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Synthesis of the core ring system of the sclerophytin diterpenes utilizing a Lewis acid-promoted [4+3] annulation strategy

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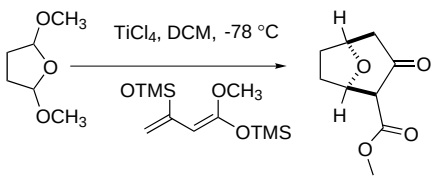
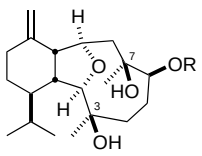
Abstract—The synthesis of the core ring system of the sclerophytin diterpenes is described. The key tetrahydrofuran-containing intermediate is assembled via a Lewis acid-promoted [4+3] annulation reaction between a mixed dimethyl acetal and a bis-TES dienol ether. The resulting β-keto ester was homologated, cyclized, and ring expanded to afford the sclerophytin ring system.

Recent reports from the arena of cladiellin natural product synthesis[1] have prompted us to report part of our efforts in this area, specifically our work toward the synthesis of the sclerophytin diterpenes (Fig. 1). Our work was directed toward the previously assigned structures—molecules with an oxygen bridge between C-3 and C-7 forming a tetrahydropyran ring. The successful synthesis of sclerophytin analogs reported in this communication pre-date recent corrections to the structure of the sclerophytins.[2]

Novel annulation methods developed in these laboratories have been shown to have utility for synthesizing medium-sized ring-containing natural products.[3] These annulation methods employ bis(trimethylsilyl)dienyl ethers with diketones or keto-aldehydes to assemble oxygen-bridged, seven- and eight-membered ring systems. It was our goal to extend this method toward the synthesis of cladiellin natural products, namely the diterpenes sclerophytins A and B. Our initial plan was to assemble the tetrahydrofuran-containing nucleus of the sclerophytins through the use of a [4+3] annulation reaction employing a 1,4-dialdehyde. However, because of the inherent instability of 1,4-dialdehydes and their propensity to form cyclic hydrates, our efforts met with little success. As an alternative to using a dialdehyde, Chan and Brownbridge used a tetrahydrofuran-1,4-dimethyl acetal, a 1,4-dialdehyde surrogate, as a substrate in a [4+3] annulation reaction (Eq. (1)).[4] The synthetic viability of a dimethyl acetal-containing intermediate was appealing, thus we began investigating a route to cyclic acetal **1** (Scheme 1).



(1)



Sclerophytin A (R=H)
Sclerophytin B (R=Ac)

Figure 1.

Our efforts to construct the mixed acetal **1** began with racemic cryptone (**2**)—the substrate for a 1,4-vinyl addition reaction promoted by a copper bromide–dimethyl sulfide complex.[5] The resulting enolate was trapped with chlorotrimethylsilane to afford dienol ether **3**. Exposure of **3** to Lewis acid in the presence of trimethyl orthoformate[6] resulted in dimethyl acetal **4**. The *trans–trans*-stereochemistry about the cyclohexanone ring of **4** was assigned based on the ^{1}H NMR spectrum that displayed axial–axial coupling constants between the adjacent stereogenic center methine protons ($J=10.8$ Hz for each relationship). The vinyl group of **4** was cleaved using ozone, and a dimethyl

