JOC Article

Total Synthesis and Bioactivity of an Unnatural Enantiomer of Merrilactone A: Development of an Enantioselective Desymmetrization Strategy

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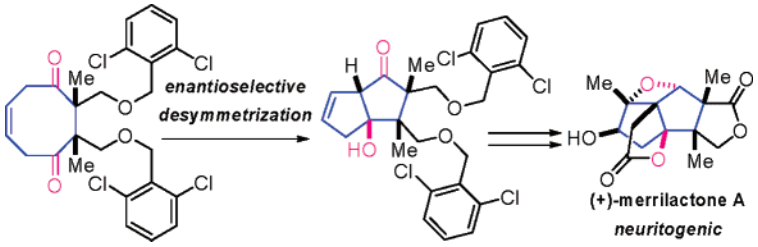

(−)-Merrilactone A [(−)-**1**], isolated from *Illicium merrillianum* in 2000, possesses neurite outgrowth activity in cultures of fetal rat cortical neurons, and, therefore, is expected to show therapeutic potential for the treatment of neurodegeneration associated with Alzheimer's and Parkinson's diseases. Apart from its biological aspects, the caged pentacyclic skeleton of **1** poses interesting synthetic challenges. Here, we report the total synthesis of the unnatural enantiomer of merrilactone A [(+)-**1**], based on a novel desymmetrization strategy. The chiral lithium amide **16g** promoted an enantioselective transannular aldol reaction of eight-membered *meso*-diketone **3d**, establishing the absolute stereochemistries of four chiral centers of the *cis*-bicyclo[3.3.0]octane framework of **1** in a single step. The obtained compound **4d** served as a platform for the subsequent functional group manipulations necessary for the construction of (+)-**1**. Surprisingly, both the natural and unnatural enantiomers of synthetic merrilactone A equally promoted neurite outgrowth in primary neuronal cultures.

Introduction

Neurotrophic factors (NTF) are endogenous proteins that regulate neuronal survival, neurite outgrowth, differentiation of nerve cells and synaptic connectivity, and maintenance of structural integrity.[1] Over the past two decades, NTFs have served as potent therapeutic agents for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. However, their clinical use has been limited because of their relatively poor bioavailability and pharmacokinetics: NTF proteins are easily metabolized and unable to cross the blood−brain barrier. Stable, nonpeptidal small molecules have been the subject of intense attention as NTF alternatives.[2]

In this context, Fukuyama and co-workers isolated and determined the structure of a series of natural products with NTF-like activities.[3] One of the most potent compounds, (−)-merrilactone A [(−)-**1**, Figure 1], promoted neurite outgrowth and exerted a neuroprotective effect at low concentrations (0.1−10 μM) in primary cultures of fetal rat cortical neurons.[4] Interestingly, **1** is the only neurotrophic member of the structur-

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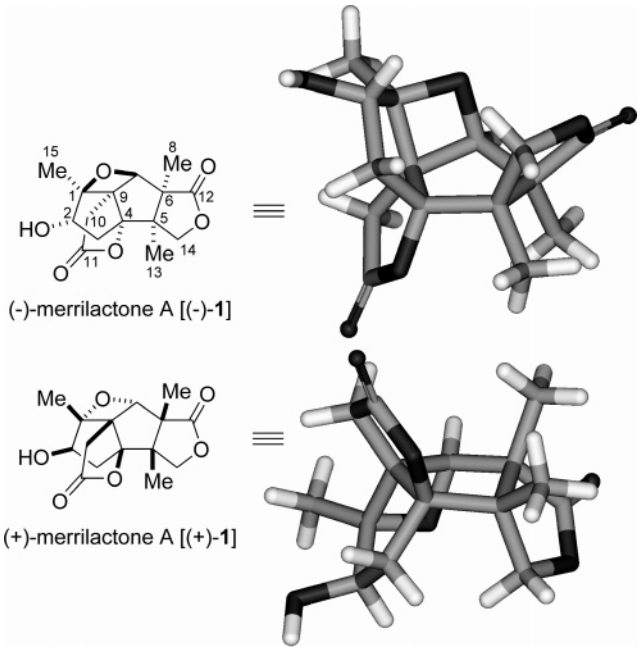
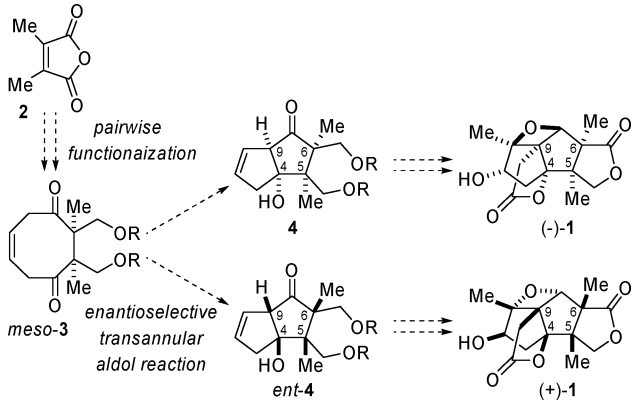


FIGURE 1. Structures of both enantiomers of merrilactone A.

ally related anislactone-type sesquiterpenoids.[5] Despite its promising activity, its mode of action in neuronal cells and the structural features necessary for activity have not been elucidated.

In addition to significant biological activity, **1** possesses interesting architecture from a synthetic point of view. The highly oxygenated caged structure is composed of a central *cis*-bicyclo[3.3.0]octane carbon framework, two γ-lactones, a unique oxetane ring, and seven contiguous stereogenic carbon centers, three of which are quaternary carbons (C5, C6, C9). This challenging structure has been the target of intense synthetic investigations,[6] which led to the total synthesis of (±)-merrilactone A independently by our group,[7] and the laboratories of Danishefsky,[8] Mehta,[9] and Frontier.[10] The asymmetric synthesis of **1** also has been accomplished by Danishefsky et al.[11] Recently, we reported the asymmetric total synthesis of the natural enantiomer (−)-**1** from a chiral starting material, and confirmed the absolute configuration.[12]

SCHEME 1. Synthetic plan of both enantiomers of merrilactone A



As a consequence of the potent activity of the natural product and the uncertainty surrounding its mechanism of action, we were especially keen to evaluate both enantiomers of **1**, because examination of the unnatural enantiomer should provide seminal structural information about factors contributing to the biological effects of the natural product. Here, we report the concise total synthesis of the unnatural enantiomer of merrilactone A [*ent*-(+)-**1**] based on a novel enantioselective desymmetrization strategy, and provide a preliminary biological comparison of the synthetic enantiomers.

Synthetic Plan

Merrilactone A (**1**) possesses a densely oxygenated carbon framework fused with two γ-lactones and an oxetane ring (Scheme 1). To simplify an asymmetric synthetic route to both enantiomers of **1**, we exploited a hidden structural symmetry of the framework in **1**: the plan involved assembly of the pivotal *cis*-bicyclo[3.3.0]octane skeleton **4** or *ent*-**4** by an enantioselective transannular aldol reaction of the common *meso*-eight-membered diketone **3**.[13,14] Installation of the absolute stereochemistry of four centers (C4, C5, C6, C9) from an achiral

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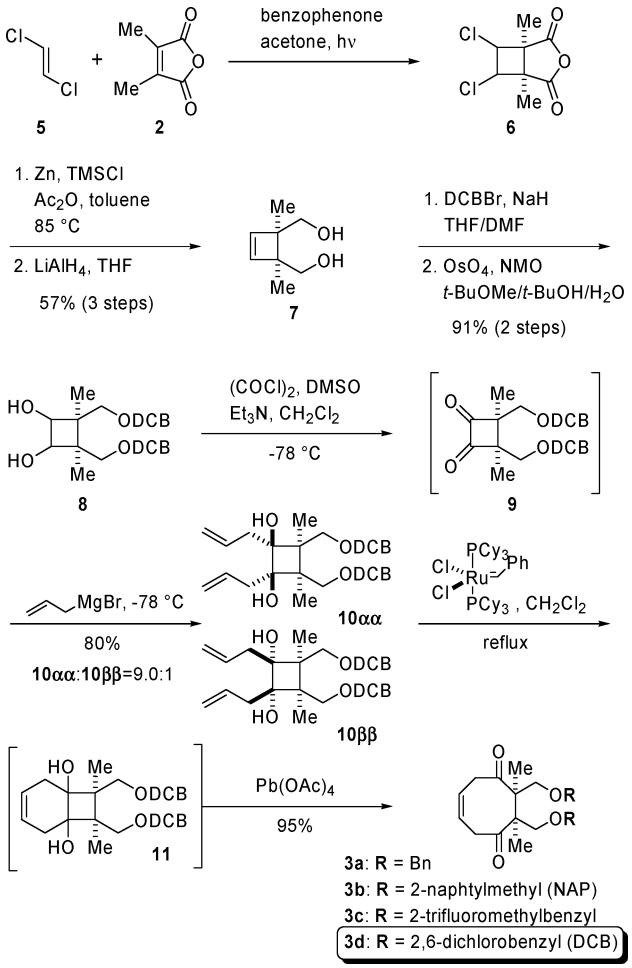
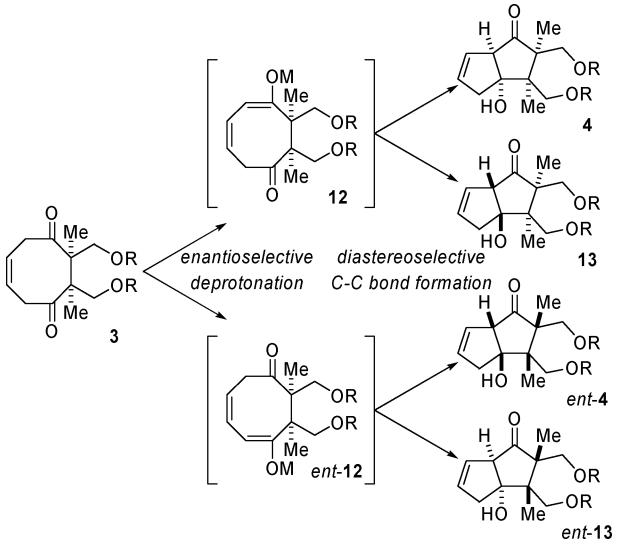
SCHEME 2. Synthesis of *meso*-Eight-Membered Diketone



material was considered the most prominent, yet challenging, feature of this reaction.[15] By taking advantage of its symmetry, an efficient synthesis of *meso*-**3** could be attained by applying pairwise functionalization to *meso* intermediates after starting with **2**.[16] This strategy allows readily available **4** and *ent*-**4** to serve as a platform structure for subsequent functional group transformations necessary for the chemical construction of (−)-**1** and *ent*-(+)-**1**, respectively.

