Formation of Highly Oxygenated [4.4]Spirononenes via Lewis Acid-Catalyzed Isomerization of Adducts to Squarate Esters. Total Synthesis of Dimethyl Gloiosiphone A

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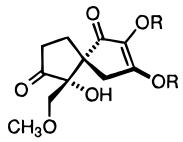
Red marine algae continue to be intensively scrutinized for medicinally useful metabolites since these organisms have proven to be a rich source of unique natural products. Recent collections of *Gloiosiphonia verticillaris* off the Oregon coast were found to exhibit powerful antimicrobial activitiy against several *Staphylococcus*, *Bacillus*, and *Salmonella* species. The causative agent was recognized to be highly unstable when attempts to accomplish isolation resulted in very rapid loss of activity.[1] Pretreatment of the bioactive fractions with diazomethane provided the more robust **2**, which is obviously produced by O-methylation of the enolic protons of gloiosiphone A (**1**). These compounds comprise a new structural class

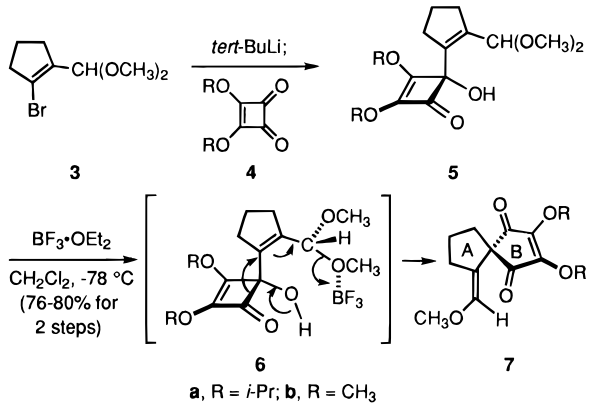


1, R = H
2, R = CH_3

featuring a substantially oxygenated [4.4]spirononenedione system. Herein we disclose a very direct means for the elaboration of this framework in the context of a total synthesis of dimethyl gloiosiphone A (**2**).

The key elements of our strategy involve the condensation of bromide **3** with an equivalent of a squarate ester **4** and subsequent deployment of a regiocontrolled ring expansion to generate the critical spirocyclic center (Scheme 1).[2−4] The synthesis of **3** is readily achieved by sequential Vilsmeier−Haack bromoformylation and acetalization of cyclopentanone.[5] Halogen−metal exchange with *tert*-butyllithium and addition to **4a** or **4b** in THF at −78 °C provides **5a** or **5b**, respectively, in quantitative yield. Treatment of either α-hydroxy ketone with boron trifluoride etherate in cold CH_2Cl_2 induces ring expansion with loss of methanol. As reflected in **6**, the carbonyl carbon migrates exclusively, thus providing the desired 1,3-diketone array.[6] The exocyclic vinyl ether is formed with high stereoselectivity. The spirocyclic end products **7a** and **7b**, isolated in 76% and 80% yield, were fully characterized on the basis of COSY, NOE, and long-range DEPT NMR analyses.

Scheme 1



Advantage was now taken of the C_s symmetry of **7**. Specifically, controlled reduction of either of the equivalent ketone carbonyls in its B ring to the methylene level was recognized to relegate stereoselective introduction of the stereogenic center in ring A to a later stage of the synthesis. This ordering of events was considered to be advantageous. After a survey of several reductive schemes, the three-step protocol outlined in Scheme 2 was adopted. Once sequential reaction with cold (0 °C) sodium borohydride[7] and esterification with acetic anhydride had been performed in order to produce **9**, NOE measurements established that H_a and H_b were in close spatial proximity (4% signal enhancement). Thus, hydride delivery had occurred syn to the exocyclic double bond. Careful exposure of **9** to samarium iodide in a THF/methanol solvent system at −78 °C[8] led in excellent yield to **10**.

Proper functionalization of the A ring was now initiated by oxidation of **10** with ceric ammonium nitrate in aqueous acetonitrile.[9] Although this transformation proved problematic at times, a significant rate difference in favor of attack at the enol ether double bond was noted. In effect, the conversion to **11** can be considered to be a highly chemoselective process. Subsequent arrival at **12** could be achieved regioselectively

