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A Bidirectional Approach to the Synthesis of a Complete Library of Adjacent-Bis-THF Annonaceous Acetogenins

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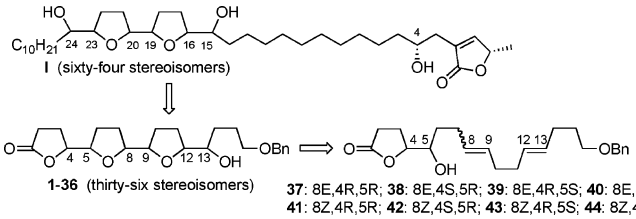

Thirty-six stereoisomers of bifunctional adjacent bis-THF (tetrahydrofuran) lactones have been synthesized, which can afford a complete library of the adjacent bis-THF Annonaceous acetogenins. The bis-THF lactones were synthesized, starting from the enantioselectively pure 8,9:12,13-(*E*,*E* and *Z*,*E*)-16-benzyloxy-5-hydroxy-hexadeca-1,4-olide, in a highly distereoselective manner using oxidative reactions, including rhenium(VII) oxides-mediated oxidative cyclization, Shi's asymmetric epoxidation, and Sharpless asymmetric dihydroxylation reactions. Using the nonsymmetrical bis-THF lactones, syntheses of two nonnatural acetogenins were achieved.

Introduction

Many Annonaceous acetogenins, especially the adjacent bis-THF (tetrahydrofuran) acetogenins are known for their impressive antitumor activities.[1] Few of these compounds, including asimicin (**Ia**),[2] bullatacin (**Ib**),[3] trilobacin (**1c**),[4] and rolliniastatin-1 (**Id**)[5] (Figure 1), have shown in vitro antitumor potency 10^8 times greater than that of adriamycin. The antitumor properties of these molecules originate from their ability to strongly inhibit the complex **I** in the mitochondria,[6] which also make these compounds an interesting tool to investigate the structure−function problems of complex **I**.[7] These natural products share very similar carbon skeletons, in that a

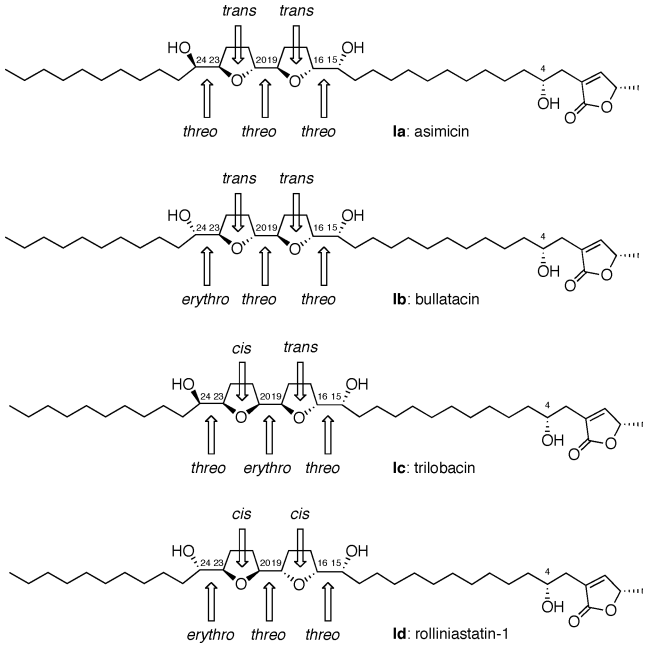

FIGURE 1. Structure of the representative adjacent bis-THF acetogenins.

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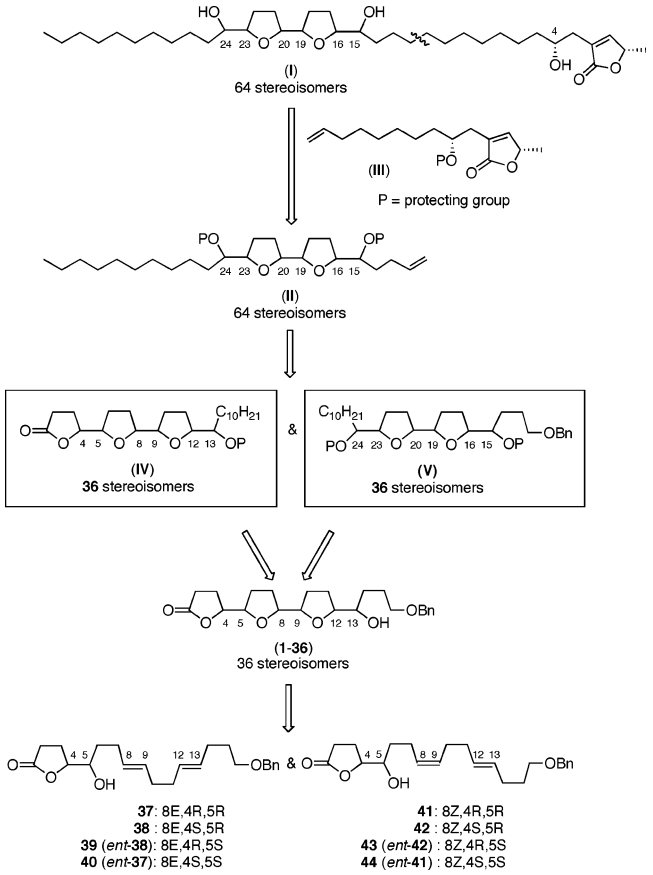
long alkyl chain tethers THF fragments to a butenolide group, which represents the conserved part of most acetogenins. Yet, they exhibit remarkable structural diversity with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. An adjacent bis-THF acetogenin can exist in as many as 64 diastereomeric forms due to six stereogenic centers of the bis-THF fragment. The cytotoxicity and selectivity of these molecules to the specific cell lines are expected to be highly dependent upon the stereo- and regiochemistry of all stereogenic centers, including the bis-THF fragment. Hence, to properly address the relationship between the stereochemistry of this fragment and the biological activity of these acetogenins, it is imperative that all 64 diastereomeric acetogenins be produced and evaluated.

Production of a library of the adjacent bis-THF acetogenins has remained a challenging goal despite numerous reports on the syntheses of natural and nonnatural acetogenins.[8] Only recently, synthesis of all 16 stereoisomers of a mono-THF acetogenin has been reported.[9] Also, there has been some advancement toward the library of the adjacent bis-THF acetogenins.[10] Earlier, we also designed the synthetic strategies that could give 32 of the 64 adjacent bis-THF acetogenins.[11] Nevertheless, there is no report yet on the synthesis of the complete library of the adjacent bis-THF acetogenins. Here, we report the synthesis of 36 stereoisomeric bifunctional lactones that can afford all 64 stereoisomers of the adjacent bis-THF acetogenins, **I**. We also describe the total synthesis of two nonnatural diastereomeric acetogenins, **Ie** and **If**, starting from a common bis-THF lactone to show the viability of our approach for the generation of the combinatorial library of the 64 stereoisomers of **I** and their analogues.

SCHEME 1. Partial *retro*-Synthetic Analysis of Adjacent Bis-THF Libraries[a]



[a] Compounds **39**, **40**, **43**, and **44** are the enantiomers of **38**, **37**, **42**, and **44**, respectively, and they can be named as *ent*-**38**, *ent*-**37**, and so on. However, for simplicity, hereon we used a new number for each enantiomer.

Results and Discussion

An examination of the adjacent bis-THF acetogenin molecules reveals that a complete library of 64 stereoisomers of **I** can be synthesized by the coupling of 64 bis-THF fragments (such as **II**) with a single butenolide precursor (Scheme 1). The coupling reaction can be achieved using a number of methodologies, including the intramolecular and cross-metathesis reaction,[12] palladium-catalyzed coupling processes,[13] and the Wittig reaction.[14] Earlier, we had successfully utilized the palladium-catalyzed coupling processes, and the Wittig reaction for the synthesis of a number of Annonaceous acetogenins, such as, solamin, reticulatacin, asimicin, bullatacin, trilobacin, trilobin, uvaricin, rolidecin C and D, and

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mucocin.[15] Here, we decided to test the utility of cross metathesis reaction for the assembly of **I**.[16] Thus, using all possible stereoisomers of **II** and the butenolide alkene **III**, one may produce the 64 stereoisomers of **I** in a parallel combinatorial synthesis. Obviously, synthesis of all stereoisomers of **II** remains the major determining factor for the production of the bis-THF acetogenin library considering that there exists a number of synthetic methods[8] for the synthesis of the butenolide fragment, **III**.[15b] We anticipated that all 64 stereoisomeric **II** could be obtained via the intermediates **IV** and/or **V** in two ways. In one case, 64 stereoisomers of the intermediates **IV** or **V** will be used, which will be obtained from the identical number of their precursors. Alternatively, all 64 stereoisomers of **II** can be prepared starting from the 36 stereoisomeric bifunctional lactones (**1**−**36**, Table 1) using a combination of intermediates **IV** and **V**.

