Pergamon

Tetrahedron 58 (2002) 1921–1942

TETRAHEDRON

Synthesis and biological studies of flexible brevetoxin/ciguatoxin models with marked conformational preference

M. L. Candenas,[a,*] Francisco M. Pinto,[a] Cristina G. Cintado,[a] Ezequiel Q. Morales,[a,*] Ignacio Brouard,[a] M. Teresa Díaz,[a] Milagros Rico,[b] Elsa Rodríguez,[b] Rosa M. Rodríguez,[a] Ricardo Pérez,[a] Ruby L. Pérez[a] and Julio D. Martín[a,*]

[a]*Instituto de Investigaciones Químicas, CSIC, Avda. Américo Vespucio, s/n, Isla de la Cartuja, 41092 Seville, Spain*
[b]*Departamento de Química, Universidad de Las Palmas, Campus de Tafira, 35107 Las Palmas de Gran Canaria, Spain*

Received 8 October 2001; accepted 20 November 2001

Abstract—A comparison of the more active polyether toxins which are selective activators of voltage-sensitive sodium channels (VSSC), indicate that these molecules are mostly flat, with a hinge part around the middle of the molecules and a large curvature at one of the ends. Assuming that the receptor is topographically complementary to the active molecules, from the result reported here we could conclude, that the specific requirements of the receptor region can be achieved by synthetic polyether models based on exclusive participation of oxane/oxepane moieties. A new convergent approach to give oxepene rings via double reduction of methyl diacetals is explored. In searching for biological models to further characterize Na^+ channels, our studies show that different voltage-dependent Na^+ channels are expressed in the rat uterus and activated by brevetoxin-B. However, selected compound models synthesized in this work, failed to inhibit or activate Na^+ channel function.

1. Introduction

The propagation of electrical signals in excitable cells is mediated through the gating of membrane-associated ion channels. These proteins, that show ion selectivity for K^+, Na^+ or Ca^{2+}, are all composed of four identical or similar subunits, each containing six transmembrane segments in a roughly four-fold symmetric structure.[1] Among them, voltage-dependent Na^+ channels are a main component for the generation of the rapid depolarization during the initial phase of the action potential.[2] At least 10 different voltage-operated Na^+ channel subtypes have been cloned in mammals and the number will probably increase.[3] Changes in the expression and/or function of these proteins represent an important step in the development of different pathologies and, consequently, it is essential to find compounds able to act selectively as openers or inhibitors of a certain Na^+ channel subtype.[4]

Probably due to their central role in neurotransmission, voltage-gated Na^+ channels are the target of many natural toxins, that are able to interact with the protein or even to mimic its membrane disposition, forming artificial ion channels.[5] These Na^+ channel-specific natural toxins have been very useful tools for understanding the structure and function of the channel. However, most of these toxins and other presently known compounds are not able to discriminate between different Na^+ channel subtypes.[6] This is one of the reasons justifying our presently poor knowledge of Na^+ channel characterization and classification. In searching for selective compounds for a certain Na^+ channel, a main objective would be the chemical modification of these known compounds, in order to establish structure–activity relationships and look for analogues with increasing selectivity, able to discriminate between different Na^+ channel isoforms. A second objective would be to find simple biological models that would permit us to study the activity of different compounds on a particular channel subtype. As an example to illustrate the complexity of the subject, Fig. 1 shows Na^+ channel messenger RNA (mRNA) expression in the non-pregnant rat uterus. The myometrium is unique among most mammalian visceral smooth muscles in that it contains voltage-gated Na^+ channels.[7] Fig. 1 shows that many Na^+ channels are expressed in the uterus, giving an idea of the difficulty of establishing a precise correlation between a functional response and the specific Na^+ channel(s) subtype(s) involved in this response.

Examples of molecules of interest to us include the conformationally constrained polyethers: brevetoxins (BTXs) and ciguatoxins (CTXs),[8,9] which are selective activators of voltage-sensitive sodium channels (VSSC) in nerves, heart and muscle.[10] The binding of both groups of polyethers induces a conformational change in the organization of the protein which tends to stabilize a multiplicity of different open and/or preopen states of the channel. In

Keywords: sodium channels; uterus; toxins; conformation; polyethers.
* Corresponding authors. Tel.: +34-95-4489565; fax: +34-95-4460565; e-mail: mluz@cica.es; ezequiel@iiq.cartuja.csic.es; jdelgado@cica.es

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00047-9

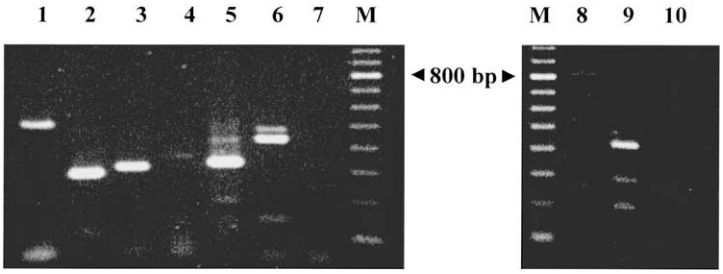


Figure 1. Agarose gel showing products of reverse-transcriptase-polymerase chain reaction (RT-PCR) assay for cDNA from non-pregnant rat uterus in the estrous stage of the ovarian cycle. Equal amounts of uterine cDNA, as determined from the previous amplification of the housekeeping genes glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and β-actin, were amplified with primers specific for each of the rat voltage-dependent Na^+ channel α subunits. Single transcripts corresponding to the sizes predicted for the tetrodotoxin (TTX)-sensitive Na^+ channels from skeletal muscle *SKM*1μ_1 (lane 2), *PN4*a (lane 3), and brain type II (lane 6) and III (lane 5) were expressed in the uterus. The TTX-insensitive *SNS*2 (lane 9) and the atypical *SCL*11 (lane 1) were also detected. The specific bands corresponding to the TTX-sensitive channels *SCN*9A (lane 4) and brain type I (lane 7) and the TTX-insensitive *SKM*2 (lane 8) and *SNS* (lane 10) channels were undetected. *M* represents molecular size standards.

consequence, BTXs and CTXs shift the voltage dependence of the activation kinetics and eliminate the inactivation of the Na^+ current inducing a persistent activation of the channel. Both groups of lipid-soluble toxins are *trans*-fused polycyclic systems composed of a single carbon chain that winds the length of the molecule. In each toxin structure, the chain is linked by ether oxygens into a series of *trans*/*syn*-fused cyclic arrays, with ring sizes ranging from five- to nine-membered oxacycles. The structural requirements for the toxicity are complex, involving stereochemistry, length and conformational flexibility of the whole molecule. Because polyether size (~30 Å long) and flexibility (seven- to nine-membered oxacycles) strongly influences receptor binding, internal motions of natural toxins have been thoroughly investigated by experimental and computational methods.[6,11] It has been proposed that the 'ideal' pharmacophore is a roughly 'hair-pin' shaped lipid soluble molecule, >30 Å long, bound to its receptor primarily with hydrophobic and non-polar solvation forces, possible aided by strategically placed ether oxygens acting as hydrogen bond acceptors being their effectiveness (CTXs≫BTXs) depending on their selectivity for the active conformation of the receptor.

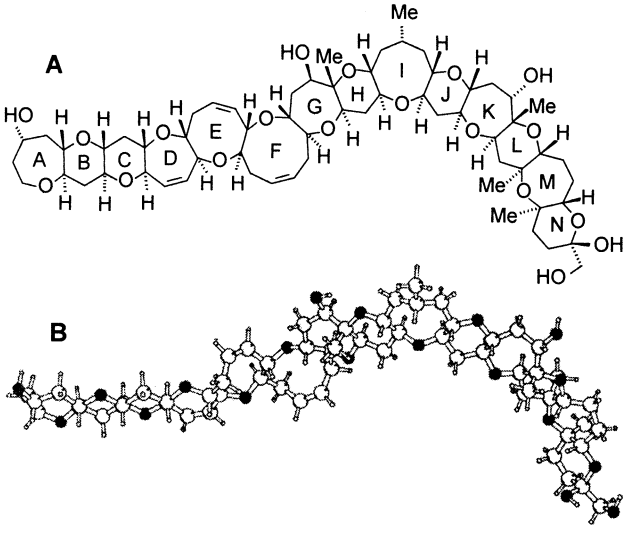


Figure 2. (A) Caribbean ciguatoxin-1 (C-CTX-1). (B) Conformational behavior of the lower energy conformer.[9k] Copyright (1998) American Chemical Society. Reprinted with permission.

BTXs and CTXs are thus examples of flexible molecules with a defined shape; that is, compounds that essentially populate a single conformation, whilst maintaining full conformational flexibility. Because ligand flexibility strongly influences receptor binding, an important question concerns the biological relevance of the compact folded region in the more active polyethers; i.e. H/N-rings segment of the C-CTX-1[9k] (Fig. 2). The results reported later represent an attempt to discover easily accessible structural oxane/oxepane segments that, in the context of *trans*-fused polyethers, form the basis for the design of BTX/CTX mimetics.

2. Results and discussion

2.1. Conformational background

In general, modeling structurally complex compounds for a biological study requires parallel consideration of conformation and synthetic principle, to ensure a successful outcome. Because of the extra ring bond, oxepane has one more degree of torsional freedom as compared with its lower oxane homologue and, therefore, no rigid conformation of oxepane exists.[12] There are, however, two conformational families that cannot be interconverted without increasing bond angles, just as in an oxane. One family consist of the *chair*, the *twist-chair* and all the intermediate forms between these; the other family may be similarly described in terms of a *boat* and *twist-boat*. According to molecular mechanics calculations, there is a substantial barrier, about 9.0 kcal/mol, preventing the interconversions belonging to the two families, but very low barriers to pseudorotation (2–3 kcal/mol) within either family. However, all the evidence is consistent with the oxepane existing largely in the *twist-chair* conformations.[13]

When torsional constrains are introduced in a seven-membered ring, the conformational picture becomes analogous to that of cyclohexane, and both geometrically rigid and flexible forms occur. Dreiding molecular models show that in tricyclic *trans*, *syn*, *trans*-fused oxane/oxepane/oxane systems, only *chair* and *twist-chairs* are possible for the internal oxepane ring.[14] Non-eclipsed *twist-chair* forms of oxepane are in fact the minimum-energy conformations,

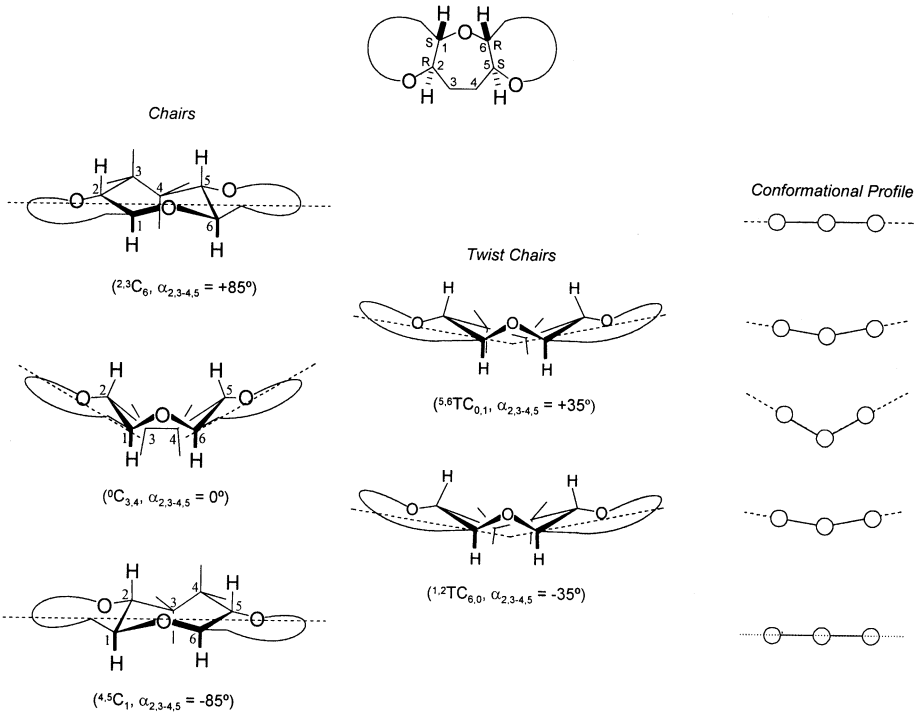


Figure 3. Possible conformers for an oxatricyclic *trans*,*syn*,*trans*-fused polyether possessing an internal oxepane ring.

whereas the *chairs* are transition states for the slightly hindered pseudorotations that occur to relieve the eclipsing strains. Fig. 3 illustrates the three possible chair conformers for the internal oxepane in a *trans*, *syn*, *trans*-fused oxatricyclic system.[15] Each of these *chairs* ($^{2,3}C_6$, $\alpha_{2,3-4,5}$= +85° and $^{0}C_{3,4}$, $\alpha_{2,3-4,5}$=0°; $^{4,5}C_1$, $\alpha_{2,3-4,5}$=−85°) and their minimum energy *twist-chair* conformers ($^{5,6}TC_{0,1}$, $\alpha_{2,3-4,5}$=+35° and $^{1,2}TC_{6,0}$, $\alpha_{2,3-4,5}$=−35°), may be interconverted by folding the oxatricyclic molecule in a direction depending on the configuration of the oxepanyl moiety. Consequently, the introduction of seven-membered ring oxacycles in the middle of rigid *trans*-fused polyethers should be a way to create flexible polyethers with predictable conformational profiles (Fig. 4).

Related flexible moieties in the middle of rigid backbones are a common feature of brevetoxins and ciguatoxins and are suspected to play a role in the bioactivity of these toxins. However, no conformational studies in solution have yet been performed, probably due to the scarcity of these polyethers from natural sources.

Fused oxepane rings present an interesting conformational problem. Although each ring might be expected to have a number of accessible *chair* and *twist-chair* conformation, we are unsure what effect their fusion might have on the potential energies of various (reasonable) conformations. While fused oxane rings always gave rigid and extended conformations, by virtue of their *trans* decalin-like geometry, we were uncertain about fused oxepanes flanked by flexible (oxepanes and higher size rings) or rigid (oxanes) moieties. We decided to first address this question by synthesis and conformational study of a wide range of model compounds, a selection of which are included in Table 1.

2.2. Synthesis and conformational profile of *trans*-fused oxane/oxepane systems

The synthesis of *ortho*-condensed compounds containing oxepane rings flanked by different sized oxacycles would be useful for the thermodynamic analysis of their characteristic conformational behavior described earlier. As a part of our studies directed toward the synthesis of brevetoxin/

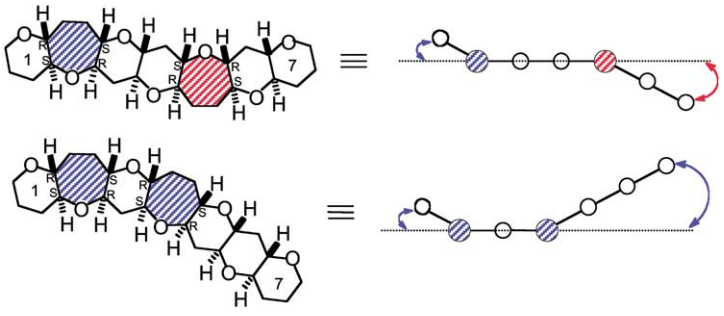
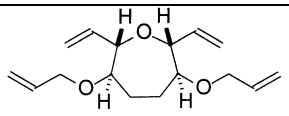
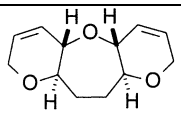
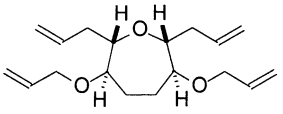
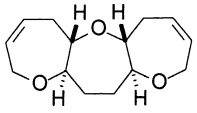
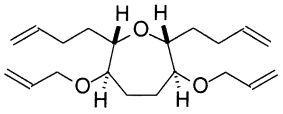
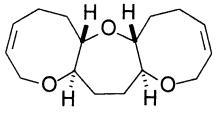
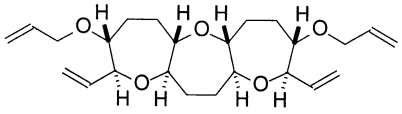
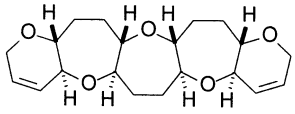
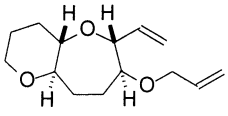
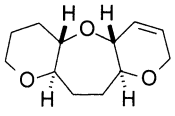
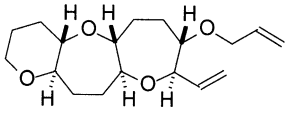
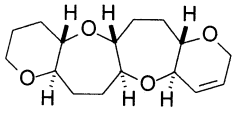
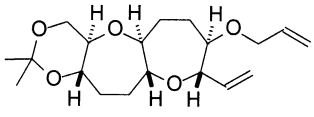
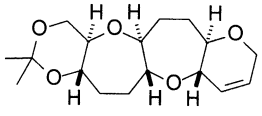
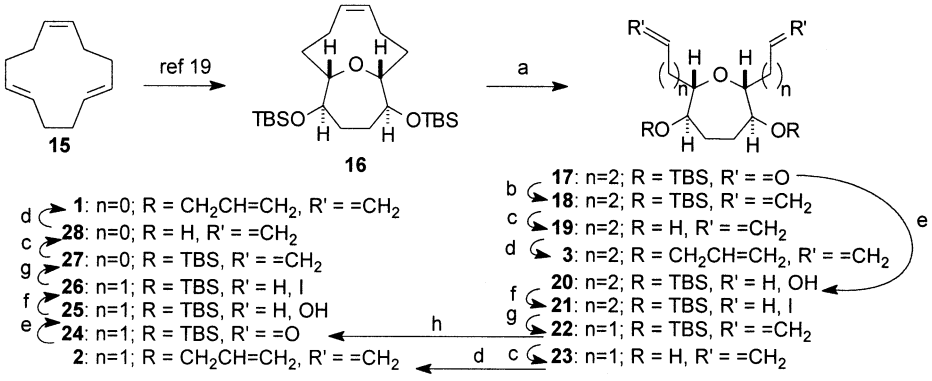


Figure 4. Conformational profile of *trans*,*syn*,*trans*-fused oxane/oxepane polyethers and their folded dependence with the configuration of the oxepane rings. Colors associated with *twist-chairs* in the direction in which molecules are folded (● blue, up; ● red, down).

Table 1. Conditions: 0.2–0.5 mmol scale, 10–30 mol% of $[(PCy_3)_2RuCHPh]Cl_2$, 6×10^{-3} M (CH_2Cl_2), 25°C, 2–4 h

Entry	Substrate	Product	Yield (%)
1	 **1**	 **8**	>95
2	 **2**	 **9**	>95
3	 **3**	 **10**	>95
4	 **4**	 **11**	>95
5	 **5**	 **12**	>95
6	 **6**	 **13**	>95
7	 **7**	 **14**	>95

ciguatoxin mimetics, we have developed a cyclization methodology for assembling ether rings of various sizes from simple cycloalkenes, in the *trans*-relationship that is found in natural polyethers.[16] Herein, we describe first the synthesis of selected tri- tetra- and penta-cyclic model compounds (Table 1), including studies related to their conformational behavior at room temperature based on NMR spectroscopy. As illustrated in Table 1, compounds **8**–**14** were achieved, in essentially quantitative yield, by ring-closing metathesis (RCM) from their respective alkylidene precursors **1**–**7**,[17] using bis (tricyclohexyl-phosphine) benzylidene ruthenium dichloride as catalyst.[18] The *meso*



Scheme 1. *Reagents and conditions*: (a) (i) 0.2 equiv. OsO_4, 5.0 equiv. NMO, acetone/H_2O (4:1); (ii) 1.5 equiv. $NaIO_4$, acetone/H_2O (9:1), 88% (two steps); (b) 2.5 equiv. of PPh_3CH_3Br, 2.5 equiv. of *n*-BuLi, THF, 0–25°C, 8 h, 84%; (c) 2.5 equiv. of *n*-Bu_4NF, THF, 25°C, 2 h (**19**: 98%; **23**: 98%; **28**: 97%); (d) 10.0 equiv. of allyl bromide, 2.5 equiv. of NaH, *n*-Bu_4NI catalyst, THF, 0–25°C, 8 h (**3**: 88%; **2**: 92%; **1**: 89%); (e) 6.0 equiv. of $NaBH_4$, MeOH, 0°C, 1 h (**20**: 94%; **25**: 96%); (f) 4.0 equiv. of I_2, 3.0 equiv. of imidazole, 5.0 equiv. of PPh_3, C_6H_6, 4°C, 1 h (**21**: 98%; **26**: 96%); (g) 2.5 equiv. of KO–*t*-Bu, THF, 25°C, 30 min (**22**: 93%; **27**: 89%); (h) O_3, CH_2Cl_2, −78°C, 20 min, then 3.0 equiv. of PPh_3, 20°C, 1 h, 87%.

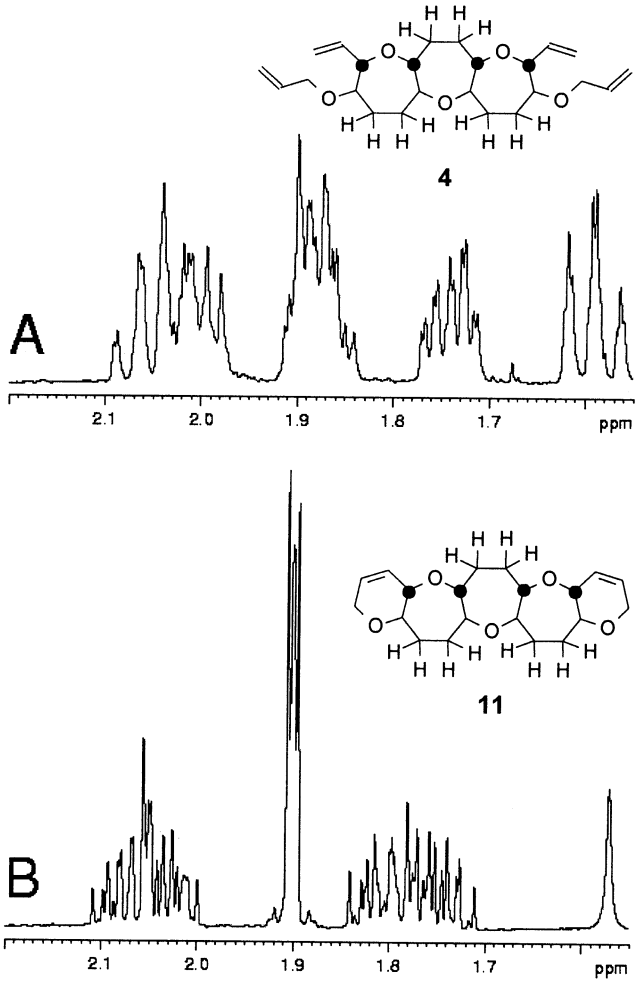


Figure 5. ^{1}H NMR ($CDCl_3$) corresponding to methylene oxepane protons of compounds **4** (A) and **11** (B).