Synthesis of Eight-Membered *meso*-Diketone. As shown in Scheme 2, the synthesis of **3** started with [2+2] photocycloaddition between 2,3-dimethylmaleic anhydride **2**[17] and *trans*-dichloroethylene **5** to install the two contiguous quaternary stereocenters (C5, C6).[18] Reductive dechlorination of **6** with Zn/AcOH, followed by $LiAlH_4$ reduction of the anhydride, provided *meso*-diol **7**. After protection of the primary alcohols of **7** by their dichlorobenzyl (DCB) ethers, dihydroxylation of the olefin

SCHEME 3. Two Distinct Steps in the Enantioselective Transannular Aldol Reaction



afforded **8**. Although Swern oxidation[19] of the obtained diol **8** generated diketone **9**, the aqueous workup of **9** readily resulted in its hydrated form, which turned out to be unreactive toward various nucleophilic reagents. Thus, allyl magnesium bromide was added directly to the Swern oxidation mixture containing **9**,[20] leading to **10αα** and **10*ββ*** as major isomers in high yield. The cis-arrangement of allyl groups effectively facilitated the ring-closing metathesis reaction[21] of **10** to produce the bicyclo-[4.2.0]octyl system **11**, which was treated with $Pb(OAc)_4$ in situ[22] to yield the *meso*-eight-membered diketone **3d**. Therefore, **3d** was synthesized in only seven steps through pairwise symmetrical functionalization. To evaluate the effect of the protective group on the outcome of the next aldol reaction, various other *meso*-eight-membered diketones **3a**−**c** were prepared in a similar manner.

Enantioselective Transannular Aldol Reaction. As shown in Scheme 3, the crucial asymmetric aldol reaction of **3** contained two distinct steps: enantioselective deprotonation and diastereoselective C−C bond formation, both of which need to be highly selective for obtaining **4** or *ent*-**4** out of the four possible cis-fused isomers.[23] First, we evaluated the outcome of the C−C bond formation (the second step) by varying two elements: the reaction conditions (Table 1) and the protective group of the primary alcohols (Table 2). As shown in Table 1, treatment of **3a** with $LiN(TMS)_2$ in THF at −100 °C led to the cis-fused products (±)-**4a** and (±)-**13a**, favoring the desired isomer (±)-**4a** (entry 1). Higher temperatures (entries 2 and 3) resulted in lower selectivity, suggesting the kinetic nature of

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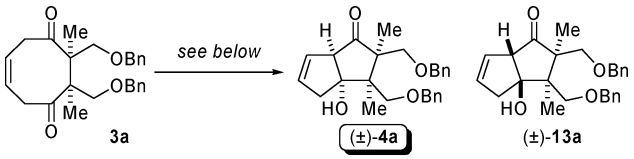
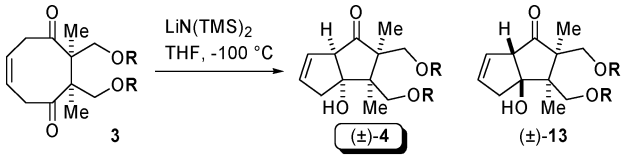
TABLE 1. Diastereoselective C−C Bond Formation: Base Effect

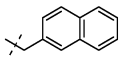


entry	reagents and conditions	(±)-**4a** : (±)-**13a**	combined yield
1	$LiN(TMS)_2$, THF, -100 °C	3.1 : 1	85%
2	$LiN(TMS)_2$, THF, -78 °C	2.9 : 1	86%
3	$LiN(TMS)_2$, THF, -40 °C	2.6 : 1	78%
4	$MgBrN(TMS)_2$, Et_2O, rt	1 : 3.0	81%
5	$LiN(TMS)_2/Et_3N$, toluene, -78 °C	1 : 5.1	79%
6	DBU, CH_2Cl_2, 0 °C	1.1 : 1	63%
7	LiNMePh, THF, -100 °C	5.7 : 1	99%[a]
8	LiNMe(*m*-ClPh), THF, -100 °C	5.8 : 1	87%[a]
9	LiNMe(*p*-ClPh), THF, -100 °C	11.2 : 1	89%

[a] The yields were based on recovered starting material [80% conversion (entry 7), 92% conversion (entry 8)].

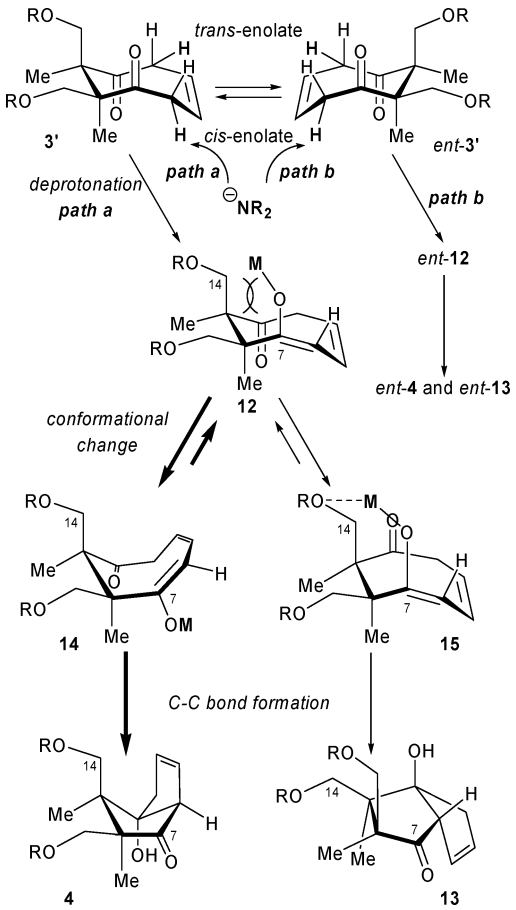
TABLE 2. Diastereoselective C−C Bond Formation: Protective Group Effect



entry	**3**	(±)-**4** : (±)-**13**	combined yield
1	**3a**: R = 	3.1 : 1	85%
2	**3b**: R = 	3.2 : 1	92%
3	**3c**: R = 	3.9 : 1	93%
4	**3d**: R = 	6.0 : 1	88%

(±)-**4a** under these conditions. This hypothesis was reinforced by the absence of isomerization of **4a** to **13a** upon re-treatment with $LiN(TMS)_2$. Interestingly, both $MgBrN(TMS)_2$ (entry 4) and $LiN(TMS)_2/Et_3N$[24] in toluene (entry 5) induced the opposite selectivity, favoring the undesirable diastereomer (±)-**13a**, whereas DBU did not exhibit a preference for either product (entry 6). Since the lithium amide in THF (entry 1) gave the most promising result, a number of other lithium bases were applied to **3a**. Lithium anilides[25] (entries 7−9) improved selectivity with lithium 4-chloro-*N*-methylanilide providing the best results [(±)-**4a**:(±)-**13a** 11.2:1].

SCHEME 4. Mechanistic Consideration of the Aldol Reaction



As shown in Table 2, the yield of (±)-**4** also was improved by increasing the steric bulk of the protective group (R). Whereas replacement of the benzyl group with a 2-naphthyl group (NAP) (entry 2) gave a result comparable to that shown in entry 1 under the same conditions [$LiN(TMS)_2$, THF], **3c** bearing a 2-trifluoromethylbenzyl group showed higher selectivity for (±)-**4c** (entry 3). The preference for (±)-**4** was improved further when substrates with doubly *ortho*-substituted benzyl groups, 2,6-dichlorobenzyl (DCB, entry 4), were subjected to the same reaction conditions. In this way, we successfully developed highly diastereoselective C−C bond formation by controlling the reaction conditions and protective groups.

