Natural Products Synthesis

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Total Synthesis of (±)-Merrilactone A**

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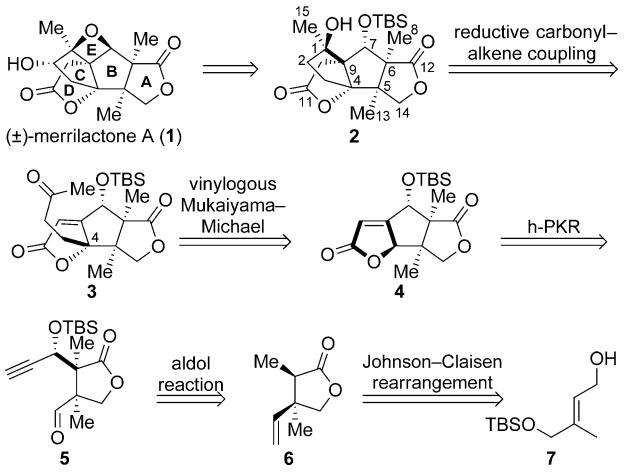
Merrilactone A (**1**, Scheme 1), a complex cage-shaped pentacyclic sesquiterpene, was isolated from pericarps of *Illicium merrillianum* by Fukuyama and co-workers in 2000.[1] Its structure was established by NMR spectroscopic and X-ray crystallographic analyses, and the absolute configuration was determined by using the Mosher protocol.[1a,2] In addition to an oxetane moiety, two γ lactone functionalities, and a highly substituted cyclopentane ring at its core, this molecule contains seven contiguous chiral centers, including five quaternary ones. Moreover, this sesquiterpene was identified as a nonpeptidal neurotrophic factor that promoted neurite outgrowth in the culture of fetal rat cortical neurons.[1a] Owing to its unique structure as well as the potential officinal value for neurodegenerative diseases, merrilactone A has attracted considerable attention from the synthetic community.[3] So far, Danishefsky,[3a,b] Inoue and Hirama,[3c–e] Mehta,[3f] Frontier,[3g,h] Greaney[3i] and their respective co-workers have accomplished its total or formal syntheses. Relevant synthetic studies have been documented for this natural product.[3j–m] Herein we wish to report a novel and efficient approach to the synthesis of (±)-**1**.



Scheme 1. Retrosynthetic analysis of (±)-merrilactone A. TBS = *tert*-butyldimethylsilyl.

The Pauson–Khand reaction (PKR)[4] and hetero-Pauson–Khand reaction (h-PKR)[5] have been increasingly applied to the total syntheses of natural products. Having realized an expeditious assembly of (+)-mintlactone through an intramolecular ynal h-PKR,[5c] we have recently completed an efficient total synthesis of (±)-merrilactone A, further showcasing the power of this key transformation. We envisioned that **1** could be generated from **2** after inversion of the configuration at C7 and dehydration of the tertiary alcohol followed by oxetane formation;[1b] **2** should be accessible from **5** by intramolecular h-PKR (**5**→**4**), vinylogous Mukaiyama-Michael reaction[6] (**4**→**3**), and SmI_2-mediated reductive carbonyl–alkene coupling[7] (**3**→**2**; Scheme 1). Finally, ynal **5** could be obtained from the known alcohol **7**[8] through a combined Johnson–Claisen rearrangement[9] and lactonization (**7**→**6**) followed by a series of reactions, including an aldol reaction,[10] hydroxyl silylation, and alkene ozonolysis (**6**→**5**).

Our synthesis started from the known alcohol **7**,[8] which was treated with triethyl orthopropionate and propionic acid to afford the Johnson–Claisen rearrangement[9] product **8** (d.r. = 3.8:1), which was desilylated and lactonized to form **6** (d.r. = 2.9:1, 89% over two steps from **7**) in the presence of $TsOH{\cdot}H_2O$ (Scheme 2). Sequential treatment of **6** with LDA, $Ti(OiPr)_3Cl$, and 3-trimethylsilylpropynal led to a 1:1 mixture of inseparable aldols **9a** and **9b** in 81% combined yield along with two other isomers (inseparable mixture, 9% in total).[10] The presence of the methyl and vinyl substituents at C5 does not have a steric influence on the aldol reaction of **6**, thus resulting in essentially no facial selectivity on the lactone ring. Nevertheless, **9a** and **9b** were both useful for the subsequent transformations. After hydroxyl protection, alkyne desilylation,[11] and selective ozonolysis,[12] alcohols **9a** and **9b** were smoothly converted into the two separable ynals **10a** and **10b** (1:1). Transformation of **10b** into **10a** was realized through reversal of configuration at C5 by reduction of **10b** with $NaBH_4$ and intramolecular transesterification (an equilibrium process), separation of **11a** and **11b** (1.9:1) by flash chromatography, and subsequent oxidation of **11a** with DMP. Gratifyingly, **11a** was also obtained from **11b** by initial conversion into a mixture of **11a** and **11b** (1.6:1) using a Cs_2CO_3-promoted intramolecular transesterification, and subsequent separation of the isomers by flash chromatography.

