ORGANIC LETTERS

2006
Vol. 8, No. 13
2847−2850

Total Synthesis of the Interleukin-1β Converting Enzyme Inhibitor EI-1941-2 Using Tandem Oxa-electrocyclization/Oxidation[1]

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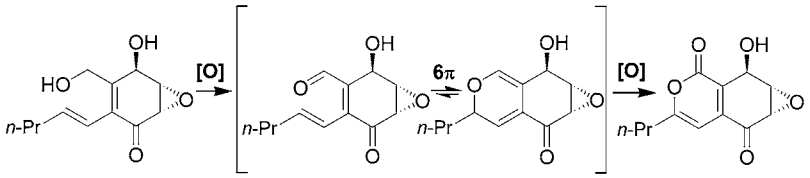
Received April 20, 2006

ABSTRACT



The total synthesis of the interleukin-1β converting enzyme inhibitor EI-1941-2 was achieved utilizing tandem oxidation/oxa-electrocyclization/oxidation to access a key α-pyrone intermediate. Support for the tandem reaction mechanism was obtained by evaluation of a stepwise oxidation protocol.

Koizumi and co-workers recently reported the isolation[2] and structure elucidation[3] of the interleukin-1β converting enzyme (ICE) inhibitors EI-1941-2 (**1**) and EI-1941-1 (**2**) (Figure 1). ICE is a cysteine protease which functions to cleave the biologically inactive precursor of interleukin-1β, an enzyme implicated in inflammatory disease.[4] In light of our interest[5] in the synthesis of epoxyquinoid natural products,[6] we have targeted these compounds for synthesis. Recently, the Hayashi group[7] reported the enantioselective synthesis of both **1** and **2**, and Mehta and Roy[8] completed an enantioselective synthesis of **1**. Herein, we report the enantioselective synthesis of EI-1941-2 (**1**) utilizing a tandem oxidation/oxa-electrocyclization/oxidation cascade to access a key α-pyrone intermediate.

Our synthetic approach to **1** arose serendipitously during studies toward the synthesis of epoxyquinol A (**3**)[5f] and related natural products (Scheme 1).[5] In these studies, selective oxidation of primary alcohol **4** to the corresponding aldehyde **5** was attempted. Previous work in our group showed that dienal **5** should readily undergo 6π-oxa-electrocyclization[9,10] to the corresponding diastereomeric 2*H*-pyrans (**6**/**6′**) and further dimerization to **3**.[5c,f] However, when

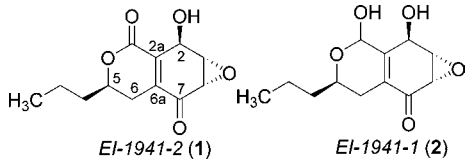


Figure 1. EI-1941 natural products.

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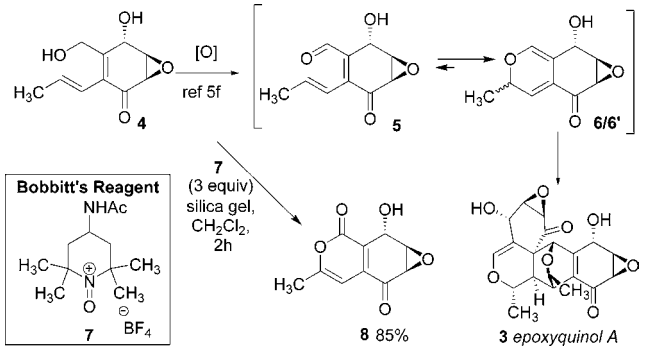
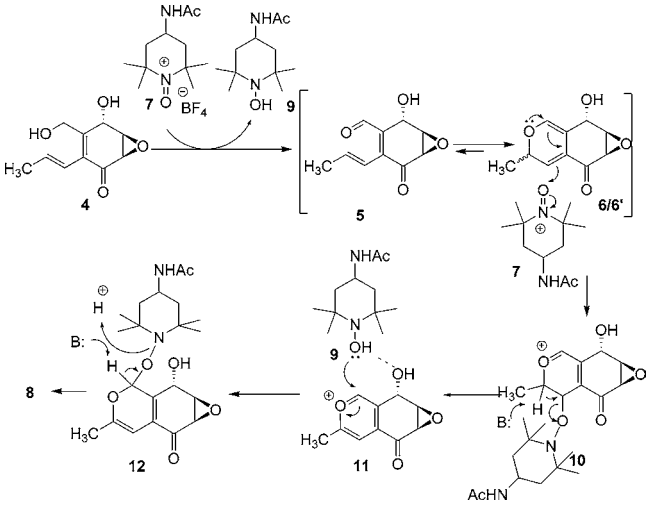
10.1021/ol060954f CCC: $33.50
Published on Web 05/27/2006

