Total Synthesis

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Asymmetric Total Synthesis of (−)-Merrilactone A: Use of a Bulky Protecting Group as Long-Range Stereocontrolling Element**

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(−)-Merrilactone A ((−)-**1**, Figure 1), a sesquiterpenoid isolated from *Illicium merrillianum* in 2000 by Fukuyama and coworkers,[1,2] has been shown to possess neuroprotective and

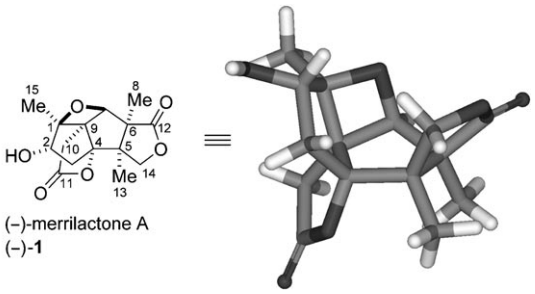
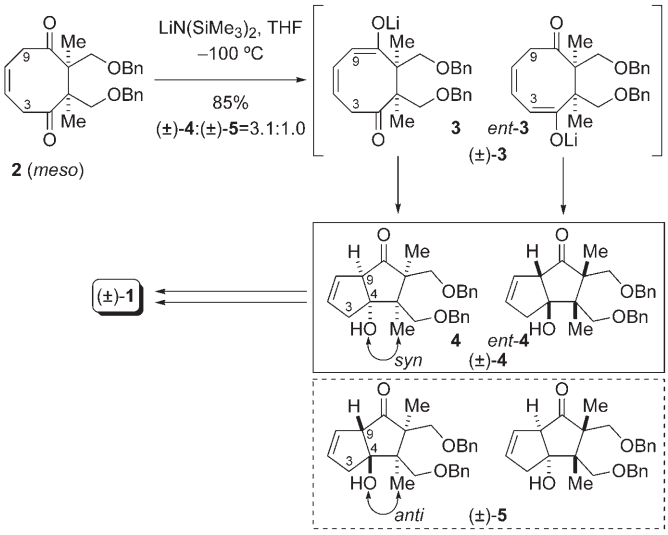


Figure 1. Structure of (−)-merrilactone A.

neuritogenic activity in cultures of fetal rat cortical neurons. Small molecules with these neurotrophic effects are expected to be useful as metabolically stable alternatives to endogenous neurotrophic factors, and thus as therapeutic agents for the neurodegeneration associated with Alzheimer's and Parkinson's diseases.[3] By X-ray crystallographic analysis together with extensive NMR spectroscopic studies, **1** was determined to possess a unique pentacyclic cage structure comprising a central bicyclo[3.3.0]octane framework, two δ-lactone rings, and an oxetane ring. The absolute configuration of **1** was established on the basis of the modified Mosher method[4] by using MTPA derivatives at C2–OH.[1] In addition to its evident architectural complexity, **1** is also very complex from a stereochemical point of view: Five of its seven asymmetrically substituted carbon atoms are contiguous and carry only non-hydrogen substituents (C6, C5, C4, C9, C1). The molecular architecture of **1** is a daunting challenge for chemical synthesis.

Motivated by the important biological activity and unusual structure of **1**, we began a synthetic study, which resulted in the total synthesis of racemic merrilactone A ((±)-**1**) in 2003.[5] To date, two other chemical routes to (±)-**1** have been developed by the Danishefsky and Mehta research groups,[6,7] and Danishefsky and co-workers have reported an elegant asymmetric synthesis of a key intermediate en route to **1**.[8] Herein, we report an asymmetric total synthesis of the natural enantiomer (−)-**1** in which a remote bulky protecting group is used to control the stereochemistry. This study also confirmed the assigned absolute configuration for the first time.

