Natural Products

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Synthesis of (±)-Merrilactone A and (±)-Anislactone A**

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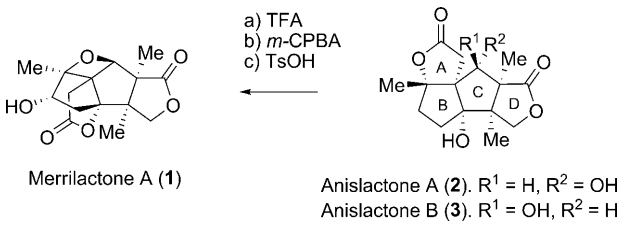
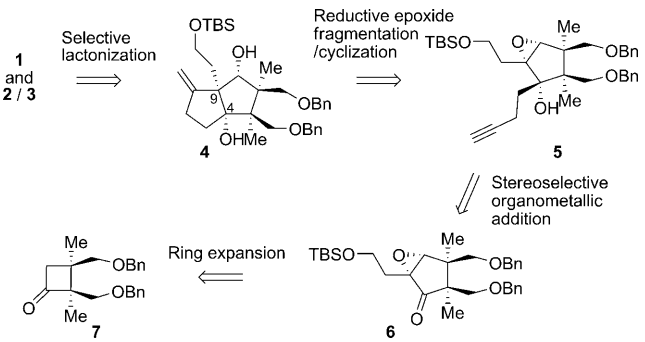
Plants of the *Illicium* genus native to southeast Asia are rich sources of biologically active sesquiterpenoid natural products. Merrilactone A, isolated in 0.004% yield from the dried pericarps of *Illicium merrillianum* by Fukuyama and co-workers in 2000, has become one of the most studied compounds of this class.[1] Characterized as the novel oxetane-containing structure **1**, it displays potent neurotrophic activity at low concentration (0.1 μmol L^{-1}) (Scheme 1). Structurally, merrilactone A is related to anislactones A and B, a pair of epimeric sesquiterpene dilactones discovered ten years earlier by Kouno and co-workers from the related *Illicium anisatum* plant.[2] Fukuyama has shown that anislactone B can be converted into merrilactone A using a simple three-step sequence,[1b] suggesting that the anislactones may be biogenetic precursors to merrilactone A.



Scheme 1. Merrilactone A and anislactones A and B. **1** can be synthesized from **3** using the following sequence:[1b] a) TFA, reflux, 90%; b) *m*-CPBA, DCM, 64%; c) TsOH, DCM; 78%. TFA = trifluoroacetic acid, *m*-CPBA = *m*-chloroperoxybenzoic acid, DCM = dichloromethane, Ts = *p*-toluenesulfonyl.

The potential of non-peptide neurotrophic factors as bioavailable therapeutics for neurodegenerative disease has stimulated extensive synthetic studies on merrilactone A. Its compact sesquiterpene architecture, featuring five rings and seven chiral centers, five of which are contiguous fully substituted carbon atoms, places stringent demands on stereoselective C–C bond formation in sterically congested environments. This challenge has been met to date with four total syntheses, from the research groups of Danishefsky,[3] Inoue and Hirama,[4] Mehta,[5] and Frontier,[6] in addition to synthetic studies on subsections of the merrilactone A structure.[7] Anislactones A and B, by contrast have received little attention from synthetic chemists with only a single report from Hong et al. on an approach to the tricyclic BCD framework.[8]

We envisaged a direct route to an advanced BC intermediate that would enable regiodivergent synthesis of both anislactone A/B and merrilactone A (Scheme 2). Compound **4** has the complete carbon skeleton of both natural products and can be directed to either one by orthogonal lactonization sequences. We planned to access **4** from the fully functionalized C ring **6** using two key C–C bond constructions. First, the tertiary alcohol at C4 arises from a stereoselective 1,2-addition of an organometallic to the ketone in **6**. Second, the highly congested C9 quaternary stereocenter would be installed by reductive epoxide opening of **5** and radical cyclization onto the pendant alkyne, forming the B ring of the natural products. The five-membered C ring at the heart of the approach would be accessed through regioselective ring-expansion of a cyclobutane derivative **7**.



Scheme 2. Retrosynthetic analysis. TBS = *tert*-butyldimethylsilyl.

