Tetrahedron Letters 49 (2008) 6613–6616

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A novel α,β-unsaturated nitrone-aryne [3+2] cycloaddition and its application in the synthesis of the cortistatin core

Mingji Dai [a], Zhang Wang [a], Samuel J. Danishefsky [a,b,*]

[a] Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA
[b] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065, USA

ARTICLE INFO

Article history:
Received 26 August 2008
Accepted 2 September 2008
Available online 9 September 2008

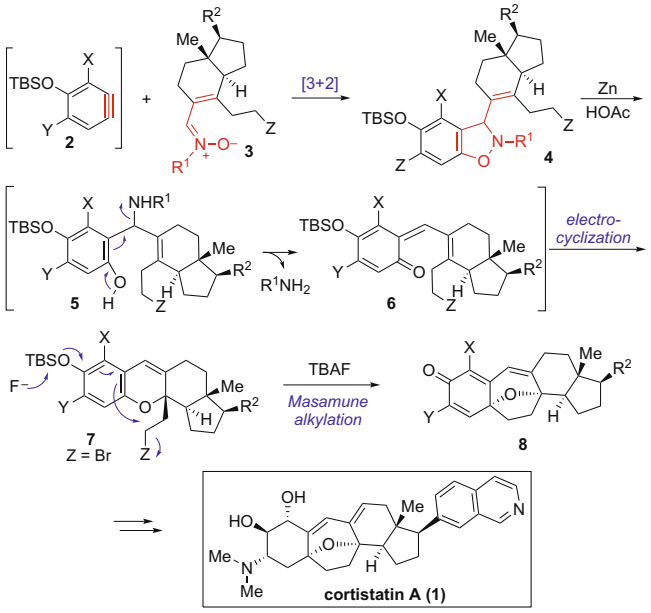
ABSTRACT

We describe here a novel α,β-unsaturated nitrone-aryne [3+2] cycloaddition. The resulting benzoisoxazolines underwent N–O bond reduction–elimination–electrocyclization sequence to furnish a variety of polysubstituted 2*H* or 2-alkylated-1-benzo-pyrans. The application of this methodology was further demonstrated in the synthesis of the oxa[3.2.1]octene moiety of cortistatin A.

As described in the previous Letter, we have been pursuing a total synthesis of cortistatin A (**1**) in the context of an aggressive program directed to the discovery of even more valuable cortistatin analogs. Isolated by Kobayashi and co-workers,[1] cortistatin A has received a great deal of attention from the synthetic community, due to its promising biological activity and unusual structural features.[2] These efforts culminated in the first synthesis of cortistatin A by Baran and co-workers.[3] A total synthesis of **1** was recently accomplished by the Nicolaou group.[4] In designing a synthetic strategy toward **1** that would be amenable to a program of diverted total synthesis,[5] we envisioned an intermediate of the type **8** to be a key launching point, from which we could prepare a range of cortistatin analogs.[6] In the preceding Letter, we demonstrated an efficient route to the cortistatin pentacyclic core via a Snieckus reaction and subsequent Masamune alkylation.[7] Herein, we explore a very different approach to compound **7**.

As shown in Scheme 1, we envisioned employing a defining 1,3-dipolar cycloaddition reaction[8] between generic aryne **2** and α,β-unsaturated nitrone **3**, to generate benzoisoxazoline **4**. The latter would be advanced to the desired benzopyran **7** through sequential reductive N–O bond cleavage, 1,4-elimination, and 6π-electrocyclization. Finally, Masamune alkylation of **7** would afford intermediate **8**. Interestingly, there is little precedent for the type of [3+2] cycloaddition proposed herein (**2** + **3** → **4**). To the best of our knowledge, only one example of an α,β-unsaturated nitrone-aryne [3+2] cycloaddition[9] has been reported. Furthermore, there are a paucity of examples of even simple nitrone-aryne [3+2] cycloadditions.[10] Recognizing the potential general applicability of this type of reaction to the synthesis of complex molecules, and hoping to apply this general strategy to the synthesis of cortistatin A, we sought to develop and optimize a generally useful α,β-unsaturated nitrone-aryne [3+2] cycloaddition protocol.