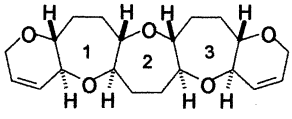
compounds **1**–**4** (entries 1–4) were prepared from (*E*, *E*, *Z*) cyclododecatriene (**15**)[19] following the synthetic sequence outlined in the Scheme 1. Compounds **5**–**7** (entries 5 and 6) were synthesized[20] starting from tri-*O*-acetyl-D-glucal (for compounds **5**, **6**) and 2-deoxy-D-ribose (for compound **7**).

Analysis by NMR spectroscopy reveal that, with exception of compounds **13** and **14**, cyclization to give terminal oxane rings occurs with concomitant sharpening of the ^{1}H NMR signals. As an example, Fig. 5 show the ^{1}H NMR spectra corresponding to the methylene protons of oxepane rings of the pentacyclic compound **11** in comparison with its tricyclic precursor **4**. Since sharpened peaks are thought to be derived from single conformers, oxepane rings in **11** are assumed to mostly exist in a dominant conformation at room temperature.

Modeling of compound **11** reveals a marked conformational preference for the whole molecule, which is due to an ordered alternation of *twist-chair*/*chair* conformers for the oxepane rings. Table 2 includes calculated lower-energy conformers of **11** which show *twist-chair* conformations for both oxepanes adjacent to oxene rings (ring 1, 3 in **11**), whereas the middle oxepane (ring 2 in **11**) appears to be fixed in *chair* conformations. Since change among *twist-chair*, $^{5,6}TC_{0,1}$ and $^{1,2}TC_{6,0}$ or extended *chairs* $^{2,3}C_6$ and $^{4,5}C_1$ does not alter the overall profile of the molecule (Fig. 3), the minimum-energy conformers should be virtually superimposable, which results in a semirigid C-shaped profile for the whole structure.

Furthermore, NOE and coupling-constant data were used together with molecular modeling to establish the average conformation in solution for the pentacyclic compound **11** (Fig. 6). Low-energy conformer were obtained in all cases from a Monte Carlo search as it is implemented in Macromodel.[21] Examination of the low-energy population revealed that 97.9% is occupied by two essentially isoenergetic (ΔE=0.03 kcal/mol) and almost superimposable conformers, which correspond to the C-shaped structure depicted in Fig. 6a. A comparison of **11** with its tricyclic precursor **4** (diacetate), Fig. 6b, shows that the absence of the strain imposed by fusion with external oxane rings, allows a mostly flat and flexible oxepanyl segment due to

Table 2. Low-energy conformers for compound **11** (C=*chair*; TC=*twist-chair*), T_1, T_2, T_3 are torsion angle $\alpha_{2,3-4,5}$ for oxepane rings 1, 2, 3, respectively; color (blue) associated with *twist-chairs* in the direction in which the molecule is folded



11

Conf.	ΔE (kJ/mol)	T_1	T_2	T_3	Conformational profile
1	0	−36.7 ●	88.0	−29.7 ●	TC C TC
2	0.03	29.7 ●	−88.3	37.3 ●	TC C TC
3	2.64	32.9 ●	−90.0	−29.9 ●	TC C TC
4	2.65	29.9 ●	−90.0	32.9 ●	TC C TC

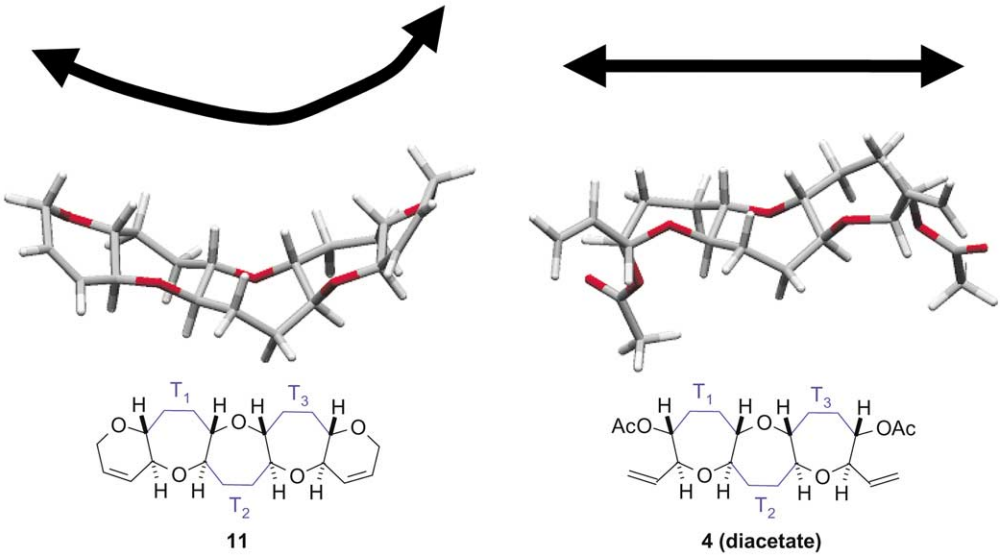
TC C TC C-shaped structure (semi-rigid)

(A)

Conformers	E_T (kJ/mol)	T1	T2	T3	Population %
1	490.16	-29.7	88.3	-37.3	50.2
2	490.19	37.3	-88.3	29.7	47.7
Others					2.1

(B)

Conformers	E_T (kJ/mol)	T1	T2	T3	Population %
1	390.97	69.6	84.4	-70.4	41.6
2	390.98	70.4	-84.4	-69.6	40.6
Others					17.8



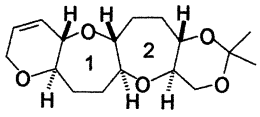
11 4 (diacetate)

Figure 6. (A) Low-energy conformation of compound **11**. (B) Low-energy conformation of compound **4** (diacetate).

preferentially extended *chair* conformations $^{2,3}C_6$ and $^{4,5}C_1$ of the seven-membered oxacycles (conformer population 82.2%).

Compound **14** possesses two fused oxepanes flanked by two distinguishable six-membered (oxene and 1,3-dioxane) rings. For compound **14**, as occurs with its related **13**, although the average structure can be determined with fidelity, detailed proton signals of each oxepane cannot be quantified by ^{1}H NMR spectra. The broadened proton resonance of the methylene hydrogens in compound **14** indicated the conformational change of the oxepane rings on a millisecond time scale. Table 3 shows the lower-energy conformers calculated for compound **14**. As expected several *chairs* and *twist-chair* conformations for each oxepane were indiscriminately found forming a highly flexible S-shaped structure. Indeed, this result is in agreement with the reported modeling of brevetoxin-B,[22] which shows a flexible backbone around the two seven-membered moieties.

Table 3. Low-energy conformers for compound **14** (C=*chair*; TC=*twist-chair*), T_1,T_2 are torsion angle $\alpha_{2,3-4,5}$ for oxepane rings 1, 2, respectively; color associated with *twist-chairs* and the direction in which molecule is folded (● blue, up; ● red, down)

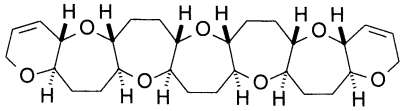


14

Conf.	ΔE (kJ/mol)	T_1	T_2	Conformational profile
1	0	−83.3	29.3 ●	C TC
2	2.73	28.7 ●	81.7	TC C
3	4.54	−83.1	−11.2 ●	C TC
4	5.45	45.9 ●	−46.0 ●	TC C
5	9.33	79.2	34.8 ●	C TC

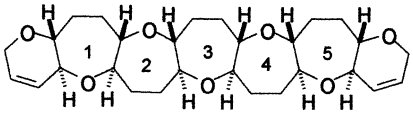
S-shaped structure (flexible)

In consonance with the earlier results, a semirigid C-shaped structure should be expected for the heptacyclic derivative **29**, where five oxepanes are flanked by two terminal oxenes. Indeed, both ^{1}H and ^{13}C NMR signals arising from the oxepanyl moiety in **29**,[23] were observed without significant peak broadening. As the individual conformation of these oxepanes is important in order to stabilize the overall shape of the molecule, molecular mechanics studies were carried out. Table 4 shows the calculated lower energy conformers for compound **29**, which reveal *twist-chairs* conformers for the middle oxepane and the two oxepanes adjacent to oxenes (rings, 1, 3, 5 in **29**), and extended *chair* conformations for the two others seven-membered rings (rings 2, 4 in **29**). These results reveal a monoconformational and semirigid C-shaped structure for compound **29**.



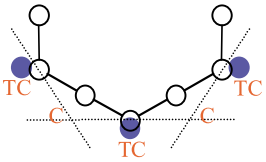
29

Table 4. Low-energy conformers for compound **29** (C=*chair*, TC=*twist-chair*), *T*1, *T*2, *T*3, *T*4, *T*5 torsion angle $\alpha_{2,3-4,5}$ for oxepane rings 1, 2, 3, 4, 5, respectively. Color, (blue) associated with *twist-chairs* show the direction in which the molecule is folded



29

Conf.	ΔE (kJ/mol)	T_1	T_2	T_3	T_4	T_5	Length (Å)[a]
1	0	−36.8	88.0	33.0	88.1	−29.7	15.92
2	1.6	−36.6	88.2	−25.1	−86.6	35.5	15.65
3	1.6	−36.8	88.0	−31.9	86.4	28.8	15.86
4	4.0	29.7	−88.0	37.2	89.7	−29.9	16.60
5	4.3	−36.6	88.2	−25.7	−88.3	−32.3	15.77
6	4.3	32.9	89.7	−33.6	88.2	−29.7	16.18
7	4.5	−29.5	−88.1	−36.4	88.1	−29.7	16.47
8	5.4	−35.7	86.7	24.3	89.7	−29.9	16.28
9	5.5	32.8	89.8	−23.8	−86.8	38.5	25.80
10	5.9	−28.9	−86.4	35.7	89.7	−29.9	16.45
11	5.9	−35.6	86.6	25.7	88.1	29.3	16.28
12	6.1	−28.9	−86.5	32.4	−89.7	−33.0	16.11
13	6.2	−28.9	−86.4	35.0	88.1	29.4	16.31

Conformational profile 

C-shaped structure (semi-rigid)

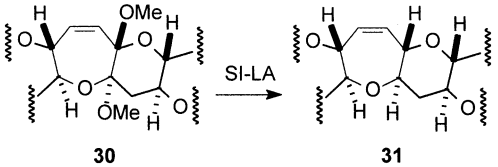
[a] Length refers to distance among oxene oxygens and was calculated by molecular mechanics routine.

In conclusion, the study reported here provides logical starting points for the development of flexible (S-shaped) or semirigid (C-shaped) polycycles. From these results we can expect that the specific topographical requirements present in natural polyethers may be achieved in synthetic models based on oxane/oxepane segments.

In order to reach the required polyether size (~30 Å long), pairs of the above fragments can be coupled with version of convergent approaches[24] to give series of polycyclic models with different lengths and conformational mobility. This knowledge could, in principle, be used to limit the structures of synthetic molecules to those optimally fit for binding. We next report on the synthesis of oxepane rings following a convergent methodology.[25–27]

2.3. Synthesis of oxane/oxepane models via a convergent approach

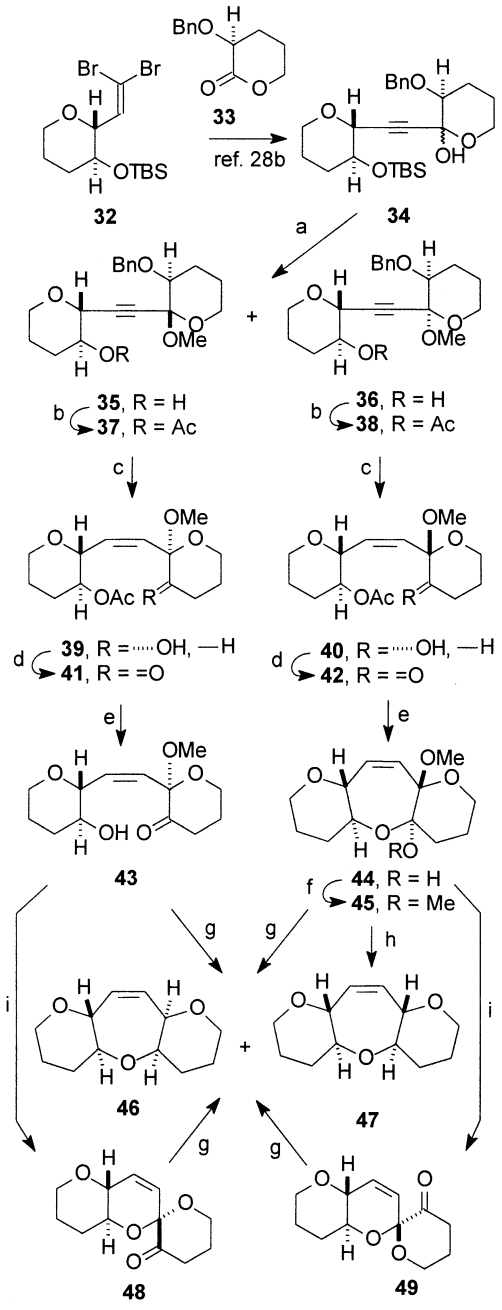
The reductive intramolecular coupling of hydroxy-ketones in reactions with silane-Lewis acids (SI-LA) to generate cyclic ethers is affected by the conformational preference of the hemiacetal (or mixed acetal or thioacetal) intermediates.[24] Although this method has presented a powerful tool for efficient convergent synthesis of *trans*-fused polyethers via reductive etherification to oxane[26] and oxocene[25] ring systems, cyclization to oxepanes is a limitation of the method due to the difficulty in directing the stereoselectivity toward the required *trans–syn–trans*-epimer.[28] We report below studies related to the steroselective construction of the *trans*-fused mixed diacetal **30** and double reductive etherification to the *trans*-fused oxepanyl system **31** (Scheme 2).



30 **31**

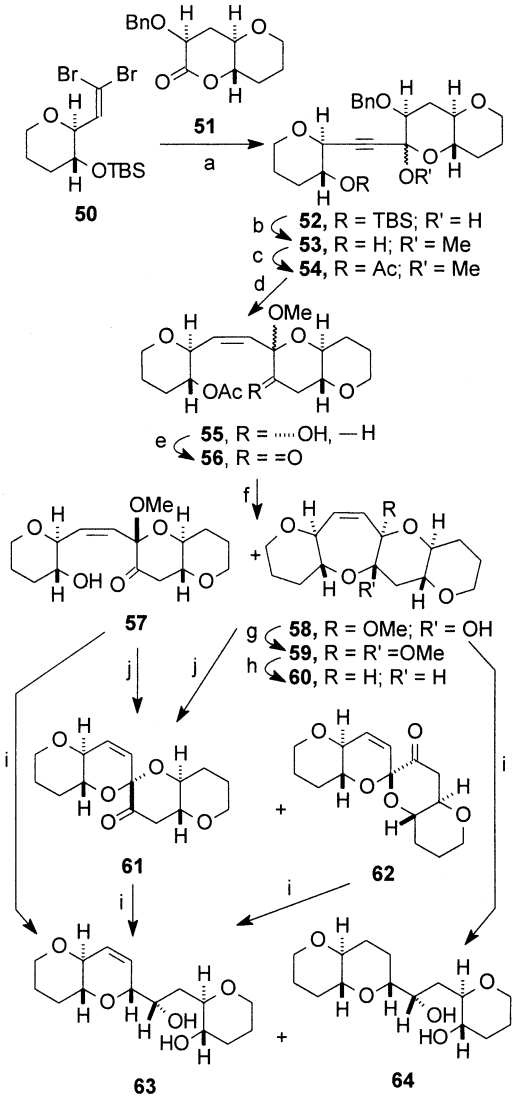
Scheme 2.

The coupling of intermediates **32**[29] and **33**[30] and elaboration of the resulting product to compound **47** is summarized in Scheme 3. The lithium acetylide obtained from *n*-butyllithium addition to **32** (*n*-BuLi, THF, −78 to 40°C) was quenched with lactone **33** to afford **34** as an inseparable mixture of diastereomers at C-1 in 90% yield.[28b] Treatment of the 1:1 mixture of hemiacetals **34** with CSA in methanol at 0°C gave a 1:1 mixture of mixed acetals **35** and **36** which were separated by flash column chromatography. The acid catalyzed reaction occurs with concomitant loss of TBS group in 98% yield. Acetylation of **35** (or **36**) afforded **37** (or **38**), which were then further treated with 10% Pd–$BaSO_4$ under hydrogen atmosphere to give **39** (or **40**) in 64% yield. Compounds **39** and **40** were oxidized to ketones **41** and **42** which were, respectively, hydrolyzed by base treatment to the hydroxy-ketone **43** (74% yield, two steps) and hemiacetal **44** (68% yield, two steps). When compounds **43** and **44** were independently subjected to reductive (SI-LA) conditions using $Et_3SiH/BF_3{\cdot}OEt_2$, an identical mixture of oxatricycles **46** and **47** (82% yield; ca 9:1) was obtained. The stereochemistry of compounds **46** and **47** was easily determined by 2D COSY and NOESY NMR experiments. The manner of fusion and stereochemistry in **46** were clarified by 1D ^{1}HNOE difference measurements and $J_{H,H}$ data. Prominent enhancements in



Scheme 3. *Reagents and conditions*: (a) 0.3 equiv. of CSA, MeOH, 25°C, 24 h, 98%, compounds **35** and **36** (1:1 ratio); (b) 3.0 equiv. of Ac_2O, 4.0 equiv. of Et_3N, DMAP catalyst, CH_2Cl_2, 25°C, 6 h (**37**: 97%; **38**: 94%); (c) 10% Pd–$BaSO_4$, catalyst, 0.1 equiv. of quinoline, H_2, EtOAc, 25°C, 6 h (**39**: 64%; **40**: 59%); (d) 3.4 equiv. of oxalyl chloride, 5.7 equiv. of DMSO, 11.4 equiv. of Et_3N, CH_2Cl_2, −78°C, 1 h (**41**: 76%; **42**: 79%); (e) 0.4 equiv. of MeONa, MeOH, 25°C, 30 min (**43**: 80%; **44**: 94%); (f) 2.5 equiv. of NaH, 5.0 equiv. of MeI, DMF, 0°C, 8 h, 61%; (g) from **43**, 15.0 equiv. of Et_3SiH, 15.0 equiv. of $BF_3{\cdot}Et_2O$, MeCN, 0°C, 3 h (**46**: 73%; **47**: 8%); from **44** (**46**: 72%; **47**: 8%); from **48** (**46**: 74%; **47**: 9%); from **49** (**46**: 74%; **47**: 9%); (h) 15.0 equiv. of Et_3SiH, 15.0 equiv. of $BF_3{\cdot}Et_2O$, MeCN, −78 to −15°C, 2 h, 78%; (i) from **43**, 2.0 equiv. of $BF_3{\cdot}Et_2O$, CH_3CN, −30°C, 30 min (**48**: 87%; **49**: 12%); from **44** (**48**: 87%; **49**: 12%).

the NOE difference spectra of **46** were observed on Ha_2/H_{11a}, H_{4a}/H_{5a}, H_{5a}/H_{9a} and H_{9a}/Ha_8. Coupling constants between angular methines H_{4a}/H_{11a}=8.3 Hz and H_{5a}/H_{9a}=4.0 Hz, were typical values for interaction between antiperiplanar and synclinal oxymethines, respectively, indicating a *trans*, *syn*, *cis* fusion for either rings. Furthermore, compound **46** was hydrogenated (H_2, $Pd(OH)_2$/C) to a previously reported compound.[28b] The ^1H and ^{13}C NMR spectra of **47** clearly showed its *meso*-symmetry, all the methine protons having an axial orientation. An explanation of these results might involve the spirocycles **48** and **49** which can be isolated when the reductive process is interrupted after 4–5 min of reaction at −78°C and independently subjected to reduction to give **46** and **47** in identical yield and relative proportions as given earlier for **43** or **44**.



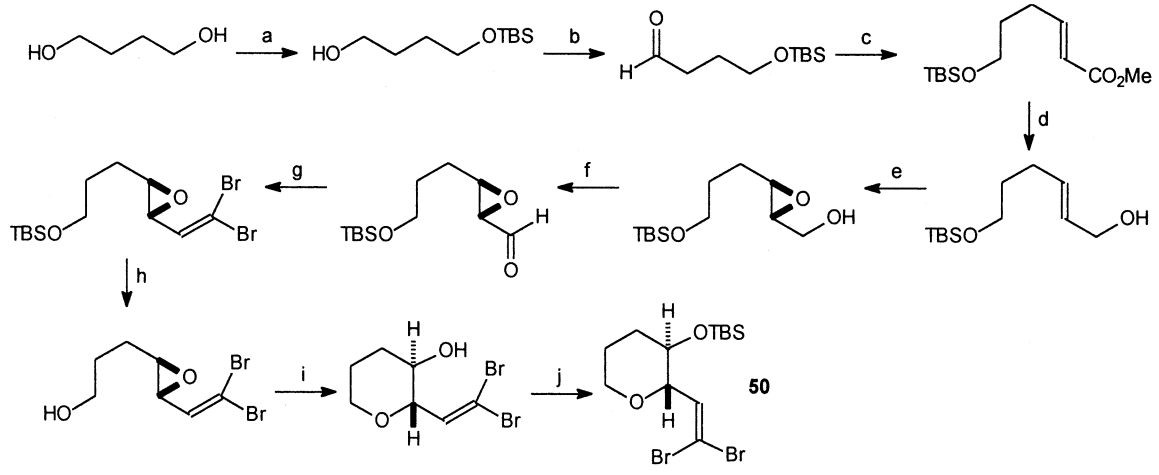
Scheme 4. *Reagents and conditions*: (a) 2.0 equiv. of *n*-BuLi, THF, −78 to −35°C, 1 h, then 0.96 equiv. of **51**, 25°C, 1.5 h, 93%; (b) 0.3 equiv. of CSA, MeOH, 25°C, 12 h, 96%; (c) 3.0 equiv. of Ac_2O, 3.0 equiv. of Et_3N, DMAP catalyst, CH_2Cl_2, 25°C, 6 h, 98%; (d) 10% Pd–$BaSO_4$ catalyst, 0.1 equiv. of quinoline, H_2, EtOAc, 25°C, 5 h, 59%; (e) 3.4 equiv. of oxalyl chloride, 5.8 equiv. of DMSO, 11.0 equiv. of Et_3N, CH_2Cl_2, −78°C, 1.5 h, 82%; (f) 0.5 equiv. of MeONa, MeOH, 25°C, 30 min, **57** and **58** (1:1 ratio), 86%; (g) 2.5 equiv. of NaH, 5.0 equiv. of MeI, DMF, 0°C, 6 h; 53%; (h) 14.5 equiv. of Et_3SiH, 15.0 equiv. of $BF_3{\cdot}OEt_2$, MeCN, −78 to −30°C, 2 h, 57%; (i) from **57**, 15.0 equiv. of Et_3SiH, 15.0 equiv. of $BF_3{\cdot}OEt_2$, MeCN, 0°C, 12 h (**63**: 66%; **64**: 11%); from **58** (**63**: 75%; **64**: 9%); (j) from **57**, 15.0 equiv. of $BF_3{\cdot}OEt_2$, MeCN, −15°C, 1 h, **61** and **62** (1:1 ratio), 100%.

