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Formal Synthesis of Merrilactone A Using a Domino Cyanide 1,4-Addition–Aldol Cyclization

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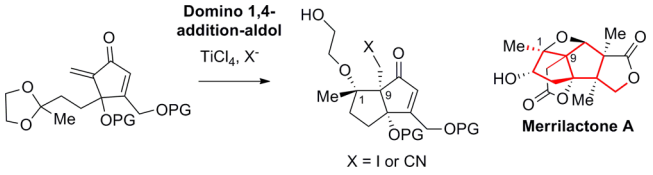
ABSTRACT



A formal synthesis of merrilactone A has been completed using a domino 1,4-addition–aldol process as the key step. Both iodo- and cyano-1,4-addition–aldol cyclizations were productive in forming the highly hindered C1–C9 bond linking *vic*-quaternary and tertiary stereocenters. The latter method was used to complete a formal total synthesis of the natural product.

The neurotrophic sesquiterpene merrilactone A, **1**, was isolated by Fukuyama in 2000 from the pericarps of *Illicium merrilianium*.[1] The highly congested terpenoid structure, featuring five contiguous, fully substituted carbon centers, has inspired total syntheses from the groups of Danishefsky,[2] Inoue and Hirama,[3] Mehta,[4] Frontier,[5] ourselves,[6] and Zhai.[7,8] In each case, creative strategies were necessary to achieve stereocontrolled C–C bond formation in such a sterically hindered architecture, with the cyclopentane C-ring, containing four fully substituted carbons plus a secondary stereocenter, being a particular challenge. Our first synthesis used a reductive epoxide cyclization of the highly functionalized cyclopentane **3** as the key step (Scheme 1). Treatment of **3** with Ti(III) affords the bicycle **4** having the complete carbon skeleton of merrilactone A. Two orthogonal functionalization sequences then afforded merrilactone A, **1**, or the related sesquiterpene anislactone A, **2**. We now wish to report a second synthesis of the merrilactone A structure, based on a domino conjugate

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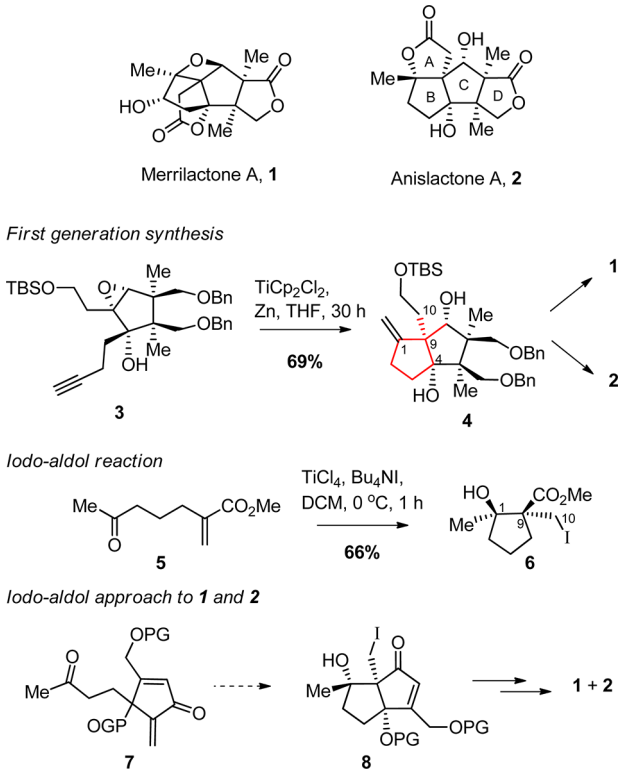
addition–aldol process for the installation of the key C9 quaternary stereocenter.

Scheme 1. Synthesis of Merrilactone A and Anislactone A. First-Generation Route and Proposed Domino-Aldol Approach

