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A Highly Efficient Iterative Approach to Fused Ether Ring Systems

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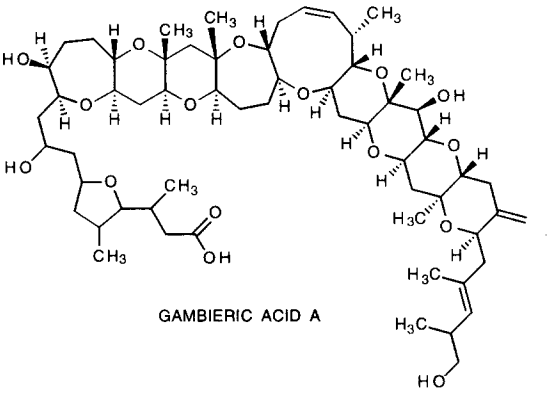
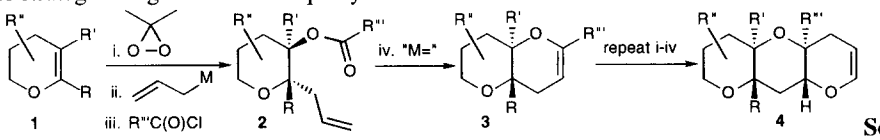
Abstract: *An iterative synthesis of fused ether ring systems has been developed. This strategy couples a cyclic enol ether oxidation and carbon-carbon bond forming reaction in one flask with an acid catalyzed cyclic acetal formation and alkoxide elimination in another flask. The result is a general and highly efficient two flask synthesis of fused ethers as are present in a wide variety of bioactive natural products.*

The marine "ladder" toxins consist of bioactive agents whose skeletons incorporate highly regular oxygenated heterocycles. Although this family is most commonly associated with neurotoxicity and "red tide" catastrophes,[1] some members have shown potent anti-microbial activity and lack neurotoxicity (cf. Gambieric Acid).[2,3] When coupled with their complex yet highly regular architecture, the very interesting bioactivity of this class of molecules would seem to warrant an efficient and general approach to their synthesis if they are to be fully evaluated.[4-12]



GAMBIERIC ACID A

As part of our program toward these ring systems, we have recently communicated a five-step iterative approach to fused pyran rings.[13] Central to this strategy was the stereoselective epoxidation and nucleophilic ring opening of cyclic enol ethers (**1** → **2**, Scheme 1). From our perspective, the subsequent annulation sequence (**2** → **3**) was somewhat less critical for two reasons. First, nearly all of the stereocenters in the fused ethers reside at the ring junctions; it is precisely these centers that the epoxidation and carbon-carbon bond forming reaction address. Second, we felt that there were several possible cyclization methods at our disposal. Consequently, while our first generation annulation approach employed ring-closing metathesis reactions to carry out the **2** → **3** transformation, we were confident that other strategies might be at least equally successful.



Scheme 1

While generally pleased with the overall efficiency of the strategy outlined in Scheme 1, we felt that there was clearly room for improvement. For one, the annulation sequence had required stoichiometric amounts of transition metals and three synthetic steps. For another, the yields for the epoxidation and subsequent coupling reaction of bicyclic enol ethers had been moderate and/or had given an undesirable stereochemical outcome. This communication describes our second generation approach to these ring systems which focuses on the annulation sequence while also examining the epoxidation of bicyclic fused ether rings in more detail.

As envisioned, our new approach would combine the very promising cyclic enol ether epoxidation and carbon-carbon bond forming reaction of our first strategy with an acid-catalyzed cyclization[14] and enolization (**5** → **7**, Scheme 2). If successful, we felt that an approach of this type would be a dramatic improvement as it would not only minimize the number of transformations required for each iteration but it would also avoid the use of stoichiometric and/or expensive transition metals. While precedent suggested that the conversion of **6** into **7** could be carried out in two separate reactions,[14-17] we were interested in maximizing efficiency by effecting the formation of the cyclic acetal and the subsequent elimination in a single flask.

