Synthetic Methods

A Synthetic Pathway to Either Enantiomer of Merrilactone A**

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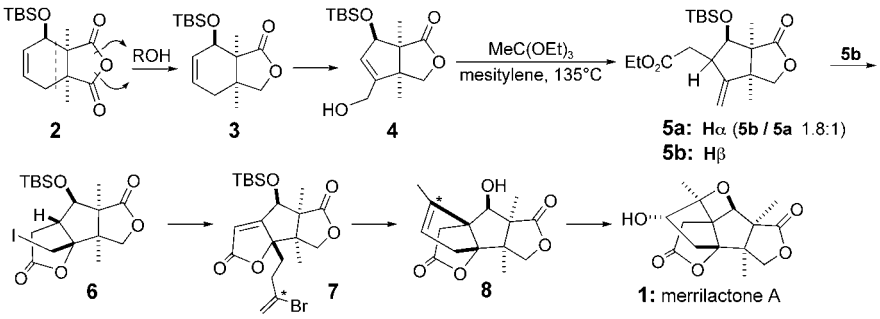
In 2002, our group reported the total synthesis of merrilactone A (racemic **1**).[1] Aesthetically, one is attracted to this molecule by virtue of its propeller-like topology, crafted from five interlocking *cis* fusions (including two γ-lactones and an oxetane). Six stereogenic bridgehead centers serve as the anchor points of these fusions. Attempts to synthesize structures such as **1** often enrich the field of organic chemistry.

In the case of merrilactone A, additional considerations argued for a program directed to its total synthesis. Compound **1** is a member of a class of nonpeptidal neurotrophic factors. Maintenance of appropriate levels of polypeptidal neurotrophic factors in the central nervous system can be critical in promoting neuronal cell viability.[2a] Administration of polypeptidal neurotrophic factors to damaged neuronal cells can lead to substantially restored phenotypes in vitro.[2b–d] Unfortunately, however, the natural factors have performed poorly as therapeutic agents in vivo.[2e] These failures have been ascribed to the usual transport and pharmacostability issues that beset the use of polypeptides. Thus, we have been studying the synthesis of potential nonpeptidal small molecules with neurotrophic activity. Through such compounds, some of the pharmacostability issues that plague polypeptidal neurotrophic factors might be overcome. Fukuyama and co-workers described promising activity for merrilactone A in a neurite growth assay.[3] It would be of considerable interest to investigate the mechanism of this in vitro activity as well as its relevance to in vivo settings. These considerations prompted our first experiments directed toward the total synthesis of merrilactone A, which were indeed successful (Scheme 1).[1]

There are several areas of our initial synthesis in which significant improvements would be helpful. Whereas compound **2** could be synthesized in reasonable yields through Diels–Alder cycloaddition (Scheme 1, dotted line in **2**), its conversion into γ-lactone **3** was not straightforward. Various attempted ring openings of the anhydride were nonregioselective; the isomeric products that arose from both modes of ring opening (Scheme 1, arrows in **2**) could be converted individually into the desired **3**.

A second difficulty arose at the level of relative stereochemistry. The transformation of **4** into **5b** by Claisen rearrangement was never realized in a selective fashion, despite many attempts. At best, we could obtain only a 1.8:1 ratio of **5b**/**5a** favoring the desired isomer. Moreover, the synthesis produced racemic merrilactone. In the context of launching a structure–activity relationship study on this family of compounds, it would certainly be of interest to evaluate merrilactone A in its enantiomerically pure form.



Scheme 1. Birman–Danishefsky synthesis of merrilactone A.

As shown in Scheme 1, chirality was introduced initially in our first-generation synthesis in the Diels–Alder reaction leading to **2**. Since this reaction can only be accomplished at high temperatures, the prospects for strong margins of catalytically mediated enantioselectivity are not promising. These considerations, particularly the goal of generating the enantiopure antipodes of merrilactone A for biological assessment, led us to explore a new total synthesis route. As the previous route to merrilactone A from **6** onward is rather concise and efficient, we planned for compound **6** to be a milestone in a new route.

We therefore set diester **12** as our first subgoal compound. It could not be reached by Diels–Alder reaction of **10a** (R = Me) with **9**. A solution around this problem was required. Fortunately, cycloaddition was possible with the monomethyl compound **10b**[4] (R = H) with *endo* specificity (Scheme 2). Methanolysis of the anhydride and esterification of the free acid afforded **11**. The key point was the *endo* configuration of the quaternary ester in **11**. Lithiation generated the enolate of the other ester (asterisk on **11**). In the event, stereospecific C-methylation[5] of this enolate gave rise to **12**. The latter was advanced in a straightforward manner to *meso* structure **14**.

