ORGANIC LETTERS

2004
Vol. 6, No. 9
1477−1480

Construction of a C(30–38) Dioxabicyclo[3.2.1]octane Subtarget for (+)-Sorangicin A, Exploiting a Regio- and Stereocontrolled Acid-Catalyzed Epoxide Ring Opening

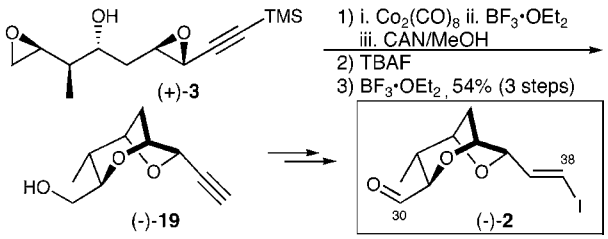
Amos B. Smith, III* and Richard J. Fox

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received February 27, 2004

ABSTRACT



In this paper, we report assembly of the novel dioxabicyclo[3.2.1]octane subtarget (–)-2, comprising the signature structural element of the potent antibiotic (+)-sorangicin A (1). The synthesis was achieved in 15 steps (1.5% overall yield) via a series of acid-catalyzed epoxide ring openings. The first, facilitated by the complex of alkyne (+)-3 with $Co_2(CO)_8$, proceeded in a highly regio- and stereoselective fashion.

In a world of ever-increasing antibiotic resistance, the discovery and development of new, potent antibiotics is of utmost importance. In 1985, Höfle and co-workers described the isolation of a family of novel macrolide antibiotics termed the sorangicins from *Sorangium cellulosum*, the same bacterial strain that furnished the epothilone antitumor agents.[1] Sorangicin A (**1**), the most potent congener, proved to be highly effective against a broad panel of both Gram-positive and Gram-negative bacteria, displaying average MIC values of 10 ng/mL and 10 μg/mL, respectively. At the molecular level, sorangicin A inhibits RNA polymerase in *Escherichia coli* and *Staphylococcus aureus*. Importantly, eukaryotic cells are unaffected. Thus, rats infected with virulent *E. coli* underwent marked improvement when dosed with sorangicin A.[2]

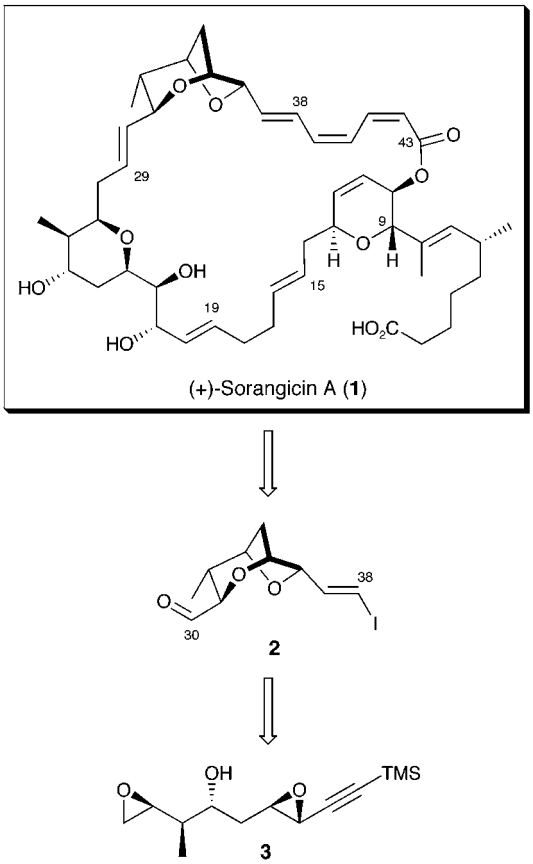
Given the novel architecture, including the signature dioxabicyclo[3.2.1]octane ring moiety, the *cis*,*cis*,*trans*-trienoate and the 31-membered macrolide ring, in conjunction with the reported, significant instability of the natural product to a variety of reagents (e.g., fluoride ion, DDQ, and the dissolving metal sodium amalgam),[3] the sorangicin class of natural products, and in particular sorangicin A (**1**), represent timely synthetic targets. In this paper, we disclose an effective, stereocontrolled assembly of a C(30−38) dioxabicyclo-[3.2.1]octane subtarget **2**.