A possible mechanism of the present transannular reaction is explained by the conformations of **3** and subsequent enolate intermediates. As depicted in Figure 2, X-ray crystallographic analysis of **3d** revealed that the two ketones are perpendicular to the eight-membered ring and are oriented in the opposite direction. The ^1H NMR signals of **3d** at −100 °C separated into two sets of peaks, representing two alternating conformers (1:1, see the Supporting Information). Thus, it is very likely that the eight-membered ring **3** exists as an equimolar mixture of the two enantiomeric conformers **3′** and *ent*-**3′** (Scheme 4). Since *cis*-enolate formation from the eight-membered ring is energetically more favorable than *trans*-enolate formation, only one of the two protons orthogonal to the C═O bonds (indicated

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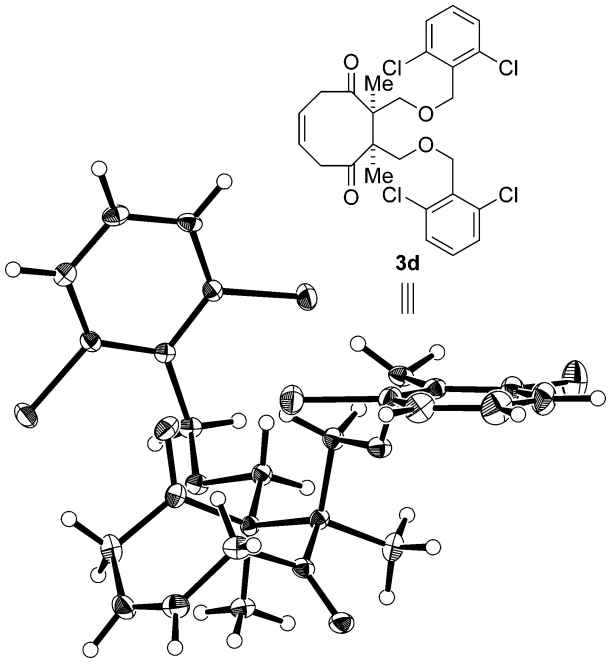
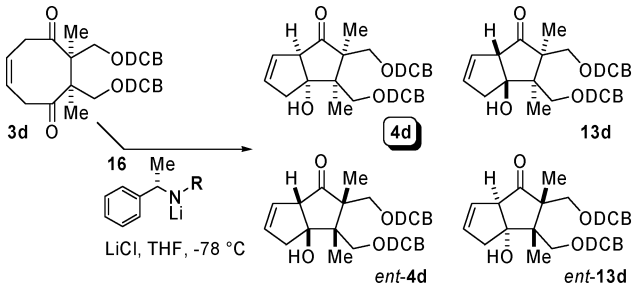


FIGURE 2. X-ray crystallographic analysis of compound **3d**.

in bold face) is considered to be abstracted by the base ($^{-}NR_2$). Consequently, conformers **3′** and *ent*-**3′** would lead to **4**/**13** and *ent*-**4**/*ent*-**13** via **12** and *ent*-**12**, respectively; only the former path is shown in Scheme 4. After enolate formation from **3′**, the strong 1,3-diaxial-like steric interaction between the bulky protected oxymethylene and C7−O bond in **12** would enforce a conformational flip of the olefin to form **14**, from which the enolate reacts with the ketone to generate the desired cis-fused 5−5 ring system **4**. The proposed mechanism agrees well with the observation that a bulkier protecting group is beneficial in obtaining **4** (Table 2). However, metal chelation could fix the orientation between C7−O and C14−O in intermediate **15** that leads to the undesired diastereomer **13**. In fact, **13** was obtained selectively in entries 4 and 5 (Table 1), where Li^+ in nonpolar solvent and Mg^{2+}, respectively, would stabilize the seven-membered chelate in **15**, unlike Li^+ in ethereal solvent. Hence, the diastereoselectivity of the C−C bond formation appears to be controlled by a balance between steric interaction and chelation of C7-OM and C14-oxymethylene.

With the establishment of an efficient procedure for the synthesis of (±)-**4** using bulky protective groups and lithium amide as controlling elements, efforts turned toward the development of a procedure for the synthesis of either **4** or *ent*-**4** via an enantioselective deprotonation[26] (path a or path b in Scheme 4). We envisaged that a chiral lithium amide would differentiate path a and path b through selective recognition of the two enantiomeric conformers **3′** and *ent*-**3′**, respectively. To realize the enantioselective transformation, DCB-protected diketone **3d** was treated with a substituted lithium (*R*)-1-phenylethylamide **16a**−**g** with lithium chloride[27] in THF (Table 3).[28] As expected, all entries showed a diastereoselectivity for **4d** + *ent*-**4d** over **13d** + *ent*-**13d**. In contrast, the enantiomer ratio between **4d** and *ent*-**4d** was highly sensitive to the lithium amide

TABLE 3. Enantioselective Transannular Aldol Reaction



entry	R		(**4d**+*ent*-**4d**) : (**13d**+*ent*-**13d**)	**4d** : *ent*-**4d**	combined yield
1		**16a**	19 : 1	1 : 2.4	87%
2		**16b**	15 : 1	1 : 1.3	73%
3		**16c**	6.0 : 1	1 : 1	100%
4		**16d**	7.0 : 1	1.9 : 1	88%
5		**16e**	8.1 : 1	2.2 : 1	94%
6		**16f**	3.0 : 1	2.7 : 1	94%
7		**16g**	6.0 : 1	4.7 : 1	90%

structures: while enantioselectivity was not observed upon treatment of **3d** with **16b**[29] and **16c**[30] (entries 2 and 3), **16d**,[31] **16e**,[32] **16f**,[31] and **16g**,[33] selectively generated **4d** (entries 4−7), and **16a**[34] induced the opposite selectivity (entry 1). The absolute structure of **4d** was unambiguously determined by X-ray crystallographic analysis (Supporting Information). Most importantly, the enantiomer ratio obtained in the case of **16g** (**4d**: *ent*-**4d** 4.7:1, entry 7) was practically sufficient for the asymmetric total synthesis of enantiopure merrilactone, because of the crystalline nature of **4d** (vide supra). Overall, the selective formation of **4d** among the four isomers was achieved by using the novel enantioselective desymmetrization strategy.

Total Synthesis of (+)-Merrilactone A. Having developed a flexible new route to **4d** and *ent*-**4d**, our effort focused on

(26) For reviews of enantioselective deprotonation, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1. (b) Koga, K. *Pure Appl. Chem*. **1994**, *66*, 1487. (c) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (d) Plaquevent, J.-C.; Perrard, T.; Cahard, D. *Chem. Eur. J*. **2002**, *8*, 3300.

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(28) When **16g** was used without lithium chloride, the ratio of **4d**/*ent*-**4d** was changed into 1.7:1 [(**4d** + *ent*-**4d**):(**13d** + *ent*-**13d**) 8.0:1)].

(29) Yamamoto, K.; Takemae, M. *Bull. Chem. Soc. Jpn*. **1989**, *62*, 2111.

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(31) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.

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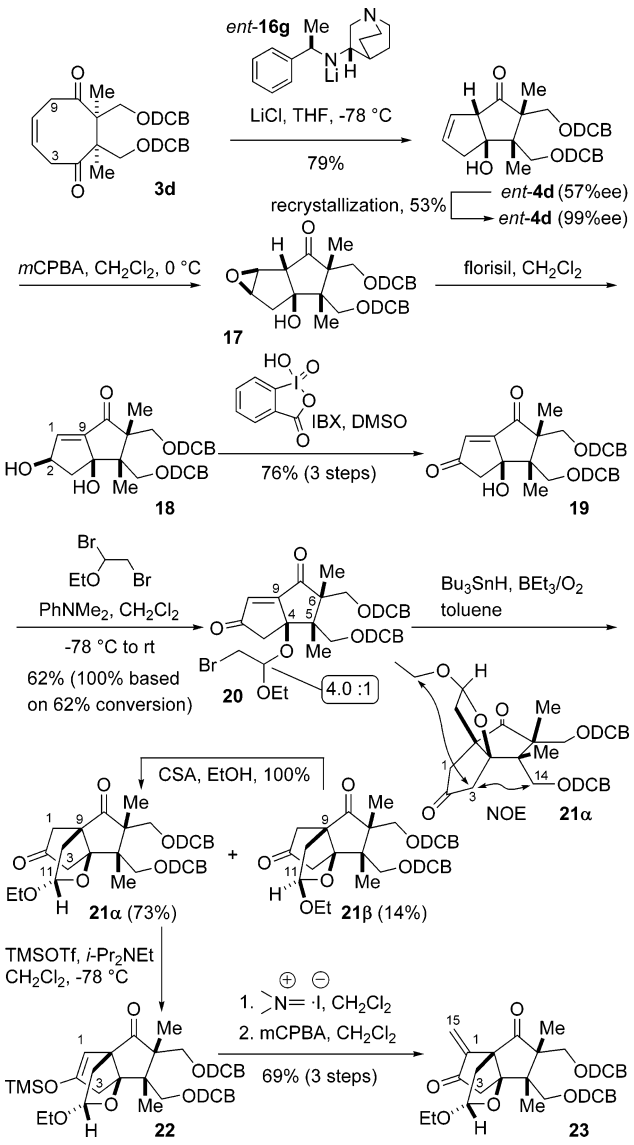
(33) Although **16g** and *ent*-**16g** are commercially available, these bases have not been applied to enantioselective deprotonation reaction to the best of our knowledge. For their preparation, see: Kowalczyk, B. A.; Rohloff, J. C.; Dvorak, C. A.; Gardner, J. O. *Synth. Commun*. **1996**, *26*, 2009.