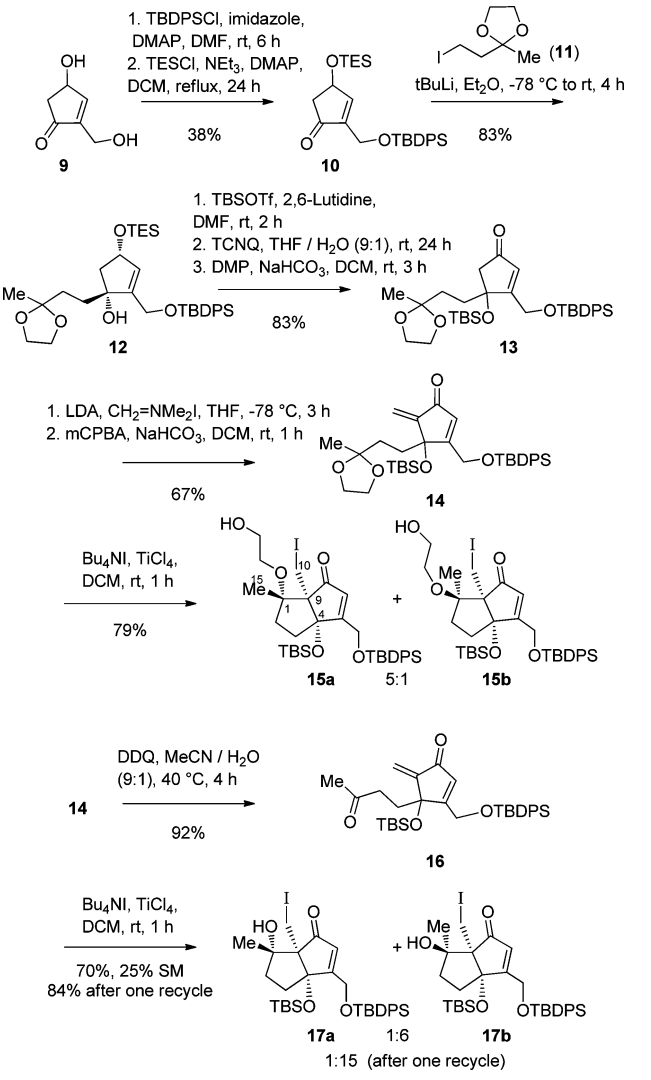


Previous work in our group established the iodo-aldol reaction as a useful protocol for the synthesis of highly hindered *vic*-quaternary and tertiary alcohol stereocenters.[9,10] Compound **5**, for example, undergoes treatment with iodide and $TiCl_4$ to afford the cyclopentane **6** in good yield and excellent selectivity for the *trans* diastereoisomer.

This motif is embedded in the merrilactone structure (highlighted in red on structure **4**), with the quaternary center corresponding to the key C9 position at the heart of the molecule. A domino conjugate addition–aldol approach to **1** would offer a direct construction of the highly hindered 5–5 system with good prospects for relative stereocontrol across the tertiary–quaternary–tertiary stereotriad of C1, 9, and 4. A protected dienone such as **7** is an appropriate substrate to test this approach, affording an iodo-aldol adduct **8** containing functionality that may be further advanced toward either of the merrilactone or anislactone structures.

We began by synthesizing the TES- and TBDPS-protected enone **10** starting from the known cyclopentenone **9** (Scheme 2).[11] Selective protection of the primary alcohol in **9** proceeded in rather low yield (40%) due to competitive disilylation under a range of conditions. TES protection at

Scheme 2. Iodo-aldol Reaction



the secondary alcohol was then followed by addition of the organolithium prepared from iodide **11**, affording tertiary alcohol **12** in high yield. TBS protection, selective removal of the TES group with tetracyanoquinone (TCNQ),[12] and oxidation with the Dess–Martin periodinane (DMP) gave the enone **13**, which was then methylenated with Eschenmoser's reagent/*m*-CPBA to afford the ketal-protected dienone **14**.

Ketal **14** is a potentially viable substrate for the iodo-aldol reaction, although precedent for acetals or ketals acting as electrophiles in iodo-aldol chemistry is limited to one example.[10f] We were pleased, therefore, to find that exposure of **14** to tetrabutylammonium iodide (TBAI) in the presence of $TiCl_4$ over 1 h at room temperature gave the iodo-aldol adducts **15a** and **15b** in 79% combined yield and a 5:1 ratio (stereochemistry assigned by NOESY). Both compounds have the expected *cis*-relationship between C4 and C9 at the ring fusion and differ according to the C1 and

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C9 relative stereochemistry. The ketone substrate **16** was then prepared by way of comparison. Iodo-aldol reaction with a ketone electrophile offers a potentially more expedient synthesis, as the resultant tertiary alcohol product is unencumbered by the hydroxyethyl group present in the ketal-derived products.

