The Utility of Furan-, Pyrrole-, and Thiophene-Based 2-Silyloxy Dienes As Demonstrated by Modular Synthesis of Annonaceous Acetogenin Core Units and Their Pyrrolidine and Thiolane Analogues

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We report a modular strategy for obtaining the core units of annonaceous acetogenins and their nitrogen and sulfur analogues, which generates great structural diversity. This synthesis is based on the application of a reiterative vinylogous addition protocol involving a unique triad of silyloxy diene modules, 2-[(*tert*-butyldimethylsilyl)oxy]furan (TBSOF), *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (TBSOP), and 2-[(*tert*-butyldimethylsilyl)oxy]thiophene (TBSOT) and suitable heteroatom-stabilized carbenium ions. By combining TBSOF, TBSOP, and TBSOT nucleophilic synthons with certain tetrahydrofuran, pyrrolidine, and thiolane acceptors, the construction of varied, adjacently linked oligo-heterocyclic motifs related to the core segments of the annonaceous acetogenins is assured. At first, the reliability of the pivotal coupling maneuver was certified, by assembling a collection of 18 model constructs, covering all oxygen, nitrogen, and sulfur heteroatom combinations (i.e., compounds **7**−**9**, **13**−**15**, and **19**−**21**). This uniformed protocol was then suited to forge advanced bis-tetrahydrofuran, bis-pyrrolidine, and bis-thiolane scaffolds encompassing the heterocyclic core portion of various binuclear annonaceous acetogenins and relatives. The utility of this synthesis was demonstrated by the preparation of a repertoire of eight isomeric bis-tetrahydrofuran units, **41**−**48**, two bis-pyrrolidine units, **62** and **63**, and four bis-thiolane units, **78**−**81**.

Introduction

The annonaceous acetogenins are a class of C_{35} or C_{37} plant metabolites isolated, as to date, only from the archaic family of the Annonaceae.[1] Since 1982, when uvaricin was first isolated from *Uvaria acuminata*,[2] this class of compounds has grown to include over 250 individual representatives. The structural hallmark of annonaceous acetogenins is an oxygenated core consisting of either a tetrahydrofuran ring,[3] an assembly of tetrahydrofuran rings (both adjacent and not), or a biogenetically equivalent element (polyepoxide or epoxyolefin moieties). This oxygenated core carries two alkyl chains, one of which terminates with a γ-methyl-γ-lactone ring, whereas both are generally oxygenated in the vicinity of the central core and the lactone head (Figure 1). The molecular diversity within the annonaceous acetogenins is impressive, since the variability of the constitutional elements (type of oxygen core and location of the oxygen functions on the alkyl branches) is further magnified by the diverse disposition of the numerous stereocenters present.

The economic relevance of several plants from the Annonaceae family is paralleled by the broad biological activity of several of their acetogenins. Of special interest is their cytotoxicity which, seemingly mediated by inhibition of mitochondrial respiratory complex I, ultimately results in ATP depletion.[4] Furthermore, several annonaceous acetogenins display an anticancer activity several orders of magnitude greater than that of some chemotherapeutic agents in current clinical use.[1,4] However,

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(1) For recent comprehensive reviews, see: Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Ed.; Springer-Verlag: Wien, New York, 1997; Vol. 70, pp 81−288. Gu, Z.-M.; Zhao, G.-X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. In *Recent Advances in Phytochemistry*; Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, 1995; Vol. 29, Chapter 11, pp 249−310. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275−306. Cavé, A.; Cortes, D.; Figadère, B.; Hocquemiller, R.; Laprévote, O.; Laurens, A.; Lebœuf, M. In *Phytochemical Potential of Tropical Plants*; Downum, K. R., Romeo, J. T., Stafford, H. E., Eds.; Plenum Press: New York, 1993; pp 167−202. Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. Recent Developments in the Synthesis of Annonaceous Acetogenins. *Isr. J. Chem.* **1997**, *37*, 97−107. Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts Org. Chem.* **1998**, *11*, 803−827 and references therein.

(2) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151−3153.

(3) Recently, a few tetrahydropyran-containing analogues have been isolated and synthesized: Schaus, S.; Brånalt, J.; Jacobsen, E. *J. Org. Chem.* **1998**, *63*, 4876−4877. Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279−11284. Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723−726. Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* **1999**, *40*, 1253−1256.

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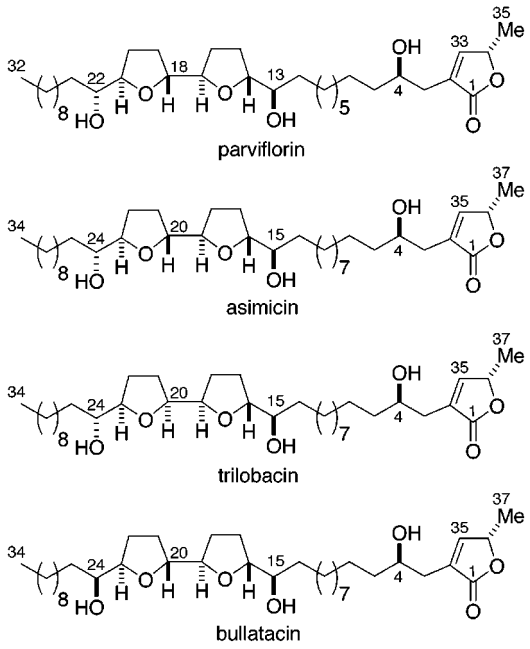


Figure 1. Representative adjacent bis-tetrahydrofuran acetogenins of the Annonaceae.

their very narrow therapeutic index necessitates optimization if their toxicity is to be reduced. This, coupled with the failure to identify a common pharmacophore, the challenging chemical architecture of the natural products, their limited availability and their resistance to chemical modification, justifies the interest shown in the total synthesis of these compounds.[1]

The aim of this work is (1) to design an adaptable, chemically uniform methodology for obtaining the multichiral heterocyclic annonaceous acetogenin core components and (2) to exploit this methodology to assemble a repertoire of adjacently linked bis-tetrahydrofuran acetogenin scaffolds and their modified bis-pyrrolidine and bis-thiolane unnatural relatives. The synthesis of these densely functionalized chiral constructs provides a new application for the triad of vinylogous heterocyclic silyl enol ethers, 2-[(*tert*-butyldimethylsilyl)oxy]furan (hereafter TBSOF), *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (TBSOP), and 2-[(*tert*-butyldimethylsilyl)oxy]thiophene (TBSOT).[5] This paper describes a novel, unified strategy that allows for the synthesis of 14 individual adjacently linked binuclear acetogenin core units, comprising eight isomeric bis-tetrahydrofuran representatives, **41**−**48**, two bis-pyrrolidine analogues, **62**−**63**, and four bis-thiolane congeners, **78**−**81**.

Results and Discussion

Planning. As a continuation of our program targeted at developing a methodology relevant to the asymmetric synthesis of important multifunctional biomolecules, we have devised a modular approach of assembling both binuclear annonaceous acetogenins **A** and mononuclear relatives **B** by exploiting furan-, pyrrole-, and thiophene-based silyloxy dienes TBSOF, TBSOP, and TBSOT and using glyceraldehyde **H** as the chiral starter molecule. As shown in the retrosynthetic plan in Scheme 1, disconnection of the generic C_{37} binuclear acetogenin **A** along the bonds C11−C12 and C25−C26 defines the subtarget lactone **C** as the basic scaffold of the C12−C25 core backbone, which contains the two adjacently linked heterocycles. Attachment of the methyl butenolide frame and the saturated aliphatic chain at the north and south orthogonally masked termini (or vice versa) guarantees formation of the acetogenin targets. Installation of the lactone moiety within **C** may arise via a vinylogous juncture of the silyloxy furan TBSOF to the "anomeric" carbon of the binuclear intermediate **D**. The C16−C25 unit **D**, in turn, originates from **E**, an intermediate common to the synthesis of mononuclear annonaceous acetogenins of type **B**. Disconnection of **E** along the bond C19−C20 reveals the mononuclear lactol-type synthon **F**, which, in the forward sense, leads to **E** via vinylogous coupling with one of the three silyloxy diene heterocycles TBSOF, TBSOP, or TBSOT. Lactol **F** readily traces back to **G**, which may derive from the vinylogous Mukaiyama aldol addition between glyceraldehyde **H** and one of the silyloxy diene modules already mentioned.

On the whole, this synthesis, which exploits a readily available triad of four-carbon modules and uses a uniform and reiterative chemistry, outlines the stepwise elongation of the easily accessible three-carbon "chiron" **H** via three sequential vinylogous additions.[6] The choice of the heteroatoms combined in the first and the second vinylogous aldol couplings, the chirality of the chosen aldehyde starter **H** (*R* vs *S*), and the chirality transmittal during the molecular growth (*erythro* vs *threo*, *cis* vs *trans*) all ensure the generation of ample chemical diversity during this synthesis. In addition, the synthetic flexibility can be increased during the final union of subtargets **C** and **E** to the butenolide and aliphatic fragments by simply switching the poles onto which these side chains are installed (C12 and C25 in **C**, or C16 and C25 in **E**). As a result, preparation of a highly diverse repertoire of natural annonaceous acetogenins, as well as their structural and stereochemical variants is, in principle, feasible.

Initial Studies.[7] The work initiated by assembling a number of unsaturated and saturated model constructs **4**−**21** (Scheme 2) covering all the diverse X,Y heteroatom combinations. In order for the coupling chemistry to be

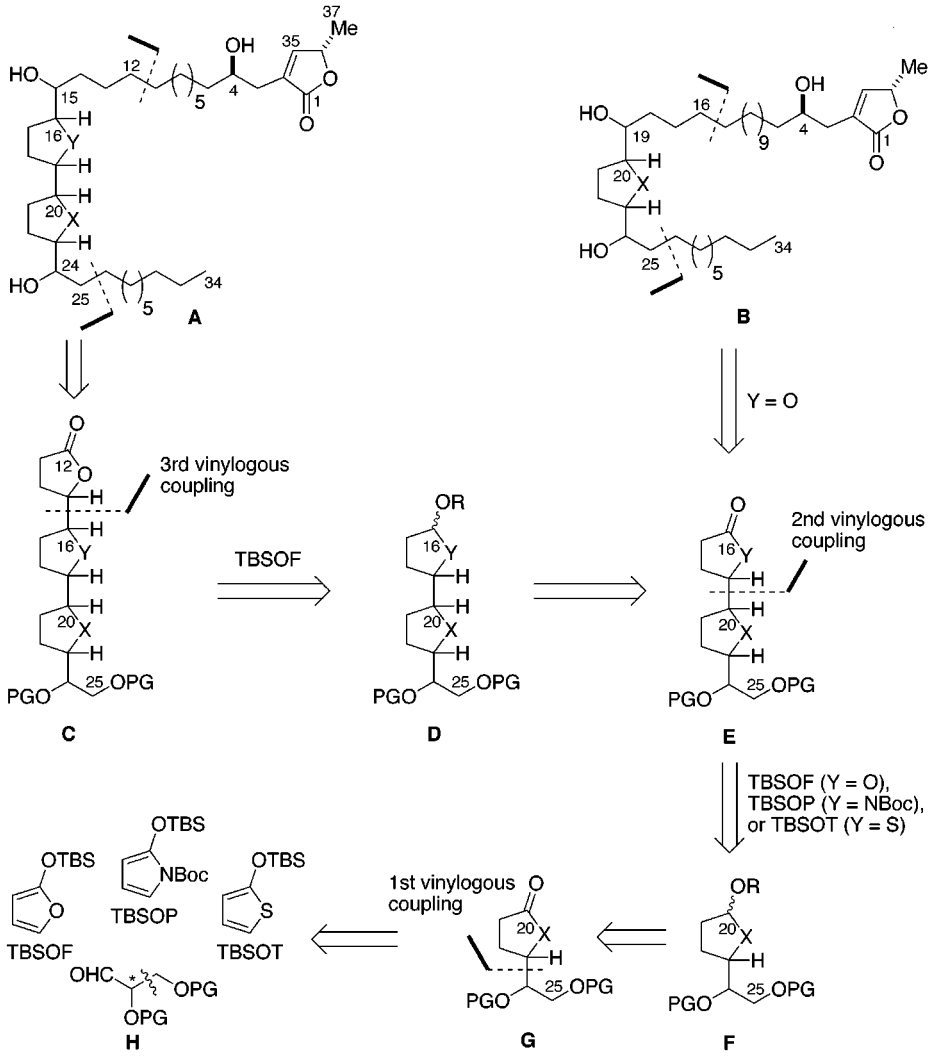
(4) Holschneider, C. H.; Johnson, M. T.; Knox, R. M.; Rezai, A.; Ryan, W. J.; Montz, F. J. *Cancer Chemother. Pharmacol.* **1994**, *34*, 166−170. Degli Esposti, M.; Ghelli, A.; Ratta, M.; Cortes, D.; Estornell, E. *Biochem. J.* **1994**, *301*, 161−167. Oberlies, N. H.; Jones, J. L.; Corbett, T. H.; Fotopoulos, S. S.; McLaughlin, J. L. *Cancer Lett.* **1995**, *96*, 55−62. Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1995**, *56*, 343−348. Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73−79. Wang, X.-W.; Xie, H. *Drugs Future* **1999**, *24*, 159−165.

(5) For general reviews: Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−629. Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford; 1998; Vol. 3, pp 113−189. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350.

(6) For leading references concerning the reactivity of vinylogous carbon nucleophiles, see, for example: Christoffers, J. *J. Org. Chem.* **1998**, *63*, 4539−4540. Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813−814. Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013−7016. Saito, S.; Yamamoto, H. *Chem. Eur. J.* **1999**, *5*, 1959−1962. Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949−8953. Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072−3082. Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816−6826.

(7) For a preliminary account of the work in this section, see: Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368−1369.

