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Synthetic studies toward merrilactone A: a short synthesis of AB ring motif

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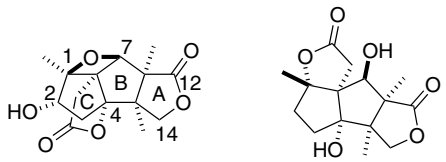
Abstract—An efficient route to the AB ring motif of merrilactone A has been established by remarkable regioselective reduction of cyclic anhydrides **3** and **8** to the γ-lactone moiety, followed by the successive Stille and Heck reactions of 1,1-dibromo-1-alkene.

In 2000,[1] we reported the isolation of merrilactone A (**1**) from the pericarps of *Illicium merrillianum* indigenous to southern China and determined its absolute structure, which belongs to an anislactone-type sesquiterpene consisting of the highly oxygenated pentacyclic skeleton with one oxetane, two γ-lactones, and successive seven stereogenic centers. In addition to this architecture, **1** significantly promotes neurite outgrowth in the primary cultures of fetal rat cortical neurons at concentrations from 0.1 to 10 μM and, therefore, is expected to be a lead compound for the development of therapeutic agents in the treatment of neurodegenerative diseases such as Alzheimer's disease. These unique structure and intriguing biological properties of **1** have stimulated extensive efforts of synthetic works. We already showed that **1** can be readily converted from anislactone B (**2**) in three steps.[2] To date, three elegant syntheses of **1** were reported by Danishefsky and co-workers,[3,5] and Inoue et al.,[4] and recently one synthetic approach appeared.[6] In continuation of our synthetic efforts, we present here our studies toward the construction of the AB motif of **1** featuring regioselective reduction of anhydride and successive Stille–Heck reactions of 1,1-dibromo-1-alkene (see Fig. 1).



Merrilactone A (**1**) Anislactone B (**2**)

Figure 1. Structure of merrilactone A (**1**) and anislactone B (**2**).

In designing our synthetic route, we selected a functionalized bicyclic lactone **7** as the key intermediate, since it contains appropriate functionalities for conversion to merrilactone A (Fig. 2). We envisioned that **7** would be readily derived from compound **6** by oxidizing its diene moiety. Thus, we initially focused on the synthesis of **6** corresponding to the AB motif of merrilactone A. A 1,1-dibromo-1-alkene **5**, which could be derived in several steps from Diels–Alder adduct **3** or **8** if crucial regioselective reduction of anhydride could be succeeded, would be converted to **6** by applying palladium-catalyzed Stille and Heck reactions.

The slightly modified Diels–Alder reaction[7] of the Danishefsky diene with 2,3-dimethylmaleic anhydride gave silyl enol ether **3** and ketone **8** in 63% and 12% yield, respectively (Scheme 1). Deprotection of the silyl group in **3** yielded **8** under acidic conditions. Regioselective reduction[8] of the cyclic anhydride moiety in **3** or **4** to the desired γ-lactone **4** or **10** is likely to be an attractive attempt, since in the previous syntheses, Danishefsky spent three steps for the conversion of the cyclic anhydride to the requisite γ-lactone,[3] whereas Inoue et al. converted the cyclic anhydride to the lactone via diol by regioselective oxidation.[4]

Keywords: Merrilactone A; Regioselective reduction; Stille and Heck reactions; 1,1-Dibromo-1-alkene.
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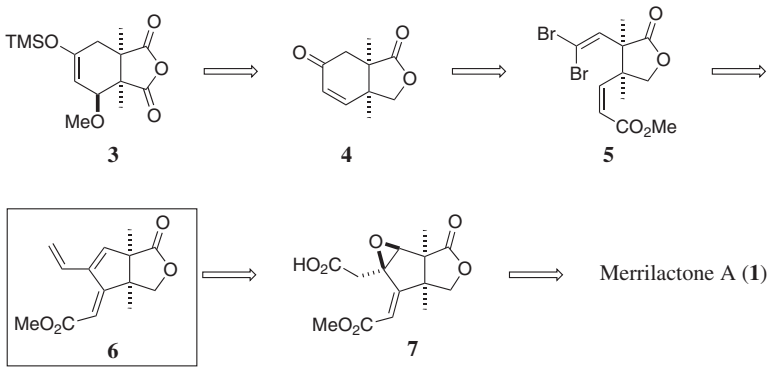
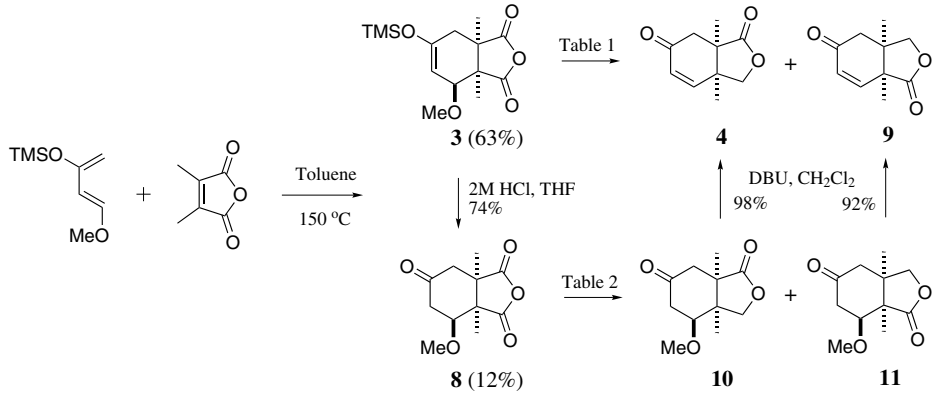