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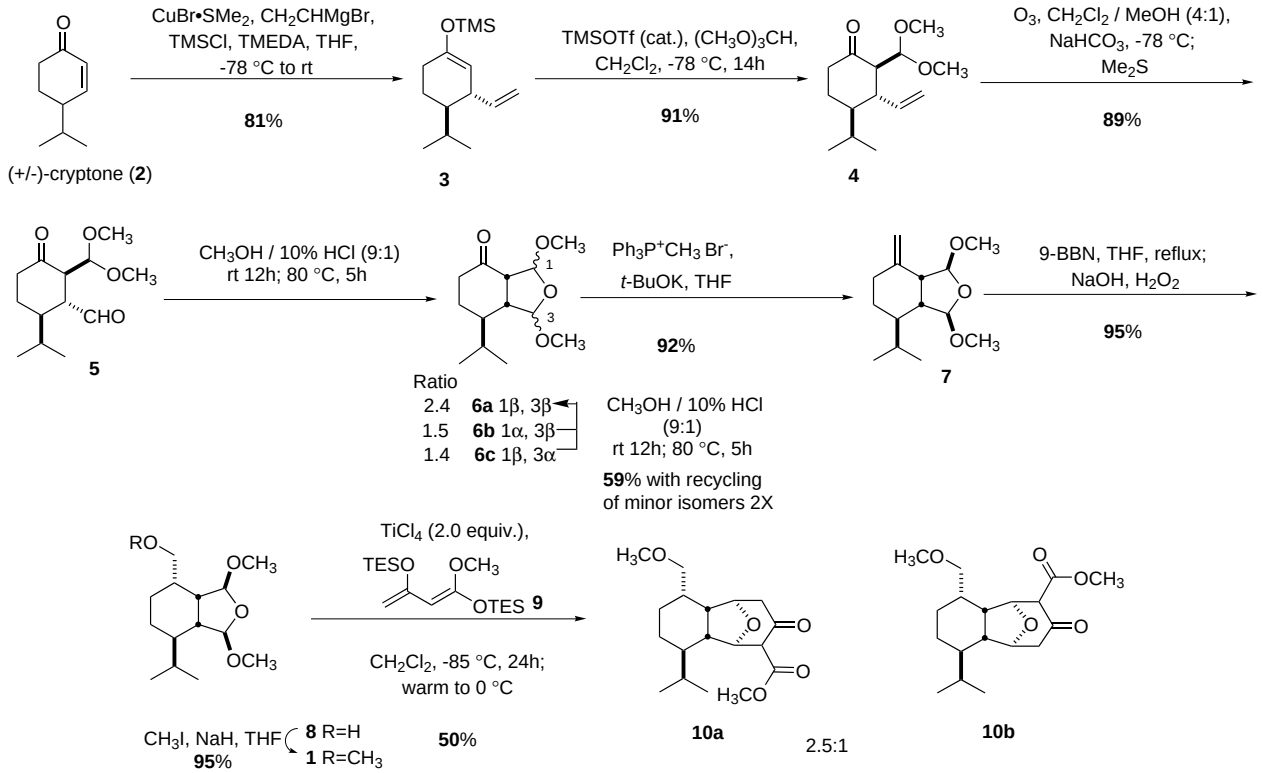


Scheme 1.

sulfide workup provided the aldehyde **5** in high yield. This acetal was isomerized under acidic conditions to a 2.5:1.5:1.4 mixture of tetrahydrofuran dimethyl acetals **6a–c**, respectively. Only material derived from the major isomer **6a**, i.e. methyl ether **1**, proved to be a suitable substrate for the key [4+3] annulation reaction (vide infra). Isomeric acetals of **1**, derived from **6b** and **6c**, gave little, if any desired product in the [4+3] annulation reaction. Thus, the major isomer **6a** was isolated from the mixture of acetals **6a–c** via chromatography and the minor isomers **6b** and **6c** were combined and resubmitted to the isomerizing conditions. Two iterations of minor isomer recycling and chromatography afforded the *cis*-isomer **6a** in good yield for the combined material. The *cis*-ring fusion and acetal carbon stereochemistry of **6a** was confirmed through single crystal X-ray analysis of a 2,4-dinitrobenzoate ester derived from **6a**. Olefination of **6a** using triphenylphosphine methylide gave **7**, which was converted to the primary carbinol through a hydroboration and oxidation sequence. The free hydroxyl of **8** was capped as its methyl ether (**1**), which was the substrate for the [4+3] annulation reaction. The best results in the annulation reaction were achieved by treating a cold solution of acetal **1** with freshly distilled titanium tetrachloride, added dropwise. This was followed by the slow addition of bis(triethylsilyl)dienyl ether **9**.[7] The mixture was kept cold and allowed to react for 24 h, at which time it was allowed to warm to an ambient temperature and was then poured into a saturated solution of sodium bicarbonate. An extractive workup afforded a modest yield of a 2.5:1 mixture of bicyclic keto esters **10a** and **10b**, with the desired keto ester **10a** being the major product. Single crystal X-ray analysis of **10a** demonstrated that the five stereogenic centers of **10** had been set, as depicted (Fig. 2).