Scheme 1



uniform and validated, vinylogous Mukaiyama aldol-type reactions of the silyloxy diene triad TBSOF, TBSOP, and TBSOT with simple tetrahydrofuran, pyrrolidine, and thiolane electrophilic modules **1**−**3** were investigated. The results are summarized in Scheme 2 and Chart 1.

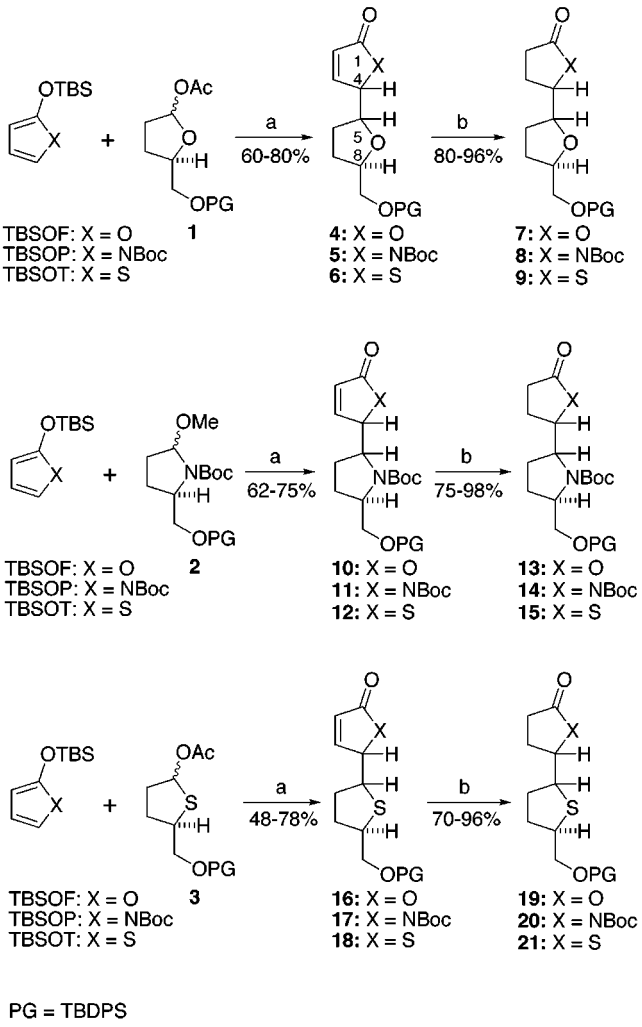
Efficient, stereoselective synthesis of the lactol-type modules **1**, **2**, and **3** had been previously achieved using the same silyloxy diene triad TBSOF, TBSOP, and TBSOT and using 2,3-*O*-isopropylidene-D-glyceraldehyde as the chiral hydroxymethyl surrogate.[8] Addition of TBSOF to the activated lactol **1** in the presence of 0.6 equiv of *tert*-(butyldimethylsiloxy)trifluoromethanesulfonate (TBSOTf) in CH_2Cl_2 at −90 °C afforded a separable 1:1 mixture of two epimeric butenolide intermediates **4tt** and **4et**, which were individually hydrogenated, to provide the corresponding saturated 4,5-*threo*-5,8-*trans*- and 4,5-*erythro*-5,8-*trans*-configured counterparts **7tt** and **7et** (67% combined yield for two steps).[9] The saturated binuclear models **7**−**9**, **13**−**15**, and **19**−**21** shown in Chart 1 were assembled according to a set of parallel protocols that reproduced the catalytic system and procedure used for the *all*-oxygen series. The results reveal that the nine processes behaved in the same way under TBSOTf catalysis, irrespective of the heteroatom composition, providing, after hydrogenation, reasonable yields (46−74%) of the expected saturated adducts **7**−**9**, **13**−**15**, and **19**−**21**. With the exception of the coupling between TBSOP and **1**, which gave rise to all four possible stereoisomers, the other reactions displayed partial or complete diastereocontrol, yielding either a couple of stereoisomers or a single component, as indicated.

Structural diagnosis of the different isomers isolated proved nontrivial, especially for the scantily precedented 2,5-disubstituted pyrrolidine-containing units (e.g., **10**−**15**). Stereochemical assignment was mainly based on the following data. **(1) Chiro-Optical Evidence.** As a guideline, 4*R*-configured 4-hydroxyalkyl-substituted 2,3-unsaturated butenolides and relatives are dextrorotatory,

(8) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168−180. Conveniently, preparation of **1** and **2** may also be achieved adopting conventional chemistry by starting with commercially available (*R*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone and (*R*)-5-(hydroxymethyl)-2-pyrrolidinone, respectively. The reaction sequence to **1** encompasses proper silylation of the free hydroxyl (TBDPSCl, imidazole, DMF), followed by carbonyl reduction to a lactol (DIBAL-H, CH_2Cl_2, −80 °C) and acetylation (Ac_2O, pyridine, DMAP) (65% yield over three steps). For **2**, the protocol includes hydroxyl silylation, *N*-Boc protection (Boc_2O, DMAP, MeCN), carbonyl reduction ($LiEt_3BH$, THF, −80 °C), and methylation ($CH(OMe)_3$, $BF_3 \cdot OEt_2$, Et_2O, 4 Å molecular sieves) (52% yield over four steps).

(9) The suffixes associated to conventional numbering in model compounds **4**−**21** relate to the relative stereodisposition of the C4−C5 and C5−C8 stereocenters: e.g., **4tt** = 4,5-*threo*-5,8-*trans*-**4**; **14ec** = 4,5-*erythro*-5,8-*cis*-**14**, etc.

Scheme 2[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF.

while their 4*S*-configured counterparts are levorotatory.[10] A more reliable piece of evidence came from circular dichroic measurements, where positive or negative signs of the Cotton effect of the $\pi-\pi^*$ transitions are directly correlated to right-handed (P) or left-handed (M) helicity of the chromofore.[11] **(2) Base-Promoted C4 Epimerization.** When an unsaturated adduct is exposed to Et_3N, deprotonation at C4 takes place, directly assessing the epimeric relationship for a given isomeric couple. Quite unexpectedly, the N,N-couple **11ec** and **11et** proved particularly base-resistant, thus preventing us from being able to use this diagnostic criterion. **(3) H4−H5 Vicinal Coupling Constants [^3J(H4,H5)].** Evaluation of ^{1}H−^{1}H coupling constants between the H4 and H5 protons within both unsaturated and saturated products is a sure guide for assigning the 4,5-*threo*/*erythro* relative disposition of the two heteroatom substituents, with *erythro* compounds exhibiting larger *J* values than the corresponding *threo* counterparts.[12] **(4) H3 Chemical Shift Values of Butenolide-Type Adducts.** With the exception of *N*-Boc-containing compounds exhibiting controversial results, 4,5-*erythro*-configured butenolides and relatives may be distinguished from their 4,5-*threo* counterparts by the downfield chemical shift of the H3 proton within the unsaturated ring.[13]

Where controversy arose, as in the case of the N,N-binuclear adducts **11** and **14**, recourse to bidimensional ^{1}H NMR NOESY and ROESY experiments proved decisive, allowing for the unequivocal assignment of the stereostructures through analysis of interproton NOE contact sequences. For example, for the saturated lactams **14ec** and **14et**, whose ^{1}H NMR spectra were barely readable due to considerable *N*-Boc rotameric contamination, analysis of the corresponding N-deprotected counterparts, deBoc-**14ec** and deBoc-**14et**, was necessary. This analysis showed well resolved resonances for all diagnostic protons. The compounds deBoc-**14ec** and deBoc-**14et** were cleanly obtained in yields of 85% and 81%, respectively, upon exposure of the corresponding protected derivatives **14ec** and **14et** to *B*-bromocatecholborane in CH_2Cl_2.[14] As shown in Figure 2, the contacts H8/H6β, H9a/H6α, and H5/H6β for deBoc-**14ec** and H8/H6β, H9a/H6α, and H5/H6α for deBoc-**14et** were crucial for structural diagnosis. This study also revealed the existence of a major conformation for both isomers, where the H4 and H5 protons involving the inter-ring juncture are located in an antiperiplanar relationship, reflected by the large vicinal H4−H5 coupling constant ($J_{4,5}$ = 8.8 Hz for deBoc-**14ec**, and $J_{4,5}$ = 7.1 Hz for deBoc-**14et**). In particular, the slightly smaller value of the $J_{4,5}$ coupling constant for deBoc-**14et**, compared with that of the deBoc-**14ec** isomer, may be attributed to the coexistence of a minor conformation where the H4 and H5 protons are in a gauche relationship. This conclusion is also supported by a significant NOE contact between these two protons, which is almost negligible for the deBoc-**14ec** isomer.

Taken together, these data allowed us to assign with confidence the stereochemistry of all 18 compounds shown in Chart 1.[15] Overall, our optimized synthetic protocols and the set of criteria used for the structural diagnosis of the various stereostructures represent the sound foundations onto which the synthesis of C12−C25 acetogenin subtargets could be based.

Synthesis of Bis-Tetrahydrofuran C12−C25 Units.[16] Successful preparation of model structures **4**−**21** via the flexible synthesis just described prompted us to exploit a similar methodology to assemble bis-tetrahydrofuran units of type **C** (Scheme 1), where X and Y are atoms of oxygen. These scaffolds encompass the C12−C25 core portion of a myriad of biologically important

(10) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807−5824.

(11) Gawronski, J. K.; van Oeveren, A.; van der Deen, H.; Leung, C. W.; Feringa, B. L. *J. Org. Chem.* **1996**, *61*, 1513−1515. Cuiper, A. D.; Brzostowska, M.; Gawronski, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567−2570.

(12) For some representative binuclear fragments, a molecular mechanics calculation was performed, simulating a rotation around the C4−C5 bond. The calculation of the relative populations of *anti* and *gauche* conformations allowed the prediction of the mean *J* values, which were in good accordance with the experimental ones. See note 12 in ref 7.

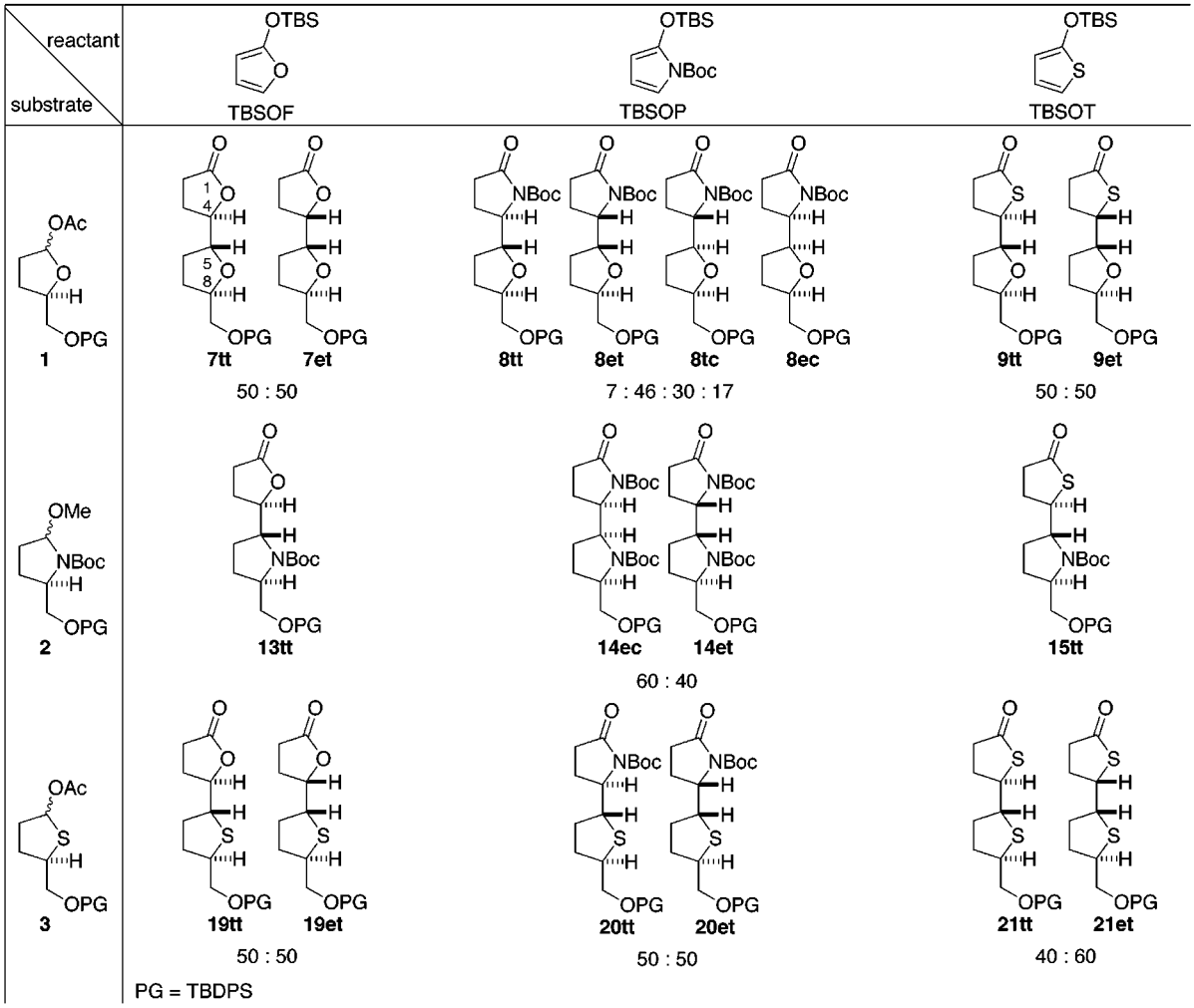
(13) Figadère, B.; Chaboche, C.; Peyrat, J.-F.; Cavé, A. *Tetrahedron Lett.* **1993**, *34*, 8093−8096. Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037−4040.