The adjacent bis-THF acetogenins can be divided into two sets, which differ from each other being the *threo* (set I) or *erytho* (set II) configuration of C-19/C-20 joining the bis-THF rings (Table 1). Each set is comprised of 32 compounds and can further be divided into three subsets on the basis of the stereochemistry of bis-THF rings, *trans*−*trans*, *cis*−*cis*, and *trans*−*cis* or *cis*−*trans*. As shown in Table 1, four *trans*−*trans* and four *cis*−*cis* acetogenins in set I are pseudo-symmetric at C-19/C-20 center, whereas the remaining 56 acetogenins are nonsymmetrical. Likewise, 8 bis-THF lactones (**1**−**4** and **7**−**10**) are pseudo-symmetric at C-8/C-9 center, and the remaining 28 (**5**,**6** and **11**−**36**) are nonsymmetrical. The nonsymmetrical bis-THF lactones (**5**,**6** and **11**−**36**) can flip along the *x*-axis to afford the identical number of stereoisomers. Thus, lactones **5**,**6** and **11**−**36** can be functionalized at the two alternative ends to give each 28 stereoisomeric intermediates of **IV** and **V**, thereby leading to a total of 56 stereoisomers of **II**. Functionalization of the remaining eight lactones **1**−**4** and **7**−**10**, at either end, will afford an additional eight stereoisomers of **II** via **IV** or **V**.

Earlier, we synthesized a number of Annonaceous acetogenins starting from the "naked" carbon skeletons, in that all of the oxygen functions were installed using enantioselective and diastereoselective reactions, including Sharpless asymmetric dihydroxylation (AD)[17] and asymmetric epoxidation (AE)[18] reactions, and the rhenium(VII) oxides-mediated oxidative cyclization (OC)[19] reactions. These reactions were combined with Williamson's type etherification[20] and Mitsunobu inversion[21] to produce various bis-THF compounds. An analysis of compounds **1**−**36** suggested that they could be synthesized by stereospecific oxidative cyclizations of the isomeric diene-lactones **37**−**40** using five key reactions, which include Shi mono- or bis-asymmetric epoxidation (AE),[22] beside the rhenium(VII) oxides mediated mono- or bis-OC, Sharpless AD, Williamson's etherification, and the Mitsunobu inversion reactions. However, using the above-described key reactions, several bis-THF compounds could be accessed better starting from diene-lactones **41**−**44**. Hence, we used diene-lactones **37**−**44** to synthesize **1**−**36**. Table 2 shows the specific sets of reactions used to convert **37**−**44** to **1**−**36**. Here, rhenium(VII) oxides-mediated OC reaction was conducted on both cis and trans double bonds, whereas Shi AE and Sharpless AD were executed with trans double

TABLE 1. Stereochemical Correlation of All 64 Adjacent Bis-THF Acetogenins of the General Structure I with Bis-THF Lactones, 1−36[a]

configurations of **I** or **1-36**			stereochemistry		starting bis-THF compounds
C-19,C-20 or C-8,C-9	bis-THF rings		**I**	**1-36**	
			15,16,19,20,23,24	4,5,8,9,12,13	
threo	*trans-trans*		RRRRRR	RRRRRR	**1**
			SSSSSS	SSSSSS	**2** (*ent*-**1**)
			SRRRRS	SRRRRS	**3**
			RSSSSR	RSSSSR	**4** (*ent*-**3**)
			RRRRRS; SRRRRR	RRRRRS	**5**
			SSSSSR; RSSSSS	SSSSSR	**6** (*ent*-**5**)
	cis-cis		RSRRSR	RSRRSR	**7**
			SRSSRS	SRSSRS	**8** (*ent*-**7**)
			SSRRSS	SSRRSS	**9**
			RRSSRR	RRSSRR	**10** (*ent*-**9**)
			SRSSRR; RRSSRS	SRSSRR	**11**
			RSRRSS; SSRRSR	RSRRSS	**12** (*ent*-**11**)
	trans-cis or *cis-trans*		RRRRSR; RSRRRR	RRRRSR	**13**
			SSSSRS; SRSSSS	SSSSRS	**14** (*ent*-**13**)
			RRRRSS; SSRRRR	RRRRSS	**15**
			SSSSRR; RRSSSS	SSSSRR	**16** (*ent*-**15**)
			RSSSRR; RRSSSR	RSSSRR	**17**
			SRRRSS; SSRRRS	SRRRSS	**18** (*ent*-**17**)
			SRRRSR; RSRRRS	SRRRSR	**19**
			RSSSRS; SRSSSR	RSSSRS	**20** (*ent*-**19**)
erythro	*trans-trans*		RRRSSS; SSSRRR	RRRSSS	**21**
			RSSRRS; SRRSSR	RSSRRS	**22**
			RSSRRR; RRRSSR	RSSRRR	**23**
			SRRSSS; SSSRRS	SRRSSS	**24** (*ent*-**23**)
	cis-cis		RRSRSS; SSRSRR	RRSRSS	**25**
			SRSRSR; RSRSRS	SRSRSR	**26**
			RRSRSR; RSRSRR	RRSRSR	**27**
			SSRSRS; SRSRSS	SSRSRS	**28** (*ent*-**27**)
	trans-cis or *cis-trans*		RRRSRR; RRSRRR	RRRSRR	**29**
			SSSRSS; SSRSSS	SSSRSS	**30** (*ent*-**29**)
			RRRSRS; SRSRRR	RRRSRS	**31**
			SSSRSR; RSRSSS	SSSRSR	**32** (*ent*-**31**)
			SRRSRR; RRSRRS	SRRSRR	**33**
			RSSRSS; SSRSSR	RSSRSS	**34** (*ent*-**33**)
			RSSRSR; RSRSSR	RSSRSR	**35**
			SRRSRS; SRSRRS	SRRSRS	**36** (*ent*-**35**)

[a] Compounds **2**, **4**, **6**, etc. are the enantiomers of **1**, **3**, **5**, and so on, and they can be named as *ent*-**1**, *ent*-**3**, *ent*-**5**, etc. However, for simplicity, hereon we used a new number for each enantiomer.

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TABLE 2. Synthesis of Bis-THF Lactones 1−36[a]

com-pounds	starting materials	methods	com-pounds	starting materials	methods
1	**41**	D-2	**21**	**41**	A
2	**44**	D-1	**22**	**43**	C-1
3	**38**	C-1	**23**	**43**	A
4	**39**	C-2	**24**	**42**	A
5	**37**	C-1	**25**	**27**	E
6	**40**	C-2	**26**	**38**	B-2
7	**12**	E	**27**	**37**	B-2
8	**11**	E	**28**	**40**	B-1
9	**40**	F-1	**29**	**37**	D-2
10	**37**	F-2	**30**	**40**	D-1
11	**38**	F-2	**31**	**37**	B-1
12	**39**	F-1	**32**	**40**	B-2
13	**37**	C-2	**33**	**38**	D-2
14	**40**	C-1	**34**	**39**	D-1
15	**37**	A	**35**	**39**	B-2
16	**40**	A	**36**	**38**	B-1
17	**39**	A			
18	**38**	A			
19	**38**	C-2			
20	**39**	C-1			

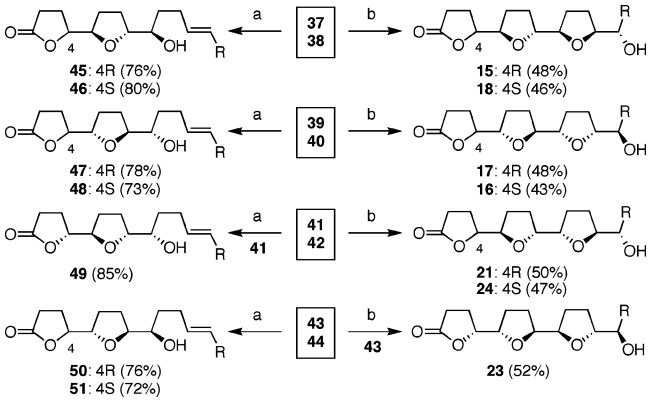
[a] Key: (A) bis-OC, (B-1) bis-α-AE, (B-2) bis-*β*-AE, (C-1) mono-OC, then mono-α-AE, (C-2) mono-OC, then mono-*β*-AE, (D-1) mono-OC, then α-AD, (D-2) mono-OC, then *β*-AD, (E) Mitsunobu inversion, (F-1) mono-α-AE, then α-AD, (F-2) mono-*β*-AE, then *β*-AD.

bonds only. Both one-step tandem and stepwise oxidation of the two double bonds using rhenium(VII) oxides and Shi AE were applied. Finally, Mitsunobu reaction was carried out to invert the stereochemistry of C-13 in the selected bis-THF compounds.

Using the one-step tandem reactions of **37**−**44**, 14 bis-THF lactones were synthesized, whereas the remaining 22 compounds required stepwise reactions, in that the double bond nearer to the lactone ring was first oxidized followed by the next double bond. Interestingly, many of the bis-THF lactones **1**−**36** are potentially accessible from **37**−**44** using more than one method. Hence, the choice of method was based on the number of steps required to accomplish the synthesis of the bis-THF compounds from the starting diene lactones, **37**−**44**. Therefore, rhenium(VII) oxides-mediated bis-OC and Shi bis-AE methods were applied as the first and second choice, which afforded the bis-THF compounds from the starting dienes in one and two steps, respectively. The next set of bis-THF compounds was synthesized by rhenium(VII) oxides-mediated mono-OC followed by Shi-AE or the combination of Sharpless AD and Williamson's etherification. Finally, the remaining compounds were prepared by using a combination of Shi-AE and Sharpless AD, and by the Mitsunobu inversion of other bis-THF compounds.

