for their support of this work.

Supporting Information Available: Complete experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901537N

(16) Khuong-Huu, F.; Herlam-Gaulier, D.; Khuong-Huu, M.; Stanislas, E.; Goutarel, R. *Tetrahedron* **1966**, *22*, 3321–3327.