(14) Boeckman, R. K. Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411−1414.

(15) In the preliminary account of this work (ref 7) the stereostructures of compounds **14ec** and **14et** were misassigned as *threo,trans* and *threo,cis* isomers, respectively.

(16) For easy reference, the atom numbering of the various target and intermediary compounds adopted in Schemes 3−11 relate to the conventional numbering of the generic C_{37} annonaceous acetogenin **A** in Scheme 1.

Chart 1. Synthesized Saturated Binuclear Models and Stereochemistry

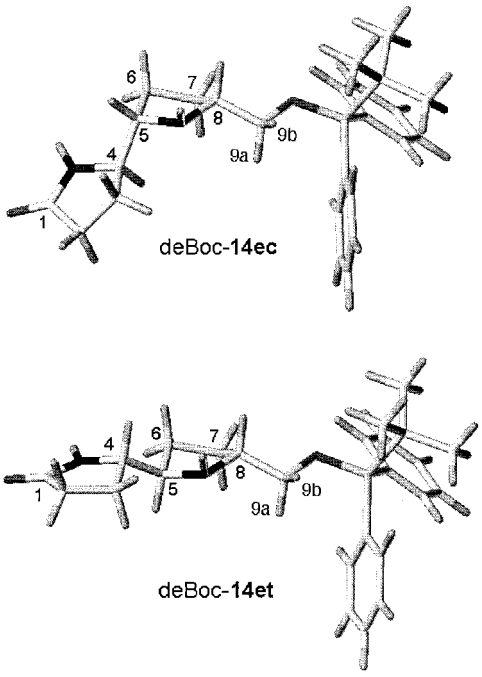


adjacently linked bis-THF annonaceous acetogenins of natural origin. Our project started with the preparation of the C20−C25 lactol precursor **26**, via $BF_3{\cdot}OEt_2$-promoted vinylogous Mukaiyama aldol coupling of TBSOF to 2,3-*O*-isopropylidene-D-glyceraldehyde (**22**) (Scheme 3). This addition produced the unsaturated butenolide adduct **23**, in high yield (75%) and with a high diastereoselectivity (94%), which was converted to **24** by catalytic hydrogenation and silylation (85%, two steps). The precursor for this project, **26**, was prepared from **24** by a sequence involving (1) selective acetonide deblocking, (2) $NaIO_4$ oxidative one-carbon shortening, (3) $NaBH_4$ reduction of the aldehyde formed, (4) protection of the primary hydroxyl to **25**, and (5) lactone-to-lactol reduction followed by acetylation (54% yield from **24**).

Homologation of **26** to C16−C25 subunits **31** and **32** utilized the same furan-based silyloxy diene TBSOF under TBSOTf catalysis (Scheme 4). The reaction was conducted in CH_2Cl_2 at −90 °C and furnished a 1:1 mixture of *threo,trans,threo* butenolide **27** and its *erythro,trans,threo* C19-epimer **28** (70% combined yield). After chromatographic separation, **27** and **28** were individually subjected to parallel three-stage protocols, consisting of hydrogenation to the corresponding saturated adducts **29** and **30**, followed by lactone-to-lactol reduction and acetylation. In this case, bis-THF donor units **31** and **32** were formed in 78% and 71% isolated yields from **27** and **28**. Stereochemical assignment for **27** and **28** was then carried out following the guidelines previously disclosed (vide supra), with both epimers fully matching the diagnostic chiro-optical, chemical, and spectral requirements.

Completion of the bis-tetrahydrofuran C12−C25 acetogenin units was effected in a parallel manner by reiterating the addition of TBSOF to the *threo,trans,threo* lactol **31** (Scheme 5, left side) and its *erythro,trans,threo* counterpart **32** (right side). Each TBSOTf-catalyzed vinylogous addition did not display substantial stereocontrol, affording all four expected trinuclear butenolide isomers **33**−**36** and **37**−**40**, respectively. The unsaturated compounds **33**−**40** were individually hydrogenated, leading to the final eight bis-THF scaffolds **41**−**48** in yields ≥95% for this step.

Assignment of the relative stereochemistry for all the components was based mainly on analysis of the unsaturated congeners **33**−**40**. Thus, **33**/**36**, **34**/**35**, **37**/**40**, and **38**/**39** are C15 epimeric couples (Et_3N-promoted epimerization); **33**, **35**, **37**, and **39** are 15*R*-configured (positive $[\alpha]_D$ values and $\pi-\pi^*$ CD Cotton effects), while **34**, **36**, **38**, and **40** are 15*S*-configured (negative $[\alpha]_D$ values and $\pi-\pi^*$ CD Cotton effects); and **33**, **34**, **37**, and **38** possess a 15,16-*threo* relative configuration ($J_{15,16} = 3.6-4.6$ Hz), while **35**, **36**, **39**, and **40** possess a 15,16-*erythro* configuration ($J_{15,16} = 6.5-7.9$ Hz). Since the relative and absolute configuration of the remainder three stereo-



compd.	proton	NOE (intensity)[a]
deBoc-**14ec**	H8	H6β (m)
	H9a	H6α (m)
	H5	H6β (s)
	H4	H6α (s)
	H5	H3β (s)
	H5	H2β (w)
deBoc-**14et**	H8	H6β (m)
	H9a	H6α (m)
	H5	H6α (s)
	H4	H6β (s)
	H5	H3α (s)
	H5	H2α (w)

[a] s = strong; m = medium; w = weak

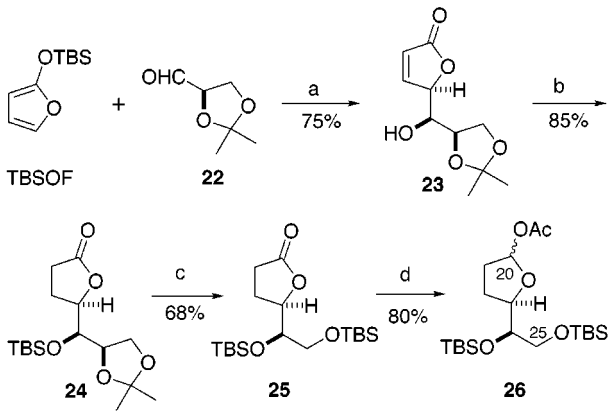
Figure 2. Possible minimum-energy conformations of isomers deBoc-**14ec** and deBoc-**14et** consistent with the NOE peaks reported. The structures represented were selected among families of minimum energy conformations, obtained by geometry optimization applying the Tripos force field, with the molecular modeling program Sybyl 6.5 (Tripos Inc., St. Louis, MO).

centers (C20, C23, and C24) were previously established, the overall assignment could be made with confidence.

The lack of selectivity encountered during the synthesis of compounds **41**−**48**, though chemically unappealing, guarantees the generation of chemical diversity. Thus, **41** could be the subtarget of asimicin, when the proper butenolide appendage is attached to the north terminal of the scaffold (C12) and the aliphatic chain to the south terminal (C25). Interestingly, **44** could represent the core component of both squamocin I and bullatacin, whereas **45** could be the scaffold of trilobacin via south−north homologation. On the other hand, the remaining units bearing "unnatural" stereochemistry could lead to a number of novel bis-THF acetogenin candidates.

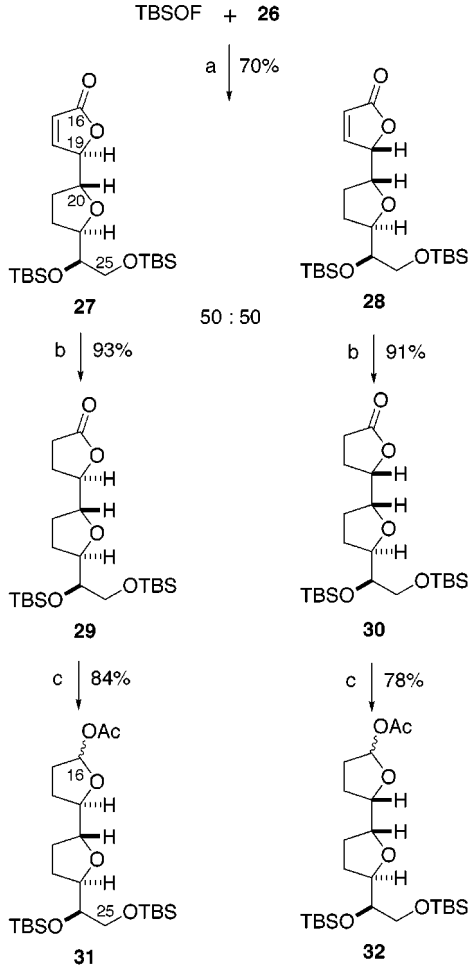
Synthesis of Bis-Pyrrolidine C12−C25 Units. Synthesis of the bis-pyrrolidine scaffolds of type **C** (Scheme 1, X = Y = NBoc) called for C20−C25 *N*,*O*-acetal **53** as the pivotal precursor. Thus, as depicted in Scheme 6, **53** arose from a vinylogous Mukaiyama-type aldol addition

Scheme 3[a]



[a] Key: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −80 °C; (b) (i) H_2, Pd/C, THF, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) (i) 80% aq AcOH, 50 °C, (ii) aq $NaIO_4$, CH_2Cl_2, (iii) $NaBH_4$, MeOH, −30 to −15 °C, (iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) (i) DIBAL-H, CH_2Cl_2, −80 °C, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2.

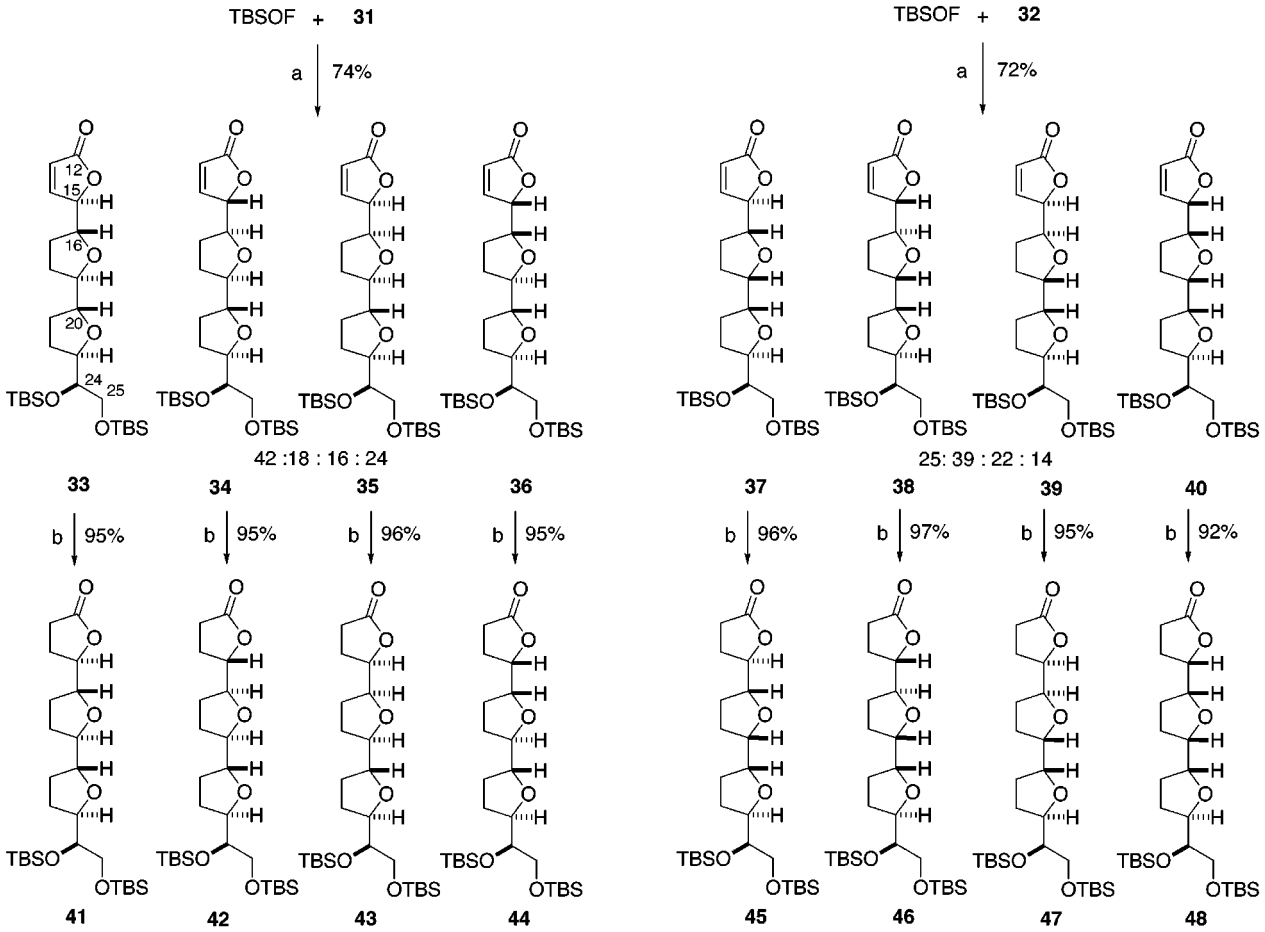
Scheme 4[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF; (c) (i) DIBAL-H, CH_2Cl_2, −80 °C, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2.

