Useful Designs in the Synthesis of *Trans*-Fused Polyether Toxins

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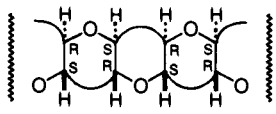
Contents

I. Introduction and General Remarks

Marine dinoflagellates are attracting more and more attention as a source of compounds with unique structures and useful biological activity.[1] Many are polyethers recognized as valuable reagents in biomedical research, e.g. okadaic acid,[2] halichondrins,[3] brevetoxins,[4] or ciguatoxins.[5]

Hemibrevetoxin (**2**),[4f] brevetoxin B (GB-2) (**3**),[4a] and brevetoxin A (GB-1) (**7**)[4d] (Chart 1) are three examples of potent lipid-soluble toxins with a *trans*-fused polyether skeleton (general structure **1**) found in cultured cells of the extremely deleterious organism *Gymnodinium breve* (=*Ptychodiscus brevis*).[4]



1

This toxic dinoflagellate is the causative organism of the red tides along the Gulf coast of Florida, which accompany massive fish kills and human intoxications.[6] Several other toxins isolated from this organism were grouped in the brevetoxin B (**4**–**6**) and brevetoxin A series (**8** and **9**) according to their skeleton type.

After the brevetoxins had proved to have the unprecedented polycyclic ether structure generalized as **1**, more compounds were found with similar skeletons. The main toxins held responsible for ciguatera poisoning,[7] ciguatoxin (**10**),[5d] and its congeners (Chart 2) are closely related to the brevetoxins, at least as far as their ladder-shaped structural organization and toxicity are concerned. Ciguatoxin congeners have been isolated from cultures of the epiphytic dinoflagellate *Gambierdiscus toxicus*,[5] data which suggest that the less oxidized congeners produced by the dinoflagellate are precursors to the more polar toxins isolated from poisoned fish. A phenomenon worth noting is that oxidized metabolites show augmented toxicity, as is the case of ciguatoxin (**10**) itself, which is 11 times more toxic than **11**, its probable precursor.[8]

Virtually all the stereocenters in the brevetoxins and ciguatoxins are contained in vicinally oxygenated carbons which suggests that the stereocontrolled functionalization of a polyolefinic precursor may be involved in their biosynthesis.[9] The *all-trans* cyclic structure **1** can be formed by a cascade of opening of *all-trans* epoxides formed by epoxidation of a *trans* double-bond polyene precursor (Scheme 1). The geometry of the possible transition states for the intramolecular oxirane ring enlargement to give the apparently unfavored[10] *fused* polyether **1** should overcome the energy barriers and the strain necessary to bring the epoxide oxygen into a geometry that allows nucleophilic attack in the appropriate C–O bond direction. Stepwise cyclization via the intermediacy of oxocarbenium ions such as **16** and their behavior when cyclized[11] provided chemical support for the stereochemical outcome of the polyepoxide approach.

The epoxide cascades mentioned above are of interest in view of the present state of knowledge about polyether antibiotic biosynthesis[12] and Townsend's theories[13] concerning oxidative cyclization and polyene stereochemistry. Other polyethers produced by the cultured medium of *G. toxins* (Chart 3), maitotoxin (**19**),[14] a potent Ca^{2+} ion channel activator, and gambieric acids A–D[15,16] [gambieric acid A (**17**) and C (**18**), Chart 3], strong antifungal agents, possess a long chain linked with polycyclic ethers and polyhydroxy moieties. This suggests that

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the carbon chains of the polycyclic ether compounds found in dinoflagellates have a similar biogenetic origin and structural differences may be due to the different modes of epoxide opening.[9c]

II. Biofunctionality

The brevetoxins (BTXs) and ciguatoxin (CTX) are selective activators of voltage-sensitive sodium channels in nerves, heart, and muscle.[17–22] Nerves and heart are more sensitive to the toxins than the latter as is shown by the significantly higher concentration needed to active Na^+ channels present in the sarcolemma of muscle cells.[19,21] The binding of both groups of toxins induces a conformational change in the disposition of the channel which tends to stabilize a multiplicity of different open and/or preopen states of the ion channels.[18,23] In consequence, BTXs and CTX shift the voltage dependence of the activation process in the hyperpolarizing direction, slow down the activation kinetics, and eliminate the inactivation of the Na^+ current, inducing a persistent activation of the channel.[23,24] Prolonged depolarization produces a continuous Ca^{2+} influx and neurotransmitter release[20,22,25,26] and leads finally to blockage of impulse conduction and a failure in transmitter release,[19,27–30] actions that can explain the biological effects observed after exposure to the toxins.

Radioligand binding studies carried out with [^{3}H] BTX have shown that other molecules known to act selectively on the Na^+ channel such as tetrodotoxin and saxitoxin (occluders), veratridine, batrachotoxin, α- and β-scorpion venoms (Na^+ channel activators), or the polypeptide toxins from sea anemone (Na^+ channel stabilizers) do not displace [^{3}H] BTX from its specific binding site.[23,24,31]

Conversely, CTX competitively inhibits the binding of [^{3}H] BTX and binds even more strongly to the same site.[32] This suggests that BTXs and CTX act at a site, called site 5, distinct from the four other known toxin

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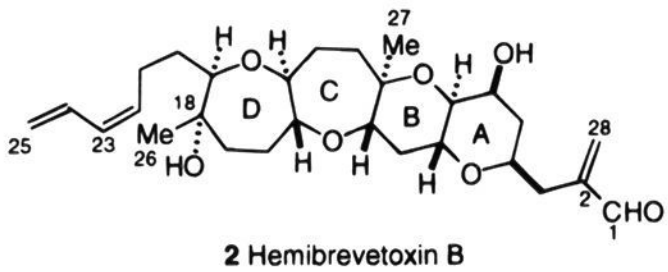
binding sites of the Na^+ channel. Voltage-gated Na^+ channels are heteromeric proteins consisting of α and β subunits and the specific site of BTX and CTX interaction is always located in the α-subunit.[33,34] Further studies intended to identify the peptides labeled by [^{3}H] BTX suggest that the transmembrane segments IS6 and IVS5 in the α subunit are important components of the receptor site recognized by BTXs (Figure 1).[34]

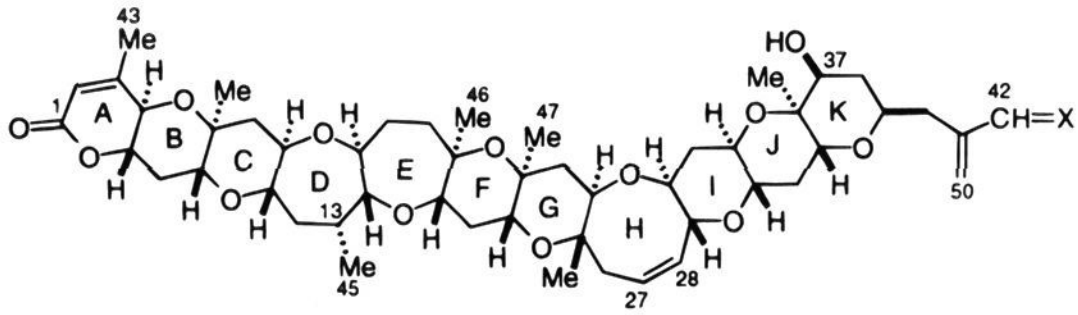
An attempt to increase understanding of receptor–ligand interactions involved conformational analysis of BTX-2[35,38] and BTX-1[36] backbones, followed by comparison of the theoretical conformations of both toxins and led to the conclusion that the most stable conformation is a roughly cigar-shaped molecule, approximately 30 Å long, which binds to the receptor by both the "head" (i.e., the lactone ring) and the "tail" (the aldehydic aliphatic chain) with the lactone carbonyl also playing an important role in the *ligand–receptor interaction*.[36,38]

Toxicological studies showed an increase in lethal potency against mice in the sequence hemibrevetoxin B ≪ BTX-2 ≪ BTX-1 ≪ CTX, indicating that the toxicity of these molecules is associated with two main structural factors: (i) the molecular size of the polyether[36,37] and (ii) its conformational flexibility.[35,38] The first of these factors accounts for the low toxicity of hemibrevetoxin B (**2**) and the second, for the lower activity of BTX-2 (**3**) which, compared with BTX-1 (**7**) and CTX (**10**), has a more rigid conformation mainly imposed by the longer *trans*-fused sequence of oxane rings (Figure 2). Both **10** and **7** have flexible conformations associated with the oxepane, oxocane, and oxonane rings in the middle of the molecules (hinge parts), which bring about slow conformational changes. These conformational changes may be responsible for the alteration of the gating mechanism (or the inactivation mechanism) of the voltage-sensitive sodium channel. A further important de-

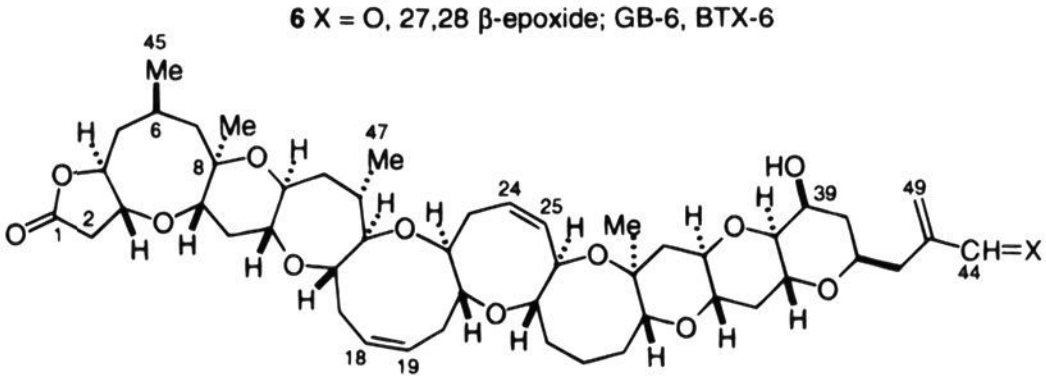
Chart 1



2 Hemibrevetoxin B

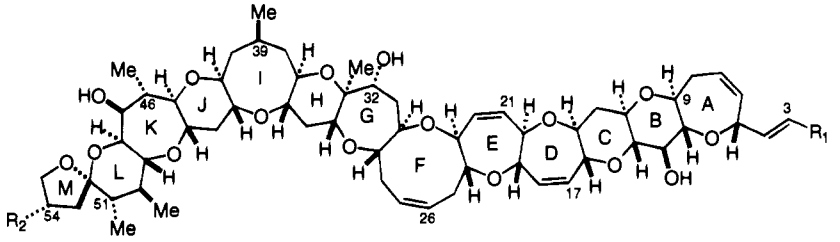


3 X = O; Brevetoxin B; GB-2, BTX-2
4 X = H, OH; GB-3, BTX-3
5 X = O, 37-OAc; GB-5, BTX-5
6 X = O, 27,28 β-epoxide; GB-6, BTX-6

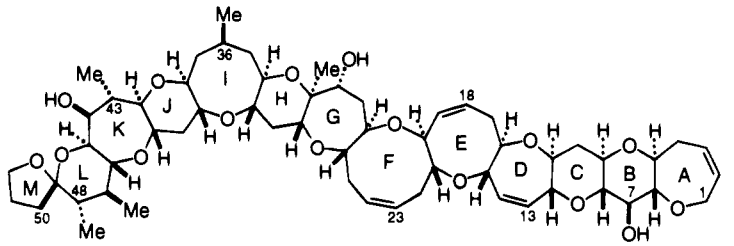


7 X = O; Brevetoxin A; GB-1, BTX-1
8 X = H, OH; GB-7, BTX-7
9 X = $(OCH_3)_2$

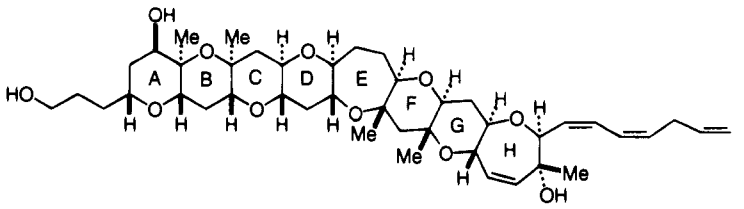
Chart 2



10 Ciguatoxin (CTX) (R_1= -CH(OH)CH_2OH, R_2 = OH)
11 CTX-4B; R_1 = -CH=CH_2, R_2 = H

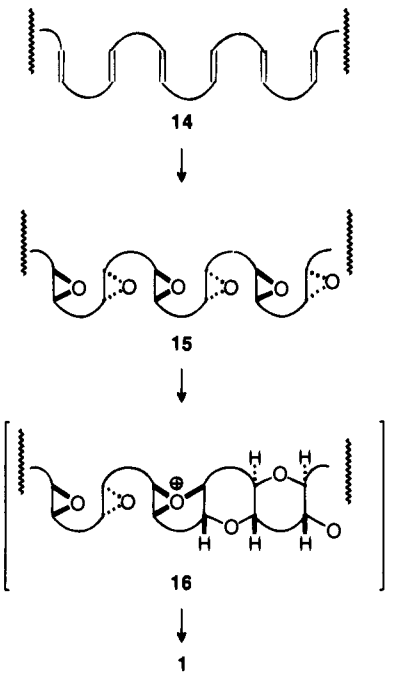


12 CTX-3C



13 Gambierol

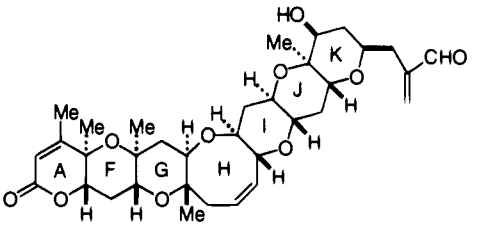
Scheme 1. Proposed Stepwise Cyclization for the Biosynthesis of *Trans*-Fused Polyethers



14
15
16
1

terminant of bioactivity is the hydrophobic nature of the polyether since the most hydrophobic members of the BTXs family (BTX-1 and BTX-7) are also the most potent. If the C-42 aldehyde group in BTX-2 is oxidized to the carboxylic acid function, reducing the hydrophobic nature of the toxin, both potency and affinity for the receptor site are diminished.[38,39]

