Synthetic Methods

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Synthesis of Macroheterocycles through Intramolecular Oxidative Coupling of Furanoid β-Ketoesters**

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Furanocembranoids are an intriguing class of marine diterpenoids characterized by a C_{14} cembrane skeleton with an embedded furan heterocycle.[1] Derived from these structures are various more advanced secondary metabolites arising through biooxidation of their furan moieties into more complex cembranoids which often undergo transannular transformations involving carbon–carbon and/or carbon–oxygen bond formations.[1] Bielschowskysin (**1**),[2] verrillin (**2**),[3] and plumarellide (**3**)[4] are three such molecules (Figure 1 a). Their origins can be traced back to *exo*-enol ether/cyclic hemiacetal precursors **4**, **5**, and **6**, respectively, as shown in Figure 1 a. Methods for the synthesis of the latter precursors are, therefore, crucial to testing such biosynthetic hypotheses and to synthetic strategies toward these natural products. In addition to the cytotoxic and antimalarial properties that many furanocembranoids exhibit,[1a] these macrocyclic *exo*-enol ether/cyclic hemiacetal structural motifs (see **A**, Figure 1 b) may be of interest to chemical biology and medicinal chemistry as novel molecular diversity whose biological properties remain largely unexplored.

As part of a program directed toward the synthesis of complex furanocembranoids, we recently reported[5] a synthesis of a bielschowskysin model system that featured an intermolecular oxidative coupling[6,7] of a furan and a β-ketoester as a means to form the *exo*-enol ether/cyclic acetal functionality.[8] Herein we describe the intramolecular version of this reaction which can be fine-tuned to provide either the monomeric or dimeric macrocyclic systems. A salient feature of this novel macrocyclization is its tolerance for various functional groups and structural motifs, including certain nitrogen and oxygen heterocycles.

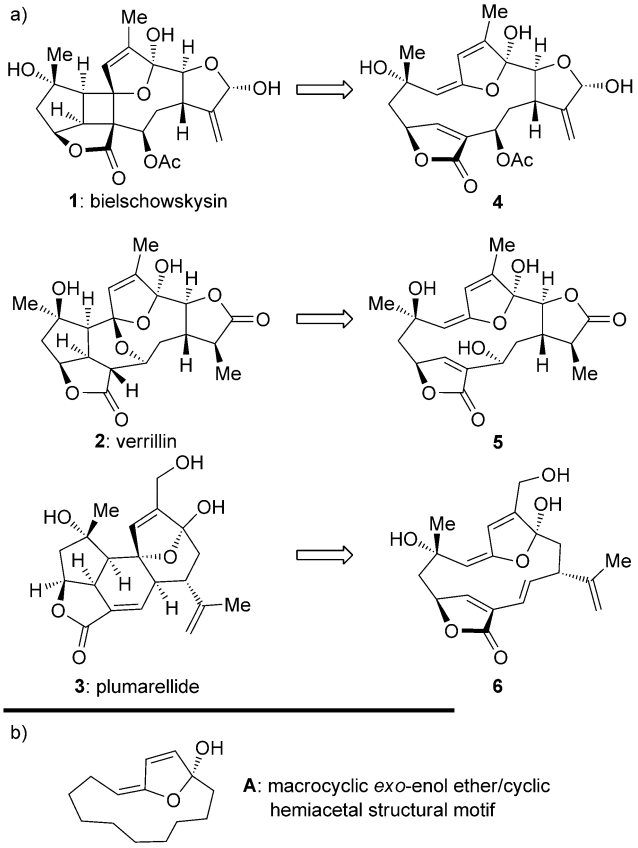

Figure 1. a) *exo*-Enol ether/cyclic acetal derived furanocembranoids (**1**, **2**, and **3**) and their hypothetical biosynthetic precursors (**4**, **5**, and **6**) and b) *exo*-enol ether/cyclic hemiacetal structural motif (**A**).