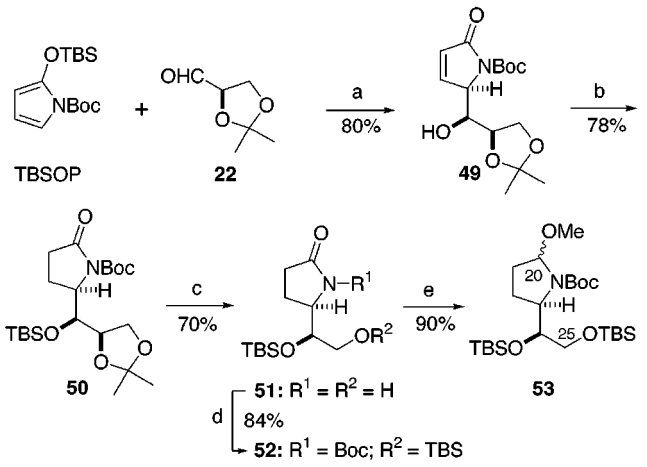
between the pyrrole-based TBSOP and D-glyceraldehyde **22**. The reaction was performed in the presence of $SnCl_4$ in diethyl ether at −80 °C and furnished the crystalline unsaturated adduct **49** as the major product in an 80% isolated yield. Next, hydrogenation and protection of the secondary hydroxyl led to the fully protected lactam

Scheme 5[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF.

Scheme 6[a]



[a] Key: (a) $SnCl_4$, Et_2O, −80 °C; (b) (i) H_2, Pd/C, THF, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) (i) 80% aq AcOH, 50 °C, (ii) aq $NaIO_4$, CH_2Cl_2, (iii) $NaBH_4$, MeOH, −30 to −15 °C; (d) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, (ii) Boc_2O, DMAP, MeCN, 40 °C; (e) $LiEt_3BH$, THF, −80 °C, (ii) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, Et_2O.

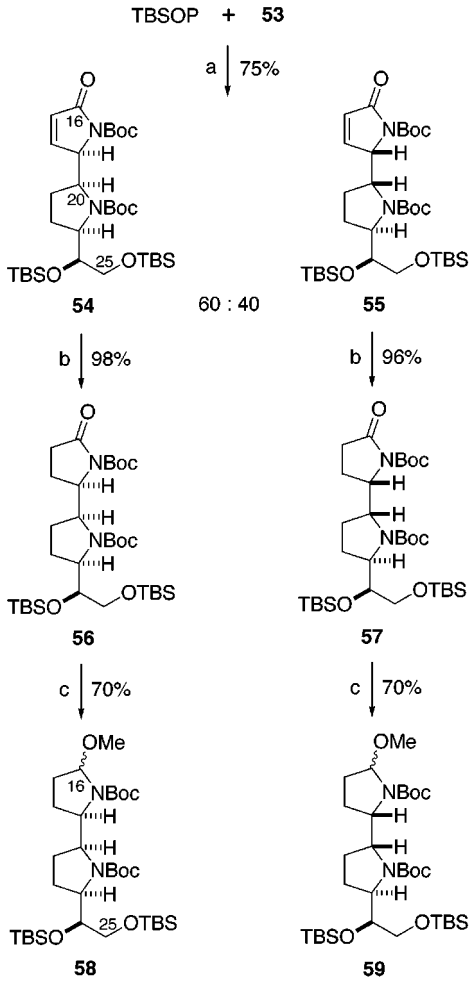
50 (78%)[17] which was sequentially exposed to 80% aqueous acetic acid, sodium periodate, and $NaBH_4$ to deliver pyrrolidinone **51** in a 70% yield. Suitable protection of the primary hydroxyl and reprotection of the pyrrolidine nitrogen gave rise to **52** (84%), which was promptly converted to the *N*,*O*-acetal **53** via selective carbonyl reduction ($LiEt_3BH$) followed by methylation (90%).

The advanced subunits **58** and **59** were obtained from **53** and TBSOP, as shown in Scheme 7. The vinylogous Mannich addition was catalyzed by TBSOTf as usual and furnished two out of four possible bicyclic constructs, namely, *erythro*,*cis*,*threo* unsaturated lactam **54** and its *erythro*,*trans*,*threo* diastereoisomer **55**, in a 75% combined yield (60:40 ratio).[17] Once separated by silica gel chromatography, each isomer was saturated to **56** and **57** and transformed into C16−C25 subunits **58** and **59** by $LiEt_3BH$ reduction and methylation (69% and 67%, three steps). The final stages of this synthesis paralleled the chemistry, previously disclosed, used for the bis-THF units. Elongation of both **58** and **59** with furan-based TBSOF (TBSOTf as a catalyst) proved highly diastereoselective (Scheme 8), butenolides **60** and **61** being solely produced in 90% and 98% yields, respectively. As expected (vide infra), both reactions behaved similarly, favoring a relative *threo*,*trans* arrangement for the newly formed stereocenters at C15 and C16. Catalytic hydrogenation of the individual compounds **60** and **61** eventually completed the diastereoselective synthesis of the bis-pyrrolidine units **62** and **63** in 95% and 88% yields, respectively.

As with the model pyrrolidine compounds **11ec** and **11et** (and **14ec** and **14et**), direct NMR structural diagnosis for the binuclear compounds **54** and **55**, and the trinuclear congeners **60** and **61** (and related saturated

(17) Although TBSOTf is actually a reagent for cleaving *N*-Boc linkages, no traces of N-deprotected compounds were found in this and similar instances.

Scheme 7[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF; (c) $LiEt_3BH$, THF, −80 °C, (ii) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, Et_2O.

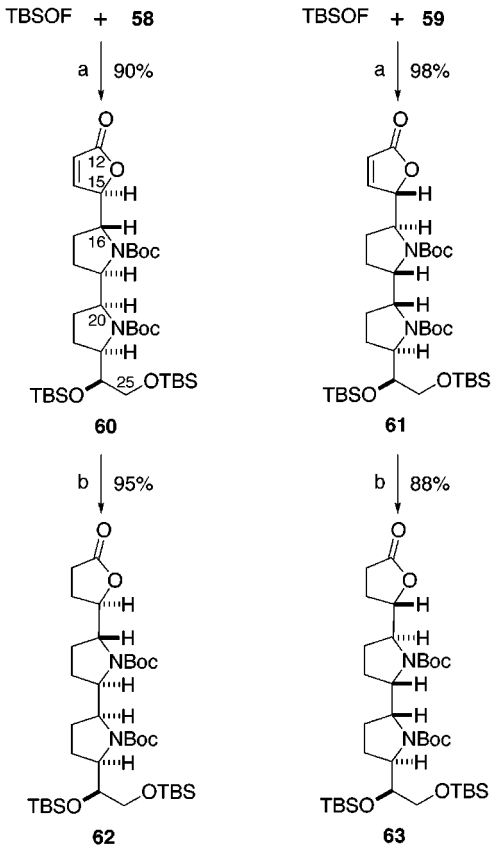
counterparts) proved difficult as the analysis was hampered, in all instances, by conformational heterogeneity reflecting rotameric coexistence. Nevertheless, guided by chiro-optical considerations and in view of the strong spectral analogy with the models **11ec** and **11et**, we were able to assign an *erythro,cis,threo* configuration to **54** and an *erythro,trans,threo* configuration to **55**, whereas the relative stereodisposition of the two additional stereocenters C15 and C16 of the trinuclear targets **60** and **61** (and **62** and **63**), which lacked suitable comparison models, was determined by circular dichroic measurements, by examination of $^1H-^1H$ coupling constants between H15 and H16, and by synthetic conjectures.[18]

Thus, a positive Cotton effect for compound **60** led us to assign a 15*R*-absolute configuration, whereas a negative value for **61** defined its 15*S*-configuration. These data, coupled with the observed $^3J_{15,16}$ values (3.6 Hz for **60**, 3.1 Hz for **61**), established the final assignment indicated.

With the two bis-pyrrolidine subtargets **62** and **63** at hand, the exciting perspective of obtaining nitrogen

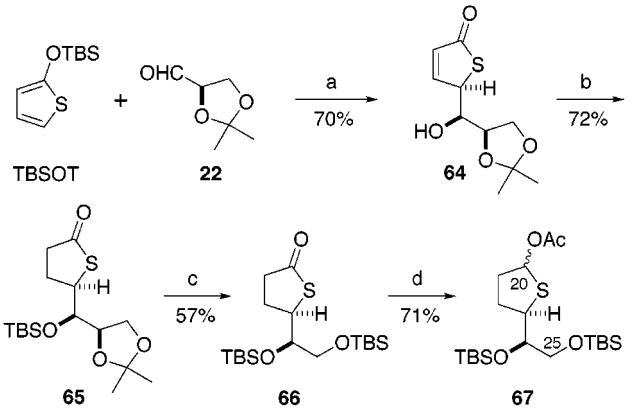
(18) Owing to the high diastereoselectivity observed in the model coupling reaction between TBSOF and *N,O*-acetal **2**, favoring *threo,trans*-configured adduct **10tt**, one can reason that a similar behavior is here followed, too. See also: Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567−1572. Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990−6997.

Scheme 8[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF.

Scheme 9[a]

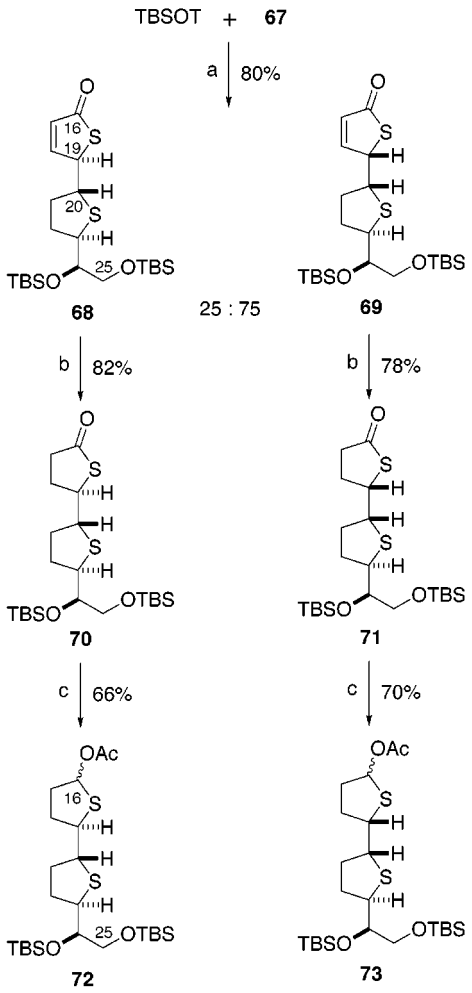


[a] Key: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −80 °C; (b) (i) H_2, Pd/C, THF, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) (i) 80% aq AcOH, 50 °C, (ii) aq $NaIO_4$, CH_2Cl_2, (iii) $NaBH_4$, EtOH, −30 °C, (iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) (i) $NaBH_4$, MeOH, −15 °C, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2.

acetogenin analogues now emerged. Indeed, by tethering a butenolide moiety to C12 and an alkyl chain to C25, aza-trilobacin can easily be prepared from compound **62**.

Synthesis of Bis-Thiolane C12−C25 Units. Preparation of the disubstituted thiolane precursor **67**, encompassing the C20−C25 frame of the bis-thiolane targets **78**−**81**, echoes the previous experiments involving its oxygen and nitrogen congeners **26** and **53** (vide supra). Thus, as shown in Scheme 9, BF_3-mediated Mukaiyama aldol addition of thiophene-based silyloxy diene TBSOT to D-glyceraldehyde **22** afforded the expected adduct **64**

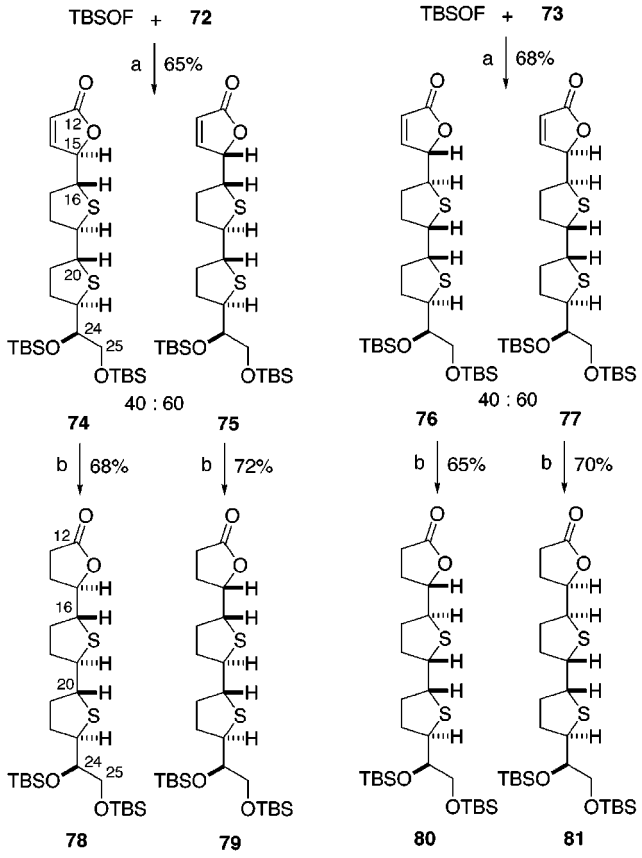
Scheme 10[a]



[a] Key: (a) TBSOTf, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF; (c) (i) $NaBH_4$, MeOH, −15 °C, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2.

(70%), which was catalytically hydrogenated and protected to saturated thiolactone **65** (72%, two steps). One-carbon shortening of the lactone side chain was then carried out, as per usual, by deacetonidation followed by periodate fission. In the event, a six-carbon aldehyde was formed (not shown), which was selectively reduced to an alcohol ($NaBH_4$, EtOH, −30 °C) and protected to afford thiolactone **66** in a 57% yield (four steps). Further reduction of the carbonyl function within **66** was efficiently effected by exposure to $NaBH_4$ in MeOH at −15 °C to furnish a thiolactol that was promptly acetylated to **67** (71%, two steps). The binuclear subunits C16−C25, **72** and **73**, were obtained by a vinylogous addition involving TBSOT and **67** (Scheme 10), carried out in the presence of catalytic TBSOTf at −90 °C, to give a 1:3 mixture of two epimeric unsaturated adducts **68** and **69** in a 80% combined yield. In this case, verification of the *threo*,*trans*,*threo* arrangement for **68** and the *erythro*,*trans*,*threo* arrangement for **69** proved straightforward and was based on the usual chemical, chiro-optical, and ^1H NMR spectroscopic criteria (vide supra). For **68**, dextrorotation coupled with a 6.2 Hz $^3J_{19,20}$ coupling constant indicated its C(19*R*)/C19−C20 *threo* configuration, whereas for **69** levorotation and a large H19−H20 coupling constant (9.3 Hz) corroborated its C(19*S*)/C19−C20 *erythro* configuration.