(34) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

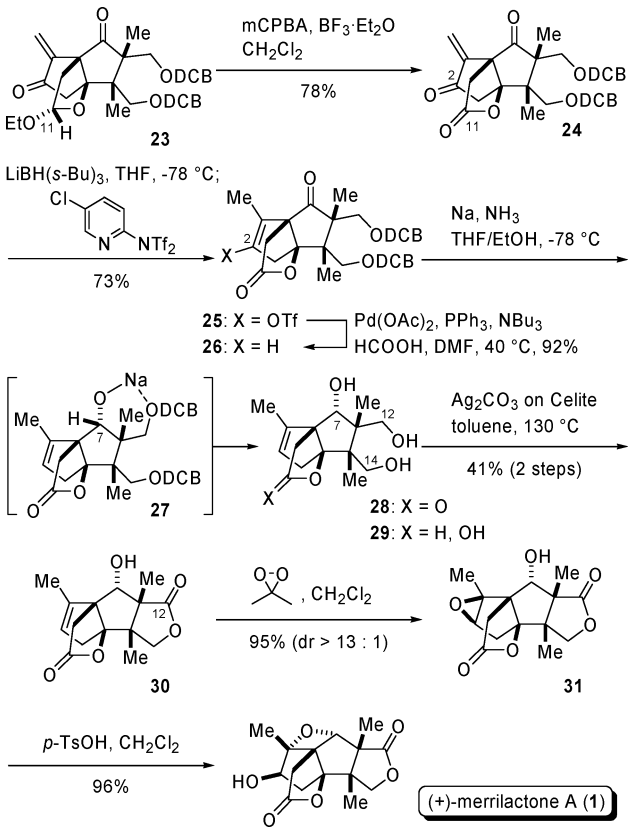
SCHEME 5. Synthesis of the Carboskeleton of Merrilactone A



synthesis and biological evaluation of the unnatural enantiomer of merrilactone A [(+)-**1**]. Diketone **3d** was first treated with *ent*-**16g** (Scheme 5) to selectively produce *ent*-**4d** (57% ee, 79% yield); one recrystallization afforded enantiopure *ent*-**4d** (99% ee). The C1−C9 olefin and C2−oxygen functionality then were introduced in two steps: α-selective epoxidation of *ent*-**4d** and subsequent florisil-mediated epoxide opening of **17**, to provide allylic alcohol **18**.

To synthesize the entire carboskeleton of **1**, introduction of the C9-quaternary center and a C15-carbon was necessary (Scheme 5). The former was particularly problematic, owing to the large steric hindrance of three proximal tetrasubstituted carbon centers (C4, C5, C6). After attempting a number of unsuccessful reactions, we conducted intramolecular radical cyclization of α-bromoacetal **20**[35,36] because of its powerful yet mild nature. Oxidation of allylic alcohol **18** was attained by using IBX[37] to yield enedione **19**. α-Bromoacetal then was

SCHEME 6. Total Synthesis of (+)-Merrilactone A



introduced to the hindered tertiary alcohol **19** by using 1,2-dibromoethyl ethyl ether and *N*,*N*-dimethylaniline to provide **20**. Treatment of **20** with Bu_3SnH and BEt_3 under the air[38] at room temperature successfully led to 5-exo product **21α** and C11-epimer **21*β*** in 87% combined yield. When subjected to acidic conditions, **21*β*** was selectively isomerized to **21α**. NOESY experiments indicated the three-dimensional structure of **21α**, with the ethoxy and C14-O-benzyl groups located in spatial proximity with the C3 carbon center. This arrangement of functional groups was beneficial for the next site-selective installation of C15 at C1: a combination of TMSOTf and *i*-Pr_2-NEt enabled the regioselective enolization of ketone **21α** at the C1 position in the presence of the sterically shielded C3 methylene, leading to silyl enol ether **22** as a single isomer. Then, exposure of **22** to Eschenmoser's salt and subsequent elimination of amine via *N*-oxide furnished the carboskeleton **23**.[39]

Seven selective functional group transformations yielded the targeted (+)-**1** from **23** (Scheme 6). Ethyl acetal **23** was converted to lactone **24** by the action of *m*CPBA in the presence of BF_3·Et_2O.[40] Then, lithium enolate formation from enone **24**,

(35) For recent reviews on radical reactions, see: (a) Zhang, W. *Tetrahedron* **2001**, *57*, 7237. (b) Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, *1903*. (c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377.

(36) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

(37) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(38) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. For a review, see: (b) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

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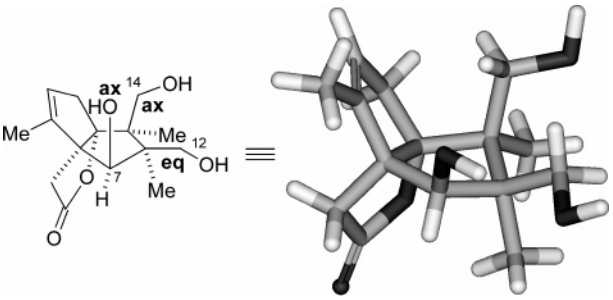

FIGURE 3. Three-dimensional molecular model (MM2*, MacroModel Version 6.0) of compound **28**.

using LiBH(*s*-Bu)$_3$ followed by in situ triflation,[41,42] afforded enol triflate **25**, whose palladium-mediated hydrogenolysis proceeded smoothly to give trisubstituted olefin **26**.[43,44] Exposure of **26** to Na in NH_3[45] effected stereoselective reduction of the hindered C7-ketone to α-alcohol, presumably via six-membered chelate **27**. Then the removal of both DCB groups gave rise to lactol **29** along with lactone **28**. This mixture was subjected to Fetizon oxidation[46] to produce the desired bis-γ-lactone **30** as the exclusive isomer via **28**. It appears that the reactivity toward oxidation of the C12 alcohol is greater than that toward the C7 and C14 alcohols because of its more exposed nature: molecular modeling (Macro Model Version 6.0)[47] of **28** suggested that only the C12-hydroxy methyl group adopts the pseudoequatorial conformation depicted in Figure 3.

Last, epoxidation of **30** with dimethyldioxirane[48] selectively furnished **31**, which was subjected to acid-promoted oxetane formation to produce (+)-**1**. Comparison of ^{1}H NMR, ^{13}C NMR, IR, and HRMS data revealed that the synthetic product was identical with an authentic sample from a natural source except for the optical rotation [[α]$^{27}_D$ +15.7 (*c* 0.19, CH_3OH); nat.: [α]$^{18}_D$ −16.7 (*c* 1.10, CH_3OH)]].[4,49]

Neurite Outgrowth Activity of (-)- and *ent*-(+)-Merrilactone A. We evaluated the neuritogenic activity of both enantiomers of synthetic merrilactone [(-)-**1**^{12}, (+)-**1**] using primary cultures of fetal rat cortical neurons (Figure 4).[50] Surprisingly, both enantiomers of merrilactone A stimulated neurite outgrowth to a similar extent, in a dose-dependent manner between 0.1 μM and 1 μM. This unexpected but informative comparable potency of the two enantiomers of **1** promotes elucidation of the mechanism of action; such studies are in progress.

Conclusion

Concise total synthesis of (+)-merrilactone A has been achieved based on the novel enantioselective desymmetrization strategy (1.3% overall yield, 23 steps). Key transformations in the total synthesis include the following: (i) seven-step pairwise symmetrical functionalization to synthesize **3d** by taking advantage of its *meso*-symmetry; (ii) a new enantioselective transannular aldol reaction of *meso*-**3d** to construct the bicyclo-[3.3.0]octane core **4d**; (iii) radical cyclization to establish the sterically congested C9-quaternary carbon of **21α**; (iv) highly selective substrate-controlled reactions to introduce three functional groups (the C15-methylene of **23**, C7-α-alcohol of **29**, and C12-γ-lactone of **30**). Furthermore, synthetic (−)- and *ent*-

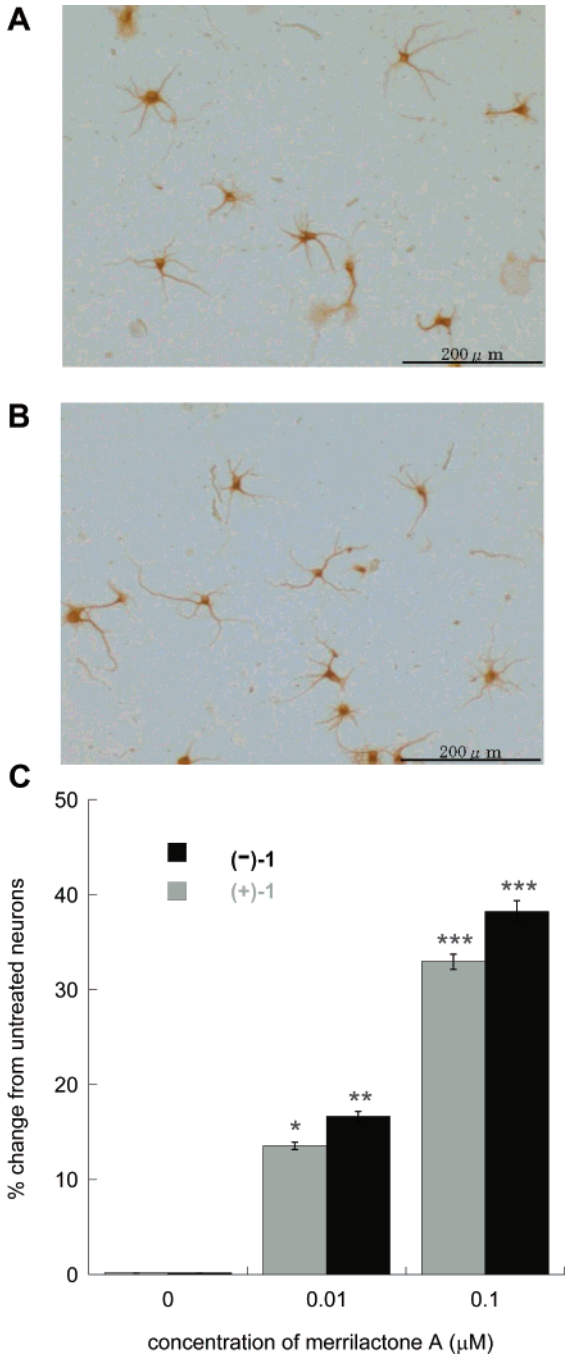

FIGURE 4. Neurite outgrowth-promoting activity of (+)-merrilactone A and (−)-merrilactone A in primary cultures of fetal rat cortical neurons: (A) control, (B) (−)-merrilactone A 0.1 μM, and (C) percent change from untreated neurons. Key for part C: ***, $p < 0.001$ compared with control; **, $p < 0.01$ compared with control; and *, $p < 0.05$ compared with control.

