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An efficient synthesis of the CD rings model for merrilactone A

Kenichi Harada, Hitoshi Ito, Hideaki Hioki and Yoshiyasu Fukuyama*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

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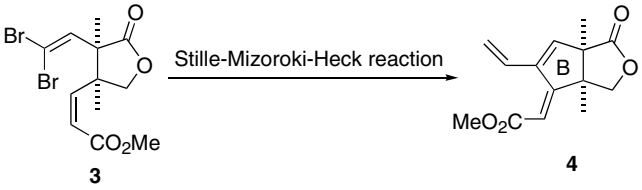
Abstract—A synthetic route to the CD rings of merrilactone A was explored by using the model system **9a**, which was easily converted from 7,7-dibromohepta-2,6-dienoic acid ethyl ester (**8**) by the successive Stille–Mizoroki–Heck reaction. The D ring **14** was constructed by applying the intramolecular Tsuji–Trost reaction to the formation of a γ-lactone, whereas the formation of the C ring **18** was effectively accomplished in one step by methylation and conjugate addition toward 1,1-dibromo-1-alkene **17** using Miyashita's protocol.

Merrilactone A (**1**),[1] isolated from the pericarps of *Illicium merrillianum* indigenous to the Southern China, has attracted synthetic attention because of its challenging structure, combined with intriguing neurite outgrowth promoting activity in the primary cultured rat cortical neurons. Additionally, **1** is the only neurotrophic anislactone-type sesquiterpene possessing the highly oxygenated pentacyclic skeleton with one oxetane, two γ-lactones, and successive seven stereogenic centers.[2] This interesting molecule has been the focus of several synthetic studies,[3] which culminated in the total synthesis of (±)-**1** by Danishefsky,[4] Inoue,[5] Metha,[6] and Frontier.[7] Recently, the excellent asymmetric synthesis of **1** has been also reported.[8] In connection of our independent synthetic studies of merrilactone A, we have recently developed a new strategy for construction of the AB rings **4** in **1** based on successive Pd(0)-catalyzed Stille and Mizoroki–Heck reactions of 1,1-dibromo-1-alkene **3** (Scheme 1).[9] Subsequently, in this Letter, we describe an effective synthesis of the CD rings model in **1** featuring intramolecular Tsuji–Trost reaction[10] for D ring formation as well as a one-step construction of D ring through 1,1-dibromo-1-alkene by Miyashita's protocol.[11]

In 2001, we showed that **1** was readily derived from anislactone B in three steps,[2] which included ester exchange, epoxidation, and an oxetane formation of **2** that is

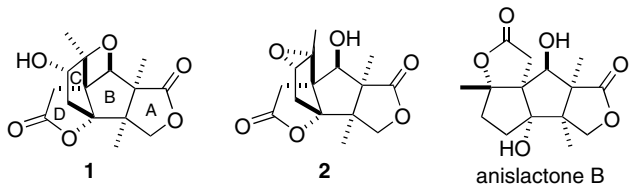


3 4

Scheme 1. The construction of the A and B rings of **1** using successive Stille–Mizoroki–Heck reaction.

essentially targeted to the most syntheses of **1** (Fig. 1).[4,5] To develop a new route to the key intermediate **2** from the AB rings **4**, we explored the potentials of intramolecular Tsuji–Trost reaction for D ring formation as well as of Miyashita's protocol (Me_2CuLi) through 1,1-dibromo-1-alkene for C ring construction by using the model compound **9a** as an equivalent of **4**.

First of all, the model compound **9a** was prepared from 1,4-butanediol (**5**). A hydroxyl group of **5** was protected as the MOM group, and the other one was oxidized with



1 2 anislactone B

Figure 1. Structures of merrilactone A (**1**), the key intermediate **2** of synthesis of **1** and anislactone B.

Keywords: Merrilactone A; Tsuji–Trost reaction; 1,1-Dibromo-1-alkene; Miyashita's protocol.
* Corresponding author. Tel.: +81 88 622 9611; fax: +81 88 655 3051; e-mail: fukuyama@ph.bunri-u.ac.jp

