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Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization

Wei He, Jie Huang, Xiufeng Sun,† and Alison J. Frontier*

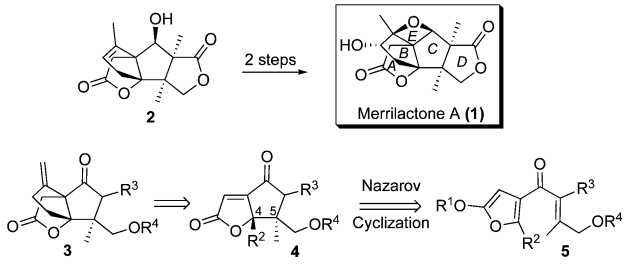
Department of Chemistry, University of Rochester, Rochester, New York 14627

Received November 14, 2006; E-mail: frontier@chem.rochester.edu

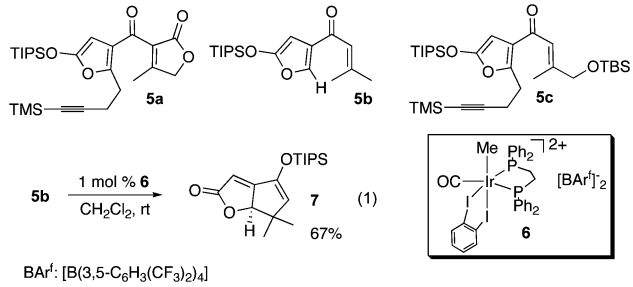
Merrilactone A (**1**, Scheme 1) is a structurally unique pentacyclic sesquiterpene dilactone isolated in 2000 by Fukuyama and coworkers from the *Illicium merrillianum*. It was identified as a potent nonpeptidal neurotrophic factor that promotes neurite outgrowth in the culture of fetal rat cortical neurons at a remarkably low concentration of 0.1 μmol/L.[1] In addition to its promising bioactivity, the merrilactone A pentacycle is riddled with synthetic challenges. The molecule sports seven contiguous chiral centers, of which three are quaternary, and bears a highly substituted cyclopentane ring at its core (see ring C, Scheme 1). This densely functionalized yet compact structure has captured the attention of a number of synthetic chemists. Danishefsky and Birman achieved the first total synthesis of (±)-merrilactone A, based on a Diels−Alder cycloaddition.[2] A year later, Inoue, Sato, and Hirama reported a strategy based on the ring contraction of a 1,4-cyclooctenedikетone,[3] and more recently, Mehta and Singh reported a third synthesis based on the desymmetrization of 1,4-cyclopentenedione.[4] Other novel approaches to this unique carbocyclic system have also been disclosed.[5,6] In this communication, we report an efficient stereoselective synthesis of (±)-merrilactone A featuring the Nazarov cyclization of a silyloxyfuryl enone as the key step.

Our laboratory has been involved in developing Nazarov cyclizations of polarized divinyl ketones.[7] This research direction was spawned by the synthetic strategy targeting merrilactone A described herein (Scheme 1). Our overall strategy involved elaboration of an intermediate of type **3** into intermediate **2**, which Birman and Danishefsky were able to convert into merrilactone A in two steps.[2] Intermediate **3** would be accessible from cyclization of a cyclopentanoid derivative of type **4**. We imagined that the adjacent stereocenters at C-4 and C-5 of **4** could arise from the Nazarov cyclization of an achiral precursor **5**. This idea was attractive because the 4π electrocyclization is expected to follow a conrotatory pathway,[8] which would allow stereospecific creation of both chiral centers.

Scheme 1. General Synthetic Strategy Targeting Merrilactone A



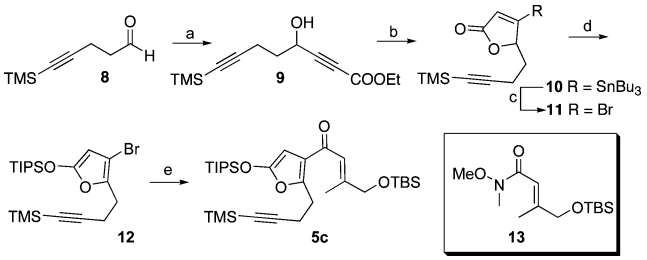
Initial experiments focused on silyloxyfuran **5a**, which has an electron-rich aromatic donor and an electron-poor butenolide acceptor. Unfortunately, no cyclization of **5a** was observed upon exposure to a wide range of Lewis acid promoters. However, it was found that the simpler ketone **5b** underwent smooth Nazarov cyclization catalyzed by the dicationic catalyst $[Ir(CO)(Me)(dppe)(DIB)]^{2+}$-$(BAr^f)^-_2$ (**6**)[9] to give the enol silane **7** (eq 1). Copper triflate did not catalyze the cyclization of **5b**, possibly because it lacks the electron-withdrawing group important for reactivity in polarized Nazarov cyclizations.[7] Triisopropylsilyl triflate also did not catalyze the cyclization of **5b**, underlining how important the strong Lewis acid character of Ir^{III} complex **6** is to the success of the cyclization.[10]



To our knowledge, these are the first examples of Nazarov cyclizations involving a silyloxyfuran component.[11] We were also pleased to note that a quaternary center was formed during the cyclization of **5b**, which was an important prerequisite for application to merrilactone A. These results encouraged us to embark upon the synthesis and cyclization of the fully functionalized silyloxyfuran **5c**.