At this stage, the global task was the degradation of **14** to reach **15**. The latter would intersect **6** by iodolactonization. Overall, this required the oxidation of the 1,4-diol of **14** to a butyrolactone, degradation of the etheno linkage with interpolation of an oxygen function at a former bridgehead center, and attachment of an exocyclic methylene to the other (asterisks on **14** and **15**). The crux of the more subtle challenge of specificity at the regiochemical level is that the interpolated oxygen functional group appears "*ortho*" to the oxidized

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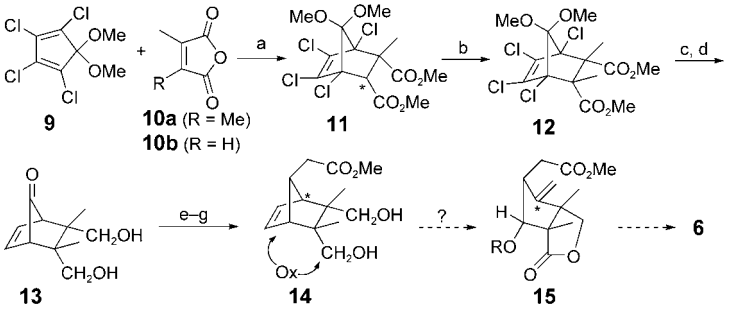
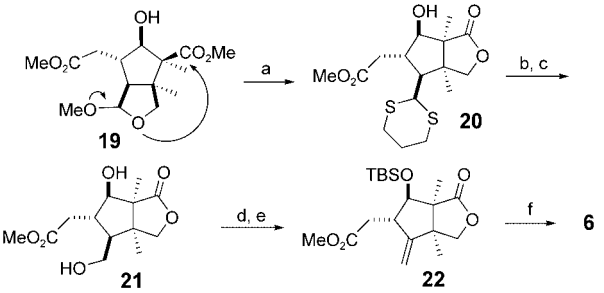


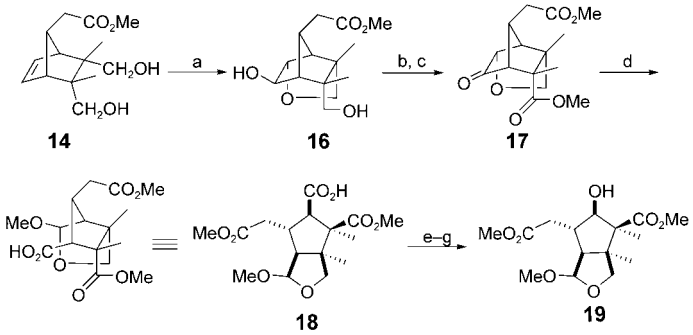
Scheme 2. Synthesis of key intermediate **14**: a) 180 °C, neat; then MeOH, reflux, PhH/MeOH, $TMSCHN_2$, 92% for one-pot reaction; b) LDA, HMPA, MeI, THF, −78 °C→RT, 95%; c) LAH, THF, reflux; d) Na, NH_3, THF/EtOH, 72% over two steps; e) 2,2-dimethoxypropane, acetone, *p*TsOH; f) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 86% over two steps; g) Mg, MeOH, acidic workup, 77%. LAH = lithium aluminum hydride; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide; TMS = trimethylsilyl Ts = toluenesulfonyl.



Scheme 4. Completion of the synthesis of racemic intermediate **6**: a) $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$, CH_2Cl_2, 50%; b) $PhI(OCF_3CO_2)_2$, CH_3CN/H_2O, 50%; c) $NaBH_4$, MeOH, 0 °C; d) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, then H_2O_2 (30%), 86%; e) TBSOTf, Et_3N, CH_2Cl_2, 76%; f) LiOH, $MeOH/H_2O$; then I_2, saturated $NaHCO_3$/THF, (75%). TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl.

carbon of the lactone, leaving the *exo* methylene group to emerge "*ortho*" to the unoxidized hydroxymethyl equivalent (structure **15**).