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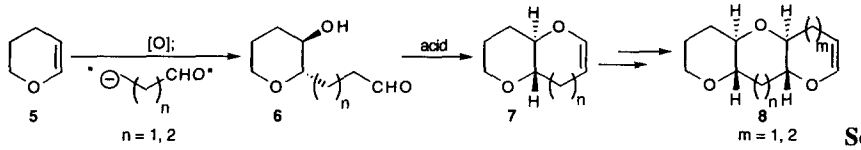


Scheme 2

With this strategy in mind, 3,3-dimethoxypropylmagnesium bromide was coupled with epoxide **10**[18] at various temperatures. As illustrated, the yield for these transformations ranged from 51% at 0°C to 29% at -40°C with rather low selectivity favoring the desired anti isomer **11** (entries 1 and 2, Table 1). In contrast, 3-propenylmagnesium chloride adds to **10** in an 83% yield with complete anti selectivity at 0°C.[13,19] Fortunately, we were able to overcome these moderate yields and lack of selectivity by using the corresponding cuprate. Thus, in the presence of 0.5 equivalents of CuI, 3,3-dimethoxypropyl magnesium bromide added to **10** at -30°C to give a >9:1 ratio of anti:syn products in a 63% overall yield.[20]

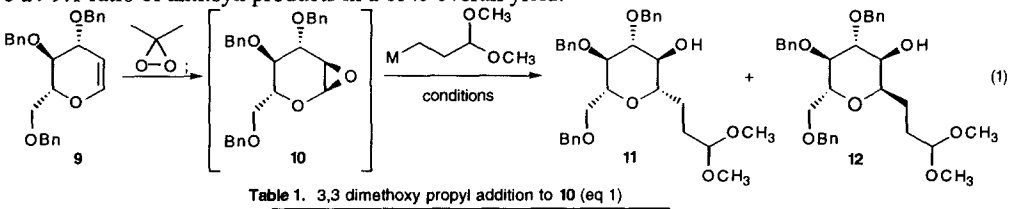


Table 1. 3,3 dimethoxy propyl addition to **10** (eq 1)

entry	M	temperature	11:12	yield
1	MgBr	0°C	1:1	51%
2	MgBr	-40°C	1.7:1	29%
3	CuMgX	-30°C	6:1	63%

With a reasonably efficient synthesis of **11** in hand, we turned our attention to the formation of the mixed acetal and the subsequent elimination of methanol. In spite of our stated goal of identifying a single flask cyclization and elimination sequence, we initially investigated a two step approach. As illustrated (eq 2), addition of TMSOTf to **11** at -65°C resulted in the generation of cyclic acetal **13** in 56% yield.[15] When **13** was subjected to either TMSOTf and pyridine at 40 °C [17] or PPTS, pyridine, and dichlorobenzene at 140 °C[16] we were able to efficiently isolate bicyclic enol ether **14** in a 91% yield. Encouraged by these results, we investigated the single flask conversion of **11** into **14**. To this end, hydroxy acetal **11** in dichlorobenzene was subjected to PPTS at 60°C until its complete consumption was observed by TLC. Subsequent addition of pyridine followed by further heating resulted in the isolation of the desired cyclic enol ether **14**.[21] To the best of our knowledge, the sequence described above is the simplest and most efficient approach to fused ethers to date. To summarize, we have been able to accomplish the synthesis of fused bicycle **14** in two flasks and 57% overall yield using readily available reagents. In contrast, our previous synthesis required 4 flasks and resulted in a 37% overall yield using much more costly reagents.

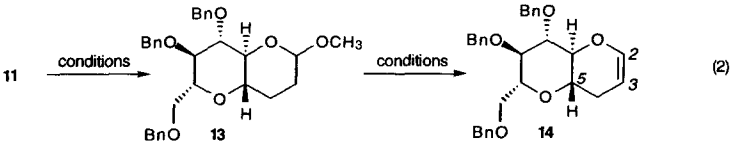


Table 2. Acyclic Acetal to Cyclic Enol Ether Conversion (eq 2)

entry	11 → 13	13 → 14	yield[a]
1	TMSOTf, CH_2Cl_2, -65°C	TMSOTf, NEt_3, CH_2Cl_2, 40°C, 14 h	28%
2	TMSOTf, CH_2Cl_2, -65°C	PPTS, pyridine, PhCl, 140°C, 4h	51%
3	----------	PPTS, dichlorobenzene, pyridine 60-140°C, 6h ----------	91%

