An Iterative Approach to Biologically Important Fused Polycyclic Ethers *via* Acyl Radical Cyclizations

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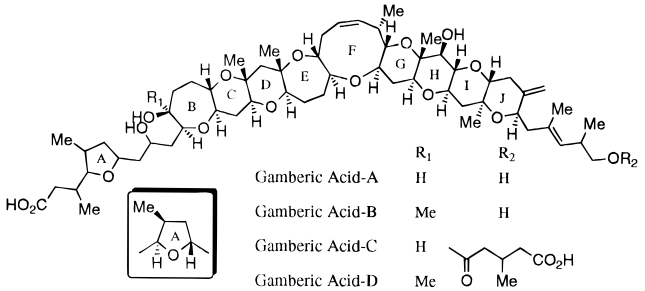
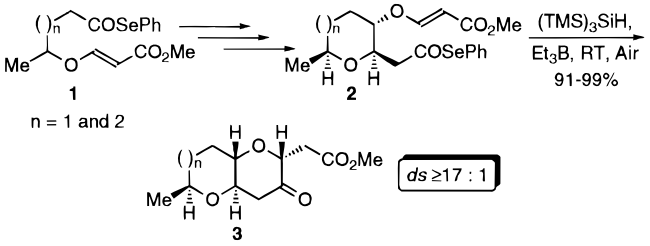
Fused polycyclic ether containing natural products present formidable synthetic targets owing to their inherent structural complexity.[1] A variety of elegant approaches have been developed for this class of compounds with an increasing emphasis on iterative strategies.[2] The gamberic acids A−D, recently isolated by Yasumoto and co-workers from a culture medium of *Gambierdiscus toxicus*, are particularly interesting. They



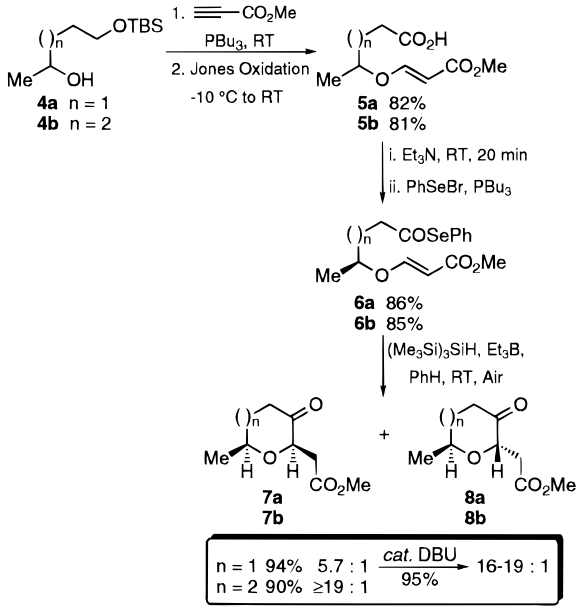
have a unique ladder-like polycyclic molecular framework, consisting of nine contiguous *trans*-fused polyether rings with an isolated tetrahydrofuran ring. Furthermore, they have antifungal activity exceeding that of amphotericin B by more than 3 orders of magnitude, making them of significant therapeutic interest. The biological activity exhibited by these agents has been attributed to the symbiotic combination of all four gamberic acids, providing an intriguing question with regard to the mechanism of action.[3]

In this paper, we describe an iterative acyl radical cyclization strategy for the synthesis of the key left hand (BC segment) **3** (n = 2) and right hand (IJ segment) **3** (n = 1) components of this extremely important molecule.[4−6] Our retrosynthetic analysis envisioned the molecule being disconnected into two complex tetracyclic units, namely the BCDE and GHIJ subunits, each of which should be accessible *via* the strategy outlined in Scheme 1.

Scheme 1



Scheme 2



Scheme 2 summarizes the initial sequence devised for the synthesis of the tetrahydropyran-3-one and oxepin-3-one systems.[6] Treatment of the secondary alcohols **4a**[7] and **4b**[8] with methyl propiolate and tributylphosphine furnished the vinylogous carbonates,[9] which were oxidized directly with Jones reagent to the corresponding carboxylic acids **5a** and **5b** in 82% and 81% overall yield, respectively.[10] The carboxylic acids **5a** and **5b** were then converted to the acyl selenides **6a** and **6b** in 86% and 85% yield, using the Crich protocol.[11] Treatment of the acyl selenides **6a** and **6b** with tris(trimethylsilyl)silane and triethylborane at room temperature, in the presence of air, furnished the cyclic ethers **7a/8a** and **7b/8b** in 94% and 90% yield as 5.7:1 and ≥19:1 mixture of stereoisomers, respectively, as previously reported.[6] The stereochemical assignments were confirmed by NOE studies, and the mixture of tetrahydropyran-3-ones **7a/8a** equilibrated to the thermodynamically more stable *cis*-diastereoisomer **7a** (16−19:1) using a catalytic amount of diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene in 95% yield.