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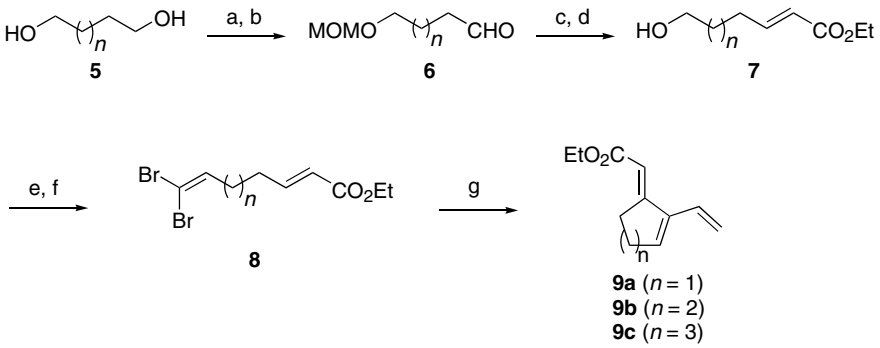
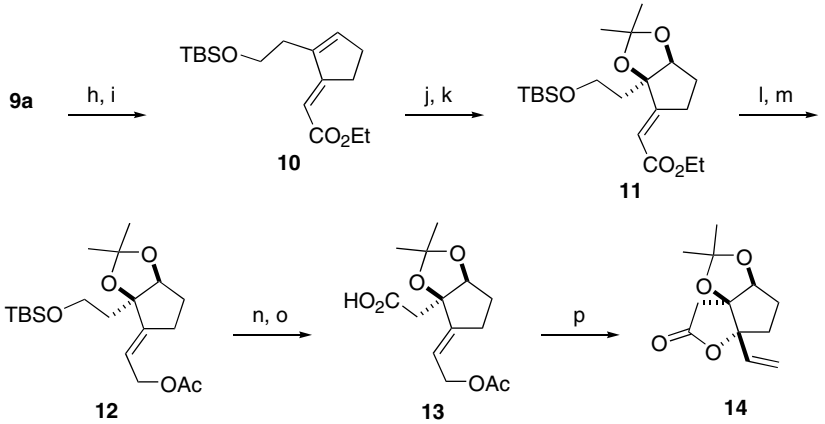


Scheme 2. Reagents and conditions: (a) MOMCl, Et_3N, CH_2Cl_2, 50%; (b) PCC, 4 ÅMS, CH_2Cl_2, 80%; (c) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF; (d) conc HCl, EtOH, 95% (two steps); (e) PCC, 4 ÅMS, CH_2Cl_2, 67%; (f) CBr_4, PPh_3, CH_2Cl_2, 80%; (g) tri-*n*-butylvinyltin, 10 mol % Pd_2dba_3–$CHCl_3$, 60 mol % tri(2-furyl)phosphine, toluene, then Et_3N, DMF, 78%.

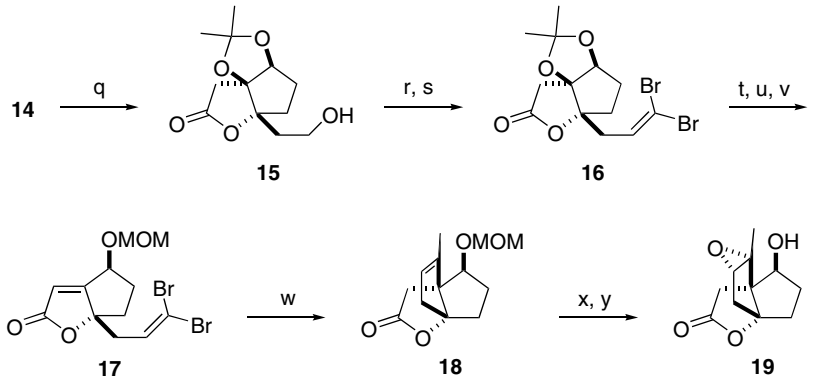
PCC to give aldehyde **6**, which was converted to alcohol **7** in 95% yield using a Horner–Wadsworth–Emmons reaction, followed by deprotection of MOM group under acidic conditions. Oxidation of **7** followed by the Corey–Fuchs reaction[12] yielded 1,1-dibromo-1-alkene **8**. Next, Stille–Mizoroki–Heck reaction toward **8** was employed under the same conditions reported previously,[9] that is, 10 mol % tris(dibenzylideneacetone)-dipalladium chloroform adduct, 60 mol % tri(2-furyl)-phosphine and 1.1 equiv of tri-*n*-butylvinyltin in 0.1 M toluene and then adding triethylamine and 0.01 M DMF to the reaction mixture, giving rise to the model compound **9a** in 78% yield. It is worthy of note that this successive Stille–Mizoroki–Heck protocol[13] could be utilized for the formation of 6- and 7-membered rings with the vinyl functional group to give rise to **9b** and **9c** in good yields (see Scheme 2).