In our total synthesis of (±)-**1**, the bicyclo[3.3.0]octane framework was constructed in the form of (±)-**4** through an intramolecular aldol reaction of the benzyl-protected *meso* diketone **2** (Scheme 1).[9,10] Importantly, by controlling the



Scheme 1. Diastereoselective transannular aldol reaction of the *meso* diketone **2** in the total synthesis of (±)-**1**.[5] Bn = benzyl.

reaction conditions (using $LiN(SiMe_3)_2$ in THF) it was possible to favor the selective formation of the desired *syn* isomer (±)-**4** over that of the *anti* isomer (±)-**5**. The key intermediate (±)-**4** was then converted into (±)-**1** through a series of functional-group transformations.

Our plan for preparing enantiomerically pure merrilactone A (−)-**1** was based on the transannular aldol chemistry described above. Theoretically, exclusive deprotonation of C9 of diketone **2** would lead to the bicyclo[3.3.0]octane system **4** with the absolute configuration found in the natural product (**2**→**3**→**4** versus **2**→*ent*-**3**→*ent*-**4**, Scheme 1). We were intrigued by the possibility of differentiating the deprotona-

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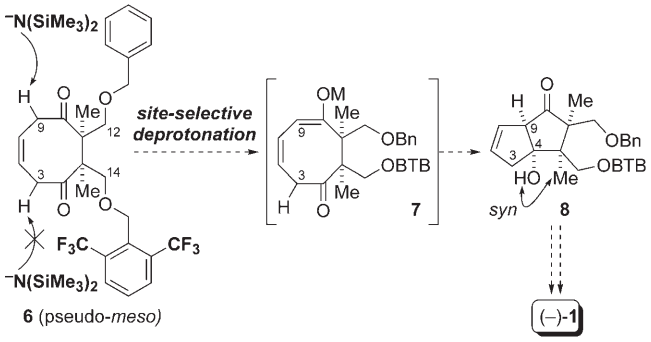
tion rates at C9 and C3 by utilizing a pseudo-*meso* substrate: The attachment of a bulky protecting group at C14–OH would effectively shield C3–H through a long-range steric interaction (Scheme 2).[11] To apply the reaction sequence

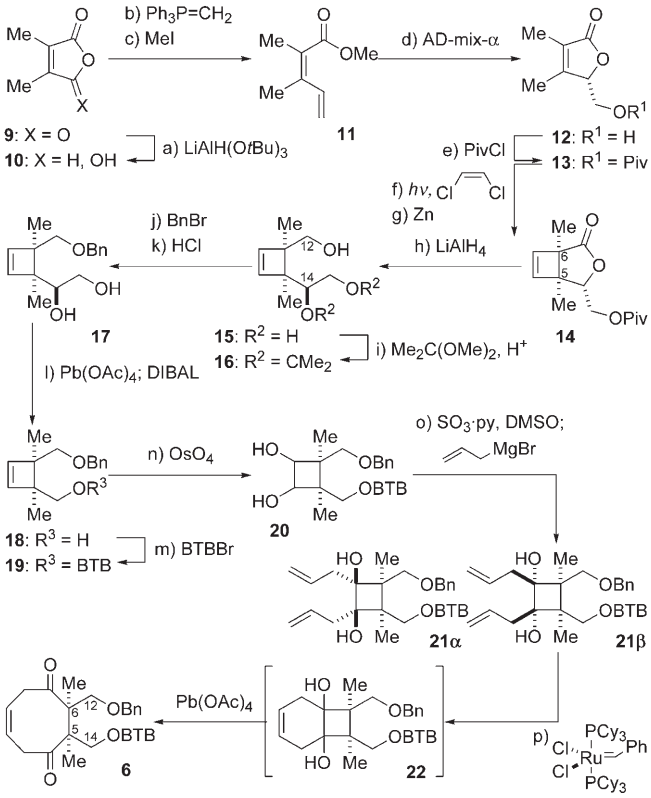


Scheme 2. Strategy for the asymmetric synthesis of the core bicyclo-[3.3.0]octane framework of (−)-merrilactone A from a pseudo-*meso* diketone.

developed from (±)-**4** to (±)-**1**, this bulky protecting group needed to be as stable as Bn in a variety of reactions and to be removed simultaneously with Bn in the final stage of the total synthesis. Since no existing alcohol protecting group met these requirements, we designed a new benzyl ether, 2,6-bis(trifluoromethyl)benzyl (BTB) ether, which has chemically inert CF_3 groups at the two *ortho* positions to impose a large steric effect.[12] Thus, our subsidiary goals in the asymmetric total synthesis were to prepare the differentially protected diketone **6** and to evaluate the BTB group as a remote stereocontrolling element for the selective generation of **7** and **8**.