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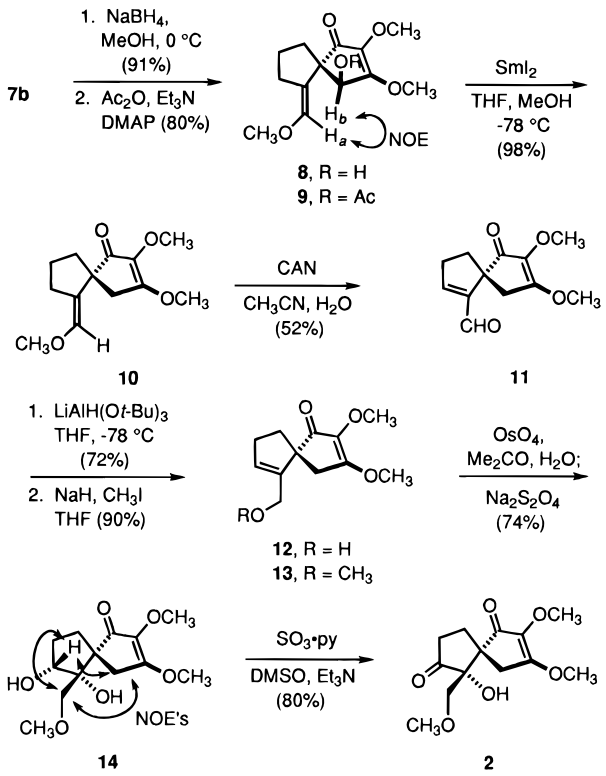
Scheme 2



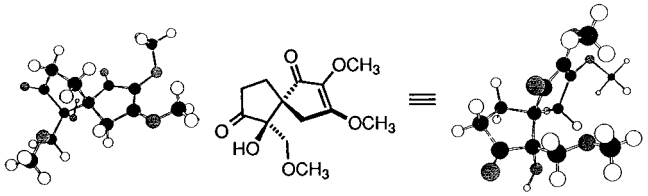
provided that lithium tri(*tert*-butoxy)aluminum hydride[10] was employed only at −78 °C or below. The subsequent transformation of this sensitive alcohol into its methyl ether **13** was accomplished with methyl iodide and silver(I) oxide in acetonitrile[11] (61%) or preferably with sodium hydride in THF (90%).

Dihydroxylation of the homoallylic ether double bond in **13** was next required to enhance to level of A ring oxygenation. Although attempts to effect this transformation with catalytic amounts of osmium tetroxide failed, success was achieved under stoichiometric conditions. The resulting osmate ester was most satisfactorily cleaved with sodium dithionite.[12] A single diastereomer was obtained as evidenced by ^{1}H and ^{13}C NMR spectroscopies. This diol was established to be **14** on the basis of prevailing NOE effects.

Implementation of the final step necessary for completion of the synthetic goal was initailly thwarted because several oxidants of the perruthenate or periodinane type proved destructive of **2**. Fortunately, dimethyl gloiosiphone A was tolerant of the sulfur trioxide−pyridine complex[13] and delivered **2** in 80% yield. The ^{1}H and ^{13}C NMR spectra of the synthetic and natural samples proved identical.[14]

Significantly, gloiosiphone A occurs as a racemic compound in the saline environment in which it is produced. The speculation can be advanced that **1** might be capable of ready and reversible retroaldol cleavage of its A ring. Were this to occur, the original sense of absolute and relative configuration at both stereogenic centers would be eradicated. The preference for **1** on reclosure could be attributed to the ability of this diastereomer to engage in intramolecular hydrogen bonding.

The following facts argue against this otherwise attractive proposal. MM3-minimized structures of **2** and **15** (MacroModel 5.0) were subjected to a Monte-Carlo multiconformational search involving 1000 different arrangements for each structure.



This procedure was repeated several times while varying the final ring closure bond and torsional angles. The lowest energy conformation from each Monte-Carlo search was subjected to full-matrix Newton−Raphson minimization using the modified MM3 force field. The total energies were thereby determined to be 42.22 and 41.36 kcal/mol, respectively, indicating **15** to be thermodynamically *more stable* by 0.86 kcal/mol. The stabilizing effect of the interring hydrogen bond in **2** involving the OH and enone carbonyl is offset by significant nonbonded steric interaction involving the CH_2OCH_3 substituent and proximate methylene group from the B ring. In a control experiment conducted with K_2CO_3 in methanol, **2** exhibited no detectable tendency for equilibration with **15**. Consequently, the absence of optical activity in **1** likely may not arise from operation of a retroaldol−aldol ring fragmentation scheme. Unfortunately, the extreme sensitivity of **1** precludes a more direct assessment of this matter.

To conclude, a convergent total synthesis of dimethyl gloiosiphone A has been accomplished in 10 steps and in 11.4% overall yield from dimethyl squarate. The approach underscores the latent synthetic potential of squarate esters as well as the capacity for accomplishing chemocontrolled transformations in small, densely oxygenated spirocyclic frameworks.

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