Scheme 11[a]



[a] Key: (a) TBSOTf, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −90 °C; (b) H_2, Pd/C, THF.

Synthesis of the sulfur subunits **72** and **73** proceeded nicely from **68** and **69**, via double-bond saturation to thiolactones **70** and **71** (82% and 78%), followed by lactone-to-lactol reduction ($NaBH_4$, MeOH, −15 °C) and acetylation (66% and 70%, two steps). To establish the lactone moiety, furnishing the C12−C15 portion of our sulfur units, **72** and **73** were separately coupled to TBSOF (TBSOTf/$BF_3{\cdot}OEt_2$ as a catalyst mixture) to provide trinuclear butenolides **74**/**75** and **76**/**77**, respectively (65% and 68% combined yields) (Scheme 11).

Each couple consisted of C15-epimers (Et_3N-promoted equilibration) with a C(15*R*)-configuration for **74** and **77** (positive Cotton effects) and a C(15*S*)-configuration for **75** and **76** (negative Cotton effects). Once again, evaluation of the vicinal coupling constant values between H15 and H16 for the four isomers **74**−**77** sustained the relative arrangement of these two stereocenters, with *threo* isomers **74** and **76** displaying smaller constants ($^3J_{15,16}$ = 6.0 and 5.2 Hz) than the *erythro* counterparts **75** and **77** ($^3J_{15,16}$ = 9.8 and 9.6 Hz). Completion of individual sulfur subtargets **78**−**81** was finally accomplished by catalytic hydrogenation of the respective isolated precursors with 68%, 72%, 65%, and 70% yields. It will not go unnoticed that scaffold **78** may well constitute the basic substructure of either an asimicin- or a parviflorin-sulfur analogue, whereas **79** may be used to forge the core construct of unnatural thio-bullatacin.

Conclusion

The synthesis of a repertoire of annonaceous acetogenin core units has been accomplished, encompassing

eight members of the "natural" bis-tetrahydrofuran family, two representatives of "unnatural" bis-pyrrolidine analogues, and four bis-thiolane surrogates. This project proved highly reliable, allowing all the synthetic paths to be pursued with comparable efficacy according to the same protocol. Starting from a common chiral substance, D-glyceraldehyde **22**, the parallel synthetic sequences leading to **41**−**48**, **62**−**63**, and **78**−**81** entailed preparation of the mononuclear synthons **26**, **53**, and **67** (first vinylogous addition, nine steps), elongation to the binuclear scaffolds **31**−**32**, **58**−**59**, and **72**−**73** (second vinylogous addition, four steps), and, common to all processes, installation of the terminal butenolide ring (third vinylogous coupling, two steps). Through this study, we have convincingly demonstrated both the utility and malleability of the vinylogous version of the Mukaiyama aldol and Mannich-type addition reactions involving TBSOF, TBSOP, and TBSOT, an ideal triad of five-membered heterocyclic building modules.

The possibility of totally synthesizing naturally occurring acetogenins and, hopefully, nitrogen and sulfur surrogates, using intermediates rationally selected from our repertoire of trinuclear scaffolds, is an exciting prospect that has now opened. The convergence of **62** into aza-trilobacin is currently being studied in our laboratories, and the completed synthesis will be reported in due course. With such a series of varied acetogenin candidates we hope to provide impetus for a better understanding of their important, yet not completely understood, structure−activity relationship.

Experimental Section

Unsaturated Lactone 23. To a solution of TBSOF (3.05 mL, 15.4 mmol) in anhydrous CH_2Cl_2 (60 mL) under argon atmosphere was added 2,3-*O*-isopropylidene-D-glyceraldehyde (**22**) (2.60 g, 20.0 mmol), and the resulting mixture was cooled to −80 °C. BF_3 etherate (1.89 mL, 15.4 mmol), cooled to the same temperature, was added dropwise to the stirring solution, and the reaction was allowed to proceed for 6 h at −80 °C. The reaction was then quenched at the same temperature by the addition of saturated aqueous $NaHCO_3$, and after ambient temperature was reached, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum to give a solid crude residue that was subjected to flash chromatographic purification (hexanes/EtOAc 60:40). Pure lactone **23** was obtained (2.47 g, 75%) as white crystals: mp 125 °C; $[\alpha]^{20}_D$ +69.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.8, 1.7 Hz, 1H), 6.17 (dd, J = 5.8, 1.9 Hz, 1H), 5.27 (m, 1H), 4.18 (m, 2H), 4.05 (m, 1H), 3.67 (m, 1H), 2.94 (d, J = 6.6 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 154.3, 122.1, 109.8, 84.2, 75.5, 72.9, 67.1, 26.7, 25.1. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.71.

Lactone 24. Palladium on carbon (10%, 0.3 g) was added to a solution of α,β-unsaturated lactone **23** (2.4 g, 11.2 mmol) in anhydrous THF (60 mL) in the presence of a small amount of NaOAc (0.09 g) at room temperature. The reaction vessel was evacuated by aspirator and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under a balloon of hydrogen. After 24 h, the hydrogen was evacuated, the catalyst filtered off, and the filtrate concentrated under vacuum to give a crude residue that was subjected to flash chromatographic purification (EtOAc/hexanes 60:40). There was obtained 2.35 g (97%) of a saturated lactone as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (td, J = 7.5, 2.1 Hz, 1H), 4.14 (m, 2H), 4.01 (m, 1H), 3.53 (bs, 1H), 3.35 (bs, 1H), 2.5−2.7 (m, 2H), 2.31 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H). The saturated lactone was subjected to suitable TBS protection. Thus, a stirred solution of the lactone intermediate (2.35 g, 10.9 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled with an ice bath and sequentially treated with 2,6-lutidine (2.0 mL, 17.4 mmol) and TBSOTf (3.5 mL, 15.3 mmol), under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with 5% aqueous citric acid and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to afford a crude residue that was purified by flash chromatography (hexanes/EtOAc 50:50). Protected lactone **24** (3.17 g, 88%) was obtained as a colorless oil: $[\alpha]^{20}_D$ −9.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (dt, J = 6.6, 3.6 Hz, 1H), 4.13 (m, 1H), 4.06 (dd, J = 8.1, 6.3 Hz, 1H), 3.87 (dd, J = 8.1, 6.9 Hz, 1H), 3.78 (dd, J = 6.0, 3.6 Hz, 1H), 2.51 (m, 2H), 2.21 (m, 2H), 1.41 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 109.0, 81.2, 76.3, 74.3, 66.6, 28.4, 26.5, 25.8 (3C), 27.2, 23.6, 18.1, −4.0 (2C). Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.15. Found: C, 58.20; H, 9.09.

Lactone 25. Protected lactone **24** (3.0 g, 9.1 mmol) was dissolved in 10 mL of 80% aqueous acetic acid, and the resulting mixture was warmed to 50 °C and allowed to stir for 24 h. The reaction mixture was then concentrated under vacuum, furnishing a crude diol intermediate (2.51 g, 95%) as a white solid. To a stirred solution of the crude diol (2.51 g, 8.6 mmol) in CH_2Cl_2 (30 mL) were added chromatography grade SiO_2 (15 g) and a 0.65 M aqueous $NaIO_4$ solution (17.3 mL, 11.18 mmol). The resulting slurry was vigorously stirred at room temperature for 45 min, after which time the reaction mixture was filtered under suction and the silica was thoroughly washed with CH_2Cl_2 and EtOAc. The filtrates were evaporated, affording a crude aldehyde intermediate (2.13 g, 96%) as colorless crystals.

A stirred solution of the aldehyde intermediate (2.13 g, 8.24 mmol) in methanol (40 mL) under nitrogen atmosphere was cooled to −30 °C and treated with $NaBH_4$ (620 mg, 16.4 mmol). After being stirred for 1 h at −30 °C, the temperature of the reaction mixture was allowed to rise to −15 °C, while a further portion of $NaBH_4$ (312 mg, 8.24 mmol) was added. After 2 h at −15 °C, the reaction mixture was quenched by addition of acetone (10 mL) and 5% aqueous citric acid. The mixture was then extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum, furnishing a crude alcohol that was purified by flash chromatography (hexanes/EtOAc 50:50). A pure alcohol intermediate was obtained (2.0 g, 94%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (ddd, J = 7.7, 6.4, 3.8 Hz, 1H), 3.6−3.7 (m, 3H), 3.55 (dd, J = 10.4, 4.1 Hz, 1H), 2.52 (ddd, J = 17.7, 10.0, 6.4 Hz, 1H), 2.42 (ddd, J = 17.6, 9.6, 7.6 Hz, 1H), 2.23 (dddd, J = 12.7, 9.4, 7.7, 6.5 Hz, 1H), 2.01 (m, 1H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

A stirred solution of the alcohol intermediate (2.0 g, 7.7 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled with an ice bath and sequentially treated with 2,6-lutidine (1.26 mL, 10.8 mmol) and TBSOTf (2.1 mL, 9.24 mmol), under nitrogen atmosphere. After being stirred at 0 °C for 30 min, the reaction mixture was quenched with 5% aqueous citric acid and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated under vacuum, providing an oily crude residue that was subjected to flash chromatographic purification (hexanes/EtOAc 85:15). Pure lactone **25** was obtained (2.28 g) in 79% yield (68% overall yield from **24**) as a colorless oil: $[\alpha]^{20}_D$ −44.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (ddd, J = 8.2, 5.1, 1.6 Hz, 1H), 3.58 (m, 2H), 3.49 (dd, J = 13.7, 9.5 Hz, 1H), 2.49 (ddd, J = 17.6, 10.3, 7.2 Hz, 1H), 2.36 (ddd, J = 17.4, 9.9, 6.0 Hz, 1H), 2.19 (m, 1H), 2.03 (m, 1H), 0.82 (bs, 18H), −0.02 (bs, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 79.4, 74.9, 63.5, 28.3, 25.8 (3C), 25.6 (3C), 23.4, 18.1, 17.8, −3.7, −4.5, −5.0, −5.6. Anal. Calcd for $C_{18}H_{38}O_4Si$: C, 62.38; H, 11.05. Found: C, 62.19; H, 11.23.

Oxygen Precursor 26. To a stirred solution of lactone **25** (2.0 g, 5.3 mmol) in anhydrous CH_2Cl_2 (30 mL) cooled at −80 °C was added DIBAL-H (7 mL of a 1.5 M solution in toluene, 10.6 mmol) dropwise. The reaction was stirred at −80 °C under nitrogen atmosphere for 30 min and quenched at the same

temperature by addition of methanol (15 mL) and water (15 mL). Once warmed to room temperature, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated, providing a crude lactol intermediate (1.94 g, 97%). The crude lactol (1.94 g, 5.14 mmol) was dissolved in dry CH_2Cl_2 (30 mL) under nitrogen atmosphere and sequentially treated with pyridine (1.24 mL, 15.42 mmol), acetic anhydride (0.9 mL, 0.28 mmol), and DMAP (catalytic) at room temperature. After being stirred for 1 h, the mixture was treated with further portions of pyridine (0.62 mL, 7.7 mmol), Ac_2O (0.46 mL, 5.14 mmol), and DMAP (catalytic). After 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (hexanes/EtOAc 80:20) to give **26** (1.76 g, 82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 75:25 anomeric mixture) δ 6.27 (dd, J = 5.0, 1.1 Hz, 0.75H), 6.20 (dd, J = 3.7, 1.1 Hz, 0.25H), 4.29 (m, 0.75H), 4.04 (m, 0.25H), 3.4−3.7 (m, 3H), 1.9−2.1 (m, 2H), 1.96 (s, 3 × 0.75), 1.94 (s, 3 × 0.25H), 1.8−1.9 (m, 2H), 0.85 (s, 9 × 0.25H) 0.84 (s, 9 × 0.25H), 0.83 (s, 9 × 0.75H), 0.82 (s, 9 × 0.75H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major anomer) δ 170.2, 99.2, 80.2, 74.8, 64.4, 31.9, 25.8 (3C), 25.7 (3C), 24.3, 21.2, 18.2, 18.0, −4.4, −4.6, −5.5 (2C). Anal. Calcd for $C_{20}H_{42}O_5Si_2$: C, 57.37; H, 10.11. Found: C, 57.45; H, 10.24.

Unsaturated Lactones 27 and 28. General Procedure A. To a stirred solution of acetyl lactol **26** (1.76 g, 4.2 mmol) in anhydrous CH_2Cl_2 (50 mL) under an inert atmosphere (N_2) cooled to −90 °C were added dropwise enol ether TBSOF (1.0 g, 5.04 mmol) and TBSOTf (0.58 mL, 2.5 mmol). After being stirred for 1 h at −90 °C, the reaction mixture was neutralized at the same temperature by addition of Et_3N (2.5 mL of a 1.0 M solution in CH_2Cl_2, 2.5 mmol) and quenched with water. After room temperature was reached, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to furnish an oily crude residue that was subjected to flash chromatographic purification (hexanes/EtOAc 85:15). Two pure stereoisomeric butenolides were obtained, namely, **27** (650 mg) and **28** (648 mg), each in 35% yield.