O-Methylation of hemiacetal **44** under the base conditions reported by Mori[26l] (THF, MeI/NaH) gave the methyl

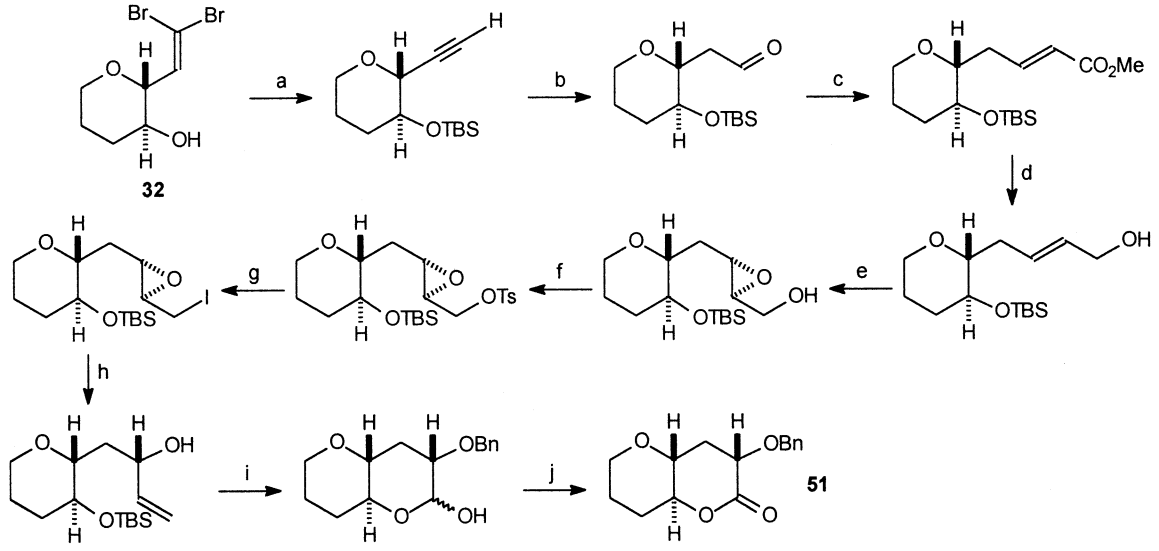
diacetal **45**, which was doubly reduced by SI-LA treatment (CH_2Cl_2, $Et_3SiH/BF_3{\cdot}OEt_2/CH_3CN/-75$ to $-30°C$) to compound **47** in 78% yield.

Finally, the earlier method was applied to the synthesis of tetracyclic compound **60** as an advanced model system for this convergent approach (Scheme 4). Generation of the lithium acetylide of **50**,[†] followed by condensation with lactone **51**,[‡] yielded an inseparable mixture (1:1 ratio) of diastereoisomers **52**. Subsequent treatment with CSA/MeOH gave, with loss of TBS group, a 1:1 mixture of methyl acetals **53**, which was further acetylated to give **54** (1:1 mixture). Partial hydrogenation (10% Pd–$BaSO_4$, H_2) gave **55**, which was further oxidized to afford the ketone **56** (1:1 mixture). Base hydrolysis gave hydroxy-ketone **57** and hemiacetal **58** that were separated by column chromatography.

O-Methylation of the hemiacetal **58** following the earlier described conditions gave the methyl diacetal **59**, which was reduced to compound **60** in 57% yield.[27f] Then, we envisioned the reductive etherification of hydroxy-ketone **57** and hemiacetal **58** to fused oxepane systems. Reduction of **57** and **58** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ resulted in the formation of diols **63** and **64** in the relative proportions of (6:1), respectively. In order to check the



Reagents and conditions: (a) TBSCl (0.3 equiv.), CH_2Cl_2, 64%; (b) $SO_3{\cdot}$py complex (3.0 equiv.), Et_3N (7.0 equiv.), DMSO/CH_2Cl_2 (1:1), 3 h, 98%; (c) $Ph_3P{=}CHCO_2Me$ (1.2 equiv.), NaH (1.0 equiv.), benzene, 1 h, 95%; (d) DIBALH (2.0 equiv.), THF, 2 h, 82%; (e) −DET (0.12 equiv.) $(^iPro)_4Ti$ (0.1 equiv.), ^{t}BuOOH (1.8 equiv.), CH_2Cl_2, 3 h, 90%; (f) NMO (1.5 equiv.), TPAP catalyst, CH_2Cl_2, 91%; (g) PPh_3 (4.0 equiv.), Br_4C (2.0 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2, 78%; (h) TBAF (1.5 equiv.), THF, 3 h, 98%; (i) CSA catalyst, CH_2Cl_2, 0–25°C, 93%; (j) TMSCl (1.5 equiv.), imidazole (1.5 equiv.), CH_2Cl_2, 96%.



Reagents and conditions: (a) *n*-BuLi (2.0 equiv.), −78°C, THF, 30 min, then H_2O, 81%; (b) $(Sia)_2BH$ (2.0 equiv.), THF, 0°C, 12 h, then 3N NaOH (10.0 equiv.), 30% H_2O_2 (20.0 equiv.), 0°C, 2 h, 88%; (c) NaH (1.3 equiv.), $(MeO)_2POCH_2CO_2Me$ (1.2 equiv.), benzene, 25°C, 15 min, 88%; (d) DIBALH (5.0 equiv.), Et_2O, 0°C, 1.5 h; quench with NaOH–H_2O, 98%; (e) (+)DET (0.4 equiv.), ^{t}BuOOH (1.8 equiv.), 4 Å MS, CH_2Cl_2, −20°C, 12 h, 95%; (f) TosCl (1.1 equiv.), 4-DAMP (0.05 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, 25°C, 8 h, 93%; (g) NaI (2.3 equiv.), $NaHCO_3$ (2.0 equiv.), butanone, 60°C, 1 h, 97%; (h) ^{t}BuLi (2.0 equiv.), Et_2O, −78°C, 2 h, 99%; (i) BnCl (2.0 equiv.), $(^iPr)_2EtN$ (4.0 equiv.), 4-DAMP (0.1 equiv.), CH_2Cl_2, 25°C, 6 h, 96%, (ii) NMO (3.0 equiv.), OsO_4 catalyst, THF/H_2O/acetone (1:1:1), 25°C, 12 h, 75%, (iii) TBAF (1.2 equiv.), THF, 25°C, 6 h, (iv) $(n\text{-}Bu)_4NIO_4$ (2.5 equiv.), MeOH/H_2O (4:1), 20°C, 3 h, 81% for two steps; (j) PCC (1.5 equiv.) NaOAc (0.2 equiv.), CH_2Cl_2, 25°C, 6 h, 73%.

[†] Dibromoolefin **50**, $[\alpha]_D^{25}=+9.2°$ (*c* 2.08, $CHCl_3$), was readily prepared as illustrated following a standard methodology.[31]

[‡] Lactone **51**, $[\alpha]_D^{25}=-122°$ (*c* 1.77, $CHCl_3$), was prepared starting from the dibromoolefin **32** following the synthetic sequence outlined.[32]

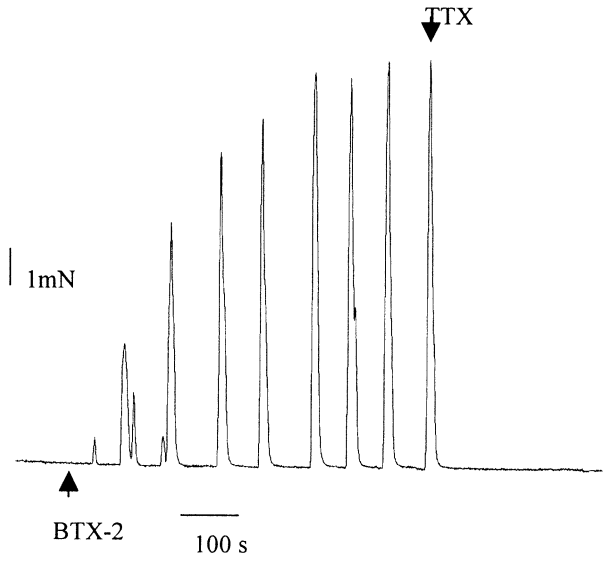
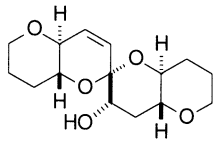
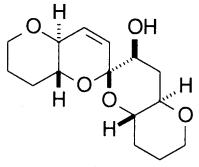


Figure 7. Typical tracing showing the rhythmic contractions elicited by brevetoxin B (BTX-2, 30 nM) in isolated uterine strips from non-pregnant rats. The rhythmic contractions were abolished by TTX (0.1 μM). The record is representative of typical results in five different animals.

intermediacy of spiroketones **61** and **62** in this unexpected reductive process, compounds **57** and **58** were independently treated with $BF_3{\cdot}OEt_2$/MeCN to give, in a 1:1 ratio, spiroketones **61** and **62**, which were separated and their configurations at the spiroketal carbon determined by 2D COSY and 1D ^{1}HNOE difference experiments. Reduction of **61** or **62** using $BF_3{\cdot}Et_2O$ and a large excess of Et_3SiH gave diols **63** and **64**, as the only compounds to be isolated. Unexpectedly, in compounds **61** and **62**, the SI-LA induced reduction of carbonyl group occurred prior to the dioxaspirocyclic functionality to give the hydroxy derivatives **65** and **66**, which precluded the reductive etherification coupling to oxepene rings.



65



66

3. Biological studies

RT-PCR was used to investigate Na^+ channel subtypes mRNA expression in the rat uterus. As shown in Fig. 1, six of the 10 voltage-gated Na^+ channels cloned in the rat are expressed in the uterus. The high-affinity and selective Na^+ channel activator brevetoxin-B (BTX-2, ≥30 nM) caused the development of rhythmic contractions in isolated strips of rat myometrium (Fig. 7). The contractions were rapidly and completely abolished by tetrodotoxin (TTX, 0.1 μM). These data provide evidence that functionally active voltage-gated Na^+ channels exist in the non-pregnant rat uterus.

Although none of the polyethers synthesized in this work reach the required size (~30 Å long), some of them, i.e. compounds **11** and **29** (1 nM–1 μM), were tested on the isolated uterus, showing no induction of any significant contractile effect on myometrial preparations under resting tone. It has been shown that some brevetoxin derivatives act as Na^+ channel antagonists,[6d] therefore, we analyzed the possible inhibitory effects of a high concentration (1 μM) of each of the selected polyethers on rhythmic contractions elicited by BTX-2 (30 nM). The compounds assayed inhibited neither the frequency nor the amplitude of contractions elicited by BTX-2, which revealed no binding to the BTX-2 receptor site. In these same experiments, addition of TTX (0.1 μM) caused the abolition of rhythmic contractions. These data demonstrate that compounds **11** and **29** are also devoid of antagonist activity on Na^+ channels.

3.1. Biological assays

All experiments were conducted in accordance with NIH guidelines for the care and use of laboratory animals. Uterine horns from virgin rats in the oestrous stage of the hormonal cycle were removed and carefully cleaned. mRNA expression of voltage-gated Na^+ channels was analyzed by reverse transcription-polymerase chain reaction (RT-PCR). Total RNA from uterine tissue was isolated, treated with DNase I and reverse-transcribed as previously described.[33] First strand cDNA was obtained and amplified by PCR using specific oligonucleotide primers designed from the sequences of rat Na^+ channel subtypes. Glyceraldehyde 3-phosphate dehydrogenase and β-actin were used as housekeeping genes. Functional studies were performed on isolated strips of rat uterine smooth muscle, essentially as described.[34] Strips of longitudinal smooth muscle were prepared and mounted in tissue baths containing 4 mL of Krebs solution of the following composition (mM): NaCl 118; KCl 5.6; $CaCl_2$ 1.1; $MgSO_4$ 0.95; $NaHPO_4$ 1.0; $NaHCO_3$ 25 and glucose 11. A physiological solution with a low concentration of Ca^{2+} was used to avoid development of myometrial spontaneous contractions.[35] Uterine strips were suspended under an initial tension of 0.5 g, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Mechanical responses were recorded isometrically by means of force-displacement transducers (Grass FT-03). Preparations were allowed to equilibrate for a 60 min period before addition of cumulative concentrations of compounds **11** and **29** (1 nM–1 μM) or of the selective Na^+ channel activator brevetoxin B (BTX-2, 0.1 nM–0.1 μM). Only one product was tested on each tissue. When rhythmic contractions appeared, the selective Na^+ channel blocker tetrodotoxin (TTX, 0.1 μM) was added to the bath in the continuous presence of the analyzed compound. In another set of experiments, the response to BTX-2 (30 nM) was studied in the presence of a single concentration (1 μM) of compounds **11** and **29**, which were added to the bath 20 min before BTX-2 and maintained in contact with the tissue during exposure to BTX-2. Only one compound was tested in each strip. Contractile responses were measured as peak increases in force and expressed in mN.

4. Conclusions

Model structures of several ciguatoxins indicated that these

molecules are ~30 Å long and mostly flat, with a hinge part around the middle of the molecule and a large semi-rigid curvature at one of the ends. From the results achieved here, we can conclude that a similar mono-conformational situation can be reached by exclusive participation of oxane and oxepane rings. *trans*-Fused polyethers with an odd number of oxepane rings flanked by oxanes at both ends (i.e. **11** or **29**) present a 'folded' shape conformation. The small number of minima characterized for the compounds investigated indicates that they are quite rigid. Accordingly, the conformational preference can be explained by one-state rather than a two-state equilibrium like in polycyclic oxepane systems (i.e. **4**). However, an even number of oxepanes flanked by oxanes in both ends (i.e. **13** or **14**) introduces drastic changes in the pseudorotational preferences given to highly flexible structures.

Convergent approaches to series of *ortho*-condensed systems, via intermolecular coupling of polycyclic segments can be used for the syntheses of oxane/oxepane models with controlled size and conformational mobility. Input from biological studies should provide additional guiding principles.

5. Experimental

5.1. General experimental procedures

^{1}H NMR spectra were recorded on Bruker spectrometers Avance DPX300 (300 MHz), Avance DRX400 (400 MHz) or Avance DRX500 (500 MHz). Chemical shifts are reported in parts per million from TMS with the solvent resonance as the internal standard. Data are reported as follows: chemical shift multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), integration, coupling constants (Hz) and assignment. ^{13}C NMR spectra were recorded Bruker on spectrometers Avance DPX300 (75 MHz), Avance DRX400 (100 MHz) or Avance DRX500 (125 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from TMS with the solvent as the internal reference. IR spectra were recorded on a Bruker Vector 22 spectrosphotometer. High resolution mass spectra were provided by the Universities of Seville and Cordoba Mass Spectrometry Facilities and were performed on Kratos MS80RFA, Finnigan MAT 95 or Micromass AutoSpec Q spectrometers. Melting points were determined on a Buchi 241 melting points apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 341 polarimeter, using the sodium D line at 25°C. TLC was performed using Merck silica gel 60F254 precoated plates (0.25 mm thickness) with a fluorescent indictor, visualization was accomplished with one or more of the following: UV light (254 nm), 10% ethanolic phosphomolybdic acid or H_2O/H_2SO_4/AcOH (1:4:20) solution and heat as a developing agent. Column chromatography was performed using Merck silica gel 60 (70–230 mesh) and, for flash chromatography, Merck silica gel 60 (234–400 mesh) was used. All chromatographic separations were monitored by TLC analyses. Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride was purchased from Strem Chemicals, stored in a dry-box and used under argon atmosphere with standard Schlenk techniques. All other reagents were purchased from Aldrich and used without further purification unless otherwise stated. All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2), acetonitrile (MeCN), triethylamine (Et_3N), diisopropylamine, pyridine, benzene and toluene from calcium hydride, dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) from calcium hydride under reduced pressure.

5.2. General procedure for *O*-alkylation

In a typical experimental procedure, the corresponding alcohol (0.3 mmol) was dissolved in dry THF (3.0 mL) and allyl bromide (0.45 mmol) and a catalytic amount of *n*-Bu_4NI was added. The reaction mixture was cooled to 0°C and NaH (0.36 mm, 1.2 equiv., 60% dispersion in mineral oil) was added and left overnight, allowing the temperature to rise. The reaction mixture was cooled again to 0°C and water (2 mL) was added. The aqueous layer was extracted with EtOAc (3×3 mL), combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed in vacuo and the residue was purified by flash chromatography.

5.2.1. *meso*-(2*R*,3*S*,6*R*,7*S*)-3,6-Bis-allyloxy-2,7-divinyl-oxepane (1). Colorless oil; R_f=0.72 (hexane/EtOAc, 4:1); IR (neat) 3693, 3012, 1726, 1640, 1220, 1084 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92–5.81 (m, 2H, $H_{1'}$, $H_{2''}$), 5.30 (ddd, J=17.5, 2.0, 2.0 Hz, 1H, $H_{3''}$), 5.25 (ddd, J=17.2, 3.5, 2.0 Hz, 1H, $H_{2'}$), 5.14 (ddd, J=10.5, 3.5, 2.0 Hz, 1H, $H_{3''}$), 5.06 (ddd, J=10.6, 2.0, 2.0 Hz, 1H, $H_{2'}$), 4.02 (dddd, J=12.5, 5.5, 2.0, 2.0 Hz, 1H, $H_{1''}$), 4.01 (dddd, J=11.4, 6.4, 2.0, 2.0 Hz, 1H, H_2), 3.83 (ddd, J=5.5, 2.0, 2.0 Hz, 1H, $H_{1''}$), 3.42 (ddd, J=6.4, 5.0, 4.0 Hz, 1H, H_3), 1.88–1.81 (m, 1H, H_4), 176–1.68 (m, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6 (d, $C_{1'}$), 135.4 (d, $C_{2''}$), 117.0 (t, $C_{3''}$), 114.5 (t, $C_{2'}$), 83.9 (d, C_2), 81.4 (d, C_3), 69.9 (t, $C_{1''}$), 24.2 (t, C_4); HRMS Calcd for $C_{16}H_{24}O_3$ (M^+): 264.17253; Found: 264.17261.

5.2.2. *meso*-(2*R*,3*S*,6*R*,7*S*)-2,6-Diallyl-3,6-bis-allyloxy-oxepane (2). Colorless oil; R_f=0.42 (hexane/EtOAc, 2:1); IR (neat) 3014, 1726, 1640, 1410, 1230, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J=17.2, 10.2, 5.7, 5.3 Hz, 1H, $H_{2''}$), 5.85 (dddd, J=17.2, 10.2, 8.0, 7.0 Hz, 1H, $H_{2'}$), 5.23 (d, J=17.2 Hz, 1H, $H_{3''}$), 5.13 (d, J=10.2 Hz, 1H, $H_{3''}$), 5.05 (d, J=17.2 Hz, 1H, $H_{3'}$), 5.02 (d, J=10.2 Hz, 1H, $H_{3'}$), 4.03 (brdd, J=12.5, 5.3 Hz, 1H, $H_{1''}$), 3.83 (brdd, J=12.5, 5.7 Hz, 1H, $H_{1''}$), 3.31 (brddd, J=8.2, 8.0, 3.2 Hz, 1H, H_2), 3.22–3.16 (m, 1H, H_3), 2.43 (brddd, J=14.5, 8.0, 3.2 Hz, 1H, $H_{1'}$), 2.16 (ddd, J=14.5, 8.0, 7.2 Hz, 1H, $H_{1'}$), 1.83–1.76 (m, 1H, H_4), 1.75–1.67 (m, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (d, $C_{2''}$), 135.0 (d, $C_{2'}$), 117.1 (t, $C_{3''}$), 116.8 (t, $C_{3'}$), 84.7 (d, C_2), 82.2 (d, C_3), 70.1 (t, $C_{1''}$), 38.9 (t, $C_{1'}$), 24.5 (t, C_4); HRMS Calcd for $C_{18}H_{28}O_3$ (M^+): 292. 20383; Found: 292.20379.

5.2.3. *meso*-(2*R*,3*S*,6*R*,7*S*)-Bis-allyloxy-2,7-di-but-3′-enyl-oxepane (3). Colorless oil; R_f=0.43 (hexane/EtOAc, 2:1); IR (neat) 3693, 3011, 1726, 1640, 1420, 1084 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, J=17.2, 10.4, 5.8, 5.6 Hz, 1H, $H_{2''}$), 5.83 (dddd, J=17.1, 10.1, 8.0, 5.0 Hz, 1H, $H_{3'}$), 5.23 (brd, J=17.2 Hz, 1H, $H_{3''}$), 5.12 (brd, J=10.4 Hz, 1H, $H_{3''}$), 5.00 (brd, J=17.1 Hz, 1H, $H_{4'}$), 4.93 (brd, J=10.1 Hz, 1H, $H_{4'}$), 4.04 (brdd, J=12.6, 5.5 Hz, 1H, $H_{1''}$), 3.84 (brdd, J=12.6, 5.8 Hz, 1H, $H_{1''}$), 3.27 (ddd, J=9.5, 8.0, 3.2 Hz, 1H, H_2), 3.15 (brddd, J=8.0, 7.5, 3.5 Hz, 1H, H_3), 2.28 (brddd, J=14.2, 8.0, 4.8, 2.0 Hz, 1H, $H_{2'}$), 2.10 (brddd, J=14.2, 11.0, 5.0, 3.0 Hz, 1H, $H_{2'}$), 1.83 (brddd, J=14.3, 11.0, 4.8, 3.0 Hz, 1H, $H_{1'}$), 1.81–1.74 (m, 1H, H_4), 1.73–1.66 (m, 1H, H_4), 1.46 (dddd, J=14.3, 9.5, 5.0, 4.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0 (d, $C_{3'}$), 135.7 (d, $C_{2''}$), 117.0 (t, $C_{3''}$), 114.4 (t, $C_{4'}$), 84.0 (d, C_2), 82.5 (d, C_3), 70.2 (t, $C_{1''}$), 34.3 (t, $C_{1'}$), 30.7 (t, $C_{2'}$), 24.6 (t, C_4); HRMS Calcd for $C_{20}H_{32}O_3$ (M^+): 320.23513; Found: 320.23547.