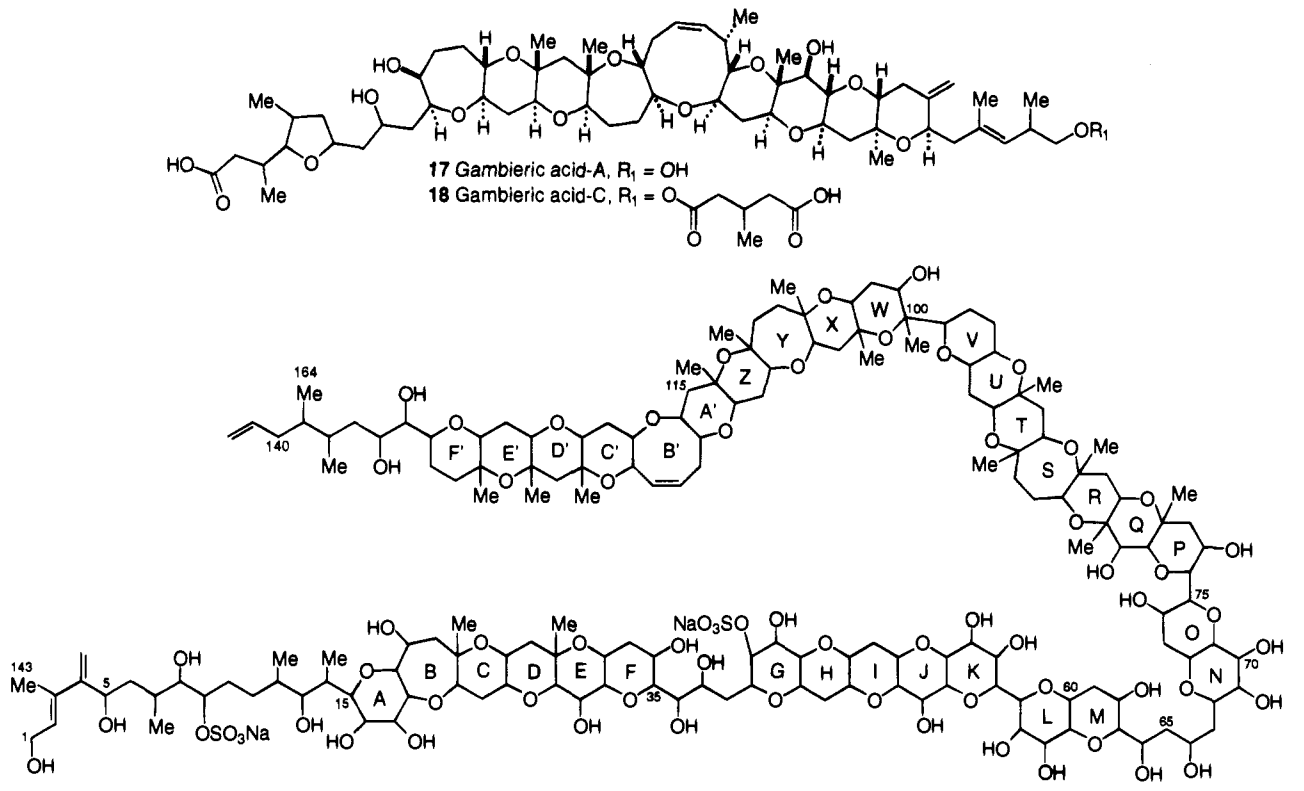
Recently, Nicolaou and co-workers have synthesized truncated brevetoxin B [AFGHIJK] (**20**),[37] in which all the functionality of the natural compound is present, except for the interval rings BCDE. While **20** is conformationally preorganized for binding in the



20 Truncated brevetoxin B [AFGHIJK]

same form as the natural product **3**, biological studies revealed no binding to the brevetoxin B receptor.[37] One likely reason for the absence of biofunctionality in **20**, is that while the parent compound **3** is conformationally flexible with a vast array of distinct low-energy forms around the seven-membered rings D and E, it is evident that the complexity of the conformational networks decreases in the truncated model **20** (Figure 2). This conformational restriction induces a notable change in the gross shape of the molecule which significantly affects its affinity and toxicity and might be responsible for the loss of its binding properties. This study suggests new ways of controlling toxicological/pharmacological properties in *trans*-fused polyethers by structural modifications at a distance from the binding sites.

Chart 3



19 Maitotoxin (Most of the ether rings are *trans*-fused except for rings L/M and N/O which are *cis*-fused).

III. Synthetic Designs

The structural complexity of these molecules and the novelty of their polyether systems make them most attractive from the synthetic point of view. A considerable amount of effort is presently being devoted to the laboratory preparation of simplified models and the total synthesis of these substances. Moreover, as problems in isolating significant quantities of these polyether toxins have limited pharmacological investigation of this class of compounds, the development of efficient strategies for their synthesis will make these interesting molecules available for further testing.

The great number and variety of cyclic ethers that have been synthesized in the last 10 years, even in a form suitable for incorporation into synthetic schemes of fused polyethers, enables some strategic principles, methods, and synthetic procedures to be generalized. The aspects which have most interested synthetic chemist are the isolated medium and large ring ether system in which the *cyclization reaction* is often the key step in the synthesis, and the polycyclic frameworks where the most salient phase of the synthetic sequence is generally that during which the *ether subunit is assembled.* The first group of compounds is currently the subject of intensive research and excellent reviews are appearing.[40] The varied methodologies and the diversity of the already synthesized fused polyether frameworks fully justify the inclusion of these compilations in the bibliography.

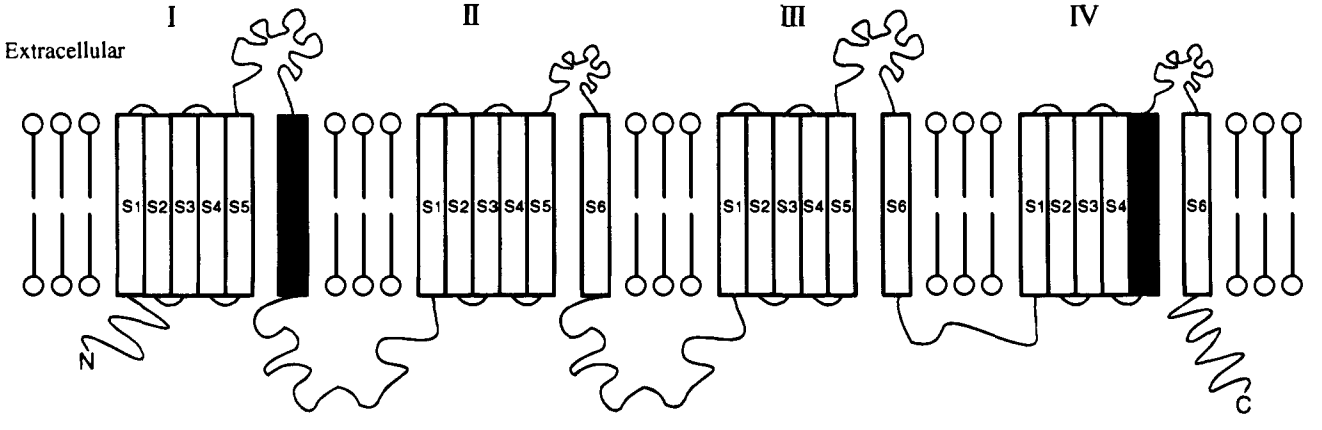


Figure 1. Schematic representation of the Na^+ channel α-subunit. Transmembrane domains IS6 and IVS5 (shown in black) have been identified as specific sites of brevetoxin interaction.[34]

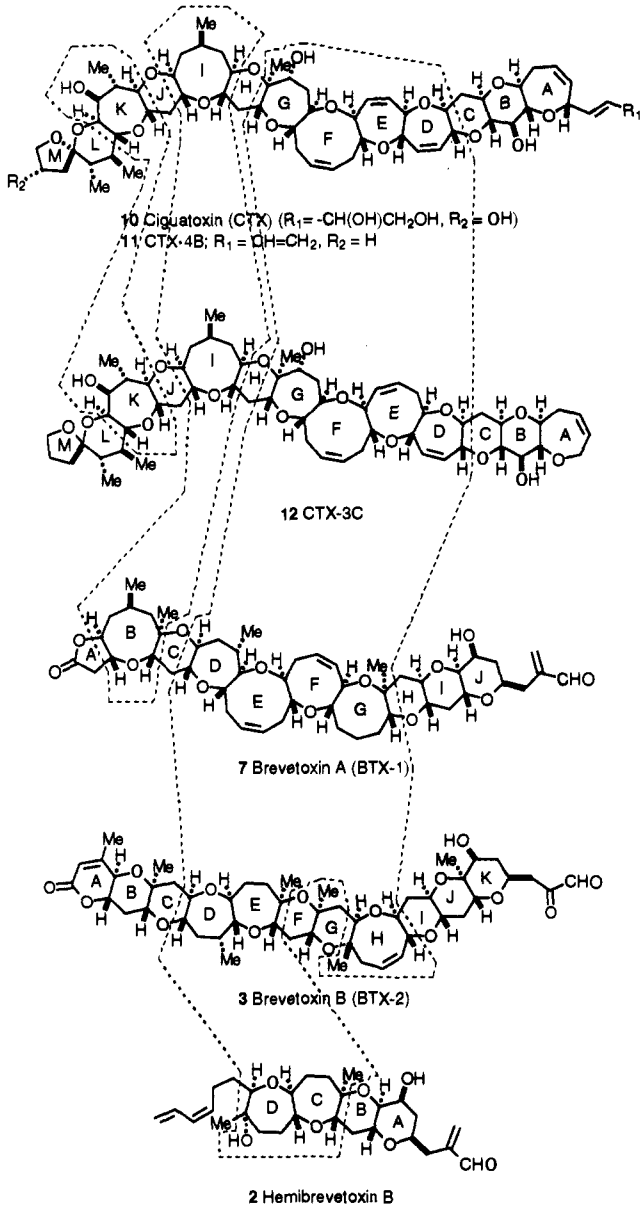


Figure 2. *Trans*-fused polyether compounds with rotatable bonds in the middle of the molecules.

Syntheses are classified in the different sections of this report according to the mode of formation of the strategic bonds. Whenever possible, the strategic principles are grouped under a common heading to allow the reader to compare the different methods used to assemble the same or closely related oxacyclic frameworks during the crucial stages.

Another important strategy for the construction of fused-polyether systems consists of modifying oxacycles already in existence. A number of oxygen heterocyclic compounds are available, and these may represent a convenient starting point for synthesis. In principle, a new oxacyclic system can be created in one or two ways either by a *de novo* synthesis from an acyclic precursor, or by modifying an already existing ring system, e.g. by contraction or expansion. The first route is depicted in Figure 3. It should be noted here that oxacyclic rings can be closed either by forming a C–O bond or by establishing a C–C bond, provided the chain already contains the oxygen atom (Figure 3).

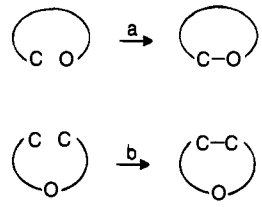


Figure 3.

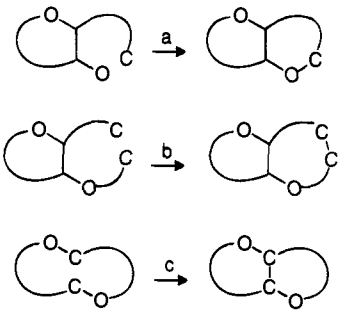


Figure 4.

If the rings of a bicyclic system can be constructed sequentially by pointing another ring to an already existing oxacycle (Figure 4, a or b), another potentially efficient manner would be that shown in c, bisecting a ring by a cross-piece bond to enlarge the number of cycles by one. The former method is used more frequently, although the latter proves advantageous under certain conditions. The synthetic approach to these systems may also involve cyclization at or outside the annulation sites.

This chapter lays down the principles and most important methods for building up the various medium-sized cyclic ethers in a form suitable for incorporation into synthetic schemes of *trans*-fused polyethers (since methods are often applicable to either system). It should be mentioned here that these methods can often be applied not only to monocyclic compounds, but also to fused-condensed polyethers.

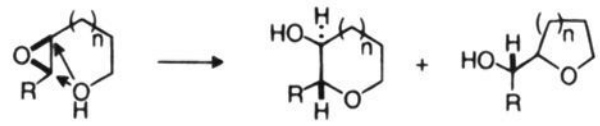
IV. Heterocyclization by Intramolecular C–O Bond-Forming Reactions

Of the two modes of cyclization depicted in Figures 3 and 4, C–O bond formation and C–C bond formation, the former is the more common, requiring intramolecular nucleophilic attack by an oxygen atom on a suitable activated carbon center.

A. Hydroxy–Epoxide Cyclizations

A high degree of stereocontrol can be achieved in the synthesis of substituted tetrahydropyrans by acid-induced simultaneous hydroxy ring closure epoxide opening reactions.[41,42] The cornerstone of this work is the facile construction of *trans*-substituted oxane rings via 6-*endo* activated ring closure of *trans* hydroxy epoxides. The results, summarized in Table 1 (entries 1–3), are readily explained in terms of the authors' original strategy for controlling the mode of cyclization. As is shown in Scheme 2, which describes an acid-assisted cyclization of *trans* hydroxy epoxide **21** (n = 1), an *endo* ring closure would preferentially proceed at the allylic position to pro-

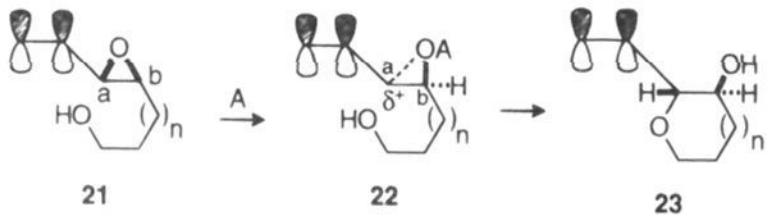
Table 1. Acid-Catalyzed Cyclization of *Trans* Hydroxy Epoxides



24 **25** (endo) **26** (exo)

Entry	Hydroxyepoxides	Conditions	Products (Ratio)	Yield (%)	Ref.
1	**24a (n=1)**; R = (E)CH=CHCO$_2$Me	0.1 equiv. CSA, CH_2Cl_2, -40 to 25 °C	**25a (n=1) : 26a (n=1)** (60:40)	96	42
2	**24b (n=1)**; R = CH=CH$_2$	"	**25b (n=1) : 26b (n=1)** (100:0)	95	42
3	**24c (n=1)**; R = CH=CBr$_2$	"	**25c (n=1) : 26c (n=1)** (100:0)	90	42
4	**24a (n=2)**; R= (E)CH=CHCO$_2$Me	"	**25a (n=2) : 26a (n=2)** (22:78)	75	43
5	**24b (n=2)**; R = CH=CH$_2$	"	**25b (n=2) : 26b (n=2)** (82:18)	75	43
6	**24c (n=2)**; R = (Z)CH=CHCl	"	**25c (n=2) : 26c (n=2)** (60:40)	70	43
7	**24d (n=2)**; R = (E)CH=CHCl	"	**25d (n=2) : 26d (n=2)** (98:2)	75	43

Scheme 2



21 **22** **23**

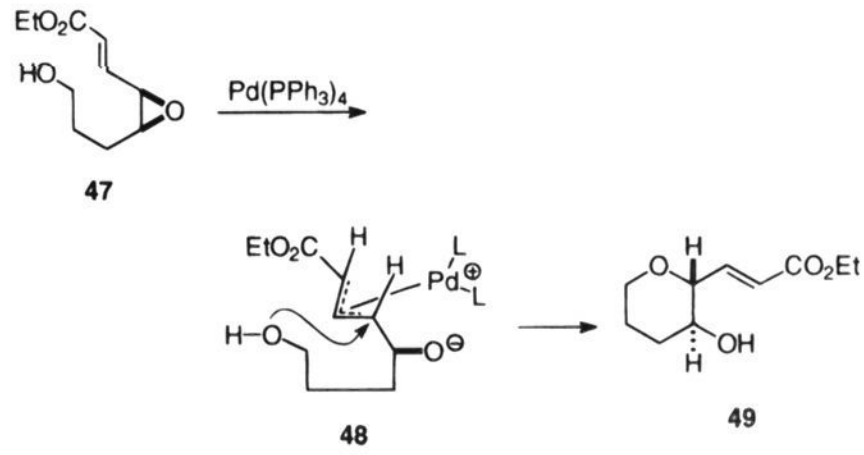
duce the *trans*-substituted oxane **23** ($n = 1$), via transition state **22** ($n = 1$), in which the developing electron-deficient orbital on carbon *a* would be stabilized by electron donation from the adjacent π orbital in a parallel orientation. This fact was successfully exploited by Nicolaou et al.[42,44-47] in synthetic work on the *trans*-fused oxanyl systems of brevetoxin and related compounds (Table 2).