(41) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.
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(48) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.
(49) The reported optical rotation of merrilactone A [[α]$^{21}_D$ +11.8 (*c* 1.20, CH_3OH), ref 4] was found to be an error. The correct value of the natural product is [α]$^{18}_D$ −16.7 (*c* 1.10, CH_3OH). For unambigrous determination of the absolute structure of merrilactone A, see ref 12.
(50) Brewer, G. J. *J. Neurosci. Res.* **1995**, *42*, 674.

(+)-merrilactone A equally promoted neurite outgrowth in primary neuronal culture. The unanticipated biological behavior of *ent*-(+)-**1** provided a rewarding culmination to the present synthesis of the unnatural enantiomer. The flexible asymmetric route described here would provide practical access not only to both enantiomers, but also to analogous structures for future detailed biological and SAR studies.

Experimental Section

Diol 7. Benzophenone (3.63 g, 19.8 mmol) and *trans*-1,2-dichloroethene **5** (60.8 mL, 793 mmol) were dissolved in acetone (2.6 L). 2,3-Dimethylmaleic anhydride **2** (25.0 g, 198 mmol) was divided into three portions and the first portion was added into a flask. The solution was irradiated at room temperature for 60 min. The second portion of 2,3-dimethylmaleic anhydride **2** was added into the reaction mixture, which was then irradiated for 60 min. Then, the last portion was added into the reaction mixture, which was then irradiated for 70 min. Concentration gave the crude **6**, which was directly used in the next reaction.

Zinc dust was successively washed with 2% HCl, H_2O, EtOH, and Et_2O, and then dried under reduced pressure. The freshly activated zinc (205 g, 3.13 mol) was added into a flask equipped with a mechanical stirrer, and toluene (150 mL) and TMSCl (30.0 mL, 235 mmol) were then introduced. To a suspension was added a solution of **6** in toluene (150 mL) and acetic anhydride (192 mL). The mixture was stirred at 85 °C for 2 d, then concentrated to give the crude olefin, which was used directly in the next reaction: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 6H), 6.46 (s, 2H).

To a suspension of $LiAlH_4$ (23.8 g, 626 mmol) in THF (300 mL) at 0 °C was added the above olefin in THF (100 mL). The reaction mixture was stirred at room temperature for 5 h, then quenched with 2 M HCl. The aqueous layer was extracted with EtOAc twice. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with open column chromatography (hexane/EtOAc 5:1 to 3:1), and recrystallized from EtOAc/hexane to give 16.0 g of diol **7** (57% for 3 steps): colorless crystals: mp 98−99 °C (hexane/EtOAc); R_f 0.31 (silica gel, 1:1 hexane/EtOAc); IR (film) 3226, 2915, 1469, 1291, 1029, 769 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, 6H), 2.70 (s, 2H), 3.48 (d, J = 11.6 Hz, 2H), 3.90 (d, J = 11.6 Hz, 2H), 6.01 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 52.9, 68.2, 140.9; HRMS (ESI) calcd for $C_8H_{14}O_2Na^+$ 165.0886 (M + Na^+), found 165.0886.

Diol 8. To a suspension of NaH (1.2 g, 50.6 mmol) in DMF (116 mL) at 0 °C were added diol **7** (3.6 g, 25.3 mmol) in DMF (200 mL), and then DCBBr (18.2 g, 75.9 mmol). The reaction mixture was stirred at room temperature for 1 d, quenched with H_2O, and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with open column chromatography (hexane/Et_2O 10:1) to give 11.6 g of the bis-DCB ether (100%): colorless solid; mp 120−122 °C; R_f 0.48 (silica gel, 3:1 hexane/EtOAc); IR (film) 2864, 1454, 1094, 1074, 736, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 6H), 3.47 (d, J = 9.0 Hz, 2H), 3.60 (d, J = 9.0 Hz, 2H), 4.46 (d, 12.0 Hz, 2H), 4.50 (d, J = 12.0 Hz, 2H), 6.15 (s, 2H), 7.29−7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 51.8, 73.2, 75.4, 127.3, 127.5, 128.2, 138.8, 141.1; HRMS (ESI) calcd for $C_{22}H_{22}Cl_4O_2Na$ 481.0272 (M + Na^+), found 481.0266.

A solution of the above bis-DCB ether (2.43 g, 5.28 mmol) in *t*-BuOMe (7 mL), *t*-BuOH (7 mL), and H_2O (7 mL) was treated with NMO (0.5 M in H_2O, 1.3 mL, 15.8 mmol) and OsO_4 (38 mM in *t*-BuOH, 1.4 mL, 0.05 mmol), and the mixture was stirred at room temperature for 1 d. Then, the solution was diluted with H_2O and extracted three times with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with open column chromatography (hexane/Et_2O 6:1) to give 2.37 g of diol **8** as a mixture of diastereomers (91%, 1.2:1). **Major isomer**: colorless solid; mp 263−266 °C; R_f 0.35 (silica gel, 3:1 hexane/EtOAc); IR (film) 3420, 2931, 1582, 1564, 1437, 1199, 1097, 998, 768, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 6H), 3.34 (d, J = 8.5 Hz, 2H), 3.67 (d, J = 9.5 Hz, 2H), 3.72 (d, J = 9.5 Hz, 2H), 3.90 (d, J = 8.5 Hz, 2H), 4.69 (d, J = 11 Hz, 2H), 4.72 (d, J = 11 Hz, 2H), 7.19 (m, 2H), 7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6, 45.6, 67.2, 70.1, 75.1, 128.2, 129.7, 133.5, 136.8. **Minor isomer**: colorless solid ; mp 263−266 °C; R_f 0.30 (silica gel, 3:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (s, 6H), 2.75 (s, 2H), 3.44 (d, J = 9 Hz, 2H), 3.47 (d, J = 9 Hz, 2H), 4.00 (d, J = 3 Hz, 2H), 4.61(d, J = 11 Hz, 2H), 4.64 (d, J = 11 Hz, 2H), 7.14 (m, 2H), 7.27 (m, 4H).

Diene 10. To a solution of DMSO (5.4 mL, 76 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added oxalyl chloride (5 mL, 57 mmol). After 5 min, diol **8** (4.7 g, 9.5 mmol) in CH_2Cl_2 (90 mL) was introduced, and the resultant mixture was stirred for 30 min at −78 °C, before being treated with triethylamine (21.2 mL, 152 mmol). The resultant mixture was stirred vigorously for 1 h at −78 °C. Allylmagnesium bromide (0.7 M in Et_2O, 95 mL, 66.5 mmol) was then added to the solution. The reaction mixture was stirred for 15 min at −78 °C, quenched with saturated aqueous ammonium chloride, and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/Et_2O 30:1 to 10:1) to give 4.3 g of diene **10** as a mixture of two diastereomers (80% for 2 steps, **10**$\alpha\alpha$:**10**$\beta\beta$ 9:1). **10**$\alpha\alpha$: colorless solid; mp 90−92 °C; R_f 0.61 (silica gel, 3:1 hexane/EtOAc); IR (film) 3448, 2976, 1582, 1563, 1437, 1199, 1097, 777, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 6H), 2.28 (m, 2H), 2.41 (m, 2H), 3.72 (d, J = 9.5 Hz, 2H), 3.75 (d, J = 9.5 Hz, 2H), 4.67 (d, J = 10.5 Hz, 2H), 4.71 (d, J = 10.5 Hz, 2H), 4.99 (d, J = 10.5 Hz, 2H), 5.05 (dd, J = 10.5, 2 Hz, 2H), 5.84 (m, 2H), 7.19 (t, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.1, 38.4, 47.1, 67.4, 74.0, 77.9, 117.4, 128.3, 129.9, 133.4, 134.6, 136.8; HRMS (ESI) calcd for $C_{28}H_{32}Cl_4O_4Na$ 595.0952 (M + Na^+), found 595.0947.

Diketone 3d. To a solution of diene **10** (3.88 g, 6.76 mmol) in CH_2Cl_2 (560 mL) was added $(PCy_3)_2Cl_2Ru$=CHPh (0.6 g, 0.68 mmol), and the resultant mixture was heated to reflux for 5 h. After being cooled to room temperature, the solution was treated with $Pb(OAc)_4$ (3.60 g, 8.2 mmol). Then, the mixture was filtrated through a pad of silica gel to give 3.50 g of diketone **3d** (95%). The obtained **3d** was recrystallized from EtOAc for the X-ray crystallographic analysis (see Figure 2): colorless crystals; mp 168−170 °C; R_f 0.48 (silica gel, 3:1 hexane/EtOAc); IR (film) 2937, 2360, 1693, 1563, 1437, 1097, 1066, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (s, 6H), 2.96 (m, 2H), 3.14 (m, 2H), 3.45 (d, J = 8.5 Hz, 2H), 4.09 (d, J = 8.5 Hz, 2H), 4.65 (d, J = 10.5 Hz, 2H), 4.68 (d, J = 10.5 Hz, 2H), 5.63 (m, 2H), 7.18 (m, 2H), 7.29 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.919, 40.9, 56.2, 67.5, 73.6, 125.0, 136.8, 210.9; HRMS (ESI) calcd for $C_{26}H_{26}Cl_4O_4Na$ 565.0483 (M + Na^+), found 565.0477.