We began the synthesis with [2+2] photocycloaddition of 4,5-dimethylmaleic anhydride **8** and dimethylketene acetal **9**, which proceeded in excellent yield to afford cyclobutane **10** displaying the requisite *cis*-methyl groups at newly formed quaternary centers C5 and C6 (Scheme 3). Reduction of the anhydride, benzyl protection, and ketal hydrolysis gave the cyclobutanone **7**, the substrate for a regioselective ring-enlargement transformation. To access the required cyclopentanone we require the least substituted methylene carbon to migrate preferentially in a Tiffeneau–Demjanov type reaction. Ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$ proved effective,[9] yielding the cyclopentanone **11** in very

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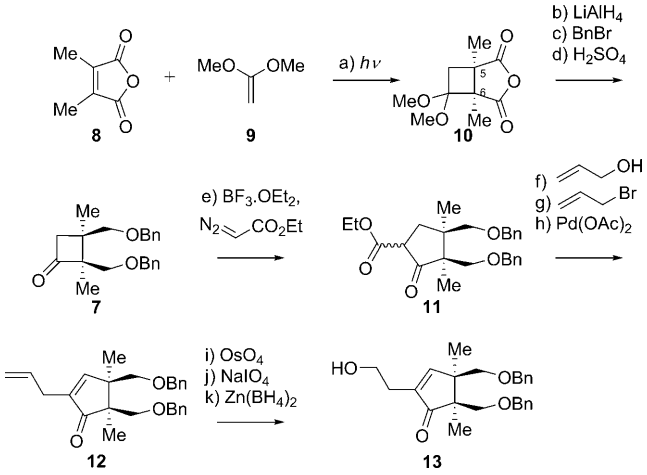
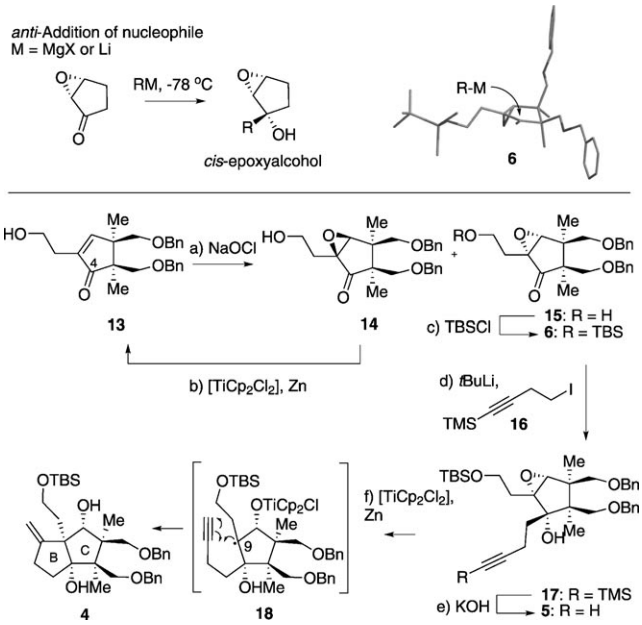


Scheme 3. Synthesis of cyclopentenone C ring, **13** (principle reagents shown in scheme): a) *hν*, pyrex, MeCN/acetone (9:1), 96%; b) $LiAlH_4$, Et_2O, 0°C 97%; c) BnBr, TBAI, NaH, THF; d) H_2SO_4 (aq), MeCN, 90% (two steps); e) N_2CHCO_2Et, $BF_3{\cdot}Et_2O$ (2.5 equiv), DCM, 0°C, 88%; f) allyl alcohol, toluene, reflux, 93%; g) allyl bromide, K_2CO_3, acetone, 89%; h) $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), MeCN, reflux, 90%; i) OsO_4 (2 mol%), NMO (1 equiv), acetone/H_2O (4:1), 96%; j) $NaIO_4$, THF/H_2O (1:1), k) $ZnBH_4{\cdot}$py, isopropyl alcohol, 0°C, 76% (2 steps). TBAI = tetrabutylammonium iodide, py = pyridine, NMO = *N*-methylmorpholine *N*-oxide.



Scheme 4. BC ring synthesis (principle reagents shown in scheme): a) NaOCl (aq), pyridine, 0°C, 90%, d.r. 2.2:1; b) $[Cp_2TiCl_2]$ (2 equiv), Zn (6 equiv), THF, 70%; c) TBSCl, imidazole, DCM, 0°C, 98%; d) **16**, *t*BuLi, Et_2O, −78°C, 94%; e) KOH, MeOH, 98%; f) $[Cp_2TiCl_2]$ (3 equiv), Zn (9 equiv), THF, 69%, 10% starting material recovered.

good yield (88%). The ethyl ester group in **11** was then transesterified with allyl alcohol, followed by C-alkylation of the β-keto ester with allyl bromide to set up a Tsuji–Trost decarboxylation–dehydrogenation sequence.[10] Treatment with catalytic $Pd(OAc)_2$ and PPh_3 worked reliably (5 g scale) and in high yield to give the enone **12**. Oxidative cleavage of the terminal alkene followed by immediate reduction of the aldehyde with freshly prepared zinc borohydride–pyridine complex[11] gave the cyclopentanone **13**.