Figure 2. Synthetic plan of **1**.



Scheme 1.

At first, the silyl enol ether **3** was subjected to several reduction conditions using metal hydride reagents (Table 1). As hydride reduction of **3** reduced simultaneously both the cyclic anhydride and the liberated ketone, the generated secondary alcohol was oxidized back to the ketone with Dess–Martin periodinane before terminating the reaction. $NaBH_4$ and $LiAlH_4$ reduced **3** to a mixture of **4** and **9** in low yields with low selectivity (entries 1 and 2), whereas reductions of **3** by Red-Al and Dibal-H afforded a mixture of **4** and **9** in favor of the desired product **4** with the accompanying desilylation and elimination of the methoxy group (entries 4 and 5) after Dess–Martin oxidation. We were pleased to find that the reduction of **3** by Super-Hydride proceeded in a high regioselective manner to give rise to the desired γ-lactone **4**[9] in 74% yield without oxidation process (entry 3). It should be noted that the ketone group remained being untouched even using 5 equiv of Super-Hydride because these reductive conditions presumably left the silyl group intact before work up.

On the other hand, reductions of the ketone **8** using metal hydride reagents (Table 2) showed opposite regioselectivity. $NaBH_4$ and $LiAlH_4$ reductions of **8** gave **10** and **11** in 32% and 15% yield with a poor regioselectivity, respectively (entries 1 and 2). However, all powerful hydride reagents such as L-Selectride, Super-Hydride, Red-Al, and Dibal-H enhanced regioselectivity as well as overall yield, giving rise to a mixture of **10** and **11** in favor of the undesired product **11**. In particular, Super-Hydride gave **11** in 78% yield with a high regioselectivity, again (entry 4). The treatment of **10** and **11** with DBU readily provided **4** and **9** in good yields, respectively.

Accounting for these remarkable regioselectivities in the reduction of the cyclic anhydride, we first envisaged the chelation effects of metal ions.[10] However, there is no experimental evidence for the involvement of metal chelation in these hydride reductions. Thus, steric hindrance appears to be the most important factor as

Table 1. Regioselective reduction of **3**

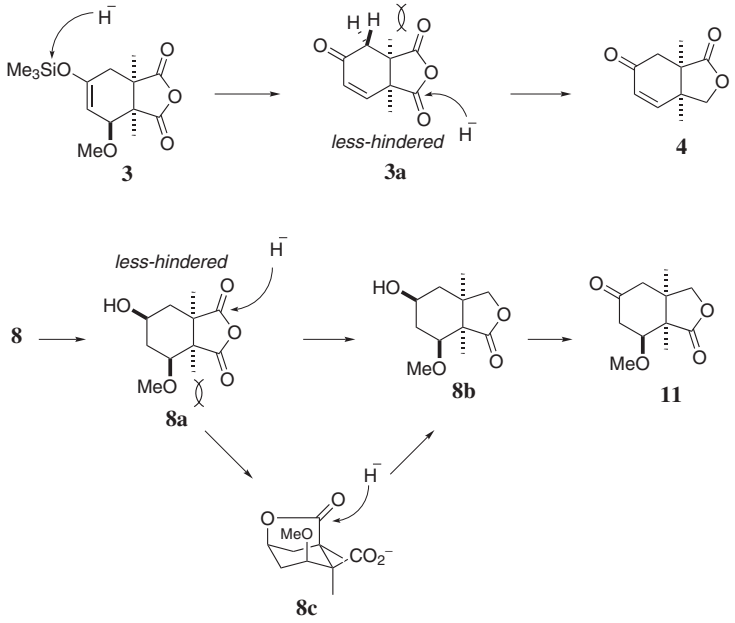
Entry	Reductant (3.5 equiv)	Solvent	Temperature	Oxidant (2 equiv)	**4** (%)	**9** (%)
1	$NaBH_4$	MeOH	rt	Dess–Martin	21	18
2	$LiAlH_4$	THF	−78 °C → rt	Dess–Martin	Trace	32
3	Super-Hydride	THF	rt	—[a]	74	0
4	Red-Al	THF	rt	Dess–Martin	48	15
5	Dibal-H	THF	rt	Dess–Martin	69	9

[a] Under the absence of Dess–Martin periodinane.