Acid-induced cyclizations of type **21** ($n = 2$) *trans* hydroxy epoxides are set out in Table 1 (entries 4−7).[43] In general, *trans* epoxides of type **21** ($n = 2$) exhibited less selectivity to the *endo* cyclization than their corresponding homologues **21** ($n = 1$). In an attempt to enhance this selectivity, the chloro olefins **24c** ($n = 2$) and **24d** ($n = 2$) were utilized in this reaction (Table 1, entries 6 and 7). Interestingly, the *Z*-chloro olefin **24c** ($n = 2$) exhibited lower selectivity to the oxepane system [**25c** ($n = 2$):**26** ($n = 2$) ca. 60:40], whereas the corresponding *E* isomer **24d** ($n = 2$) gave **25d** ($n = 2$) and **26d** ($n = 2$) in an ca. 92:8 ratio. While the increased selectivity toward the oxepane in the case of **24d** ($n = 2$) was in line with the higher electron density of its alkene π system, the behavior of **24c** ($n = 2$) could be attributed to its inability to attain planarity, due to allylic strains, resulting in lower stabilization of the developing positive charge, and loss of selectivity.

Nicolaou's strategy to control the acid-catalyzed cyclization of hydroxy epoxides in the 6-*endo* mode by activation through the vinyl substituent achieved regio- and stereocontrol for the *trans* epoxides. *Cis* epoxides, however, suffered from 5-*exo* mode cyclization and gave a mixture of the tetrahydropyran and the tetrahydrofuran rings.[41,42] A rational approach using palladium-catalyzed cyclization of hydroxy vinyl epoxides via π-allylpalladium intermediates was developed by Trost[48] and Hirama.[49] As shown in Scheme 3, the *cis* isomer **47** should produce the *trans*-substituted oxepanyl system **49** via **48** if the process proceeds with double stereochemical inversion.[49]

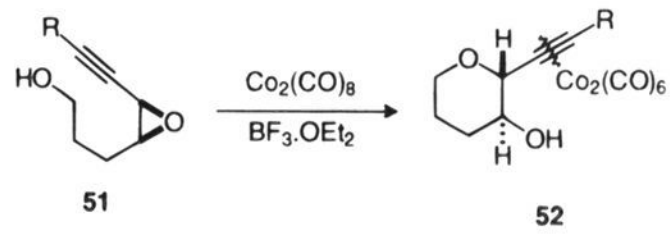
The cyclization results are summarized in Table 3. Surprisingly, these palladium-catalyzed reactions are dramatically affected by the solvent used. With

Scheme 3



47 **48** **49**

Scheme 4



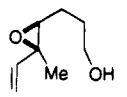
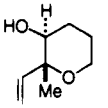
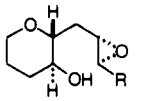
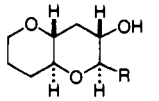
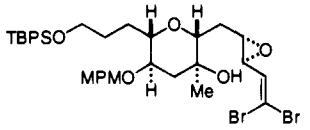
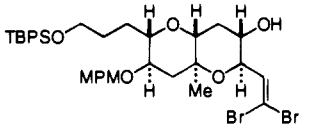
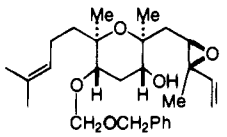
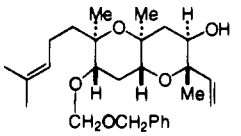
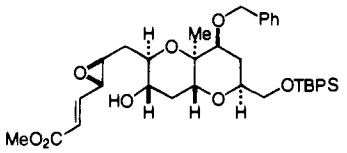
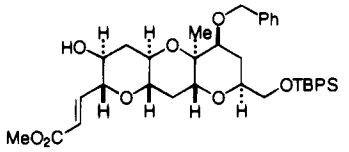
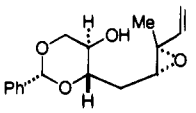
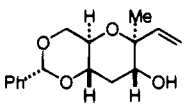
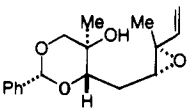
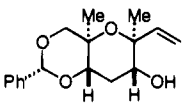
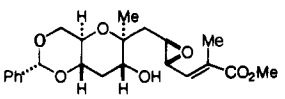
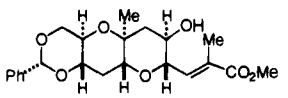
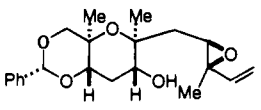
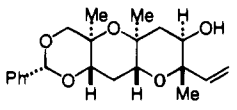
51 **52**

halogenated solvents such as chloroform and dichloromethane (entries 4 and 5), the reactions proceeded rapidly, and gave excellent yields (~90%) as well as full stereoselectivity (~98%). Another successful contribution on the same line as this strategy, giving efficient access to tetrahydropyran derivatives via highly regio- and stereoselective 6-*endo* mode ring opening, was recently reported by Hanaoka and coworkers.[50] When cobalt complexes derived from *cis*-4,5-epoxy-6-heptyn-1-ols (**51**) and dicobalt octacarbonyl were treated with a catalytic amount of $BF_3{\cdot}OEt_2$ in dichloromethane at −78 °C, the reaction occurs exclusively with *configuration retention at the propynyl position* leading to the *trans*-substituted tetrahydropyran system **52** with high selectivity (Scheme 4). Preliminary results are described in Table 4.

A second example of efficient access to *trans*-substituted tetrahydropyrans via highly selective 6-*endo* mode cyclization of epoxy acetylenes has also been reported by Hanaoka[51] (Scheme 5).

If *trans*-acetylenic epoxides **54** with electron-donating groups at the acetylene terminus were treated with a catalytic amount of $BF_3{\cdot}OEt_2$, *trans*-substituted tetrahydropyrans **55** were obtained with high regio- and stereoselectivity (Table 5, entries 3−5). Under similar conditions, *trans*-acetylenic epoxides possessing electron-withdrawing substituents at the acetylene terminus afforded the corresponding tetrahydrofuran derivatives in a highly selective way (Table 5, entry 6). *Inversion of the stereochemistry*

Table 2. Acid-Catalyzed Cyclization of *Trans* Hydroxy Epoxides Leading to *Trans,Syn,Trans*-Substituted Oxanyl Systems

Entry	Substrate	Conditions*	Product	Yield (%)	Ref.
1	 **27**	A	 **28**	96	42
2	 **29**, R = (E)CH=CHCO$_2$Me	A	 **30**, R = (E)CH=CHCO$_2$Me	92	42
3	**31**, R = CH=CH$_2$	A	**32**, R = CH=CH$_2$	100	42
4	 **33**	A	 **34**	83	44
5	 **35**	A	 **36**	85	45
6	 **37**	A	 **38**	70	46
7	 **39**	B	 **40**	86	47
8	 **41**	B	 **42**	94	47
9	 **43**	B	 **44**	84	47
10	 **45**	B	 **46**	92	47

* Method A: 0.1 equiv CSA, CH_2Cl_2, -40 to 25 °C; Method B: 0.8 - 0.9 equiv PPTS, CH_2Cl_2, 0 - 25 °C

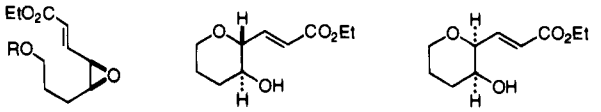
at the *propynyl position* was observed in all cases studied.[51]

Janda, Sevlin, and Lerner recently reported[52] the generation of an antibody which catalyzes the hydroxy–epoxide cyclization of **59** to give **60** (Scheme 6). This catalytic antibody overwhelms the normal preference for five-membered ring formation and causes the six-membered **60** to become the major product. Its energetic advantage has been estimated[53] and must lower the 6-*endo* activation energy by 3.6 kcal/mol more than the 5-*exo* activation energy.

B. Oxirane Ring Enlargement in Epoxycycloalkenes

Reports from our own laboratories[54-67] have described the synthesis of *trans*-fused medium-sized oxacycles by iodine-assisted transannular ring expansion in epoxycycloalkenes **61** followed by silver ion-induced solvolysis to give initially bridged oxacyclic systems type **62** (Scheme 7). Further oxidative cleavage in **62** with simultaneous construction of C–O (**62** → **64**) or C–C (**62** → **66**) bonds would result in the generation of *trans*-fused oxacyclic substruc-

Table 3. Ring Closure by Palladium-Catalyzed Intramolecular Reaction of Hydroxy Vinyl Epoxides

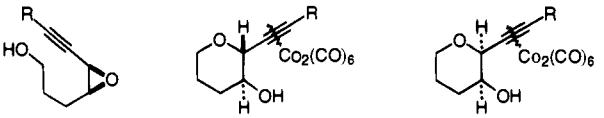


47 49 50

Entry	Substrate	Solvent	Reaction time[c]	Yield (%)[d]	49 : 50 ratio	Ref.
1	**47a** (R = H)[a]	THF	45 min	42	64:36	49
2	**47b** (R = TBPS)	THF	23 h	71	88:12	49
3	**47b** (R = TBPS)	CH_3CN[b]	17.5 h	80	97:3	49
4	**47b** (R = TBPS)	$CHCl_3$[b]	5 min	89	98:2	49
5	**47b** (R = TBPS)	CH_2Cl_2[b]	6 min	86	98:2	49

[a] Directly treated with $Pd(PPh_3)_4$. [b] Desilylation was carried out in THF. After the solvent was removed *in vacuo*, the residue was dissolved in a relevant solvent and treated with $Pd(PPh_3)_4$. [c] Reaction time of palladium catalyzed reaction. [d] Combined yield of **49** and **50**.

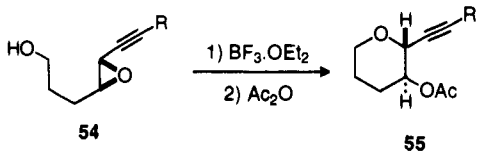
Table 4. Ring Closure of Cobalt-Complexed Acetylenic Epoxides



51 52 53

Entry	Substrate	R	Products (Ratio)	Yield (%)	Ref.
1	**51a**	H	**52a : 53a** (99:1)	92	50
2	**51b**	TMS	**52b : 53b** (100:0)	88	50
3	**51c**	Bu[n]	**52c : 53c** (99:1)	92	50
4	**51d**	C_6H_5	**52d : 53d** (99:1)	93	50
5	**51e**	*p*-CH_3-C_6H_4	**52e : 53e** (97:3)	95	50
6	**51f**	C_6H_5CO	**52f : 53f** (97:3)	89	50

Scheme 5



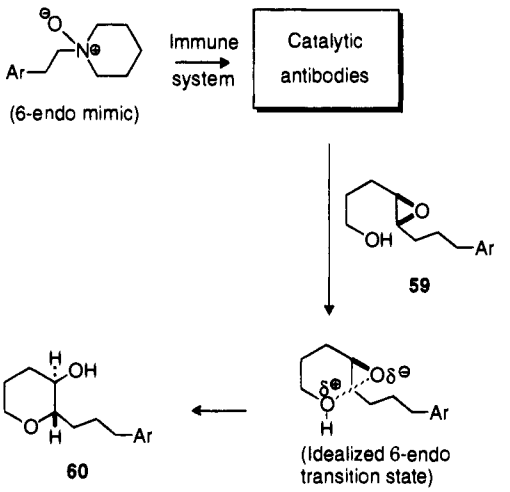
54 55

tures, capable by further chemical modifications of increasing their number of rings by convergent processes through intermolecular couplings, or by one- or two-way linear sequences which would generate external oxacycles in single reactions steps. Table 6 summarizes some of the findings of these studies in connection with the synthesis of *trans,-syn,trans* systems.

C. Hydroxy–Aldehyde (Acetal) Coupling Reactions

An interesting synthesis of oxacycles entails intramolecular acid-assisted hydroxy–aldehyde (acetal) cyclization in the presence of thiophenol to give 2-thiophenyl ethers in excellent yields (<90%).[69] The methodology is equally useful for the synthesis of medium and large rings and has been applied to the

Scheme 6

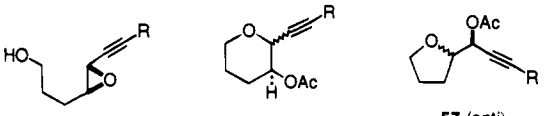


(6-endo mimic) 59 60 (Idealized 6-endo transition state)

synthesis of *trans*-fused polyether frameworks related to the brevetoxins[62-63,69] (Table 7).