Scheme 1. Serendipitous α-Pyrone Formation



Scheme 2. Proposed Mechanism for α-Pyrone Formation

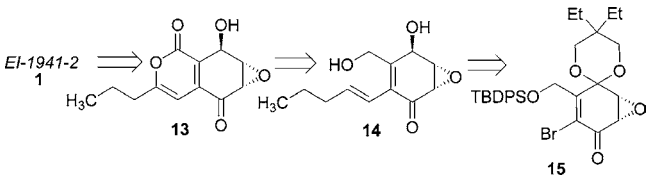


4 was treated with oxoammonium salt **7** (Bobbitt's Reagent, Scheme 1, inset),[11] α-pyrone[12,13] **8** was obtained unexpectedly in 85% yield.[14]

A proposed mechanism for the formation of α-pyrone **8** involves initial oxidation of primary alcohol **4** to aldehyde **5** followed by oxa-electrocyclization to afford 2*H*-pyrans **6/6′** (Scheme 2). The electrophilic oxoammonium salt **7** may then react with the 2*H*-pyran[15] moiety, resulting in intermediate **10** which may undergo elimination generating pyrylium salt **11**. Alternate pathways for pyrylium generation may entail an ene-type mechanism[16] or direct hydride abstraction.[17,18] Nucleophilic hydroxylamine **9**, the reduced form of **7** generated in the initial oxidation step (**4** → **5**),[19] may then condense[20] with **11**, resulting in formation of intermediate **12** followed by elimination[21] to provide the observed α-pyrone **8**. Mehta and Roy[8] have proposed an alternate mechanism for a related α-pyrone formation involving initial oxidation with an oxoammonium species to a carboxylic acid followed by electrophilic cyclization−elimination.

On the basis of the oxa-electrocyclization/oxidative α-pyrone formation process, a retrosynthetic analysis of EI-1941-2 was developed (Scheme 3). EI-1941-2 (**1**) may be derived from hydrogenation of the C5−C6 olefin of α-pyrone **13**. Compound **13** may be prepared by α-pyrone formation from diol **14** utilizing the tandem oxa-electrocyclization/oxidation protocol. Epoxyquinol **14** may result from global deprotection of **15**, followed by selective reduction of the resulting C2 carbonyl. The unsaturated side chain in **14** may be installed by Stille cross-coupling of vinyl bromide **15** and the corresponding *E*-vinylstannane. The antipode of **15** has been previously reported by our laboratory.[5b]

Scheme 3. Retrosynthetic Analysis for EI-1941-2



The synthesis was initiated beginning with the known quinone monoketal **16** (Scheme 4). Tartrate-mediated nu-