Rhenium(VII) Oxides-Mediated Oxidative Cyclization (OC) of 37−44.[23] The rhenium(VII) oxides-mediated oxidative cyclization[24] of the bis-homoallylic and poly-bis-homoallylic alcohols affords THF and poly-THF compounds with very high selectivity.[25] The selectivity and the stereochemistry of the THF rings depend on the

SCHEME 2. Rhenium(VII) Oxides Mediated Oxidative Cyclization (OC) of 37−44 To Produce Mono- and Bis-THF Lactones[a]



[a] Key: (R = −$CH_2CH_2CH_2OBn$) (a) $TFAOReO_3$, lutidine, CH_2Cl_2, 0 °C to rt, 6 h; (b) $TFAOReO_3$, TFAA, CH_2Cl_2, 0 °C to rt, 6 h.

reagents used as well as the substrates. In general, OC reaction of the bis-homoallylic and poly-bis-homoallylic alcohols using $TFAOReO_3$−lutidine or $TFAOReO_3$−TFAA has been found to be highly selective.[26] $TFAOReO_3$−lutidine system is suitable for the production of mono-THF compounds from the bis-homoallylic and poly-bis-homoallylic alcohols, whereas $TFAOReO_3$−TFAA affords a poly-THF compound from the poly-bis-homoallylic alcohol. Based on previous reports as well as our studies,[25b] we have also derived the empirical rules for the mono- and bis-oxidative cyclization of the isomeric diene alcohols. The rules state that the first THF ring is always trans irrespective of the reagents and substrates, whereas the second THF ring depends on the stereochemistry of the first double bond and reagents used. Using $TFAOReO_3$−TFAA as a reagent, the second THF-ring is cis with substrates possessing the first trans double bond and trans THF-ring with the cis double bond. Thus, it was anticipated that the mono- and bis-OC reactions of dienes **37**−**44** using $TFAOReO_3$−lutidine and $TFAOReO_3$−TFAA, respectively would also afford the corresponding mono- and bis-THF compounds, the steroselectivity of which could be predicted.

As required by our design (Table 2), we carried out the mono-OC of dienes **37**−**41** and **43**,**44**, and bis-OC of **37**−**43** (Scheme 2). The mono OC reaction of **37**−**41** and **43**,**44** was carried out with $TFAOReO_3$−lutidine to afford seven mono-THF compounds, **45**−**51**. The latter products became the precursors of several bis-THF compounds (see latter). The bis-OC reaction of **37**−**43** was carried out using $TFAOReO_3$−TFAA to give seven bis-THF compounds **15**, **18**, **17**, **16**, **21**, **24**, and **23**, respectively (Scheme 2). As expected, both mono-OC and bis-OC reactions were found to be highly stereoselective, and the bis-THF compounds obtained from **37**−**40** and **41**−**43** had *trans*,*cis* and *trans*,*trans* configurations, respectively. The *cis*-stereochemistry of the second THF ring in *trans*,*cis*-bis-THF compounds, such as **16** and **18**, was

(23) For the synthesis of starting materials, see the Supporting Information.

(24) (a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133.

(25) (a) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (b) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076.

(26) (a) McDonald, F. E.; Town, B. T. *J. Org. Chem.* **1995**, *60*, 5750. (b) Towne, B. T.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (c) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633.

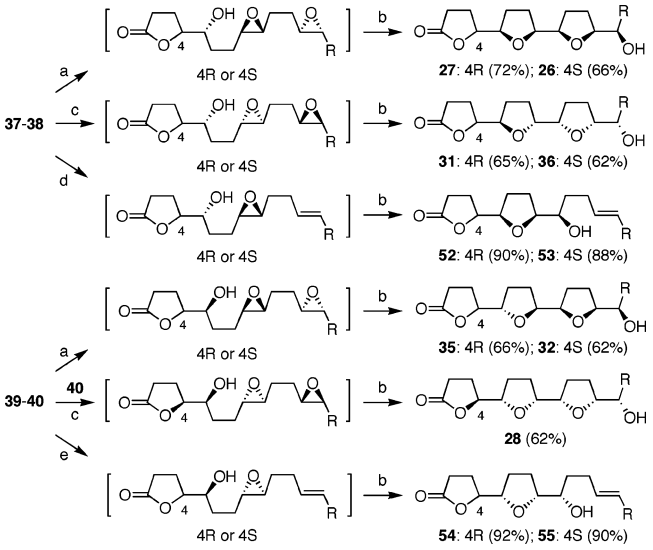
verified by an NOE experiment on the corresponding benzoate ester, which showed an NOE between the signals for H-9 and H-12 (see Scheme 1 for the numbering). In contrast, the benzoate ester of compound **21**, which possesses both trans THF rings, did not display any NOE between the signals for H-9 and H-12.

Synthesis of the Mono- and Bis-THF Lactones by the Enantioselective Shi Bis-Epoxidation Followed by Regioselective Epoxide Opening Reactions. Next, we examined the application of Shi enantioselective epoxidation for the synthesis of the mono- and bis-THF lactones. Based on the reported literature,[22] it was expected that the Shi epoxidation of trans olefins would afford the corresponding epoxides with high enantioselectivities, and accordingly we executed the Shi AE on trans alkenes only. As shown in Table 2, seven bis-THF lactones were designed using Shi bis-AE reactions on the trans dienes **37**−**40**. Thus, dienes **37**−**40** underwent asymmetric epoxidation in the presence of D-fructose-based (−)-Shi catalyst to give the corresponding desired bisepoxides contaminated with the bis-THF compounds (5−10%). Cycloetherification of the respective bisepoxides using the catalytic amount of camphorsulfonic acid (CSA) afforded the bis-THF compounds **27**, **26**, **35**, and **32** as the major products (Scheme 3). A minor amount of the byproducts with high polarity was also detected in each cycloetherification reaction, which was found to be devoid of the benzyl protecting groups. The ratio of the major and minor products after the completion of reactions remained virtually identical even after a prolong reaction time, confirming that the minor products were a result of the competitive side reaction. Similarly, starting from dienes, **37**, **38**, and **40**, three more bis-epoxides were prepared using the L-fructose-based (+)-Shi catalyst,[27] which underwent cycloetherification to afford the bis-THF compounds, **31**, **36**, and **28**, respectively. In general, the bis-THF compounds so obtained had very high diastereomeric purity.

Our design for the synthesis of several other bis-THF lactones required the regioselective Shi AE of compounds **37**−**40** (Table 2). Thus, two mono-THF compounds had to be prepared using (−)-Shi on **37**,**38** and two from **39**,**40** using (+)-Shi catalysts at the C-8,C-9 double bond (Scheme 3). We anticipated that this could be achieved by using half equivalents of the reagents and catalysts that were required for the bis-AE of **37**−**40**. As expected, epoxidation of **37**,**38** using (−)-Shi catalyst afforded the mixture of desired epoxides together with their regioisomers (epoxides at C-12,C-13) and the bis-epoxides. Interestingly, the desired mono-epoxides were the major products, as the crude epoxides underwent acid-catalyzed cyclization to afford the mono-THF lactones **52** and **53** in 54% and 48% yields (two steps), respectively. A minor amount of unreacted dienes and bis-epoxides was also isolated. Similarly, compounds **39**,**40** were epoxidized using (+)-Shi catalyst, and the crude epoxides were cyclized using CSA to afford the mono-THF lactones **54**,**55**.

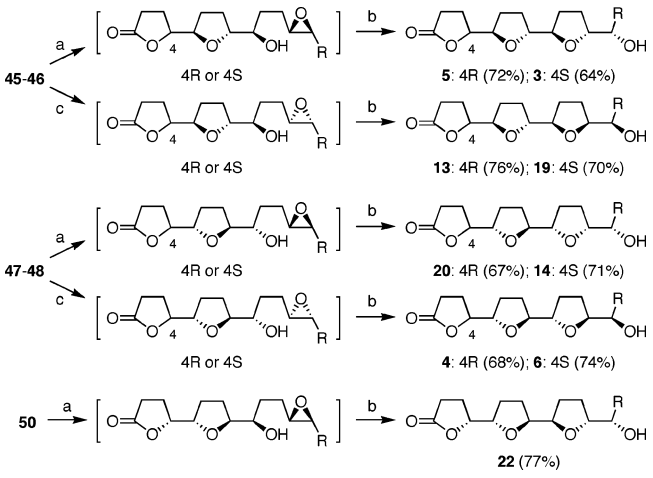
Synthesis of the Bis-THF Lactones from Mono-THF Lactones and Other Bis-THF Lactones. For the synthesis of the major portion of the remaining bis-THF lactones, we used the mono-THF compounds that were prepared by the rhenium(VII) oxides mediated mono-OC and Shi mono-AE reactions. The mono-THF compounds underwent either Shi AE reaction or Sharpless AD and Williamson's type etherification as required (Table 2). Thus, mono-THF lactones **45**−**48** and **50** were epoxidized using (+)-Shi catalyst, and the resultant epoxides were cyclized with CSA to afford the bis-THF compounds **5**, **3**, **20**, **14**, and **22** (Scheme 4). Similarly, compounds **45**−**48** were epoxidized using (−)-Shi catalyst and the products were cyclized to afford bis-THF compounds **13**, **19**,

SCHEME 3. Synthesis of Mono- and Bis-THF Lactones via the Enantioselective Shi Mono- and Bis-Epoxidation Reactions[a]



[a] Key: (R = $-CH_2CH_2CH_2OBn$) (a) (−)-Shi catalyst (60 mol %), nBu_4NHSO_4, oxone, K_2CO_3, buffer, CH_3CN−DMM; (b) CSA, CH_2Cl_2−MeOH; (c) (+)-Shi catalyst (60 mol %), reagents same as step A; (d) (−)-Shi catalyst (30 mol %), 1/2 equiv of the reagents used in step a; (e) (+)-Shi catalyst (30 mol %), 1/2 equiv of the reagents used in step c.