Scheme 8 outlines the general concepts that led to the synthesis of *trans,syn,trans*-substituted tetrahy-

Table 5. Ring Closure of Acetylenic Epoxides

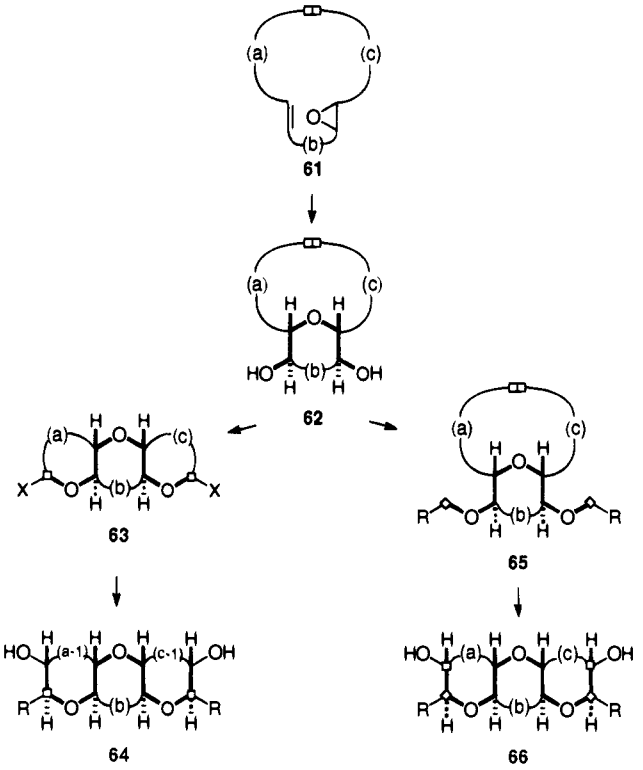


54 55 (*trans*) 56 (*cis*) 57 (anti) 58 (syn)

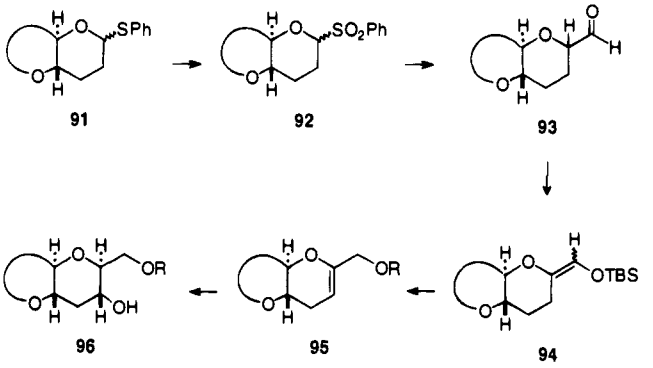
Entry	Substrate	R	6-endo / 5-exo[a]	55 : 56	57 : 58	yield(%)[b]	Ref.
1	**54a**	H	10 / 90	100 : 0	100 : 0	92	51
2	**54b**	TMS	62 / 38	98 : 2	90 : 10	91	51
3	**54c**	Bu[n]	95 / 5	100 : 0	100 : 0	96	51
4	**54d**	C_6H_5	100 / 0	96 : 4	------	94	51
5	**54e**	*p*-CH_3-C_6H_4	100 / 0	83 : 17	------	96	51
6	**54f**	C_6H_5CO	1 / 99	100 : 0	100 : 0	96	51

[a] Ratio of total amount of **55** and **56** to that of **57** and **58**. [b] The specific yields are total yields of **55** - **58**.

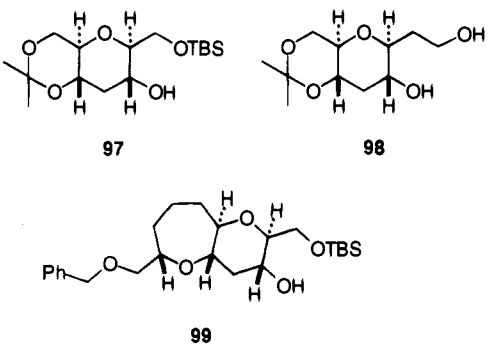
Scheme 7



Scheme 8



dropyranyl system **96** starting from thioether **91**. Oxidation of **91** gave the 2-benzenesulfonyl ether **92** which, by substitution at the anomeric position by masked carbonyl nucleophiles, yielded aldehyde **93**.[70] Dehydrogenation of **93** through the silyl enol ether **94** using $Pd^{II}(OAc)_2$ in acetonitrile[71] gave, after carbonyl reduction, the cyclic hydroxymethyl enol ether **95**, which can easily be hydrated to **96**. Because of the *syn* specificity of the hydroboration reaction, the newly introduced hydroxyl of the pyran ring in the **95** → **96** hydration emerges *trans* to the hydroxymethyl group, making the whole process an especially handy and clean method of preparing substituted tetrahydropyranyl oxacycles with a *trans,syn,trans* stereochemistry. Application of the described technology to the synthesis of the tetrahydropyranyl derivatives **97**–**99** has also been reported.[64]



D. Reductive Hydroxy–Ketone Coupling Reactions

Reductive coupling of hydroxy–ketones in reactions with silane–Lewis acid (SI-LA) to generate

Table 6. Oxirane Ring Enlargement in Epoxycycloalkenes Followed by Carbon–Carbon or Carbon–Oxygen Bond-Forming Cyclizations

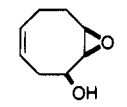
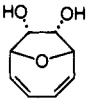
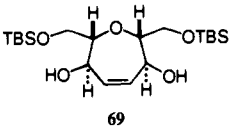
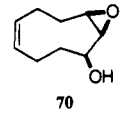
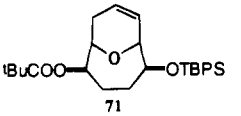
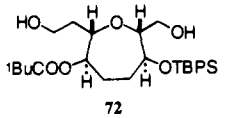
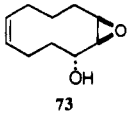
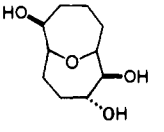
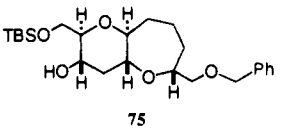
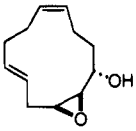
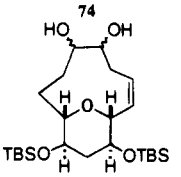
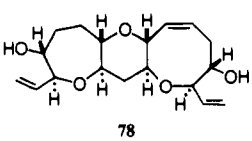
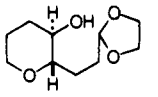
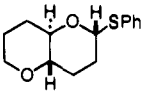
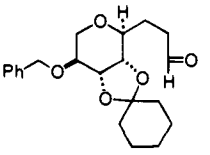
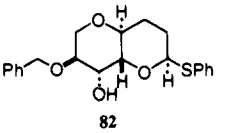
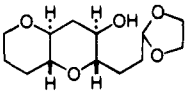
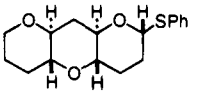
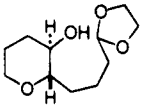
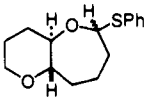
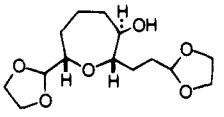
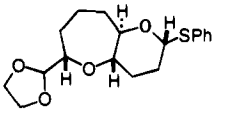
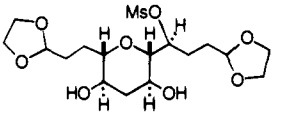
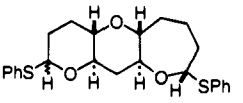
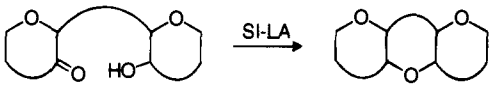
Entry	Epoxycycloalkenes	Bridged Oxabicycle	Fused-Oxacycles	Ref.
1	 67	 68	 69	61
2	 70	 71	 72	68
3	 73	 74	 75	62,64
4	 76	 77	 78	66,67

Table 7. Hydroxy–Aldehyde (Acetal) Coupling Reactions

Entry	Substrate	Conditions	Product	Yield (%)	Ref.
1	 **79**	PhSH (1.5 equiv), CSA (cat.), CH_2Cl_2, 25 °C	 **80**	97	69
2	 **81**	"	 **82**	93	69
3	 **83**	"	 **84**	93	69
4	 **85**	"	 **86**	96	69
5	 **87**	"	 **88**	91	62
6	 **89**	PhSH (2.5 equiv), CSA (cat.), CH_2Cl_2, reflux.	 **90**	96	63

Scheme 9



100 **101**

ethers[72] is a tried and tested methodology in the synthesis of oxacyclic *ortho*-condensed model polyethers[73] (Scheme 9).

Earlier experiments with simple hydroxy ketones such as **105** and **106** (entries 3 and 4, Table 8) suggested that complete *syn* selectivity might be achieved in the more complex systems, since oxepane **108** was obtained in high yield (>80%) with complete diastereomeric purity, upon treatment with triethylsilane and trimethylsilyl triflate.[73] However, in the case of *trans*-fused polyethers of marine origin, the strict *R*/*S* alternation of the stereogenic centers in the carbon skeleton of these substances (see general structure **1**) limits the applicability of this reaction due to the difficulty in directing stereoselectivity toward the required *trans,syn,trans* epimer, at least in the reported cyclization of two-carbon-linked oxacyclic models[73–76] to yield oxepanyl systems (entries 10–15, Table 8). The methodology nonetheless could well be valid in other areas of oxepane natural products synthesis.

E. Hydroxy–Dithioketal Coupling Reactions

A highly efficient cyclization reaction of hydroxy dithioketals leading to oxocene and related systems has been reported by Nicolaou and co-workers.[37,77–79] The Ag^+-induced ring closures occur in high yield under mild conditions and the resulting cyclic systems may be desulfurized via homolytic or heterolytic C–S cleavage leading to a variety of cyclic ethers with defined *trans*-fused stereochemistry and flexible substitution. Table 9 includes products and yields for cyclization and replacement of the sulfur group with a hydrogen (H) (entries 1, 3–5, 8, 10) and methyl groups (Me) (entries 2, 6, 7, 9), with stereochemistry retention. As can be seen from these data, substrates with a *cis* double bond in three-carbon linked oxacycles, led efficiently to oxocene systems with *trans,syn,trans* stereochemistry. Systems of higher rigidity and steric demand, due to the presence of additional rings, cyclized at lower rates,[37,78–79] but in excellent yields (entries 5, 9, 10) making this methodology practical and suitable for a highly convergent approach to natural polyethers.

However, when the double bond is absent, cyclization fails, leading only to the hydrolysis of the dithioketal and isolation of the carbonyl compound as the major product.[78] It thus appears that a *cis* double bond is essential for the success of this reaction, showing that a reduction in the number of rotational degrees of freedom is necessary for cycliza-

Table 8. Reductive Hydroxy–Ketone Coupling Reactions

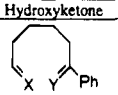
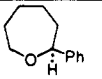
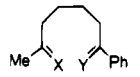
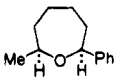
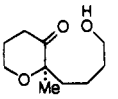
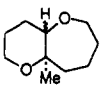
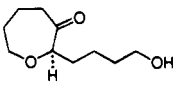
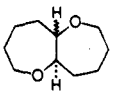
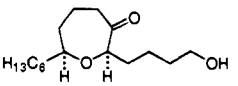
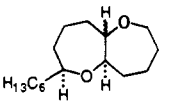
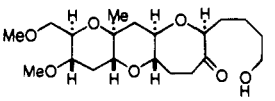
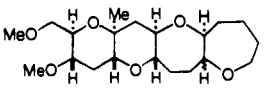
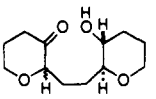
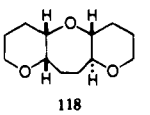
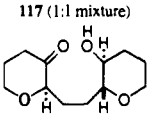
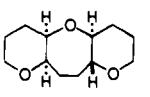
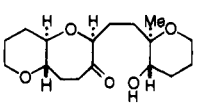
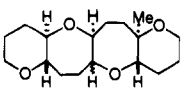
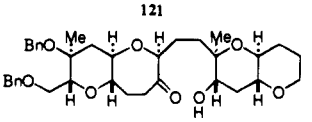
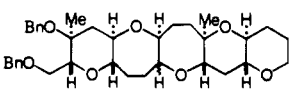
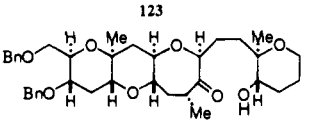
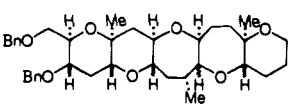
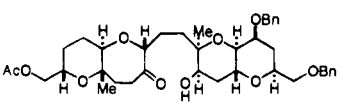
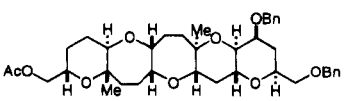
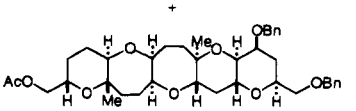
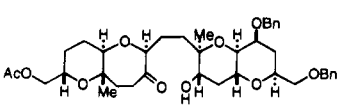
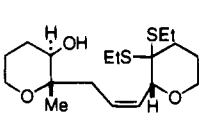
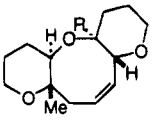
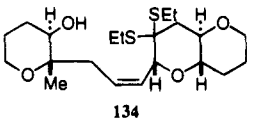
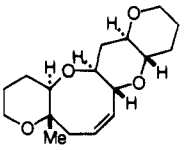
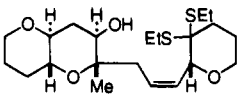
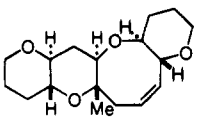
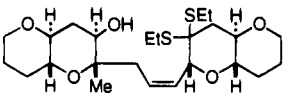
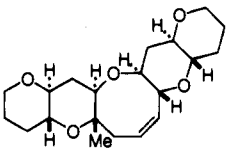
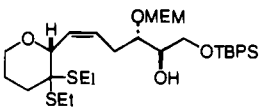
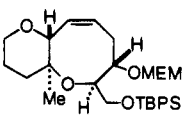
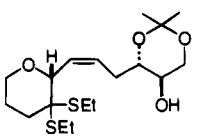
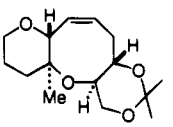
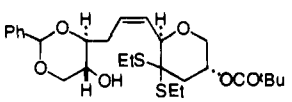
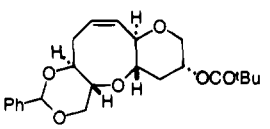
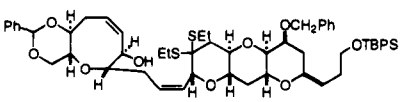
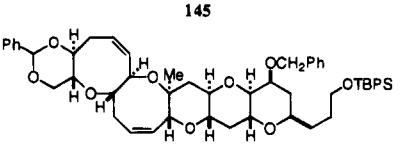
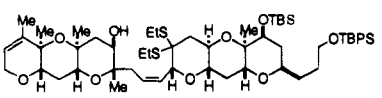
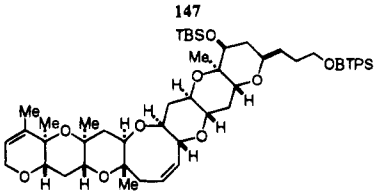
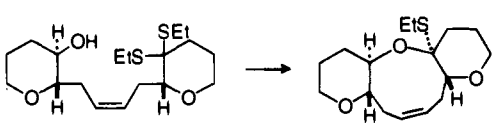
Entry	Hydroxyketone	Oxepane	Yield (%)	Ref.
1	 **102**: X = H, OH; Y = O	 **104**	90	73
2	**103**: X = O; Y = H, OH		79	73
3	 **105**: X = H, OH; Y = O	 **108**	83	73
4	**106**: X = O; Y = H, OH		85	73
5	**107**: X = Y = O		83	73
6	 **109**	 **110** (*trans:cis* ca 1:1 ratio)	50	73
7	 **111**	 **112** (*trans*:cis ca 2:1 ratio)	79	74
8	 **113**	 **114** (*trans: cis* ca 3:1 ratio)	51	74
9	 **115**	 **116** (*trans:cis* ca 3:1 ratio)	75	73
10	 **117** (1:1 mixture)	 **118**	77	75
11	 **119**	 **120**	89	75
12	 **121**	 **122** (*trans:cis* ca 3:1 ratio)	81	73
13	 **123**	 **124** (*trans:cis* ca 3:1 ratio)	55	73
14	 **125**	 **126** (*trans:cis* ca 6:1 ratio)	62	73
15	 **127**	 **128** +  **129** (**128:129** ca 6:1 ratio)	81	76
16	 **130**	---	0	76

Table 9. Hydroxy–Dithioketals Coupling Reactions

Entry	Hydroxythioketal	Cyclized-desulfurized Product	Yield (%)	Ref.
1	 **131**	 **132**: R = H	88	77,78
2		**133**: R = Me	86	77,78
3	 **134**	 **135**	76	78
4	 **136**	 **137**	77	78
5	 **138**	 **139**	83	77,78
6	 **140**	 **141**	55	78
7	 **142**	 **143**	62	78
8	 **144**	 **145**	63	79
9	 **146**	 **147**	82	79
10	 **148**	 **149**	88	37

tion to occur. An interesting cyclization is presented by substrate **150**, a four-carbon linked dioxanyl system which cyclized to the sterically congested oxonene system **151**, albeit in low yield (30%).