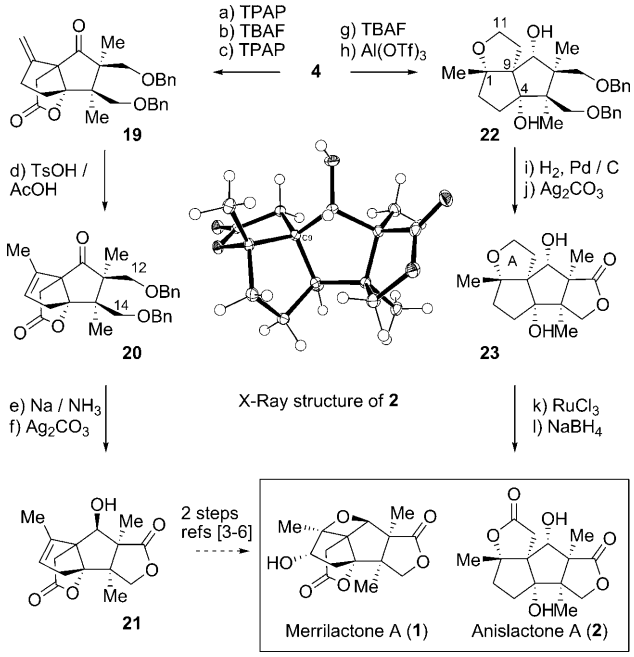
Our plan for stereocontrolled construction of the C4 stereocenter was to carry out a 1,2-addition to an epoxycyclopentanone derived from **13**. The epoxide group is known to exert powerful stereocontrol in this reaction for simple five-membered ring systems, enforcing exclusive *anti* addition of organometallics to the carbonyl group to produce the *cis*-epoxyalcohol (Scheme 4).[12]

The required α-epoxide could be prepared through NaOCl treatment of enone **13**, a reaction that proceeded in excellent overall yield (90%) but only moderate diastereoselectivity (**15**/**14** = 2.2:1; stereochemical configuation established by NOESY on downstream intermediates, see the Supporting Information). The efficiency of the overall transformation could, however, be improved by recycling the unwanted minor β-epoxide **14** through reductive deoxygenation using $[Cp_2TiCl_2]$ (Cp = cyclopentadienyl) and zinc.[13] Protection of the primary alcohol as a TBS ether then gave ketone **6**.

We envisaged that the epoxide group would be the dominant element of stereocontrol in 1,2-addition to **6**, presenting a sterically more accessible convex face of the bicycle to the incoming nucleophile, *anti* to the epoxide C–O bond (shown in Scheme 4 for an MM2-minimized structure of **6**). This proved to be the case: addition of excess homopropargyl lithium reagent prepared from **16** to the highly hindered ketone proceeded in excellent yield and diastereoselectivity, affording the tertiary alcohol **17** as essentially a single stereoisomer in 94% yield.

Desilylation of **17** then set the stage for the key step in the synthesis—a reductive epoxide cleavage with Ti^{III} and subsequent 5-*exo*-dig cyclization onto the pendant alkyne. Using $[Cp_2TiCl_2]$ and excess zinc, under more dilute conditions than Rajanbabu and Nugent's original procedure,[14,15] we were pleased to see successful formation of the BC bicycle **4** in approximately 69% yield (79% based on recovered starting material), containing a small amount (< 5%) of an unknown contaminant, suspected to be a deoxygenation by-product. Dilute conditions, along with dropwise addition of reagent to epoxide, were found to be essential in minimizing the build-up of deoxygenation products over the course of the reaction. The highly congested C9 quaternary stereocenter is formed through selective scission of the C9–O bond to form the more stable tertiary radical (**18**). Cyclization and quenching of the subsequent vinyl radical by the THF solvent[14] gives the bicyclic product. This sequence contrasts with the earlier application of $[Cp_2TiCl_2]$/Zn to epoxide **14**, where the lack of a cyclization pathway, coupled with the formation of a stable enone, leads to smooth deoxygenation. Compound **4** has the full carbon skeleton of both merrilactone and anislactone, enabling a regiodivergent approach to both natural products by selective formation of the A-ring lactone.