Scheme 1 summarizes the mechanistic rationale[5a,7] for the designed ring closure of furan β-ketoester substrates (**I**) to the desired macrocyclic *exo*-enol ether/cyclic acetals (**VIII**) through postulated intermediate species **II**–**VII**, in the presence of cerium ammonium nitrate (CAN) as an oxidant and methanol as a nucleophile.

Table 1 shows our investigations to optimize conditions for the formation of the desired macrocyclic *exo*-enol ether/cyclic acetal system **8** from the corresponding substrate, furan β-ketoester **7**. Under the initially employed conditions of adding a slight excess of oxidant (i.e. CAN) to a solution of substrate **7** in methanol (0.05 M, entry 1) at 0 °C, it was striking to observe the formation of the dimeric 22-membered macrocyclic product **9** in 45 % yield (ca. 1:1 diastereomeric ratio) as the only isolated product. Carrying out the reaction under high dilution conditions (i.e. 0.001 M, entry 5) led to the isolation of the desired monomer **8** in 25 % yield as a single

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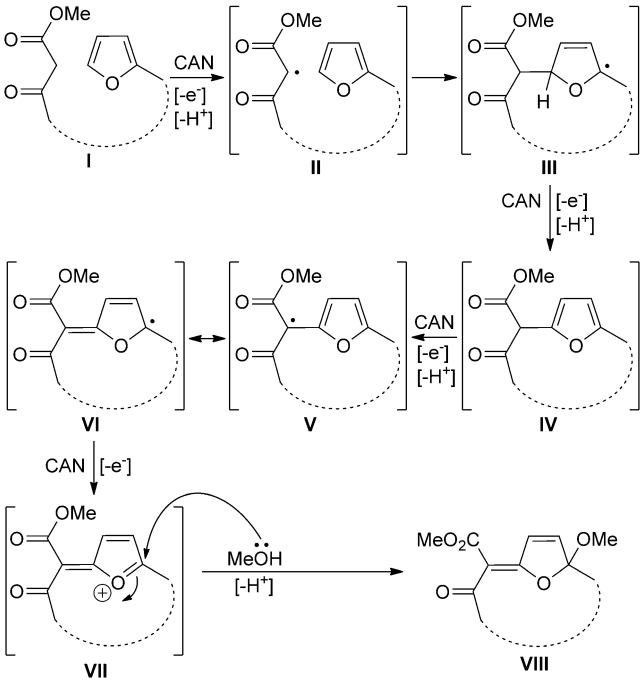
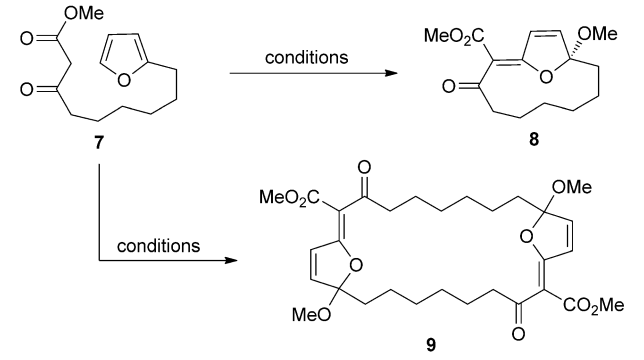


Scheme 1. Mechanistic rationale for the oxidative macrocyclization of furan β-ketoester **I** to macrocycle **VIII**.

Table 1: Screening of conditions.[a]