Our synthetic analysis, illustrated in Scheme 1, called initially for construction of **2** via an acid-catalyzed cascade of epoxide openings, the first facilitated and stereocontrolled by an alkyne−$Co_2(CO)_6$ complex of bis-epoxide **3**. Subsequent installation of the vinyl iodide and oxidation would then complete construction of the bicyclic fragment.

(1) (a) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Höfle, G. *Tetrahedron Lett.* **1985**, *26*, 6031. (b) Jansen, R.; Irschik, H.; Reichenbach, H.; Schomburg, D.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1989**, 111.
(2) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1987**, *40*, 7.
(3) Schummer, D.; Irschik, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 293.

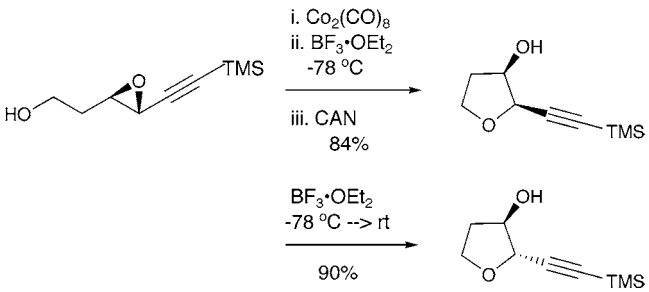
10.1021/ol049644s CCC: $27.50
Published on Web 03/30/2004

Scheme 1



In 1994, Mukai, Hanaoka, and co-workers[4] reported the regio- and stereoselective formation of 2-ethynyl-3-hydroxytetrahydrofuran derivatives via an endo-ring closure of 3,4-epoxy-6-substituted-5-yn-1-ols (Scheme 2). They discovered

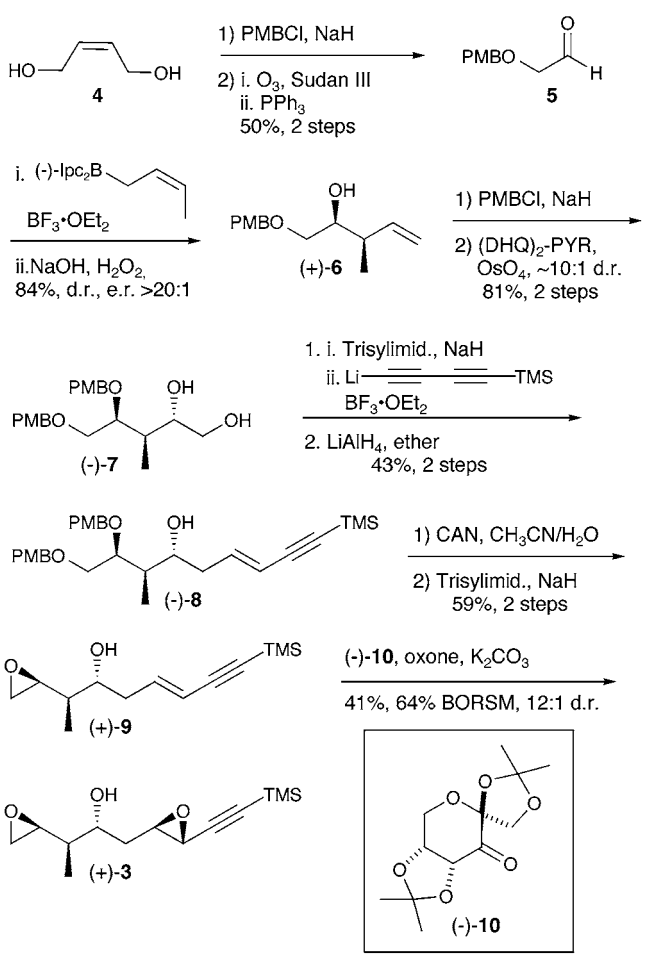
Scheme 2



that the epoxide opening can proceed either by retention or by inversion of stereochemistry at the propargylic stereocenter, depending on the reaction conditions.