SCHEME 4. Synthesis of Bis-THF Lactones from the Mono-THF Lactones via the Enantioselective Shi Epoxidation Reactions[a]



[a] Key: (R = $-CH_2CH_2CH_2OBn$) (a) (+)-Shi catalyst, nBu_4NHSO_4, oxone, K_2CO_3, buffer, CH_3CN−DMM; (b) CSA, CH_2Cl_2−MeOH; (c) (−)-Shi catalyst, reagents same as step A.

(27) (−)-Shi catalyst was purchased from Aldrich (cat. # 52016-0), and (+)-Shi catalyst was synthesized as described in the literature, see: Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

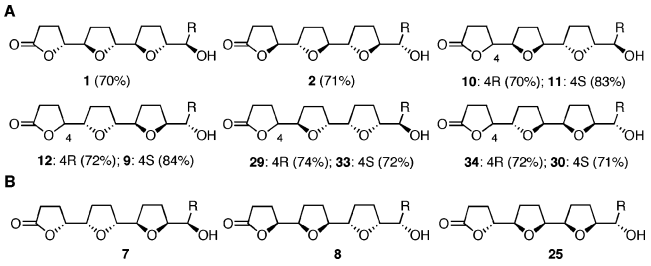


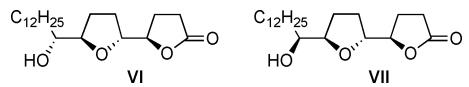
FIGURE 2. (R = $-CH_2CH_2CH_2OBn$) Bis-THF lactones prepared (A) from the mono-THF lactones via the enantioselective Sharpless AD and Williamson's type etherification reactions, and (B) by Mitsunobu inversion reaction of bis-THF lactones.

4, and **6**, respectively. This way, a total of nine bis-THF lactones were prepared.

The Sharpless AD and Williamson's type etherification were carried out on the mesylate derivatives of mono-THF compounds **45**−**49** and **51**−**55**. For this, the latter compounds were mesylated using mesyl chloride and triethylamine. The mesylates of compounds **45**, **46**, **49**, and **52**, **53** underwent Sharpless AD using the dihydroquinidine-based PHAL-DHQD ligand, whereas the mesylates of **47**, **48**, **51**, and **54**, **55** were dihydroxylated using the dihydroquinine-based PHAL-DHQ ligand. The resultant mesyloxy-diols were cyclized using the Williamson-type etherification by heating them in pyridine at elevated temperature, affording the bis-THF lactones **29**, **33**, **1**, **10**, **11**, **34**, **30**, **2**, **12**, and **9**, respectively (Figure 2). Interestingly, compounds **1** and **2** can also be obtained by the second oxidative cyclization of the mono-THF lactones **45** and **48**, respectively, using $TFAReO_3$. This preliminary finding, if general, can open a new approach to prepare the *trans*,*trans* bis-THF compounds from the *trans*,*trans* dienes in a stepwise manner. Finally, the remaining three bis-THF lactones **7**, **8**, and **25** were obtained by Mitsunobu inversion of **12**, **11**, and **27**, respectively, followed by base-acid treatment.

Structure Analysis of the Bis-THF Lactones. All of the bis-THF compounds, **1**−**36**, were synthesized starting from the stereochemically defined substrates, **37**−**44**, in that the stereochemistry of the C-4/C-5 hydroxy functions was set by the Sharpless AE or AD reactions. These reactions are known to produce epoxides and diols with defined absolute stereochemistry depending upon the ligands used. Besides Sharpless AD, the other methodologies used for the production of new stereogenic centers, C-8/C-9 and/or C-12/C-13, in compounds **1**−**36** from **37**−**44**, included Shi AE and/or rhenium(VII) oxides-mediated oxidative cyclization (OC). The Shi AE and OC reactions have also been shown earlier to follow certain rules and trends, which were taken into account when Table 2 was drafted. The fact that the bis-THF lactones, **1**−**36**, possessed the expected structures was confirmed by a comparative analysis of the ^1H and ^{13}C NMR of the mono- and bis-THF lactones, as well as the tetracetates derived from **1**−**36**. In addition, NOE experiments were carried out on the representative compounds (the benzoate esters of compounds **16**, **18**, and **21**, vide supra).

First, we confirmed the trans stereochemistry of the mono THF compounds **45** and **49** (or their enantiomers) with the previously known *trans*-THF compounds **VI**[15a] and **VII**,[25a] respectively, which showed a close match of the signals for the diagnostic protons (H-4, H-5, H-8, and H-9) and the related oxy-carbons in their NMR spectra. Because the C-4/C-5 relationship was not expected to affect the outcome of relative stereochemistry of the THF ring or the newly generated C-8/C-9 centers, the above-made observations also supported the structure of the diastereomeric trans mono-THF compounds. Similarly, a comparison of **52** and **54** (or their enantiomers) with the alternate feasible trans stereoisomers **49** and **50**, respectively, revealed that they were not identical, confirming the cis stereochemistry in **52**−**55**, as expected. The foregoing data also supported the expected stereochemistry of the first THF ring and C-8/C-9 centers in the bis-THF lactones **1**−**36**, as the latter were synthesized via the mono-THF lactones, **45**−**55**, or by the processes similar to that used in their syntheses.



Next, comparison of the ^1H NMR and ^{13}C NMR spectra of the bis-THF lactones (altogether 20 spectra excluding the corresponding enantiomers) allowed us to reaffirm the relative stereochemistry of the C-4/C-5 and C-12/C-13 centers. It should be noted that stereochemistry of the C-4/C-5 centers was already established in the starting materials, and that of the C-12/C-13 center depended upon the olefin configuration. Thus, the following trends are obvious in the NMR spectra: (i) All compounds, which possess *threo* stereochemistry between C-4/C-5 centers, display H-2/H-2′ of the butyrolactone ring separated by about 0.3 ppm, and 0.1 ppm for those with *erythro* stereochemistry; and (ii) compounds with the expected *threo* stereochemistry between C-12/C-13 show H-13 signals at δ 3.32−3.42, and C-13 at $>\delta$ 73 in the ^1H NMR and ^{13}C NMR spectra, respectively, and at δ 3.74−3.82 and $<\delta$ 73 in erythro compounds. Using this information, we could compare the compounds possessing identical C-4/C-5, C-8/C-9 centers, but the reverse C-12/C-13 absolute stereochemistry. Here, the comparison was made between compounds **1/15**, **5/13**, **23/34**, **22/35**, and **20/4** (or the corresponding enantiomers; see Table 3). There were no counterparts for the remaining compounds in our list of bis-THF lactones. As shown in the table, the compounds in each group display different ^1H and/or ^{13}C NMR spectral properties, suggesting that the second THF ring in these compounds possesses the expected stereochemistry, or else those of both compounds are incorrect. The latter is less likely.

Finally, the ^1H NMR spectral properties of the tetraacetate derivatives[28] of compounds **1**−**36** (designated by letter "T" after the number of bis-THF lactones used for the synthesis of the tetraacetates; only one enantiomer was used in cases when both enantiomers of the lactones were present) show trends that are similar to the previously reported analogous bis-THF diacetates[29] (Table 4). Moreover, the signals for the diagnostic protons of 12

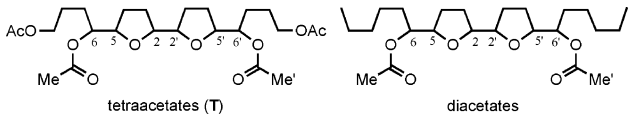
(28) The tetraacetates were synthesized in a sequence of three steps, including LAH reduction of lactones to the corresponding triols, deprotection of the benzyl protecting group by hydrogenolysis in the presence of H_2/Pd−C, and esterification of the resultant tetra hydroxy bis-THF compounds using Ac_2O/pyridine.

(29) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc*. **1987**, *109*, 4402.