Table 2. Regioselective reduction of **8**

Entry	Reductant (3.5 equiv)	Solvent	Temperature	**10**[a] (%)	**11**[a] (%)
1	$NaBH_4$	MeOH	rt	32	15
2	$LiAlH_4$	THF	rt	13	18
3	L-Selectride	THF	rt	22	58
4	Super-Hydride	THF	rt	>1	78
5	Red-Al	THF	rt	24	67
6	Dibal-H	THF	rt	13	70

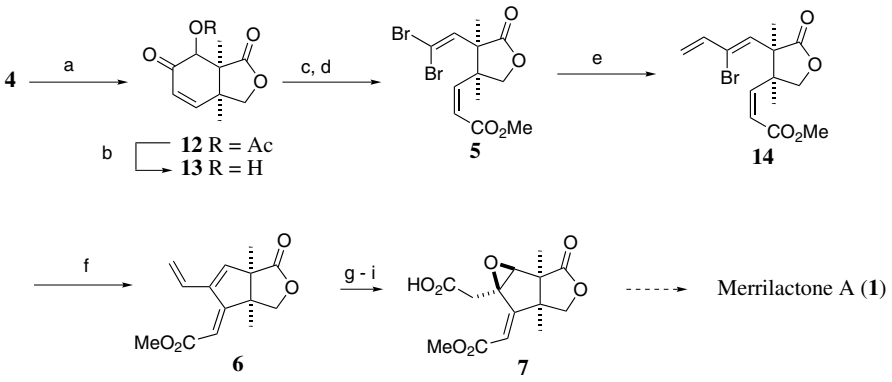
[a] Isolated yield after oxidizing the resultant alcohol with Dess–Martin periodinane.



Scheme 2. Plausible mechanism of regioselective reduction of **3** and **8**.

outlined in Scheme 2. In the case of **3**, hydride attack from the less-hindered lower side of **3a**, which would be presumably the first production by the reduction of **3**, can explain highly favorable regioselectivity for the reduction with concomitant loss of TMS and MeO groups. It remains unclear, however, as to why Super-Hydride gives directly the desired lactone **4** without subsequent oxidation. On the other hand, the opposite regioselectivity for the reduction of **8** would be explained as the following. Hydride attack to the ketone in **8** first occurs from the convex face of *cis*-fused anhydride resulting in the formation of an axial alcohol **8a**. Subsequent hydride reduces the less-hindered upper carbonyl group to give rise to γ-lactone **8b**.[11] There appears to be another possibility that **8a** first forms a γ-lactone **8c** and then its carbonyl is chemoselectively reduced. Anyhow, we have established the highly regioselective reduction of the anhydride moiety to the desired γ-lactone by using Super-Hydride.

Next, compound **4** reacted with $Pb(OAc)_4$ in benzene followed by acidic hydrolysis to give alcohol **13** in good yield (Scheme 3). Oxidative cleavage of the α-hydroxyketone moiety of **13** by $Pb(OAc)_4$ afforded an aldehyde, which was transformed according to the Corey–Fuchs protocol[12] to 1,1-dibromo-1-alkene **5** in 74% yield. 1,1-Dibromo-1-alkenes can provide a convenient route for the preparation of stereospecifically trisubstituted alkenes by palladium-catalyzed stepwise coupling of both bromides.[13] This advance prompted us to apply successive Stille and Heck reactions of **5** for the preparation of the AB ring system of merrilactone A. As results, the first Stille reaction of **5** with vinyltributyltin using a 10 mol % Pd_2dba_3–$CHCl_3$ and 20 mol % trifurylphosphine system afforded (*Z*)-vinylalkene **14** exclusively in 62% yield. The second intramolecular Heck reaction of **14** in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % $(o\text{-tol})_3P$, and 2 equiv of Et_3N in DMF proceeded smoothly to give rise to **6**, corresponding to the AB motif of merrilactone A in 78% yield. Since both the Stille and the intramolecular Heck reactions were performed in the presence of palladium(0) catalysts, we attempted to shorten the two-steps procedure. After several trials, we found that both the reactions proceeded smoothly only by diluting a toluene solution of the first Stille reaction with DMF. Namely, to a solution of **5** in toluene (0.1 M) was added 10 mol % Pd_2dba_3–$CHCl_3$ and 20 mol % trifurylphosphine. After being stirred at 100 °C for 4 h, DMF (0.01 M) and 2 equiv of Et_3N was added for initiating Heck reaction and then the reaction mixture was stirred at the same temperature for additional 10 h. Under these conditions, **6**[14] was obtained in 52% yield in a one-pot procedure. Compound **6** was readily functionalized by several operations (hyd-