With this precedent in mind, our point of departure for the construction of **3** entailed bis-protection of *cis*-2-butene-1,4-diol (PMBCl, NaH), followed by ozonolysis to afford aldehyde **5**[5] (Scheme 3, 50%, two steps). Asymmetric Brown

Scheme 3



crotylation[6] then furnished homoallylic alcohol (+)-**6**[7] in excellent yield and with high stereoselectivity (84%; d.r., e.r. >20:1).[8] Protection of the homoallylic hydroxyl and Sharpless dihydroxylation[9] led to diol (−)-**7** in good yield, after careful removal of the minor diastereomer by flash chromatography.

Enyne (−)-**8** was next prepared by one-flask Fraser-Reid epoxide formation,[10] followed by reaction with the lithium anion derived from 1,4-bis(trimethylsilyl)-1,3-butadiyne,[11] and in turn chemo- and stereoselective reduction of the

(4) (a) Mukai, C.; Sugimoto, Y.-i.; Ikeda, Y.; Hanaoka, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1161. (b) Mukai, C.; Sugimoto, Y.-i.; Ikeda, Y.; Hanaoka, M. *Tetrahedron* **1998**, *54*, 823.

(5) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 231.

(6) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(7) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946.

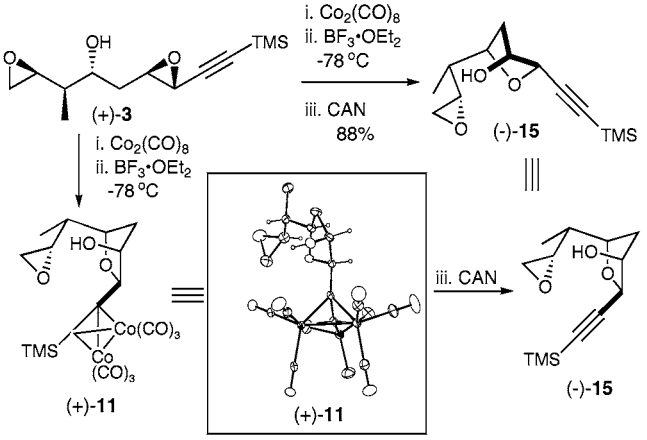
(8) The absolute stereochemistry and enantiomeric ratio of (+)-**6** was determined via the Kakisawa analysis of the derived Mosher esters: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. Also see the Supporting Information.

(9) (a) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (b) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

internal triple bond.[12] With (−)-**8** in hand, removal of the PMB groups, followed by a second Fraser-Reid[10] protocol led to epoxide (+)-**9**. Reagent-controlled diastereoselective epoxidation exploiting the elegant Shi conditions[13] furnished a mixture of diastereomers (12:1), which upon HPLC purification afforded the requisite cyclization precursor bis-epoxide (+)-**3** (41%, 64% BORSM).

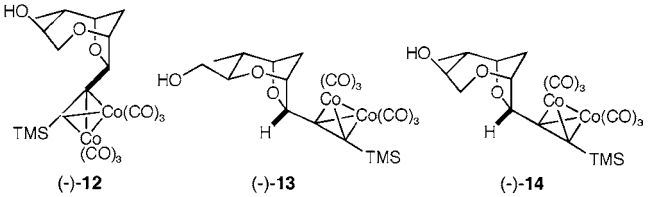
We initiated cyclization studies with the expectation of retention of configuration based on the precedent of Mukai, Hanaoka, and co-workers.[4] To this end, treatment of (+)-**3** with 1.1 equiv of $Co_2(CO)_8$ at ambient temperature, followed at −78 °C by a catalytic amount of $BF_3{\cdot}OEt_2$, yielded alkyne−cobalt complex (+)-**11** (Scheme 4). Importantly, the

Scheme 4



reaction proceeded with complete chemoselectivity at the activated propargylic epoxide. Single-crystal X-ray analysis verified that the first epoxide opening had indeed proceeded with retention of stereochemistry.[14]