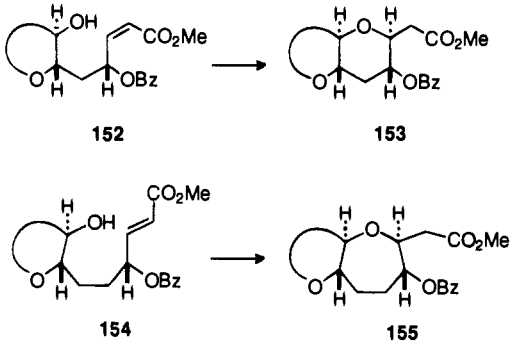


150 **151**

F. Hetero-Michael Cyclizations

Reversibility of the hetero-Michael cyclization was expected to lead to the less sterically encumbered equatorial disposition of the carboalkoxyl appendage.[80] An efficient methodology based on intramolecular hetero-Michael addition of properly functionalized alkoxy-γ-benzoyloxy-α,β-unsaturated esters has been developed by V. S. Martín et al. for the enantioselective construction of *trans*-fused tetrahydropyran and oxepan systems.[81-83] As illustrated in Scheme 10, the cyclization stereochemistry is con-

Scheme 10

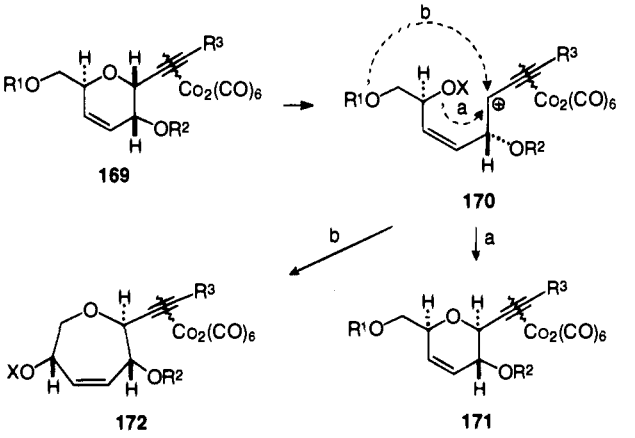


trolled by the geometry of the double bond. Evidence for this is provided by the results in Table 10.

G. Hydroxy–Carbon Electron-Deficient Intermediate Cyclizations

Acid-induced ring-opening cyclizations at the anomeric position in dihydropyrans with C-1 alkynyl groups as dicobalt hexacarbonyl complexes, can be controlled taking advantage of the highly stabilized propargylic carbocation generated as intermediate.[84] Recently, Isobe and co-workers[85,86] reported an approach to enantiomeric synthesis of *syn,trans*-substituted dihydropyran subunits **171** by acid-assisted epimerization of dicobalt hexacarbonyl complexes of **169**, readily prepared from 2,3,4,6-tetracetyl-D-glucal under carbohydrate synthon (Scheme 11). Three

Scheme 11



steps involving complexation, acid transformation and decomplexation afforded overall epimerization.[85,86]

The results are summarized in Table 11 (entries 1–5). Changing the C-6 protecting group to a benzoyl (entry 2) did not greatly affect the ratio while if the C-2 protecting group were changed to an acetyl (entry 3) or TBPS (entries 4 and 5), the ratio dramatically improved, due to greater 1,2 interaction by the α complex as opposed to the β complex, as shown in a Newman projection (Figure 5).

Trapping of the Nicholas[84] intermediate **170** with the acylinium ion gave the corresponding linear

Table 10. Hetero-Michael Cyclizations

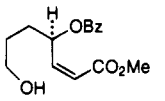
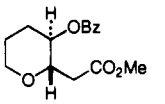
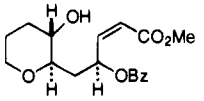
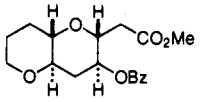
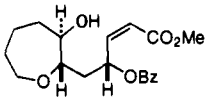
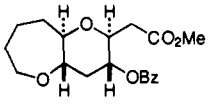
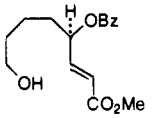
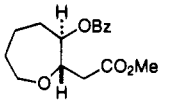
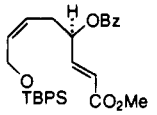
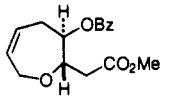
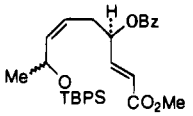
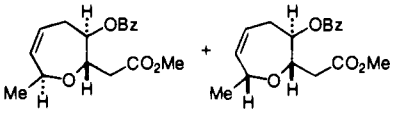
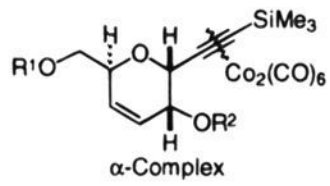
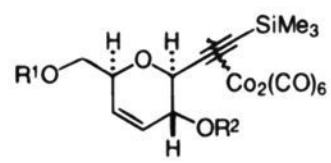
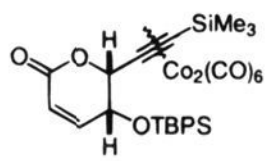
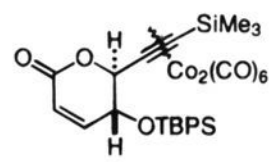
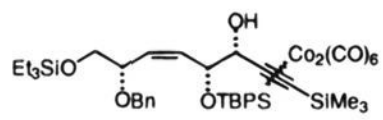
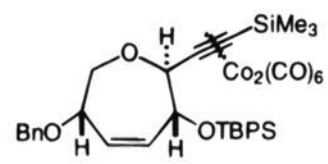
Entry	Substrate	Conditions	Product	Yield (%)	Ref.
1	 **156**	NaH, THF -78 - 0 °C	 **157**	>95	81
2	 **158**	"	 **159**	>90	82
3	 **160**	"	 **161**	91	83
4	 **162**	"	 **163**	12	83
5	 **164**	TBAF, THF	 **165**	75	83
6	 **166**	"	 **167** + **168** (1:1 ratio)	72	83

Table 11. Isomerization of α Complex to β Complex

Entry	Substrate	TfOH (eq)	Product	ratio (α:β)	Yield (%)	Ref.
	 α-Complex		 (β-Complex)			
1	**169a**, R^1 = Ac; R^2 = H	0.3	**171a**	1:10	86	86
2	**169b**, R^1 = Bz; R^2 = H	0.2	**171b**	1:12	95	86
3	**169c**, R^1 = Ac; R^2 = Ac	0.2	**171c**	1:27	94	86
4	**169d**, R^1 = Ac; R^2 = TBPS	0.2	**171d**	1:100	84	86
5	 **173**	0.1	 **174**	1:>100	97	86
6	 **175**	0.2	 **176**	-------	57	87

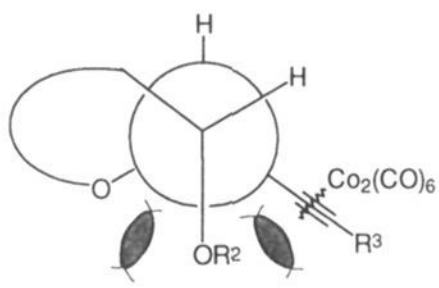


Figure 5.

molecule which, after further recyclization through the primary hydroxy group, afforded a *trans*-substituted dehydrooxepane **172**[87] (Scheme 11), Table 11, entry 6.

A highly efficient, mild, general cyclization reaction of hydroxy *exo*-(propargyl)$Co_2(CO)_6$ cations leading to medium-sized cyclic ethers has been described by Palazón and Martín[88] (Table 12). The reaction is highly stereoselective when defined stereocenters are encountered in the linear precursor, providing a means of obtaining fused cyclic ethers in their enantiomeric forms. As indicated in Table 12, the procedure works smoothly, forming six- to nine-membered rings (entries 1−4) using 1 equiv of acid (HBF_4 or $BF_3{\cdot}OEt_2$). Although the reaction can also be carried out catalytically (entry 1), the best yields were obtained when 1.0 equiv of acid was used.

Another successful contribution in line with this strategy, giving efficient access to six-, seven-, and eight-membered cyclic ethers, is the rhodium carbenoid-mediated cyclization of hydroxy α-diazo β-keto esters.[89−98] The diazo alcohol intermediate **195** readily loses nitrogen upon treatment with catalytic amounts of rhodium(II) salts, usually dirhodium tetraacetate, in dichloromethane or refluxing benzene, and cyclic ethers **196** are formed in good yields (Scheme 12). Although the reaction formally requires an intramolecular insertion into the O−H bond, the mechanism of medium ring ether formation can be regarded as a nucleophilic attack by the hydroxy group on the highly electron-deficient rhodium carbenoid intermediate, generated by Rh(II)-catalyzed loss of nitrogen from the diazo compound.[98] The methodology is particularly useful for oxepane formation and easily tolerates α substitution to the hydroxy group. The functionality of the medium ring ether which is formed offers possibilities for incorporation in synthetic schemes to do with *trans*-fused polyethers.

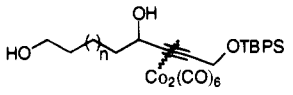
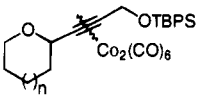
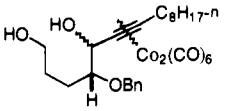
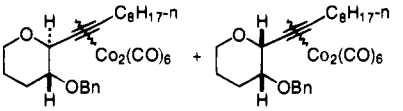
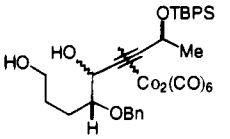
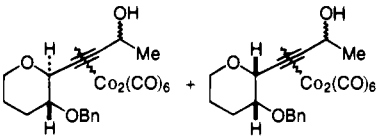
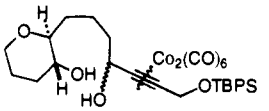
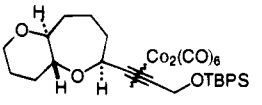
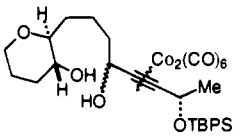
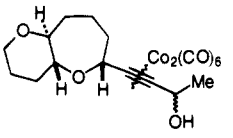
Modifications of the above route constitute a *general method to syn-dialkylated 3-oxooxacycles*.[74] Scheme 13 illustrates the procedure for a seven-membered series. 3-Oxooxepan-2-ylphosphonates **198**, prepared by rhodium carbenoid cyclization of the diazophosphonates **197**, are readily transformed into the keto alcohol **200** by Wadsworth−Emmons reaction, hydrogenation, and epimerization.[74]

In a related sequence,[99] cyclic ethers (ring sizes 6−8) have been prepared in good yield and with high levels of diastereocontrol by intramolecular insertion of allyl ethers into copper carbenoids generated from α-diazo carbonyl compounds such as **201**, and rearrangement of the resulting ylide-type species to give **204** (Scheme 14).

V. Heterocyclization by Intramolecular C–C Bond-Forming Reactions

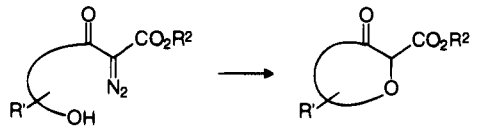
Over the last few years various new synthetic methodologies have been developed for the specific construction of *ortho*-condensed polyether systems by

Table 12. Cyclization of Hydroxy *exo*-(Propargyl)$Co_2(CO)_6$ Cations

Entry	Substrate	Product[a]	Yield[b]	Ref.
				
1	**177**, n = 1	**178**, n = 1	85, 78[c]	88
2	**179**, n = 2	**180**, n = 2	78	88
3	**181**, n = 3	**182**, n = 3	72	88
4	**183**, n = 4	**185**, n = 4	55	88
5	 **185**	 **186** (3 : 1 ratio) **187**	82	88
6	 **188**	 **189** (1 : 3 ratio) **190**	80	88
7	 **191**	 **192**	73	88
8	 **193**	 **194**	71	88

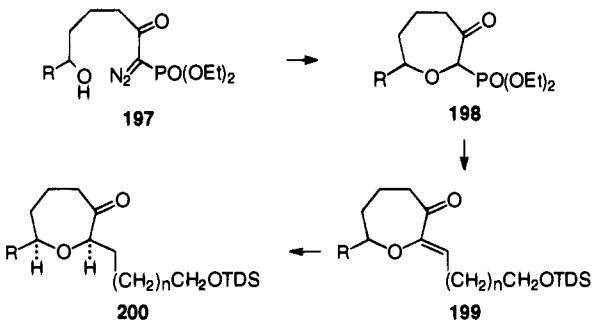
[a] The cyclizations have been performed at -30 °C using 1 equiv of BF_3OEt_2 following the reaction by TLC (1 to 9 h) and quenching the reaction with saturated aqueous $NaHCO_3$ solution; [b] Isolated yields; [c] The reaction has been performed in a catalytic manner (0.1 equiv of HBF_4).