Hydroboration with Sia_2BH and oxidative work-up of **9a**, followed by TBS protection produced silyl ether **10** in 88% yield. The γ,δ-double bond in dienyl ester **10** was regioselectively dihydroxylated by oxidation with OsO_4, giving rise to acetonide **11** in 56% yield after acetal formation. Allyl acetate **12** was obtained from **11** by reduction with Dibal-H and then acetylation under general conditions. Desilylation of **12** by treatment with TBAF and PDC oxidation in DMF afforded **13** that serves as a substrate of the Pd(0)-catalyzed Tsuji–Trost reaction. For the desired formation of the γ-lactone in **13** by the Tsuji–Trost reaction, the carboxylate nucleophile must attack at the more hindered quaternary center on π-allyl Pd complex.[14] Upon treatment of **13** in DMF at 80 °C with 10 mol % tetrakis(triphenylphosphine)palladium and 1.1 equiv of sodium hydride, the reaction smoothly proceeded to give the desired **14**[15] with high regioselectivity in 75% yield. It should be emphasized that no side product was observed in this reaction, in which the carboxylate attacked at the more hindered position on π-allyl Pd complex due to favor formation of γ-lactone (see Scheme 3).

Subsequently, we focused on construction of the C ring through 1,1-dibromo-1-alkene by applying Stille–Mizoroki–Heck reaction. Hydroboration of **14** with various dialkyl boranes did not proceed presumably due to the highly hindered double bond. However, the use of less hindered BH_3–THF complex resulted in the formation of an alcohol **15** in 58% yield. Oxidation of **15** with Dess–Martin periodinane gave the aldehyde, which was subjected to the Corey–Fuchs reaction giving rise to dibromoalkene **16**. Successive treatment of **16** with 1 M HCl, methanesulfonyl chloride/triethylamine, and



Scheme 3. Reagents and conditions: (h) Sia_2BH, THF, then aq. NaOH, H_2O_2, 88%; (i) TBSCl, imidazole, DMF, 95%; (j) 3 mol % OsO_4, NMO, THF; (k) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, 56% (two steps); (l) Dibal-H, CH_2Cl_2; (m) Ac_2O, DMAP, pyridine, 89% (two steps); (n) TBAF, THF; (o) PDC, DMF, 67% (two steps); (p) $Pd(PPh_3)_4$, NaH, DMF, 75%.



Scheme 4. Reagents and conditions: (q) BH_3–THF complex, THF, then aq. NaOH, H_2O_2, 58%; (r) Dess–Martin periodinane, CH_2Cl_2, quant.; (s) CBr_4, PPh_3, CH_2Cl_2, 64%; (t) 1 M HCl, THF, 71%; (u) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 76%; (v) MsCl, Et_3N, CH_2Cl_2, 67%; (w) Me_2CuLi, ether, 78%; (x) DOWEX® 500WX2-100, MeOH, 88%; (y) *m*-CPBA, CH_2Cl_2, 66%.

MOMCl gave an α,β-unsaturated lactone **17**. With a precursor **17** for the construction of the C ring in hand, at first, we attempted successive Pd(0)-catalyzed reactions such as Stille–Mizoroki–Heck reaction toward the 1,1-dibromo-1-alkene **17** to realize one-step formation of the ring C. However, Stille reaction with tetramethyltin[16] and Suzuki–Miyaura reaction with trimethylboroxine[17] gave no monomethylated product but the totally recovered starting material. In contrast, Negishi reaction[18] with dimethylzinc and Kumada reaction[19] with methylmagnesium bromide afforded dimethylated compound as a sole product in good yields. After making several vain trials, we were pleased to find that Miyashita's protocol[11] was quite suitable for our system. When **17** was reacted with 3.0 equiv of dimethyl lithium cuprate in ether at −78 °C, highly regioselective methylation on the *trans*-Br in the 1,1-dibromo-1-alkene and the subsequent Michael type cyclization to the conjugated lactone moiety proceeded smoothly in one-pot to give rise to the tricylic compound **18**[20] in 78% yield. Finally, deprotection of MOM group of **18**, followed by stereospecific oxidation with *m*-CPBA gave epoxide **19**,[21] which is an equivalent of the synthetic target **2** leading to merrilactone A (**1**) (see Scheme 4).