Entry	Oxidant	Conc.	Temperature	Time	Yield [%]
1	$Ce(NO_3)_6(NH_4)_2$	0.05 M	0 °C	15 min	45 (**9**)[b]
2	$Ce(NO_3)_6(NH_4)_2$	0.05 M	−78–0 °C	60 min	42 (**9**)[b]
3	$Ce(SO_4)_2{\cdot}8H_2O$	0.05 M	0 °C	30 min	11 (**9**)[b]
4	$Ce(NH_4)_4(SO_4)_4$	0.05 M	0 °C	15 min	12 (**9**)[b]
5[d]	$Ce(NO_3)_6(NH_4)_2$	0.001 M	0 °C	60 min	25 (**8**)[c]
6[e]	$Ce(NO_3)_6(NH_4)_2$	0.025 M	0 °C	90 min	55 (**8**)[c]
7	$Ce(OTf)_4$	0.05 M	0–25 °C	18 h	n.d.[f]
8	$Mn(OAc)_3$	0.05 M	0–60 °C	48 h	n.d.[f]
9	$Mn(OAc)_3/Cu(OTf)_2$	0.05 M	0–60 °C	18 h	n.d.[f]
10	$(Cp_2Fe)PF_6$	0.05 M	0–25 °C	18 h	n.d.[f]
11	$Co(OAc)_2$	0.05 M	0–60 °C	18 h	n.r.[g]

[a] Reactions were performed on ca. 50 mg scale. [b] Yield refers to spectroscopically pure, ca. 1:1 mixtures of diastereomers. [c] Yield refers to spectroscopically and chromatographically homogenous material. [d] The substrate in methanol (0.01 M) was added into a solution of CAN in methanol (0.001 M). [e] The substrate in methanol (0.05 M) was added by syringe pump over 1.5 h to a solution of the oxidant at 0 °C. [f] Not detected by TLC or crude ^{1}H NMR analysis. [g] No reaction observed.

olefinic isomer. Based on the observation that these reactions were extremely rapid, we reasoned that slow addition of the substrate to a solution of CAN in methanol would achieve even higher dilution conditions, thereby increasing the yield of **8**. We therefore resorted to a syringe pump addition mode of substrate **7** to a methanolic solution of CAN. Indeed, under such extremely high dilution conditions (0.05 M methanolic solution of **7** added to a 0.23 M methanolic solution of CAN, at 0 °C, over 1.5 h) cyclic product **8** was obtained in 55 % yield (entry 6). Several other commercially available cerium(IV) complexes, as well as other known single electron oxidants, failed to surpass CAN as the reagent of choice in terms of efficiency (entries 3, 4, 7–11). It is noteworthy that the manganese(III),[9] iron(III),[10] and cobalt(II)[11] complexes shown in entries 8–11 failed to produce any of the monomeric or dimeric macrocycles.

In order to explore the generality and scope of this macrocyclization reaction, we constructed a range of substrates and subjected them first to the optimized conditions for monomer formation, and then for dimer formation. Table 2 summarizes the results of these investigations leading to a variety of macrocyclic systems containing the *exo*-enol ether furanoid structural motif. Not surprising, but of interest,

Table 2: Synthesis of monomeric *exo*-enol ether/cyclic acetals.[a]

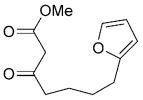
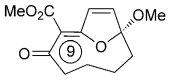
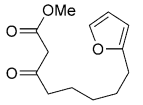
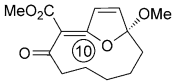
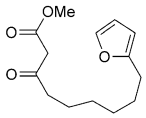
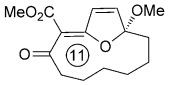
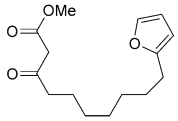
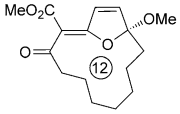
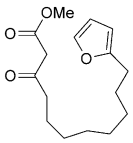
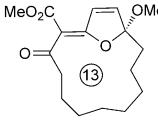
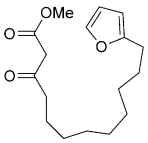
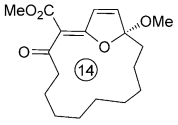
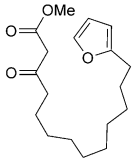
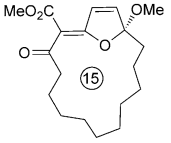
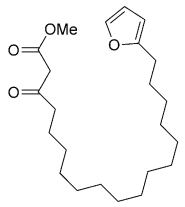
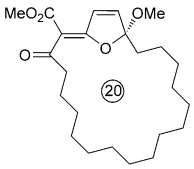
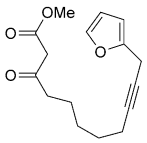
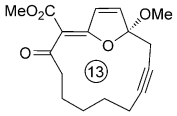
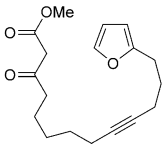
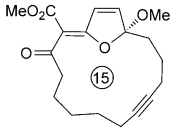
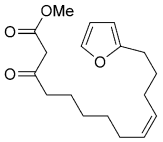
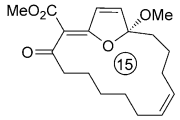
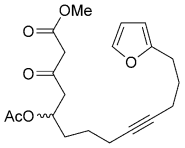
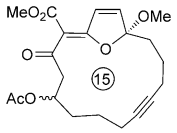
Entry	Substrate		Product		Yield [%][b]
1	**10**		**21**		0
2	**11**		**22**		21
3	**7**		**8**		55
4	**12**		**23**		57
5	**13**		**24**		53
6	**14**		**25**		71
7	**15**		**26**		76