To determine the feasibility of performing the second epoxide opening without isolation of (+)-**11**, we explored a variety of added acids and bases. Unexpectedly, (+)-**11** failed to produce any of the desired bicycle resulting from 6-exo-tet cyclization. Instead, with either CSA or PPTS, only selective formation of bicycle (−)-**12**, resulting from 7-endo-tet cyclization, was observed! Surprisingly, treatment of (+)-**11** with $BF_3{\cdot}OEt_2$ led to mixtures of the 7-membered bicycle (−)-**12**, along with the 6- and 7-membered bicycles (−)-**13** and (−)-**14**, respectively, both epimerized at the propargylic center! Bicycles (−)-**12**, (−)-**13**, and (−)-**14** were distinguishable through ^1H, COSY, and D_2O exchange experiments. Reexposure of the individual bicycles to the $BF_3{\cdot}$

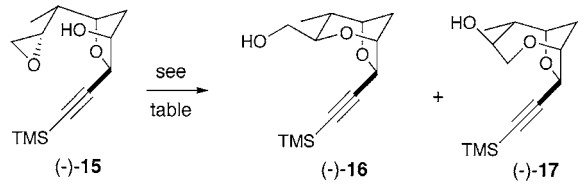


OEt_2 reaction conditions did not result in any change, thus suggesting that the cyclizations proceed under kinetic control.

Based on the X-ray crystal structure of (+)-**11**, we reasoned that the steric bulk of the cobalt complex might disfavor the desired 6-exo-tet pathway. To reduce the steric incumbrance, as well as to attenuate the ease of epimerization, we removed the cobalt moiety from the alkyne prior to attempting the second cyclization (Scheme 4). This three-step operation, performed in a single flask, furnished epoxide (−)-**15** in 88% yield.

With epoxide (−)-**15** in hand, ring opening of the second epoxide was reinvestigated (Table 1). Initially, we explored

Table 1. Examining the 6-exo- and 7-endo-tet Cyclizations of (−)-**15**



entry	conditions[a]	*t* (°C)	time (h)	(−)-**16**/(−)-**17**[b]	conv[b] (%)
1	CSA (0.1 equiv)	25	28	1:1	97
2	$BF_3{\cdot}OEt_2$ (0.1 equiv)	−78	25	1:6	10
3	$BF_3{\cdot}OEt_2$ (0.1 equiv)	0	1	1:1	100
4	$BF_3{\cdot}OEt_2$ (0.1 equiv)	40	0.5	1:1	100
5	$BF_3{\cdot}OEt_2$ (1.0 equiv)	−78	1	1:3	80
6	$BF_3{\cdot}OEt_2$ (2.0 equiv)	−78	0.75	1:3	93
7	$BF_3{\cdot}OEt_2$ (2.0 equiv)	0	0.3	1:1	100
8	5 M $LiClO_4{\cdot}OEt_2$, CSA (0.1 equiv)	25	1.5	1:1.1	10

[a] Entries 1−7 were run in CH_2Cl_2. [b] Ratios and conversions determined by 500 MHz ^1H NMR.

the cyclization under "standard" acidic conditions (see entries 1−7, Table 1). Unlike cobalt complex (+)-**11**, exposure of (−)-**15** to either CSA or $BF_3{\cdot}OEt_2$ furnished the desired 6-exo-tet product (−)-**16**, *albeit* at best as a mixture (ca. 1:1) with the 7-endo-tet bicycle (−)-**17**. Importantly, no epimerized products were observed. Attempts to increase this ratio with other Lewis acids (ca. $TiCl_4$ or $CeCl_3$) or under basic conditions (ca. KH, DMSO) proved unsuccessful. In an attempt to increase the amount of carbocation character in the ring-opening transition state, anticipated to favor attack at the epoxide secondary carbon, we explored the extremely polar solvent system of Grieco and co-workers[15] ($LiClO_4{\cdot}OEt_2$) (see entry 8, Table 1). Although these conditions dramatically increased the reaction rate (entry 1 vs 8, Table 1), the ratio of (−)-**16** to (−)-**17** did not improve.

(10) (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122.

(11) (a) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H. *Chem. Commun.* **1979**, 840. (b) Holmes, A. B.; Jones, G. E. *Tetrahedron Lett.* **1980**, *21*, 3111.

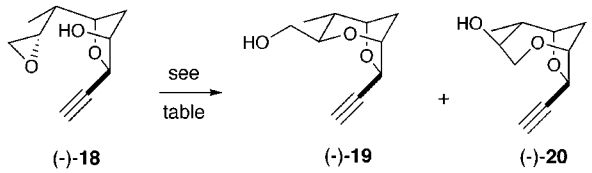
(12) Doolittle, R. E. *Synthesis* **1984**, 730.