5.2.4. *meso*-(2*R*,3*S*,5a*R*,6a*S*,9*R*,10*S*,11a*R*,13a*S*)-3,9-Bis-allyloxy-2,10-divinyl-tetradecahydro-1,6,11-trioxa-cyclohepta[1,2-*b*]-heptalene (4). Colorless oil; R_f=0.65 (hexane/EtOAc, 4:1); IR (neat) 3693, 3011, 2360, 1726, 1220, 1084 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, J=17.2, 10.6, 4.7 Hz, 1H, $H_{1'}$), 5.80 (dddd, J=17.2, 10.5, 5.3, 5.3 Hz, 1H, $H_{2''}$), 5.47 (ddd, J=17.2, 2.0, 2.0 Hz, 1H, $H_{2'}$), 5.21 (ddd, J=17.2, 3.4, 1.8 Hz, 1H, $H_{3''}$), 5.08 (ddd, J=10.6, 2.0, 1.9 Hz, 1H, $H_{2'}$), 5.02 (ddd, J=10.5, 3.4, 1.6 Hz, 1H, $H_{3''}$), 4.23 (ddd, J=8.2, 5.3, 1.9 Hz, 1H, H_2), 3.78 (dddd, J=12.9, 5.3, 1.7, 1.6 Hz, 1H, $H_{1''}$), 3.71 (ddd, J=9.1, 6.9, 4.9 Hz, 1H, H_{11a}), 3.62 (dddd, J=12.9, 5.3, 1.6, 1.6 Hz, 1H, $H_{1''}$), 3.39 (ddd, J=8.2, 6.3, 2.2 Hz, 1H, H_3), 3.37 (brddd, J=10.4, 9.1, 4.7 Hz, 1H, H_{5a}), 2.06 (dddd, J=15.6, 12.9, 10.4, 2.3 Hz, 1H, H_5), 2.01 (brdd, J=14.5, 6.9 Hz, 1H, H_{12}), 1.89 (brddd, J=15.9, 6.5, 4.7 Hz, 1H, H_5), 1.85 (brdd, J=14.4, 4.9 Hz, 1H, H_{12}), 1.72 (brddd, J=14.7, 6.5, 6.3 Hz, 1H, H_4), 1.59 (brdd, J=14.7, 12.5 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4 (d, $C_{1'}$), 135.2 (d, $C_{2''}$), 115.7 (t, $C_{3''}$), 113.9 (t, $C_{2'}$), 85.6 (d, C_{5a}), 82.9 (d, C_2), 82.4 (d, C_{11a}), 81.7 (d, C_3), 69.5 (t, $C_{1''}$), 29.9 (t, C_{12}), 28.2 (t, C_5), 22.8 (t, C_4); ^{1}H NMR (500 MHz, C_6D_6) δ 5.87 (dddd, J=17.2, 10.5, 5.6, 5.3 Hz, 1H, $H_{2''}$), 5.78 (ddd, J=17.2, 10.6, 5.2 Hz, 1H, $H_{1'}$), 5.28 (ddd, J=17.2, 2.0, 2.0 Hz, 1H, $H_{2'}$), 5.23 (dddd, J=17.2, 2.0, 2.0, 2.0 Hz, 1H, $H_{3''}$), 5.13 (ddd, J=10.5, 2.0, 2.0 Hz, 1H, $H_{3''}$), 5.07 (ddd, J=10.6, 2.0, 2.0 Hz, 1H, $H_{2'}$), 4.07 (ddd, J=8.0, 5.3, 2.0 Hz, 1H, H_2), 3.99 (dddd, J=12.7, 5.6, 2.0, 2.0 Hz, 1H, $H_{1''}$), 3.83 (dddd, J=12.2, 5.3, 2.0, 2.0 Hz, 1H, $H_{1''}$), 3.58–3.54 (m, 1H, H_{5a}), 3.47 (ddd, J=6.0, 4.0, 2.0 Hz, 1H, H_3), 3.29 (brddd, J=15.3, 15.3, 9.0 Hz, 1H, H_{11a}), 1.90–1.82 (m, 3H, H_4, 2×H_5), 1.81–1.75 (m, 2H, 2×H_{12}), 1.61–1.52 (m, 1H, H_4); ^{13}C NMR (125 MHz, C_6D_6) δ 137.8 (d, $C_{2''}$), 134.8 (d, $C_{1'}$), 116.7 (t, $C_{2'}$), 114.7 (t, $C_{3''}$), 85.7 (d, C_{5a}), 83.0 (d, C_2), 82.3 (d, C_{11a}), 81.9 (d, C_3), 69.7 (t, $C_{1''}$), 29.7 (t, C_{12}), 27.9 (t, C_5), 22.8 (t, C_4); HRMS Calcd for $C_{24}H_{36}O_5$ (M^+): 404.25628; Found: 404.25514.

5.2.5. (4a*S*,6*R*,7*S*,9a*R*)-7-Allyloxy-6-vinyl-octahydro-1,5-dioxa-benzocycloheptene (5). Colorless oil; R_f=0.57 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=+24.0° (*c* 0.31, $CHCl_3$); IR (neat) 3685, 3013, 1731, 1602, 1232, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91–5.80 (m, 2H, $H_{2'}$, $H_{1''}$), 5.28 (ddd, J=17.3, 1.8, 1.8 Hz, 1H, $H_{3'}$), 5.24 (ddd, J=17.3, 3.5, 5.3, 1.8 Hz, 1H, $H_{2''}$), 5.13 (ddd, J=10.4, 3.1, 1.5 Hz, 1H, $H_{3'}$), 5.07 (ddd, J=10.6, 1.8, 1.7 Hz, 1H, $H_{2''}$), 4.02 (dddd, J=12.7, 5.4, 1.5, 1.5 Hz, 1H, $H_{1'}$), 3.99 (dddd, J=11.2, 5.2, 1.7, 1.7 Hz, 1H, H_6), 3.85 (ddd, J=5.7, 1.4, 1.4 Hz, 1H, H_2), 3.82 (ddd, J=5.7, 1.6, 1.6 Hz, 1H, $H_{1'}$), 3.43 (ddd, J=4.9, 4.9, 2.9 Hz, 1H, H_7), 3.28 (brdddd, J=14.8, 11.3, 9.0, 6.2 Hz, 1H, H_2), 3.23 (ddd, J=11.1, 9.2, 4.6 Hz, 1H, H_{4a}), 2.98 (brddd, J=9.3, 9.2, 5.2 Hz, 1H, H_{9a}), 2.05 (dddd, J=12.8, 6.6, 4.6, 3.6 Hz, 1H, H_4), 1.93 (brddd, J=13.4, 9.0, 4.5 Hz, 1H, H_8), 1.84–1.73 (m, 2H, 2×H_9), 1.69–1.60 (m, 3H, 2×H_3, H_8), 1.43 (brdd, J=12.4, 11.1, 7.0 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (d, $C_{2'}$), 134.8 (d, $C_{1''}$), 116.8 (t, $C_{3'}$), 114.5 (t, $C_{2''}$), 83.9 (d, C_6), 82.7 (d, C_{9a}), 81.3 (d, C_7), 80.5 (d, C_{4a}), 69.9 (t, $C_{1'}$), 67.6 (t, C_2), 31.4 (t, C_4), 26.9 (t, C_9), 27.5 (t, C_3), 23.8 (t, C_8); HRMS Calcd for $C_{14}H_{22}O_3$ (M^+): 238.99491; Found: 238.99468.

5.2.6. (4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-8-Allyloxy-9-vinyl-dodecahydro-1,5,10-trioxa-benzo[*b*]heptalene (6). Colorless oil; R_f=0.91 (hexane/EtOAc, 13:7); $[\alpha]_D^{25}$=+24.4° (*c* 0.43, $CHCl_3$); IR (neat) 3008, 1162, 1378, 1087, 763 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, J=17.3, 10.4, 5.7, 5.7 Hz, 1H, $H_{2'}$), 5.79 (ddd, J=17.2, 10.5, 5.3 Hz, 1H, $H_{1''}$), 5.28 (ddd, J=17.2, 1.8, 1.8 Hz, 1H, $H_{2''}$), 5.24 (ddd, J=17.2, 1.7, 1.7 Hz, 1H, $H_{3'}$), 5.12 (dddd, J=10.4, 1.5, 1.5 Hz, 1H, $H_{3'}$), 5.07 (dddd, J=10.5, 1.7, 1.7 Hz, 1H, $H_{2''}$), 4.04 (dddd, J=5.4, 3.7, 1.8, 1.8 Hz, 1H, H_9), 4.00 (dddd, J=12.7, 5.3, 1.5, 1.5 Hz, 1H, H_1), 3.86–3.81 (m, 2H, $H_{1'}$, H_2), 3.66 (ddd, J=9.0, 5.4, 5.3 Hz, 1H, H_{10a}), 3.43 (ddd, J=6.1, 3.7, 2.0 Hz, 1H, H_8), 3.35 (brdd, J=14.6, 4.6 Hz, 1H, H_{5a}), 3.27 (ddd, J=9.1, 6.8, 6.8 Hz, 1H, H_{12a}), 3.14 (ddd, J=11.5, 9.1, 4.0 Hz, 1H, H_{4a}), 2.95 (ddd, J=9.1, 6.8, 6.8 Hz, 1H, H_{12a}), 2.03 (brdd, J=12.1, 3.9 Hz, 1H, H_4), 1.98–1.86 (m, 2H, 2×H_{11}), 1.86–1.77 (m, 5H, 2×H_{12}, H_7, 2×H_6), 1.67–1.58 (m, 3H, 2×H_3, H_7), 1.41 (brdd, J=12.1, 11.5 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8 (d, $C_{2'}$), 134.9 (d, $C_{1''}$), 116.7 (t, $C_{3'}$), 114.8 (t, $C_{2''}$), 84.4 (d, C_{5a}), 83.3 (d, C_{12a}), 83.2 (d, C_9), 82.3 (d, C_{4a}), 82.0 (t, C_{10a}), 81.5 (d, C_8), 69.8 (t, $C_{1'}$), 67.9 (t, C_2), 31.6 (t, C_4), 30.7 (t, C_{11}), 28.9 (t, C_{12}), 27.9 (t, C_6), 26.1 (t, C_3), 23.1 (t, C_7); HRMS Calcd for $C_{18}H_{28}O_4$ (M^+): 308.19876; Found: 308.19883.

5.2.7. (4a*R*,5a*S*,8*R*,9*S*,10a*R*,12a*S*)-8-Allyloxy-2,2-dimethyl-9-vinyl-decahydro-1,3,5,10-tetraoxabenzo[*b*]heptalene (7). Colorless foam; R_f=0.48 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$=−26.6° (*c* 0.35, $CHCl_3$); IR (KBr) 3017, 2933, 1601, 1455, 1011, 876 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91–5.80 (m, 2H, $H_{2'}$, $H_{1''}$), 5.28 (ddd, J=17.8, 1.7, 1.7 Hz, 1H, $H_{2''}$), 5.24 (dd, J=17.7, 1.7 Hz, 1H, $H_{3'}$), 5.15 (dd, J=10.4, 1.5 Hz, 1H, $H_{3'}$), 5.08 (ddd, J=10.6, 1.7, 1.7 Hz, 1H, $H_{2''}$), 4.03–3.96 (m, 3H, H_4, H_9, $H_{1'}$), 3.90–3.82 (m, 3H, H_4, H_{4a}, $H_{1'}$), 3.47 (brdd, J=7.6, 4.7 Hz, 1H, H_8), 3.24–3.18 (m, 2H, H_{10a}, H_{12a}), 3.04 (ddd, J=10.0, 10.0, 5.0 Hz, 1H, H_{5a}), 2.08 (brddd, J=12.7, 4.5, 4.5, 4.0 Hz, 1H, H_{11}), 1.94–1.89 (m, 2H, H_7, H_{12}), 1.79 (brddd, J=12.3, 11.8, 10.5, 10.5 Hz, 1H, H_6), 1.76–1.71 (m, 1H, H_6), 1.62 (dddd, J=13.4, 12.7, 2.4, 2.4 Hz, 1H, H_7), 1.46 (dddd, J=13.4, 12.7, 12.5, 4.0 Hz, 1H, H_{11}), 1.38 (s. 3H, CH_3-2), 1.36–1.33 (m, 1H, H_{12}), 1.32 (s, 3H, CH_3-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2 (d, $C_{1''}$), 135.3 (d, $C_{2'}$), 117.2 (t, $C_{3'}$), 115.0 (t, $C_{2''}$), 109.7 (s, C_2), 84.3 (d, C_9), 82.8 (d, C_{5a}), 81.7 (d, C_8), 80.8 (d, C_{10a}), 78.5 (d, C_{12a}), 78.3 (d, C_{4a}), 70.3 (t, $C_{1'}$), 67.7 (t, C_4), 31.2 (t, C_{11}), 28.1 (t, C_{12}), 27.2

(t, C_6), 27.1 (q, *C*H_3-2), 25.7 (q, *C*H_3-2), 24.2 (t, C_7); HRMS Calcd for $C_{19}H_{30}O_5$ (M^+): 338.20930; Found: 338.20936.

5.3. General procedure for olefin metathesis

The amount of catalyst necessary in each case was weighted and dissolved in dry CH_2Cl_2 in a flame-dried vessel (10–30 mol% of catalyst). A solution of the corresponding diene in CH_2Cl_2 was then added dropwise via cannula to the above solution under an atmosphere of dried argon (final concentration of diene 6×10^{-3} M). When addition finished, the vessel was sealed and the reaction mixture was stirred at room temperature (2–4 h). Progress of reaction was tested by TLC and NMR. When the reaction finished or when no further progress was observed, solvent was removed in vacuo and the residue was purified by flash chromatography, affording the expected unsaturated heterocycle.

5.3.1. *meso*-(2*R*,3*S*,6*R*,7*S*)-2,4a,5a,8,9a,10,11,11a-Octahydro-1,5,9-trioxa-dibenzo[*a*,*d*]cycloheptane (8). Colorless oil; R_f=0.71 (hexane/EtOAc, 4:1); IR (neat) 3017, 2941, 1610, 1460, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J*=11.0, 4.5, 2.5 Hz, 1H, H_4), 5.75 (ddd, *J*=11.0, 2.0, 2.0 Hz, 1H, H_3), 4.18 (ddd, *J*=12.0, 4.5, 2.0 Hz, 1H, H_2), 4.14 (ddd, *J*=12.0, 2.5, 2.0 Hz, 1H, H_2), 4.01 (dd, *J*=8.4, 2.0 Hz, 1H, H_{4a}), 3.36 (ddd, *J*=8.4, 7.8, 6.5 Hz, 1H, H_{9a}), 1.95–1.88 (m, 2H, 2×H_{10}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.1 (d, C_4), 128.0 (d, C_3), 80.1 (d, C_{9a}), 75.7 (d, C_{4a}), 65.7 (t, C_2), 29.4 (t, C_{10}); HRMS Calcd for $C_{12}H_{16}O_3$ (M^+): 208.10993; Found: 208.10982. Compound **8** was hydrogenated (10% Pd–C cat/H_2/EtOAc/25° C/2 h) to give tetrahydro derivative: *meso-(4aR,5aS,9aS,11aR)-2,3,4,4a,5a,6,7,8,9a,10,11,11a-dodecahydro-1,5,9-trioxa[a,d]cycloheptane* (**8′**). Colorless oil; R_f=0.73 (hexane/EtOAc, 3:1); IR (neat) 3002, 2980, 1604, 1242, 1085, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (ddd, *J*=11.5, 4.0, 2.0 Hz, 1H, H_2), 3.24 (ddd, *J*=11.5, 10.0, 4.5 Hz, 1H, H_2), 3.22 (ddd, *J*=9.0, 9.0, 4.5 Hz, 1H, H_{4a}), 3.11 (ddd, *J*=9.0, 8.5, 4.6 Hz, 1H, H_{9a}), 2.10 (dddd, *J*=11.5, 9.0, 4.0, 2.0 Hz, 1H, H_4), 1.98–1.91 (m, 2H, 2×H_{11}), 1.68–1.62 (m, 2H, 2×H_3), 1.45 (ddd, *J*=12.5, 11.5, 6.0 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.0 (d, C_{9a}), 81.0 (d, C_{4a}), 67.8 (t, C_2), 32.1 (t, C_4), 30.6 (t, C_{10}), 26.0 (t, C_3); HRMS Calcd for $C_{12}H_{20}O_3$ (M^+): 212.14123; Found: 212.14224.

5.3.2. *meso*-(5a*S*,6a*R*,11a*S*,13a*R*)-2,5,5a,6a,7,10,11a,12,13,13a-Decahydro-1,6,11-trioxa-cyclohepta[*b*]heptalene (9). Colorless oil; R_f=0.72 (hexane/EtOAc, 4:1); IR (neat) 3018, 2940, 1726, 1610, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, *J*=11.0, 2.0, 2.0 Hz, 1H, H_3), 5.67 (ddd, *J*=11.0, 2.0, 2.0 Hz, 1H, H_4), 4.20 (brdd, *J*=14.5, 2.0 Hz, 1H, H_2), 3.97 (brdd, *J*=14.5, 2.0 Hz, 1H, H_2), 3.38 (ddd, *J*=10.0, 8.0, 4.0 Hz, 1H, H_{5a}), 3.29 (brddd, *J*=8.0, 3.0, 3.0 Hz, 1H, H_{11a}), 2.58 (ddd, *J*=12.0, 4.0, 2.0 Hz, 1H, H_5), 2.24 (dd, *J*=12.0, 10.0 Hz, 1H, H_5), 1.98–1.92 (m, 2H, 2×H_{12}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.2 (d, C_3), 125.8 (d, C_4), 86.0 (d, C_{11a}), 83.5 (d, C_{5a}), 68.4 (t, C_2), 36.7 (t, C_5), 29.3 (t, C_{12}); HRMS Calcd for $C_{14}H_{20}O_3$ (M^+): 236.14123; Found: 236.14224. Compound **9** was hydrogenated (10% Pd–C cat/H_2/EtOAc/25°C/2 h) to give the tetrahydro derivative: *meso-(5aS,6aR,11aS,13aR)-2,3,4,5,5a,6a,7,8,9,10,11a,12,13,13a-tetradecahydro-1,6,11-trioxa-cyclohepta[b]heptalene* (**9′**). Colorless oil; R_f=0.81 (hexane/EtOAc, 4:1); IR (neat) 3002, 2940, 1726, 1610, 1234, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (ddd, *J*=12.0, 8.8, 6.0 Hz, 1H, H_2), 3.66 (ddd, *J*=12.0, 10.5, 4.8 Hz, 1H, H_2), 3.30 (ddd, *J*=14.0, 9.0, 4.8 Hz, 1H, H_{5a}), 3.27 (brs, 1H, H_{11a}), 2.08–2.03 (m, 1H, H_5), 1.85–1.81 (m, 2H, 2×H_{12}), 1.75–1.70 (m, 1H, H_4), 1.67–1.60 (m, 2H, H_3, H_4), 1.54–1.46 (m, 1H, H_3), 1.42–1.37 (m, 1H, H_5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.4 (d, C_{11a}), 80.9 (d, C_{5a}), 68.9 (t, C_2), 36.0 (d, C_5), 29.3 (t, C_{12}), 28.7 (t, C_4), 20.9 (t, C_3); HRMS Calcd for $C_{14}H_{24}O_3$ (M^+): 240.17253; Found: 240.17338.

5.3.3. *meso*-(1*S*,3*R*,10*S*,13*R*)-2,9,14-Trioxa-tricyclo-[11.6.0.0^{3,10}]nonadeca-6,16-diene (10). Colorless oil; R_f=0.68 (hexane/EtOAc, 4:1); IR (neat) 3017, 2940, 2341, 1724, 1610, 1422, 1284, 980 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, *J*=11.0, 2.0, 2.0 Hz, 1H, H_3), 5.72 (brddd, *J*=9.7, 9.4, 8.3 Hz, 1H, H_6), 5.26 (brddd, *J*=9.7, 3.0, 2.0 Hz, 1H, H_7), 4.37 (brd, *J*=6.8 Hz, 1H, H_8), 4.01 (brdd, *J*=6.8, 3.0 Hz, 1H, H_8), 3.48 (brs, 1H, H_1), 3.39 (ddd, *J*=10.7, 10.0, 5.0 Hz, 1H, H_{10}), 2.57 (brddd, *J*=11.4, 10.8, 9.5 Hz, 1H, H_5), 2.06 (brddd, *J*=11.4, 9.3, 9.2 Hz, 1H, H_5), 2.02–1.96 (m, 1H, H_4), 1.83–1.78 (m, 1H, H_{11}), 1.74–1.68 (m, 1H, H_{11}), 1.45 (brddd, *J*=12.0, 11.4, 10.8 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.8 (d, C_6), 127.0 (d, C_7), 81.2 (d, C_1), 84.2 (d, C_{10}), 68.4 (t, C_8), 34.1 (t, C_4), 27.3 (t, C_{11}), 23.1 (t, C_5); HRMS Calcd for $C_{16}H_{24}O_3$ (M^+): 264.17253; Found: 264.17354.

5.3.4. *meso*-(4a*S*,5a*R*,7a*S*,8a*S*,12a*S*,14a*R*,15a*S*,17a*R*)-2,4a,5a,6,7,7a,8a,11,12a,13,14,14a,15a,16,17,17a-Hexadecahydro-1,5,8,12,15-pentaoxa-dibenzocyclohepten-[6,7-*a*:6′,7′-*e*]cycloheptene (11). Colorless oil; R_f=0.23 (hexane/EtOAc, 4:1); IR (neat) 3017, 2941, 2341, 1726, 1442, 1284, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, *J*=10.3, 3.0, 1.6, 1.6 Hz, 1H, H_4), 5.73 (ddd, *J*=10.3, 3.5, 1.9 Hz, 1H, H_3), 4.12 (dddd, *J*=16.7, 3.5, 2.1, 1.4 Hz, 1H, H_2), 4.06 (dddd, *J*=16.7, 2.6, 2.6, 1.4 Hz, 1H, H_2), 3.78 (ddd, *J*=8.5, 3.0, 1.3 Hz, 1H, H_{4a}), 3.40 (dddd, *J*=8.7, 5.3, 3.5, 1.8 Hz, 1H, H_{5a}), 3.32 (ddd, *J*=8.8, 8.7, 5.0 Hz, 1H, H_{14a}), 3.22 (ddd, *J*=9.2, 8.3, 4.6 Hz, 1H, H_{12a}), 2.08 (dddd, *J*=13.0, 7.5, 5.0, 2.9 Hz, 1H, H_{13}), 2.04 (dddd, *J*=13.0, 7.5, 4.6, 4.6 Hz, 1H, H_{14}), 1.92–1.88 (m, 2H, 2×H_6), 1.80 (dddd, *J*=13.0, 9.1, 7.8, 4.6 Hz, 1H, H_{13}), 1.74 (dddd, *J*=13.0, 9.0, 7.8, 2.9 Hz, 1H, H_{14}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.9 (d, C_4), 127.4 (d, C_3), 85.7 (d, C_{14a}), 83.6 (d, C_{5a}), 77.2 (d, C_{4a}), 77.1 (d, C_{12a}), 65.7 (t, C_2), 30.8 (t, C_{14}), 29.3 (t, C_{13}), 29.2 (t, C_6); HRMS Calcd for $C_{20}H_{28}O_5$ (M^+): 348.19367; Found: 348.19311. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.96; H, 8.04. Found: C, 68.93; H, 8.10.