Scheme 12



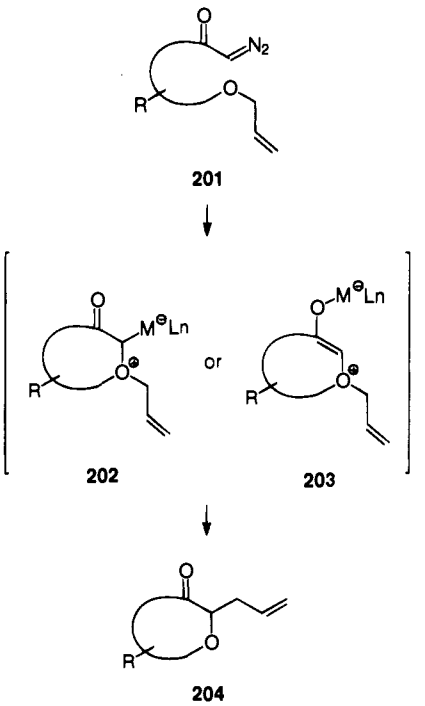
195 **196**

Scheme 13



197 **198** **199** **200**

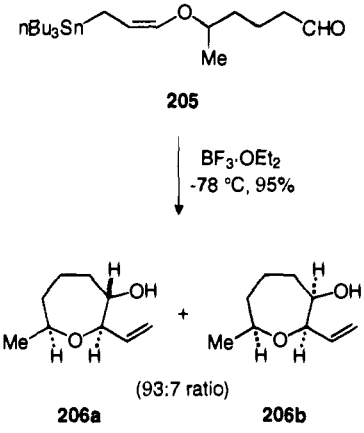
Scheme 14



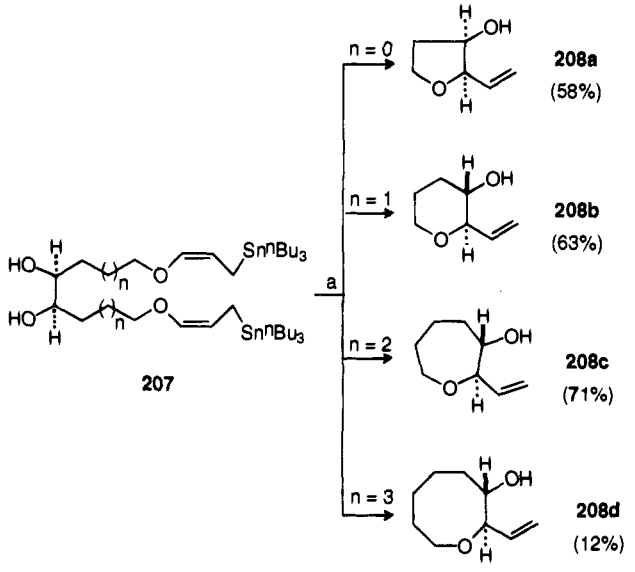
201 **202** **203** **204**

C–C bond-forming reactions. The synthetic approach to these systems may employ cyclization at or outside the annulation sites. As well as *de novo* methods of construction of cyclic systems, it is possible to start from a compound which already contains the basic cyclic skeleton and then enlarge or contract the existing rings. These methods can often be applied not only to *trans*-fused frameworks, but also to monocyclic compounds, as will be shown in the following sections.

Scheme 15



Scheme 16



A. Allylstannane–Aldehyde (Acetal) Cyclizations

Allylstannane–aldehyde condensation is one of the most important synthetic methods for regio- and stereoselective C–C bond forming and its mechanism has been extensively studied during the last decade.[100] The utility of the intramolecular approach of this reaction for making *trans*-substituted oxepanes was illustrated recently by Yamamoto and coworkers.[101] As indicated in Scheme 15, a high level of stereocontrol between the α-vinyl and β-hydroxy groups was attained, making it clear that intramolecular acid-assisted cyclization of the aldehyde–allylic tin system is an efficient way for *de novo* generation of *syn,trans*-fused oxepanyl systems.

A general approach using a similar strategy involves the intramolecular addition of a stable γ-alkoxy-substituted allylstannane to a masked aldehyde carbonyl group[66,67] (Scheme 16).

The entire reaction is conducted in a one-pot process which includes *vic*-diol fragmentation and Lewis acid-induced cyclization of the resulting aldehyde–allylic tin system. The examples shown in Scheme 16 reflect conformational preferences in the S_E' transition state which are a composite of conformational constraints and electronic effects.[102] Although the reason for the observed *cis* stereoselectivity between the α-vinyl and β-hydroxy groups in

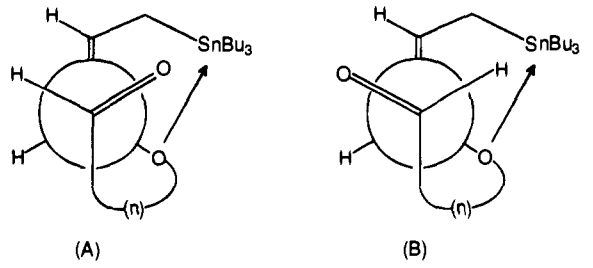
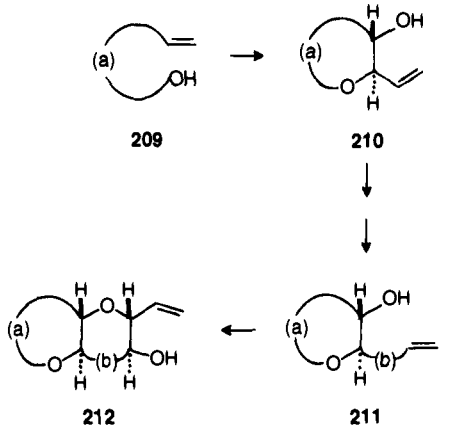


Figure 6.

Scheme 17



oxolane **208a** is not fully understood, the thermodynamically more stable *trans* hydroxy–vinyl arrangement observed in the series **208b–d** indicates a marked preference for the less crowded and more flexible synclincal transition state of type B (Figure 6).[103]

The transition-state structure required for the intramolecular reaction seems then to be fundamentally related to the length of the connecting chain. It has been also reported that acid-induced cyclization of ω-stannyl ether aldehydes to give tetrahydropyranyl systems depend strongly upon the double-bond geometry.[104]

This cyclization was of particular interest in the context of *trans*-fused polyether synthesis as is shown in Scheme 17, since the resulting compound is a latent version of the original material. That is, inspection of the monocyclic compound **210** readily reveals that protection of the free hydroxy group followed by homologation of the vinyl appendage regenerates the initial conditions for continuing with the cyclization process. Table 13 demonstrates the generality and scope of these reactions in the construction of *trans*-fused polycyclic structures. These results demonstrate the viability of utilizing this methodology in a reiterative manner since the required *trans,syn,trans* stereochemistry is generated through the more favorable transition state of type B (Figure 6), independently of the size of the ring (6 or 7) supporting the cyclized appendages. Applications of this technology to substructures of *trans*-fused marine natural toxins have, therefore, considerable potential. As an extension of this methodology in a two-directional way, oxatricyclic systems **234** (Table 13, entry 11) were synthesized from the diallylstannane **233** by a one-pot double carbon–carbon bond-forming strategy.[66,67]

In 1990, Yamamoto's group reported[107] that Lewis acid-mediated cyclization of ω-trialkylstannyl ether

Table 13. Allylstannane–Aldehyde Cyclizations

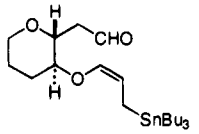
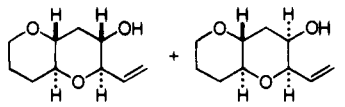
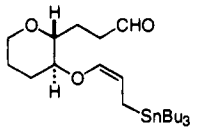
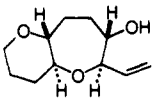
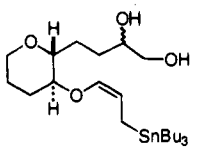
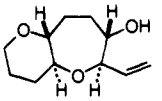
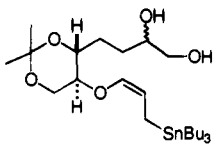
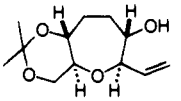
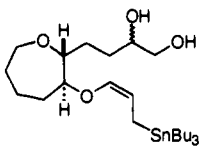
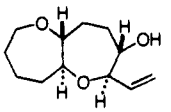
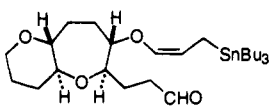
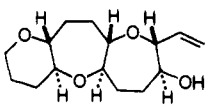
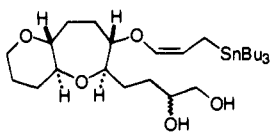
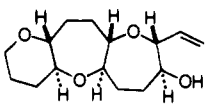
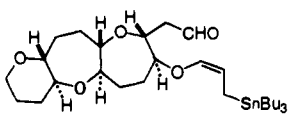
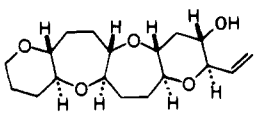
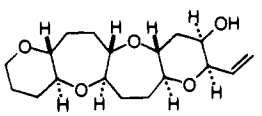
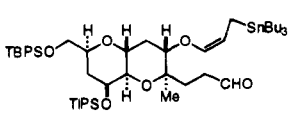
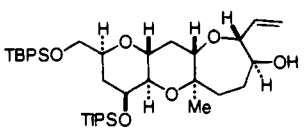
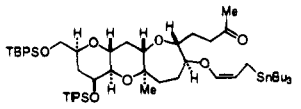
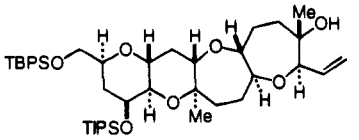
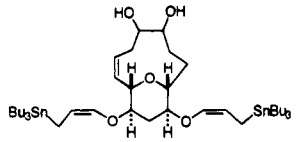
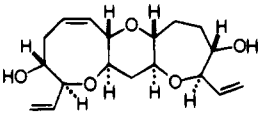
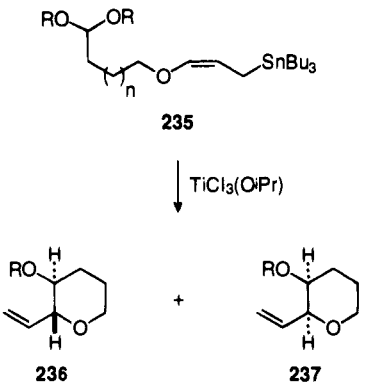
Entry	Allylstannane	Conditions[a]	Products	Yield (%)	Ref.
1	 **213**	A	 (33:67 ratio) **214** **215**	-----	101
2	 **216**	A	 **217**	99	101
3	 **218**	B	 **217**	65	66,67
4	 **219**	B	 **220**	95	105
5	 **221**	B	 **222**	98	67
6	 **223**	A	 **224**	97	101
7	 **225**	B	 **224**	94	105
8	 **226**	A	 **227** +  **228** (ca 1:1 ratio)	83	101
9	 **229**	A	 **230**	95	106

Table 13. (Continued)

Entry	Allylstannane	Conditions*	Products	Yield (%)	Ref.
10	 **231**	C	 **232**	55	106
11	 **233**	B	 **234**	63	66,67

* Method A: $BF_3.OEt_2$, CH_2Cl_2, -78 °C. Method B: nBu_4NIO_4, CH_2Cl_2, 0-25 °C, then add $BF_3.OEt_2$, -78 °C. Method C: $AlCl_3.OEt_2$, CH_2Cl_2, -78 °C.

Scheme 18



acetals **235** gave the desired cyclic ethers **236**, **237** in good yields (Scheme 18). Unfortunately, however, the *trans*/*cis* stereoselectivity was not particularly high (Table 14).

Recently, the synthetic possibilities of this pioneering work were reexamined and extended.[108] Table 15 summarizes the cyclization reactions of ω-trialkylstannyl ether acetals leading to α-vinyl β-oxyalkenyl ethers with high *trans*/*cis* stereoselectivity. Even more interestingly, acetals **247** and **249** (Table 15, entries 7 and 8) underwent facile Lewis acid cyclization to give the *trans*-substituted O-linked ethers **248** and **250**, respectively. Two new stereogenic centers are produced by a single cyclization process which appears ideal for the synthesis of *trans*-fused polyethers since the cyclization reproduces the strict *R*/*S* alternation of the stereogenic centers found in the carbon skeleton of natural polyethers (see general structure **1**).

B. Nucleophilic Addition to Lactones (Thionolactones)

A classic path to medium ring oxacycles involves the lactonization of hydroxy acids. Further manipulation of the resulting alkanolides allows entry into cyclic ether systems. Using such an approach, Nicolaou's group has developed a new method for the construction of medium-sized cyclic ethers from the readily available lactones[109] via their corresponding thionolactones.[110] The thionolactones undergo nucleophilic attack with organolithium reagents at low temperature, giving alkylated thioacetals upon

Table 14. Allylstannane–Cyclic Acetal Cyclizations

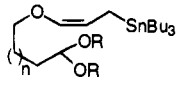
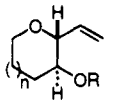
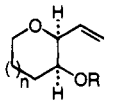
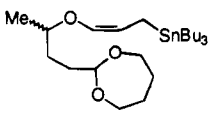
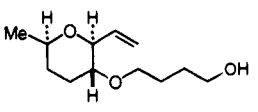
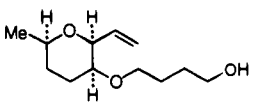
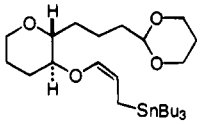
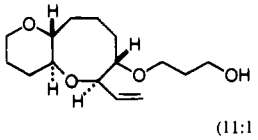
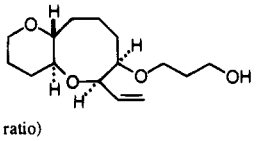
Entry	Allylstannane	Products		Yield (%)	Ref.
					
1	**235a**, n = 1, R-R = $(CH_2)_2$	**236a**, R = $(CH_2)_2OH$	(1.3:1.0 ratio) **237a**, R = $(CH_2)_2OH$	84	107
2	**235b**, n = 1, R-R = $(CH_2)_3$	**236b**, R = $(CH_2)_3OH$	(1.5:1.0 ratio) **237b**, R = $(CH_2)_3OH$	57	107
3	**235c**, n = 1, R-R = $(CH_2)_4$	**236c**, R = $(CH_2)_4OH$	(3.1:1.0 ratio) **237c**, R = $(CH_2)_4OH$	86	107
4	**235d**, n = 2, R-R = $(CH_2)_4$	**236d**, R = $(CH_2)_4OH$		57	107
5	**235e**, n = 3, R-R = $(CH_2)_4$	**236e**, R = $(CH_2)_4OH$		8	107
6	 **238**	 **239**	(1.4:1.0 ratio)  **240**	85	107
7	 **241**	 **242**	(11:1 ratio)  **243**	30	107

Table 15. Allylstannane–Acetal Cyclizations

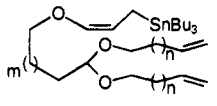
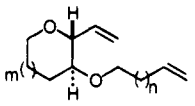
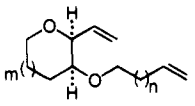
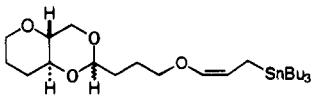
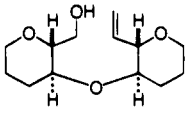
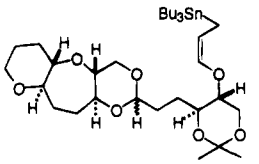
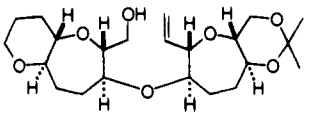
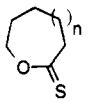
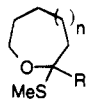
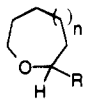
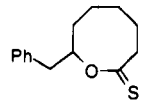
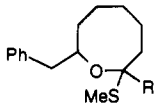
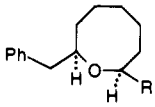
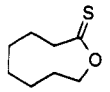
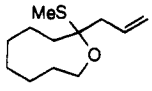
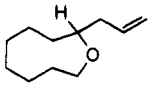
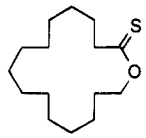
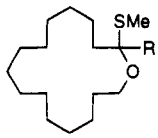
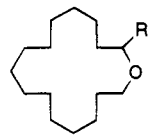
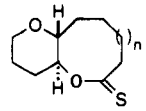
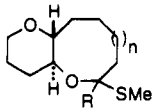
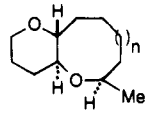
Entry	Allylstannane	Products			Yield (%)	Ref.
						