To this end, known aldehyde **8**[12] was coupled with the lithium anion of ethyl propiolate to give alcohol **9** (Scheme 2).[13] Addition of a higher order stannylcuprate to the alkynyl ester accompanied by in situ lactonization gave the vinyltin compound **10** in one synthetic operation.[14] It was then possible to convert **10** to the vinyl bromide **11** through very slow addition of bromine in dichloromethane. The desired silyloxyfuran **12** was ultimately obtained in quantitative yield by treatment with triisopropylsilyl triflate under basic conditions. The lithium anion of **12** was generated using

Scheme 2. Synthesis of Silyloxyfuran **5c**[a]



[a] Reagents and conditions: (a) ethyl propiolate with *n*-BuLi, THF, −78 °C, then **8**, 88%; (b) $Bu_3Sn(Bu)(CN)CuLi_2$, THF/MeOH, −78 °C, 90%; (c) Br_2, CH_2Cl_2, rt, 93%; (d) Et_3N, triisopropylsilyl triflate, CH_2Cl_2, −78 to 0 °C, quantitative; (e) *t*-BuLi, ether, then **13**, 82%.

† Present address: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877.

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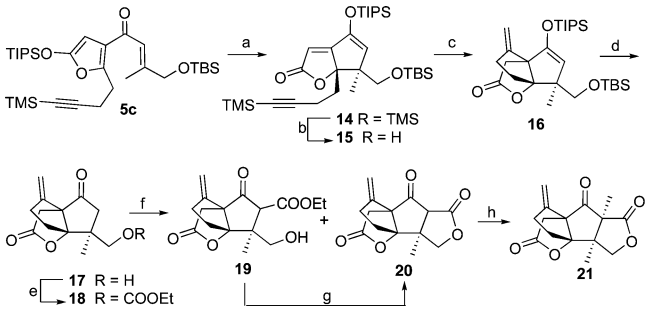
Scheme 3. Construction of Rings B, C, and D[a]



[a] Reagents and conditions: (a) **6** (2 mol %), CH_2Cl_2, 87%; (b) $AgNO_3$, KCN, THF/EtOH/H_2O, 83%; (c) AIBN, Bu_3SnH, benzene, reflux, then *p*-TsOH, rt, 91%; (d) TBAF, THF, rt, 99%; (e) pyridine, DMAP, ethylchloroformate, 95%; (f) NaH, THF, rt; (g) *p*-TsOH, benzene, reflux, 0.5 h, 90% from **18**; (h) NaH, CH_3I, HMPA, THF, rt, 97%.

t-BuLi, and addition to the α,β-unsaturated Weinreb amide **13**[15] gave rise to **5c** in satisfactory yield.

As hoped, Nazarov cyclization of **5c** proceeded smoothly with the dicationic iridium catalyst **6** in dichloromethane to give a single diastereoisomeric product **14** (Scheme 3). In this event, the stereocenters at both C-4 and C-5 were created stereospecifically, setting the stage for the assembly of the multiple fused rings of target **2** (rings A−D, Scheme 1).

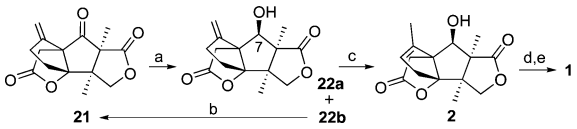
Approaches involving cyclization of the protected alkyne **14** did not provide access to ring B. However, removal of the trimethylsilyl group allowed smooth radical cyclization of the resultant 1,6-enyne **15**, and treatment with acid led to protiolysis of the intermediate vinyl stannane to give the exocyclic olefin (**16**).[16] Fluoride-induced deprotection of the resultant **16** furnished the hydroxyketone **17**, which was easily converted to the carbonate **18**.[17] Treatment of **18** with excess NaH in THF triggered intramolecular nucleophilic lactonization[18] to give a 1:1 mixture of desired bislactone **20** and its open counterpart **19**. Treatment of this mixture with *p*-toluenesulfonic acid (*p*-TsOH) under reflux effected cyclization of **19**, delivering tetracyclic lactone **20** in 90% overall yield from carbonate **18**.[17] α-Methylation of ketone **20** was accomplished with sodium hydride and iodomethane in the presence of HMPA, affording **21** in nearly quantitative yield (Scheme 3).[19]

The necessary adjustments to the carbon skeleton were carried out as shown in Scheme 4. Reduction of **21** was a bit problematic: use of either L-Selectride or diisobutylaluminum hydride resulted in overreduction, and sodium borohydride gave a 1.2:1 ratio of the desired alcohol **22a** and the undesired C-7 epimer **22b**. Fortunately, the yield of the **22a**/**22b** mixture was 93%, and it was possible to separate the isomers and achieve nearly quantitative oxidation of the undesired **22b** (Scheme 4). This recycling procedure enabled us to regenerate ketone **21** and funnel all material toward **22a**.

Tetracycle **22a** was then isomerized into **2** by refluxing with *p*-TsOH in benzene. Finally, **2** was converted into merrilactone A following the known procedures. The spectroscopic data of both intermediate **2** and our synthetic (±)-**1** were identical to those previously reported.[2a]

Further studies of this new variant of the Nazarov cyclization are underway, as well as investigation of methods that would allow asymmetric synthesis of merrilactone A.

Scheme 4. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 93% (**22a**:**22b** = 1.2:1); (b) Dess−Martin periodinane, CH_2Cl_2, 98%; (c) *p*-TsOH, benzene, reflux, 4 h, 92%; (d) *m*-CPBA, CH_2Cl_2, rt; (e) *p*-TsOH, CH_2Cl_2, rt, 68% over two steps.

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

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