27: an oil; $[\alpha]^{20}_D$ +28.1 (c 0.3, $CHCl_3$); CD (CH_3OH, 1.4 × 10^{-4} M) $[\theta]_{215}$ +3140 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 5.8, 1.6 Hz, 1H), 6.12 (dd, J = 5.8, 2.0 Hz, 1H), 5.03 (dt, J = 3.7, 1.8 Hz, 1H), 4.25 (td, J = 6.9, 3.9 Hz, 1H), 4.07 (td, J = 6.8, 3.2 Hz, 1H), 3.4−3.6 (m, 3H), 2.02 (m, 1H), 1.93 (m, 1H), 1.7−1.9 (m, 2H), 0.86 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 153.7, 122.8, 84.6, 80.6, 77.8, 75.6, 64.7, 27.6, 27.1, 26.0 (3C), 25.9 (3C), 18.3 (2C), −4.3, −4.8, −5.4 (2C). Anal. Calcd for $C_{22}H_{42}O_5Si_2$: C, 59.68; H, 9.56. Found: C, 59.71; H, 9.64.

28: an oil; $[\alpha]^{20}_D$ −40.7 (c 0.4, $CHCl_3$); CD (CH_3OH, 1.4 × 10^{-4} M) $[\theta]_{216}$ −5660 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 5.8, 1.6 Hz, 1H), 6.12 (dd, J = 5.8, 1.9 Hz, 1H), 4.82 (dt, J = 7.1, 1.7 Hz, 1H), 4.14 (td, J = 6.8, 3.5 Hz, 1H), 3.85 (app q, J = 6.8 Hz, 1H), 3.61 (dd, J = 11.4, 8.9 Hz, 1H), 3.52 (m, 2H), 2.10 (m, 1H), 1.97 (m, 1H), 1.7−1.9 (m, 2H), 0.87 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 155.3, 122.0, 85.2, 80.3, 79.5, 75.5, 64.7, 29.2, 27.2, 25.9 (3C), 25.8 (3C), 18.4, 18.2, −4.4, −4.8, −5.4 (2C). Anal. Calcd for $C_{22}H_{42}O_5Si_2$: C, 59.68; H, 9.56. Found: C, 59.53; H, 9.69.

Saturated Lactone 29. General Procedure B. Butenolide **27** (600 mg, 1.36 mmol) was dissolved in anhydrous THF (50 mL) and treated with 10% Pd on carbon (60 mg) and a small amount of sodium acetate (15 mg) at room temperature. The reaction vessel was evacuated and purged with hydrogen, and the resulting heterogeneous mixture was stirred under a balloon of hydrogen for 24 h. After hydrogen evacuation, the catalyst was filtered off, and the filtrate was concentrated under vacuum to afford a crude oily residue that was subjected to flash chromatographic purification (hexanes/EtOAc 80:20). Pure lactone **29** was obtained (560 mg, 93%) as a colorless oil: $[\alpha]^{20}_D$ −15.0 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (td, J = 6.8, 2.6 Hz, 1H), 4.06 (m, 1H), 4.00 (td, J = 7.0, 2.5 Hz, 1H), 3.61 (dd, J = 11.4, 8.5 Hz, 1H), 3.52 (m, 2H), 2.65 (ddd, J = 17.3, 9.6, 7.6 Hz, 1H), 2.39 (dt, J = 17.6, 7.9 Hz, 1H), 2.21 (m, 2H), 1.7−2.0 (m, 4H), 0.86 (s, 18H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 81.2, 80.8, 80.4, 75.8, 64.9, 28.2, 27.9, 27.6, 26.0 (3C), 25.9 (3C), 24.6, 18.4, 18.1, −4.3, −4.8, −5.4 (2C). Anal. Calcd for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.35; H, 10.05.

Saturated Lactone 30. The reaction was carried out according to general procedure B, by starting with butenolide **28** (600 mg, 1.36 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), pure lactone **30** was obtained (550 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ −11.0 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (dt, J = 7.3, 6.0 Hz, 1H), 4.0−4.1 (m, 2H), 3.61 (dd, J = 11.2, 8.3 Hz, 1H), 3.51 (dd, J = 11.1, 4.8 Hz, 1H), 3.50 (m, 1H), 2.54 (ddd, J = 17.7, 9.9, 6.4 Hz, 1H), 2.44 (ddd, J = 17.6, 9.3, 7.5 Hz, 1H), 2.24 (m, 1H), 2.08 (m, 2H), 1.94 (m, 1H), 1.81 (m, 1H), 1.66 (m, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.04 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 82.0, 80.3, 79.9, 75.7, 64.7, 28.7, 28.1, 27.3, 25.9 (3C), 25.8 (3C), 23.8, 18.3, 18.1, −4.4, −4.8, −5.5 (2C). Anal. Calcd for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.49; H, 10.09.

Oxygen Subunit 31. The above two-step protocol to transform **25** into **26** was adopted, by starting with lactone **29** (560 mg, 1.26 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), pure acetylated lactol **31** was obtained (515 mg, 84%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, major anomer) δ 6.31 (d, J = 4.6 Hz, 1H), 4.18 (quint, J = 3.8 Hz, 1H), 4.02 (m, 1H), 3.93 (m, 1H), 3.62 (m, 1H), 3.53 (m, 2H), 2.18 (m, 1H), 2.00 (m, 1H), 1.99 (s, 3H), 1.7−2.0 (m, 6H), 0.87 (s, 9H), 0.86 (s 9H), 0.04 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major anomer) δ 170.3, 99.1, 82.6, 81.2, 80.5, 75.3, 64.8, 31.9, 28.4, 27.5, 26.0 (3C), 25.8 (3C), 24.2, 22.6, 18.3, 18.2, −4.3, −4.8, −5.4 (2C). Anal. Calcd for $C_{24}H_{48}O_6Si_2$: C, 58.97; H, 9.90. Found: C, 59.05; H, 9.78.

Oxygen Subunit 32. The above two-step protocol to transform **25** into **26** was adopted, by starting with lactone **30** (550 mg, 1.24 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), pure acetylated lactol **32** was obtained (470 mg, 78%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, 50:50 anomeric mixture) δ 6.26 (bd, J = 4.5 Hz, 0.5H), 6.20 (t, J = 2.6 Hz, 0.5H), 3.7−4.1 (m, 3H), 3.63 (m, 1H), 3.52 (m, 2H), 1.99 (s, 3 × 0.5H), 1.97 (s, 3 × 0.5H), 1.7−2.1 (m, 8H), 0.86 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, one anomer) δ 170.2, 99.2, 82.0, 80.9, 80.2, 75.7, 64.7, 31.9, 28.2, 27.1, 27.0, 25.9 (3C), 25.8 (3C), 21.2, 18.3, 18.1, −4.4, −4.8, −5.4 (2C). Anal. Calcd for $C_{24}H_{48}O_6Si_2$: C, 58.97; H, 9.90. Found: C, 58.89; H, 9.76.

Unsaturated Oxygen Units 33, 34, 35, and 36. The reaction was carried out according to general procedure A, using TBSOF (250 mg, 1.26 mmol) and acetyl furanose **31** (500 mg, 1.02 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), pure butenolides **33** (162 mg, 31%), **34** (70 mg, 13%), **35** (62 mg, 12%), and **36** (93 mg, 18%) were obtained in a 74% combined yield.

33: colorless oil; CD (CH_3OH, 4.9 × 10^{-5} M) $[\theta]_{214}$ +26920 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, J = 5.8, 1.6 Hz, 1H), 6.15 (dd, J = 5.6, 2.1 Hz, 1H), 5.06 (dt, J = 3.6, 1.8 Hz, 1H), 4.30 (m, 1H), 4.02 (m, 1H), 3.88 (m, 2H), 3.6−3.7 (m, 1H), 3.5−3.6 (m, 2H), 2.09 (m, 1H), 1.7−2.0 (m, 6H), 1.61 (m, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 153.6, 122.6, 84.3, 80.6, 80.2, 79.4, 77.8, 75.7, 65.0, 28.0, 27.7, 27.4, 26.0 (3C), 25.0 (3C), 24.0, 18.4, 18.2, −5.4 (4C); HRMS (CI, CH_4) m/z 513.3081 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

34: an oil; CD (CH_3OH, 1.3 × 10^{-5} M) $[\theta]_{215}$ −15780 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.8, 1.6 Hz, 1H), 6.13 (dd, J = 5.4, 2.0 Hz, 1H), 5.09 (dt, J = 4.6, 1.7 Hz, 1H), 4.30 (m, 1H), 4.02 (m, 1H), 3.85 (m, 2H), 3.6−3.7 (m, 1H), 3.5−3.6 (m, 2H), 2.10 (m, 1H), 1.6−2.0 (m, 7H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 153.7, 122.8, 84.3, 80.6, 80.2, 79.5, 77.9, 75.6, 64.9, 27.9, 27.7, 27.4, 26.0 (3C), 25.9 (3C), 24.7,

18.3, 18.2, −4.3, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3074 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

35: an oil; CD (CH_3OH, 1.2×10^{-5} M) $[\theta]_{218}$ +12530 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 5.9, 1.7 Hz, 1H), 6.12 (dd, J = 5.4, 1.8 Hz, 1H), 4.86 (dt, J = 7.9, 1.6 Hz, 1H), 3.8−4.1 (m, 4H), 3.5−3.7 (m, 3H), 2.10 (m, 1H), 1.7−2.0 (m, 6H), 1.60 (m, 1H), 0.88 (s, 18H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 155.0, 122.0, 84.9, 80.3, 80.0, 79.8, 78.2, 75.5, 64.7, 28.2, 27.6, 27.2, 26.0 (3C), 25.9 (3C), 24.3, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3042 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

36: an oil; CD (CH_3OH, 3.9×10^{-5} M) $[\theta]_{216}$ −15180 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J = 6.0, 1.7 Hz, 1H), 6.14 (dd, J = 5.9, 2.1 Hz, 1H), 4.89 (dt, J = 6.8, 1.8 Hz, 1H), 3.9−4.1 (m, 4H), 3.5−3.8 (m, 3H), 2.10 (m, 1H), 1.7−2.0 (m, 6H), 1.60 (m, 1H), 0.88 (s, 18H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 154.9, 122.1, 84.7, 80.5, 80.1, 79.7, 78.1, 75.5, 64.7, 27.9, 27.7, 27.3, 26.0 (3C), 25.9 (3C), 24.1, 18.4, 18.1, −4.3, −4.8, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3051 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

Unsaturated Oxygen Units 37, 38, 39, and 40. The reaction was carried out according to general procedure A, using TBSOF (200 mg, 1.01 mmol) and acetyl furanose **32** (450 mg, 0.92 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), pure butenolides **37** (84 mg, 18%), **38** (133 mg, 28%), **39** (75 mg, 16%), and **40** (48 mg, 10%) were obtained in a 72% combined yield.

37: an oil; $[\alpha]^{20}_D$ +4.4 (*c* 0.2, $CHCl_3$); CD (CH_3OH, 1.2×10^{-4} M) $[\theta]_{212}$ +5870 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 5.8, 1.6 Hz, 1H), 6.13 (dd, J = 5.8, 2.0 Hz, 1H), 5.05 (dt, J = 4.0, 1.8 Hz, 1H), 4.21 (ddd, J = 7.0, 5.9, 4.0 Hz, 1H), 3.99 (td, J = 7.1, 3.9 Hz, 1H), 3.85 (m, 2H), 3.61 (dd, J = 11.8, 8.0 Hz, 1H), 3.52 (m, 1H), 3.51 (dd, J = 11.5, 5.0 Hz, 1H), 1.7−2.0 (m, 6H), 1.5−1.7 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 153.7, 122.8, 84.6, 80.7, 80.3, 79.8, 77.8, 75.8, 65.2, 28.1, 27.6, 26.8, 26.0 (3C), 25.9 (3C), 24.5, 18.4, 18.2, −4.4, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3089 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

38: an oil; $[\alpha]^{20}_D$ −17.2 (*c* 0.2, $CHCl_3$); CD (CH_3OH, 1.8×10^{-4} M) $[\theta]_{216}$ −6490 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 5.8, 1.6 Hz, 1H), 6.15 (dd, J = 5.8, 2.0 Hz, 1H), 5.02 (dt, J = 3.8, 1.8 Hz, 1H), 4.28 (m, 1H), 4.00 (m, 1H), 3.85 (m, 2H), 3.5−3.7 (m, 3H), 1.7−2.1 (m, 6H), 1.5−1.7 (m, 2H), 0.86 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 153.8, 122.6, 84.3, 80.9, 80.2, 79.7, 77.9, 75.7, 65.0, 28.1, 27.7, 27.0, 26.0 (3C), 25.9 (3C), 24.6, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3055 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

39: an oil; CD (CH_3OH, 1.3×10^{-4} M) $[\theta]_{219}$ + 11170 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.8, 1.6 Hz, 1H), 6.13 (dd, J = 5.7, 1.9 Hz, 1H), 4.86 (dt, J = 6.5, 1.8 Hz, 1H), 4.02 (m, 1H), 3.8−4.0 (m, 3H), 3.61 (m, 1H), 3.53 (m, 2H), 1.9−2.1 (m, 3H), 1.7−1.9 (m, 3H), 1.5−1.7 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 155.2, 122.0, 84.9, 80.7, 80.3, 79.8, 78.0, 75.7, 65.0, 28.1, 27.9, 27.4, 26.0 (3C), 25.9 (3C), 23.9, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3084 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

40: an oil; CD (CH_3OH, 1.1×10^{-4} M) $[\theta]_{220}$ −10500 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.5, 1.4 Hz, 1H), 6.12 (dd, J = 5.7, 1.9 Hz, 1H), 4.84 (m, 1H), 4.02 (m, 1H), 3.8−4.0 (m, 3H), 3.60 (m, 1H), 3.50 (m, 2H), 1.9−2.1 (m, 3H), 1.7−1.9 (m, 3H), 1.5−1.7 (m, 2H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 155.3, 122.4, 84.7, 80.6, 80.3, 79.5, 78.1, 75.8, 64.9, 28.2, 27.6, 27.2, 26.0 (3C), 25.9 (3C), 23.6, 18.3, 18.2, −4.3, −4.7, −5.4 (2C); HRMS (CI, CH_4) *m/z* 513.3087 (MH, 513.3068 calcd for $C_{26}H_{49}O_6Si_2$).