TABLE 3. A Comparative Study of the ^{1}H NMR Data of Compounds 1−36

compounds	stereochemistry (4,5,8,9,12,1 3)	configuration	chemical shifts H-4	H-5	(H-8,9)[a]	H-12	H-13	H-2,2′	C-13
1 (or **2**)	*RRRRRR* (or *SSSSSS*)	th-t-th-t-th	4.46	4.09	3.89, 3.86	3.80	3.41	2.69, 2.44	73.6
15 (or **16**)	*RRRRSS* (or *SSSSRR*)	th-t-th-c-th	4.44	4.10	3.91, 3.91	3.91	3.38	2.67, 2.42	74.4
5 (or **6**)	*RRRRRS* (or *SSSSSR*)	th-t-th-t-er	4.48	4.11	3.89, 3.88	3.87	3.80	2.70, 2.45	72.9
13 (or **14**)	*RRRRSR* (or *SSSSRS*)	th-t-th-c-er	4.48	4.11	3.95, 3.92	3.89	3.78	2.67, 2.43	72.9
21	RRRSSS	th-t-er-t-th	4.46	4.08	3.94, 3.89	3.78	3.40	2.67, 2.44	73.7
29 (or **30**)	*RRRSRR* (or *SSSRSS*)	th-t-er-c-th	4.47	4.04	4.06, 3.96	3.84	3.37	2.67, 2.42	74.3
31 (or **32**)	*RRRSRS* (or *SSSRSR*)	th-t-er-c-er	4.46	4.08	4.13, 3.96	3.90	3.75	2.64, 2.43	72.9
27 (or **28**)	*RRSRSR* (or *SSRSRS*)	th-c-er-c-er	4.50	4.00	3.94, 3.92	3.85	3.78	2.71, 2.44	72.8
25	RRSRSS	th-c-er-c-th	4.50	4.01	3.94, 3.91	3.76	3.41	2.71, 2.41	73.8
10 (or **9**)	*RRSSRR* (or *SSRRSS*)	th-c-th-c-th	4.48	4.06	3.85, 3.83	3.78	3.41	2.70, 2.40	73.7
23 (or **24**)	*RSSRRR* (or *SRRSSS*)	er-t-er-t-th	4.43	4.08	3.96, 3.92	3.81	3.40	2.55, 2.48	73.6
34 (or **33**)	*RSSRSS* (or *SRRSRR*)	er-t-er-c-th	4.40	4.02	4.08, 3.94	3.84	3.38	2.55, 2.48	74.1
22	RSSRRS	er-t-er-t-er	4.43	4.09	4.00, 3.98	3.87	3.74	2.56, 2.49	72.9
35 (or **36**)	*RSSRSR* (or *SRRSRS*)	er-t-er-c-er	4.40	4.02	4.17, 3.97	3.91	3.75	2.54, 2.48	72.8
4 (or **3**)	*RSSSSR* (or *SRRRRS*)	er-t-th-t-er	4.47	4.08	3.94, 3.91	3.88	3.80	2.55, 2.49	72.9
20 (or **19**)	*RSSSRS* (or *SRRRSR*)	er-t-th-c-er	4.44	4.05	3.98, 3.88	3.92	3.80	2.54, 2.49	72.8
17 (or **18**)	*RSSSRR* (or *SRRRSS*)	er-t-th-c-th	4.43	4.05	3.97, 3.90	3.88	3.39	2.55, 2.50	74.2
8 (or **7**)	*SRSSRS* (or *RSRRSR*)	er-c-th-c-er	4.43	3.97	3.90, 3.88	3.86	3.80	2.56, 2.49	72.9
11 (or **12**)	*SRSSRR* (or *RSRRSS*)	er-c-th-c-th	4.42	3.95	3.90, 3.88	3.85	3.40	2.55, 2.49	73.9
26	SRSRSR	er-c-er-c-er	4.39	3.95	4.06, 3.98	3.89	3.75	2.54, 2.48	72.8

TABLE 4. A Comparative Study of the ^{1}H NMR Data of Tetraacetates (T)



compounds	configuration	^{1}H NMR chemical shifts H-2/H-2′	H-5/H-5′	H-6/H-6′	Me/Me′
1T	th-t-th-t-th	3.91	4.00	4.90	2.08
3T	er-t-th-t-er	3.87	3.97	4.90	2.05
6T	th-t-th-t-er	3.91	3.98	4.90	2.08, 2.05
7T	er-c-th-c-er	3.79	3.93	4.89	2.04
10T	th-c-th-c-th	3.86	3.94	5.00	2.07
12T	er-c-th-c-th	3.85, 3.80	3.99, 3.93	4.92	2.08, 2.05
14T	th-t-th-c-er	3.88, 3.82	4.00, 3.91	4.90	2.09, 2.06
16T	th-t-th-c-th	3.96, 3.83	4.09, 3.90	4.91	2.08
18T	er-t-th-c-th	3.89, 3.81	4.05, 3.96	4.92	2.08, 2.06
19T	er-t-th-c-er	3.88, 3.79	3.99, 3.92	4.91	2.05
21T	th-t-er-t-th	3.83	3.96	4.87	2.06
22T	er-t-er-t-er	3.86	3.96	4.91	2.06
24T	er-t-er-t-th	3.85	3.98	4.90	2.08, 2.06
25T	th-c-er-c-th	3.76	3.94	4.88	2.07
26T	er-c-er-c-er	3.74	3.90	4.94	2.05
28T	th-c-er-c-er	3.78, 3.73	3.94, 3.90	4.95, 4.89	2.08, 2.05
30T	th-t-er-c-th	3.82	3.98, 3.93	4.88	2.08, 2.07
32T	th-t-er-c-er	3.82	3.99, 3.90	4.95, 4.88	2.08, 2.06
33T	er-t-er-c-th	3.82	3.97, 3.94	4.89	2.07, 2.06
36T	er-t-er-c-er	3.82	3.98, 3.90	4.96, 4.90	2.07, 2.06

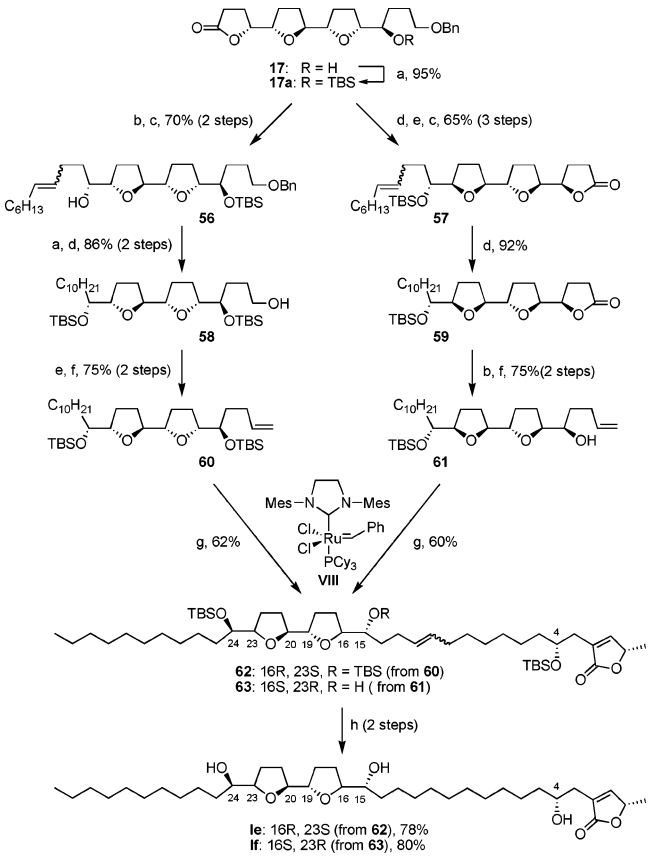
tetraacetate derivatives (T) match closely with the 12 reported diastereochemically equivalent THF diacetates. As shown in Table 4, the following trends were noticed: signals for (i) H-2 and H-5 are downfield shifted ($\Delta\delta$ 0.03−0.09 ppm) in a trans/trans compound than the corresponding cis/cis isomer; (ii) H-2 in a given cis/cis or trans/trans bis-THF compound is downfield shifted ($\Delta\delta$ 0.02−0.10 ppm) when C-2/C-2′ relationship is *threo* compared with that of *erythro*; (iii) H-2 and H-2′ in an unsymmetrical cis/trans isomer are nearly superimposed in the C-2/C-2′ *erythro* isomers and significantly separated ($\Delta\delta$ 0.06−0.09 ppm) in the C-2/C-2′ threo compounds; and (iv) methyl protons of the secondary acetate groups in compounds possessing an *erythro* configuration between C-5(5′)/C-6(6′) are upfield shifted ($\Delta\delta$ 0.02−0.03 ppm) in comparison to those with the *threo* stereochemistry. The only exception was observed with compound **22T**, where the acetate methyl protons resonated at the same δ value in comparison to the corresponding *threo* isomer, **21T**.

Synthesis of the Adjacent Bis-THF Acetogenin Stereoisomers. To show that each of the 28 nonsymmetrical lactones (**5**, **6** and **11**−**36**) would afford two adjacent bis-THF acetogenin analogues, we used lactone **17** to synthesize **Ie** and **If** as shown in Scheme 5. Thus, lactone **17** was protected as TBS ether to afford **17a**. Alkyl group was introduced at the two alternative ends of **17a** affording **56** and **57**, respectively. The latter compounds were hydrogenated to give compounds **58** and **59**. Methylenation of the aldehyde or lactol products of **58** and **59**, respectively, afforded two diastereomeric alkenes, **60** and **61**. The alkenes were subjected to the cross-metathesis reaction with butenolide alkene **III** (P = TBS) in the presence of Grubbs' second-generation catalyst **VIII**,[30] and the products **62** and **63** underwent deprotection with dilute HF in CH_3CN followed by diimide reduction to afford **Ie** (19,23-bis-*epi*-trilobacin) and **If** (16,19-bis-*epi*-trilobacin), respectively.

