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A synthesis of cyclohexanoid butenolides isolated from *Sinomenium acutum*

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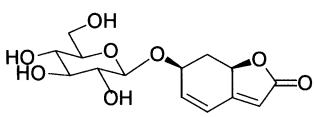
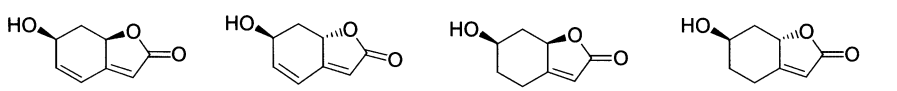
Abstract—Starting from an enantiopure building-block serving as the chiral equivalent of 4-hydroxycyclohexa-2,5-dien-1-one, a diastereocontrolled synthesis of four cyclohexanoid butenolides has been investigated. The inherent convex-face selectivity exerted by the chiral building block was a key aspect of this method which afforded three of the five known butenolides, with only one losing its original chiral integrity during the conversion.

(−)-Phyllanthurinolactone[1] **1**, the leaf-closing factor of a large tamarind tree (*Tamarindus indica* L.), has as its aglycone (−)-menisdaurilide[2,3] **2**, which is one of several cyclohexanoids isolated from *Sinomenium acutum* containing a butenolide moiety; others include (−)-aquilegiolide[3,4] **3**, (−)-dihydromenisdaurilide[4] **4** and (+)-dihydroaquilegiolide[4] **5** (Fig. 1). Otsuka and co-workers[4] established the absolute structure of natural (−)-menisdaurilide **2** by X-ray analysis. More recently, Mori and co-workers[5] proved that the aglycone menisdaurilide **2** has the same absolute structure to that of natural (−)-menisdaurilide **2** by synthesis of (−)-phyllanthurinolactone **1** from D-glucose and racemic menisdaurilide (±)-**2**. However, the enantiocontrolled syntheses of both can still be improved upon. Until now, only (−)-dihydromenisdaurilide **4** and (+)-dihydroaquilegiolide **5** have been obtained in enantioenriched forms by Majewski and co-workers.[6,7] Since, by use of either a catalytic[8] or an enzymatic[9] procedure, we had already developed a versatile chiral building-block[10] **6** serving as the synthetic equivalent of chiral 4-hydroxycyclohexa-2,5-dien-1-one, we decided to extend its utilization by exploring an enantiocontrolled route to these natural butenolides in enantiomerically pure form. The high functionality and inherent convex-face selectivity of the chiral building block **6** would play a pivotal role in this approach. We report here our results leading to the formation of the enantiomerically pure natural (+)-dihydroaquilegiolide **5** and unnatural (+)-dihydromenisdaurilide *ent*-**4**, along with the unexpected generation of racemic menisdaurilide (±)-**2**.

Thus, the enantiopure (+)-**6** was transformed into the *exo*-epoxide **7**, mp 65–66°C, $[\alpha]_D^{31}$ +56.2 (*c* 1.2, $CHCl_3$), diastereoselectively, using *tert*-butyl hydroperoxide in the presence of Triton B.[11] Reaction of **7** with the carbanion generated from ethyl acetate with LDA proceeded without reaction with the epoxy functionality to



(–)-phyllanthurinolactone **1**



(–)-menisdaurilide **2** (–)-aquilegiolide **3** (–)-dihydromenisdaurilide **4** (+)-dihydroaquilegiolide **5**

Figure 1.

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give the tertiary alcohol **8** as a single diastereomer, $[\alpha]_D^{22}$ +33.4 (*c* 1.2, $CHCl_3$). In order to carry out regioselective cleavage of the epoxide functionality, the alcohol **8** was first deprotected to give the diol **9**, mp 71–72°C, $[\alpha]_D^{24}$ +32.8 (*c* 1.2, $CHCl_3$), the secondary hydroxyl functionality of which was oxidized under Dess–Martin conditions[12] to afford the keto-alcohol **10**, $[\alpha]_D^{22}$ −11.7 (*c* 1.4, $CHCl_3$). After some experimentation, it was found that the regioselective cleavage was best carried out using aluminum amalgam[13] to give the keto-3,4-diol **11**, mp 71–72°C, $[\alpha]_D^{29}$ −104 (*c* 1.1, $CHCl_3$), as a single product. Unfortunately, complete convex-face selectivity was no longer exhibited by **11** on reaction with sodium borohydride. An inseparable mixture (10:3) of the *endo*- and *exo*-hydroxy-lactones **12** formed by in situ lactonization, was obtained under these reaction conditions. Since the intramolecular bromo-etherification of **11** prior to the reduction failed, giving rise instead to a complex mixture, we decided to use the crude alcohol mixture **12**. The retro-Diels–Alder reaction of both **12** and its secondary monosilyl ether **13**, in refluxing diphenyl ether however resulted in decomposition. Moreover, attempted dehydration of the ether **13** into the corresponding butenolide under several conditions also failed. Therefore, **13** was silylated to give the disilyl ether **14**, which was heated in refluxing diphenyl ether to furnish the cyclohexene **15** as an inseparable mixture in good yield (Scheme 1).