General Procedure for the Transannular Aldol Reaction. [*S*-(*R**,*S**)]-(+)-*N*-(1-Phenylethyl)-1-azabicyclo[2.2.2]octan-3-amine (**16g**, 145 mg, 630 μmol) and LiCl (26.7 mg, 630 μmol) were dissolved in THF (4 mL). To this solution at −78 °C was added *n*-butyllithium (1.57 M in hexane, 401 μL, 630 μmol), and the mixture was allowed to warm to room temperature. After 20 min, the solution was recooled to −78 °C and stirred for 1 h. In a separate flask, diketone **3d** (34.3 mg, 63.0 μmol) was dissolved in THF (4 mL) and cooled to −78 °C. The solution of lithium amide was transferred to the solution of **3d**. After being stirred for 10 min at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 2:1) to give 26.9 mg of **4d** (78%, 65%ee), along with 4.1 mg of the undesired isomer **13d** (12%).

Enantiomeric excess were determined with HPLC (DAICEL CHIRALCEL, OD, 250 × 4.6 mm, UV 254 nm, hexane/*i*-PrOH 85:15, 1.0 mL/min, **4d**: T_R = 15 min, *ent*-**4d**: T_R = 9 min).

Aldol Product *ent*-4d. [*R*-(*R**,*S**)]-(−)-*N*-(1-Phenylethyl)-1-azabicyclo[2.2.2]octan-3-amine (*ent*-**16g**, 4.12 g, 17.9 mmol) and LiCl (759 mg, 17.9 mmol) were dissolved in THF (70 mL). To this solution at −78 °C was added *n*-butyllithium (1.57 M in hexane, 11.4 mL, 17.9 mmol), and the mixture was allowed to warm to room temperature. After 20 min, the solution was recooled to −78 °C and stirred for 1 h. In a separate flask, diketone **3d** (2.73 g, 5.02 mmol) was dissolved in THF (100 mL) and cooled to −78 °C. The solution of lithium amide was transferred to the solution of **3d**. After being stirred for 10 min at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 2:1) to give 2.16 g of *ent*-**4d** (79%, 57% ee), along with 473 mg of the undesired isomer *ent*-**13d** (17%). The obtained *ent*-**4d** was recrystallized from 1:1 hexane/EtOAc to give 1.15 g of enantiopure *ent*-**4d** (53%, 99% ee). Enantiopure *ent*-**4d**: colorless crystals; mp 150−151 °C; R_f 0.40 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{26}_D$ +208.7 (*c* 1.00, $CHCl_3$); IR (film) 2928, 2359, 1737, 1564, 1437, 1199, 1100, 768 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.09 (s, 1H), 1.14 (s, 3H), 2.44 (s, 1H, br), 2.45 (d, J = 18.5 Hz, 1H), 2.95 (dd, J = 18.5, 2 Hz, 1H), 3.10 (d, J = 9 Hz, 1H), 3.19 (d, J = 2.5 Hz, 1H), 3.46 (d, J = 10 Hz, 1H), 3.48 (d, J = 10 Hz, 1H), 4.11 (d, J = 9 Hz, 1H), 4.62 (d, J = 11 Hz, 1H), 4.66 (d, J = 11 Hz, 1H), 4.70 (s, 2H), 5.55 (dd, J = 5.5, 2 Hz, 1H), 5.58 (dd, J = 5.5, 2.5 Hz, 1H), 7.21 (m, 2H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 19.1, 47.8, 50.2, 59.7, 60.4, 65.9, 67.2, 67.4, 73.2, 75.0, 86.9, 126.6, 128.4, 128.4, 130.0, 131.4, 133.0, 133.2, 136.7, 137.0, 215.4; HRMS (ESI) calcd for $C_{26}H_{26}Cl_4O_4Na$ 565.0477 $(M + Na)^+$, found 565.0477. *ent*-**13d**: colorless crystals; mp 150.5−152 °C; R_f 0.36 (silica gel, 3:1 hexane/EtOAc); IR (film) 3537, 2877, 1737, 1582, 1564, 1437, 1199, 1100, 1065, 767, 732 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.00 (s, 3H), 1.04 (s, 3H), 2.47 (d, J = 19.5 Hz, 1H), 2.92 (dd, J = 19.5, 2.5 Hz, 1H), 2.99 (s, br, 1H), 3.06 (d, J = 2.5 Hz, 1H), 3.56 (d, J = 9.5 Hz, 1H), 3.58 (d, J = 9.5 Hz, 1H), 3.66 (d, J = 9.5 Hz, 1H), 3.70 (d, J = 9.5 Hz, 1H), 4.51 (d, J = 10.5 Hz, 1H), 4.54 (d, J = 10.5 Hz, 1H), 4.70 (d, J = 11 Hz, 1H), 4.74 (d, J = 11 Hz, 1H), 5.66 (dd, J = 5.5, 2.5 Hz, 1H), 5.68 (dd, J = 5.5, 2.5 Hz, 1H), 7.20 (m, 2H), 7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 19.5, 45.6, 50.2, 55.8, 67.0, 67.5, 69.4, 73.5, 74.2, 86.7, 128.2, 128.5, 130.0, 130.3, 130.8, 132.4, 133.1, 136.5, 136.9, 216.6; HRMS (ESI) calcd for $C_{26}H_{26}Cl_4O_4Na$ 565.0477 $(M + Na)^+$, found 565.0477.

Epoxide 17. A solution of *ent*-**4d** (6.30 g, 11.6 mmol) in CH_2Cl_2 (580 mL) was cooled to 0 °C and treated with mCPBA (3.6 g, 34.7 mmol). The reaction mixture was stirred at room temperature for 4 h, and then quenched with saturated aqueous sodium thiosulfate. The aqueous layer was extracted three times with EtOAc. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated to give epoxide **17**, which was used in the next reaction without further purification: R_f 0.35 (silica gel, 3:1 hexane/EtOAc); IR (film) 3401, 2932, 1714, 1563, 1437, 1247, 1199, 1098, 1079, 767, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.10 (s, 3H), 1.69 (d, J = 15 Hz, 1H), 2.85 (dd, J = 15, 2 Hz, 1H), 2.87 (s, 1H), 3.00 (dd, J = 2, 2 Hz, 1H), 3.50 (d, J = 2 Hz, 1H), 3.52 (d, J = 9.5 Hz, 1H), 3.60 (d, J = 9.5 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.72 (d, J = 9.5 Hz, 1H), 4.54 (d, J = 10 Hz, 1H), 4.57 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 10 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 7.20 (m, 2H), 7.31 (m, 2H), 7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.1, 19.7, 39.2, 50.1, 57.2, 59.1, 59.1, 60.4, 62.1, 67.2, 73.7, 74.8, 86.4, 128.3, 128.4, 128.4, 130.0, 130.1, 132.8, 133.1, 136.7, 136.8.

Allylic Alcohol 18. To a solution of the above epoxide **17** in CH_2Cl_2 (580 mL) was added florisil (63 g). After being stirred for 2 h, the solution was filtrated and concentrated to give allylic alcohol **18**, which was used in the next reaction without further purification: colorless crystals; mp 191−192.5 °C; R_f 0.26 (silica gel, 1:1 hexane/EtOAc); IR (film) 3467, 2934, 2877, 1736, 1581, 1563, 1437, 1199, 1100, 837, 768, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 3H), 1.45 (s, 3H), 1.66 (d, J = 14.5 Hz, 1H), 2.31 (dd, J = 14.5, 5.5 Hz, 1H), 2.48 (s, br, 2H), 3.32 (d, J = 9.5 Hz, 1H), 3.56 (d, J = 9.5 Hz, 1H), 3.62 (d, J = 9 Hz, 1H), 3.83 (d, J = 9 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 4.38 (d, J = 10.5 Hz, 1H), 4.68 (d, J = 10 Hz, 1H), 4.73 (d, J = 10 Hz, 1H), 4.90 (dd, J = 5.5, 2.5 Hz, 1H), 6.37 (d, J = 2.5 Hz, 1H), 7.18 (m, 2H), 7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 20.8, 43.4, 47.9, 59.5, 66.6, 67.5, 73.8, 74.3, 79.8, 88.5, 128.3, 128.3, 128.3, 129.8, 130.0, 132.5, 133.6, 136.5, 136.9, 153.6, 204.2; HRMS (ESI) calcd for $C_{26}H_{26}Cl_4O_5Na$ 581.0432 $(M + Na^+)$, found 581.0427.

Enedione 19. A solution of allylic alcohol **18** in DMSO (50 mL) was treated with IBX (0.7 M in DMSO, 30.0 mL, 23.2 mmol), and the mixture was stirred for 1 h at room temperature. Then, the solution was diluted with H_2O and Et_2O, and filtrated through Celite. The aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 4:1) to give 4.90 g of enedione **19** (76%, 3 steps): colorless crystals; mp 195−198 °C; R_f 0.65 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{26}_D$ −49.2 (*c* 1.00, $CHCl_3$); IR (film) 3462, 2877, 1718, 1582, 1564, 1437, 1199, 1098, 779, 732 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.50 (s, 3H), 2.35 (d, J = 17 Hz, 1H), 2.70 (d, J = 17 Hz, 1H), 3.40 (d, J = 9.5 Hz, 1H), 3.60 (d, J = 9.5 Hz, 1H), 3.73 (d, J = 9.5 Hz, 1H), 3.80 (d, J = 9.5 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 4.36 (d, J = 10.5 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 6.15 (s, 1H), 7.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.6, 21.0, 48.1, 49.2, 56.5, 66.8, 67.5, 73.6, 74.3, 83.1, 128.0, 128.3, 128.4, 129.9, 130.2, 132.0, 133.3, 136.5, 136.9, 171.3, 204.4, 208.4; HRMS (ESI) calcd for $C_{26}H_{24}Cl_4O_5Na$ 579.0275 $(M + Na^+)$, found 579.0270.