Table 2: (Continued)

Entry		Substrate		Product	Yield [%][b]
8[c]	**16**		**27**		40
9	**17**		**28**		11
10	**18**		**29**		75
11	**19**		**30**		71
12[d]	**20**		**31**		72[e]

[a] Reactions were performed on ca. 50 mg scale as follows: a methanolic solution of the substrate (0.05 M) was added by syringe pump over ca. 1.5 h to a 0 °C methanolic solution of CAN (4.5 equiv, 0.23 M). [b] Yields refer to spectroscopically and chromatographically homogenous material unless otherwise noted. [c] The substrate was added as a solution in methanol:CH_2Cl_2 5:3 (for solubility purposes). [d] Reaction was performed on 35 mg of substrate. [e] Yield refers to a spectroscopically pure ca. 3:2 mixture of diastereomers.

was the failure of substrate **10** to furnish any of the corresponding 9-membered ring monomer (i.e. **21**, entry 1) under the high dilution conditions, undoubtedly due to the severe strain and transannular interactions associated with this medium-sized ring. Other medium-sized rings (10- to 13-membered) notable for their intransigence to be formed (i.e. **8**, **22**–**24**, entries 2–5) were generated, however, in low to respectable yields as shown in Table 2. Gratifyingly, compound **8** yielded crystals suitable for X-ray crystallographic analysis [m.p. = 93–95 °C ($CHCl_3$), see ORTEP, Figure 2], thus confirming its connectivity as well as its *E* enol ether configuration.[12] Larger rings (i.e. 14- and 15-membered) were formed in higher yields, as we expected (compounds **25** and **26**, 71 % and 76 %, respectively, entries 6 and 7). The introduction of an acetylenic bond in the aliphatic tether of the precursor leading to the 13-membered ring (i.e. **24**, 53 % yield, entry 5) had a detrimental effect on the cyclization yield, leading to product **28** (11 %, entry 9), presumably due to the strain associated with the acetylenic linkage and/or oxidation of the methylene between the furan and acetylene

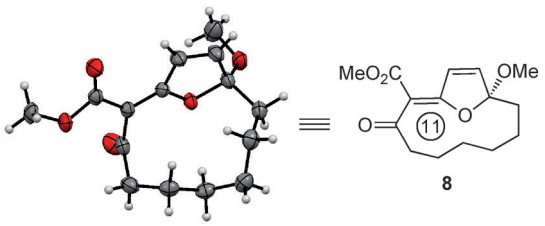
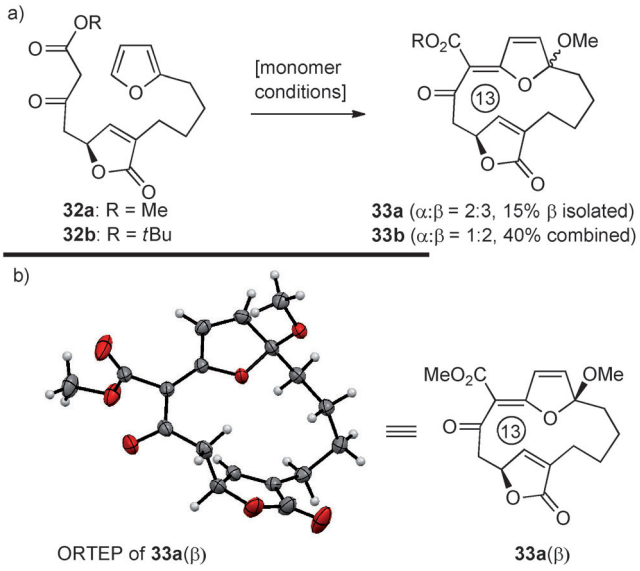