1	**244a**, m = 1, n = 1	**245a**, m = 1, n = 1			32	108
2	**244b**, m = 1, n = 2	**245b**, m = 1, n = 2	(7:1 ratio)	**246b**, m = 1, n = 2	98	108
3	**244c**, m = 2, n = 1	**245c**, m = 2, n = 1			42	108
4	**244d**, m = 2, n = 2	**245d**, m = 2, n = 2	(9:1 ratio)	**246d**, m = 2, n = 2	80	108
5	**244e**, m = 3, n = 1	**245e**, m = 3, n = 1			21	108
6	**244f**, m = 3, n = 2	**245f**, m = 3, n = 2			58	108
7	 **247**	 **248**			80	108
8	 **249**	 **250**			60	105

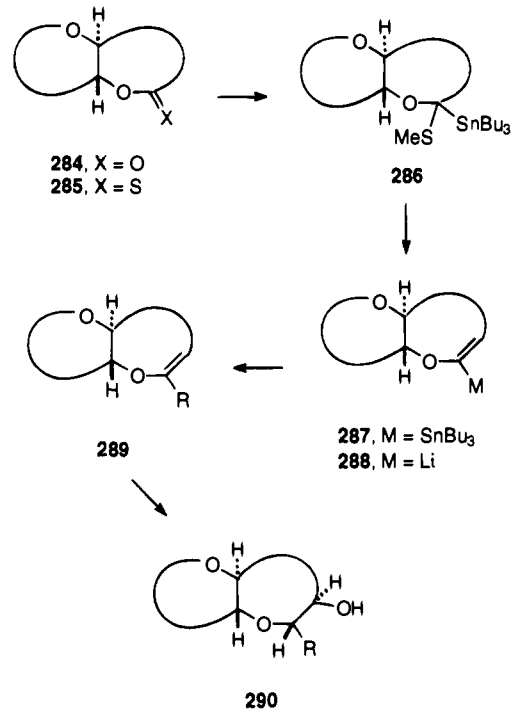
Table 16. Synthesis of Cyclic Ethers by Nucleophilic Addition to Thionolactones

Entry	Thionolactone	Nucleophile	Addition Product	Yield (%)	Reduction Product	Yield (%)	Ref.
							
1	**251**, n = 1	MeLi	**252**, n = 1, R = Me	83	**253**, n = 1, R = Me	85	111
2	**251**, n = 1		**254**, n = 1, R = 	86	**255**, n = 1, R = 	85	111
3	**256**, n = 2	nBuLi	**257**, n = 2, R = nBu	96	**258**, n = 2, R = nBu	84	111,112
4	**259**, n = 3		**260**, n = 3, R = 	94	**261**, n = 3 R = 	85	112
5	**259**, n = 3	nBuLi	**262**, n = 3, R = nBu	96	**263**, n = 3, R = nBu	84	111
							
6	**264**	nBuLi	**265**, R = nBu	56	**266**, R = nBu	85	111
7	**264**	EtLi	**267**, R = Et	84	**268**, R = Et	92	112
8	 **269**		 **270**	94	 **271**	88	111
							
9	**272**	MeLi	**273**, R = Me	78	**274**, R = Me	90	111,112
10	**272**		**275**, R =	81	**276**, R = 	...	111,112
							
11	**277**, n = 1	MeLi	**278**, n = 1, R = Me	83	**279**, n = 1	90	111,112
12	**277**, n = 1	$LiEt_3BH$	**280**, n = 1, R = H	74	**279**, n = 1 (via sulfone and $AlMe_3$)	82	111,112
13	**281**, n = 2	MeLi	**282**, n = 2, R = Me	96	**283**, n = 2, R = Me	84	112

quenching with alkyl iodide.[111,112] Reductive desulfurization using triphenyltin hydride under radical conditions afforded the corresponding cyclic ethers rapidly and efficiently and, in most cases, with complete stereocontrol (Table 16). The methodology is equally useful for the synthesis of large rings (entries 8–10) and has been applied to the synthesis of *trans*-fused polyether frameworks related to the brevetoxins (entries 11–13).

Scheme 19 outlines the general concepts that led to the synthesis of *trans,syn,trans*-substituted oxacyclic systems **290** starting from thionolactone **285**.

Scheme 19

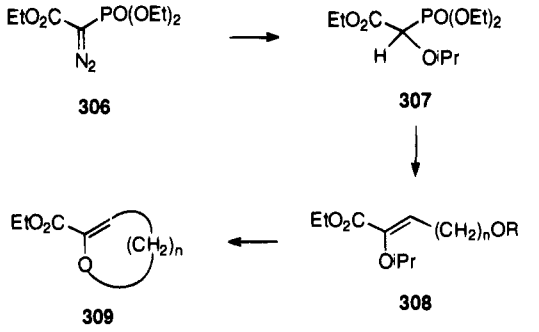


Addition of *n*-Bu_3SnLi to **285** followed by quenching with excess methyl iodide gave the methyl ether **286**. Elimination of methyl mercaptan from **286** induced by cuprous triflate, followed by transmetalation with *n*-BuLi gave the lithio derivative **288**, which could be trapped with alkyl triflate to give the vinyl ether **289**, and further hydrated to the *trans,syn,trans* system **290**. A direct and efficient one-pot entry into the enol ether **289** from **285** was obtained by addition of organocopper reagents to **285** followed by quenching with 1,4-diiodobutane and warming up in the presence of a nonnucleophilic base. An efficient application of the described technology to the synthesis of several medium-sized *trans*-fused polyether frameworks has been reported by Nicolaou and co-workers[113-116] (Table 17). The alternative procedure via the enol triflate of **284** involving side-chain addition developed by Murai[117] has also proved to be a successful method to the synthesis of the enol ether **289**.

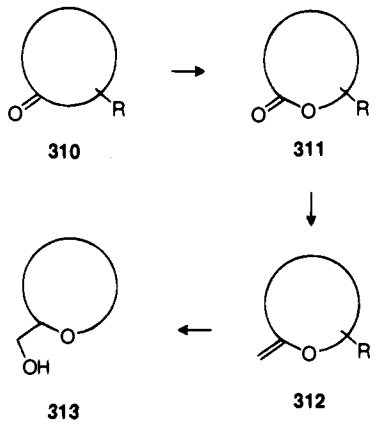
A new route to cyclic enol ethers based on diazophosphonates has been described by Moody et al.[118] The reaction involves the rhodium(II)-catalyzed O–H insertion of 2-propanol by Wadsworth-Emmons reaction to give enol ethers **308**, and deprotection and cyclization to afford the cyclic enol ethers **309** (Scheme 20). Although the dihydropyran **309** ($n = 3$) is formed in only modest yield (47%), the cyclization to the tetrahydrooxepin **309** ($n = 4$) gives 81% yield.

The Baeyer–Villiger oxidation of cyclic ketones is a classic example of lactone synthesis and has been extensively exploited by Holmes and co-workers in their approach to several medium ring ether systems[119-122] (Scheme 21). By using standard asymmetric alkylation techniques, chiral cyclic ketones and hence optically active lactones can be obtained, widening the scope on this methodology.[121] The

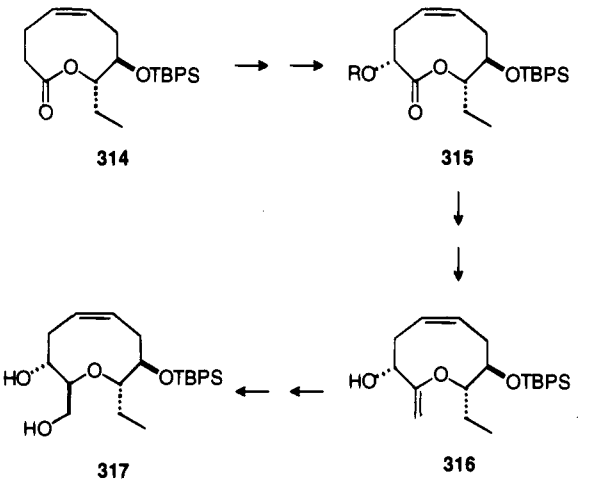
Scheme 20



Scheme 21



Scheme 22

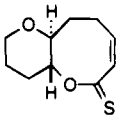
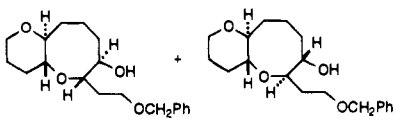
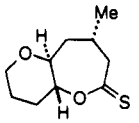
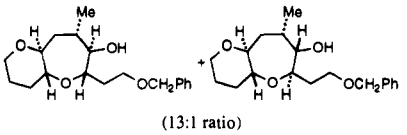
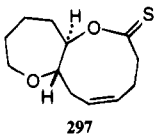
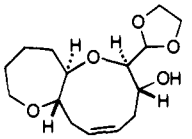
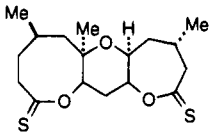
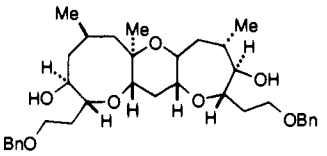
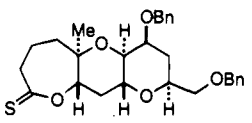
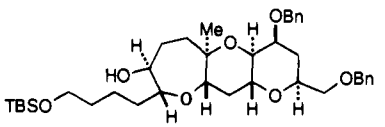
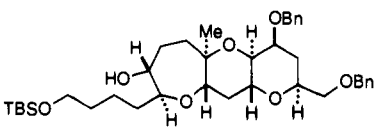
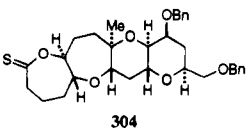
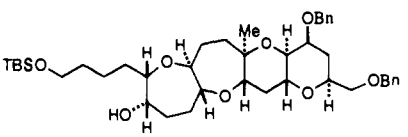


general procedure involves oxidation of a substituted cyclic ketone, followed by Tebbe methylenation of the resulting alkanolide and rapid hydroboration of the labile enol ether. The hydroxymethylated cyclic ethers are then suitable for further manipulation.

This protocol for functionalized ring ether construction appears quite general. Holmes used this method to synthesize highly substituted oxonenyl system **317**[124,125] (Scheme 22) by selective hydroxylation of lactone **314**,[123] Tebbe methylenation, and hydroxyl-directed intramolecular hydrosilation of the enol ether **316** in 30% overall yield. Application of this methodology to the synthesis *trans*-fused ethers related to brevetoxin or ciguatoxin systems is an attractive possibility.

As shown in Charts 1–3, the frameworks of *trans*-fused polyethers is dominated by the presence of

Table 17. Synthesis of Cyclic Ethers by Nucleophilic Addition to Thionolactones

Entry	Thionolactone	Products	Yield (%)	Ref.
1	 **291**	 (5:1 ratio) **292** **293**	37	112
2	 **294**	 (13:1 ratio) **295** **296**	38	112
3	 **297**	 **298**	40	114
4	 **299**	 **300**	19	113
5	 **301**	 **302** +  **303** (4:1 ratio)	76	115,116
6	 **304**	 **305**	76	115,116

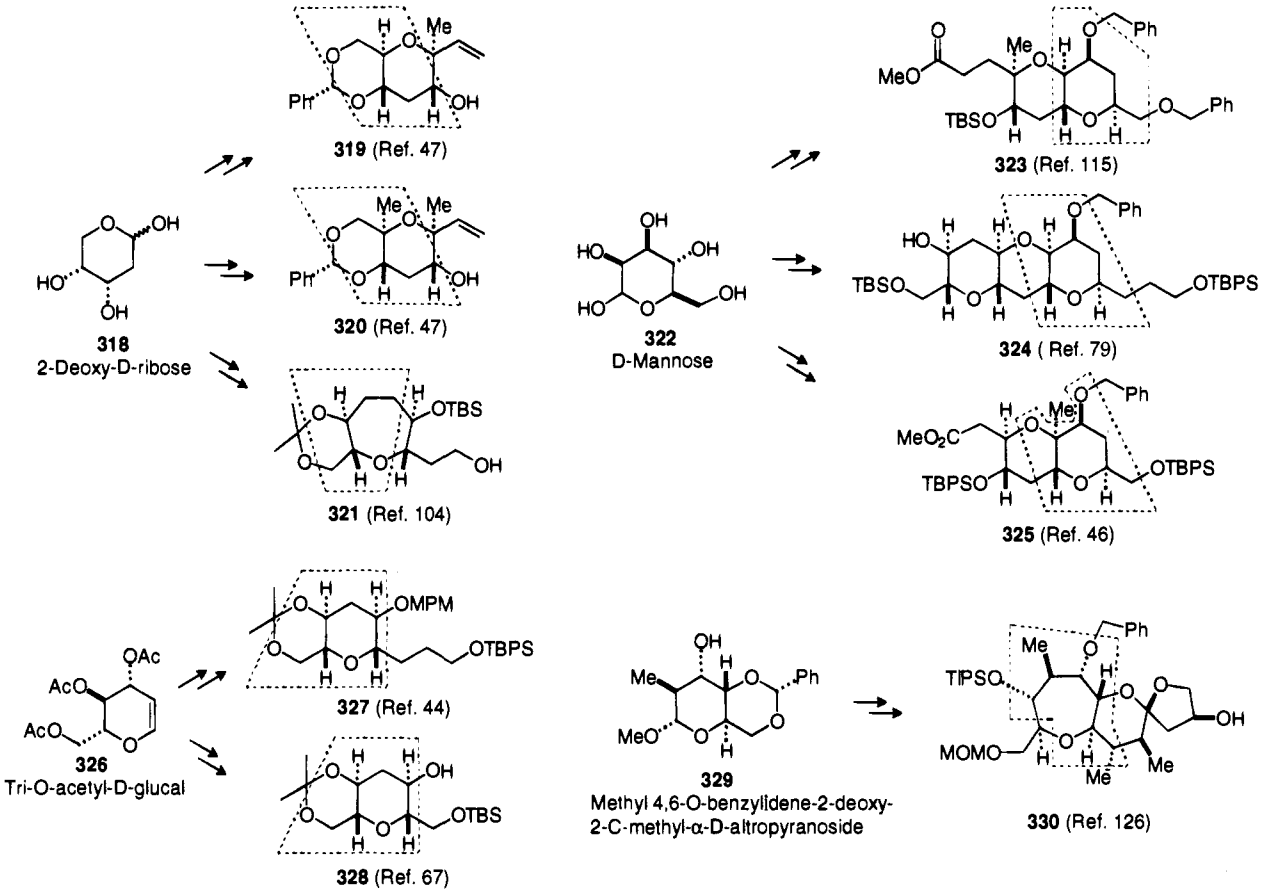
highly functionalized tetrahydropyrans. It is clear that considerable attention has been focused on development of efficient and stereochemical routes related to the synthesis of C-glycoside fragments. Recent developments in C-glycoside synthesis are currently the subject of intensive research and excellent accounts are appearing.[126] Here we will present only a few illustrative examples which are intended to highlight the use of C-glycoside in the strategy of stereoselective synthesis of *trans*-fused polyethers (Scheme 23).