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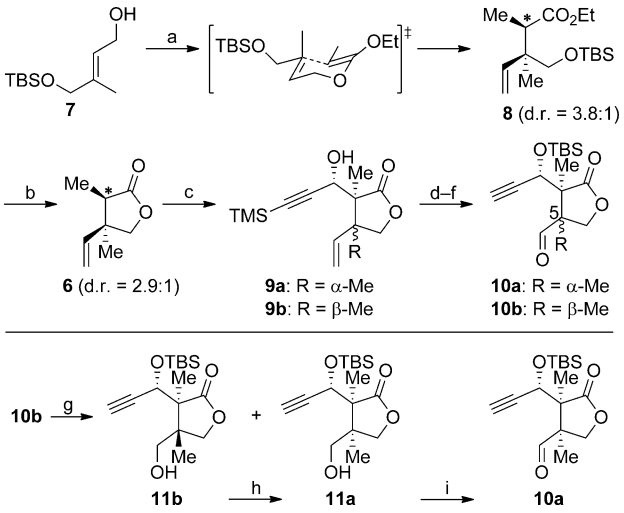
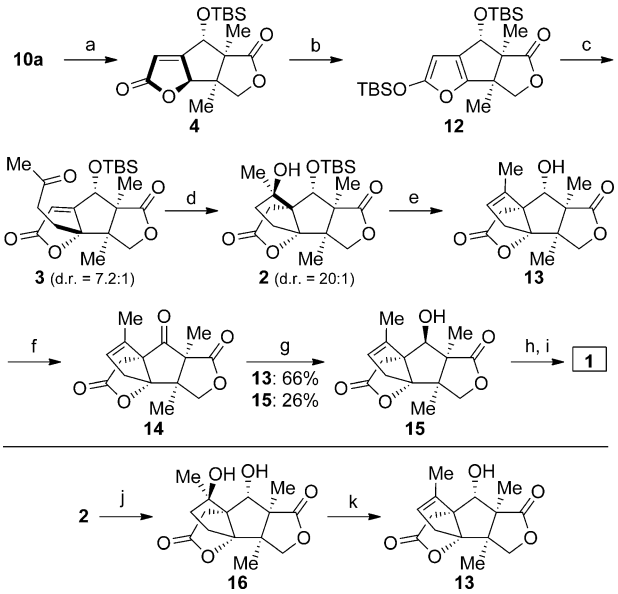


Scheme 2. Synthesis of aldehyde **10a**. a) Triethyl orthopropionate, propionic acid, 135 °C, 8 h, d.r. = 3.8:1; b) $TsOH{\cdot}H_2O$, MeOH, 20 °C, 3 h, 89% (2 steps, d.r. = 2.9:1); c) LDA, $Ti(OiPr)_3Cl$, 1.5 h, 3-trimethylsilylpropynal, −78 °C to −30 °C, 0.5 h, 81%, **9a**:**9b** = 1:1; d) TBSOTf, 2,6-lutidine, 30 °C, 3 h, 92%; e) K_2CO_3, MeOH, RT, 2 h, 96%; f) O_3, MeOH, CH_2Cl_2, −78 °C, 5 min, then Me_2S, −78 °C→RT, 8 h, 97%, **10a**:**10b** = 1:1; g) $NaBH_4$, $CHCl_3$, RT, 16 h, 89%, **11a**:**11b** = 1.9:1; h) Cs_2CO_3, $CHCl_3$, RT, 12 h, 89%, **11a**:**11b** = 1.6:1; i) DMP, CH_2Cl_2, RT, 5 h, 80%. DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 3. Synthesis of (±)-merrilactone A (**1**). a) $[Mo(CO)_3(DMF)_3]$, THF, then CO, RT, 5 h, 69%; b) TBSOTf, Et_3N, CH_2Cl_2, RT, 15 h, 87%; c) MVK, $Tf_2CHCH_2CHTf_2$, CH_2Cl_2, −78 °C→−20 °C, 3 h, 69%, (d.r. = 7.2:1); d) SmI_2, THF, RT, 2 h, 88% (d.r. = 20:1); e) $TsOH{\cdot}H_2O$, benzene, reflux, 2 d, 91%; f) DMP, CH_2Cl_2, RT, 2 h, 94%; g) $NaBH_4$, MeOH, 0 °C, 1 h, **13**: 66%, **15**: 26%; h) DMDO, CH_2Cl_2, acetone, RT, 7 h; i) $TsOH{\cdot}H_2O$, CH_2Cl_2, RT, 1 d, 74% (2 steps); j) TBAF/AcOH, THF, 0 °C, 1 h, 82%; k) $TsOH{\cdot}H_2O$, benzene, reflux, 7 h, 90%. DMDO = dimethyl dioxirane, MVK = methyl vinyl ketone, TBAF = tetrabutylammonium fluoride.