Figure 2. X-ray derived ORTEP of *exo*-enol ether **8**. Thermal ellipsoids at 30 % probability.

moieties. However, the acetylene functionality had no significant effect on the cyclization leading to the 15-membered macrocycle **29** (75 % yield, entry 10) as compared to the saturated chain counterpart (i.e. **26**, 76 % yield, entry 7). Similarly, the introduction of a *cis* olefinic bond within the aliphatic linker as shown in substrate **19** (entry 11) had little effect on the efficiency of the ring closure (71 % yield of **30** vs. 76 % yield of **26**, entry 7). Additional oxygenation in the backbone was also tolerated, as evidenced by the formation of acetoxy macrocycle **31** (72 % yield, entry 12).[13]

Encouraged by these results, we proceeded to examine the tolerance of heterocycles within our substrates to the reaction conditions. Scheme 2 shows the results of macrocyclization of butenolide-containing substrates **32a** (R = Me) and **32b** (R = *t*Bu). We anticipated that ring closure of these substrates

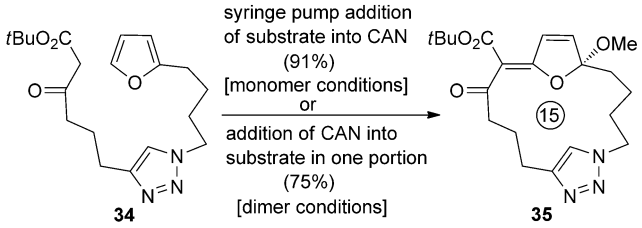


Scheme 2. a) Macrocyclic *exo*-enol ether/cyclic acetal formation of butenolide furan β-ketoesters **32a** and **32b** and b) X-ray derived ORTEP representation of **33a**(β). Thermal ellipsoids at 30 % probability.

might be more challenging than their saturated counterparts (see **13**, Table 2, entry 5), due to an additional ring within the carbon framework. We were pleased to find in a preliminary experiment that ring closure of **32a** occurred, furnishing product **33a** as a ca. 2:3 mixture of α- and β-methoxy isomers, of which the major β-isomer [**33a**(β)] was isolated in 15 % yield. The latter compound crystallized from chloroform in

suitable crystals for X-ray crystallographic analysis (m.p. = 188–190 °C, see ORTEP, Scheme 2b),[12] which allowed the relative configuration of the newly generated stereocenter to be assigned as shown in **33a**(β).[14] Switching the ester from methyl to *tert*-butyl in the substrate (**32b**) led to an increased overall yield of the product (**33b**, 40 %, ca. 1:2 α:β, chromatographically separated, Scheme 2a).

Scheme 3 shows the results of the ring closure of triazole-containing substrate **34** under both the high and low dilution conditions. Impressively, the high dilution conditions (syringe pump addition of substrate into CAN) led to the expected 15-membered macrocyclic system **35** in 91 % yield. More strikingly, the high concentration conditions also led to the



Scheme 3. Monomer formation of triazole substrate **34** under both monomer and dimer conditions.

monomeric macrocycle **35** (75 % yield) with no dimer being detected. Apparently, the overwhelming rigidification effect of the triazole ring on the backbone of precursor **34** renders rapid and exclusive ring closure to afford 15-membered ring macrocycle **35** in preference to intermolecular coupling. The latter compound (i.e. **35**) crystallized from Et_2O:CH_2Cl_2 (10:1, m.p. = 142–144 °C) and was subjected to X-ray crystallographic analysis (see ORTEP, supporting information), thereby confirming its connectivity, enol ether configuration, and triazole-ring integrity under the reaction conditions.[12]