To obtain (−)-menisdaurilide **2**, **15** was treated with potassium carbonate in methanol to induce β-elimination. The expected reaction occurred to give the butenolide **16** as an inseparable mixture. Exposure of **16** to hydrofluoric acid in acetonitrile afforded an inseparable mixture **17** of menisdaurilide **2** and aquilegiolide **3**. Interestingly, the ratio changed from 10:3 to 2:3 during the elimination reaction as evidenced by ^1H NMR. A similar epimerization has previously been reported[3] during the isolation of (−)-aquileginolide **3**. The mixture was oxidized with pyridinium chlorochromate (PCC) to give the single enone[5] **18**, which was found to be completely racemic. As a result, menisdaurilide **2** obtained from **18** by diastereoselective reduction was racemic. The resulting racemization may be due to a facile enolization of the butenolide moiety at the β-elimination step via the hydroxyfuran **19** or in the oxidation step via the trienone **20**. These concluded us that the route involving the β-elimination of **15** was inappropriate for the enantioselective synthesis of menisdaurilide **2** (Scheme 2).

We next explored a route to the (+)-dihydroaquilediolide **5** utilizing the same intermediate **15**. Thus, **15** was hydrogenated under catalytic conditions to afford the separable 1,4-*syn*-ether **21** and the 1,4-*anti*-ether **23** in yields of 78 and 21%, respectively. The major compound **21** gave the tertiary alcohol **23** on exposure to dilute hydrochloric acid, which was dehydrated with methanesulfonyl chloride and triethylamine to give the butenolide **25**. Under these conditions, epimerization did not take place with the dihydro-derivative. Desilylation of **25** with hydrofluoric acid in acetonitrile furnished (+)-dihydroaquilediolide **5**, mp 107–108°C, $[\alpha]_D^{26}$ +125 (*c* 0.9, MeOH){lit.:[6] $[\alpha]_D^{24}$ +113 (*c* 1.0, MeOH) (90% ee)}, the spectroscopic data of which were identical with those of the natural product. The overall yield of **5** from **21** was 55%. On the other hand, the minor isomer **22**, under the same conditions, afforded (+)-dihydromenisdaurilide *ent*-**4**, mp 79–80°C, $[\alpha]_D^{26}$ +123 (*c* 0.2, MeOH), the enantiomer of the natural (−)-dihydromenisdaurilide **4**, $[\alpha]_D^{26}$ −112 (*c* 2.0, MeOH) (90% ee),[6] in 35% overall yield from **22** without epimerization (Scheme 3).

