Natural Product Synthesis

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Total Synthesis of (±)-Merrilactone A**

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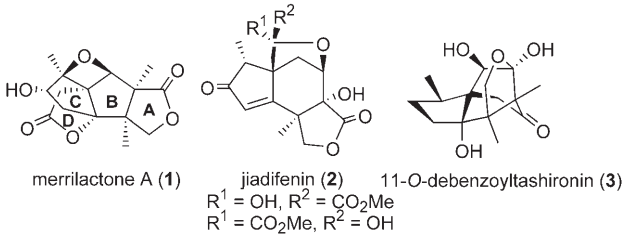
As a consequence of the advancing age profile of the global population, particularly in developed nations, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases have emerged as a major public health concern. In this regard, neurotrophic agents, which have been implicated in the maintenance and growth of neurons as well as prevention of neuronal death, are being considered as potential leads for therapeutic development.[1] While earlier efforts in the area have focused on the naturally occurring polypeptides, pharmacokinetics and bioavailability considerations have kindled interest in exploring small-molecule-based natural product entities as neurotrophic factors.[1b]

Recent pioneering efforts from Fukuyama and co-workers[2] have unraveled a series of densely oxygenated, neurotrophically active polycyclic sesquiterpenoid natural products from a variety of exotic *Illicium* species, thus making available enchanting platforms and opportunities for chemical explorations. These include merrilactone A (**1**),[2a] jiadifenin (**2**),[2b] and 11-*O*-debenzoyltashironin (**3**)[2d] to name a few (Scheme 1). The isolation of merrilactone A (**1**) from the

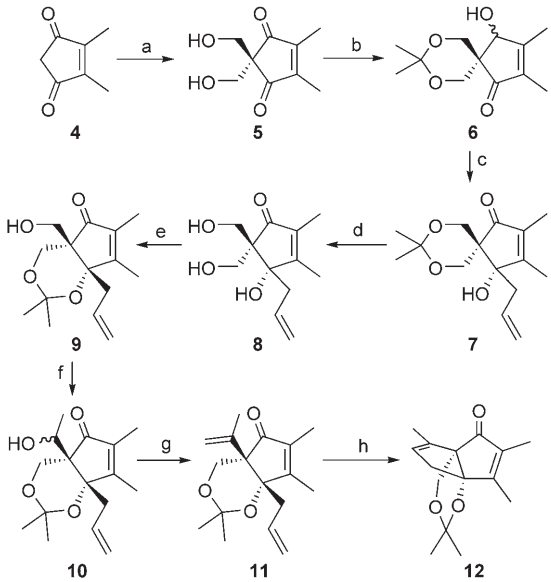


Scheme 1. a) Neurotrophic natural products isolated from *Illicium* sp.

pericarps of *Illicium merrillianum* was reported a few years ago, and in addition to the determination of its crystal structure (X-ray) and absolute configuration (Mosher), **1** was shown to significantly promote neurite outgrowth in the primary cultures of fetal rat cortical neurons at concentrations from 0.1 to 10 μM.[2a] This novel bioactivity profile coupled with the compact pentacyclic caged architecture of merrilactone A, which comprises two γ-lactone moieties, an oxetane ring, an oxa[3.3.3]propellane moiety, and seven contiguous stereogenic centers, make it an alluring synthetic target that has captivated widespread attention. Indeed, two elegant total synthesis of merrilactone A by Danishefsky and co-workers[3a] and Hirama and co-workers[3b] have appeared along with several model synthetic studies[3c,d] including our own[3e] in the past few years. More recently, Meng and Danishefsky have also unveiled an asymmetric approach to **1**.[3f] Herein, we report a total synthesis of **1** that follows a very different conceptual design, embedded in a flexible and diversity-oriented mould.

In our approach towards the synthesis of merrilactone A (**1**), we recognized the centrality of the choice of the starting synthon, keeping in mind the prime importance of setting up the key five-membered ring B of the natural product which includes four contiguous quaternary centers and much of the stereochemistry of the molecule. After screening several candidates, we opted for the readily available 2,3-dimethyl-2-cyclopentene-1,4-dione (**4**)[4] as its symmetry was readily exploitable for stereocontrol and it was intrinsically poised towards an asymmetric adaptation.[5]

Double hydroxymethylation of **4**, mediated by DBU, was nearly quantitative to furnish **5**, whose 1,3-diol moiety was then protected as the acetonide (Scheme 2). Luche reduction[6] of **5** furnished **6** as a single hydroxyenone. Careful addition of the in situ generated allylcerium reagent to **6** followed by MnO_2 oxidation of the allylic secondary hydroxy group led to the hydroxyenone **7** as a single isomer.