5.3.5. (4a*S*,6*R*,7*S*,9a*R*)-2,3,4,4a,5a,8,9a,10,11,11a-Decahydro-1,5,9-trioxa-dibenzo[*a*,*b*]cycloheptene (12). Colorless oil; R_f=0.41 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=+32° (*c* 0.22, $CHCl_3$); IR (neat) 3696, 3016, 1727, 1600, 1443, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=10.4, 4.3, 2.8 Hz, 1H, H_7), 5.74 (ddd, *J*=10.4, 1.7, 1.7 Hz, 1H, H_6), 4.11 (dd, *J*=14.4, 2.8 Hz, 1H, H_8), 4.10 (dd, *J*=14.4, 4.4 Hz, 1H, H_8), 3.95 (dd, *J*=8.6, 1.7 Hz, 1H, H_{5a}), 3.83 (ddd, *J*=11.3, 3.9, 1.8 Hz, 1H, H_2), 3.33 (ddd, *J*=8.6, 7.4, 7.0 Hz, 1H, H_{9a}), 3.25 (ddd, *J*=11.2, 7.3, 4.9 Hz, 1H,

H_2), 3.18 (ddd, J=11.0, 8.8, 4.0 Hz, 1H, H_{4a}), 3.03 (ddd, J=8.8, 8.4, 4.1 Hz, 1H, H_{11a}), 2.14 (dddd, J=14.3, 10.2, 7.0, 5.2 Hz, 1H, H_{10}), 2.08 (dddd, J=12.4, 8.1, 4.2, 1.7 Hz, 1H, H_4), 1.95 (dddd, J=14.7, 6.3, 5.2, 4.1 Hz, 1H, H_{11}), 1.88 (dddd, J=14.7, 10.2, 5.0 Hz, 1H, H_{11}), 1.79 (dddd, J=14.3, 7.4, 6.3, 5.0 Hz, 1H, H_{10}), 1.67–1.61 (m, 2H, 2×H_3), 1.43 (ddd, J=12.5, 11.0, 5.8 Hz, 1H, H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.9 (d, C_6), 127.8 (d, C_7), 81.7 (d, C_{11a}), 80.9 (d, C_{4a}), 77.8 (d, C_{9a}), 75.3 (d, C_{5a}), 67.7 (t, C_2), 65.8 (t, C_8), 31.2 (t, C_4), 30.4 (t, C_{11}), 29.2 (t, C_{10}), 25.8 (t, C_3); HRMS Calcd for $C_{12}H_{18}O_3$ (M^+): 210.12560; Found: 210.12581.

5.3.6. (4a*S*,6a*R*,7a*S*,11a*R*,12a*S*,14a*R*)-2,3,4,4a,5a,6,7,7a,9,11a,12a,13,14,14a-Tetrahydro-1,5,8,12-tetraoxa-dibenzo-[*b*,*h*]heptalene (13). Colorless oil; R_f=0.42 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$=+59.1° (*c* 0.81, $CHCl_3$); IR (neat) 3696, 3012, 2930, 1726, 1463, 1211, 837, 686 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 2H, H_3, H_4), 4.10 (brd, J=15.7 Hz, 1H, H_2), 4.07 (brd, J=15.7 Hz, 1H, H_2), 3.83 (dddd, J=11.3, 5.1, 1.8, 1.8 Hz, 1H, H_9), 3.74 (brdd, J=8.2, 2.9 Hz, 1H, H_{4a}), 3.55 (ddd, J=8.3, 4.8, 4.8 Hz, 1H, H_{5a}), 3.47 (ddd, J=8.3, 8.3, 5.8 Hz, 1H, H_{12a}), 3.26 (ddd, J=11.3, 9.4, 6.8 Hz, 1H, H_9), 3.19 (ddd, J=10.2, 8.2, 3.4 Hz, 1H, H_{14a}), 3.04 (ddd, J=11.2, 9.0, 4.2 Hz, 1H, H_{11a}), 2.90 (ddd, J=9.0, 7.6, 6.3 Hz, 1H, H_{7a}), 2.08 (brdddd, J=11.7, 7.2, 5.8, 4.5 Hz, 1H, H_{13}), 2.05–1.94 (m, 2H, 2×H_{11}), 1.94–1.90 (m, 2H, H_{13}, H_{14}), 1.83–1.73 (m, 4H, 2×H_7, H_6, H_{14}), 1.65–1.58 (m, 2H, 2×H_{10}), 1.40 (brddd, J=11.1, 9.5, 2.8 Hz, 1H, H_{11}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.0 (d, C_3), 127.2 (d, C_4), 84.0 (d, C_{5a}), 83.8 (d, C_{11a}), 83.2 (d, C_{7a}), 82.7 (d, C_{12a}), 79.0 (d, C_{4a}), 77.3 (d, C_{14a}), 67.8 (t, C_9), 65.8 (t, C_2), 31.5 (t, C_{11}), 30.1 (t, C_6), 30.1 (t, C_{13}), 28.9 (t, C_{14}), 28.4 (t, C_7), 25.9 (t, C_{10}); HRMS Calcd for $C_{16}H_{24}O_4$ (M^+): 280.16746; Found: 280.16763.

5.3.7. (4a*R*,5a*S*,7a*R*,11a*S*,12a*R*,14a*S*)-2,2-Dimethyl-4,4a,5a,6,7,7a,9,11a,12a,13,14,14a-dodecahydro-1,3,5,8,12-pentaoxa-dibenzo[*b*,*h*]heptalene (14). Following the described earlier protocol for RCM, **7** (5.58 mg, 0.018 mmol) was converted to **14**[20] (5.46 mg, 0.018 mmol, 98%).

5.3.8. (2*R*,3*S*,2″*R*,3″*S*)-2-[3″-(Benzyloxy-2″-methoxy-tetrahydropyran-2″-yl)ethynyl]-tetrahydropyran-3-ol (35). To a stirred solution of hemiacetals **34** (800 mg, 1.79 mmol) in dry MeOH (18 mL) was added CSA (125 mg, 0.54 mmol) at 0°C. After being stirred for 24 h at 25°C, the reaction mixture was diluted with ether (50 mL) and water (2× 20 mL), and then dried ($MgSO_4$). Concentration followed by flash chromatography (silica, 50% EtOAc in *n*-hexane) gave **35** and **36** (609 mg, 1.76 mmol, 98%) as a 1:1 mixture of α/β anomers, which were separated by successive chromatographic purifications (silica, 20–30% EtOAc in *n*-hexane). **35**: colorless oil; R_f=0.24 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$=−23.9° (*c* 1.33, $CHCl_3$); IR (neat) 3604, 3019, 1453, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.73 (s, 2H), 4.09 (d, J=6.7 Hz, 1H), 3.94 (ddd, J=11.7, 5.2, 2.8 Hz, 1H), 3.62–3.58 (m, 1H), 3.58–3.47 (m, 4H), 3.47 (s, 3H), 3.46 (ddd, J=11.7, 8.5, 3.2 Hz, 1H), 2.66 (brs, 1H, D_2O-exchangeable), 2.12–2.08 (m, 1H), 1.86–1.74 (m, 3H), 1.66–1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (s), 128.3 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.6 (d), 95.8 (s), 83.8 (s), 82.3 (s), 79.0 (d), 72.3 (d), 72.2 (t), 69.2 (d), 65.9 (t), 60.5 (t), 50.8 (q), 29.3 (t), 24.5 (t), 24.4 (t), 23.1 (t). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.29; H, 7.80.

5.3.9. (2*R*,3*S*,2″*S*,3″*S*)-2-[3″-(Benzyloxy-2″-methoxy-tetrahydropyran-2″-yl)ethynyl]-tetrahydropyran-3-ol (36). Colorless oil; R_f=0.46 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$=−42.7° (*c* 0.8, $CHCl_3$); IR (neat) 3604, 3019, 2867, 1464, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 4.78 (d, J=12.2 Hz, 1H), 4.66 (d, J=12.2 Hz, 1H), 4.07 (d, J=7.0 Hz, 1H), 3.94 (ddd, J=11.8, 4.4, 4.4 Hz, 1H), 3.75–3.69 (m, 2H), 3.61 (ddd, J=11.0, 7.0, 3.9 Hz, 1H), 3.49 (s, 3H), 3.44 (ddd, J=11.8, 9.1, 2.4 Hz, 1H), 3.37 (dd, J=7.8, 3.9 Hz, 1H), 3.09 (brs, 1H, D_2O-exchangeable), 2.12–2.07 (m, 1H), 1.91–1.87 (m, 1H), 1.77–1.70 (m, 3H), 1.62–1.57 (m, 1H), 1.53–1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (s), 128.3 (d), 128.6 (d), 127.9 (d), 127.8 (d), 127.6 (d), 99.1 (s), 85.1 (s), 77.4 (d), 72.7 (d), 72.7 (t), 72.6 (d), 69.5 (d), 66.3 (t), 62.8 (t), 51.2 (q), 29.5 (t), 26.1 (t), 23.4 (q), 22.3 (t). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.17; H, 7.73.

5.3.10. (2*R*,3*S*,2″*R*,3″*S*)-Acetic acid-2-[3″-(benzyloxy-2″-methoxytetrahydropyran-2″-yl)ethynyl]-tetrahydropyran-3-yl ester (37). To a stirred solution of methyl acetal **35** (250 mg, 0.72 mmol) in dry CH_2Cl_2 (7 mL) was added Et_3N (0.4 mL, 2.89 mmol), Ac_2O (0.20 mL, 2.16 mmol), and a catalytic amount of DMAP (5 mg). After the mixture was stirred for 6 h at 25°C, the reaction was quenched with a saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined CH_2Cl_2 phases were washed with water (2×30 mL) and brine (2×20 mL) prior to drying ($MgSO_4$) and solvent evaporation. Chromatography of the crude residue on silica gel (eluant: 30% EtOAc in *n*-hexane) gave **37** (270 mg, 0.68 mmol, 97%). **37**: colorless oil; R_f=0.52 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=+15.2° (*c* 1.05, $CHCl_3$); IR (neat) 3019, 2957, 1734, 1376, 1209 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 4.83 (br dd, J=9.0, 4.5 Hz, 1H), 4.72 (d, J=12.3 Hz, 2H), 4.48 (d, J=4.5 Hz, 1H), 3.95 (ddd, J=11.7, 8.9, 2.9 Hz, 1H), 3.62–3.59 (m, 1H), 3.58–3.54 (m, 3H), 3.46 (s, 3H), 2.13–2.10 (m, 1H), 2.07 (s, 3H), 1.87–1.81 (m, 3H), 1.71–1.51 (m, 3H), 1.52–1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 138.3 (s), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.6 (d), 95.8 (s), 84.4 (s), 80.8 (s), 79.0 (d), 72.4 (t), 70.1 (d), 68.1 (d), 64.3 (t), 60.6 (t), 50.8 (q), 25.5 (t), 24.6 (t), 24.3 (t), 21.8 (t), 21.1 (q). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.05; H, 7.38.

5.3.11. (2*R*,3*S*,2″*S*,3″*S*)-Acetic acid-2-[3″-(benzyloxy-2″-methoxytetrahydropyran-2″-yl)ethynyl]-tetrahydropyran-3-yl ester (38). Prepared from **36** (250 mg, 0.72 mmol) by the same procedure used to convert **35** to **37**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **38** (262 mg, 0.68 mmol, 94%). **38**: colorless oil; R_f=0.66 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=+5.70° (*c* 0.84, $CHCl_3$); IR (neat) 3019, 2957, 1734, 1245, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 4.84–4.82 (m, 1H), 4.77 (d, J=12.1 Hz, 1H), 4.63 (d, J=12.1 Hz, 1H), 4.48 (d, J=4.5 Hz, 1H), 3.95 (ddd, J=11.6, 9.1, 2.9 Hz, 1H), 3.71–3.68 (m, 1H), 3.66 (ddd, J=14.8, 11.6, 3.4 Hz, 1H), 3.57 (ddd, J=11.6, 4.4, 4.4 Hz, 1H), 3.46 (s, 3H), 3.35 (dd,

J=7.7, 3.8 Hz, 1H), 2.11–2.08 (m, 1H), 2.04 (s, 3H), 1.90–1.81 (m, 4H), 1.67–1.63 (m, 1H), 1.45–1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 138.7 (s), 128.2 (d), 128.1 (d), 127.8 (d), 127.7 (d), 127.4 (d), 98.9 (s), 83.1 (s), 82.5 (s), 77.5 (d), 72.6 (t), 70.2 (d), 68.2 (d), 64.3 (t), 62.7 (t), 51.0 (q), 25.9 (t), 25.6 (t), 22.2 (t), 21.8 (t), 21.1 (q). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.01; H, 7.38.

5.3.12. (2*R*,3*S*,2″*R*,3″*S*)-Acetic acid-2-[-2′-(-3″-hydroxy-2″-methoxytetrahydropyran-2″-yl)vinyl]-tetrahydropyran-3-yl ester (39). 10% Pd–$BaSO_4$ catalyst (50 mg) was added to a stirred solution of **37** (250 mg, 0.64 mmol) in EtOAc (10 mL) and quinoline (0.1 equiv.) under H_2 atmosphere. After the mixture was stirred for 6 h at 25°C, the catalyst was filtered off and the solvent was removed under vacuum to give, after flash column purification (50% EtOAc in *n*-hexane) compound **39** (123 mg, 0.41 mmol, 64%). **39**: colorless oil; R_f=0.66 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−69.4° (*c* 1.01, $CHCl_3$); IR (neat) 3400, 2949, 1732, 1246, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dd, J=12.1, 9.0 Hz, 1H), 5.55 (d, J=12.1 Hz, 1H), 4.65 (ddd, J=10.5, 9.0, 4.8 Hz, 1H), 4.43 (dd, J=9.0, 9.0 Hz, 1H), 3.87 (ddd, J=10.8, 2.5, 1.9 Hz, 1H), 3.55 (ddd, J=11.1, 3.0, 1.6 Hz, 1H), 3.47–3.35 (m, 3H), 3.34 (brs, 1H, D_2O-exchangeable), 3.24 (s, 3H), 2.13 (br ddd, J=12.1, 4.5, 3.4 Hz, 1H), 1.97 (s, 3H), 1.83–1.55 (m, 6H), 1.50 (dddd, J=12.1, 11.2, 10.5, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (s), 135.1 (d), 131.7 (d), 100.4 (s), 73.9 (d), 72.1 (d), 71.2 (d), 67.2 (t), 59.8 (t), 48.8 (q), 28.8 (t), 26.6 (t), 25.1 (t), 24.8 (t), 21.0 (q). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.10; H, 8.24.

5.3.13. (2*R*,3*S*,2″*S*,3″*S*)-Acetic acid-2-[-2′-(-3″-hydroxy-2″-methoxytetrahydropyran-2″-yl)vinyl]-tetrahydropyran-3-yl ester (40). Prepared from **38** (250 mg, 0.64 mmol) following the same procedure used to convert **37** to **39**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **40** (115 mg, 0.38 mmol, 59%). **40**: colorless oil; R_f=0.21 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=+8.3° (*c* 1.42, $CHCl_3$); IR (neat) 3400, 3013, 1734, 1247, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dd, J=11.9, 9.0 Hz, 1H), 5.43 (d, J=11.9 Hz, 1H), 4.56 (ddd, J=10.0, 10.0, 4.5 Hz, 1H), 4.43 (dd, J=10.0, 9.0 Hz, 1H), 3.91 (ddd, J=11.2, 2.2, 2.2 Hz, 1H), 3.65–3.63 (m, 2H), 3.57 (brs, 1H), 3.41 (ddd, J=11.2, 11.2, 3.0 Hz, 1H), 3.20 (s, 3H), 2.73 (brs, 1H, D_2O-exchangeable), 2.15 (br ddd, J=12.0, 4.5, 3.6 Hz, 1H), 1.99 (s, 3H), 1.98–1.96 (m, 2H), 1.75–1.68 (m, 3H), 1.48 (dddd, J=12.0, 11.0, 10.0, 4.6 Hz, 1H), 1.29–1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 134.3 (d), 132.8 (d), 100.7 (s), 74.5 (d), 71.7 (d), 68.5 (d), 67.2 (t), 60.6 (t), 49.2 (q), 29.1 (t), 25.5 (t), 25.0 (t), 21.0 (q), 18.4 (t). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.86; H, 8.05.

5.3.14. (2*R*,3*S*,2″*R*)-Acetic acid-2-[-2′-(-2″-methoxy-3″-oxo-tetrahydropyran-2″-yl)vinyl]-tetrahydropyran-3-yl ester (41). Oxalyl chloride (0.10 mL, 1.2 mmol) was slowly added to a cold (−78°C) and stirred solution of DMSO (0.14 mL, 2.0 mmol) in dry CH_2Cl_2 (5 mL) under argon. After the solution was stirred for 10 min, the alcohol **39** (104 mg, 0.35 mmol) in CH_2Cl_2, (5 mL) was dropwise added at −78°C, and stirring was continued at that temperature for 1 h. Et_3N (0.56 mL, 4.0 mmol) was then added at −78°C. The mixture was allowed to warm to 25°C over a 1 h period, diluted with CH_2Cl_2 (10 mL), and washed with brine (2×10 mL). The organic solution was dried ($MgSO_4$) and concentrated to afford a crude product that was purified by flash column chromatography (silica, 20% EtOAc in *n*-hexane) to yield the ketone **41** (79 mg, 0.27 mmol, 76%). **41**: colorless oil; R_f=0.45 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−57.2° (*c* 0.77, $CHCl_3$); IR (neat) 3031, 1733, 1602, 1247, 1091, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dd, J=12.2, 9.0 Hz, 1H), 5.60 (d, J=12.2 Hz, 1H), 4.55 (ddd, J=11.8, 8.9, 4.3 Hz, 1H), 4.46 (dd, J=8.9, 8.9 Hz, 1H), 4.01 (ddd, J=11.5, 11.5, 2.9 Hz, 1H), 3.97 (ddd, J=11.3, 1.9, 1.9 Hz, 1H), 3.84 (ddd, J=11.5, 2.5, 2.5 Hz, 1H), 3.38 (ddd, J=11.3, 11.3, 3.7 Hz, 1H), 3.29 (s, 3H), 2.84 (ddd, J=14.8, 12.2, 6.6 Hz, 1H), 2.44 (ddd, J=14.8, 3.4, 3.4 Hz, 1H), 2.18–2.16 (m, 1H), 2.10–2.06 (m, 2H), 1.95 (s, 3H), 1.74–1.68 (m, 2H), 1.47 (dddd, J=17.3, 12.1, 11.8, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3 (s), 170.2 (s), 134.4 (d), 128.9 (s), 100.9 (s), 75.2 (d), 71.6 (d), 66.8 (t), 59.7 (t), 49.4 (q), 35.6 (t), 28.9 (t), 27.4 (t), 24.9 (t), 21.2 (q). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.93. Found: C, 60.51; H, 7.71.

5.3.15. (2*R*,3*S*,2″*S*)-Acetic acid-2-[-2′-(-2″-methoxy-3″-oxo-tetrahydropyran-2″-yl)vinyl]-tetrahydropyran-3-yl ester (42). Prepared from **40** (129 mg, 0.43 mmol) following the same procedure used to convert **39** to **41**. Flash column chromatography (silica, 20% EtOAc in *n*-hexane) gave **42** (101 mg, 0.34 mmol, 79%). **42**: colorless oil; R_f=0.57 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−1.3° (*c* 0.71, $CHCl_3$); IR (neat) 3026, 3018, 1733, 1446, 1218, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dd, J=12.0, 9.0 Hz, 1H), 5.46 (d, J=12.0 Hz, 1H), 4.66 (ddd, J=10.2, 9.0, 4.5 Hz, 1H), 4.27 (dd, J=9.0, 9.0 Hz, 1H), 3.99 (ddd, J=11.7, 11.7, 3.0 Hz, 1H), 3.87 (brd, J=11.2 Hz, 1H), 3.76 (ddd, J=11.7, 3.1, 2.0 Hz, 1H), 3.37 (ddd, J=11.2, 11.2, 4.2 Hz, 1H), 3.30 (s, 3H), 2.84 (ddd, J=14.3, 12.3, 6.6 Hz, 1H), 2.43 (dddd, J=14.3, 4.9, 3.2, 1.6 Hz, 1H), 2.19 (ddddd, J=13.4, 12.3, 11.7, 4.9, 3.1 Hz, 1H), 2.07 (s, 3H), 2.06–2.03 (m, 2H), 1.96–1.71 (m, 2H), 1.54 (ddddd, J=11.2, 10.2, 10.2, 5.5, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7 (s), 170.5 (s), 134.4 (d), 128.9 (s), 101.3 (s), 74.9 (d), 71.4 (d), 66.7 (t), 59.6 (t), 49.5 (q), 35.6 (t), 28.7 (t), 27.9 (t), 24.8 (t), 21.2 (q). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.93. Found: C, 60.58; H, 7.71.

5.3.16. (2*R*,3*S*,2″*R*)-2-[-2′-(-2″-Methoxy-3″-oxo-tetrahydropyran-2″-yl)vinyl]-tetrahydropyran-3-ol (43). A mixture of acetate **41** (50 mg, 0.17 mmol), MeONa catalytic (4 mg, 0.07 mmol), and MeOH (10 mL) was stirred at 25°C for 30 min. Evaporation of the solvent followed by flash chromatography (silica, 30% EtOAc in *n*-hexane) gave hydroxy-ketone **43** (35 mg, 0.14 mmol, 80%). **43**: colorless oil; R_f=0.32 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$=−32.4° (*c* 0.82, $CHCl_3$); IR (neat) 3605, 3018, 2942, 1720, 1604, 1162, 988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, J=12.0, 9.0 Hz, 1H), 5.62 (d, J=12.0 Hz, 1H), 4.06 (ddd, J=11.4, 11.4, 3.0 Hz, 1H), 3.92 (brdd, J=11.3, 4.2 Hz, 1H), 3.83 (ddd, J=11.4, 2.5, 2.5 Hz, 1H), 3.57 (dd, J=9.8, 9.0 Hz, 1H), 3.45 (brs, 1H, D_2O-exchangeable), 3.36 (ddd, J=11.3, 11.3, 3.2 Hz, 1H), 3.29 (s, 3H), 3.02 (ddd, J=10.0, 9.8, 4.3 Hz, 1H), 2.86 (ddd, J=14.5, 12.3, 7.0 Hz, 1H), 2.43

(ddd, J=14.5, 3.5, 3.5 Hz, 1H), 2.19–2.15 (m, 2H), 2.08–2.04 (m, 1H), 1.66–1.63 (m, 2H), 1.36 (dddd, J=12.5, 12.5, 11.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (s), 134.4 (d), 128.9 (d), 100.8 (s), 81.4 (d), 78.2 (d), 67.4 (t), 59.7 (t), 49.3 (q), 35.6 (t), 29.8 (t), 27.4 (t), 25.3 (t). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.82; H, 7.90.