α-Bromoacetal 20. To a solution of bromine (11.0 mL, 214 mmol) in CH_2Cl_2 (60 mL) at −78 °C was added ethyl vinyl ether (22.4 mL, 229 mmol). The resultant mixture was stirred at −78 °C for 15 min, warmed to room temperature over 5 min, and then recooled to −78 °C. This mixture was added to a solution of enedione **19** (6.0 g, 10.7 mmol) and *N*,*N*-dimethylaniline (68.2 mL, 537 mmol) in CH_2Cl_2 (540 mL). The mixture was allowed to warm to room temperature, and stirred for 4 d. Then, the solution was diluted with 1 M HCl and CH_2Cl_2. The organic layer was washed with 1 M HCl (3×), saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 17:1 to 5:1) to give 4.36 g of an inseparable diastereomeric mixture of α-bromoacetal **20** (62%, 4:1), along with recovered enedione **19** (2.06 g, 38%).

Cyclized Product 21. To a solution of bromide **20** (1.0 g, 1.41 mmol) and Bu_3SnH (1.15 mL, 8.5 mmol) in toluene (140 mL) was added BEt_3 (1.0 M in hexane, 4.25 mL, 8.5 mmol) at room temperature under air. After being stirred for 30 min, the mixture was concentrated to 1/3 of total volume, and purified with flash column chromatography (hexane/Et_2O 3:1) to give 648 mg of cyclized product **21α** (73%) and 131 mg of **21*β*** (14%). **21α**: colorless solid; mp 160−162.5 °C; R_f 0.40 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ −22.2 (*c* 1.00, $CHCl_3$); IR (film) 2976, 2928, 2878, 1739, 1582, 1564, 1438, 1199, 1099, 769, 732 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.0 (s, 3H), 1.13 (t, J = 6.5, 3H), 1.28 (s, 3H), 2.20 (d, J = 14 Hz, 1H), 2.49 (dd, J = 14, 5 Hz, 1H), 2.51 (d, J = 19 Hz, 1H), 2.63 (d, J = 19 Hz, 1H), 2.80 (d, J = 19 Hz, 1H), 2.96 (d, J = 19 Hz, 1H), 3.26 (d, J = 10 Hz, 1H), 3.37 (d, J = 10 Hz, 1H), 3.40 (dq, J = 9, 6.5 Hz, 1H), 3.42 (d, J = 10 Hz, 1H), 3.56 (d, J = 10 Hz, 1H), 3.72 (dq, J = 9, 6.5 Hz, 1H), 4.10 (d, J = 11 Hz, 1H), 4.36 (d, J = 11 Hz, 2H), 4.47 (d, J = 11 Hz, 1H), 5.24 (d, J = 5 Hz, 1H), 7.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

14.2, 14.7, 21.0, 46.3, 49.6, 50.3, 60.4, 62.7, 65.2, 65.7, 67.1, 72.9, 73.6, 95.5, 105.2, 116.8, 128.2, 129.8, 130.1, 131.8, 133.2, 136.8, 137.2, 148.1, 171.2, 202.6, 216.0; HRMS (ESI) calcd for $C_{30}H_{32}Cl_4O_6Na$ 651.0851 ($M + Na^+$), found 651.0845. **21α**: colorless solid; mp 201−203 °C; R_f 0.25 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ −80.5 (*c* 1.00, $CHCl_3$); IR (film) 2676, 2878, 1741, 1581, 1564, 1437, 1198, 1099, 769, 731 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.02 (s, 3H), 1.19 (t, J = 7 Hz, 3H), 1.46 (s, 3H), 2.34 (m, 4H), 2.85 (d, J = 19.5 Hz, 1H), 2.99 (d, J = 19.5 Hz, 1H), 3.25 (d, J = 9.5 Hz, 1H), 3.32 (d, J = 9.5 Hz, 1H), 3.42 (d, J = 9.5 Hz, 1H), 3.55 (dq, J = 9.5, 6 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.80 (dq, J = 9.5, 6 Hz, 1H), 4.07 (d, J = 10 Hz, 1H), 4.34 (d, J = 10 Hz, 1H), 4.45 (d, J = 12 Hz, 1H), 5.24 (dd, J = 6, 6 Hz, 1H), 7.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 15.3, 20.8, 46.5, 48.1, 49.2, 49.8, 54.1, 60.1, 65.7, 66.0, 67.1, 73.4, 73.7, 94.9, 104.4, 128.2, 128.5, 129.8, 130.3, 131.7, 133.3, 136.7, 137.2, 212.9, 219.6; HRMS (ESI) calcd for $C_{28}H_{32}Cl_4O_4Na$ 651.0851 ($M + Na^+$), found 651.0844.

Isomerization of 21β to 21α. A solution of acetal **21β** (15.0 mg, 23.8 μmol) in EtOH (1.2 mL) was treated with camphorsulfonic acid (17.0 mg, 71.4 μmol), and the mixture was heated to 40 °C for 1 d. The reaction mixture was quenched with saturated aqueous sodium bicarbonate, and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/Et_2O 3:1) to give 15.0 mg of **21α** (100%).

Enone 23. A solution of ketone **21α** (500 mg, 793 μmol) in CH_2Cl_2 (8 mL) was cooled to −20 °C and treated with $EtN(i\text{-}Pr)_2$ (2.2 mL, 12.7 mmol) and TMSOTf (1.44 mL. 7.93 mmol). The reaction mixture was stirred for 4 h at the same temperature, quenched with saturated aqueous sodium bicarbonate, and extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give silyl enol ether **22**, which was used in the next reaction without further purification.

A solution of the above silyl enol ether in CH_2Cl_2 (8.0 mL) was treated with $Me_2NCH_2{}^+I^-$ (900 mg, 4.76 mmol), and the mixture was stirred for 3 h at 35 °C, then the reaction mixture was cooled to 0 °C and quenched with 1 M HCl. Potassium carbonate was introduced to neutralize the mixture. The aqueous layer was extracted three times with EtOAc. The organic layer was washed with brine and concentrated to give a mixture of the β-amino ketone and enone **23**, which was used directly in the next reaction.

A solution of the above mixture in CH_2Cl_2 (8.0 mL) was treated with mCPBA (65%, 400 mg, 2.4 mmol), and the mixture was stirred for 1 h at room temperature. Then, the reaction was quenched with saturated aqueous thiosulfate. The aqueous layer was extracted twice with EtOAc. The organic layer was washed with aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/Et_2O 3:1 to hexane/EtOAc 3:1) to give 356 mg of enone **23** (69% for 3 steps): colorless crystals; mp 108−111 °C; R_f 0.48 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{26}_D$ −3.6 (*c* 1.00, $CHCl_3$); IR (film) 2878, 1731, 1640, 1582, 1564, 1438, 1201, 1080, 1060, 767, 733 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) δ 1.0 (s, 3H), 1.10 (t, J = 7 Hz, 3H), 1.29 (s, 3H), 2.26 (d, J = 13.5 Hz, 1H), 2.63 (dd, J = 13.5, 5.5 Hz, 1H), 2.64 (d, J = 19.5 Hz, 1H), 3.04 (d, J = 19.5 Hz, 1H), 3.25 (d, J = 9.5 Hz, 1H), 3.35 (d, J = 10.5 Hz, 1H), 3.59 (d, J = 9.5, 7 Hz, 1H), 3.41 (d, J = 9.5 Hz, 1H), 3.52 (d, J = 10.5 Hz, 1H), 3.69 (dq, J = 9.5, 7 Hz, 1H), 4.10 (d, J = 10.5 Hz, 1H), 4.24 (d, J = 12 Hz, 1H), 4.35 (d, J = 12 Hz, 1H), 5.23 (d, J = 5.5 Hz, 1H), 5.54 (s, 1H), 5.70 (s, 1H), 7.22 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7, 21.0, 46.3, 49.6, 50.3, 60.4, 62.7, 65.1, 65.7, 67.1, 72.9, 73.6, 95.5, 105.2, 116.8, 128.2, 128.3, 129.8, 130.1, 131.8, 133.2, 136.8, 137.2, 148.1, 202.6, 216.0; HRMS (ESI) calcd for $C_{31}H_{32}Cl_4O_6Na$ 663.0851 ($M + Na^+$), found 663.0845.

γ-Lactone 24. To a solution of enone **23** (189 mg, 294 μmol) and mCPBA (329 mg, 1.47 mmol) in CH_2Cl_2 was added $BF_3{\cdot}Et_2O$ (150 μL, 1.18 mmol). The mixture was stirred at room temperature for 10 min and quenched with saturated aqueous thiosulfate. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with aqueous sodium bicarbonate three times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 5:1) to give 140 mg of γ-lactone **24** (78%): colorless solid; R_f 0.31 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{25}_D$ −12.0 (*c* 1.00, $CHCl_3$); IR (film) 2929, 1785, 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.22 (s, 3H), 2.55 (d, J = 19.5 Hz, 1H), 2.78 (d, J = 19.5 Hz, 1H), 3.11 (d, J = 19.5 Hz, 1H), 3.28 (d, J = 9.5 Hz, 1H), 3.31 (d, J = 19.5 Hz, 1H), 3.41 (d, J = 10.0 Hz, 1H), 3.46 (d, J = 9.5 Hz, 1H), 3.61 (d, J = 10.0 Hz, 1H), 4.09 (d, J = 10.5 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 10.5 Hz, 1H), 5.62 (s, 1H), 5.78 (s, 1H), 7.19 (m, 2H), 7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 19.7, 43.0, 45.8, 50.8, 60.1, 65.8, 67.3, 72.8, 73.3, 95.4, 118.4, 128.4, 128.5, 130.1, 130.5, 131.3, 133.0, 136.8, 137.4, 146.5, 174.1, 198.6, 214.2; HRMS (ESI) calcd for $C_{29}H_{26}Cl_4O_6Na$ $(M + Na)^+$ 633.0376, found 633.0375.