Oxidation of **14** with *m*CPBA resulted, not surprisingly, in the formation of **16** (Scheme 3). Compound **16** was subjected



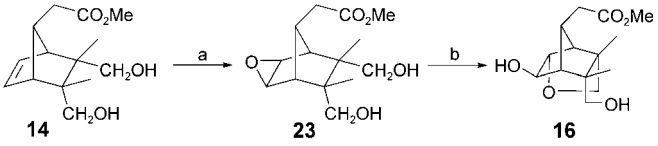
Scheme 3. Baeyer–Villiger oxidation of **17**: a) *m*CPBA, CH_2Cl_2, 90%; b) PDC, DMF; c) K_2CO_3, MeI, acetone, reflux, 70% over two steps; d) MMPP, MeOH, 0 °C→RT, 88%; e) DCC, *m*CPBA, 0 °C→RT, 83%; f) PhH, reflux; g) K_2CO_3, MeOH, 70%. DCC = *N*,*N*-dicyclohexylcarbodiimide; DMF = *N*,*N*-dimethylformamide; *m*CPBA = *meta*-chloroperoxybenzoic acid; MMPP = magnesium monoperoxyphthalate hexahydrate; PDC = pyridinium dichromate.

to oxidation with PDC, which, followed by esterification, led to the formation of ketoester **17**. As expected, Baeyer–Villiger oxidation of **17** gave rise to **18**.[6] The resulting carboxylic acid in **18** was transformed into the requisite secondary alcohol **19** with retention of stereochemistry through carboxy inversion.[7]

The methoxytetrahydrofuran ring moiety of **19** was opened by trapping its masked aldehyde, which prompted lactonization to produce **20** (Scheme 4, arrows). The latter was subsequently converted into **21**. In this way, the regiochemical issues delineated above had been settled in a most favorable manner.

Upon exposure to the protocols of Grieco and co-workers,[8] compound **21** underwent selective reaction at the primary alcohol to provide a transient selenide, which afforded the desired exocyclic olefin after oxidative elimination. Silyl protection of the secondary alcohol gave rise to **22**. The latter was hydrolyzed and the resultant carboxylic acid underwent iodolactonization to afford the advanced intermediate **6**, whose spectroscopic properties were in complete accord with those previously reported.[1]

With a controlled synthesis of **6** in place, we could focus on our final and most critical goal, that is, an enantioselective synthesis of merrilactone A. It was not by chance that this second-generation synthesis was built around a series of *meso* intermediates that culminated in **14**, and thence its *exo* epoxide **23** (Scheme 5). It was at this point that we hoped to



Scheme 5. Desymmetrization of *meso*-**14**: a) DMDO, CH_2Cl_2, 0.5–1 h; b) (*S*,*S*)-[Co^{III}(salen)]-OAc, −78 °C, two days; then −25 °C, two days, THF, 86% over two steps. DMDO = 2,2-dimethyldioxirane; salen = *N*,*N*′-bis(salicylidene)ethylenediamine.

make use of highly innovative asymmetric epoxide-ring-opening (ARO) methodology. Compound **14** was treated with dimethyldioxirane to form the discrete epoxide, **23**. The latter was exposed to catalytic amounts of (*S*,*S*)-[Co^{III}(salen)]-OAc as described by Jacobsen and co-workers[9] (Scheme 5). We were pleased to find that this treatment led to the formation of enantioenriched **16**, with 86% ee and in 86% yield. As expected, use of the *R*,*R* Jacobsen catalyst led to *ent*-**16**.[10]

One of the key teachings of this synthesis lies in the construction of **12**. Thus, we were able to compensate for the resistance of dimethyl maleic anhydride **10a** to undergo cycloaddition by performing a series of straightforward transformations with Diels–Alder adduct **11** which led to the formation of **12**. A second important feature of this synthesis is the chemical degradation pathway from **14** to **18**, which proceeded with full regiocontrol and promising enantiocontrol.

In summary, a route to the enantioenriched merrilactone antipodes has been charted. Parenthetically, the chemistry described above serves to ameliorate the regio- and diastereoselectivity awkwardness of the earlier effort,[1] while retaining its particularly clean and convergent features. With the advances reported above, a full-scale investigation of the effects of absolute configuration on the performance of a potent, nonpeptidal neurotrophic factor will go forward.

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[10] Compounds **16** and *ent*-**16** were converted into the corresponding benzyl esters, and the optical rotations were determined: $[\alpha]_D^{23} = -10.9$ ($CHCl_3$, $c = 0.19$) for the benzyl ester of **16** and $[\alpha]_D^{23} = 7.9$ ($CHCl_3$, $c = 0.34$) for the benzyl ester of *ent*-**16**. Although the HPLC data show the enantiospecificity of each reaction that arises from the antipodal catalysts to be identical, the rotations, though opposite, are not equal in magnitude. This suggests the presence of an impurity in one of the specimens. This matter is currently under investigation.

