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Synthesis of a C4-*epi*-C1–C6 Fragment of FR901464 Using a Novel Bromolactolization

Brian J. Albert and Kazunori Koide*

Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260

koide@pitt.edu

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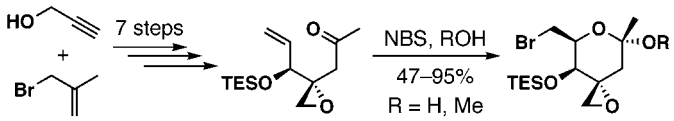
ABSTRACT



A synthesis of a C4-*epi*-C1–C6 fragment of the antitumor agent FR901464 is reported. The advanced intermediate prepared in this study contains two of the three correct stereocenters found in the C1–C6 moiety of FR901464. For the preparation of this intermediate, we have developed a highly diastereoselective bromolactolization of a *δ*-alkenyl ketone.

Discoveries of antitumor agents with novel mechanisms continue to be important in oncology and medicine.[1] In the quest for an anticancer agent with new modes of actions, scientists at Fujisawa Pharmaceutical Co. isolated FR901464 (Figure 1) from the culture broth of *Pseudomonas* sp. No. 2663.[2,3] FR901464 increases the transcriptional activity of a reporter gene driven by the SV40 promoter at 10 nM concentration.[3] This compound also exhibits cytotoxicity against various human solid tumor cell lines at low nanomolar concentrations.[3] Despite these unique biological activities of FR901464, the mode of action of FR901464 is poorly understood. To prepare various FR901464 analogues for biological studies, it is essential to develop a convergent synthetic strategy for this natural product. In this paper, we report the preparation of a highly functionalized C4-*epi*-C1−C6 fragment of FR901464.[4]

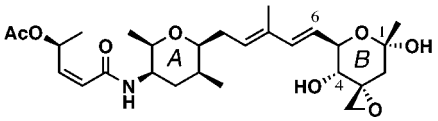


Figure 1. Structure of FR901464.

Chemical syntheses of FR901464 have been accomplished by two groups. The first total synthesis of FR901464 by the Jacobsen group[5] involves the application of a powerful enantioselective hetero-Diels−Alder reaction.[6] The second total synthesis by the Kitahara group uses the chiral pool for starting materials.[7] Both groups further functionalized the B-ring after the union of advanced intermediates, and installation of the spiroepoxide in the late stages of the syntheses proved problematic. To prepare various analogues of FR901464 for biological studies, a convergent synthetic approach using highly functionalized coupling intermediates would be desirable.

(1) (a) Ferrante, K.; Winograd, B.; Canetta, R. *Cancer Chemother. Pharmacol.* **1999**, *43*, S61−S68. Gibbs, J. B. *Science* **2000**, *287*, 1969−1973. (b) Darnell, J. E., Jr. *Nat. Rev. Cancer* **2002**, *2*, 740−749. (c) Pompetti, F.; Pilla, D.; Giancola, R. *BioEssays* **2003**, *25*, 104−107.

(2) (a) Nakajima, H.; Sato, B.; Fujita, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 1196−1203. (b) Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96−99.

(3) Nakajima, H.; Hori, Y.; Terano, H.; Okuhara, M.; Manda, T.; Matsumoto, S.; Shimomura, K. *J. Antibiot.* **1996**, *49*, 1204−1211.

(4) The numbering in this paper follows ref 2b.

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(6) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.

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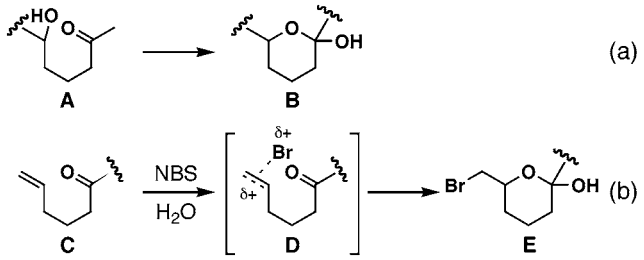
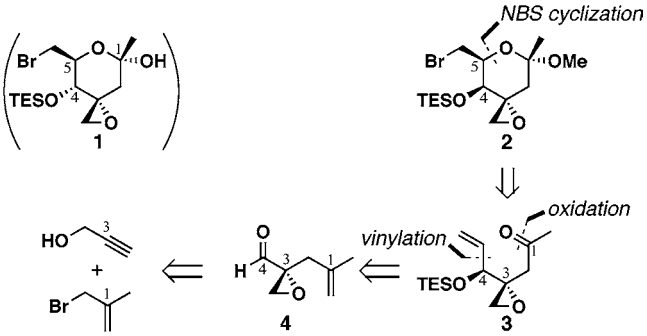
Scheme 1. Lactol Formations