Of the numerous existing methods for C-glycoside construction,[126] intramolecular free radical cyclization employing temporary silicon connection lends itself as the most attractive in this context since the reaction conditions are mild and complete stereochemical control at the anomeric center can be achieved.[128]

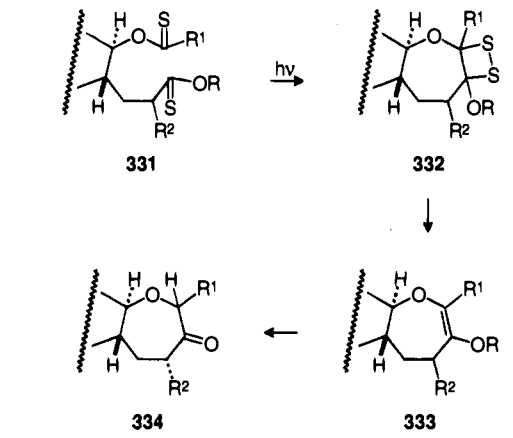
C. Photolytic Cyclization of Dithionoesters

Nicolaou's group reported an interesting and successful route to functionalized oxepane systems related to brevetoxin fragments.[129] According to the strategy shown in Scheme 24, the dithionoester **331** is converted to the 1,2-dithietane intermediate **332** via diradical coupling under photolytic conditions. Sulfur extrusion under the reaction conditions leads to the didehydrooxepane **333** which may be selectively deprotected to afford the oxepanone **334**. Table 18 demonstrates the generality and scope of this method in the construction of oxepanes of the type present in brevetoxin B and hemibrevetoxin B. Nevertheless, it does seem that a preexisting ring in the substrate **331** is necessary for this photolytic closure to be successful.[129]

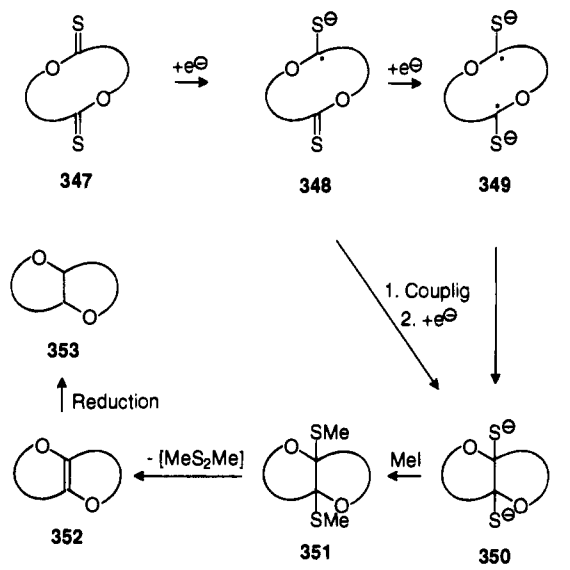
Scheme 23



Scheme 24



Scheme 25

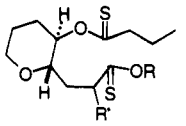
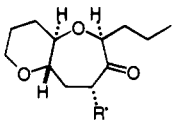
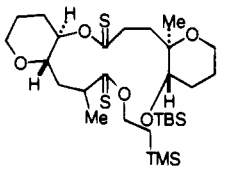
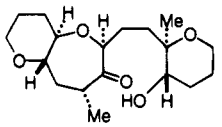
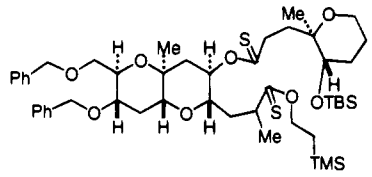
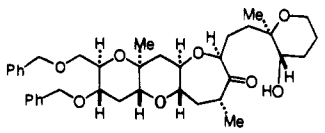
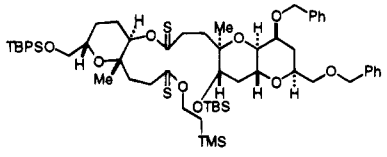
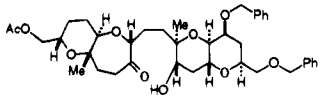


D. Bridging of Macrodithionolactones to Oxopolycyclic Systems

An intriguing and powerful alternative procedure for ring closure is that of bridging macrodithionolactones to unsaturated bicyclic systems.[130,131] It was anticipated, Scheme 25, that electron transfer to a thionocarbonyl group of the macrodithionolide system **347** would generate a radical anion **348** initiating a sequence leading to a bridge product **350**. Quenching of the resulting dianion **350** with an electrophile such as methyl iodide was then expected to lead to a stable disulfide **351** which could be chemically manipulated to form a variety of systems including the olefinic compound **352** and the *cis*- and *trans*-fused polycycles **353** (Scheme 25).

Table 19 demonstrates the generality and scope of these reactions in the construction of *ortho*-condensed olefinic polyethers **352** containing common and medium-sized rings. Subsequent reduction of the double bond in **352** to generate fully hydrogenated polyethers **353** under the conditions selected up to now give mostly *cis*-fused oxacycles.[131]

Table 18. Synthesis of Oxepanes from Dithionoesters

Entry	Dithionoester	Conditions[a]	Oxepane	Yield (%)	Ref.
					
1	**335a**: R = $CH_2CH_2SiMe_3$, R' = Me	A	**336a**: R' = Me	63	129
2	**335b**: R = CH_2CCl_3, R' = Me	A	**336a**: R' = Me	51	129
3	**335c**: R = R' = Me	A	**336a**: R' = Me	50	129
4	**335d**: R = Me, R' = H	A	**336d**: R' = H	51	129
5	 **337**	A	 **338**	58	129
6	**339**: R = Me, R' = $CH_2CH_2CH_3$, R^1 = Me	A	**340**: R' = $CH_2CH_2CH_3$, R^1 = Me	56	129
7	**341**: R = CH_2CH_2TMS, R' = $(CH_2)_4OCH_2Ph$, R^1 = H	A	**342**: R' = $(CH_2)_4OCH_2Ph$, R^1 = H	69	129
8	 **343**	A	 **344**	63	129
9	 **345**	B	 **346**	36	116

[a] Method A: i) irradiation using a Hanovia quartz lamp at 450 nm in toluene solution, for 2 h at 70 °C; ii) TBAF, THF, 45 °C, 8 h. Method B: i) hν, $NaHCO_3$, benzene, 70 °C, 2 h; ii) TBAF, THF, 25 °C, 12 h; iii) 1.1 equiv of Ar_2O, 3 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 2 h (selective desilylation of TPS); iv) HF-py, CH_2Cl_2, 0 °C, 1 h, 90%.

E. Synthesis of *Trans*-Fused Polyether Frameworks via O-Linked Oxacycles

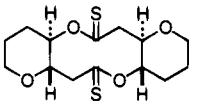
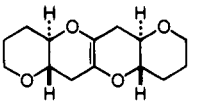
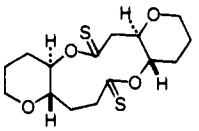
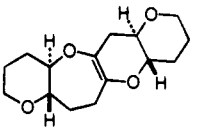
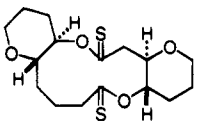
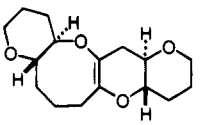
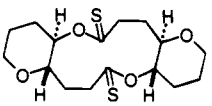
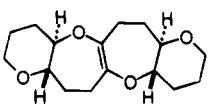
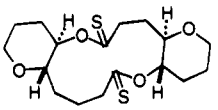
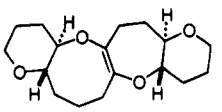
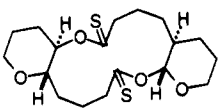
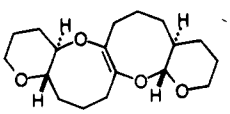
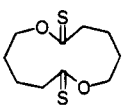
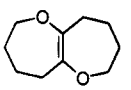
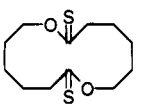
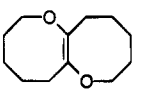
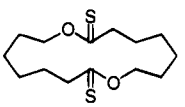
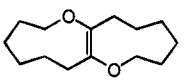
A general way of building up an *ortho*-condensed system is by cyclization outside the annulation sites. This alternative requires the existence of an easily accessible cyclic structural unit furnished with two vicinal substituents. The substituents should have a defined relative configuration and should be equipped with functional groups which enable the new ring closure. This being the case, cyclization outside the annulation sites may be more advantageous than the methods described in the preceding sections. The problem of stereoselective annulation is then of course narrowed to the specific introduction of the substituents onto the first ring.

In this section we shall present a selection of our own results.[108] According to this strategy, *trans*-fused oxacycles are generated from O-linked oxacyclic precursors via thioannulation and successive α halogenation and sulfur oxidation, followed by a Ramberg–Bäcklund reaction.[132] One of the great strengths of the reaction is that there is no ambiguity about the position of the newly introduced double bond; it is fixed by the position of the sulfone group in the heterocycle and does not isomerize under the reactions conditions. Table 20 summarizes representative examples of thioannulation and SO_2-extrusion reactions leading to medium-sized unsaturated oxacycles.

VI. Conclusions and Future Directions

The intense research directed at finding new bioactive substances in microalgae will probably afford novel *trans*-fused polyethers, which in turn will present new challenges to synthetic chemists. The immediate future will almost certainly involve applying the recently developed methodology for the

Table 19. Synthesis of Oxapolycyclic Systems by Reductive Bridging of Dithionolides Followed by Free Radical Desulfurization[a]

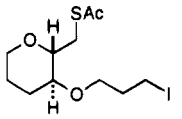
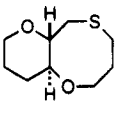
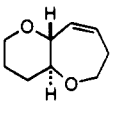
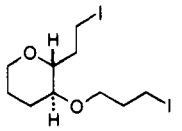
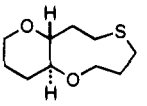
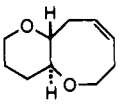
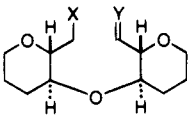
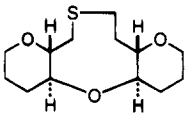
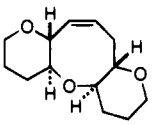
Entry	Dithionolide	Enol Ether	Yield (%)	Ref.
1	 **354**	 **355**	82	130,131
2	 **356**	 **357**	76	130,131
3	 **358**	 **359**	44	130,131
4	 **360**	 **361**	79	130,131
5	 **362**	 **363**	51	130,131
6	 **364**	 **365**	60	130,131
7	 **366**	 **367**	49	131
8	 **368**	 **369**	50	131
9	 **370**	 **371**	11	131

[a] Reactions conditions: i) 2.2 equiv of sodium naphthalene, THF, -78 °C, 30 s, then 10 equiv of MeI, -78 to 25 °C, 30 min; ii) 1.2 equiv of nBu_3SnH, 0.1 equiv of AIBN, toluene, 120 °C, 15 min; or 1.2 equiv of nBu_3SnH, hv, toluene, 25 °C, 1 h; or Raney Ni, EtOH, 25 °C, 30 min.

preparation of medium-sized oxacycles to the synthesis of *trans,syn,trans* polyethers. In this context, the elegantly reviewed[40] contributions from the groups of Kocienski,[133] Kotsuki,[134] Masamune,[135] Overman,[136] Paquette,[137] or Schreiber[138] deserve special mention. Grubbs'[139] or Masuyama's[140] recent achievements also provide strategies of general applicability for the synthesis of medium ring ethers.

The excellent chemistry published by Nicolaou et al.[141] has single handedly made it possible for any natural *trans*-fused polyether to be synthesized. Nonetheless, for greater ease of access from the synthetic point of view, the size and complexity of the natural products do require efficient convergent methodologies, as yet to be designed, since synthesis is envisaged as a better source of these substances than the frequently laborious process of culturing the microorganisms which produce them. It is hoped that new designs of this type will see the light of day in the near future.

Table 20. Synthesis of Unsaturated Polyethers by Successive Thioannulation/SO_2–Extrusion Reactions

Entry	Compound	Thioannulation conditions[a]	Thioxacycle	Yield (%)	SO_2-extrusio Product 1[b]	Yield (%)	Ref.
1	 372	A	 373	87	 374	41	108
2	 375	B	 376	70	 377	37	108
3	 **378**: X = Sac; Y = H, -CH_2I	A	 **379**	78	 **380**	52	108
4	**381**: X = I, Y = H, CH_2I	B	**379**	63	**380**	47	108

[a] Method A: MeONa (3.0 equiv), MeOH (0.1 M), H_2 atmosphere, 0 - 25 °C, 12 h. Method B: Na_2S over Al_2O_3 (1.0 equiv), HMPA (0.01 M), 100 °C, 24 h. [b] i) NCS (1.5 equiv), CCl_4, 0 °C, 4 - 5 h; ii) MCPBA (1.4 equiv), CH_2Cl_2, 25 °C, 8 - 10 h; iii) ^{t}BuOK (1.2 equiv), THF, 0 °C, 4 - 5 h.

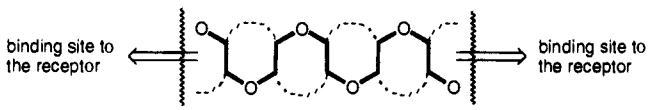


Figure 7.

The search for bioactive synthetic models, as an alternative to the complex natural structures, will also be a priority among the objectives in organic chemistry. If the biofunctionality of the polyether is based on the special tridimensional organization originated by the carbon bridges (Figure 7), alternatives to this dependency that are simpler structurally, more accessible synthetically and that do not invalidate its selective capacity of action will be sought. *Trans*-fused polyethers and their biofunctionality constitute an area of confluence between biology and chemistry, and will be developed in the future on both fronts.

Note Added in Proof

Since this paper was written several new insights have been published in the literature on the subject. Nicolaou et al.[142,143] have reported the total synthesis of brevetoxin B (**3**) and Hoffman[144,145] has described a new method for the synthesis of medium ring ethers. *7-Endo-tet* ring closure to hydroxyoxepane rings from the corresponding hydroxy epoxides by means of catalytic antibodies has been also recently published.[146]

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