Our initial investigations were focused on the sterically unencumbered nitrone substrates **9a–c** and the benzyne derived from 2-bromophenyl triflate **10**. The α,β-unsaturated nitrones were prepared from the corresponding α,β-unsaturated aldehydes by treatment with alkylated hydroxylamine (see supplementary data for details). As shown in Table 1, when a solution of α,β-unsaturated

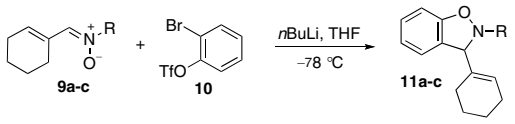


Scheme 1. Proposed nitrone-aryne [3+2] cycloaddition en route to cortistatin A (**1**).

* Corresponding author. Tel.: +1 212 639 5501; fax: +1 212 772 8691.
E-mail address: danishes@mskcc.org (S. J. Danishefsky).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.019

Table 1
Cycloaddition of α,β-unsaturated aldehydes (**9**) with benzyne derived from **10**[a]



9a-c **10** **11a-c**

Entry	–R	Ratio **9**:**10**	Yield (**11**)	RSM (**9**)
1	–*t*Bu (**9a**)	2:1	49% (**11a**)	54%
2	–*t*Bu (**9a**)	1:1	47% (**11a**)	28%
3	–*t*Bu (**9a**)	1:1.2	51% (**11a**)	37%
4	**–*t*Bu (9a)**	**1:2**	**74% (11a)**	**10%**
5	–Me (**9b**)	1:2	50% (**11b**)	ND
6	–Bn (**9c**)	1:2	38% (**11c**)	ND

[a] Cycloaddition reaction condition optimization: To a solution of **9** and **10** in THF at −78 °C was added *n*BuLi (1 equiv to **10**). After workup, product **11** was purified by silica gel chromatography. RSM: recovered starting material (**9**); ND: not determined.

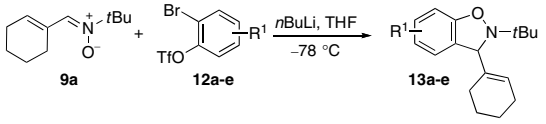
nitrone **9a** and 2-bromophenyl triflate **10** was treated with *n*BuLi at –78 °C, the desired benzoisoxazoline **11a** was isolated in moderate to good yields, with recovery of starting material **9a** (entries 1–4). The best yield (74%) was observed when a 1:2 ratio of **9a**:**10** was employed (entry 4). In this case, the reaction was complete within 5 min, and longer reaction times did not lead to improvements in yield. Methylated (**9b**) and benzylated (**9c**) nitrones gave significantly lower reaction yields in comparison to the *t*Bu nitrone (**9a**), presumably due to acidic protons located α to the nitrogen center (entries 5 and 6).

With these improved conditions in hand, we sought to probe the generality of the reaction with respect to the nature of the bromoaryl triflate component (see supplementary data for synthetic details). As shown in Table 2, the reaction is capable of efficiently accommodating a range of functionalities. While all reactions proceeded in moderate to good yield, we did observe poor product regioselectivities when 2-bromo-4-methoxyphenyl triflate **12b** or 1-bromonaphthalen-2-yl triflate **12c** was used (entries 2 and 3). These findings were not unexpected, since the conjugation effect does not influence the electronic properties of the aryne's reactive orbitals, due to their perpendicular relationship to the aromatic π-electron system. Based on this theory, electron-withdrawing or electron-donating groups *ortho* to the aryne could polarize the frontier orbital of the aryne dipolarophile, and therefore help to control the regioselectivity. Steric factors must also be taken into account. In fact, when 2-bromo-3-methoxyphenyl triflate **12d** was used, only product **13d** was obtained in 74% yield. The structure of **13d** was unambiguously verified by X-ray crystallography.[11] The electron donating—TMS group (**12e**) served to completely invert the regioselectivity, furnishing **13e** as the only cycloadduct in modest yield (41%).

We next prepared a range of α,β-unsaturated nitrone substrates. Nitrones **14a–c** were combined with **10**, under the standard reaction conditions. Each substrate smoothly underwent cycloaddition to furnish products **15a–c** in good yield (Table 3). However, almost no stereoselectivity was observed with nitrones **14a** and **14b**, presumably reflecting the remoteness of the resident stereocenter. We note that the lack of stereocontrol observed in these cases will not permanently impact our own synthetic efforts toward cortistatin A, since our strategy calls for the elimination of the newly generated stereocenter in subsequent steps.

Having established the substrate scope of the 1,3-dipolar cycloaddition between α,β-unsaturated nitrones and arynes, we now sought to develop an efficient protocol to convert the cycloadduct to a compound of the general type **16** (Table 4). First, reductive cleavage of the N–O bond was accomplished through exposure to Zn/AcOH. The resulting amino-phenol was heated in toluene.