Enol Triflate 25. A solution of γ-lactone **24** (139 mg, 227 μmol), Commins reagent (267 mg, 681 μmol), and 4 Å molecular sieves in THF (7.5 mL) was cooled to −78 °C and treated with L-selectride (1.06 M in THF, 642 μL, 681 μmol). The resultant solution was stirred at the same temperature for 15 min. Then, the reaction mixture was quenched with H_2O, and extracted twice with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 20:1 to 10:1) to give 124 mg of enol triflate **25** (73%): yellow oil; R_f 0.26 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{26}_D$ +71.7 (*c* 1.00, $CHCl_3$); IR (film) 2930, 1787, 1743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.14 (s, 3H), 1.52 (m, 3H), 2.62 (d, J = 19.0 Hz, 1H), 2.66 (d, J = 19.0 Hz, 1H), 2.74 (dq, J = 17.5, 2.5 Hz, 1H), 3.30 (dq, J = 17.5, 2.5 Hz, 1H), 3.49 (d, J = 9.5 Hz, 1H), 3.54 (d, J = 9.5 Hz, 1H), 3.66 (d, J = 10.0 Hz, 1H), 3.72 (d, J = 10.0 Hz, 1H), 4.52 (d, J = 10.0 Hz, 1H), 4.53 (d, J = 10.0 Hz, 1H), 4.59 (d, J = 10.0 Hz, 1H), 4.60 (d, J = 10.0 Hz, 1H), 7.22 (m, 2H), 7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.9, 17.6, 18.9, 37.4, 40.0, 50.2, 57.6, 64.6, 67.2, 67.6, 73.6, 74.3, 95.0, 118.4 (q, J = 319 Hz, 1C), 127.4, 128.5, 128.6, 130.3, 130.6, 132.4, 132.7, 136.8, 136.9, 141.1, 173.9, 214.7; HRMS (ESI) calcd for $C_{30}H_{27}Cl_4F_3O_8SNa$ $(M + Na)^+$ 767.0025, found 767.0023.

Olefin 26. A solution of enol triflate **25** (124 mg, 166 μmol) and tributylamine (236 μL, 996 μmol) in DMF (5.0 mL) was degassed by using the freeze−pump−thaw technique (3×). To this mixture were added PPh_3 (43.5 mg, 166 μmol) and $Pd(OAc)_2$ (19.8 mg, 88.0 μmol) and then formic acid (31.3 μL, 830 μmol) in DMF (1.0 mL), which was separately degassed by using the freeze−pump−thaw technique (3×) beforehand. The mixture was stirred at 40 °C for 2 h, and then diluted with H_2O. The aqueous solution was extracted twice with EtOAc. The organic layer was washed with H_2O two times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 20:1 to 10:1) to give 90.9 mg of olefin **26** (92%): colorless solid; R_f 0.40 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{25}_D$ +148.4 (*c* 1.00, $CHCl_3$); IR (film) 2938, 1775, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.13 (s, 3H), 1.55 (m, 3H), 2.48 (m, 1H), 2.55 (d, J = 19.0 Hz, 1H), 2.61 (d, J = 19.0 Hz, 1H), 3.00 (m, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.47 (d, J = 9.0 Hz, 1H), 3.63 (d, J = 9.5 Hz, 1H), 3.69 (d, J = 9.5 Hz, 1H), 4.57 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 10.5 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 4.63 (d, J = 10.5 Hz, 1H), 4.82 (m, 1H), 7.20 (m, 2H), 7.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ12.7, 14.2, 17.9, 20.9, 29.2, 37.0, 41.7, 49.8, 54.0, 59.1, 67.2, 67.3, 69.2, 73.0, 73.9, 100.0, 125.21, 125.24, 128.38, 128.40, 130.0, 130.1, 132.9, 133.1, 136.9, 137.0, 137.8, 175.4, 214.8; HRMS (ESI) calcd for $C_{29}H_{28}Cl_4O_5Na$ $(M + Na)^+$ 619.0583, found 619.0583.

Bis-γ-lactone 30. To a solution of olefin **26** (9.8 mg, 16.4 μmol) in THF (680 μL) and EtOH (140 μL) at −78 °C was introduced liquid ammonia (1.6 mL). Then, sodium (37.0 mg, 1.64 mmol) was added to this solution, and the mixture was stirred at −78 °C for

30 min. The reaction mixture was quenched with ammonium chloride, stirred at −78 °C for 40 min, and allowed to warmed to room temperature. After liquid ammonia was removed, the resultant solution was filtrated through a pad of florisil to give 3.4 mg of lactone **28** and lactol **29** (**28**:**29** 1.0:3.9).

A solution of the above mixture in toluene (3.2 mL) was treated with 50% Ag_2CO_3 on Celite (181 mg, 328 μmol) and heated to 130 °C. The mixture was stirred at the same temperature for 4 h. The suspension was filtrated through Celite and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 2:1) to give 1.9 mg of bis-γ-lactone **30** (41% for 2 steps): colorless crystals; mp 166−169 °C; R_f 0.43 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{27}_D$ +141.3 (*c* 0.27, CH_3OH); IR (film) 3467, 2925, 1770 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.16 (s, 3H), 1.20 (d, J = 1.0 Hz, 3H), 1.80 (ddd, J = 2.5, 2.0, 1.5 Hz, 3H), 2.37 (ddq, J = 18.5, 2.5, 2.5 Hz, 1H), 2.58 (ddq, J = 18.5, 2.0, 2.0 Hz, 1H), 2.78 (d, J = 19.0 Hz, 1H), 2.88 (d, J = 19.0 Hz, 1H), 3.98 (d, J = 8.5 Hz, 1H), 4.09 (s, 1H), 4.17 (dd, J = 8.5, 1.0 Hz, 1H), 5.34 (ddq, J = 2.5, 2.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 15.1, 16.1, 16.9, 40.6, 41.9, 57.0, 64.0, 71.6, 74.4, 87.0, 106.5, 125.1, 143.8, 177.9, 180.2; HRMS (ESI) calcd for $C_{15}H_{18}O_5Na$ $(M + Na)^+$ 301.1052, found 301.1045.

Epoxide 31. A solution of **30** (13.0 mg, 46.7 μmol) in CH_2Cl_2 (4.0 mL) was treated with dimethyldioxirane (0.078 M in acetone, 2.5 mL, 234 μmol), and the resultant mixture was stirred at room temperature for 5 h. After concentration, the residue was purified with flash column chromatography (hexane/EtOAc 1:1) to give 12.1 mg of **31** (88%) along with 1 mg of the undesired isomer (7%): colorless crystals; mp 229−232 °C; $[\alpha]^{31}_D$ +22.6 (*c* 0.32, MeOH); R_f 0.21 (silica gel, 1:1 hexane/EtOAc); IR (film) 3435, 2981, 1768, 1258, 1190, 1020, 752 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.11 (s, 3H), 1.17 (s, 3H), 1.55 (s, 3H), 2.08 (d, J = 16.5 Hz, 1H), 2.26 (dd, J = 16.5, 2.0 Hz, 1H), 2.59 (d, J = 19.0 Hz, 1H), 3.02 (d, J = 19.0 Hz, 1H), 3.95 (d, J = 9.0 Hz, 1H), 4.13 (s, 1H), 3.66 (d, J = 2.0 Hz, 1H), 4.48 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 16.1, 16.6, 17.9, 37.3, 38.5, 57.3, 64.8, 67.4, 69.4, 71.7, 75.8, 83.9, 108.3, 177.4, 180.2; HRMS (ESI) calcd for $C_{15}H_{18}O_6Na$ $(M + Na)^+$ 317.1001, found 317.0996.

(+)-Merrilactone A (1). A solution of epoxide **31** (10.4 mg, 35.3 μmol) in CH_2Cl_2 (3.5 mL) was treated with *p*-TsOH·H_2O (33.6 mg, 177 μmol), and the mixture was stirred for 1 d at room temperature. After filtration and concentration, the residue was purified with flash column chromatography (EtOAc) to give 10 mg of (+)-merrilactone A (**1**) (96%): colorless crystals; mp 269−272 °C; R_f 0.34 (silica gel, 1:3 hexane/EtOAc); $[\alpha]^{28}_D$ +15.9 (*c* 0.22, MeOH); IR (film) 3482, 2976, 2930, 1766, 1259, 1076, 1017, 986 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.08 (s, 3H), 1.25 (s, 3H), 1.49 (s, 3H), 2.28 (dd, J = 15.5, 1.5 Hz, 1H), 2.68 (d, J = 19.5 Hz, 1H), 2.72 (dd, J = 15.5, 5.0 Hz, 1H), 2.91 (d, J = 19.5 Hz, 1H), 3.95 (dd, J = 5.0, 1.5 Hz, 1H), 4.02 (d, J = 10.0 Hz, 1H), 4.61 (d, J = 10.0 Hz, 1H), 4.74 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 16.0, 17.3, 17.5, 32.3, 44.1, 58.5, 61.2, 66.1, 75.5, 80.0, 90.4, 96.2, 107.3, 177.6, 179.3; HRMS (ESI) calcd for $C_{15}H_{18}O_6Na$ $(M + Na)^+$ 317.1001, found 317.0996.

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Supporting Information Available: General methods and spectroscopic and analytical data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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