Acknowledgements

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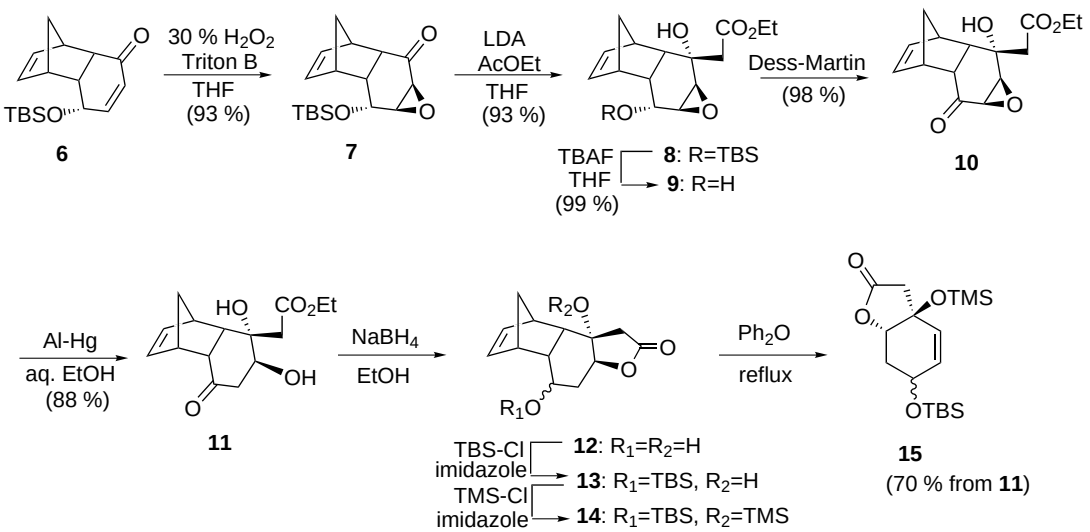
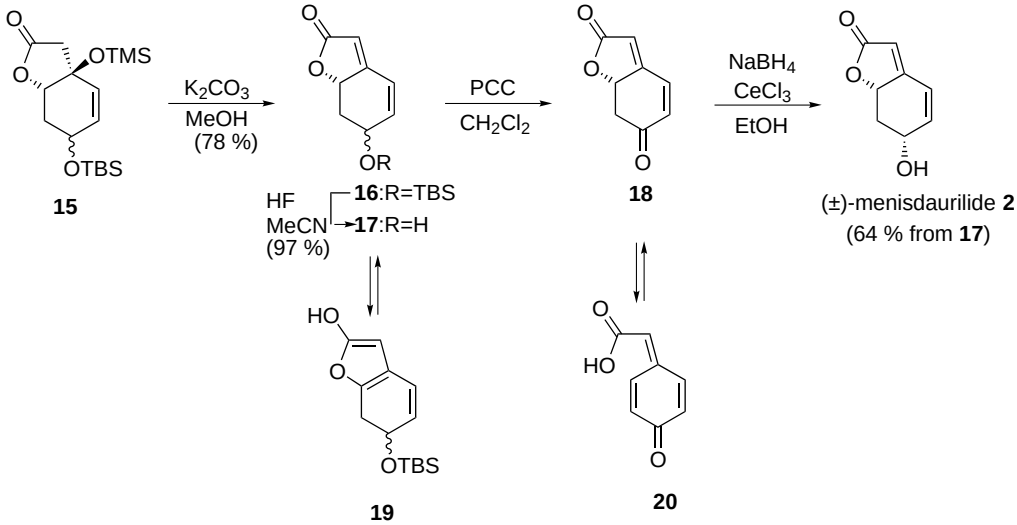
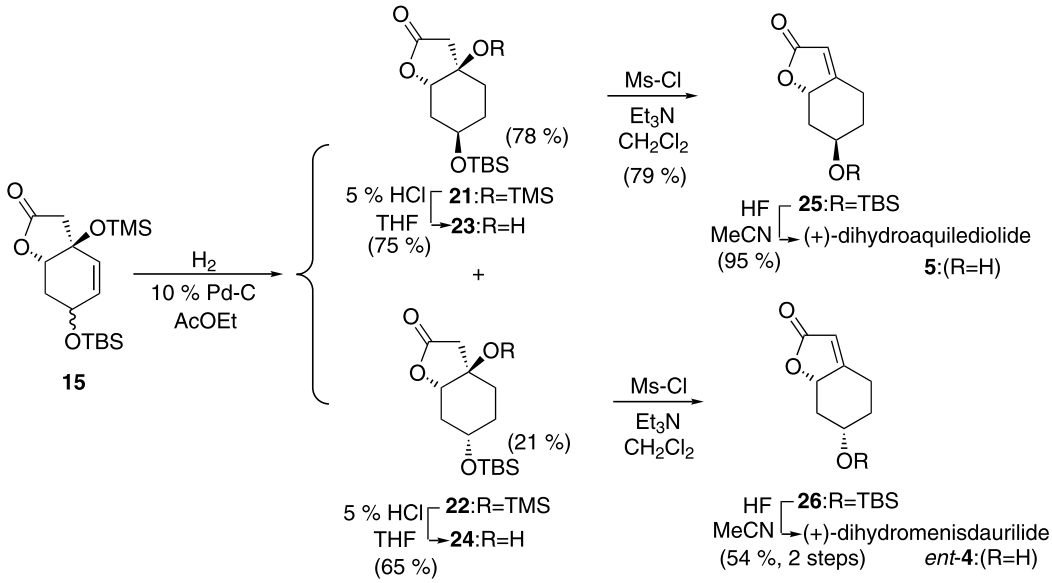


Scheme 1.



Scheme 2.



Scheme 3.

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