In conclusion, we demonstrated that intramolecular Tsuji–Trost and Miyashita's protocols are quite useful for the construction of the C and D rings of **1** using the model system. With the final objective of applying these synthetic procedures in the several elaborations of our synthesis of merrilactone A, we have set out to test them for the construction of the C and D rings. Further effort for complete synthesis of merrilactone A is currently in progress in our laboratory.

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13. Representative procedure of Stille–Mizoroki–Heck reaction: Under argon atmosphere, tris(dibenzylideneacetone)dipalladium–chloroform adduct (17.5 mg, 17.0 μmol) and tri(2-furyl)phosphine (24.0 mg, 102 μmol) were added to a solution of dibromoalkene **8** ($n = 1$, 50.6 mg, 170 μmol) and tributylvinyltin (59.0 mg, 190 μmol) in toluene (1.70 mL, 0.1 M). The reaction mixture was stirred for 4 h at 100 °C. After checking the consumption of **8** by TLC (hexane:AcOEt = 5:1, $R_f = 0.4$), the solution was diluted with DMF (15.3 mL) to 0.01 M and added triethylamine (50.0 mL, 340 μmol). After 10 h, water was added and the solution was extracted with ether. The ethereal solution was washed with water and brine and dried over $MgSO_4$. Evaporation and purification by column chromatography

(silica gel, hexane:AcOEt = 9:1) gave **9a** (21.7 mg, 78% yield).
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15. Compound **14**: colorless amorphous; ^{1}H NMR (300 MHz): δ 1.34 (3H, s), 1.48 (3H, s), 1.80–2.24 (4H, m), 2.71 (1H, d, $J = 18.1$ Hz), 3.02 (1H, d, $J = 18.1$ Hz), 4.53 (1H, d, $J = 3.8$ Hz), 5.36 (1H, dd, $J = 10.1$, 1.1 Hz), 5.42 (1H, dd, $J = 17.3$, 1.1 Hz), 5.96 (1H, dd, $J = 17.3$, 10.1 Hz); ^{13}C NMR (75 MHz): δ 24.9, 26.2, 28.5, 33.6, 37.2, 87.1, 92.3, 94.9, 111.4, 115.9, 134.6, 172.6; CIMS *m*/*z* (rel. int.): 225 [M^{+}+1] (1); HRCIMS: calcd 225.1106 for $C_{12}H_{17}O_4$; found, 225.1103; IR (cm^{-1}): 1793.
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20. Compound **18**: colorless oil; ^{1}H NMR (300 MHz): δ 1.75 (3H, dt, $J = 2.3$, 2.2 Hz), 1.83–2.22 (4H, m), 2.41 (1H, d, $J = 18.8$ Hz), 2.61 (1H, ddq, J= 17.9, 1.9, 2.2 Hz), 2.70 (1H, d, $J = 18.8$ Hz), 2.72 (1H, ddq, $J = 17.9$, 2.2, 2.2 Hz), 3.38 (3H, s), 4.01 (1H, dd, $J = 2.7$, 2.6 Hz), 4.61 (1H, d, $J = 7.0$ Hz), 4.69 (1H, d, $J = 7.0$ Hz), 5.34 (1H, ddq, $J = 2.2$, 1.9, 2.3 Hz); ^{13}C NMR (75 MHz): δ 14.5, 31.1, 35.9, 38.3, 44.4, 56.0, 68.6, 83.5, 95.5, 102.7, 124.9, 138.7, 176.5; CIMS *m*/*z* (rel. int.): 239 [M^{+}+1] (100), 207 (97), 179 (85); HRCIMS: calcd 239.1284 for $C_{13}H_{19}O_4$; found, 239.1284; IR (cm^{-1}): 1769.
21. Compound **19**: colorless amorphous; ^{1}H NMR (300 MHz): δ 1.57 (3H, s), 1.86 (1H, dt, $J = 13.9$, 2.9 Hz), 2.05–2.22 (5H, m), 2.60 (1H, d, $J = 15.8$ Hz), 2.84 (1H, d, $J = 18.3$ Hz), 3.61 (1H, s), 4.27 (1H, br s); ^{13}C NMR (75 MHz): δ 0.18, 15.2, 35.0, 35.8, 38.1, 41.6, 65.2, 67.8, 68.8, 102.8, 175.9; CIMS *m*/*z* (rel. int.): 211 [M^{+}+1] (100), 193 (32), 89 (21); HRCIMS: calcd 211.0957 for $C_{11}H_{15}O_4$; found, 211.0970; IR (cm^{-1}): 3415, 1732.