As part of our efforts toward a convergent synthesis of FR901464, we targeted the highly functionalized C1−C6 fragment of FR901464, **1**, which contains a hemiketal functionality at the C1-position and the spiroepoxide (Scheme 2). Scheme 1 illustrates two concepts of lactol formation. It

Scheme 2. Retrosynthetic Analysis

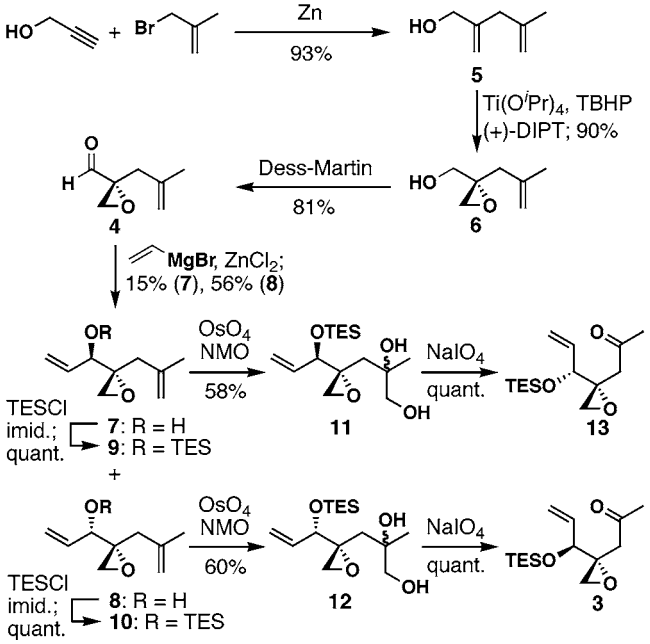


is well-documented that a six-membered hemiketal can be formed from the corresponding δ-hydroxyketone as shown in eq (a) (**A** → **B**). In contrast to this widely used approach, the conceptually different tactic shown in eq (b) has never been explored. Similar intramolecular cyclization tactics utilizing aromatic aldehydes/ketones onto alkynes[8] and amide carbonyls onto alkenes[9] exist but are conceptually different from our proposed approach. In the tactic shown in eq (b), the ketone functionality of δ-alkenyl ketone **C** is used as a nucleophile rather than an electrophile: The treatment of **C** with *N*-bromosuccinimide (NBS) provides π-complex **D** in situ, which then reacts with the carbonyl oxygen atom, and subsequent nucleophilic attack of a water molecule furnishes bromolactol **E**.

Scheme 2 shows our retrosynthetic analysis of methyl glycoside **2**, a C-4 epimer of **1**, based on this alternative approach. According to eq (b), if the olefin of **3** reacts with NBS to form the corresponding π-complex, the carbonyl oxygen atom would react with the complex intramolecularly to furnish compound **2** in the presence of methanol. To prepare alkenyl ketone **3** for this cyclization, we planned to install the olefin by the vinylation of epoxyaldehyde **4** and the ketone by the oxidation of the olefin in **4**. We expected this epoxyaldehyde to be prepared by the coupling of propargyl alcohol and methallyl bromide promoted by zinc dust followed by sequential oxidation steps (vide infra).

Scheme 3 illustrates the preparation of alkenyl ketone **3** and its diastereomer **13**. The known allyl alcohol **5** was

Scheme 3. Preparation of Alkenyl ketones **13** and **3**[a]



prepared from propargyl alcohol and methallyl bromide in the presence of zinc dust in 93% yield according to the literature.[10] The regio- and enantioselective Sharpless epoxidation of this allyl alcohol afforded the desired epoxy alcohol **6** in 90% yield and greater than 95% ee.[11] Treatment of this epoxy alcohol with Dess−Martin periodinane afforded aldehyde **4** in 81% yield.[12] With this aldehyde in hand, we examined various vinylation conditions to produce allylic alcohols **7** and **8**. Addition of vinylmagnesium bromide to aldehyde **4** in THF resulted in the formation of alcohols **7** and **8** in 23% and 28% yield, respectively, together with the formation of the primary alcohol **5** in 30% yield. A modified procedure, in which 2 equiv of $ZnCl_2$ and 4 equiv of vinylmagnesium bromide were premixed, furnished alcohols **7** and **8** in 15% and 56%, respectively. At this stage, we separated these diastereomers by standard column chromatography