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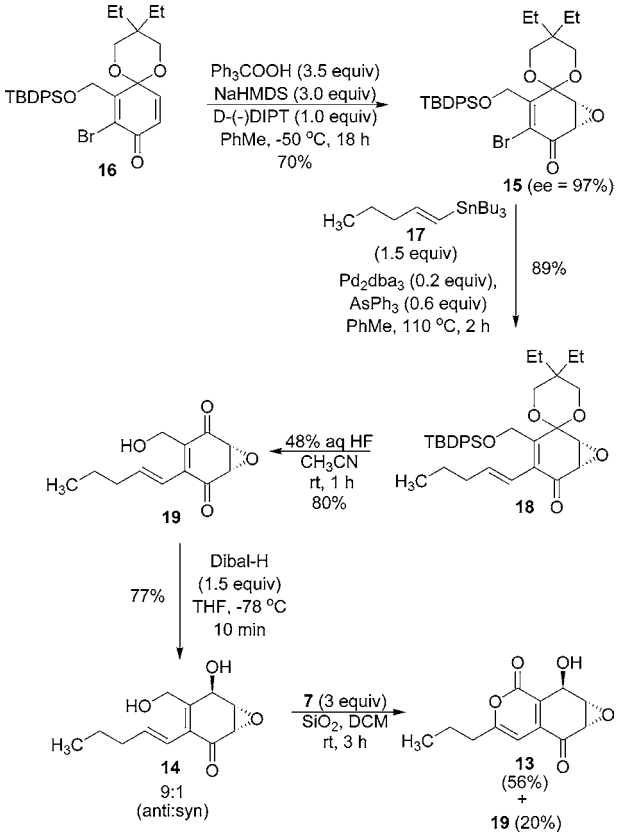
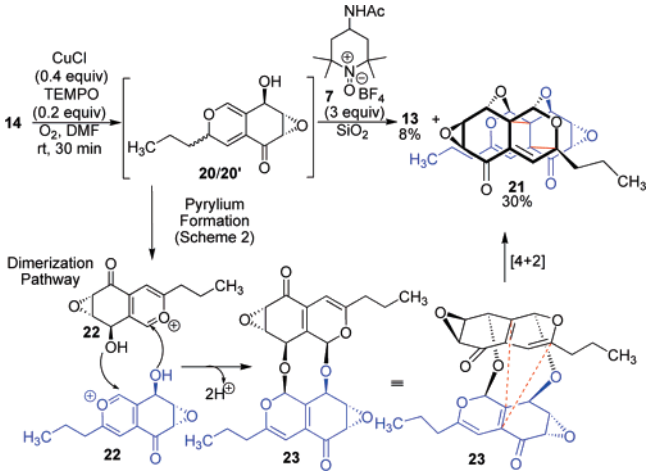
Scheme 4. Forward Synthesis of Intermediate **13**



Scheme 5. Formation of a Novel, Polycyclic Dimer



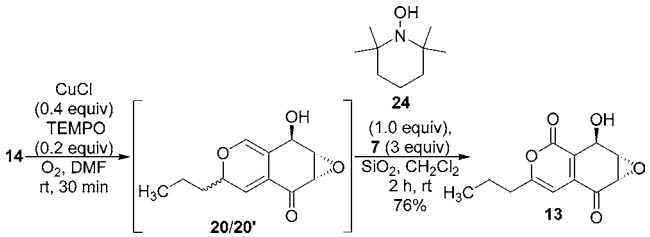
cleophilic epoxidation[5b] of **16** using diisopropyl D-tartrate, trityl hydroperoxide, and NaHMDS in toluene at −50 °C for 18 h produced the desired α-epoxide **15** in 70% yield (97% ee). Stille cross-coupling[22] with *E*-vinyltributylstannane **17**, $Pd_2(dba)_3$, and $AsPh_3$ in toluene afforded the protected epoxyquinone monoketal **18** (89%). Global deprotection with 48% HF provided epoxyquinone **19** (80%) which was reduced in a regioselective fashion with DIBAL-H to provide **14** in 77% yield with 9:1 *anti:syn* diastereoselectivity. For α-pyrone formation, we employed the oxa-electrocyclization/oxidation sequence (Scheme 1) which afforded a 56% yield of α-pyrone **13** along with 20% of secondary alcohol oxidation product **19**.