Saturated Oxygen Unit 41. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **33** (130 mg, 0.25 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **41** (124 mg) was recovered in 95% yield: an oil; $[\alpha]^{20}_D$ −10.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (td, J = 6.8, 2.2 Hz, 1H), 4.01 (m, 2H), 3.85 (m, 2H), 3.63 (m, 1H), 3.5−3.6 (m, 2H), 2.67 (dt, J = 17.1, 8.7 Hz, 1H), 2.39 (dt, J = 17.4, 7.8 Hz, 1H), 2.22 (m, 2H), 1.8−2.1 (m, 4H), 1.6−1.8 (m, 3H), 1.56 (m, 1H), 0.87 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 82.3, 81.3, 81.2, 80.8, 80.2, 75.8, 65.0, 28.6, 28.3, 28.2, 27.8, 27.7, 26.0 (3C), 25.9 (3C), 24.7, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); MS (CI, CH_4) *m/z* 515 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.48; H, 9.87.

Saturated Oxygen Unit 42. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **34** (50 mg, 0.10 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **42** (48 mg) was obtained in 95% yield: an oil; $[\alpha]^{20}_D$ −7.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (td, J = 6.8, 2.8 Hz, 1H), 4.01 (m, 2H), 3.8−3.9 (m, 2H), 3.5−3.7 (m, 3H), 2.66 (dt, J = 17.2, 8.7 Hz, 1H), 2.38 (m, 1H), 2.2−2.3 (m, 2H), 1.8−2.1 (m, 4H), 1.6−1.8 (m, 3H), 1.52 (m, 1H), 0.87 (s, 18H), 0.05 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 83.0, 81.6, 81.4, 80.9, 80.6, 76.0, 65.0, 28.6, 28.3, 27.8, 27.5, 27.2, 26.0 (3C), 25.9 (3C), 24.3, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); MS (CI, CH_4) *m/z* 515 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.76; H, 9.65.

Saturated Oxygen Unit 43. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **35** (50 mg, 0.10 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **43** (49 mg) was obtained in 96% yield: an oil; $[\alpha]^{20}_D$ −33.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J = 6.0 Hz, 1H), 4.00 (m, 2H), 3.86 (m, 2H), 3.6−3.7 (m, 1H), 3.5−3.6 (m, 2H), 2.4−2.6 (m, 1H), 2.2−2.3 (m, 2H), 1.6−2.0 (m, 8H), 1.52 (m, 1H), 0.87 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 82.0, 81.5, 81.0, 80.3, 80.2, 76.1, 65.0, 28.7, 28.5, 28.2, 27.7, 27.4, 26.0 (6C), 23.9, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); MS (CI, CH_4) *m/z* 515 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.85; H, 9.54.

Saturated Oxygen Unit 44. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **36** (80 mg, 0.16 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **44** (76 mg) was obtained in 95% yield: an oil; $[\alpha]^{20}_D$ −7.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (app q, J = 6.2 Hz, 1H), 4.01 (m, 2H), 3.8−4.0 (m, 2H), 3.64 (m, 1H), 3.54 (m, 2H), 2.4−2.6 (m, 2H), 2.2−2.4 (m, 1H), 2.0−2.2 (m, 1H), 1.6−2.0 (m, 7H), 1.54 (m, 1H), 0.87 (s, 18H), 0.05 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 82.2, 82.0, 81.4, 80.2 (2C), 75.8, 65.0, 28.6, 28.2, 28.1 (2C), 27.6, 26.0 (3C), 25.9 (3C), 24.1, 18.4, 18.2, −4.3, −4.8, −5.4 (2C); MS (CI, CH_4) *m/z* 515 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.83; H, 9.58.

Saturated Oxygen Unit 45. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **37** (70 mg, 0.14 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **45** (67 mg) was obtained in 96% yield: an oil; $[\alpha]^{20}_D$ −28.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (ddd, J = 7.9, 5.0, 2.8 Hz, 1H), 3.95 (m, 2H), 3.78 (m, 2H), 3.61 (m, 1H), 3.53 (m, 2H), 2.61 (ddd, J = 17.4, 10.0, 7.4 Hz, 1H), 2.39 (ddd, J = 17.2, 9.7, 6.0 Hz, 1H), 2.1−2.3 (m, 2H), 1.8−2.0 (m, 4H), 1.5−1.8 (m, 4H), 0.87 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 82.3, 81.2, 80.7, 80.5, 80.2, 75.9, 65.2, 29.4, 28.8, 28.2, 27.7, 26.8, 26.0 (3C), 25.9 (3C), 24.6, 18.4, 18.2, −4.4, −4.7, −5.4 (2C); MS (CI, CH_4) *m/z* 515 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.48; H, 9.89.

Saturated Oxygen Unit 46. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **38** (100 mg, 0.19 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **46** (97 mg) was obtained in 97% yield: an oil; $[\alpha]^{20}_D$ −10.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (ddd, J = 7.8, 5.1, 2.4 Hz, 1H), 3.9−4.1 (m, 2H), 3.7−3.9 (m, 2H), 3.5−3.7 (m, 3H), 2.68 (ddd, J = 17.4, 9.9, 7.5 Hz, 1H), 2.43 (ddd, J = 17.1, 9.6, 6.6 Hz, 1H), 2.23 (m, 2H), 1.6−2.1 (m, 8H), 0.88 (s, 18H), 0.07 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 82.8, 81.4, 81.1, 80.8, 80.1, 75.8, 65.0, 29.4, 28.4, 28.2, 27.8, 27.4, 26.0 (3C), 25.9 (3C), 24.7, 18.4, 18.2, −4.3, −4.7, −5.4 (2C); MS (CI, CH_4) *m/z* 515

$[M + H]^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.50; H, 9.85.

Saturated Oxygen Unit 47. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **39** (60 mg, 0.12 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **47** (57 mg) was obtained in 95% yield: an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (q, J = 6.2 Hz, 1H), 4.04 (m, 2H), 3.87 (m, 2H), 3.64 (dd, J = 11.8, 8.0 Hz, 1H), 3.5−3.6 (m, 2H), 2.4−2.6 (m, 2H), 2.2−2.4 (m, 2H), 1.6−2.2 (m, 4H), 1.6−1.9 (m, 4H), 0.89 (s, 18H), 0.07 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 82.4, 81.8, 81.5, 81.1, 80.1, 75.8, 65.0, 29.2, 28.3, 28.2, 28.0, 27.4, 26.0 (3C), 25.9 (3C), 23.9, 18.4, 18.2, −4.3, −4.7, −5.3 (2C); MS (CI, CH_4) m/z 515 $[M + H]^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.85; H, 9.59.

Saturated Oxygen Unit 48. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **40** (40 mg, 0.08 mmol). After flash chromatographic purification (hexanes/EtOAc 70:30), pure lactone **48** (36 mg) was obtained in 92% yield: an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, J = 6.2 Hz, 1H), 4.00 (m, 2H), 3.86 (m, 2H), 3.5−3.7 (m, 3H), 2.4−2.6 (m, 2H), 2.2−2.4 (m, 2H), 1.9−2.2 (m, 4H), 1.5−1.8 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 82.2, 81.8, 81.5, 80.9, 80.1, 75.9, 64.9, 29.4, 29.2, 28.3, 27.7, 27.3, 26.0 (3C), 25.9 (3C), 23.7, 18.3, 18.2, −4.3, −4.7, −5.4 (2C); MS (CI, CH_4) m/z 515 $[M + H]^+$. Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.77; H, 9.64.

Unsaturated Lactam 49. To a solution of TBSOP (2.45 g, 8.2 mmol) in anhydrous Et_2O (50 mL) under argon atmosphere was added protected D-glyceraldehyde **22** (1.39 g, 10.7 mmol), and the resulting mixture was cooled to −80 °C. A 0.1 M Et_2O solution of $SnCl_4$ (0.82 mL, 8.2 mmol), cooled to the same temperature, was added dropwise to the stirring solution, and the reaction was allowed to proceed for 5 h at −80 °C. The reaction mixture was then quenched at the same temperature by the addition of solid $NaHCO_3$ (2.7 g) followed by water (30 mL) and, after reaching room temperature, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under vacuum to furnish a crude residue, which was purified by crystallization from CH_2Cl_2/hexane. Pure lactam **49** was obtained (2.06 g) in 80% yield, accompanied by its C4-epimer (4.7% yield), which was obtained in a pure form by flash chromatography of the mother residue (hexanes/EtOAc 50:50). Compound **49**: white solid; mp 138−140 °C; $[\alpha]^{20}_D$ +197.6 (c 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 6.3, 2.1 Hz, 1H), 6.13 (dd, J = 6.3, 1.5 Hz, 1H), 4.81 (dt, J = 5.7, 2.4 Hz, 1H), 4.09 (ddd, J = 6.0, 5.7, 3.9 Hz, 1H), 4.01 (q, J = 6.0, 1H), 3.94 (dd, J = 8.1, 6.0 Hz, 1H), 3.86 (dd, J = 8.1, 6.0 Hz, 1H), 3.63 (d, J = 3.9 Hz, 1H), 1.57 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 150.9, 148.2, 126.9, 109.2, 83.8, 75.6, 72.6, 66.4, 65.6, 28.0 (3 C), 26.4, 25.1. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.31; H, 7.35; N, 4.32.

Lactam 50. The above hydrogenation procedure to transform **23** into **24** was adopted, using unsaturated lactam **49** (2.0 g, 6.38 mmol), Pd on carbon (10%, 200 mg), and NaOAc (80 mg) in dry THF (30 mL). After flash chromatographic purification (hexanes/EtOAc 60:40), a saturated lactam intermediate was obtained (1.85 g) in 92% yield as a white solid. This lactam intermediate (1.85 g, 5.87 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and sequentially treated with 2,6-lutidine (1.1 mL, 9.4 mmol) and TBSOTf (1.89 mL, 8.22 mmol), under stirring at room temperature. After 1 h, the reaction mixture was quenched with 5% citric acid and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to afford a crude residue that was purified by flash chromatography (hexanes/EtOAc 70:30). Protected lactam **50** was obtained (2.14 g, 85%, corresponding to a 78% overall yield from **49**) as a pale yellow oil: $[\alpha]^{20}_D$ +38.1 (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (ddd, J = 9.2, 3.7, 1.3 Hz, 1H), 4.10 (dd, J = 8.5, 3.7 Hz, 1H), 4.07 (dd, J = 8.0, 5.9 Hz, 1H), 3.95 (dt, J = 8.5, 6.1 Hz, 1H), 3.71 (dd, J = 8.1, 6.2 Hz, 1H), 2.57 (ddd, J = 17.8, 11.5, 9.8 Hz, 1H), 2.38 (ddd, J = 17.8, 10.3, 2.0 Hz, 1H), 2.16 (m, 1H), 1.98 (m, 1H), 1.52 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H), 0.85 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.8, 109.8, 82.3, 75.2, 71.1, 68.6, 60.2, 31.8, 29.4, 28.0 (3 C), 26.2, 25.4 (3 C), 24.9, 17.6, −4.2, −5.0. Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26. Found: C, 58.79; H, 9.20; N, 3.12.

Lactam 51. Pure lactam **50** (2.0 g, 4.65 mmol) was dissolved in 15 mL of 80% aqueous acetic acid, and the resulting mixture was warmed to 50 °C and allowed to stir for 24 h. The reaction was then concentrated under vacuum, furnishing a crude diol intermediate, which was subjected to flash chromatographic purification (EtOAc/MeOH 95:5 to 80:20). A pure diol intermediate was obtained (1.2 g, 90%) as white crystals, which was dissolved in CH_2Cl_2 (15 mL) and treated with chromatography-grade SiO_2 (6 g) and a 0.65 M aqueous $NaIO_4$ solution (8.3 mL, 5.4 mmol). The resulting slurry was vigorously stirred at room temperature for 2 h, after which time the reaction mixture was filtered under suction and the silica was thoroughly washed with CH_2Cl_2 and EtOAc. The filtrates were evaporated, affording a crude aldehyde intermediate (1.04 g, 98%) as a pale yellow oil.

A stirred solution of this aldehyde intermediate (1.04 g, 4.04 mmol) in methanol (20 mL) under nitrogen atmosphere was cooled to −30 °C and treated with $NaBH_4$ (306 mg, 8.08 mmol). After being stirred for 1 h at −30 °C, the temperature of the reaction mixture was allowed to raise to −15 °C, while further portion of $NaBH_4$ (155 mg, 4.04 mmol) was added. After 2 h at −15 °C, the reaction mixture was quenched by addition of acetone (5 mL) and 5% aqueous citric acid solution. The mixture was then extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum, furnishing a crude residue that was purified by flash chromatography (EtOAc/MeOH 98:2). Pure lactam **51** was recovered (840 mg, 80% corresponding to a 70% overall yield from **50**) as white crystals: mp 92−94 °C; $[\alpha]^{20}_D$ −22.2 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (bs, 1H), 3.82 (dt, J = 7.4, 5.2 Hz, 1H), 3.5−3.6 (m, 3H), 2.73 (bs, 1H), 2.30 (m, 2H), 2.16 (m, 1H), 1.82 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 75.3, 63.7, 56.2, 30.0, 25.7 (3C), 23.5, 17.9, −4.4, −4.8. Anal. Calcd for $C_{12}H_{25}NO_3Si$: C, 55.56; H, 9.71; N, 5.40. Found: C, 55.69; H, 9.88; N, 5.32.