With the advanced intermediate **10a** in hand, homologation and ring expansion began with the alkylation of **10a** with the primary iodide **11**, using sodium hydride as base (Scheme 2). This transformation was straightforward and gave a good yield of the sulfone **12**. As expected, the alkylation of **10a** occurred from the convex face of the bicyclic ring system. Saponification of

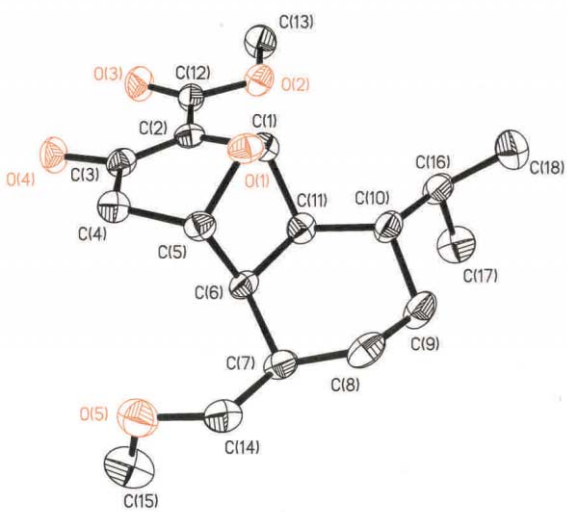
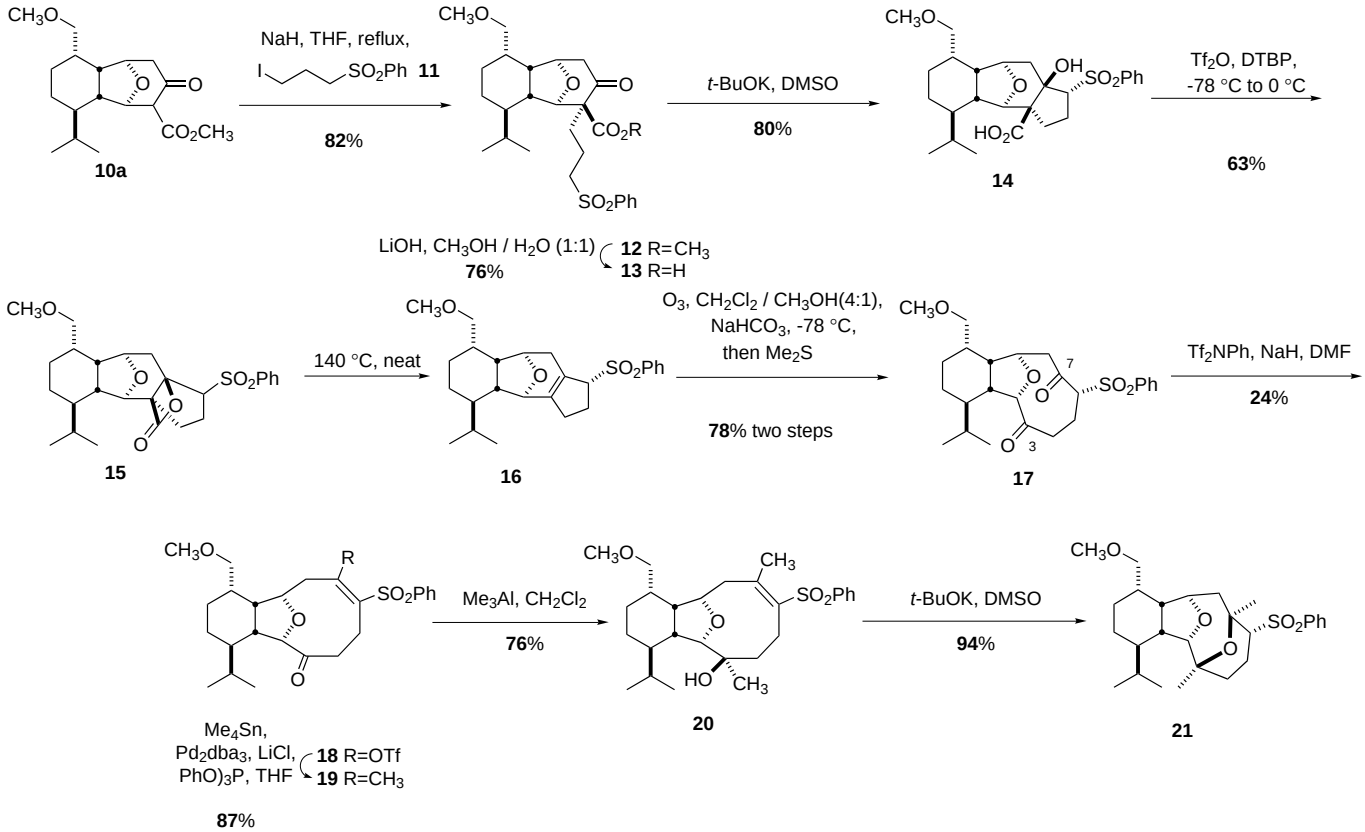