Scheme 2. a) DBU, 40% HCHO (aq.), THF, 0°C, 95%; b) i) acetone, 4 Å MS, Amberlyst-15, 92% (based on recovered starting material); ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0°C, 90%; c) i) $CeCl_3$, allyl magnesium chloride, −78°C, 85%; ii) MnO_2, CH_2Cl_2, 98%; d) THF/H_2O (5:1), 2 N HCl, 90%; e) acetone, 4 Å MS, Amberlyst-15, 94% (**7**/**9** 1:1); f) i) PDC, CH_2Cl_2; ii) MeLi, Et_2O, 62% (2 steps); g) i) PDC, CH_2Cl_2, 85%; ii) Ph_3PCH_2Br, *t*BuOK, Et_2O, 68%; h) Grubbs' catalyst (25 mol%), CH_2Cl_2, reflux, 76%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; MS = molecular sieves; PDC = pyridinium dichromate.

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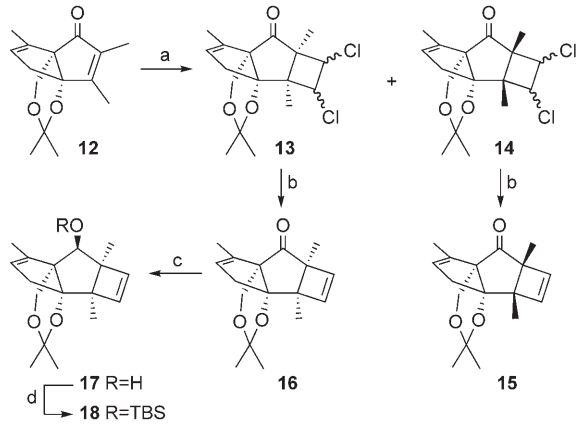
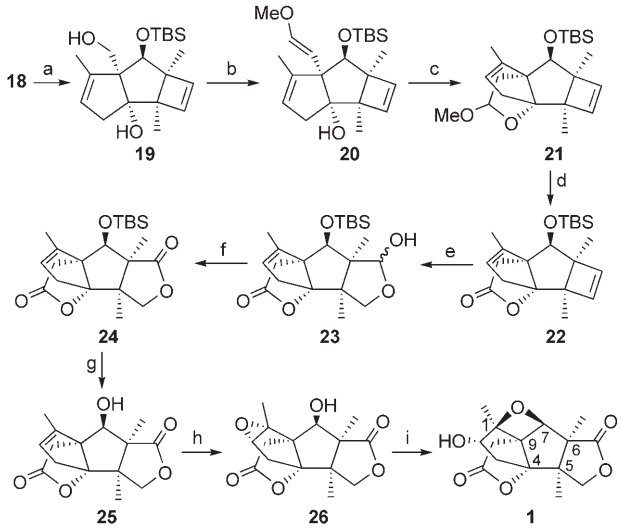
At this stage, a key acetonide deprotection–protection step positioned the four side arms on ring B for sequential annulation of the five-membered ring C and the γ-lactone ring D. Thus, acetonide deprotection in **7** led to the triol **8**, reprotection of which under equilibrating conditions furnished a readily separable (1:1) mixture of the desired acetonide **9** along with **7**, which could be readily recycled (Scheme 2). For the construction of ring C, the primary hydroxy group in **9** was oxidized to the aldehyde followed by addition of methyllithium to give **10**. PDC oxidation of **10** to the corresponding α-methylketone and further Wittig methylenation furnished **11**. The *cis*-oriented allyl and propenyl chains in **11** were suitably positioned towards a ring-closing metathesis reaction, and exposure to Grubbs' first-generation catalyst[7] delivered the diquinane **12** in satisfactory yield.