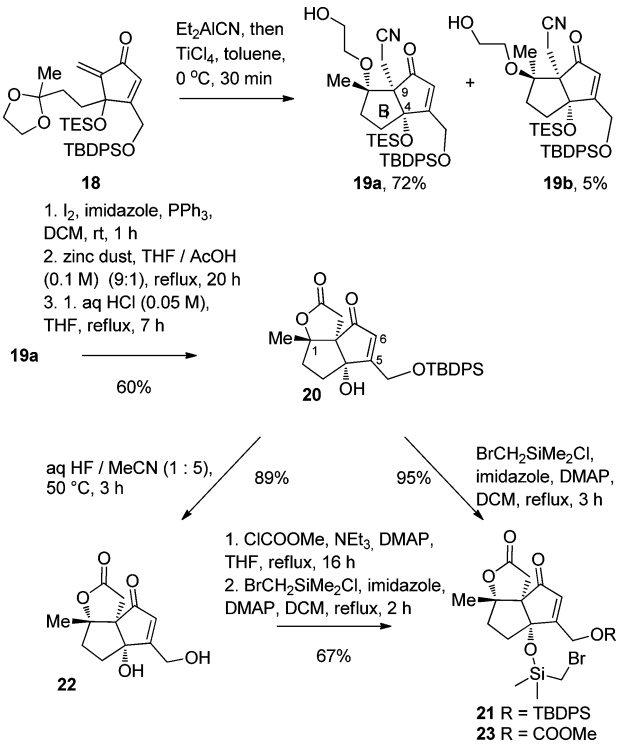
We were pleased to find that the domino reaction was again effective, giving the two adducts **17a** and **17b** in very good yield. The C1−C9 relationship, however, is reversed from the ketal substrate **14** with the *cis*−*cis* isomer dominating.[13] Iodides **17a** and **17b** were crystalline and were characterized using X-ray analysis (Supporting Information)

Disappointingly, advancement of either of the major diastereoisomers **15a** or **17b** in the synthesis was not possible. Our efforts were concentrated on substituting the iodo group with a carbon nucleophile in order to provide C11 of the merrilactone A-ring lactone. Adducts **17a** and **17b** proved unstable with respect to retro-aldol chemistry under a variety of conditions. While we could harness this feature to recycle the minor stereoisomer (Supporting Information), the substrate proved too labile to productively manipulate the iodo group. The ketal-derived iodide **15a** had no such retro-aldol problems but remained untouched by a variety of nucleophilic and radical substitution methods. Clearly, a corollary to creating such a sterically congested ring system via iodo-aldol chemistry is that the iodo group is extremely hindered for subsequent transformations.

A logical solution to this problem is to change the nucleophile in the domino conjugate addition−aldol process. If we could use a carbon-centered nucleophile such as cyanide, for example, we would have all of the necessary atoms in place to form the A-ring lactone. This combination of cyanide 1,4-addition followed by aldol reaction has not been widely deployed in synthesis, with just two existing literature reports that feature single enoate−aldehyde substrates.[14] The transformation is of potential high value, forming two C−C bonds and (in principle) three stereocenters in a single step, and installing a highly versatile nitrile functional group for further manipulation. In the event, we prepared ketal **18** (Scheme 3) using an improved route that avoided the previous selective protection problem (Supporting Information). We were delighted to find that the combination of Et_2AlCN and $TiCl_4$ afforded smooth reaction to produce the crystalline adduct **19a** in 72% yield as the major diastereoisomer (characterized by X-ray), along with 5% of **19b** as a minor component. The stereocontrol matches the previous iodo-aldol reaction of **14**, placing the cyanomethyl and hydroxyethyl ether groups on the same face of the B-ring. The utility of the nitrile group was quickly demonstrated; removal of the hydroxyethyl ketal was accomplished through iodination followed by zinc treatment.[15] This second step was optimized to achieve in situ lactonization via attack of the revealed C1 tertiary alcohol at the nitrile, followed by in situ hydrolysis of the resulting imidate. Removal of the TES group then gave enone **20**, representing the tricyclic core of the anislactone natural products.

Installation of the D-ring lactone onto **20** was now necessary, with synthesis of the C5 quaternary methyl group being the key challenge. We envisaged conjugate addition of a carbon nucleophile to the C-ring enone would provide this quaternary center at C5, followed by intramolecular acylation then methylation at C6. Unfortunately, this route foundered on the initial conjugate addition step, with a variety of intermolecular conditions failing on **20** and related substrates. Particular focus was paid to intramolecular addition using a Stork silicon-tethered radical reaction[16] from substrates **21** and **23**. This too was unsuccessful, with reduced material being the only isolated product.

Scheme 3. Cyanide Conjugate Addition−Aldol Reaction



To exploit the success of the domino aldol reaction in a completed synthesis of merrilactone, we needed to redesign the starting structure of the C-ring enone. We reasoned that two methyl groups in place from the early stages would create an opportunity for a late-stage stereocontrolled [2 + 2] photocycloaddition, installing the C5 and C6 quaternary stereocenters. There is precedent for this approach to the D-ring in Mehta and Singh's total synthesis of merrilactone A.[4]

Starting from the known hydroxycyclopentenone **24**,[17] we constructed substrate **27** in 7 steps (Scheme 4) using

(13) See the Supporting Information for a rationale of this reversal of diastereoselectivity.