To establish the absolute configuration of the two quaternary carbons atoms (C5, C6) of diketone **6**, we planned a [2+2] photocycloaddition of the chiral tetrasubstituted olefin **13** (Scheme 3).[13,14] The reduction of 2,3-dimethylmaleinic anhydride (**9**) to **10**,[15] followed by Wittig olefination and esterification, afforded methyl ester **11** in 68% yield (three steps). Chemo- and enantioselective dihydroxylation of dienone **11** under Sharpless asymmetric dihydroxylation conditions with the catalyst $(DHQ)_2PHAL$ led to enantiomerically pure **12** (>99% *ee*) in 65% yield after one recrystallization.[16] This hydroxy-γ-lactone was protected as its pivaloate ester **13**.[17] The irradiation of **13** in the presence of *cis*-1,2-dichloroethylene with a high-pressure mercury lamp, followed by Zn-promoted dechlorination then afforded **14**, the $LiAlH_4$ reduction of which gave cyclobutene **15** (75%) along with its facial diastereomer (8%). Thus, furanone **13** showed excellent facial discrimination (9.8:1) in the photocycloaddition and acted as a template for the stereoselective introduction of the two quaternary carbon atoms C5 and C6.[18] The structure of triol **15** was determined unambiguously by single-crystal X-ray analysis of **23** (Figure 2), the product of mono-*p*-bromobenzoylation of **15**.

The additional hydroxymethyl group attached to C14 of **15** made it possible to introduce the two benzyl-type protecting groups at the C12 and C14 alcohol groups in a stepwise fashion (Scheme 3). After triol **15** had been protected as its



Scheme 3. Synthesis of the pseudo-*meso* diketone **6**; (the principal reagents are also shown in the Scheme): a) $LiAlH(OtBu)_3$, DME, −15 °C→RT, 85%; b) $Ph_3PCH_3^+Br^-$, *t*BuOK, 0 °C→RT, 87%; c) MeI, K_2CO_3, THF, 50 °C, 92%; d) AD-mix-α, *t*BuOH/H_2O (1:1), 0 °C, 90%, 90% *ee*; then recrystallization: 65%, >99% *ee*; e) PivCl, py, DMAP, CH_2Cl_2, room temperature, 99%; f) *cis*-dichloroethylene, CH_3CN, −20 °C; g) Zn, Ac_2O, toluene, 120 °C; h) $LiAlH_4$, Et_2O, room temperature, 75% (**15**, 3 steps), 8% (the facial diastereomer, 3 steps); i) $Me_2C(OMe)_2$, $TsOH·H_2O$, CH_2Cl_2, room temperature, 81%; j) BnBr, NaH, THF/DMF (10:1), room temperature; k) THF/3 M HCl (5:1), room temperature, 91% (2 steps); l) $Pb(OAc)_4$, py, CH_2Cl_2, −50 °C; then DIBAL, −78 °C→−50 °C, 93% (90% conversion); m) BTBBr, KH, [18]crown-6, DMF, room temperature; n) OsO_4, NMO, *t*BuOMe/*t*BuOH/H_2O (2:1:1), room temperature, 94% (89% conversion; 2 steps); o) SO_3·Py, *i*Pr_2NEt, DMSO, CH_2Cl_2, −15 °C; then allylmagnesium bromide, −78 °C, 78% (**21α**/**21β** 2.7:1); p) $[(PCy_3)_2Cl_2Ru{=}CHPh]$, CH_2Cl_2, reflux; then $Pb(OAc)_4$, room temperature, 97%. Cy = cyclohexyl, DMAP = 4-dimethylaminopyridine, DME = dimethoxyethane, DIBAL = dibutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NMO = *N*-methylmorpholine *N*-oxide, Piv = pivaloyl, py = pyridine, Ts = *p*-toluenesulfonyl.

isopropylidene acetal **16**, Bn protection of the C12–OH group of **16** and subsequent removal of the acetonide under acidic conditions delivered the 1,2-diol **17** (91%, two steps). One-carbon-atom truncation from **17** to liberate the masked primary C14–OH functionality was carried out in a single-flask reaction involving $Pb(OAc)_4$-induced oxidative cleavage and DIBAL reduction, and led to **18** in 93% yield.[19] The BTB group was then introduced at C14–OH in **18** to afford differentially protected **19**.