In conclusion, we have developed methods to synthesize a complete library of the Annonaceous bis-THF acetogenins. Specifically, 36 stereoisomeric bis-THF lactones, **1**−**36**, have been synthesized, which can be transformed to all 64 stereoisomers of the adjacent bis-THF acetogenins. The key reactions used for the synthesis of these lactones include: rhenium(VII) oxides mediated mono- or bis-oxidative cyclization, Shi mono- or bis-asymmetric epoxidation, Sharpless asymmetric dihydroxylation, Williamson's type etherification, and Mitsunobu inversion. Using one isomeric bis-THF lactone, **17**, we accomplished the synthesis of 19,23-bis-*epi*-trilobacin (**Ie**) and 16,19-bis-*epi*-trilobacin (**If**). Synthesis of all 64 stereoisomeric library of trilobacin is in progress and will be published together with their biological data in due course.

(30) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.

SCHEME 5. Synthesis of the Adjacent Bis-THF Acetogenin Stereoisomers, Ie and If[a]



[a] Key: (a) TBSOTf, lutidine, CH_2Cl_2; (b) DIBAL-H, THF; (c) $C_7H_{15}PPh_3I$, BuLi, THF; (d) Pd−C, H_2, EtOAc; (e) TPAP, NMO, CH_2Cl_2, MS 4 Å; (f) CH_3PPh_3I, BuLi, ether; (g) (i) **III** (P = TBS), $RuCl_2$[imid-H_2-Mes_2][CHPh]PCy_3 (**VIII**, Grubbs' second generation catalyst), CH_2Cl_2, rt, (ii) 5% HF in CH_3CN, (iii) $TsNHNH_2$, NaOAc, CH_3CN−DME−H_2O.

Experimental Section

Total Synthesis of 19,23-Bis-*epi*-trilobacin, 1e. (4*R*,5*S*,8*S*, 9*S*,12*R*,13*R*)-5:8,9:12-Dioxido-13-*tert*-butyldimethylsilyl-oxy-16-benzyloxy-hexadeca-1,4-olide, 17a. TBSOTf (0.34 mL, 1.47 mmol) was added slowly to an ice-cooled solution of the alcohol **17** (495 mg, 1.23 mmol) and lutidine (0.214 mL, 1.84 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min and was quenched with aq NH_4Cl, extracted with ether, and washed successively with aq $CuSO_4$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to get the crude product, which was purified by flash chromatography to yield the pure TBS ether **17a** (603 mg, 95%) as a viscous liquid. $[\alpha]_D$ +5.83 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.29−7.22 (m, 5H), 4.45 (s, 2H), 4.36 (q, J = 5.6 Hz, 1H), 4.00 (q, J = 6.4 Hz, 1H), 3.91−3.82 (m, 2H), 3.71 (m, 1H), 3.64 (ddd, J = 8.4, 5.2, 3.2 Hz, 1H), 3.42 (t, J = 6.4 Hz, 2H), 2.52−2.36 (m, 2H), 2.23 (m, 1H), 2.07−1.92 (m, 3H), 1.78−1.53 (m, 9H), 1.32 (m, 1H), 0.82 (s, 9H), 0.01 (s, 3H), 0.005 (s, 3H). ^{13}C NMR (100 MHz): δ 177.1, 138.6, 128.2, 127.4, 127.3, 82.21, 82.2, 81.8, 81.7, 80.1, 73.9, 72.6, 70.5, 28.6, 28.2, 28.1, 28.0, 27.9, 26.2, 25.8, 25.7, 24.1, 18.1, −4.10, −4.8.

(4*R*,5*R*,8*S*,9*S*,12*S*,13*R*)-1-Benzyloxy-4-*tert*-butyldi-methylsilyloxy-5:8,9:12-dioxido-tricosa-13-hydroxy-16-en, 56. DIBAL-H (1.5 M in toluene, 0.4 mL, 0.6 mmol) was added dropwise to a solution of compound **17a** (200 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at −78 °C and stirred for 1 h at the same temperature. The reaction mixture was quenched with aq NH_4Cl and was slowly warmed to 0 °C. It was further stirred for another 1 h with Celite (until the reaction mixture became clear) and was then filtered through a sintered funnel using dichloromethane as solvent. The filtrate and washings were combined and evaporated under vacuum to obtain the crude lactol, which was taken to next step without further purification.

n-BuLi (1.6 M in hexane, 0.85 mL, 1.36 mmol) was added to an ice-cooled suspension of the heptyltriphenylphosphonium bromide[31] (688 mg, 1.56 mmol) in anhydrous THF (3 mL) and stirred for 20 min. A solution of the above-described lactol in THF (2 mL) was added slowly to the mixture and stirred for an additional 30 min. The reaction mixture was quenched with aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated to dryness to get the crude product, which was purified by flash chromatography to obtain the olefin **56** as a colorless oil (164 mg, 70%, two steps). ^{1}H NMR: δ 7.42−7.32 (m, 5H), 5.49−5.38 (m, 2H), 4.57 (s, 2H), 4.05−3.93 (m, 4H), 3.83−3.81 (m, 2H), 3.58 (t, J = 6.6 Hz, 2H), 2.20−1.34 (m, 29H), 0.96−0.94 (m, 12H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR: δ 138.5, 130.6, 128.8, 128.2, 127.5, 127.4, 82.6, 82.5, 82.2, 81.9, 73.6, 72.6, 70.7, 70.4, 32.3, 31.7, 29.6, 28.9, 28.8, 28.1, 27.9, 27.1, 26.1, 25.8, 24.6, 23.7, 22.6, 18.0, 14.0, −4.4, −4.7. MS (ESI): 603 (MH^+), 625 (MNa^+).

(4*R*,5*R*,8*S*,9*S*,12*S*,13*R*)-4,13-Di-*tert*-butyldimethylsilyl-oxy-5:8,9:12-dioxido-tricosa-1-ol, 58. Compound **56** (120 mg, 0.2 mmol) was subjected to TBS-protection, as described earlier for **17a**. Purification by flash chromatography provided the corresponding TBS derivative (136 mg, 95%) as an oil. ^{1}H NMR: δ 7.45−7.33 (m, 5H), 5.37−5.29 (m, 2H), 4.48 (s, 2H), 3.92−3.81 (m, 4H), 3.73−3.68 (m, 2H), 3.46−3.41 (m, 2H), 2.15−1.25 (m, 26H), 0.88−0.86 (m, 21H), 0.05−0.04 (m, 12H). ^{13}C NMR: δ 138.7, 130.1, 129.3, 128.2, 127.5, 127.4, 82.3, 82.2, 82.0, 81.6, 74.0, 73.0, 72.7, 70.6, 34.9, 31.7, 29.6, 29.0, 28.6, 28.5, 27.9, 27.2, 26.3, 26.0, 26.0, 25.9, 25.9, 25.6, 23.5, 22.6, 18.1, 18.1, 14.1, −4.2, −4.3, −4.6, −4.7. MS (ESI): 718 (MH^+), 740 (MNa^+).

Pd/C (10% w/w, 15 mg) was added to a solution of the above-described TBS-protected compound (80 mg, 0.11 mmol) in EtOAc (2 mL), and the mixture was stirred under H_2 atmosphere for 1 h. It was filtered through a Celite pad using EtOAc as solvent, the filtrate was evaporated to dryness, and the crude product was purified by flash chromatography to afford **58** (62 mg, 90%) as a colorless oil. $[\alpha]_D$ = +4.9 (c = 0.83, $CHCl_3$). ^{1}H NMR: δ 3.92−3.68 (m, 6H), 3.59 (t, J = 6.25 Hz, 2H), 1.90−2.22 (m, 31H), 0.85 (br s, 21H), 0.043, 0.035, 0.03 & 0.02 (4xs, together 12H). ^{13}C NMR: δ 82.4, 82.1, 81.9, 81.5, 74.0, 73.2, 63.1, 34.8, 31.9, 29.8, 29.6, 29.6, 29.3, 29.0, 28.7, 28.6, 27.9, 26.2, 26.0, 25.9, 25.5, 25.5, 22.7, 18.1, 18.1, 14.1, −4.2, −4.3, −4.6, −4.7. MS (ESI): 629 (MH^+), 651 (MNa^+).

(5*R*,6*R*,9*S*,10*S*,13*S*,14*R*)-5,14-Di-*tert*-butyldimethylsilyl-oxy-6:9,10:13-dioxi do-tetracosa-1-en, 60. Activated 4 Å molecular sieves (20 mg) was added to a solution of alcohol **58** (50 mg, 0.08 mmol) in CH_2Cl_2 (3 mL). After the mixture was stirred for 5 min at room temperature, NMO (14 mg, 0.12 mmol) and TPAP (3 mg, 0.008 mmol) were added sequentially to the reaction mixture, and the stirring was continued for additional 15 min. The crude mixture was filtered over a short silica gel column (CH_2Cl_2−MeOH, 20:1) to yield the corresponding aldehyde (45 mg, 90%) as a colorless oil.