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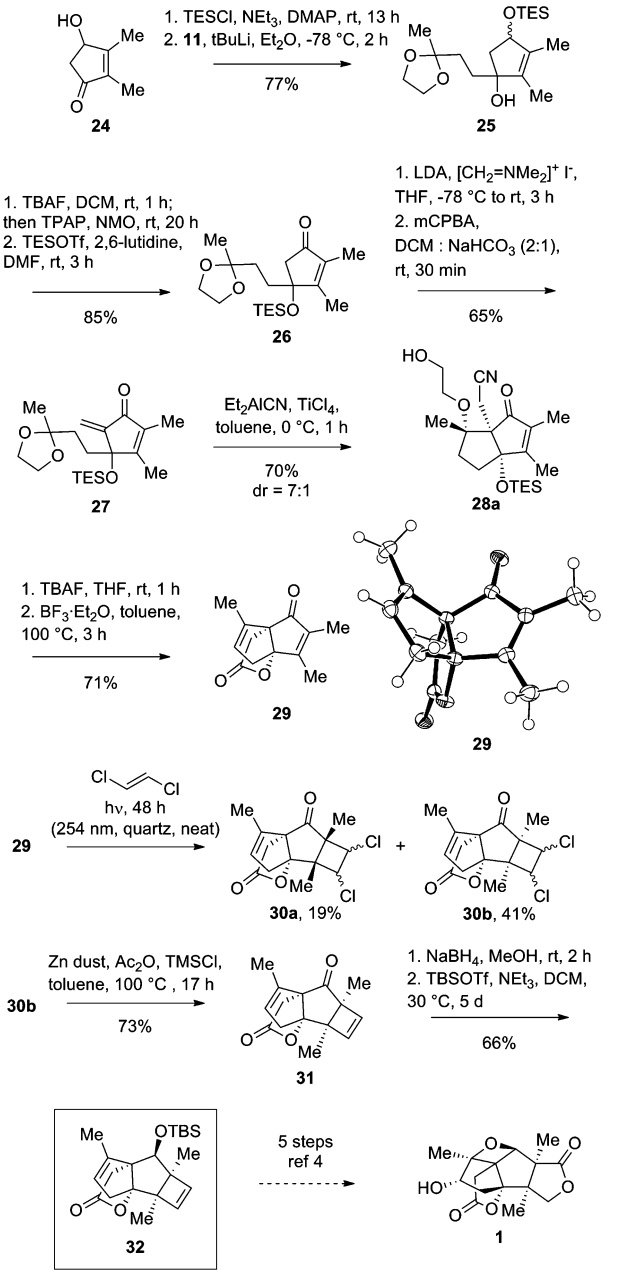
Scheme 4. Formal Synthesis of Merrilactone A



analogous chemistry to our previous routes. The cyanide domino reaction was again successful, producing adducts **28a** and **28b** in 70% combined yield, 7:1 diastereomeric ratio (major isomer shown in Scheme 4). The major isomer **28a** has the expected *cis*-relationship between the hydroxyethyl and cyanomethyl groups as per **19a** (Scheme 3). In contrast to previous routes, we directed **28a** toward merrilactone A by an alternative lactonization sequence. Desilylation gave a tertiary alcohol (characterized by X-ray), which on treatment with $BF_3 \cdot OEt_2$ at elevated temperature gave the oxatriquinane core **29** of merrilactone A in high yield (characterized by X-ray). The Lewis acid treatment is effecting an elimination of the hydroxymethyl group to a single alkene regioisomer (likely via isomerization of an initial *endo*/*exo* mixture), in addition to lactonization through alcohol attack at the cyano group. By removing the C1 stereocenter in **29**, the minor isomer **28b** in the preceding aldol reaction is now productive in this route and could be pooled with **28a** and taken forward.

Construction of the final D ring of the natural product was then attempted using [2 + 2] photocycloaddition of dichloroethylene. The reaction proceeded with moderate facial stereoselectivity to give a separable 2:1 mixture of cyclobutanes **30a** and **30b** in 60% overall yield. Stereochemical assignment was not possible at this stage, although addition from the desired β-face was expected by analogy with Mehta's work. The major diastereoisomer was dechlorinated to cyclobutene **31**, followed by stereoselective ketone reduction with $NaBH_4$. Protection of the secondary alcohol as a TBS ether gave compound **32** which has previously been prepared by Mehta and Singh in their total synthesis of merrilactone A.[4] That work accessed **32** in 20 steps, and a further five steps produced the natural product. NMR Analysis and comparison with literature data for **32** assigned the stereochemistry as shown, confirming the preference for alkene addition from the top face in the cycloaddition step.

In summary, we have completed a formal synthesis of merrilactone A. The route produces late stage intermediate **32** in 13 steps from the known cyclopentenone **24**, with a further five steps necessary for completion of the total synthesis. The domino cyanide conjugate addition–aldol reaction was key to the synthesis, forming two C–C bonds in good yield and setting three stereocenters with high levels of relative stereocontrol. Wider exemplification of this reaction will be the subject of future work in our group.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. X-ray data for compounds **17a**, **17b**, **19a**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.