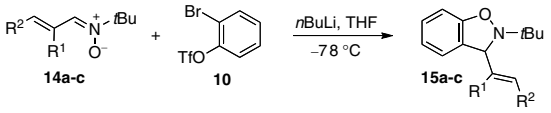
Table 2
Substrate scope of aryne component derived from **12**



9a **12a-e** **13a-e**

Entry	Substrate (**12**)	Product (**13**)	Yield (%)
1	**12a**	**13a**	56
2	**12b**	**13b** (1.5:1)	88
3	**12c**	**13c** (1.7:1)	70
4	**12d**	**13d**	74
5	**12e**	**13e**	41

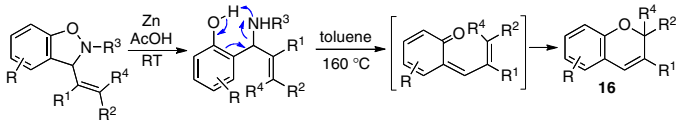
Table 3
Substrate scope of nitrone component (**14**)

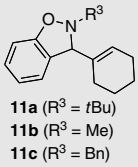
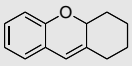
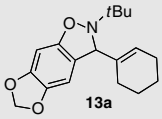
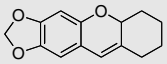
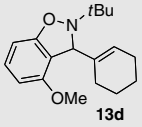
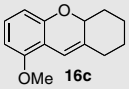
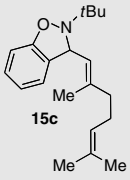
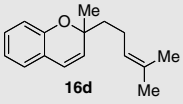
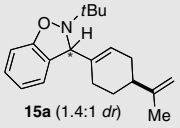
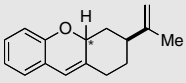
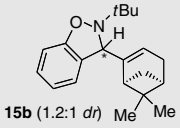
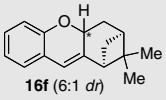


14a-c **10** **15a-c**

Entry	Nitrone (**14**)	Product (**15**)	Yield (%)
1	**14a**	**15a** (1.4:1 *dr*)	72
2	**14b**	**15b** (1.2:1 *dr*)	64
3	**14c**	**15c**	69

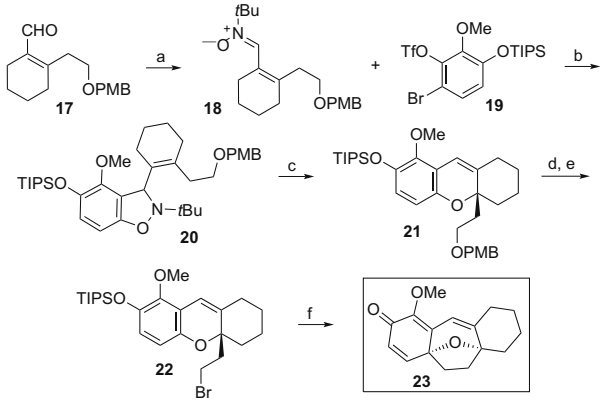
Table 4
Reduction–elimination–electrocyclization sequence



Entry	Substrate	Product	Time (h)	Yield
1	 **11a** (R^3 = *t*Bu) **11b** (R^3 = Me) **11c** (R^3 = Bn)	 **16a**	**11a**: 12 **11b**: 11 **11c**: 35	**11a**: 95% **11b**: 82% **11c**: 68%
2	 **13a**	 **16b**	1	71%
3	 **13d**	 **16c**	12	89%
4	 **15c**	 **16d**	12	83%
5	 **15a** (1.4:1 *dr*)	 **16e** (8:1 *dr*)	12	88%
6	 **15b** (1.2:1 *dr*)	 **16f** (6:1 *dr*)	12	92%

The hoped-for 1,4-elimination of the amino group proceeded smoothly, presumably assisted by intramolecular deprotonation of the phenol by the secondary amine. The quinomethide seemingly underwent spontaneous 6π-electrocyclization to furnish the desired compound **16**. It is worth noting that in generating the quinomethide, it is not necessary to activate the leaving group (for instance, through pre-formation of a quaternary ammonium salt).[12]