We then turned our attention towards establishing the γ-lactone-bearing ring A and in particular the quaternization of the two vicinal methyl groups. For this purpose, a cyclobutene ring was identified as an appropriate chemical equivalent. Photochemical [2+2] cycloaddition of *trans*-1,2-dichloroethylene to **12** proceeded with a moderate degree of β-facial selectivity, directed by the steric bulk of the acetonide methyl groups positioned on the α-face, to deliver a readily separable mixture (2:1) of **13** and **14** (Scheme 3). Eliminative dehalogenation of **13** and **14** generated the tricyclic cyclobutene-containing derivatives **15** and **16**, respectively. Reduction of **16** with DIBAL-H exclusively delivered the desired β-hydroxy epimer **17**, whose formulation was confirmed through determination of its X-ray crystal structure (Scheme 3). Stereoselectivity in this reduction reaction could be attributed to the cooperative effect of the intrinsic convex-face steric bias present in **16**, with the added possibility of intramolecular hydride delivery from the α-face, mediated through the coordination of DIBAL with the acetonide oxygen atoms. The hydroxy group in **17** was subsequently protected as its TBS derivative to give **18**.



Scheme 3. a) *trans*-Dichloroethylene, *hν* (pyrex, 400 W), 65% (**13**/**14** 2:1); b) Sodium naphthalenide, −60°C, 70% (**13**), 75% (**14**); c) DIBAL-H, −78°C, 95%; d) TBSOTf, CH_2Cl_2, Et_3N, 86%. DIBAL-H = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl.

After numerous attempts, we devised a route to elaborate **18** into the natural product merrilactone A (Scheme 4).



Scheme 4. a) THF/H_2O (5:1), 2 N HCl, 95%; b) i) TPAP, CH_2Cl_2; ii) $Ph_3PCH_2OCH_3$, *t*BuOK, THF, 54% (2 steps); c) CH_2Cl_2/THF (10:1), $HClO_4$; d) PCC, CH_2Cl_2, 62% (combined yield for steps c and d); e) i) O_3, MeOH, −78°C; ii) $NaBH_4$, MeOH, −78°C, 45%; f) PCC, CH_2Cl_2, 80%; g) TBAF, AcOH, THF, 85%; h) DMDO, 95%; i) *p*TsOH, CH_2Cl_2, 80%. TPAP = tetra-*n*-propylammonium perruthenate; PCC = pyridinium chlorochromate; TBAF = tetra-*n*-butylammonium fluoride; DMDO = dimethyl dioxirane; *p*TsOH = *p*-toluenesulfonic acid.

Acetonide deprotection in **18** led to the diol **19**, oxidation of which with TPAP furnished an intermediate aldehyde that was directly homologated through Wittig methoxymethylenation to the enol ether **20** (Scheme 4). Acid-mediated hydrolysis in **20** led to **21** with concomitant intramolecular hemiacetal formation. Direct oxidation of **21** using PCC delivered the γ-lactone-bearing ring D in **22**. The next stage was the elaboration of the cyclobutene ring in **22** to the second γ-lactone moiety; to this end, ozonolysis and in situ reduction with borohydride of **22** led to lactol **23** as the only characterizable product. The regioselective formation of **23** was somewhat anticipated, as the presence of the bulky TBS group at C7 was expected to cause steric shielding of the neighboring aldehyde group at C6 and allow borohydride to selectively attack the aldehyde group at C5 to give **23**. Oxidation of **23** with PCC delivered the second γ-lactone ring A in **24** (Scheme 4). The final stages in the synthesis of merrilactone A were implemented by following the earlier established protocols.[2c] Deprotection of the alcohol in **24** led to **25**, and epoxidation of the methyl cyclopentene double bond in the latter with DMDO furnished the α-epoxide **26** stereoselectively to set up the homo-Payne rearrangement. Brief exposure of **26** to *p*TsOH led to the target compound merrilactone A (**1**), whose ^1H and ^{13}C NMR spectra were identical to those of the natural product.[2a,3a,b]

In summary, we have delineated a total synthesis of the neurotrophic sesquiterpenoid merrilactone A (**1**) in a stereo- and regioselective diversity-oriented approach. The overall strategy is also amenable to accessing both the enantiomers of the natural product and is well poised for extension to the total synthesis of other related neurotrophic agents from *Illicium* species.

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[5] In a separate effort, we have observed that the *cis*-1,4-enediol derived from **4** can be enzymatically desymmetrized to provide access to both the enantiomers (unpublished results). Alternatively, enzymatic desymmetrization of **5** or enzymatic resolution of the keto-alcohol **6** can also provide chiral precursors for the asymmetric synthesis of merrilactone A.
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