With ynal **10a** in hand, the key h-PKR was carried out to form the B and D rings in **1** (Scheme 3). Reaction of **10a** with $Mo(CO)_3(DMF)_3$[5b,c] in THF under an argon atmosphere at room temperature for one hour indeed afforded tricycle **4** in 58% yield. Compound **10a** was not consumed completely upon replacement of argon with carbon monoxide. Delightfully, exposure of **10a** to $[Mo(CO)_3(DMF)_3]$ in THF at room temperature initially under an argon atmosphere for ten minutes and then under a CO atmosphere (balloon) for five hours produced **4** (69%),[13] the C4 configuration of which was confirmed by NOESY experiments. α,β-Unsaturated lactone **4** was converted into silyloxyfuran **12**,[14] which was treated with MVK in the presence of $Tf_2CHCH_2CHTf_2$[15] following Taguchi's protocol[6d,e] to furnish ketone **3** (61%) along with *epi*-**3** (8%) through a vinylogous Mukaiyama–Michael reaction. The good facial selectivity (7.2:1) observed for the reaction might be a result of the presence of the bulky TBS group on the α face of **12**. Switching the catalyst from $Tf_2CHCH_2CHTf_2$ to $TiCl_4$,[6c] $BF_3{\cdot}Et_2O$,[6c] or $SnCl_4$[6c] resulted in lower yields (48–57%) of **3**, the structure of which was confirmed by X-ray crystallographic analysis (see the Supporting Information).[16] As mentioned above, the C ring could be formed through a reductive carbonyl–alkene coupling reaction.[7c,d] Compound **3** was cyclized to give the desired tetracycle **2** (88%) as essentially a single diastereoisomer (d.r. = 20:1) by treatment with SmI_2 in THF. Upon treatment of **2** with $TsOH{\cdot}H_2O$ in benzene at reflux, dehydration and desilylation simultaneously took place, and the trisubstituted alkene **13** was obtained in 91% yield. In contrast, when **2** was reacted with TBAF and AcOH instead, only desilylation[3f] occurred and diol **16** was generated in 82% yield, the structure was unambiguously established by comparison of its ^1H NMR spectroscopic data with those disclosed in the literature[1b] as well as X-ray crystallographic analysis (see the Supporting Information).[16] Dehydration of **16** with $TsOH{\cdot}H_2O$ in benzene at reflux could also deliver compound **13**.

Inversion of the configuration at the hydroxy-substituted C7 was realized by following the known oxidation and reduction approach.[3g,h] Specifically, oxidation of **13** with DMP afforded ketone **14** (94%), reduction of which with $NaBH_4$ gave an easily separable mixture of **15** (26%) and **13** (66%). This process was repeated several times in order to accumulate sufficient quantities of alcohol **15**. Finally, **15** was transformed into merrilactone A by following a known procedure, including a stereoselective epoxidation and epoxide ring opening/oxetane formation (by homo-Payne rearrangement).[1b,3c] The spectroscopic data of compound **15** and our synthetically obtained (±)-merrilactone A are identical to those reported in the literature.[1a,3a,c,f,g]

In summary, we have accomplished an efficient total synthesis of (±)-merrilactone A in fifteen reaction steps for the shortest sequence from **7**, which is a known compound.[8] Key features of the current synthesis include: 1) Johnson–Claisen rearrangement and the subsequent deprotection–lactonization to generate the A ring, 2) intramolecular hetero-Pauson–Khand reaction to construct the B and D rings in one step, and 3) vinylogous Mukaiyama–Michael

reaction and reductive carbonyl–alkene coupling to assemble the C ring.

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[16] CCDC 862340 (**3**) and CCDC 862341 (**16**·H_2O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