As shown in Table 4, a number of benzoisoxazolines were subjected to the reduction–elimination–electrocyclization sequence. All substrates underwent the sequence in good to excellent overall yield (entries 1–6). The *tert*-butylated benzoisoxazoline (**11a**) again proved superior to the methylated (**11b**) and benzylated (**11c**) substrates (entry 1). When the 1.4:1 diastereomeric mixture of **15a** was subjected to the reaction sequence, the product, **16e**, was obtained with enhanced stereoselectivity (8:1) (entry 5). The predominant isomer was the thermodynamically favored product, in which the isopropenyl group is situated in the equatorial position. Interestingly, NMR monitoring of the elimination–electrocyclization sequence revealed the reaction itself to be complete within



Scheme 2. Synthesis of the core structure (**23**) of cortistatin A. (a) *t*-BuNHOH-HOAc, TEA, CH_2Cl_2, rt, 6 days, 98%; (b) *n*-BuLi, THF, 2 h; (c) Zn, HOAc, rt, overnight; 170 °C, toluene, overnight, 55% from **18**; (d) Me_2BBr, *i*-Pr_2NEt, anisole, CH_2Cl_2, −78 °C, 20 min, 84%; (e) CBr_4, PPh_3, CH_2Cl_2, 1 h, 87%; (f) TBAF, THF, rt, 5 min, then 50 °C, 20 min or rt, 2 days, 52%.

1 h, although adduct was observed with no diastereoselectivity. Prolonged heating yielded higher diastereoselectivities, with the highest selectivity (12:1) observed after 18 h of heating (see supplementary data for details). A similar result was observed in the transformation of **15b** to **16f** (entry 6).

Having developed an efficient cycloaddition/cyclization protocol, we now explored the application of the method to the synthesis of the core structure of cortistatin A. Intermediate **23** was selected as a model system. As outlined in Scheme 2, aldehyde **17** was converted to nitrone **18**. Next, 1,3-dipolar cycloaddition between **18** and the aryne generated from **19**[13] provided benzoisoxazoline **20**, which was submitted to the standard reduction–elimination–electrocyclization sequence to afford **21** in 55% overall yield from **18**. Alcohol deprotection, followed by bromination, gave compound **22**, which, upon exposure to TBAF, readily underwent cyclization to provide the target intermediate, **23**.[14]

In summary, a general method for the 1,3-dipolar cyclization between α,β-unsaturated nitrones and arynes has been developed. In addition, a highly efficient N–O bond reduction–elimination–electrocyclization sequence furnishes polysubstituted 2*H* or 2-alkylated-1-benzo-pyrans. Finally, Masamune alkylation has been used to synthesize the oxa[3.2.1]octene moiety of cortistatin A.

Acknowledgments

We are grateful to the National Institutes of Health (HL25848 and CA103823) for the financial support of this research. M.D. thanks the Guthikonda Fellowship in Organic Chemistry, the Bristol-Myers Squibb Graduate Fellowship in Synthetic Organic Chemistry, and the Sylvia & Victor Fourman Fellowship for generous support. Z. W. thanks Eli Lilly for a graduate fellowship. We thank Ms. Daniela Buccella (Parkin Group) for the crystal structure analysis and the National Science Foundation (CHE-0619638) for acquisition of an X-ray diffractometer. Ms. Rebecca Wilson is thanked for valuable help in editing this Letter.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.019.

References and notes

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.
2. When we were preparing this manuscript, three elegant syntheses of the cortistatin core were reported, see: (a) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413; (b) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650; (c) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931.
3. Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241.
4. Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310.
5. (a) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038; (b) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329.
6. Dai, M.; Danishefsky, S. J. *Heterocycles*; published online, April 17th, 2008. COM-08-S(F)6.
7. Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, preceding paper.
8. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
9. Nagy, I.; Hajos, G.; Riedl, Z. *Heterocycles* **2004**, *63*, 2287.
10. For examples of nitrone-aryne [3+2] cycloaddition: (a) Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979; (b) Bigdeli, M. A.; Tipping, A. E. *J. Fluorine Chem.* **1992**, *58*, 101; (c) Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett* **1993**, 843; (d) Cambie, R. C.; Higgs, P. I.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1994**, *47*, 1815; (e) Kitamura, T.; Todaka, M.; Shin-machi, I.; Fujiwara, Y. *Heterocycl. Commun.* **1998**, 205; (f) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842.
11. CCDC 690676 contains the supplementary crystallographic data for compound **13d**.
12. Reference for synthesis of quinomethide by 1,4-elimination of quaternary ammonium salts: (a) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 8089; (b) Breuer, E.; Melumad, D. *Tetrahedron Lett.* **1969**, *23*, 1875.
13. See Supplementary data for synthetic details.
14. (a) Masamune, S. *J. Am. Chem. Soc.* **1961**, *83*, 1009; (b) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921.