*n*BuLi (1.6 M in hexane, 0.18 mL, 0.28 mmol) was added to a suspension of $MePPh_3I$ (129 mg, 0.32 mmol) in dry ether at 0 °C. After 0.5 h, a solution of the above-described aldehyde (45 mg) in dry ether (1 mL) was added to the reaction mixture, cooling bath was removed, and the stirring was continued for 1 h at rt. The mixture was quenched with aq NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine and dried ($MgSO_4$). Inorganic material was filtered

(31) Pempo, D.; Cintrat, J.-C.; Parrain, J.-L.; Santelli, M. *Tetrahedron* **2000**, *56*, 5493−5497.

out, and the filtrate was evaporated to dryness. The resultant residue was purified by flash chromatography to afford **60** (37 mg, 75% after two steps) as a colorless oil. ^{1}H NMR: δ 5.79 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 4.99 (dq, J = 16.9, 1.8 Hz, 1H), 4.89 (dd, J = 10.3, 1.8 Hz, 1H), 3.91−3.68 (m, 6H), 2.17−1.47 (m, 12H), 1.23 (br m, 18H), 0.87−0.84 (m, 21H), 0.042, 0.035, 0.03 & 0.025 (4xs, together 12H). ^{13}C NMR: δ 139.1, 114.2, 82.4, 82.4, 81.9, 81.6, 73.5, 73.2, 34.8, 31.9, 31.1, 30.1, 29.8, 29.6, 29.6, 29.3, 28.8, 28.0, 26.1, 26.0, 25.9, 25.5, 25.4, 22.7, 18.2, 18.1, 14.1, −4.2, −4.3, −4.6, −4.7. MS (ESI): 625 (MH^+).

11,12-Dehydro-19,23-bis-*epi*-trilobacin-4,15,24-(tri-*tert*-butyldimethylsilyl) Ether, 62. Grubb's catalyst **VIII** (7 mg, 0.008 mmol) was added to a solution of compound **60** (25 mg, 0.04 mmol) and **III** (P = TBS, 59 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred for 12 h at room temperature under Ar-atmosphere. DMSO (10.6 μL, 0.15 mmol) was added, and the mixture was stirred for an additional 12 h. Solvents were removed under reduced pressure, and the crude compound was purified by flash chromatography to give the required olefin **62** (24 mg, 62%) as a viscous oil. ^{1}H NMR: δ 7.09 (d, J = 1.1 Hz, 1H), 5.40−5.31 (m, 2H), 4.97 (m, 1H), 3.94−3.67 (m, 7H), 2.40−1.40 (m, 16H), 1.39 (d, J = 6.95 Hz, 3H), 1.30−1.22 (m, 28H), 0.86−0.84 (m, 30H), 0.04−0.01 (m, 18H). ^{13}C NMR: δ 175.0, 151.6, 151.4, 130.9, 130.3, 130.2, 82.4, 81.9, 81.7, 77.4, 73.7, 73.2, 70.2, 37.0, 34.8, 31.7, 32.6, 31.9, 31.8, 29.9, 29.6, 29.6, 29.3, 29.2, 28.9, 28.7, 28.0, 26.1, 26.0, 25.9, 25.9, 25.9, 25.8, 25.5, 25.4, 25.1, 22.7, 19.2, 19.0, 18.2, 18.1, 18.0, 14.1, −4.1, −4.3, −4.4, −4.5, −4.6, −4.6. MS (ESI): 964 (MH^+), 986 (MNa^+).

19,23-Bis-*epi*-trilobacin, Ie. A solution of 5% HF[32] (CH_3CN:H_2O, 0.4 mL) was added to a solution of **62** (15 mg, 0.015 mmol) in CH_2Cl_2 (1.5 mL), and stirred for 2 h at room temperature. The reaction was quenched by saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and purified by flash chromatography to provide the corresponding desilylated triol (8 mg, 82%) as a viscous oil. ^{1}H NMR (600 MHz): δ 7.16 (s, 1H), 5.45−5.33 (m, 2H), 5.03 (q, J = 7.9 Hz, 1H), 3.93−3.81 (m, 6H), 3.37 (m, 1H), 2.51−1.69 (m, 17H), 1.41 (d, J = 7.9 Hz, 3H), 1.31−1.23 (m, 28H), 0.85 (t, J = 7.5 Hz, 3H). ^{13}C NMR: δ 174.6, 151.8, 131.2, 130.8, 130.7, 130.6, 130.3, 129.9, 129.8, 129.3, 82.9, 82.7, 82.2, 81.8, 78.0, 73.8, 71.5, 69.9, 69.9, 69.8, 37.4, 33.3, 32.5, 32.5, 31.9, 29.7, 29.6, 29.6, 29.4, 29.4, 29.3, 28.9, 28.7, 28.4, 28.2, 26.0, 25.6, 24.8, 22.7, 19.1, 19.1, 14.1. MS (ESI): 621 (MH^+), 643 (MNa^+).

A solution of NaOAc (60 mg, 0.74 mmol) in distilled water (0.7 mL) was added to a refluxing solution of the above-described desilylated triol (6 mg, 0.009 mmol) and *p*-$TsNHNH_2$ (115 mg, 0.62 mmol) in 1,2-DME (1 mL), over a period of 4 h (via syringe pump). The reaction was stirred under reflux for an additional 1 h. Finally, it was cooled to room temperature and partitioned between water and EtOAc. Organic layer was again washed with water and brine, dried over Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude material was then subjected to flash chromatography to afford the final compound **Ie** (5 mg, 95%) as a viscous oil. $[\alpha]_D$ = +3.0 (c = 0.33, $CHCl_3$). ^{1}H NMR (600 MHz): δ 7.18 (s, 1H), 5.06 (q, J = 7.2 Hz, 1H), 3.92−3.84 (m, 6H), 3.37 (m, 1H), 2.89 (m, 1H), 2.53 (dd, J = 13.8, 1.8 Hz, 1H), 2.39 (dd, J = 8.4, 15 Hz, 1H), 2.29 (bd, J = 4.8 Hz, 1H), 2.11 (br s, 1H), 2.01−1.73 (m, 9H), 1.47−1.45 (m, 7H), 1.44 (d, J = 7 Hz, 3H), 1.25 (br s, 30H), 0.87 (t, J = 7 Hz, 3H). ^{13}C NMR: δ 174.6, 151.8, 131.2, 82.9, 82.8, 82.2, 81.8, 77.9, 74.6, 71.5, 70.0, 37.4, 34.3, 33.3, 32.5, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 28.4, 28.2, 26.0, 25.8, 25.6, 24.8, 22.7, 19.1, 14.1. HRMS (ESI-TOF): calcd for $C_{37}H_{67}O_7$ = 623.4881 (MH^+), found 623.487; calcd for $C_{37}H_{66}O_7Na$ = 645.4700 (MNa^+), found 645.4692.

Total Synthesis of 16,19-Bis-*epi*-trilobacin, If. (4*R*,5*S*,8*S*,9*S*,12*R*,13*R*)-5:8,9:12-Dioxido-13-*tert*-butyldimethylsilyloxy-tricosa-16-en-1,4-olide, 57. Compound **17a** (300 mg, 0.58 mmol) was hydrogenolyzed in EtOAc (5 mL) using 10% Pd/C (60 mg) under H_2 atmosphere in 1 h as described for the synthesis of **58**. Crude product was purified by flash chromatography to afford the corresponding free primary alcohol (223 mg, 90%) as a thick liquid. $[\alpha]_D$ +3.95 (c = 2, $CHCl_3$). ^{1}H NMR (400 MHz): δ 4.41 (ddd, J = 7.6, 6.8, 5.6 Hz, 1H), 4.05 (dt, J = 8.0, 3.6 Hz, 1H), 3.92−3.84 (m, 2H), 3.73 (m, 1H), 3.68 (ddd, J = 8.0, 5.6, 3.6 Hz, 1H), 3.62−3.54 (m, 2H), 2.57−2.40 (m, 2H), 2.27 (m, 1H), 2.10−1.92 (m, 3H), 1.85−1.49 (m, 9H), 1.34 (m, 1H), 0.84 (s, 9H), 0.031 (s, 3H), 0.023 (s, 3H). ^{13}C NMR (100 MHz): δ 177.3, 82.2, 81.8, 81.6, 80.2, 74.0, 62.8, 28.9, 28.6, 28.2, 28.1, 28.1, 28.1, 26.2, 25.8, 25.8, 23.8, 18.1, −4.4, −4.7.