5.3.17. (4a*R*,5a*S*,9a*R*,11a*S*)-11a-Methoxy-3,4,5a,6,7,8,9a,11a-octahydro-2*H*-1,5,9-trioxa-dibenzo[*a*,*d*]cyclohepten-4a-ol (44). Prepared from **42** (50 mg, 0.17 mmol) following the same procedure used to convert **41** to **43**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave hemiacetal **44** (42 mg, 0.16 mmol, 94%). **44**: colorless prism; mp 142°C (hexane/ether); R_f=0.29 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−24.3° (*c* 0.74, $CHCl_3$); IR (KBr) 3400, 3010, 1719, 1463, 1306, 1211, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, J=12.2, 2.5 Hz, 1H, H_{11}), 5.38 (dd, J=12.2, 2.5 Hz, 1H, H_{10}), 4.07 (ddd, J=9.5, 2.5, 2.5 Hz, 1H, H_{9a}), 3.87–3.80 (m, 2H, H_{5a}, He_8), 3.64–3.56 (m, 2H, 2×H_2), 3.33–3.25 (m, 1H, Ha_8), 3.22 (s, 3H, OCH_3), 2.03 (s, 1H, OH), 2.00–1.91 (m, 3H, H_3, H_6, H_4), 1.68–1.58 (m, 4H, H_4, H_6, 2×H_7), 1.50–1.48 (m, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (d, C_{11}), 127.9 (d, C_{10}), 100.6 (s, C_{11a}), 94.4 (s, C_{4a}), 79.3 (d, C_{9a}), 68.0 (d, C_{5a}), 67.1 (t, C_8), 59.8 (t, C_2), 49.0 (q, OCH_3), 32.1 (t, C_4), 30.7 (t, C_6), 25.3 (t, C_7), 22.9 (t, C_3); ^{1}H NMR (400 MHz, C_6D_6) δ 6.02 (dd, J=12.2, 2.5 Hz, 1H, H_{11}), 5.40 (dd, J=12.2, 2.5 Hz, 1H, H_{10}), 4.24 (ddd, J=9.5, 2.5, 2.5 Hz, 1H, H_{9a}), 3.98 (ddd, J=13.0, 9.5, 4.6 Hz, 1H, H_{5a}), 3.68 (brd, J=12.0 Hz, 1H, He_8), 3.47 (ddd, J=11.0, 11.0, 2.5 Hz, 1H, Ha_2), 3.39–3.18 (m, 1H, He_2), 3.13 (s, 3H, OCH_3), 3.01 (ddd, J=13.0, 12.0, 2.0 Hz, 1H, Ha_8), 2.75 (s, 1H, OH), 2.28 (ddd, J=13.3, 13.3, 4.5 Hz, 1H, Ha_4), 2.00–1.94 (m, 2H, He_3, He_6), 1.83 (brd, J=13.3 Hz, 1H, He_4), 1.59 (dddd, J=13.4, 13.4, 13.0, 4.1 Hz, 1H, Ha_6), 1.44 (ddddd, J=13.4, 13.0, 13.0, 4.0, 4.0 Hz, 1H, Ha_7), 1.17–1.13 (m, 2H, He_7, Ha_3); ^{13}C NMR (100 MHz, C_6D_6) δ 140.0 (d, C_{11}), 128.1 (d, C_{10}), 100.8 (s, C_{11a}), 94.4 (s, C_{4a}), 79.6 (d, C_{9a}), 68.1 (d, C_{5a}), 66.1 (t, C_8), 59.5 (t, C_2), 48.4 (q, OCH_3), 32.3 (t, C_4), 31.1 (t, C_6), 25.4 (t, C_7), 23.0 (t, C_3). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.66; H, 7.97.

5.3.18. (4a*R*,5a*S*,9a*R*,11a*S*)-4a,11a-Dimethoxy-3,4,5a,6,7,8,9a,11a-octahydro-2*H*-1,5,9-trioxa-dibenzo[*a*,*d*]cycloheptene (45). To a stirred solution of hemiacetal **44** (85 mg, 0.33 mmol) in dry DMF (10 mL) at −30°C were added NaH (0.83 mmol, 2.5 equiv., 60% dispersion in mineral oil) and MeI (0.11 mL, 234 mg, 1.65 mmol, 5.0 equiv.). The resulting solution was stirred for 8 h at 0°C. The reaction mixture was then diluted with ether (30 mL) and washed with 5% aqueous HCl solution (2×25 mL) and brine (2×25 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, 5% EtOAc in *n*-hexane) afforded **45** (54.4 mg, 0.20 mmol, 61%). **45**: colorless prism; mp 92°C (hexane); R_f=0.61 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=−12.3° (*c* 0.93, $CHCl_3$); IR (KBr) 3012, 1604, 1353, 1110, 982 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, J=12.0, 1.5 Hz, 1H), 5.42 (dd, J=12.0, 1.5 Hz, 1H), 4.04 (ddd, J=9.5, 1.5, 1.5 Hz, 1H), 3.86–3.79 (m, 2H), 3.62–3.55 (m, 2H), 3.30 (ddd, J=11.0, 3.0, 3.0 Hz, 1H), 3.23 (s, 3H), 3.18 (s, 3H), 1.98–1.89 (m, 3H), 1.68–1.56 (m, 4H), 1.50–1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (d), 128.8 (d), 100.9 (s), 99.8 (s), 79.3 (d), 68.2 (d), 67.3 (t), 60.1 (t), 50.1 (q), 49.2 (q), 33.2 (t), 31.0 (t), 25.0 (t), 23.2 (t). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.12; H, 8.37.

5.3.19. (4a*S*,5a*R*,9a*R*,11a*R*)-2,3,4a,5a,6,7,8,9a,11a-Decahydro-1,5,9-trioxa-dibenzo [*a*,*d*]cycloheptene (46). To a solution of **43** (40 mg, 0.15 mmol) in freshly distilled CH_3CN (3.5 mL) at −30°C were added Et_3SiH (0.36 mL, 2.28 mmol) and then $BF_3{\cdot}OEt_2$ (0.3 mL, 2.28 mmol). The resulting solution was stirred for 3 h at 0°C. The reaction mixture was then diluted with ether (20 mL) and washed with saturated $NaHCO_3$ (2×10 mL), and brine (2×10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, 5–10% EtOAc in *n*-hexane) procedure **46** (24 mg, 0.11 mmol, 73%) and its less polar epimer **47** (2.6 mg, 0.012 mmol, 8%). **46**: colorless oil; R_f=0.45 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−26.0° (*c* 0.58, $CHCl_3$); IR (neat) 3011, 2950, 1263, 1220, 1040, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (brd, J=10.4 Hz, 1H, H_{10}), 5.66 (ddd, J=10.4, 2.1, 2.1 Hz, 1H, H_{11}), 4.28 (ddd, J=4.0, 2.1, 2.1 Hz, 1H, H_{9a}), 3.94 (brdd, J=11.5, 4.5 Hz, 1H, He_2), 3.89–3.82 (m, 2H, H_{5a}, He_8), 3.79 (ddd, J=14.4, 13.6, 7.0 Hz, 1H, Ha_8), 3.60 (brd, J=8.3 Hz, 1H, H_{11a}), 3.47 (ddd, J=11.5, 11.5, 4.0 Hz, 1H, Ha_2), 3.24 (ddd, J=11.5, 8.3, 4.0 Hz, 1H, H_{4a}), 2.10 (dddd, J=12.0, 4.0, 4.0, 4.0 Hz, 1H, He_4), 1.90–1.83 (m, 3H, 2×H_7, H_6), 1.78–1.70 (m, 3H, 2×H_3, H_6), 1.61–1.55 (m, 1H, Ha_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.7 (d, C_{10}), 127.5 (d, C_{11}), 80.4 (d, C_{5a}), 78.1 (d, C_{9a}), 75.6 (d, C_{11a}), 75.0 (d, C_{4a}), 68.6 (t, C_8), 68.2 (t, C_2), 29.4 (t, C_4), 27.3 (t, C_7), 25.8 (t, C_3), 25.7 (t, C_6). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.70. Found: C, 68.43; H, 9.00. Compound **46** (12 mg, 0.05 mmol) was hydrogenated (10% Pd–C cat/H_2/EtOAc/25°C/30 min) to give the known full-hydrogenated derivative.[28b]

5.3.20. *meso*-(4a*S*,5a*R*,9a*S*,11a*R*)-2,3,4a,5a,6,7,8,9a,11a-Decahydro-1,5,9-trioxa-dibenzo [*a*,*d*]cycloheptene (47). To a solution of **45** (62 mg, 0.23 mmol) in CH_3CN (10 mL) at −78°C were added Et_3SiH (0.6 mL, 3.45 mmol) and then $BF_3{\cdot}OEt_2$ (0.43 mL, 3.45 mmol). The resulting solution was stirred for 2 h at −15°C. The reaction mixture was then diluted with ether (30 mL) and washed with saturated $NaHCO_3$ (2×10 mL) and brine (2×15 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, 10% EtOAc in *n*-hexane) afforded **47** (38 mg, 0.18 mmol, 78%). **47**: colorless oil; R_f=0.50 (hexane/EtOAc, 4:1); IR (neat) 3011, 2950, 2856, 1263, 1093, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (s, 1H, H_{10}), 3.89 (brd, J=10.5 Hz, 1H, He_2), 3.73 (d, J=8.2 Hz, 1H, H_{9a}), 3.31 (ddd, J=11.0, 10.5, 4.0 Hz, 1H, Ha_2), 3.24 (ddd, J=11.5, 8.2, 4.5 Hz, 1H, H_{4a}), 2.05 (brd, J=9.0 Hz, 1H, He_4), 1.70–1.64 (m, 2H, 2×H_3), 1.51–1.43 (m, 1H, Ha_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1 (d, C_{10}), 81.2 (d, C_{9a}), 79.2 (d, C_{4a}), 67.4 (t, C_2), 31.2 (t, C_4), 25.4 (t, C_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.70. Found: C, 68.43; H, 9.10.

5.3.21. (2*S*,4a*R*,8a*S*)-Spiro[2,4a,6,7,8a-hexahydropyran-[3,2-*b*]-pyran-2,2-tetrahydropyran-3′-one] (48). To a solution of **43** (32 mg, 0.13 mmol) in freshly distilled CH_3CN (1.3 mL) at −30°C was added $BF_3{\cdot}OEt_2$

(0.03 mL, 0.26 mmol). The resulting solution was stirred for 30 min at −30°C. The reaction mixture was then diluted with ether (10 mL) and washed with saturated $NaHCO_3$ (2×5 mL) and brine (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, 20% EtOAc in *n*-hexane) gave a mixture of spiroketones **48** and **49** (28 mg, 0.12 mmol, 93%). Compounds **48** (24.3 mg, 0.11 mmol, 85%) and **49** (2.7 mg, 0.01 mmol, 8%) were isolated by successive chromatographic purifications (silica, 5–10% EtOAc in *n*-hexane). **48**: colorless oil; R_f=0.52 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=−63.9° (*c* 1.02, $CHCl_3$); IR (neat) 3019, 1732, 1306, 1271, 1068, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, *J*=10.4 Hz, 1H, H_3), 5.69 (dd, *J*=10.4, 2.4 Hz, 1H, H_4), 4.20 (ddd, *J*=12.0, 11.5, 2.8 Hz, 1H, $Ha_{6'}$), 3.94 (brd, *J*=11.3 Hz, 1H, He_6), 3.73 (brdd, *J*=11.5, 4.7 Hz, 1H, $He_{6'}$), 3.66 (ddd, *J*=11.5, 8.9, 4.1 Hz, 1H, H_{8a}), 3.59 (ddd, *J*=8.9, 2.4, 2.0 Hz, 1H, H_{4a}), 3.43 (ddd, *J*=11.3, 11.3, 3.8 Hz, 1H, Ha_6), 2.88 (ddd, *J*=14.0, 13.4, 6.7 Hz, 1H, $Ha_{4'}$), 2.42 (ddd, *J*=14.2, 4.4, 2.1, 2.1 Hz, 1H, $He_{4'}$), 2.17 (ddddd, *J*=13.4, 13.4, 12.0, 4.7, 4.4 Hz, 1H, $Ha_{5'}$), 2.10–2.06 (m, 2H, $He_{5'}$, He_8), 1.79–1.76 (m, 2H, 2×H_7), 1.57 (dddd, *J*=12.0, 12.0, 11.5, 5.5 Hz, 1H, Ha_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (d, $C_{3'}$), 132.9 (d, C_3), 125.4 (s, C_4), 96.9 (s, C_2), 75.2 (d, C_{4a}), 70.4 (d, C_{8a}), 68.3 (t, C_6), 60.2 (t, $C_{6'}$), 35.7 (t, $C_{4'}$), 28.8 (t, C_8), 28.4 (t, $C_{5'}$), 25.7 (t, C_7). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.14. Hemiacetal **44** (42 mg, 0.16 mmol), following the earlier described conditions gave compounds **48** (32 mg, 0.14 mmol, 87%) and **49** (3.6 mg, 0.02 mmol, 12%).

5.3.22. (2*R*,4a*R*,8a*S*)-Spiro[2,4a,6,7,8,8a-hexahydropyran[3,2-*b*]-pyran-2,2′-tetrahydropyran-3′-one] (49). Colorless oil; R_f=0.61 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$=+11.4° (*c* 0.22, $CHCl_3$); IR (neat) 3019, 2953, 1732, 1306, 1271, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J*=10.3 Hz, 1H, H_3), 5.69 (dd, *J*=10.3, 2.5 Hz, 1H, H_4), 4.36 (ddd, *J*=11.8, 11.8, 2.6 Hz, 1H, $Ha_{6'}$), 3.93 (brd, *J*=11.5 Hz, 1H, He_6), 3.78 (dddd, *J*=11.8, 5.0, 2.5, 2.0 Hz, 1H, $He_{6'}$), 3.73 (ddd, *J*=8.6, 2.5, 1.5 Hz, 1H, H_{4a}), 3.48–3.42 (m, 1H, Ha_6), 3.32 (ddd, *J*=10.7, 8.6, 4.5 Hz, 1H, H_{8a}), 2.94 (ddd, *J*=15.0, 13.1, 6.5 Hz, 1H, $Ha_{4'}$), 2.45 (ddd, *J*=15.0, 2.5, 2.5 Hz, 1H, $He_{4'}$), 2.16 (ddddd, *J*=18.1, 13.1, 11.8, 5.0, 5.0 Hz, 1H, $Ha_{5'}$), 2.10–2.06 (m, 1H, $H_{5'}$), 1.98 (brd, *J*=11.5 Hz, 1H, He_8), 1.76–1.71 (m, 2H, 2×H_7), 1.73–1.68 (m, 1H, Ha_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (d, $C_{3'}$), 133.0 (d, C_3), 125.2 (s, C_4), 97.0 (s, C_2), 75.3 (d, C_{4a}), 70.4 (d, C_{8a}), 68.8 (t, C_6), 60.2 (t, $C_{6'}$), 35.6 (t, $C_{4'}$), 28.8 (t, C_8), 28.6 (t, $C_{5'}$), 25.7 (t, C_7). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.14.

5.3.23. (2*R*/2*S*,3*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-(3″-*tert*-Butyldimethylsilanyloxy-tetrahydropyran-2″-yl) ethynyl-3-(benzyloxy)octahydropyran[3,2-*b*] pyran-2-ol (52). The vinyl dibromide **50** (2.0 g, 5.0 mmol) in a stirred solution of dry THF (30 mL) at −78°C was treated dropwise with *n*-BuLi (5.88 mL, 10.0 mmol, 1.7 M in THF). The reaction mixture was then warmed to −35°C, and stirring continued for 1 h. The solution was cooled to −78°C and the lactone **51** (1.26 g, 4.8 mmol) in dry THF (5 mL) was added dropwise over a 10 min period. After 1.5 h at 25°C, the reaction was carefully quenched with saturated NH_4Cl (20 mL) and diluted with ether (100 mL). The ethereal portion was dried ($MgSO_4$) and concentrated and the residue subjected to flash chromatography (silica, 30% EtOAc in *n*-hexane) to give **52** (2.33 g, 4.65 mmol, 93%) as a 1:1 mixture of isomers. **52**: colorless oil; R_f=0.45 (hexane/EtOAc, 7:3); IR (neat) 3692, 3012, 2953, 1253, 1129, 987 cm^{-1}. Anal. Calcd for $C_{28}H_{42}O_6Si$: C, 66.92; H, 8.36. Found: C, 67.12; H, 8.40.

5.3.24. (2*R*/2*S*,3*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-(3″-Hydroxy-tetrahydropyran-2″-yl) ethynyl-2-methoxy-3-benzyloxy-octatetrahydropyran[3,2-*b*] pyrane (53). The compound **53** was prepared from the hemiacetal **52** (2.33 g, 4.65 mmol) following the same procedure used to convert hemiacetal **34** to methyl acetal **35**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **53** (1.8 g, 4.46 mmol, 96%). **53**: yellowish oil; R_f=0.34 (hexane/EtOAc, 1:1); IR (neat) 3595, 3020, 2858, 1266, 1170, 989 cm^{-1}. Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.66; H, 7.46. Found: C, 68.46; H, 7.55.

5.3.25. (2*R*/2*S*,3*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-(3″-Acetoxy-tetrahydropyran-2″-yl) ethynyl-2-methoxy-3-benzyloxy-octahydropyran[3,2-*b*] pyrane (54). Prepared from **53** (1.77 g, 4.40 mmol) by the same procedure used to convert **35** to **37**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **54** (1.91 g, 4.31 mmol, 98%). **54**: yellowish oil; R_f=0.42 (hexane/EtOAc, 2:1); IR (neat) 3020, 2957, 1734, 1376, 1340, 1210 cm^{-1}. Anal. Calcd for $C_{25}H_{32}O_7$: C, 67.56; H, 7.21. Found: C, 67.66; H, 7.43.

5.3.26. (2*R*/2*S*,3*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-[2′-(3″-Acetoxy-tetrahydropyran-2″-yl) vinyl]-2-methoxy-octahydropyran[3,2-*b*]pyran-3-ol (55). Prepared from **54** (1.89 g, 4.26 mmol) by the same procedure followed to convert **37** to **39**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **55** (895 mg, 2.52 mmol, 59%). **55**: colorless oil; R_f=0.53 (hexane/EtOAc, 2:1); IR (neat) 3010, 1734, 1625, 1370, 1220 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.67; H, 7.87. Found: C, 60.60; H, 7.92.

5.3.27. (2*R*/2*S*,3*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-[2′-(3″-Acetoxy-tetrahydropyran-2″-yl) vinyl]-2-methoxy-octahydropyran[3,2-*b*]pyran-3-one (56). Prepared from **55** (890 mg, 2.50 mmol) by the same procedure to convert **39** to **41**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) afforded **56** (726 mg, 2.05 mmol, 82%). **56**: colorless oil; R_f=0.62 (hexane/EtOAc, 3:1); IR (neat) 3020, 1736, 1720, 1602, 1247, 1028 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.02; H, 7.34. Found: C, 61.33; H, 7.26.

5.3.28. (2*S*,4a*R*,8a*S*,2″*S*,3″*R*)-2-[2′-(3″-Hydroxy-tetrahydropyran-2″-yl)vinyl]-2-methoxy-octahydropyran-[3,2-*b*]pyran-3-one (57). Prepared from **56** (708 mg, 2.0 mmol) by the same procedure to convert **41** to **43**. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **57** and **58** (537 mg, 1.72 mmol, 86%) which were separated by successive chromatographic purifications (silica, 5–10% EtOAc in *n*-hexane). **57**: colorless oil; R_f=0.39 (hexane/EtOAc, 9:1); $[\alpha]_D^{25}$=−4.5° (*c* 1.18, $CHCl_3$); IR (neat) 3469, 2946, 1730, 1216, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, *J*=12.0, 8.8 Hz, 1H, $H_{2'}$), 5.71 (d, *J*=12.0 Hz, 1H, $H_{1'}$), 3.96–3.88 (m, 2H, H_{4a}, $He_{6''}$), 3.68 (dd, *J*=9.0, 8.8 Hz,

1H, $H_{2''}$), 3.44 (ddd, J=10.0, 9.0, 4.5 Hz, 1H, H_{8a}), 3.42–3.36 (m, 3H, $Ha_{6''}$, 2×H_6), 3.33 (ddd, J=12.0, 9.0, 3.5 Hz, 1H, $H_{3''}$), 3.30 (s, 3H, OCH_3), 3.05 (brdd, J=16.2, 6.4 Hz, 1H, $H_{3''}$), 2.39 (dd, J=16.2, 10.9 Hz, 1H, Ha_4), 2.20 (brdd, J=12.5, 4.5 Hz, 1H, He_8), 2.18 (brdd, J=13.0, 3.5 Hz, 1H, $He_{4''}$), 1.98 (brs, 1H, OH), 1.82–1.73 (m, 2H, 2×H_7), 1.72–1.65 (m, 2H, 2×$H_{5''}$), 1.58–1.54 (m, 1H, He_8), 1.46 (dddd, J=13.0, 13.0, 12.0, 5.2 Hz, 1H, $He_{4''}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1 (s, C_3), 134.2 (d, $C_{1'}$), 126.8 (d, $C_{2'}$), 99.9 (s, C_2), 82.4 (d, $C_{2''}$), 74.3 (d, C_{4a}), 74.2 (d, C_{8a}), 69.6 (d, $C_{3''}$), 68.3 (t, C_6), 67.4 (t, $C_{6''}$), 50.1 (q, OCH_3), 42.3 (t, C_4), 31.9 (t, $C_{4''}$), 31.0 (t, C_8), 25.8 (t, C_7), 25.1 (t, $C_{5''}$). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.71; H, 7.76.