Figure 2. ORTEP of **10a**.



Scheme 2.

the methyl ester of **12** also proceeded smoothly to afford the keto acid **13**. Brief exposure of a DMSO solution of **13** to a solution of potassium *tert*-butoxide in DMSO, followed by an acetic acid quench, afforded the polycyclic hydroxy acid **14**. Lactone formation using trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butylpyridine was followed by thermolysis of neat β-lactone **15** to afford the tetrasubstituted olefin **16**. Ozonolysis of **16** resulted in the formation of diketone **17**.

The goal at this point of the synthesis was to install the methyl groups at C-3 and C-7 followed by construction of the tetrahydropyran ring. The first step toward this goal was the selective formation of enol triflate **18**, which would set the stage for the introduction of the first methyl group through the use of a Stille reaction. Treatment of the diketone **17** with sodium hydride and *N*-phenyltriflamide as triflating reagent cleanly produced the desired enol triflate **18** in low yield.[8] Exposure of **18** to tetramethyltin and a palladium catalyst, under refluxing conditions,[9] gave the desired C-7 methylated product **19**. The second methyl group was installed by treating **19** with trimethylaluminum, thus completing the assembly of the cladiellin carbon framework.[10] Tetrahydropyran formation was accomplished through exposure of **20** to potassium *tert*-butoxide in DMSO to afford **21**. The resulting stereochemistry of both the methyl addition reaction and the tetrahydropyran ring forming reaction were inferred from crystallographic studies performed on a model system to **21** (Fig. 3).

In summary, a route to construct the core ring system of the sclerophytin diterpenes has been established. This route utilizes a Lewis acid-promoted [4+3] annulation reaction to assemble the tetrahydrofuran-containing intermediate **10a**. This key compound was further homologated and ring expanded to the core sclerophytin ring system. Additional studies in this area are in progress.

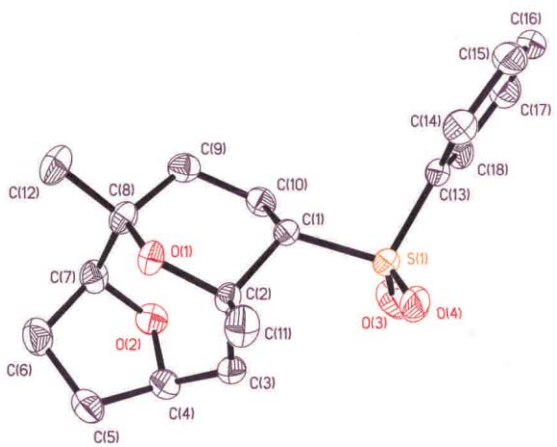


Figure 3. ORTEP plot of model **21**.

Acknowledgements

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