Natural Products Synthesis

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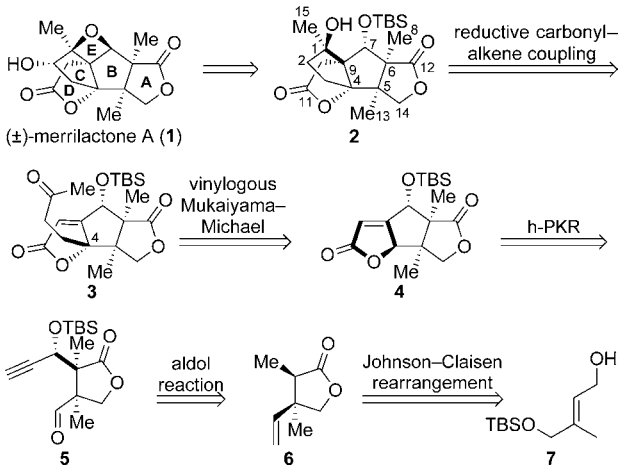
Total Synthesis of (±)-Merrilactone A**

*Jianwei Chen, Peng Gao, Fangmiao Yu, Yang Yang, Shizheng Zhu, and Hongbin Zhai**

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.

[*] J. Chen, Dr. P. Gao, Dr. F. Yu, Dr. Y. Yang, Prof. Dr. H. Zhai
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
Prof. Dr. H. Zhai
State Key Laboratory of Applied Organic Chemistry
Lanzhou University
Lanzhou 730000 (China)
J. Chen, Prof. Dr. S. Zhu
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)

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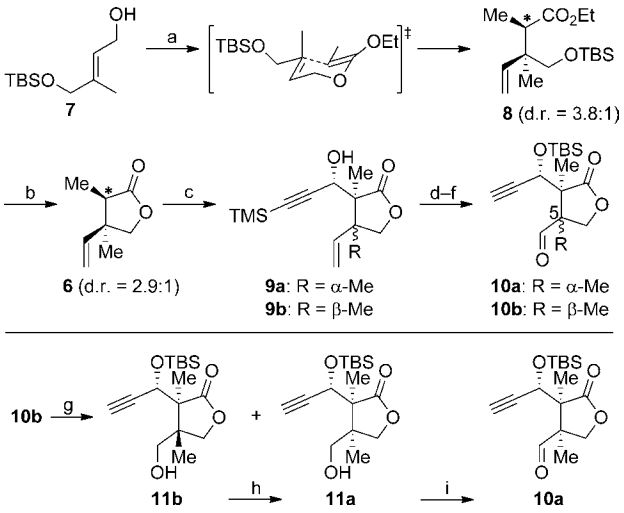
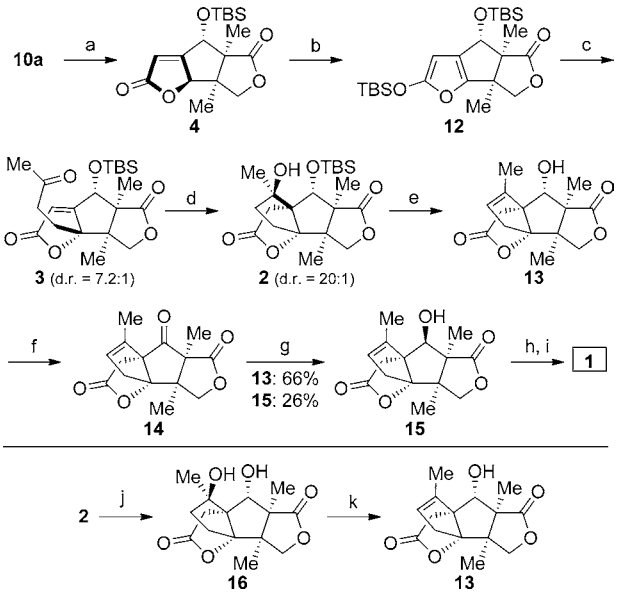


Scheme 2. Synthesis of aldehyde **10a**. a) Triethyl orthopropionate, propionic acid, 135 °C, 8 h, d.r. = 3.8:1; b) $TsOH{\cdot}H_2O$, MeOH, 20 °C, 3 h, 89% (2 steps, d.r. = 2.9:1); c) LDA, $Ti(OiPr)_3Cl$, 1.5 h, 3-trimethylsilylpropynal, −78 °C to −30 °C, 0.5 h, 81%, **9a**:**9b** = 1:1; d) TBSOTf, 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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[1] a) J.-M. Huang, R. Yokoyama, C.-S. Yang, Y. Fukuyama, *Tetrahedron Lett.* **2000**, *41*, 6111; b) J.-M. Huang, C.-S. Yang, M. Tanaka, Y. Fukuyama, *Tetrahedron* **2001**, *57*, 4691.