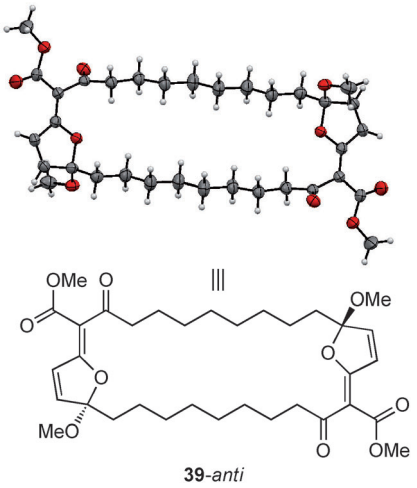
Having recognized the propensity of this reaction to form dimeric macrocyclic structures under certain conditions (i.e. **7**→**9**, Table 1, entry 1), we opted to explore the generality of the dimerization process as a means to produce new molecular diversity. As seen from Table 3, substrates **7** and **10**–**16** reacted with CAN under high concentration conditions at 0 °C to afford dimeric macrocycles **9** and **36**–**42** (sizes 18-, 20-, 22-, 24-, 26-, 28-, 30-, and 40-membered) in yields ranging from 23–45 %. Products **9** and **36**–**42** were obtained as ca. 1:1 diastereomeric mixtures.[13] Gratifyingly, 26-membered macrocyclic dimer **39** crystallized from chloroform (m.p. = 130–132 °C), yielding crystals suitable for X-ray crystallographic analysis (see ORTEP, Figure 3) that reveal its *anti* arrangement and *E* configuration of the two enol ether olefinic bonds.[12]

In conclusion, a new cyclization method was developed that renders macrocycles equipped with the *exo*-enol ether/cyclic acetal structural motif, and their dimeric counterparts, readily available from simple furanoid β-ketoester substrates. The range of products obtained through this novel cyclization include heterocycles that are relevant to biosynthetic hypotheses and total synthesis strategies for the cembranoid family

Table 3: Synthesis of dimeric *exo*-enol ether/cyclic acetals.[a]

Entry	Substrate	Product	Yield [%][b]
1	**10**	**36**	31
2	**11**	**37**	45
3	**7**	**9**	45
4	**12**	**38**	37
5	**13**	**39**	42
6	**14**	**40**	25
7[c]	**15**	**41**	26
8[d]	**16**	**42**	23

[a] Reactions were performed on ca. 50 mg scale as follows: CAN (4.5 equiv) was added to a 0 °C methanolic solution of the substrate (0.05 M) in one portion. [b] Yields refer to spectroscopically pure ca. 1:1 mixtures of diastereomers. [c] Reaction was performed on 100 mg of substrate. [d] The substrate was dissolved in methanol:CH_2Cl_2 (5:2) for solubility purposes.



39-*anti*

Figure 3. X-ray derived ORTEP of dimer **39**-*anti*. Thermal ellipsoids at 30% probability.

of natural products as well as chemical biology and medicinal chemistry investigations.

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[12] CCDC 865550 (**8**), 867307 (**33a**(β)), 865549 (**35**), and 865551 (**39**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[13] The configuration of the enol ether moiety of the products of Table 2 was tentatively assigned from their ^{1}H and ^{13}C NMR data (i.e. chemical shifts of the furanoid protons and carbons). These data were consistent with those of compound **8**, whose enol ether configuration was unambiguously assigned from its X-ray crystallographic analysis (see Figure 2). Similar observations and assignments were made for the dimeric products shown in Table 3 (see also Figure 3).
[14] It is worth noting that irradiation of **33a**(β) with UV light resulted in equilibration to a mixture (ca. 1:1, chromatographically separated) of the two olefin isomers of the enol ether moiety.