To further investigate our proposed mechanism for α-pyrone formation (Scheme 2), we considered whether the 2*H*-pyran derived from alcohol **14** may undergo further oxidation with **7** to afford α-pyrone **13**. Accordingly, treatment of **14** with TEMPO and CuCl under an oxygen atmosphere in DMF[5c,f,23] resulted in the formation of diastereomeric 2*H*-pyrans **20/20′** (Scheme 5). Immediate treatment of **20/20′** with oxoammonium salt **7** resulted in the formation of the desired α-pyrone **13** in 8% yield along with **21** (30%). An analogous dimer was formed when **4** (Scheme 1) was subjected to this series of conditions; the structural assignment was based on single-crystal X-ray analysis.[13,14] The formation of these dimeric compounds supports our initial mechanistic rationalization for α-pyrone formation (Scheme 2) and the intermediacy of both 2*H*-pyrans **20/20′** and pyrylium **22**.

A rationalization for the formation of polycyclic dimer **21** is shown in Scheme 5. 2*H*-pyrans **20/20′** undergo pyrylium formation (Scheme 2) generating intermediate **22**. Dimerization of **22** through attack of the pyrylium by the secondary alcohol of another molecule of **22** provides bis-2-alkoxy-2*H*-pyran **23**, which may undergo intramolecular [4 + 2]-cycloaddition[24] to polycyclic dimer **21**. The facial selectivity of the [4 + 2]-cycloaddition appears to be governed by the *syn* 1,3-ether tether, which directs the cycloaddition away from the epoxide moiety.

We postulated that the suppressed formation of α-pyrone **13** observed in the two-step reaction sequence may be due to reduced amounts of hydroxylamine **9** (Scheme 2). In preliminary experiments, treatment of diastereomeric 2*H*-pyrans **20/20′** with 1.0 equiv of 2,2,6,6,-tetramethylpiperidin-1-oxyl[25] **24** and 3.0 equiv of **7** afforded **13** in 76% yield without formation of polycyclic dimer **21** (Scheme 6).[13] This result highlights the likely importance of hydroxylamine byproduct **9** in the α-pyrone formation pathway.

Scheme 6. Alternate Synthesis of α-Pyrone **13**



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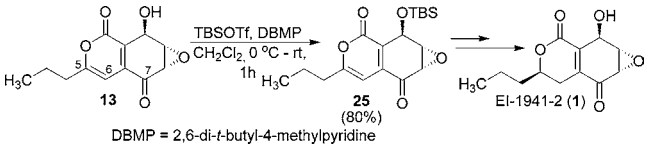
Completion of the synthesis of **1** relied on our ability to effect the selective reduction of the C5−C6 olefin of **13**. Protection of the secondary alcohol in **13** was achieved by treatment with TBSOTf/2,6-di-*tert*-butyl-4-methyl pyridine (80%, Scheme 7). As was the case in prior efforts by both

Scheme 7. Completion of the EI-1941-2 Synthesis



Hayashi[7] and Mehta,[8] we were unable to effect this reduction in the presence of the C7 carbonyl and thus completed our synthesis in an analogous fashion.[13] Synthetic EI-1941-2 (**1**) was found to be spectroscopically identical to the natural product.[3]

In conclusion, the total synthesis EI-1941-2 (**1**) has been achieved utilizing an oxoammonium salt-mediated tandem oxidation/oxa-electrocyclization/oxidation cascade for generation of a key α-pyrone intermediate. A two-step oxidation sequence helped to elucidate the mechanism of this transformation while also providing access to a novel polycyclic dimer via [4 + 2]-dimerization. Further applications of the oxa-electrocyclization/oxidation process are ongoing in our laboratory and will be reported in due course.

Acknowledgment. Financial support from the American Cancer Society (RSG-01-135-01), Bristol-Myers-Squibb, and Merck Research Laboratories is gratefully acknowledged. We thank Professor James M. Bobbitt (University of Connecticut) for providing reagent **7** and for helpful discussions, and Dr. Fumito Koizumi (Kyowa Hakko Kogyo Co., Ltd.) for providing a sample of natural EI-1941-2.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060954F