[a]Overall yield from **11** to **14**

As illustrated (eq 3), we have subjected **14** to an additional iteration. Our previous results had indicated that the epoxidation of a similar bicyclic enol ether using dimethyl dioxirane generated the undesired epoxide isomer, albeit in low yield.[13] Fortunately we had been able to overcome this by utilizing the corresponding bromohydrin. Unfortunately, when **14** was subjected to the same conditions, a very small amount of product as a mixture of diastereomers was isolated. This result, in conjunction with a recent publication by McDonald,[7] led us to re-examine the bicyclic epoxidation issue. Addition of dimethyl dioxirane at 0°C followed by 3,3-dimethoxypropyl magnesium bromide according to the conditions used in the **9** → **11** transformation resulted in a 56% yield of readily separable hydroxy acetals **15** and **16** as a 1:3 mixture. Unfortunately, the major diastereomer from this transformation proved to be the undesired **16**. In an attempt to optimize these results the epoxidation reaction was conducted at two additional temperatures. Epoxidation at -65°C resulted in a <1:9 ratio of **15** to **16** confirming our earlier speculation that the inherent facial selectivity of bicyclic ring systems like **14** is from the same face of the molecule as the C-5 ring junction hydrogen. Not unexpectedly, epoxidation at higher temperatures resulted in a decreased selectivity and an increased yield of the desired **15**. Thus, epoxidation at 24 °C gave a 1:2 ratio of **15** to **16** respectively.

With bicyclic acetal **15** in hand, we examined its conversion into the corresponding tricyclic enol ether. Much to our delight, we were able to isolate a 72% yield of tricyclic enol ether **17** by subjecting **15** to the same conditions that had been successful in the generation of bicycle **14** (eq. 3).

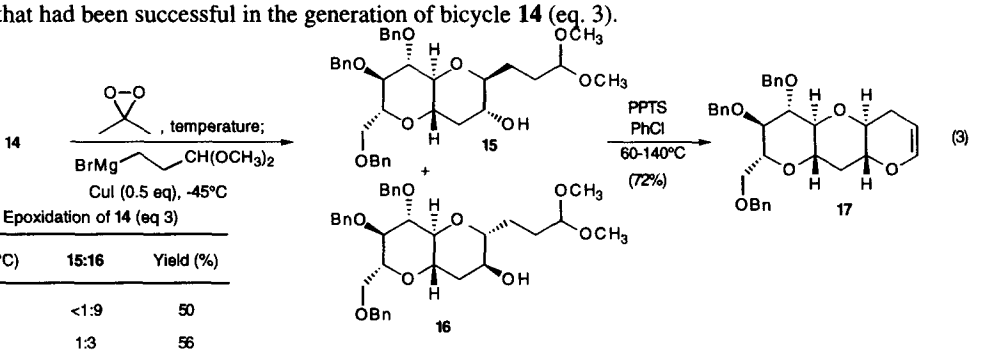
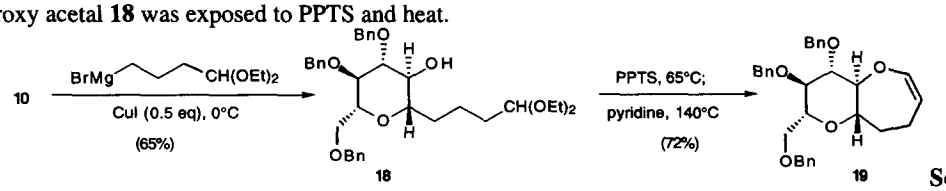


Table 3. Epoxidation of **14** (eq 3)

Temp (°C)	15:16	Yield (%)
-65	<1:9	50
0	1:3	56
24	1:2	62

As fused oxepane rings are ubiquitous throughout the marine ladder toxin family, any generally useful approach to these molecules must allow for their incorporation. From our perspective, one of the most appealing aspects of the acid catalyzed cyclization and elimination sequence was the strong possibility that we would be able to synthesize not only 7-membered but also 8- and 9-membered rings.[12] To determine whether this notion was correct, we have pursued the synthesis of [4.5.0]-fused ether **19**. To this end, the addition of the cuprate from 4,4-diethoxybutyl magnesium bromide[22] to epoxide **10** at 0°C resulted in adduct **18** as a single isomer in 65% yield. Gratifyingly, as in the formation of the [4.4.0]-ring system, we were able to isolate [4.5.0]-bicycle **19** when hydroxy acetal **18** was exposed to PPTS and heat.