By exploiting the pseudo-*meso* symmetry of **19**, diketone **6** was prepared in only three steps through pairwise functionalization.[20] Olefin **19** was subjected to dihydroxylation to afford diol **20**, the one-pot treatment of which with SO_3·py[21]

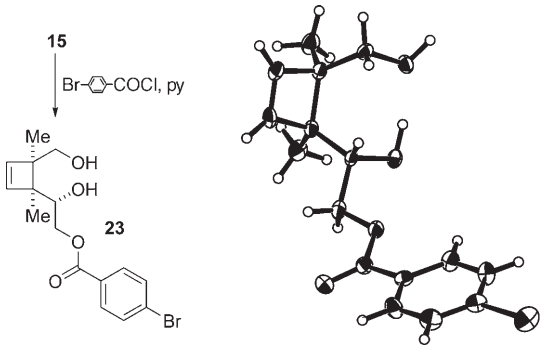
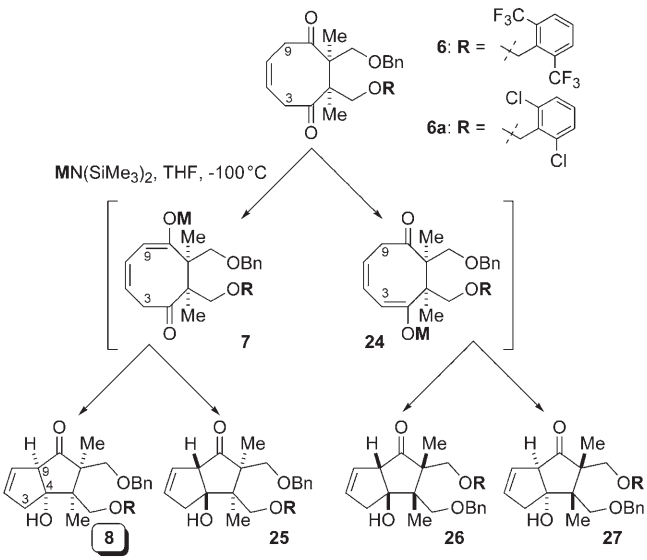


Figure 2. X-ray crystallographic analysis of compound **23** to confirm the structure of triol **15**.[41]

and an allyl Grignard reagent provided adducts **21α** and **21β** in 78% yield.[22] The *cis* relationship of the olefinic side chains of **21α** and **21β** facilitated the subsequent ring-closing metathesis reaction to produce the bicyclo[4.2.0]octyl system **22**,[23] which was subjected in situ to $Pb(OAc)_4$-promoted oxidative ring expansion[24] to yield the substituted eight-membered ring **6**.