We tackled the conversion to merrilactone A first (Scheme 5). Oxidation of the hindered secondary alcohol, desilylation, and oxidative lactonization all proceeded smoothly to afford the tricyclic compound **19**. It was then



Scheme 5. Synthesis of merrilactone A and anislactone A (principle reagents shown in scheme). Ortep of anislactone A shown with thermal ellipsoid probability of 50%. a) TPAP (0.5 equiv), NMO, M.S. 4 Å, DCM, 82%; b) TBAF, THF; c) TPAP (0.1 equiv), NMO, M.S. 4 Å, DCM, 90% (2 steps); d) TsOH, AcOH/DCM (1:1), 30°C, 78% (5% starting material recovered); e) Na, liq NH_3, THF/EtOH (5:1), −78°C; f) Ag_2CO_3 on celite, toluene, 130°C, 28% (two steps); g) TBAF, DCM/THF (5:1); h) $Al(OTf)_3$ (5 mol%), DCM, 88% (two steps); i) H_2, Pd/C, MeOH; j) Ag_2CO_3 on celite, toluene, 130°C, 73% (two steps); k) $RuCl_3$ (0.5 equiv), $NaIO_4$, $MeCN/CCl_4/H_2O$ (1:1:1), 73%; l) $NaBH_4$, THF, 95% (d.r. 5:1). TPAP = tetrapropylammonium perruthenate, TBAF = tetrabutylammonium fluoride.

necessary to isomerize the exocyclic alkene into the B ring, a reaction that proved difficult to develop as **19** was sensitive to acid at elevated temperatures. Careful treatment with a mixture of TsOH and AcOH in DCM at 30°C over 2 d proved effective, affording the internal alkene **20** in high yield. Compound **20** was very similar to a late-stage intermediate in Inoue and Hirama's synthesis, differing only slightly in the protecting group at C14 (benzyl vs. substituted benzyl).[4b] Accordingly, application of Hirama's two-step protocol of sodium in ammonia followed by Fetizon's reagent provided the tetracycle **21**. Tetracycle **21** is the antepenultimate compound in all merrilactone A syntheses to date,[3–6] and represents a formal total synthesis of this natural product.

In order to access the anislactones it was necessary to install the regioisomeric γ-lactone between C1 and C9, as opposed to C4 and C9 in merrilactone A. A hint on how to achieve this came from our development of the earlier epoxide fragmentation/cyclization, where we observed a small amount of alkene etherification product being formed from substrates having a free C11-OH group. We optimized this transformation by desilylating **4** and screening various acid catalysts for the etherification reaction. Whilst strong Brønsted acids (TfOH, MsOH, TFA) all led to decomposition, treatment with catalytic amounts of $Al(OTf)_3$ in DCM at room temperature[16] proved highly effective, producing **22** in 88% yield.

Hydrogenolysis of the benzyl protecting groups then set the stage for two selective oxidations. First, the right-hand γ-lactone was installed by regioselective oxidation with Fetizon's reagent—the weak oxidizing agent is selective for the sterically most accessible C12 primary alcohol.[4b] The remaining γ-lactone was then synthesized through RuO_4 oxidation at C11 of the cyclic ether, with concomitant oxidation of the secondary alcohol to a ketone. Reduction of this ketone with $NaBH_4$ delivered hydride from the more accessible β-face, affording anislactones A and B in 95% yield as a 5:1 mixture, from which anislactone A could be purified. The ^1H NMR, ^{13}C NMR, IR, and HRMS spectra of synthetic **2** matched those of the natural product, and the structure was confirmed unambiguously through X-ray crystallography of a single crystal which formed following chromatography.[17]

In conclusion, we have completed the first synthesis of anislactone A (22 steps, 5.7% overall yield) and a formal synthesis of merrilactone A (22 steps to known intermediate **21** in 2.4% overall yield, 24 steps to the natural product) through a common route. The synthesis describes a direct approach to all-chiral carbon B-ring cyclopentane **5** using [2+2] photocycloaddition, regioselective Tiffeneau–Demjanov ring expansion, and stereoselective 1,2-addition as key C–C bond-forming steps. The defining transformation is then the reductive epoxide cleavage–cyclization to form the C9 quaternary center at the heart of the sesquiterpene structure.

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[17] CCDC 788987 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