[2] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

[3] For total and formal syntheses, see: a) V. B. Birman, S. J. Danishefsky, *J. Am. Chem. Soc.* **2002**, *124*, 2080; b) Z. Meng, S. J. Danishefsky, *Angew. Chem.* **2005**, *117*, 1535; *Angew. Chem. Int. Ed.* **2005**, *44*, 1511; c) M. Inoue, T. Sato, M. Hirama, *J. Am. Chem. Soc.* **2003**, *125*, 10772; d) M. Inoue, T. Sato, M. Hirama, *Angew. Chem.* **2006**, *118*, 4961; *Angew. Chem. Int. Ed.* **2006**, *45*, 4843; e) M. Inoue, N. Lee, S. Kasuya, T. Sato, M. Hirama, M. Moriyama, Y. Fukuyama, *J. Org. Chem.* **2007**, *72*, 3065; f) G. Mehta, S. R. Singh, *Angew. Chem.* **2006**, *118*, 967; *Angew. Chem. Int. Ed.* **2006**, *45*, 953; g) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2007**, *129*, 498; h) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 300; i) L. Shi, K. Meyer, M. F. Greaney, *Angew. Chem.* **2010**, *122*, 9436; *Angew. Chem. Int. Ed.* **2010**, *49*, 9250; for synthetic studies, see: j) K. Harada, H. Kato, Y. Fukuyama, *Tetrahedron Lett.* **2005**, *46*, 7407; k) K. Harada, H. Ito, H. Hioki, Y. Fukuyama, *Tetrahedron Lett.* **2007**, *48*, 6105; l) J. Iriondo-Alberdi, J. E. Perea-Buceta, M. F. Greaney, *Org. Lett.* **2005**, *7*, 3969; m) G. Mehta, S. R. Singh, *Tetrahedron Lett.* **2005**, *46*, 2079; for reviews, see: n) R. M. Wilson, S. J. Danishefsky, *Acc. Chem. Res.* **2006**, *39*, 539; o) D. Urabe, M. Inoue, *Tetrahedron* **2009**, *65*, 6271.

[4] For a review, see: a) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32; for representative applications of this method in natural product synthesis, see: b) T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 4353; c) S.-J. Min, S. J. Danishefsky, *Angew. Chem.* **2007**, *119*, 2249; *Angew. Chem. Int. Ed.* **2007**, *46*, 2199; d) Q. Xiao, W.-W. Ren, Z.-X. Chen, T.-W. Sun, Y. Li, Q.-D. Ye, J.-X. Gong, F.-K. Meng, L. You, Y.-F. Liu, M.-Z. Zhao, L.-M. Xu, Z.-H. Shan, Y. Shi, Y.-F. Tang, J.-H. Chen, Z. Yang, *Angew. Chem.* **2011**, *123*, 7511; *Angew. Chem. Int. Ed.* **2011**, *50*, 7373.

[5] a) C. Mukai, T. Yoshida, M. Sorimachi, A. Odani, *Org. Lett.* **2006**, *8*, 83; b) J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 778; c) P. Gao, P.-F. Xu, H. Zhai, *J. Org. Chem.* **2009**, *74*, 2592.

[6] a) T. Fukuyama, L. Yang, *J. Am. Chem. Soc.* **1987**, *109*, 7881; b) T. Fukuyama, L. Yang, *J. Am. Chem. Soc.* **1989**, *111*, 8303; c) L. Chabaud, T. Jousseaume, P. Retailleau, C. Guillou, *Eur. J. Org. Chem.* **2010**, 5471; d) A. Takahashi, H. Yanai, T. Taguchi, *Chem. Commun.* **2008**, 2385; e) A. Takahashi, H. Yanai, M. Zhang, T. Sonoda, M. Mishima, T. Taguchi, *J. Org. Chem.* **2010**, *75*, 1259.

[7] For reviews, see: a) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371; b) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem.* **2009**, *121*, 7276; *Angew. Chem. Int. Ed.* **2009**, *48*, 7140; for representative applications of this method in natural product synthesis, see: c) G. Matsuo, K. Kawamura, N. Hori, H. Matsukura, T. Nakata, *J. Am. Chem. Soc.* **2004**, *126*, 14374; d) W. Zi, S. Yu, D. Ma, *Angew. Chem.* **2010**, *122*, 6023; *Angew. Chem. Int. Ed.* **2010**, *49*, 5887; e) J. Y. Cha, J. T. S. Yeoman, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 14964.

[8] A. Reichenberg, M. Hintz, Y. Kletschek, T. Kuhl, C. Haug, R. Engel, J. Moll, D. N. Ostrovsky, H. Jomaa, M. Eberl, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1257.

[9] a) K. Tadano, J. Ishihara, H. Yamada, S. Ogawa, *J. Org. Chem.* **1989**, *54*, 1223; b) L. Shi, X. Lei, J. Zhang, G. Lin, *Helv. Chim. Acta* **2010**, *93*, 555.

[10] M. Nerz-Stormes, E. R. Thornton, *J. Org. Chem.* **1991**, *56*, 2489.

[11] K. M. Brummond, J. Lu, *J. Am. Chem. Soc.* **1999**, *121*, 5087.

[12] A. B. Smith, G. R. Ott, *J. Am. Chem. Soc.* **1998**, *120*, 3935.

[13] The exact reason for these observations remains uncertain at this stage and more systematic investigations are ongoing in our laboratory.

[14] S. K. Bagal, R. M. Adlington, R. A. B. Brown, J. E. Baldwin, *Tetrahedron Lett.* **2005**, *46*, 4633.

[15] a) M. S. Nozari, Ger. Patent 2609148, **1976**; b) M. W. Siefken, Ger. Patent 2609150, **1976**; c) R. J. Koshar, L. L. Barber, Jr., U.S. Patent 4053519, **1977**.

[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.