The above-described alcohol (100 mg, 0.23 mmol) was oxidized in CH_2Cl_2 (5 mL) using NMO (40 mg, 0.34 mmol) and TPAP (8 mg, 0.023 mmol), by the method described for the oxidation of **58**. The resultant aldehyde (94 mg, 96%) was obtained as a colorless oil after filtration over a short silica gel column (CH_2Cl_2-MeOH, 20:1). ^{1}H NMR: δ 9.76 (t, J = 1.7 Hz, 1H), 4.11 (q, J = 6.8 Hz, 1H), 4.04 (q, J = 6.3 Hz, 1H), 3.94−3.85 (m, 2H), 3.75−3.68 (m, 2H), 2.59−2.41 (m, 4H), 2.28 (m, 1H), 2.11−2.06 (m, 2H), 1.98 (m, 1H), 1.9−1.66 (m, 6H), 1.62−1.52 (m, 2H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

Wittig reaction (method described earlier for the synthesis of **56**) of the above-described aldehyde (80 mg, 0.19 mmol) was carried out using ylide, generated from the reaction of heptyltriphenylphosphonium bromide (124 mg, 0.28 mmol) and *n*-BuLi (1.6M in hexane, 0.18 mL, 0.28 mmol) in anhydrous THF (3 mL). Olefin **57** (72 mg, 75%) was obtained as a mixture of *cis*- and *trans*-isomer after purification by flash chromatography. ^{1}H NMR: δ 5.39−5.34 (m, 2H), 4.43 (q, J = 6.6 Hz, 1H), 4.06 (q, J = 6.2 Hz, 1H), 3.96 (q, J = 6.6 Hz, 1H), 3.9 (q, J = 6.6 Hz, 1H), 3.78−3.67 (m, 2H), 2.59−2.45 (m, 2H), 2.35−1.68 (m, 14H), 1.34−1.25 (m, 10H), 0.89 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H). MS (ESI): 509 (MH^+), 531 (MNa^+).

(4*R*,5*S*,8*S*,9*S*,12*R*,13*R*)-5:8,9:12-Dioxido-13-*tert*-butyldimethylsilyloxy-tricosan-1,4-olide, 59. Olefin **57** (50 mg, 0.1 mmol) was hydrogenated using Pd/C (10% w/w, 10 mg) in EtOAc (2 mL) and under H_2 atmosphere for 20 min to afford lactone **59** (46 mg, 92%) as a viscous liquid after purification by flash chromatography. $[\alpha]_D$ +4.7 (c = 0.48, $CHCl_3$). ^{1}H NMR (500 MHz): δ 4.44 (q, J = 6.6 Hz, 1H), 4.07 (q, J = 6.6 Hz, 1H), 3.96 (q, J = 6.2 Hz, 1H), 3.89 (q, J = 6.6 Hz, 1H), 3.76 (m, 1H), 3.65 (m, 1H), 2.58−2.45 (m, 2H), 2.31 (m, 1H), 2.16−2.08 (m, 2H), 2.00 (m, 1H), 1.83−1.68 (m, 6H), 1.32−1.2 (m, 18H), 0.88 (s, 9H), 0.87 (t, J = 6.9 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz): δ 177.2, 82.4, 82.3, 81.9, 81.7, 80.2, 74.3, 32.1, 31.9, 29.9, 29.6, 29.6, 29.3, 28.2, 28.2, 28.1 (×2), 28.0, 26.3, 25.9, 25.7, 24.3, 22.6, 18.1, 14.1, −4.3, −4.7. MS (ESI): 511 (MH^+), 533 (MNa^+).

(5*R*,6*S*,9*S*,10*S*,13*R*,14*R*)-5-Hydroxy-6:9,10:13-dioxido-14-*tert*-butyldimethylsilyloxy-tetracos-1-en, 61. Compound **59** (30 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) at −78 °C was reduced using DIBAL-H (1.5 M in toluene, 60 μL, 0.09 mmol) as described for **17a** to afford the corresponding lactol. The latter in dry ether (2 mL) was added to the ylide generated from $MePPh_3I$ (73 mg, 0.18 mmol) and *n*-BuLi (1.6M in hexane, 106 μL, 0.17 mmol) at 0 °C. Workup of the reaction and purification of the crude product using flash chromatography gave olefin **61** (23 mg, 75%, after two steps) as a thick liquid. $[\alpha]_D$ +7.98 (c = 0.45, $CHCl_3$). ^{1}H NMR: δ 5.89 (m, 1H), 5.13 (dd, J = 17.2, 1.9 Hz, 1H), 5.05 (dd, J = 8.1, 1.9 Hz, 1H), 4.05−3.89 (m, 4H), 3.76−3.69 (m, 2H), 2.26 (m, 1H), 2.16 (d, J = 1.8 Hz, 1H), 2.09 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 1.81 (m, 3H), 1.62 (m, 1H), 1.5−1.42 (m, 4H), 1.29−1.22 (m, 18H), 0.88−0.86 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (150 MHz): δ 138.3, 114.8, 82.6, 82.5, 82.3, 82.1, 73.9, 70.7, 31.9, 31.6, 30.3, 29.9, 29.7, 29.6, 29.3, 28.9, 28.0, 26.0, 25.9, 24.6, 22.7, 18.1, 14.1, −4.3, −4.6. MS (ESI): 511 (MH^+), 533 (MNa^+).

11,12-Dehydro-16,19-bis-*epi*-trilobacin-4,24-(di-*tert*-butyldimethylsilyl) ether, 63. Compound **61** (15 mg, 0.03

(32) HF solution was prepared by diluting 48% aqueous HF with CH_3CN to make 5%.

mmol) and **III** (P = TBS, 43 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was metathesized using Grubb's catalyst **VIII** (5 mg, 0.006 mmol) as described earlier for the synthesis of **62**. Workup using DMSO (10.6 μL, 0.15 mmol) and purification by flash chromatography gave olefin **63** (15 mg, 60%). ^{1}H NMR: δ 7.10 (d, J = 1.5 Hz, 1H), 5.46−5.34 (m, 2H), 4.90 (qd, J = 6.9, 1.6 Hz, 1H), 3.93−3.68 (m, 6H), 2.40−1.56 (m, 20H), 1.27−1.22 (m, 28H), 0.87−0.84 (m, 21H), 0.03−0.01 (m, 12H). MS (ESI): 850 (MH^+), 872 (MNa^+).

16,19-Bis-*epi*-trilobacin, If. TBS protecting group in compound **63** (10 mg, 0.012 mmol) was removed using 5% HF[32] (CH_3CN-H_2O, 0.25 mL) in CH_2Cl_2 (1 mL) at room temperature in 2 h. The reaction was worked-up and purified as described earlier for the TBS deprotection in **62** and purified by flash chromatography to provide the corresponding desilylated triol (6.2 mg, 85%). ^{1}H NMR: δ 7.19 (d, J = 1.1 Hz, 1H), 5.52−5.36 (m, 2H), 5.05 (qd, J = 6.95, 1.45 Hz, 1H), 4.04−3.85 (m, 6H), 3.36 (m, 1H), 3.08 (br m, 1H), 2.54−1.71 (m, 20H), 1.47 (d, J = 6.6 Hz, 3H), 1.42−1.25 (m, 25H), 0.87 (d, J = 6.95 Hz, 3H). MS (ESI): 621 (MH^+), 643 (MNa^+).

The above-described triol (5 mg, 0.008 mmol) was hydrogenated (method described earlier for the synthesis of **Ie**) using and p-$TsNHNH_2$ (103 mg, 0.55 mmol) and NaOAc (54 mg, 0.66 mmol, in 1 mL of distilled water) in 1,2-dimethoxyethane (1 mL). The crude material was purified by flash chromatography to afford compound **If** (4.7 mg, 94%). $[\alpha]_D$ = +4.7 (c = 0.34, $CHCl_3$). ^{1}H NMR (600 MHz): δ 7.18 (s, 1H), 5.06 (qd, J = 7.0, 1.3 Hz, 1H), 3.96−3.84 (m, 6H), 3.37 (br m, 1H), 2.95 (br m, 1H), 2.53 (dq, J = 15.0, 1.8 Hz, 1H), 2.41 (ddd, J = 14.6, 8.3, 1.8 Hz, 1H), 2.32 (q, J = 5.4 Hz, 1H), 2.18 (br m, 1H), 2.02−1.71 (m, 8H), 1.48−1.45 (m, 5H), 1.43 (dd, J = 6.6, 0.9 Hz, 2H), 1.35−1.25 (m, 34H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 174.6, 151.8, 131.2, 82.9, 82.8, 82.2, 81.8, 78.0, 74.6, 71.5, 70.0, 37.4, 34.3, 33.3, 32.4, 31.9, 29.7, 29.6, 29.5, 29.45, 29.3, 29.2, 28.4, 29.2, 25.9, 25.8, 25.6, 24.8, 22.7, 19.1, 14.1. HRMS (ESI-TOF): calcd for $C_{37}H_{67}O_7$ = 622.4881 (MH^+), found 623.4871, calcd for $C_{37}H_{66}O_7Na$ = 645.4700 (MNa^+), found 645.469.

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Note Added after ASAP Publication: The version published June 22, 2005 contained errors in Table 3 and in the Acknowledgment. The corrected version published July 6, 2005.

Supporting Information Available: General methods, synthetic schemes, and physical data for the bis-THF lactones **1**−**36**, their starting materials **37**−**44**, mono-THF lactone intemediates **45**−**55**, and tetraacetate derivatives **1T**−**36T**, and ^{1}H and ^{13}C NMR spectra of **1**−**44**, **17a**, **60**, **61**, and **Ie**, **If**. This material is available free of charge via the Internet at http://pubs.acs.org.

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