Scheme 3. Reagents and conditions: (a) $Pb(OAc)_4$, benzene, reflux, 87%; (b) *p*-TsOH, MeOH, H_2O, 100 °C, 72%; (c) $Pb(OAc)_4$, benzene, MeOH, rt, 76%; (d) CBr_4, PPh_3, CH_2Cl_2, 74%; (e) vinyltributyltin, 10 mol % Pd_2dba_3–$CHCl_3$, 20 mol % trifurylphosphine, toluene, 100 °C, 62%; (f) 10 mol % $Pd(OAc)_2$, 20 mol % (*o*-tol)$_3$P, Et_3N, DMF, 100 °C, 78%; (g) Sia_2BH, ether, H_2O_2, 73%; (h) PDC, DMF, 62%; (i) *m*CPBA, CH_2Cl_2, 44%.

roboration, oxidation, and epoxidation) to lead to **7**, which will be brought forward to merrilactone A (**1**).

In conclusion, we have developed an efficient route for the construction of the AB ring motif of **1** by a combination of the regioselective reduction of cyclic anhydride and the successive Stille and Heck reactions of 1,1-dibromo-1-alkene. Further elaboration of this motif to the synthesis of merrilactone A is currently underway.

Acknowledgements

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9. Compound **4**: colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (3H, s), 1.27 (3H, s), 2.35 (1H, d, $J = 17.3$ Hz), 2.85 (1H, d, $J = 17.3$ Hz), 4.17 (1H, d, $J = 9.5$ Hz), 4.42 (1H, d, $J = 9.5$ Hz), 6.09 (1H, d, $J = 10.2$ Hz), 6.62 (1H, d, $J = 10.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 Hz): δ 16.4, 19.1, 40.8, 43.8, 45.1, 74.4, 130.1, 152.6, 179.1, 194.9; IR (film) 1680, 1765 cm^{-1}; EIMS *m/z* (rel. int.) 180 [M^+] (50), 122 (100), 93 (54); HREIMS *m/z* 180.0791 [M^+] (calcd 180.0813 for $C_{10}H_{12}O_3$).
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11. Compound **8b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (3H, s), 1.15 (3H, s), 1.55 (1H, dd, $J = 14.9$, 4.0 Hz), 1.81 (1H, ddd, $J = 14.4$, 3.2, 3.0 Hz), 1.94 (1H, ddd, $J = 14.9$, 4.7, 1.4 Hz), 2.08 (1H, m), 3.42 (3H, s), 3.45 (1H, dd, $J = 5.2$, 3.0 Hz), 3.86 (1H, d, $J = 8.7$ Hz), 3.99 (1H, m), 4.46 (1H, d, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 Hz): δ 16.5, 24.8, 30.5, 38.6, 39.8, 49.2, 59.0, 65.8, 76.4, 83.5, 179.6; IR (film) 1770, 3459 cm^{-1}.
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14. Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (3H, s), 1.30 (3H, s), 3.73 (3H, s), 4.02 (1H, d, $J = 9.3$ Hz), 4.11 (1H, d, $J = 9.3$ Hz), 5.21 (1H, dd, $J = 10.1$, 1.5 Hz), 5.46 (1H, dd, $J = 17.3$, 1.5 Hz), 5.73 (1H, s), 6.32 (1H, s), 6.65 (1H, dd, $J = 17.3$, 10.1 Hz); ^{13}C NMR ($CDCl_3$, 75 Hz): δ 17.1, 19.3, 51.6, 54.2, 57.2, 77.4, 113.3, 116.9, 130.8, 141.3, 142.2, 160.8, 166.2, 177.0; IR (film) 1715, 1768 cm^{-1}. CIMS *m/z* (rel. int.) 249 [M+H] (100), 204 (48), 58 (20). HRCIMS *m/z* 249.1131 [M+H] (calcd 249.1127 for $C_{14}H_{17}O_4$).