5.3.29. (4a*R*,5a*S*,6*R*,10a*R*,11a*R*,13a*S*)-11a-Methoxy-2,3,4,4a,6,6a,8,9,10,10a,11a,13a-dodecahydro-1,5,7,11-tetraoxa-benzo[4,5]cyclohepta[1,2-*b*]naphthalen-5a-ol (58). Colorless needle; mp 130°C; R_f=0.62 (hexane/EtOAc, 9:1); $[\alpha]_D^{25}$=+8.2° (*c* 0.19, $CHCl_3$); IR (KBr) 3470, 3011, 1560, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, J=11.5, 2.0 Hz, 1H, H_{12}), 5.44 (dd, J=11.5, 2.0 Hz, 1H, H_{13}), 4.08 (ddd, J=9.8, 2.0, 2.0 Hz, 1H, H_{13a}), 4.06 (ddd, J=12.0, 3.0, 3.0 Hz, 1H, He_8), 4.01 (ddd, J=10.0, 9.0, 3.5 Hz, 1H, H_{6a}), 3.88–3.82 (m, 2H, He_2, H_{4a}), 3.52 (ddd, J=11.0, 9.0, 4.0 Hz, 1H, H_{10a}), 3.42 (brdd, J=12.0, 10.0 Hz, 1H, Ha_8), 3.32–3.28 (m, 1H, Ha_2), 3.28 (s, 3H, CH_3), 2.99 (dd, J=14.0, 5.4 Hz, 1H, He_6), 2.63 (dd, J=14.0, 10.0 Hz, 1H, Ha_6), 2.18 (brdd, J=14.0, 4.0 Hz, 1H, He_{10}), 2.06 (s, 1H, OH), 1.98–1.95 (m, 1H, He_4), 1.84–1.75 (m, 2H, 2×H_9), 1.64–1.58 (m, 3H, 2×H_3, Ha_4), 1.60–1.55 (m, 1H, Ha_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (d, C_{13}), 130.2 (d, C_{12}), 101.0 (s, C_{11a}), 95.2 (s, C_{5a}), 79.5 (d, C_{13a}), 73.8 (d, C_{10a}), 73.6 (d, C_{6a}), 69.1 (t, C_8), 68.1 (d, C_{4a}), 67.8 (t, C_2), 53.0 (q, OCH_3), 38.7 (t, C_6), 31.5 (t, C_4), 31.2 (t, C_{10}), 26.0 (t, C_9), 25.3 (t, C_3). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.63; H, 7.80.

5.3.30. (4a*R*,5a*S*,6*R*,10a*R*,11a*R*,13a*S*)-5a,11a-Dimethoxy-2,3,4,4a,6,6a,8,9,10,10a,11a,13a-dodecahydro-1,5,7,11-tetraoxa-benzo[4,5]cyclohepta[1,2-*b*]naphthalene (59). Prepared from **58** (110 mg, 0.35 mmol) following the same procedure used to convert **44** to **45**. Flash column chromatography (silica, 5% EtOAc in *n*-hexane) afforded **59** (60.5 mg, 0.19 mmol, 53%). **59**: colorless oil; R_f=0.64 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$=+10.5° (*c* 0.22, $CHCl_3$); IR (neat) 3016, 1603, 1342, 1112, 960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dd, J=12.0, 2.0 Hz, 1H, H_{12}), 5.40 (dd, J=12.0, 2.0 Hz, 1H, H_{13}), 4.10 (ddd, J=10.0, 2.0, 2.0 Hz, 1H, H_{13a}), 4.06 (ddd, J=14.0, 4.5, 4.5 Hz, 1H, He_8), 3.99 (ddd, J=9.5, 9.5, 4.0 Hz, 1H, H_{6a}), 3.90–3.81 (m, 2H, He_2, H_{4a}), 3.60 (ddd, J=9.5, 9.0, 4.5 Hz, 1H, H_{10a}), 3.46 (brdd, J=14.0, 13.0 Hz, 1H, Ha_8), 3.41–3.36 (m, 1H, Ha_2), 3.28 (s, 3H, CH_3), 3.26 (s, 3H, OCH_3), 3.25 (dd, J=13.5, 4.0 Hz, 1H, He_6), 2.74 (dd, J=13.5, 9.5 Hz, 1H, Ha_6), 2.40–2.36 (m, 1H, He_{10}), 1.98–1.84 (m, 3H, 2×H_9, He_4), 1.70–1.58 (m, 3H, 2×H_3, Ha_4), 1.56–1.48 (m, 1H, Ha_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (d, C_{13}), 133.3 (d, C_{12}), 102.3 (s, C_{5a}), 101.4 (s, C_{11a}), 80.1 (d, C_{13a}), 72.4 (d, C_{10a}), 72.4 (d, C_{6a}), 70.3 (t, C_8), 70.2 (d, C_{4a}), 68.0 (t, C_2), 54.3 (q, OCH_3), 53.4 (q, OCH_3), 41.0 (t, C_6), 33.4 (t, C_{10}), 33.1 (t, C_4), 28.2 (t, C_9), 26.0 (t, C_3). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.73; H, 8.12.

Compound **59** (47 mg, 0.15 mmol) was reduced to the known compound[27f] **60** (22.5 mg, 0.085 mmol, 57%) following the same procedure to convert **45** to **47**.

5.3.31. (2*S*,4a*S*,8a*R*,4′a*R*,8′a*S*)-Spiro-(2,4a,6,7,8,8a)-hexahydro[3,2-*b*]pyran-2-2′-octahydropyran[3,2-*b*]pyran-3-one (61). Treatment of hydroxy-ketone **57** (130 mg, 0.42 mmol) under the same conditions used to convert **43** to **48** and **49**, gave a 1:1 mixture of spiroketones **61** and **62** (118 mg, 0.42 mmol, 100%). Flash column chromatography (silica, 5–15% EtOAc in *n*-hexane) gave **61** (54 mg, 0.19 mmol) and its more polar epimer **62** (52 mg, 0.19 mmol). **61**: colorless oil; R_f=0.78 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=+2.9° (*c* 0.61, $CHCl_3$); IR (neat) 3020, 3012, 1729, 1283, 1092, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, J=10.4 Hz, 1H, H_3), 5.40 (dd, J=10.4, 2.4 Hz, 1H, H_4), 4.03 (ddd, J=11.7, 10.0, 4.5 Hz, 1H, $H_{8'}$), 3.90 (brd, J=11.0 Hz, 2H, He_6, $He_{6'}$), 3.70 (brd, J=8.6 Hz, 1H, H_{4a}), 3.41–3.37 (m, 2H, Ha_6, $Ha_{6'}$), 3.31–3.24 (m, 2H, H_{8a}, $H_{4'a}$), 2.90 (dd, J=14.0, 12.3 Hz, 1H, $H_{4'}$), 2.73 (dd, J=14.0, 4.9 Hz, 1H, $H_{4'}$), 2.11 (brdd, J=11.7, 4.5 Hz, 1H, $He_{8'}$), 1.94 (brdd, J=11.9, 4.5 Hz, 1H, He_8), 1.76–1.60 (m, 4H, 2×$H_{7'}$, 2×H_7), 1.63 (dddd, J=11.9, 11.1, 11.1, 5.9 Hz, 1H, Ha_8), 1.47 (dddd, J=11.7, 11.7, 11.7, 5.5 Hz, 1H, $Ha_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7 (s, $C_{3'}$), 134.1 (d, C_3), 125.0 (d, C_4), 97.5 (s, C_2), 77.4 (d, $C_{4'a}$), 74.8 (d, C_{4a}), 74.3 (d, C_{8a}), 69.9 (d, $C_{8'a}$), 68.1 (t, C_6), 67.6 (t, $C_{6'}$), 42.3 (t, $C_{4'}$), 28.9 (t, C_8), 28.8 (t, $C_{8'}$), 25.3 (t, C_7, $C_{7'}$). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.26; H, 7.20. Found: C, 64.43; H, 7.29.

5.3.32. (2*R*,4a*S*,8a*R*,4′a*R*,8′a*S*)-Spiro-(2,4a,6,7,8,8a)-hexahydropyran[3,2-*b*]pyran-2-2′-octahydropyran[3,2-*b*]-pyran-3′-one (62). Colorless oil; R_f=0.75 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=+3.7° (*c* 0.46, $CHCl_3$); IR (neat) 3025, 3014, 2950, 1740, 1283, 1118, 960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, J=10.4 Hz, 1H, H_3), 5.77 (dd, J=10.4, 2.4 Hz, 1H, H_4), 3.94–3.88 (m, 3H, H_6, $H_{6'}$, $H_{4'a}$), 3.72 (ddd, J=11.3, 9.0, 4.1 Hz, 1H, H_{8a}), 3.58 (ddd, J=9.0, 2.4, 1.8 Hz, 1H, H_{4a}), 3.48 (ddd, J=10.7, 10.7, 4.2 Hz, 1H, $H_{8'a}$), 3.42–3.36 (m, 2H, H_6, $H_{6'}$), 3.04 (dd, J=17.2, 6.4 Hz, 1H, $H_{4'}$), 2.39 (dd, J=17.2, 10.9 Hz, 1H, $H_{4'}$), 2.18 (brdd, J=12.2, 3.0 Hz, 1H, $H_{8'}$), 2.02 (brdd, J=12.3, 3.4 Hz, 1H, He_8), 1.77–1.73 (m, 4H, 2×H_7, 2×$H_{7'}$), 1.59–1.53 (m, 2H, H_8, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 (s, $C_{3'}$), 134.2 (d, C_3), 123.9 (d, C_4), 96.8 (s, C_2), 74.9 (d, C_{4a}), 74.3 (d, $C_{4'a}$, $C_{8'a}$), 70.7 (d, C_{8a}), 68.3 (t, C_6), 67.7 (t, $C_{6'}$), 42.2 (t, $C_{4'}$), 30.8 (t, $C_{8'}$), 28.9 (t, C_8), 25.6 (t, C_7), 25.3 (t, $C_{7'}$). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.26; H, 7.20. Found: C, 64.32; H, 7.45.

5.3.33. (2*R*,3*S*,2′*S*,2″*R*,4″a*S*,8″a*R*)-2-[2′-(2″,4″a,6″,7″,8″,8″a-Hexahydropyran[3,2-*b*]pyran-2″-yl)-2′-hydroxy-ethyl]-tetrahydropyran-3-ol (63). To a solution of **57** (120 mg, 0.38 mmol) in freshly distilled CH_3CN (5 mL) at −30°C were added Et_3SiH (0.9 mL, 5.7 mmol) and then $BF_3{\cdot}OEt_2$ (0.75 mL, 5.7 mmol). The resulting solution was stirred for 12 h at 0°C. The reaction mixture was then diluted with ether (30 mL) and washed with saturated $NaHCO_3$ (2×20 mL) and brine (2×20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) produced **63** (72 mg, 0.25 mmol, 66%) and **64**

(12 mg, 0.042 mmol, 11%). **63**: colorless oil; R_f=0.55 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=+63.9° (*c* 0.93, $CHCl_3$); IR (neat) 3483, 3013, 1463, 1439, 1328, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J*=10.5 Hz, 1H, $H_{3''}$), 5.78 (dd, *J*=10.5, 1.9 Hz, 1H, $H_{4''}$), 4.19 (brs, 1H, $H_{2''}$), 3.94–3.87 (m, 3H, $He_{6''}$, He_6, $H_{2'}$), 3.59 (brd, *J*=8.3 Hz, 1H, $H_{4''a}$), 3.45 (ddd, *J*=11.4, 11.4, 4.3 Hz, 1H, $Ha_{6''}$), 3.39–3.33 (m, 2H, Ha_6, H_3), 3.28–3.23 (m, 2H, H_2, $H_{8''a}$), 2.10–2.06 (m, 3H, He_4, $H_{1''}$, $He_{8''}$), 1.74–1.68 (m, 5H, 2×H_5, 2×$H_{7''}$, $H_{1'}$), 1.54 (dddd, *J*=11.8, 11.8, 11.8, 5.4 Hz, 1H, $Ha_{8''}$), 1.40 (dddd, *J*=12.1, 12.1, 11.0, 5.8 Hz, 1H, Ha_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2 (d, $C_{3''}$), 127.5 (d, $C_{4''}$), 80.7 (d, C_2), 78.8 (d, $C_{2''}$), 75.6 (d, $C_{4''a}$), 75.1 (d, $C_{8''a}$), 72.7 (d, $C_{2'}$), 70.0 (d, C_3), 68.2 (t, $C_{6''}$), 67.7 (t, C_6), 33.8 (t, $C_{1'}$), 32.4 (t, C_4), 29.3 (t, $C_{8''}$), 25.8 (t, C_5), 25.5 (t, $C_{7''}$); ^1H NMR (400 MHz, C_6D_6) δ 6.08 (d, *J*=11.0 Hz, 2H, $H_{3''}$, $H_{4''}$), 4.24 (brs, 1H, $H_{2''}$), 4.05 (ddd, *J*=9.3, 6.5, 2.3 Hz, 1H, $H_{2'}$), 3.76 (brdd, *J*=11.2, 4.7 Hz, 1H, He_6), 3.63 (brd, *J*=8.2 Hz, 1H, $H_{4''a}$), 3.55 (brdd, *J*=11.2, 4.7 Hz, 1H, $He_{6''}$), 3.26–3.18 (m, 4H, $H_{8''a}$, H_2, H_3, H_6), 2.95 (ddd, *J*=12.2, 11.2, 1.8 Hz, 1H, $Ha_{6''}$), 2.46 (ddd, *J*=14.8, 2.3, 2.3 Hz, 1H, $H_{1'}$), 1.93 (brdd, *J*=11.5, 3.0 Hz, 1H, $He_{8''}$), 1.86–1.79 (m, 2H, Ha_4, $H_{1'}$), 1.53 (ddddd, *J*=13.0, 12.7, 12.2, 4.6, 4.1 Hz, 1H, $Ha_{7''}$), 1.44–1.39 (m, 2H, $Ha_{8''}$, H_5), 1.27 (brd, *J*=12.7 Hz, 1H, $He_{7''}$), 1.20–1.14 (m, 2H, He_4, He_5); ^{13}C NMR (100 MHz, C_6D_6) δ 128.2 (d, $C_{3''}$), 128.2 (d, $C_{4''}$), 83.1 (d, C_2), 79.1 (d, $C_{2''}$), 75.9 (d, $C_{4''a}$), 75.3 (d, $C_{8''a}$), 73.2 (d, $C_{2'}$), 69.9 (d, C_3), 67.7 (t, $C_{6'}$), 67.3 (t, $C_{6''}$), 35.0 (t, $C_{1'}$), 32.5 (t, C_4), 29.5 (t, $C_{8''}$), 25.8 (t, $C_{7''}$), 25.5 (t, C_5). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.31; H, 8.72. *Diacetate*: ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J*=10.4 Hz, 1H, $H_{3''}$), 5.66 (ddd, *J*=10.4, 2.2, 2.2 Hz, 1H, $H_{4''}$), 5.11 (ddd, *J*=8.2, 4.2, 4.2 Hz, 1H, $H_{2'}$), 4.44 (ddd, *J*=10.4, 10.4, 5.0 Hz, 1H, H_3), 4.35 (brs, 1H, $H_{2''}$), 3.94 (ddd, *J*=11.0, 2.0, 2.0 Hz, 1H, $He_{6''}$), 3.85 (ddd, *J*=11.4, 2.8, 2.8 Hz, 1H, He_6), 3.55 (brd, *J*=8.2 Hz, 1H, $H_{4''a}$), 3.45 (ddd, *J*=11.0, 11.0, 4.0 Hz, 1H, $Ha_{6'}$), 3.36 (ddd, *J*=12.0, 10.4, 4.2 Hz, 1H, H_2), 3.28 (ddd, *J*=11.4, 11.4, 2.8 Hz, 1H, Ha_6), 3.20 (ddd, *J*=11.0, 8.2, 4.0 Hz, 1H, $H_{8''a}$), 2.15 (brdd, *J*=12.0, 3.3 Hz, 1H, He_4), 2.09–2.00 (m, 7H, $He_{8''}$, 2×CH_3CO_2), 1.94 (ddd, *J*=15.0, 4.2, 4.2 Hz, 1H, $H_{1'}$), 1.78–1.70 (m, 3H, 2×$H_{7''}$, $H_{1'}$), 1.68–1.62 (m, 2H, 2×H_5), 1.51 (dddd, *J*=12.0, 11.7, 11.7, 5.6 Hz, 1H, Ha_4), 1.38 (dddd, *J*=12.4, 10.8, 10.8, 4.6 Hz, 1H, $Ha_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (s, CH_3CO_2), 170.1 (s, CH_3CO_2), 129.5 (d, $C_{3''}$), 127.0 (d, $C_{4''}$), 77.3 (d, C_2), 76.7 (d, $C_{2''}$), 75.4 (d, $C_{4''a}$), 75.1 (d, $C_{8''a}$), 72.9 (d, $C_{2'}$), 72.0 (d, C_3), 68.2 (t, $C_{6''}$), 67.4 (t, C_6), 31.7 (t, $C_{1'}$), 29.3 (t, $C_{8''}$), 29.3 (t, C_4), 25.7 (t, $C_{7''}$), 24.9 (t, C_5), 21.3 (q), 21.2 (q). Hemiacetal **58** (110 mg, 0.32 mmol), following the earlier described conditions gave **63** (69 mg, 0.24 mmol, 75%) and **64** (7 mg, 0.03 mmol, 9%).

5.3.34. (2*R*,3*S*,2′*S*,2″*R*,4″a*S*,8″)-2-[2′-Octahydropyran-[3,2-*b*]pyran-2″-yl-2′-hydroxyethyl]-tetrahydropyran-3-ol (64). Colorless oil; R_f=0.44 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$=+66.2° (*c* 0.18, $CHCl_3$); IR (neat) 3502, 3156, 2858, 1464, 1380, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89–3.83 (m, 2H, $He_{6''}$, He_6), 3.84 (ddd, *J*=5.2, 5.2, 1.6 Hz, 1H, $H_{2'}$), 3.70 (brs, 1H, D_2O-exchangeable), 3.43–3.35 (m, 3H, $Ha_{6''}$, H_3, Ha_6), 3.28 (ddd, *J*=9.4, 9.4, 5.2 Hz, 1H, $H_{2''}$), 3.24 (ddd, *J*=9.0, 9.0, 3.0 Hz, 1H, H_2), 3.05 (ddd, *J*=8.8, 8.8, 2.7 Hz, 1H, $H_{8''a}$), 2.95 (ddd, *J*=10.9, 8.8, 4.1 Hz, 1H, $H_{4''a}$), 2.13 (brs, 1H, D_2O-exchangeable), 2.12–2.05 (m, 2H, $H_{4'}$, $H_{1'}$), 2.04–1.98 (m, 2H, $H_{8''}$, $H_{4''}$), 1.86 (brd, *J*=12.9, 1H, $H_{3''}$), 1.68–160 (m, 5H, 2×$H_{7''}$, 2×H_5, $H_{3''}$), 1.58–1.53 (m, 1H, $H_{1'}$), 1.48–1.40 (m, 3H, H_4, $H_{4''}$, $H_{8''}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9 (d, C_2), 80.2 (d, $C_{2''}$), 78.5 (d, $C_{4''a}$), 78.1 (d, $C_{8''a}$), 72.6 (d, $C_{2'}$), 70.0 (d, C_3), 67.9 (t, $C_{6''}$), 67.7 (t, C_6), 34.7 (t, $C_{1'}$), 32.4 (t, C_4), 29.7 (t, $C_{8''}$), 29.1 (t, $C_{4''}$), 25.7 (t, $C_{3''}$), 25.6 (t, C_5), 25.6 (t, $C_{7''}$). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.61; H, 9.0.

5.3.35. (2*S*,4a*S*,8a*R*,3′*S*,4′a*R*,8′a*S*)-Spiro(2,4a,6,7,8,8a)-hexahydropyran[3,2-*b*]pyran-2,2′-octahydropyran[3,2-*b*]-pyran-3′-ol (65). To a solution of spiroketone **61** (50 mg, 0.18 mmol) in freshly distilled CH_3CN (3 mL) at −78°C were added Et_3SiH (0.43 mL, 2.7 mmol) and then $BF_3{\cdot}OEt_2$ (0.36 mL, 2.7 mmol). The resulting mixture was stirred for 3 h at −30°C. The reaction was then diluted with ether (15 mL) and washed with saturated $NaHCO_3$ (2×10 mL) and brine (2×10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (50–60% EtOAc in *n*-hexane) produced **65** (43 mg, 0.15 mmol, 83%). **65**: colorless oil; R_f=0.67 (EtOAc); $[\alpha]_D^{25}$=+2.7° (*c* 1.58, $CHCl_3$); IR (neat) 3599, 3017, 1468, 1223, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, *J*=10.1 Hz, 1H, H_3), 5.60 (dd, *J*=10.1, 2.1 Hz, 1H, H_4), 3.92 (brd, *J*=11.0 Hz, 1H, He_6), 3.88 (brd, *J*=11.0 Hz, 1H, $He_{6'}$), 3.65–3.72 (m, 3H, H_{4a}, $H_{3'}$, $H_{8'a}$), 3.43 (ddd, *J*=11.0, 9.5, 5.0 Hz, 1H, Ha_6), 3.40–3.37 (m, 1H, H_{8a}), 3.36 (ddd, *J*=11.0, 11.0, 4.0 Hz, 1H, $Ha_{6'}$), 2.98 (ddd, *J*=11.6, 9.4, 4.2 Hz, 1H, $H_{4'a}$), 2.18–2.12 (m, 2H, H_8, $H_{4'}$), 2.00–1.93 (m, 1H, $H_{8'}$), 1.89–1.83 (m, 1H, $H_{4'}$), 1.81–1.70 (m, 4H, 2×H_7, 2×$H_{7'}$), 1.62–1.54 (m, 1H, H_8), 1.40–1.32 (m, 1H, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, C_3), 128.1 (d, C_4), 96.3 (s, C_2), 76.9 (d, $C_{4'a}$), 76.5 (d, C_{4a}), 74.7 (d, C_{8a}), 72.6 (d, $C_{3'}$), 69.7 (t, $C_{8'a}$), 68.2 (t, $C_{6'}$), 67.9 (t, C_6), 33.9 (t, $C_{4'}$), 29.2 (t, C_8), 29.1 (t, $C_{8'}$), 25.6 (t, C_7), 25.5 (t, $C_{7'}$). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.63; H, 7.82. Compound **65** (38 mg, 0.13 mmol) under the same conditions used to convert **57** to the mixture **63** and **64**, gave diols **63** (16 mg, 0.056 mmol) and **64** (8 mg, 0.028 mmol) in 67% overall yield.