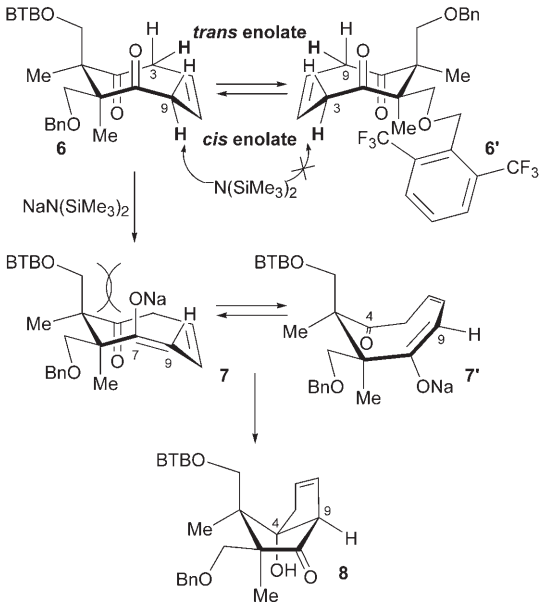
Having established a route to the differentially protected diketone **6**, we undertook the crucial transannular aldol reaction. To our gratification, the reaction of **6** with $LiN(SiMe_3)_2$ (Scheme 4, entry 1) exhibited both site-selective deprotonation (**7**/**24**) and diastereoselective C–C bond formation (**8**/**25**) to give the desired bicyclo[3.3.0]octane system **8**[25] along with smaller amounts of the other three diastereomers **25**–**27**. To enhance the formation of **8**, the effect of the counter cation of the amide base was examined (entries 2, 3): When **6** was treated with $NaN(SiMe_3)_2$, enantiomerically pure **8** was isolated in 75% yield after purification by column chromatography with SiO_2. Interestingly, the selectivity of the same base treatment of **6a**, which possesses the less sterically demanding protecting group 2,6-dichlorobenzyl (DCB; effective radii: 2.2 Å (CF_3) versus 1.7 Å (Cl)),[26] was lower in both the deprotonation and the C–C bond-forming steps (entry 4). This result clearly suggests that the steric bulk of the *ortho* substituents of the phenyl ring has a significant effect on the selectivity of the reaction. As expected, our BTB group functioned as a long-range stereocontrolling element for the aldol reaction.



Entry	R	M^+	7/24	8/25	Yield combined	Yield 8
1	BTB	Li^+	3.5 : 1	9.2 : 1	91%*	65%*
2	BTB	Na^+	4.5 : 1	17.0 : 1	97%	75%
3	BTB	K^+	2.5 : 1	9.5 : 1	78%	51%
4	DCB	Na^+	2.8 : 1	7.9 : 1	89%	58%

Scheme 4. Diastereoselective transannular aldol reaction of pseudo-*meso* diketones **6** and **6a**. The yields of entry 1 are based on recovered starting material (82% conversion).

A plausible mechanism for the reaction is shown in Scheme 5. Molecular modeling (MM2*, MacroModel Version 8.5)[27] indicated that the eight-membered ring exists as a mixture of two pseudoenantiomeric conformers **6** and **6′**.[28] Since *cis*-enolate formation from the eight-membered ring is energetically more favorable than *trans*-enolate formation, in each conformer only one of the two protons (indicated in bold face in Scheme 5) orthogonal to the C=O bonds is thought to be abstracted by the base. The selective deprotonation of **6** to generate the *cis* enolate **7** can be explained by effective insulation of C9 of **6′** by the remote bulky BTB group. After enolate formation, the severe 1,3-diaxial-like steric interaction between the large BTB-protected oxymethylene group and the C7–O bond in **7**[29] would enforce a conformational flip of the C7–C9 olefin to form **7′**, from which the enolate can react with the ketone at C4 to generate the desired *cis*-fused 5,5 ring system **8**. The proposed mechanism agrees well with the observation that the bulkier protecting group is more



Scheme 5. Plausible mechanism for the diastereoselective transannular aldol reaction of **6**.

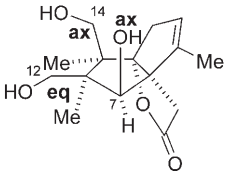
selective in both the deprotonation and C–C bond-forming steps (Scheme 4, entries 2 and 4).