Both alcohols **7** and **8** were protected as the corresponding triethylsilyl (TES) ethers in quantitative yields upon treatment with TESCl and imidazole. Subsequently, each of the resulting silyl ethers **9** and **10** were treated with catalytic OsO_4 and stoichiometric 4-methylmorpholine *N*-oxide (NMO)

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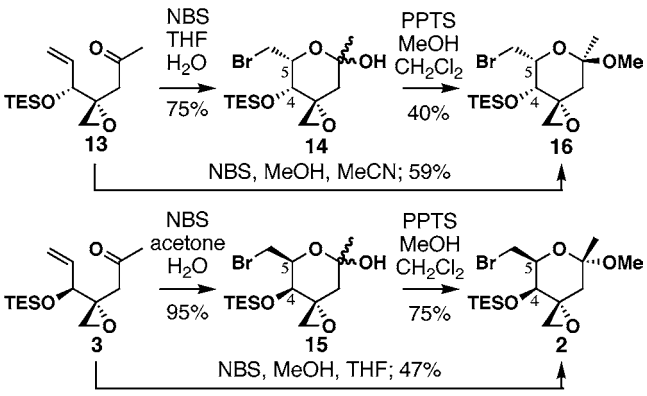
to afford the putative diols **11** and **12** as a mixture of diastereomers in 58% and 60% total yield, respectively. Oxidative cleavages of these diols with $NaIO_4$ generated alkenyl ketones **13** and **3** in quantitative yields. Thus, each of the key alkenyl ketones **13** and **3** was prepared in seven steps from commercially available propargyl alcohol and methallyl bromide.

Now the stage was set to test the chemistry shown in eq (b). Gratifyingly, upon treatment of alkenyl ketone **13** with NBS in THF/H_2O, the expected cyclization proceeded to furnish lactol **14** in 75% yield (Scheme 4). Unambiguous

Scheme 4. Bromolactolizations of **13** and **3**[a]

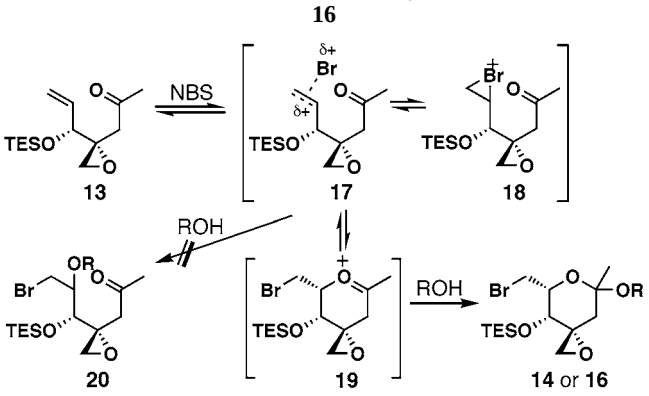


structural determination was accomplished after this lactol was converted to the corresponding methyl glycoside derivative **16** under standard conditions (cat. PPTS, MeOH) in 40% yield. Although highly diastereoselective, the NBS-promoted lactolization generated only the C5-epimer, **14**, of the desired compound **1**. Therefore, we turned our attention to alkenyl ketone **3** to generate the desired configuration at the C5-position. Under similar conditions as above (NBS, acetone/H_2O), alkenyl ketone **3** was converted to lactol **15** as a sole diastereomer in 95% yield. Compound **15** contains two of the three correct stereocenters of the desired fragment **1**. Because compound **15** exists as a mixture of anomers, methyl glycoside derivative **2** was prepared in 75% yield under the standard conditions (cat. PPTS, MeOH). The unambiguous structural characterization of **2** was accomplished by X-ray crystallographic analysis (Supporting Information).

From the conversions of **13** to **14** and **3** to **15**, it was unclear whether a bromide ion-activated olefin reacted with the oxygen atom of the ketones (or their hemiketals) or a water molecule in each transformation, followed by a spontaneous cyclization. To elucidate the mechanism of the NBS-promoted cyclizations of **13** and **3**, we employed the cyclizations of these ketones in the mixture of MeOH and MeCN or THF. Although the isolated yields are moderate, only **16** and **2** were isolated, and the NMR analysis of the reaction mixtures did not identify any methyl ethers as a result of nucleophilic attach of MeOH at the C5-positions. We also found that these NBS-promoted cyclizations proceeded smoothly in THF, acetone, and MeCN, but sluggishly in CH_2Cl_2.