It was anticipated that the differentially protected alcohols **9a/b** would allow the merit of the iterative strategy to be demonstrated. Hence, the alcohols **9a** and **9b** were prepared as outlined in Schemes 3 and 4. The

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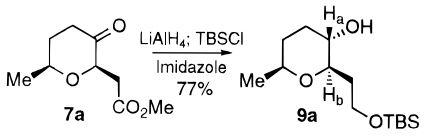
Scheme 3



tetrahydropyran derived alcohol **9a** was available in two steps from the 2,6-disubstituted tetrahydropyran-3-one **7a**. Reduction of the keto ester **7a** with lithium aluminum hydride followed by the selective protection of the primary alcohol furnished the *tert*-butyldimethylsilyl ether **9a** in 77% overall yield. The stereochemical outcome for the reduction was confirmed from the axial-axial coupling constants between H_a and H_b.

Reduction of the 2,7-disubstituted oxepin-3-one **7b** proved to be more problematic, leading to mixtures of epimeric alcohols under a variety of reaction conditions in which the desired *trans*-alcohol was inseparable and very often the minor component. In order to circumvent these difficulties, the ketone **7b** was stereoselectively reduced with L-selectride (Aldrich) to furnish the *cis*-bicyclic lactone **10** in 88% yield (Scheme 4). NOE studies were carried out in order to confirm the stereochemistry of the bicyclic lactone **10**. The bicyclic lactone **10** was then reduced to the diol and the primary alcohol protected as the *tert*-butyldimethylsilyl ether to afford the alcohol **11** in 80% overall yield. Mitsunobu inversion of the *cis*-alcohol **11**, followed by alkaline hydrolysis of the *p*-nitrobenzoyl ester, furnished the *trans*-alcohol **9b** in 83% overall yield.[12,13]

The secondary alcohols **9a** and **9b** were then converted to the corresponding acyl selenides **13a** and **13b** (Scheme 5) *via* a sequence analogous to that described for the conversion of **4a/b** to **6a/b** in Scheme 2. Treatment of the acyl selenides **13a** and **13b** with tris(trimethylsilyl)-silane and triethylborane at room temperature, in the presence of air, furnished the bicyclic ethers **14a** and **14b** in 91% and 99% yield as ≥19:1 and 17:1 mixtures of diastereoisomers, respectively. The *cis*-stereochemical assignments were confirmed by NOE studies.

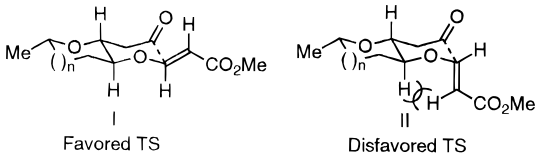
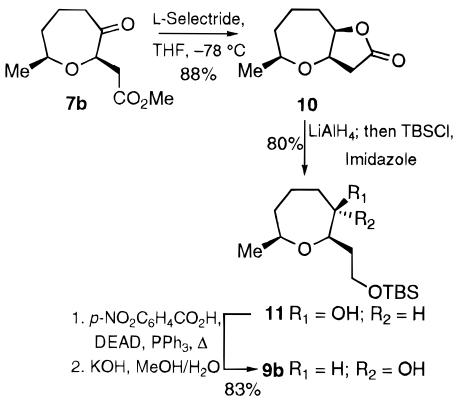


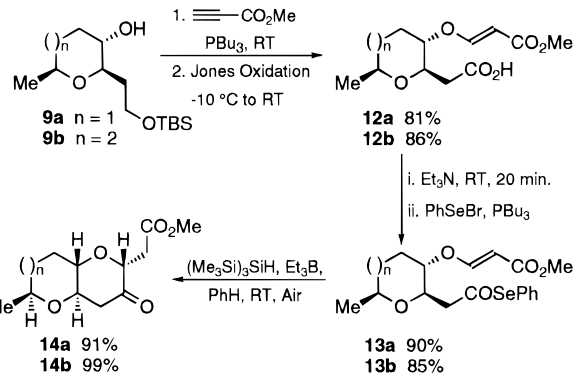
Figure 1.

The excellent stereocontrol obtained for these cyclization reactions is in sharp contrast to the modest diastereocontrol obtained in the monocyclic examples.[6] This is presumably the result of a much later transition state, in which the pyran and oxepine rings lock the components of the newly forming pyran ring in pseudo-equatorial environments. Hence, the favored transition state I (n = 1, 2) has the substituents pseudoequatorial with the vinyl ether *s-trans*, alleviating $A^{1,3}$-type allylic strain in the transition state leading to the product (Figure 1).[14]

Scheme 4



Scheme 5



In conclusion, we have demonstrated an iterative strategy, using intramolecular acyl radical cyclizations, for the efficient and stereoselective synthesis of 6,6- and 7,6-fused bicyclic ethers **14a/b**. This type of strategy is currently being applied to the synthesis of more advanced fragments applicable to the gamberic acids.

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Supporting Information Available: Experimental procedures and full characterization for compounds **5a/b**−**14a/b** (12 pages).

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(13) The Mitsunobu reaction was fairly sluggish at room temperature and required refluxing in benzene to drive the reaction to completion.[12c]

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