(13) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

(14) For a mechanistic explanation of this double-inversion process see ref 5b.

We next reasoned that, since reducing the steric bulk of the alkyne led at least to some of the desired product, performing the second epoxide opening on the terminal acetylene might improve the yield of the desired 6-exo-tet bicycle. To this end, the TMS group was removed to furnish (−)-**18** (Table 2).

Table 2. Examining the 6-exo- and 7-endo-tet Cyclizations of (−)-**18**



(-)-**18** (-)-**19** (-)-**20**

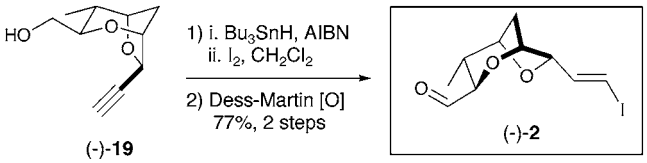
entry	conditions[a]	*t* (°C)	time (h)	(−)-**19**/ (−)-**20**[b]	conv[b] (%)
1	$BF_3{\cdot}OEt_2$ (0.1 equiv)	0	1	1.4:1	100
2	$BF_3{\cdot}OEt_2$ (10.0 equiv) (inverse addition)	40	5 min	2.1:1	100[c]
3	$BF_3{\cdot}OEt_2$ (10.0 equiv) (inverse addition)	80	4 min	1:1.2	100
4	$BF_3{\cdot}OEt_2$ (0.1 equiv)	25	1.5	1.8:1	100

[a] Entries 1 and 2 were run in CH_2Cl_2. Entries 3 and 4 were run in benzene. [b] Ratios and conversions determined by 500 MHz ^{1}H NMR. [c] Isolated yield for (−)-**19** was 65%.

Pleasingly, treatment of (−)-**18** under conditions identical to those employed in entry 3 (Table 1) increased the ratio of the desired bicycle (−)-**19** to 1.4:1 (see entry 1, Table 2). The results in Tables 1 and 2 further suggest that as the reaction rate increases, the amount of the desired 6-exo-tet bicycle increases (see entries 6 and 7, Table 1). With this in mind, our best conditions to date for the formation of (−)-**19** call for the dropwise addition of (−)-**18** to a solution of CH_2Cl_2 at reflux containing 10.0 equiv of $BF_3{\cdot}OEt_2$. Under these conditions, the ratio increased to 2.1:1 (entry 2, Table 2); the isolated yield of (−)-**19** was 65%. Again, reexposure of either (−)-**19** or (−)-**20** to the reaction conditions did not result in a change. Single-crystal X-ray analysis verified both the structure and stereochemistry of (−)-**19**.

With (−)-**19** in hand, final elaboration to coupling partner **2** was accomplished via radical-promoted hydrostannylation,[16] iodination, and Dess−Martin oxidation (Scheme 5).[17] This three step sequence furnished (−)-**2** in 77% yield.

Scheme 5



(-)-**19** (-)-**2**

In summary, an effective 15-step synthesis of dioxabicyclo[3.2.1]octane (−)-**2**, comprising the C(30−38) signature fragment of sorangicin A (**1**), has been achieved. The cornerstone of the synthetic strategy involved a kinetically controlled, regio- and stereoselective epoxide opening facilitated by the $Co_2(CO)_6$ complex of alkyne (+)-**3**. Importantly, in the second epoxide cyclization, both reducing the alkyne steric bulk and increasing the reaction rate led to a higher yield of the desired 6-exo-tet cyclization. Studies to improve the synthesis of (−)-**2** and to complete the total synthesis of (+)-sorangicin A (**1**) will be reported in due course.

Acknowledgment. Support was provided by the National Institutes of Health through Grant No. GM-29028 and an Eli Lilly and Dissertation Graduate Fellowships to R.J.F.

Supporting Information Available: Spectroscopic and analytical data for **2**−**9**, **11**, and **15**−**20** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049644S

(15) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.
(16) (a) Tolstikov, G. A.; Miftahov, M. S.; Danilova, N. A.; Vel'der, Y. L. *Synthesis* **1986**, 496. (b) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851.
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.