With the enantiomerically pure bicyclo[3.3.0]octane framework **8** in hand, we proceeded to synthesize the entire carboskeleton of (−)-**1** by introduction of the C9 quaternary center and the C15 methylene group (Scheme 6). α-Epoxidation of **8** and subsequent florisil treatment produced allylic alcohol **28**, which was converted into enedione **29**.[30] An α-bromoacetal unit was then introduced to afford **30** as a mixture of diastereomers.[31]

Despite the steric congestion induced around C9 by the three proximal tetrasubstituted carbon atoms (C4, C5, C6), radical cyclization of **30** smoothly delivered the 5-*exo* cyclized product **31** along with its C11 epimer **32** in 90% combined yield. Upon treatment with $EtOSiMe_3$ in the presence of $BF_3{\cdot}Et_2O$, the minor isomer **32** was transformed into the major isomer **31** in 72% yield. NOESY data obtained for **31** allowed the assignment of configuration and conformation (Scheme 6): The CH_2 group at position 3 was found to be in spatial proximity to the ethoxy and BTB-protected oxymethylene groups. Presumably because of low base accessibility to the sterically crowded C3 center, in the next step the reaction of **31** with Me_3SiOTf and Et_3N produced predominantly silyl enol ether **33** through site-selective deprotonation at the less-shielded C1 center. The C15 methylene group was introduced by the treatment of **33** with the Eschenmoser reagent[32] and then with *m*CPBA to give **34**.

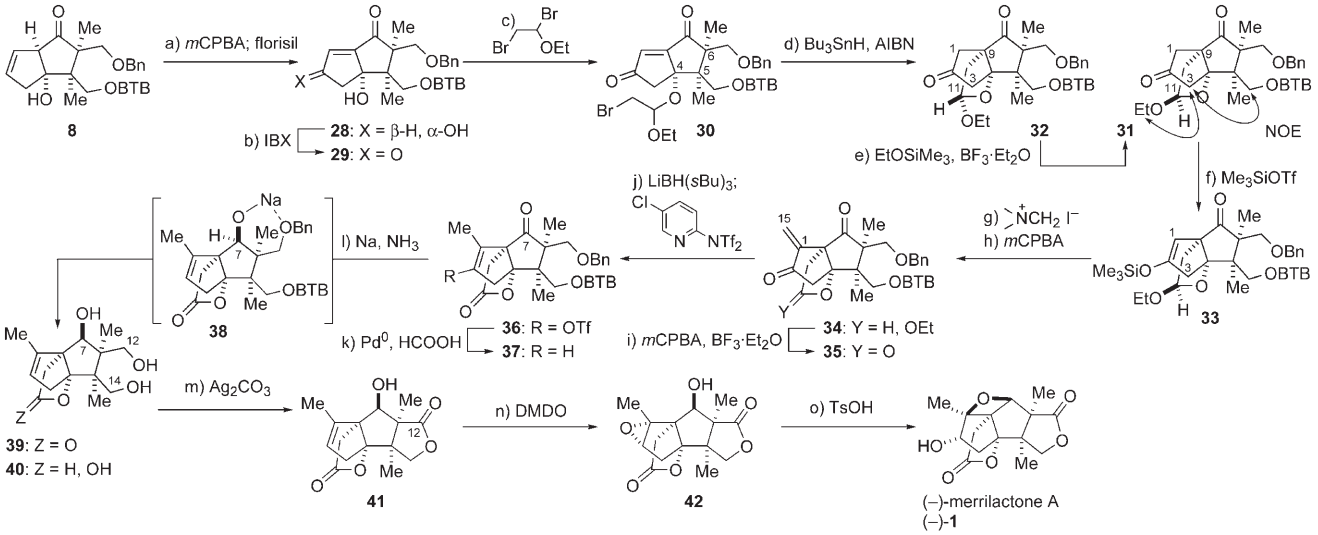
To complete the total synthesis, the remaining functional-group manipulations needed to be orchestrated judiciously. First, acetal **34** was converted quantitatively into γ-lactone **35**.[33] Hydride addition to the *exo* alkene of the unsaturated ketone **35**, followed by in situ triflation, afforded the enol triflate **36**,[34,35] which was converted into the trisubstituted alkene **37** through palladium-mediated reduction.[36] The exposure of **37** to Na in NH_3[37] effected both the stereoselective reduction of the hindered ketone at C7 to the β-hydroxy group, presumably via **38** through a six-membered chelate ring, and the removal of both benzyl-type protecting groups (Bn and BTB) to give lactol **40** along with lactone **39**.