Scheme 3

To conclude, we have now developed two highly efficient approaches to fused ether ring systems which share in common a single-flask enol ether epoxidation and C-C bond forming reaction. Future work in this area will focus on the optimization of each of these strategies, further development of the epoxidation/ring opening of C-3 unsubstituted bicyclic enol ethers, and the use of both of our strategies in the synthesis of portions of bioactive fused polyether natural products.

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(20) **Preparation of 1-(3,3-dimethoxypropyl)-3,4,6-O-tribenzyl-D-glucopyranoside, 11.** A mixture of 1-bromo-3,3-dimethoxypropane (0.75 mL, 5.5 mmol), magnesium turnings (0.27 g, 11 mmol) and THF (1.5 mL) was maintained at 24 °C for 1.75 hr by periodic cooling . To this was added CuI (0.52 g, 2.8 mmol) and THF (9 mL). The solids were allowed to settle and the supernatant was transferred via cannula to a solution of epoxide **10**[11] (0.55 mmol) and THF (12 mL) at -30 °C. After 15 min the reaction was quenched with NH_4Cl (sat. 22 mL), extracted with ether (3 X 20 mL), washed with brine (2 X 50 mL), dried (Na_2SO_4), and concentrated. Flash chromotography (2:1 hexanes/ethyl acetate) afforded 0.19 g (63%) of alcohol **11** as a colorless oil.$[\alpha]^{24}_D$= +28.17° (c=1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) ∂ 7.32-7.24 (m, 13 H, PhH), 7.18-7.15 (m, 2 H, PhH), 4.92 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.77 (d, *J* = 10.6 Hz, 1 H, OCH_2Ph), 4.72 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.60 (d, *J* = 12.2Hz, 1 H, OCH_2Ph), 4.56 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.50 (d, *J* = 12.3 Hz, 1 H, OCH_2Ph), 4.37 (t, *J* = 5.4 Hz, 1 H, $CH(OCH_3)_2$), 3.67 (d, *J* =2.9 Hz, 2 H, CH_2OBn), 3.60 (dd, *J* = 9.2, 9.2 Hz, 1 H, CHO), 3.44 (dd, *J* = 8.8, 8.8 Hz, 1 H, CHO), 3.37 (ddd, *J* = 9.7, 2.9, 2.9 Hz, 1 H, CHO), 3.32-3.23 (obs. m, 1 H, CHO), 3.26 (s, 6 H, OCH_3), 3.17-3.10 (m, 1 H, CHO), 2.42 (d, *J* = 3.0 Hz, 1 H, OH), 1.92-1.43 (m, 4H, CH_2CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) ∂ 138.6, 138.1, 138.0, 128.6, 128.3, 128.2, 127.8, 127.7, 127.5, 104.4, 86.8, 79.0, 78.4, 75.1, 74.7, 73.9, 73.4, 68.9, 52.6, 52.5, 28.1, 26.7; IR (CCl_4) 3500, 1449, 1091 cm^{-1}; MS (FAB^+) 535 ($M-H^+$), 505, 91; HRMS calcd for $C_{32}H_{39}O_7$ ($M-H^+$) 535.2696, found 535.2678.

(21) **Preparation of (4S, 5R, 6S, 7S, 8R)-1,2-anhydro-6,7,9-tribenzyloxypyrano-[4,5]-pyran, 14.**[13] To a solution of alcohol **11** (17.5 mg, 0.033 mmol) and chlorobenzene (0.9 mL) at 0 °C was added PPTS (50 mg, 0.20 mmol). The resulting solution was heated to 60 °C until all of the starting material had been consumed. After cooling, pyridine (6.8 µL, 0.085 mmol) was added and the resulting mixture was heated to 135 °C for 4h. The reaction was quenched with NaOH (1M, 2 mL), extracted with ether (3 X 3 mL), washed with brine (2 X 15 mL), dried (Na_2SO_4), and concentrated. Flash chromotography (10:1 hexanes/ethyl acetate) afforded 14.0 mg (91%) of the bicyclic skeleton **14**[13] as a colorless oil.

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