5.3.36. (2*R*,4a*S*,8a*R*,3′*S*,4′a*R*,8′a*S*)-Spiro(2,4a,6,7,8,8a)-hexahydropyran[3,2-*b*]pyran-2,2′-octahydropyran[3,2-*b*]-pyran-3′-ol (66). Prepared from **62** (50 mg, 0.18 mmol) following the same procedure to convert **61** to **65**. Flash column chromatography (silica, 50–60% EtOAc in *n*-hexane) gave **66** (36 mg, 0.13 mmol, 72%). **66**: colorless oil; R_f=0.57 (EtOAc); $[\alpha]_D^{25}$=−13.3° (*c* 0.44, $CHCl_3$); IR (neat) 3600, 3013, 1468, 1356, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, *J*=10.7, 1.6 Hz, 1H, H_4), 6.19 (d, *J*=10.7 Hz, 1H, H_3), 3.97 (brdd, *J*=11.5, 4.5 Hz, 1H, He_6), 3.92 (brdd, *J*=14.1, 1.8 Hz, 1H, $He_{6'}$), 3.82 (ddd, *J*=11.5, 9.1, 4.1 Hz, 1H, H_{8a}), 3.68 (dd, *J*=12.3, 4.7 Hz, 1H, $H_{3'}$), 3.61 (d, *J*=9.1 Hz, 1H, H_{4a}), 3.46 (ddd, *J*=11.5, 11.5, 3.5 Hz, 1H, Ha_6), 3.40–3.36 (m, 1H, $Ha_{6'}$), 3.27 (ddd, *J*=10.8, 9.3, 4.8 Hz, 1H, $H_{8'a}$), 3.12 (ddd, *J*=11.6, 9.3, 4.4 Hz, 1H, $H_{4'a}$), 2.28 (ddd, *J*=12.3, 4.7, 4.4 Hz, 1H, $He_{4'}$), 2.10 (brdd, *J*=12.3, 4.1 Hz, 1H, He_8), 2.00 (brdd, *J*=12.0, 4.8 Hz, 1H, $He_{8'}$), 1.80–1.68 (m, 5H, $Ha_{4'}$, 2×H_7, 2×$H_{7'}$), 1.66–1.62 (m, 1H, Ha_8), 1.59–1.53 (m, 1H, $Ha_{8'}$); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 134.5 (d, C_3), 122.8 (d, C_4), 98.7 (s, C_2), 76.9 (d, $C_{4'a}$), 75.9 (d, C_{4a}), 73.1 (d, $C_{8'a}$), 71.9 (d, $C_{3'}$), 70.9 (t, C_{8a}), 68.4 (t, C_6), 68.0 (t, $C_{6'}$), 33.9 (t, $C_{4'}$), 29.7 (t, $C_{8'}$), 28.9 (t, C_8), 25.6 (t, $C_{7'}$), 25.4 (t, C_7). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.83; H, 7.90. Compound **66** (31 mg, 0.11 mmol) under the conditions used to convert **57** to the mixture **63** and **64**, afforded **63** (14 mg, 0.05 mmol, 45%) and **64** (6 mg, 0.02 mmol, 18%). A 1:1 mixture of compounds **65** and **66** is quantitatively formed by base hydrolysis of **55** (MeONa cat./MeOH/ 25°C/30 min) followed by acid induced ($BF_3{\cdot}OEt_2$/ CH_3CN/−30°C/15 min) spirocyclization of the resulting diol.

Acknowledgements

We are grateful to Professor K. Nakanishi and Dr M. L. Souto, Columbia University, for providing BTX-2 (BTX-B) and to Professor T. Yasumoto and Dr M. Satake, Tohoku University, for a sample of PbTx-3. This work was supported by grants from the Ministry of Science and Technology (BQU2001-1137) and Fundación Ramón Areces. R. L. P. thanks AECI, Spain, for a fellowship. C. G. C. thanks the MEC, Spain, for a Predoctoral fellowship.

References

1. (a) Lopez-Barneo, J. *Trends Neurosci.* **1994**, *17*, 133–135. (b) Catterall, W. A. *Annu. Rev. Biochem.* **1995**, *64*, 493–531. (c) Albillos, A.; Gandia, L.; Michelena, P.; Gilabert, J. A.; del Valle, M.; Carbone, E.; Garcia, A. G. *J. Physiol.* **1996**, *494*, 687–695. (d) Sato, C.; Sato, M.; Iwasaki, A.; Doi, T.; Engel, A. *J. Struct. Biol.* **1998**, *121*, 314–325. (e) Sato, C.; Ueno, Y.; Asai, K.; Takahashi, K.; Sato, M.; Engel, A.; Fujiyoshi, Y. *Nature* **2001**, *409*, 1047–1051.
2. (a) Noda, M.; Numa, S. *J. Recept. Res.* **1987**, *7*, 467–497. (b) Cestele, S.; Scheuer, T.; Mantegazza, M.; Rochat, H.; Catterall, W. A. *J. Gen. Physiol.* **2001**, *118* (3), 291–302. (c) Cantrell, A. R.; Catterall, W. A. *Nat. Rev. Neurosci.* **2001**, *2* (6), 397–407.
3. (a) Noda, M.; Ikeda, T.; Koyano, T.; Suzuki, H.; Takeshima, H.; Kurasaki, M.; Takahashi, H.; Numa, S. *Nature* **1986**, *320*, 188–192. (b) Kayano, T.; Noda, M.; Flockerzi, V.; Takahashi, H.; Numa, S. *FEBS Lett.* **1988**, *228*, 187–194. (c) Rogart, R. B.; Cribbs, L. L.; Muglia, L. K.; Kephart, D. D.; Kaiser, M. W. *Proc. Natl Acad. Sci. USA* **1989**, *86*, 8170–8174. (d) Trimmer, J. S.; Cooperman, S. S.; Tomiko, S. A.; Zhou, J. Y.; Crean, S. M.; Boyle, M. B.; Kallen, R. G.; Sheng, Z. H.; Barchi, R. L.; Sigworth, F. J. *Neuron* **1989**, *3*, 33–49. (e) George, A. L.; Knittle, T. J.; Tamkun, M. M. *Proc. Natl Acad. Sci. USA* **1992**, *89*, 4893–4897. (f) Klugbauer, N.; Lacinova, L.; Flockerzi, V.; Hofmann, F. *EMBO J.* **1995**, *14*, 1084–1090. (g) Schaller, K. L.; Krzemien, D. M.; Yarowski, P. J.; Krueger, B. K.; Caldwell, J. H. *J. Neurosci.* **1995**, *5*, 3231–3242. (h) Belcher, S. M.; Zerillo, C. A.; Levenson, R.; Ritchie, J. M.; Howe, J. R. *Proc. Natl Acad. Sci. USA* **1995**, *92*, 11034–11038. (i) Akopian, A. N.; Sivilotti, L.; Wood, J. N. *Nature* **1996**, *379*, 257–262. (j) Toledo-Aral, J. J.; Moss, B. L.; He, Z. J.; Koszowski, A. G.; Whisenand, T.; Levinson, S. R.; Wolf, J. J.; Silos-Santiago, I.; Halegoua, S.; Mandel, G. *Proc. Natl Acad. Sci. USA* **1997**, *94*, 1527–1532. (k) Diss, J. K.; Stewart, D.; Fraser, S. P.; Black, J. A.; Dib-Hajj, S.; Waxman, S. G.; Archer, S. N.; Djamgoz, M. B. *FEBS Lett.* **1998**, *427*, 5–10.
4. (a) Rojas, C. V.; Wang, J. Z.; Schwartz, L. S.; Hoffman, E. P.; Powell, B. R.; Brown Jr., R. H. *Nature* **1991**, *354*, 387–389. (b) McClatchey, A. I.; Van den Bergh, P.; Pericak-Vance, M. A.; Raskind, W.; Verellen, C.; McKenna-Yasek, D.; Rao, K.; Haines, J. L.; Bird, T.; Brown Jr., R. H. *Cell* **1992**, *68*, 769–774. (c) Bennett, P. B.; Yazawa, K.; Makita, N.; George Jr., A. L. *Nature* **1995**, *376*, 683–685. (d) Chen, Q.; Kirsch, G. E.; Zhang, D.; Brugada, R.; Brugada, J.; Brugada, P.; Potenza, D.; Moya, A.; Borggrefe, M.; Breithardt, G.; Ortiz-Lopez, R.; Wang, Z.; Antzelevitch, C.; O'Brien, R. E.; Schulze-Bahr, E.; Keating, M. T.; Towbin, J. A.; Wang, Q. *Nature* **1998**, *392*, 293–296. (e) Cooper, E. C.; Jan, L. Y. *Proc. Natl Acad. Sci. USA* **1999**, *96*, 4759–4766. (f) Lehmann-Horn, F.; Jurkat-Rott, K. *Physiol. Rev.* **1999**, *79*, 1317–1372. (g) Gold, M. S. *Proc. Natl Acad. Sci. USA* **1999**, *96*, 7645–7649. (h) Alekov, A.; Rahman, M. M.; Mitrovic, N.; Lehmann-Horn, F.; Lerche, H. *J. Physiol.* **2000**, *529*, 533–539.
5. (a) Baden, D. G.; Mende, T. J.; Szmant, A. M.; Trainer, V. L.; Edwards, R. L.; Roszell, L. E. *Toxicon* **1988**, *26*, 97–103. (b) Cruz, L. J.; Kupryszewski, G.; LeCheminant, G. W.; Gray, W. R.; Olivera, B.; Rivier, J. *Biochemistry* **1989**, *28*, 3437–3442. (c) Trainer, V. L.; Baden, D. G.; Catterall, W. A. *J. Biol. Chem.* **1994**, *269*, 19904–19909. (d) Alvarez, E.; Candenas, M. L.; Pérez, R.; Ravelo, J.-L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953–1980. (e) Matile, S.; Nakanishi, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 757–759. (f) Linford, N. J.; Cantrell, A.; Qu, Y.; Scheuer, T.; Catterall, W. A. *Proc. Natl Acad. Sci. USA* **1998**, *95*, 13947–13952. (g) Cestèle, S.; Qu, Y.; Rogers, J. C.; Rochat, H.; Scheuer, T.; Catterall, W. A. *Neuron* **1998**, *21*, 919–931.
6. (a) Rein, K. S.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *59*, 2101–2106. (b) Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107–2113. (c) Gawley, R. E.; Rein, K. S.; Jeglitsch, G.; Adams, D. J.; Theodorakis, E. A.; Tiebes, J.; Nicolaou, K. C.; Baden, D. G. *Chem. Biol.* **1995**, *2*, 533–541. (d) Purkerson-Parker, S. L.; Fieber, L. A.; Rein, K. S.; Podona, T.; Baden, D. G. *Chem. Biol.* **2000**, *7*, 385–393. (e) Carter, A. J.; Grauert, M.; Pschorn, U.; Bechtel, W. D.; Bartmann-Lindholm, C.; Qu, Y.; Scheuer, T.; Catterall, W. A.; Weiser, T. *Proc. Natl Acad. Sci. USA* **2000**, *97*, 4944–4949. (f) Kinoshita, E.; Maejima, H.; Yamaoka, K.; Konno, K.; Kawai, N.; Shimizu, E.; Yokote, S.; Nakayama, H.; Seyama, I. *Mol. Pharmacol.* **2001**, *59*, 1457–1463.
7. (a) Ohya, Y.; Sperelakis, N. *Am. J. Physiol.* **1989**, *257*, C408–C412. (b) Inoue, Y.; Sperelakis, N. *Am. J. Physiol.* **1991**, *260*, C658–C663. (c) Martin, C.; Arnaudeau, S.; Jmari, K.; Rakotoarisoa, L.; Sayet, I.; Dacquet, C.; Mironneau, C.; Mironneau, J. *Mol. Pharmacol.* **1991**, *38*, 667–673. (d) Kao, C.; Wang, S. *Am. J. Obstet. Gynecol.* **1994**, *171*, 446–454. (e) Boyle, M. B.; Heslip, L. A. *Recept. Channels* **1994**, *2*, 249–253. (f) Knittle, T. J.; Doyle, K. L.; Tamkun, M. M. *Am. J. Physiol.* **1996**, *270*, C688–C696.
8. For a an excellent coverage of the field, see: Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49 and previous reports in this series.
9. For reviews, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (b) Scheuer, P. J. *Tetrahedron* **1993**, *50*, 3–18. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293–314. (d) Daranas, A. H.; Norte, M.; Fernández, J. J.

Toxicon **2001**, *39*, 1101–1132. Recent publications: (e) Morohashi, A.; Satake, M.; Murata, K.; Naoki, H.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 8995–8998. (f) Satake, M.; Ishihashi, Y.; Legrand, A.-M.; Yasumoto, T. *Biosci. Biochem. Biotechnol.* **1996**, *60*, 2103–2105. (g) Satake, M.; Teresawa, K.; Kadowaki, Y.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 5955–5959. (h) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 97–100. (i) Satake, M.; Fukui, M.; Legrand, A.-M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197–1198. (j) Ciminiello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Poletti, R.; Viviani, R. *Tetrahedron Lett.* **1998**, *39*, 8897–8900. (k) Lewis, R. J.; Vernoux, J.-P.; Bereton, I. M. *J. Am. Chem. Soc.* **1998**, *120*, 5914–5920. (l) Iguarashi, T.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 8499–8511. (m) Morohashi, A.; Satake, M.; Naoki, H.; Kaspar, H. F.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1997**, *7*, 45–48. (n) Yasumoto, T.; Igarashi, T.; Legrand, A.-M.; Cruchet, P.; Chinain, M.; Fujita, T.; Noaki, H. *J. Am. Chem. Soc.* **2000**, *122*, 4988–4989.

10. (a) Bidard, J. N.; Vijverberg, H. P. M.; Frelin, C.; Chungue, E.; Legrand, A.-M.; Bagnis, R.; Lazdunski, M. *J. Biol. Chem.* **1984**, *259*, 8353–8357. (b) Poli, M. A.; Mende, T. J.; Baden, D. G. *Mol. Pharmacol.* **1986**, *30*, 129–135. (c) Lombet, A.; Bidard, J. N.; Lazdunski, M. *FEBS Lett.* **1987**, *219*, 355–359. (d) Baden, D. G.; Mende, T. J.; Szmant, A. M.; Trainer, V. L.; Edwards, R. M.; Roszell, L. E. *Toxicon* **1988**, *26*, 97–103. (e) Catterall, W. A. *Science* **1988**, *242*, 50–61. (f) Baden, D. G. *FASEB J.* **1989**, *3*, 1807–1817. (g) Trainer, V. L.; Edwards, R. A.; Szmant, A. M.; Stuart, A. M.; Mende, T. J.; Baden, D. G. In *Marine Toxins: Origin, Structure and Molecular Pharmacology*, Hall, S., Trichartz, G., Eds.; *ACS Symposium Series 418*; American Chemical Society: Washington, DC, 1990; pp. 166–175. (h) Trainer, V. L.; Thomsen, W. J.; Catterall, W. A.; Baden, D. G. *Mol. Pharmacol.* **1991**, *40*, 988–994. (i) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; MacLeod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115–1127. (j) Gawley, R. E.; Rein, K. S.; Kinoshita, M.; Baden, D. G. *Toxicon* **1992**, *30*, 780–785. (k) Manger, R. L.; Leja, L. S.; Lee, S. Y.; Hungerford, J. M.; Wekell, M. M. *Anal. Biochem.* **1993**, *214*, 190–194. (l) Trainer, V. L.; Baden, D. G.; Catterall, W. A. *J. Biol. Chem.* **1994**, *269*, 19904–19909. (m) Taylor, R. *J. NIH Res.* **1994**, *6*, 100–112. (n) Manger, R. L.; Leja, L. S.; Lee, S. Y.; Hungerford, J. M.; Hokama, Y.; Dickey, R. W.; Grandole, H. R.; Lewis, R.; Yasumoto, T.; Wekell, M. M. *J. Assoc. Off. Anal. Chem.* **1995**, *78*, 521–527. (o) Benoit, E.; Juzans, P.; Legrand, A.-M.; Molgo, J. *Neuroscience* **1996**, *71*, 1121–1131. (p) Bossart, G. D.; Baden, D. G.; Ewing, R. Y.; Roberts, B.; Wright, S. D. *Toxicol. Pathol.* **1996**, *26*, 277–282. (q) Poli, M. A.; Lewis, R. J.; Dickey, R. W.; Musser, S. M.; Buckner, C. A.; Carpenter, L. G. *Toxicon* **1997**, *35*, 733–741. (r) Jeglitsch, G. A.; Rein, K. S.; Baden, D. G.; Adams, D. J. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 516–524. (s) Purkenson, S. L.; Baden, D. G.; Fieber, L. A. *Neurotoxicology* **2000**, *20*, 909–920.
11. (a) Gawley, R. E.; Rein, K. S.; Kinoshita, M.; Baden, D. G. *Toxicon* **1992**, *30*, 780–785. (b) Rein, K. S.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *52*, 2101–2106. (c) Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107–2113. (d) Gawley, R. E.; Rein, K. S.; Jeglistch, C.; Adams, D. J.; Theodorakis, E. A.; Tiebes, J.; Nicolaou, K. C.; Baden, D. G. *Chem. Biol.* **1995**, *2*, 533–541. (e) Matile, S.; Berova, N.; Nakanishi, K.; Fleischauer, J.; Woody, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 5198–5206.
12. In oxepane ring there are 14 *twist-chairs* (energy minimum) and equal number of *chairs*, *twist-boats* and *boats*: (a) Bocian, D. F.; Pickett, H. M.; Rounds, T. C.; Strauss, H. L. *J. Am. Chem. Soc.* **1975**, *97*, 687–695. (b) Bocian, D. F.; Strauss, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 2866–2876. (c) Bocian, D. F.; Strauss, H. L. *J. Mol. Struct.* **1977**, *99*, 2876–2882. (d) Favini, G. *J. Mol. Struct.* **1983**, *93*, 139–152.
13. Anet, A. L. F. In *Conformational Analysis of Medium-Sized Heterocycles*, Glass, R. S., Ed.; VCH: New York, 1988; pp. 35–95.
14. More in depth studies of the conformational restrictions imposed to oxepanes by adjacent more rigid cycles, are being carried out using ab-initio computational methodology: Morales, E. Q. To be published.
15. Stoddart's methodology for describing the conformation of seven-membered rings is used: Stoddard, J. F. *Stereochemistry of Carbohydrate*; Wiley-Interscience: New York, 1971.
16. For a full paper with indication of the used methodology, see: Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848–2876.
17. For a recent review of the synthesis of cyclic ether via ring-closing metathesis, see: Yet, L. *Chem. Rev.* **2000**, 2963–3007.
18. (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
19. Manta, E.; Scarone, L.; Hernández, G.; Mariezcurrena, R.; Suescun, L.; Brito, I.; Brouard, I.; González, M. C.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1997**, *38*, 5853–5856.
20. Brouard, I.; Hanxing, L.; Martín, J. D. *Synthesis* **2000**, 883–892.
21. Montecarlo search was performed using MM3* force field as implemented in Macromodel 6.0, 2000 steps were used, discarting conformers with energies of 50 kJ/mol above the global minimum. Macromodel V 6.0:Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrikson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–447.
22. (a) Baden, D. G.; Rein, K. S.; Kinoshita, M.; Gawley, R. E. Proceeding of the Third International Conference on Ciguatera Fish Poisoning 1990; Tosteson, T. R., Ed.; Polyscience: Morin Heights, Quebec, 1992; pp 103–114. (b) Gawley, R. E.; Rein, K. S.; Kinoshita, M.; Baden, D. G. *Toxicon* **1992**, *30*, 780–785.
23. Brouard, I.; Martín, J. D. To be published.
24. For recent reviews, see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953–1980. (b) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589–607. (c) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849–852.
25. Convergent approaches via intermolecular coupling to C-linked oxacyclic subunits, most notably arise from the Nicolaou group. Their work has led to the synthesis of brevetoxins A and B: (a) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252–10263. (b) Nicolaou, K. C.; Yang, Z.; Shi, G. Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264–269. (c) Nicolaou, K. C.; Gunzner, J. L.; Shi, G. Q.; Agrios, K. A.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1995**, *5*, 646–657.

26. Selected recent publications related to convergent approaches via C-linked oxacycles not included in Ref. 24, are: (a) Nicolaou, K. C.; Postema, M. H. D.; Clairbone, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566. (b) Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003–3016. (c) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027–9030. (d) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911–1914. (e) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075–1077. (f) Fugiwara, K.; Saka, K.; Takaoka, D.; Murai, A. *Synlett* **1999**, *64*, 1037–1040. (g) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1999**, 1063–1064. (h) Hosokaea, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37–48. (i) Fujiwara, K.; Morishita, H.; Saka, K.; Murai, A. *Tetrahedron Lett.* **2000**, *41*, 507–508. (j) Matsuo, G.; Hinou, H.; Koshino, H.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 903–906. (k) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425–1428. (l) Mori, Y.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **2000**, *41*, 4161–4164. (m) Kodowaki, C.; Chan, P. W. H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 5769–5772. (n) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371–8375. (o) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821–2824. (p) Díaz, M. T.; Pérez, R. L.; Rodríguez, E.; Ravelo, J. L.; Martín, J. D. *Synlett* **2001**, 345–348. (q) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019–3033.

27. Publications related with convergent approaches via intermolecular coupling to O-linked oxacyclic subunits, are: (a) Alvarez, E.; Díaz, M. T.; Hanxing, L.; Martín, J. D. *J. Am. Chem. Soc.* **1995**, *117*, 1437–1438. (b) Nicolaou, K. C.; Postema, M. H. D.; Clairbone, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566. (c) Alvarez, E.; Delgado, M.; Díaz, M. T.; Hanxing, L.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865–2868. (d) Oishi, T.; Nagumo, Y.; Hirama, M. *Synlett* **1997**, 980–982. (e) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *37*, 1611–1614. (f) Oishi, T.; Nagumo, Y.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1998**, 1041–1042. (g) Sasaki, M.; Inoue, M.; Naguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783–2786. (h) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 965–969. (i) Sasaki, M.; Naguchi, T.; Tacchibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337–1340. (j) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1999**, 1063–1064. (k) Oishi, T.; Nagumo, Y.; Shoji, M.; Le Brazidec, J.-Y.; Uehara, H.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1999**, 2035–2036. (l) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949–10970. (m) Inoue, M.; Sasaki, M.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9416–9429. (n) Oishi, T.; Uehara, H.; Nagumo, Y.; Shoji, M.; Le Brazidec, J.-Y.; Kosaka, M.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **2001**, 381–382. (o) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem Soc.* **2001**, *123*, 6702–6703. (p) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Muruyama, M.; Oguri, H.; Satake, M. *Science*, **2001**, *294*, 1904–1907.

28. (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Redely, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238. (b) Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003–3016.

29. Dibromoolefin **32**, $[\alpha]_D^{25}=-5.0°$ (*c* 3.2, $CHCl_3$), was prepared from tri-*O*-acetyl-D-glucal according to a previously described procedure: Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Coulados, E. A.; Abe, Y.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040–3045.

30. Lactone **33**, $[\alpha]_D^{25}=-35.2°$ (*c* 1.42, $CHCl_3$), was prepared according to a described procedure: Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003–3016.

31. Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321–5330.

32. For a different approach to the synthesis of lactone **50**, see: Zheng, W.; De Mattei, J. A.; Wu, J.-P.; Duan, J. J.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946–7968.

33. Pinto, F. M.; Armesto, C. P.; Magraner, J.; Trujillo, M.; Martín, J. D.; Candenas, M.-L. *Endocrinology* **1999**, *140*, 2526–2532.

34. Magraner, J.; Pinto, F. M.; Anselmi, E.; Hernández, M.; Pérez, R.; Martín, J. D.; Advenier, C.; Candenas, M.-L. *Br. J. Pharmacol.* **1998**, *123*, 259–268.

35. Magraner, J.; Morcillo, E.; Ausina, P.; Pinto, F. M.; Martín, J. D.; Moreau, J.; Anselmi, E.; Barrachina, M. D.; Cortijo, J.; Advenier, C.; Candenas, M.-L. *Eur. J. Pharmacol.* **1997**, *326*, 211–222.