The mixture of **39** and **40** was in turn subjected to Fetizon oxidation[38] to produce the desired bis-γ-lactone **41** as a single isomer. It appears that the reactivity of the hydroxy group at C12 in **39**/**40** towards oxidation is higher than that of the hydroxy groups at C7 and C14 as a result of its more exposed nature: Molecular modeling of **40** suggested that only the C12 hydroxymethyl group adopts a pseudoequatorial position, as depicted in Scheme 7. Thus, the remarkable selectivities of the reduction (**37**→**40**) and oxidation (**40**→**41**) steps are governed by the intrinsic three-dimensional orientation of the reacting substituents. Moreover, the stereochemical controlling factor for the aldol reaction, the BTB ether, was shown to be robust under a variety of reaction conditions up to those for the synthesis of **39**, yet was removed smoothly through Birch reduction.



Scheme 7. Conformation of **40** according to molecular modeling.

Finally, stereoselective α epoxidation of **41** with dimethyldioxirane[39] to give **42** and subsequent acid-mediated epoxide opening–oxetane formation delivered (−)-merrilactone A ((−)-**1**).[1] Synthetic (−)-**1** exhibited ^1H NMR, ^{13}C NMR, IR, and HRMS spectra that were indistinguishable



Scheme 6. Asymmetric total synthesis of (−)-merrilactone A; (the principal reagents are also shown in the Scheme): a) mCPBA, CH_2Cl_2; then florisil, CH_2Cl_2, room temperature, 75%; b) IBX, DMSO, room temperature, 91%; c) $BrCH_2Br(OEt)$, $PhNMe_2$, CH_2Cl_2, −78 °C→RT, 92% (d.r. 4.4:1, 79% conversion); d) Bu_3SnH, AIBN, toluene, 85 °C, 73% (**31**), 17% (**32**); e) $EtOSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temperature, 72%; f) Me_3SiOTf, Et_3N, CH_2Cl_2, −20 °C; g) $Me_2NCH_2{}^+I^-$, CH_3CN, room temperature; h) mCPBA, CH_2Cl_2, room temperature, 64% (3 steps); i) *m*CPBA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temperature, 100%; j) $LiBH(sBu)_3$, 2-Tf_2N-5-chloropyridine, THF, −78 °C, 73%; k) $Pd(OAc)_2$, PPh_3, NBu_3, HCOOH, DMF, 40 °C, 92%; l) Na, NH_3, THF/EtOH (5:1), −78 °C (**39**/**40** 1:1.4); m) Ag_2CO_3 on celite, toluene, 130 °C, 41% (2 steps); n) DMDO, CH_2Cl_2, room temperature, 91%; o) $TsOH{\cdot}H_2O$, CH_2Cl_2, room temperature, 96%. AIBN = *N*,*N*-azobisisobutyronitrile, DMDO = dimethyldioxirane, IBX = *o*-iodoxybenzoic acid, *m*CPBA = *m*-chloroperbenzoic acid, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

from those of the natural compound. The measured optical rotation of synthetic (−)-**1** confirmed the absolute configuration of the natural product ($[\alpha]_D^{27} = -15.7$ ($c = 0.19$, $CHCl_3$); natural (−)-**1**: $[\alpha]_D^{18} = -16.7$ ($c = 1.10$, $CHCl_3$)).[2,40]

In summary, we have completed the asymmetric total synthesis of (−)-merrilactone A (1.1% overall yield, 31 steps). The defining step in our synthesis is the diastereoselective transannular aldol reaction of **6** to construct the bicyclo[3.3.0]octane core **8**. The selectivity observed in the construction of the two new stereocenters in **8** is a long-range effect of the bulky protecting group BTB. Other remarkable features of our total synthesis include 1) a [2+2] cycloaddition to install the two contiguous quaternary carbon atoms of **14**, 2) efficient pairwise symmetrical functionalization to synthesize **6** by taking advantage of the pseudo-*meso* symmetry, 3) radical cyclization to form the sterically congested C9 quaternary carbon atom of **31**, and 4) highly selective substrate-controlled reactions to introduce three functional groups: the C15 methylene group of **34**, the β-hydroxy group at C7 of **40**, and the C12-containing γ-lactone in **41**.

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