These results indicate that the NBS-promoted bromolactolization of δ-alkenyl ketone **13** proceeds by the following manner (Scheme 5). When a bromide ion approaches

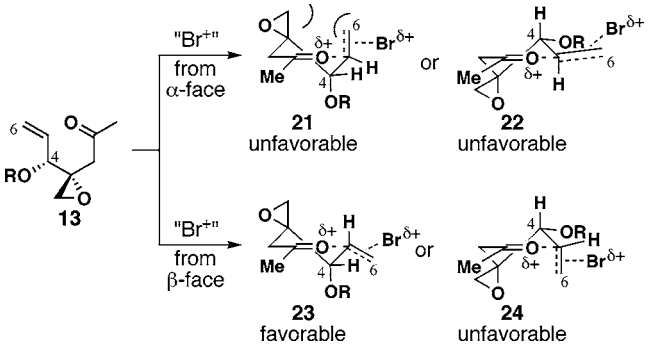
Scheme 5. Bromolactolization Pathways That Lead to **14** and **16**



compound **13**, π-complex **17** is formed. This π-complex either establishes an equilibrium with bromonium ion **18**[13] or reacts with the carbonyl oxygen atom to form oxocarbenium ion **19**. While the formation of bromonium ion **18** is possible, it has been postulated that related intramolecular haloetherifications proceed via a transition that resembles a reactant-like π-complex.[14] Therefore, we speculate that the bromolactolization proceeds via **17**, which reacts with the carbonyl oxygen atom to generate the oxocarbenium ion **19**. This oxocarbenium ion intermediate subsequently reacts with ROH (R = H or CH_3) to form hemiketal **14** (R = H) or ketal **16** (R = CH_3). As the results shown in Scheme 4 indicate, the formation of ether **20** can be ruled out.

To account for the high *cis*-diastereoselectivity of the bromolactolization, we further analyzed the possible transition states (Scheme 6). If a bromide ion approaches compound

Scheme 6. Plausible Transition States for Bromolactolization (R = TES)



13 from its α-face, the subsequent cyclization proceeds via transition state **21** or **22**. Transition state **21** appears to be more favorable than **22** by a stereoelectronic effect: the π_{C5-C6}- - -Br bond (- - -: partially formed bond) is electron deficient, so an electron-withdrawing group destabilizes the

transition state. When the C4−O bond is nearly parallel to the π_{C5-C6}- - -Br bond as shown in **22**, the orbital overlap between the π_{C5-C6}- - -Br bond and σ^*_{C4-O} destabilizes transition state **22**.[15] In contrast, in transition state **21**, the C4−O bond is nearly orthogonal to the π_{C5-C6}- - -Br bond, minimizing the destabilization of this transition state by σ^*_{C4-O}. For the same stereoelectronic reason, if a bromide ion approaches from the β-face of **13**, then transition state **23** is more favorable than **24**. Thus, transition states **21** and **23** are preferred over **22** and **24** for this stereoelectronic effect.

Comparison between transition states **21** and **23** reveals the observed preference for **23**: The *pseudo*-1,3-diaxial interaction between the epoxide methylene and the C6 methylene destabilizes **21**. In contrast, no major steric encumbrances are present in transition state **23**. Therefore, we postulate that **23** is stereoelectronically and sterically the most favorable among the four-half-chair transition states shown in Scheme 6. This preference for **23** accounts for the formation of **16** from **13**.

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In summary, we have developed an NBS-promoted bromolactolization of δ-alkenyl ketones to form the corresponding cyclic (hemi)ketals. This method provided the C4-epimer and the C5-epimer of compound **1**, and the reaction conditions are found to be compatible with a TES ether and a spiroepoxide and highly *cis*-selective in these cases. This cyclization method should be applicable to the preparation of various (hemi)ketals and acetals. To further understand the origin of the high diastereoselectivity in the transformations of **13** to **14** and **3** to **15**, we are currently investigating the NBS-promoted cyclizations of related substrates.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, HRMS, and X-ray analysis data for all new compounds in PDF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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