Lactam 52. A stirred solution of carbinol **51** (830 mg, 3.2 mmol) in anhydrous CH_2Cl_2 (15 mL) was cooled with an ice bath and sequentially treated with 2,6-lutidine (0.5 mL, 4.48 mmol) and TBSOTf (0.88 mL, 3.84 mmol) under nitrogen atmosphere. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with 5% aqueous citric acid and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated under vacuum, providing a crude residue that was purified by flash chromatography (EtOAc/hexanes 80:20). A pure silylated lactam intermediate was obtained (1.0 g, 2.68 mmol, 85%) that was dissolved in CH_3CN (20 mL) and sequentially treated with Boc_2O (385 mg, 2.68 mmol) and DMAP (16 mg, 0.13 mmol). The reaction mixture was warmed to 40 °C and allowed to stir under nitrogen atmosphere for 2 h, during which time two further portions of Boc_2O (385 mg, 2.68 mmol each) and DMAP (16 mg, 0.13 mmol) were added. The reaction mixture was then concentrated under vacuum, providing a crude residue that was purified by flash chromatography (hexanes/EtOAc 85:15). Pure protected lactam **52** was obtained (1.27 g) in almost quantitative yield (84% from **51**) as a pale yellow oil: $[\alpha]^{20}_D$ +20.1 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (ddd, J = 9.3, 4.3, 1.7 Hz, 1H), 4.11 (q, J = 5.4 Hz, 1H), 3.57 (dd, J = 10.6, 5.5 Hz, 1H), 3.52 (dd, J = 10.6, 5.4 Hz, 1H), 2.52 (ddd, J = 17.8, 10.9, 9.8 Hz, 1H), 2.35 (ddd, J = 17.8, 10.2, 2.5 Hz, 1H), 2.18 (dddd, J = 13.5, 9.6, 2.2, 2.2 Hz, 1H), 1.94 (m, 1H), 1.50 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 150.0, 82.6, 71.6, 64.0, 60.0, 32.0, 29.6 (3C), 25.9 (3C), 25.7 (4C), 18.0, 17.9, −4.6, −4.9, −5.6, −5.7. Anal. Calcd for $C_{23}H_{47}NO_5Si_2$: C, 58.31; H, 10.00; N, 2.96. Found: C, 58.26; H, 10.12; N, 2.84.

Nitrogen Precursor 53. To a stirred solution of lactam **52** (1.27 g, 2.68 mmol) in anhydrous THF (20 mL) cooled at

−80 °C was added $LiEt_3BH$ (4.02 mL of a 1.0 M solution in THF, 4.02 mmol) dropwise. After being stirred at −80 °C under nitrogen atmosphere for 2 h, the reaction mixture was treated with further portion of $LiEt_3BH$ (4.02 mL of a 1.0 M solution in THF, 4.02 mmol) and allowed to stirr at −80 °C for an additional 2 h. Methanol (10 mL), water (10 mL), and potassium sodium tartrate tetrahydrate were added, and once warmed to room temperature, the mixture was extracted with EtOAc. The combined organic layers were dried and concentrated, providing a crude aminal intermediate (1.27 g, quantitative) as a colorless oil. This *N*,*O*-acetal (1.27 g, 2.67 mmol) was dissolved at room temperature in dry Et_2O (12 mL) under nitrogen atmosphere and sequentially treated with activated 2−3 μm molecular sieves (80 mg), methyl orthoformate (590 μL, 5.34 mmol), and $BF_3{\cdot}OEt_2$ (100 μL). After being stirred for 2 h, the reaction was quenched with brine and Et_3N (some drops) and extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated under vacuum to furnish a crude oily residue that was purified by flash chromatography (hexanes/EtOAc 85:15). Pure methyl *N*,*O*-acetal **53** was obtained (1.18 g) in 90% yield (two steps) as a colorless oil: $[\alpha]^{20}_D$ +35.9 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (m, 1H), 4.27 (m, 1H), 3.84 (m, 1H), 3.70 (bd, J = 10.6 Hz, 1H), 3.50 (dd, J = 10.8, 8.2 Hz, 1H), 3.31 (s, 3H), 1.9−2.0 (m, 2H), 1.78 (m, 1H), 1.63 (m, 1H), 1.47 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 90.0, 79.5, 71.5, 64.0, 60.0, 54.9, 31.7, 28.4 (3C), 26.0 (3C), 25.8 (3C), 23.0, 18.0, 17.9, −4.3, −4.8, −5.5 (2C). Anal. Calcd for $C_{24}H_{51}NO_5Si_2$: C, 58.85; H, 10.49; N, 2.86. Found: C, 58.71; H, 10.53; N, 2.75.

Unsaturated Lactams 54 and 55. General Procedure C. To a solution of methyl aminal **53** (1.18 g, 2.41 mmol) in anhydrous CH_2Cl_2 (30 mL) cooled to −90 °C under an inert atmosphere (N_2) was added TBSOTf (0.33 mL, 1.45 mmol) dropwise. The resulting mixture was allowed to stir at −90 °C for 15 min, after which time it was treated with 856 mg (2.89 mmol) of silylenol ether TBSOP. After being stirred for an additional 1 h at −90 °C, the reaction mixture was neutralized at the same temperature with Et_3N (1.45 mL of a 1.0 M solution in CH_2Cl_2, 1.45 mmol) and quenched by the addition of water. After room temperature was reached, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide an oily residue that was purified by flash chromatography (hexanes/EtOAc 75:25). Pure unsaturated lactams **54** (695 mg, 45%) and **55** (460 mg, 30%) were obtained.

54: $[\alpha]^{20}_D$ +77.9 (*c* 0.3, $CHCl_3$); CD (CH_3OH, 1.3 × 10^{-4} M) $[\theta]_{227}$ +11474 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 60:40 rotameric mixture) δ 7.01 (dd, J = 6.0, 2.0 Hz, 0.4H), 7.00 (dd, J = 6.1, 2.0 Hz, 0.6H), 6.14 (dd, J = 5.8, 1.5 Hz, 0.4H), 6.13 (dd, J = 6.0, 1.6 Hz, 0.6H), 5.57 (dt, J = 5.1, 1.8 Hz, 0.6H), 5.28 (dt, J = 5.4, 1.9 Hz, 0.4H), 4.70 (dd, J = 7.8, 5.2 Hz, 0.6H), 4.61 (dd, J = 8.5, 5.6 Hz, 0.4H), 4.31 (q, J = 5.2 Hz, 0.4H), 4.20 (dt, J = 6.4, 4.7 Hz, 0.6H), 3.90 (dd, J = 8.3, 4.2 Hz, 0.4H), 3.80 (dd, J = 8.0, 4.8 Hz, 0.6H), 3.3−3.5 (m, 2H), 2.00 (m, 1H), 1.2−1.8 (m, 3H), 1.54 (s, 9 × 0.6H), 1.53 (s, 9 × 0.4H), 1.49 (s, 9 × 0.4H), 1.48 (s, 9 × 0.6H), 0.86 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer) δ 177.5, 153.5, 150.8, 147.8, 128.0, 83.2, 80.3, 72.1, 64.2, 61.9, 61.3, 58.5, 28.6 (3C), 28.1 (3C), 26.0 (3C), 25.7 (3C), 25.6, 25.1, 18.5, 18.0, −3.6, −4.4, −5.3 (2C). Anal. Calcd for $C_{32}H_{60}N_2O_7Si_2$: C, 59.96; H, 9.43; N, 4.36. Found: C, 60.07; H, 9.51; N, 4.32.

55: CD (CH_3OH, 1.3 × 10^{-4} M) $[\theta]_{225}$ −10270 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer) δ 7.01 (dd, J = 6.1, 2.1 Hz, 1H), 6.04 (dd, J = 6.0, 1.7 Hz, 1H), 5.74 (q, J = 1.8 Hz, 1H), 4.20 (m, 2H), 3.72 (dd, J = 8.4, 4.9 Hz, 1H), 3.43 (dd, J = 10.1, 3.8 Hz, 1H), 3.35 (dd, J = 10.1, 7.1 Hz, 1H), 2.06 (m, 1H), 1.3−1.8 (m, 3H), 1.52 (s, 9H), 1.50 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer) δ 169.6, 154.1, 150.1, 149.4, 127.2, 82.9, 80.2, 72.3, 64.1, 61.9, 60.7, 59.7, 28.7 (3C), 28.0 (3C), 26.0 (3C), 25.7 (3C), 25.2, 22.8, 18.4, 18.0, −4.3, −4.8, −5.3, −5.5. Anal. Calcd for $C_{32}H_{60}N_2O_7Si_2$: C, 59.96; H, 9.43; N, 4.36. Found: C, 59.84; H, 9.36; N, 4.28.

Saturated Lactam 56. The reaction was carried out according to general procedure B, by starting with unsaturated lactam **54** (650 mg, 1.01 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactam **56** was obtained (640 mg, 98%) as a colorless oil: $[\alpha]^{20}_D$ +19.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50:50 mixture of rotamers) δ 4.60 (dt, J = 6.7, 4.2 Hz, 0.5H), 4.35 (m, 0.5H), 4.27 (m, 0.5H), 4.13 (m, 1H), 3.93 (m, 0.5H), 3.84 (dd, J = 8.0, 4.7 Hz, 0.5H), 3.78 (dd, J = 8.2, 4.6 Hz, 0.5H), 3.42 (m, 2H), 2.77 (ddd, J = 17.5, 11.4, 8.9 Hz, 0.5H), 2.60 (ddd, J = 17.4, 12.1, 8.6 Hz, 0.5H), 2.38 (m, 1H), 2.20 (m, 1H), 1.8−2.1 (m, 3H), 1.65 (m, 2H), 1.53 (s, 9 × 0.5H), 1.51 (s, 9 × 0.5H), 1.46 (s, 9 × 0.5H), 1.43 (s, 9 × 0.5H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, one rotamer) δ 173.4, 154.0, 150.1, 83.0, 80.1, 70.0, 64.1, 61.1, 59.7, 59.4, 31.5, 28.1 (3C), 28.0 (3C), 26.0 (3C), 25.8 (3C), 24.2, 22.9, 22.4, 18.4, 18.0, −4.4, −4.7, −5.4 (2C). Anal. Calcd for $C_{32}H_{62}N_2O_7Si_2$: C, 59.77; H, 9.72; N, 4.36. Found: C, 59.61; H, 9.80; N, 4.44.

Saturated Lactam 57. The reaction was carried out according to general procedure B, by starting with unsaturated lactam **55** (450 mg, 0.7 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactam **57** was obtained (433 mg, 96%) as a colorless oil: $[\alpha]^{20}_D$ +14.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer) δ 4.96 (bd, J = 9.4 Hz, 1H), 4.30 (m, 1H), 4.02 (bd, J = 6.2 Hz, 1H), 3.74 (m, 1H), 3.3−3.5 (m, 2H), 2.58 (m, 1H), 2.42 (ddd, J = 18.1, 10.7, 3.0 Hz, 1H), 2.1−2.3 (m, 2H), 1.5−1.8 (m, 4H), 1.53 (s, 9H), 1.50 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer) δ 174.4, 154.0, 150.8, 82.9, 80.0, 72.3, 64.1, 63.1, 60.2, 57.4, 31.9, 28.7 (3C), 28.0 (3C), 26.0 (3C), 25.8 (3C), 25.0, 24.8, 21.2, 18.4, 18.0, −4.3, −4.8, −5.4, −5.5. Anal. Calcd for $C_{32}H_{62}N_2O_7Si_2$: C, 59.77; H, 9.72; N, 4.36. Found: C, 59.65; H, 9.61; N, 4.30.

Nitrogen Subunit 58. *N*,*O*-Acetal **58** was prepared according to the two-step procedure used to trasform **52** into **53**, by starting with lactam **56** (620 mg, 0.96 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), methyl aminal **58** was obtained (445 mg, 70%, two steps) as a mixture of anomers and rotamers: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 5.16 (m, 1H), 4.68 (m, 1H), 4.3−4.5 (m, 2H), 3.84 (m, 1H), 3.3−3.6 (m, 2H), 3.26 (s, 3H), 1.5−2.0 (m, 8H), 1.45 (s, 18H), 0.86 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 154.3, 154.0, 89.9, 83.1, 80.0, 71.5, 64.1, 61.2, 59.5, 59.2, 55.0, 31.4, 28.1 (3C), 28.0 (3C), 26.0 (3C), 25.9 (3C), 24.0, 22.7, 22.4, 18.3, 18.1, −4.5, −4.7, −5.5 (2C). Anal. Calcd for $C_{33}H_{66}N_2O_7Si_2$: C, 60.14; H, 10.09; N, 4.25. Found: C, 60.27; H, 10.22; N, 4.16.

Nitrogen Subunit 59. *N*,*O*-Acetal **59** was prepared according to the two-step procedure to trasform **52** into **53**, by starting with lactam **57** (410 mg, 0.64 mmol). After flash chromatographic purification (hexanes/EtOAc 80:20), compound **59** was obtained (294 mg, 70%, two steps) as a mixture of anomers and rotamers: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 5.20 (m, 1H), 4.62 (m, 1H), 4.3−4.5 (m, 2H), 3.91 (m, 1H), 3.3−3.6 (m, 2H), 3.30 (s, 3H), 1.5−2.0 (m, 8H), 1.44 (s, 18H), 0.86 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 154.5, 154.1, 89.5, 83.0, 79.9, 72.1, 64.1, 61.6, 60.0, 57.3, 55.1, 31.7, 28.5 (3C), 28.0 (3C), 26.0 (3C), 25.9 (3C), 25.0, 24.5, 21.9, 18.4, 18.0, −4.3, −4.7, −5.5 (2C). Anal. Calcd for $C_{33}H_{66}N_2O_7Si_2$: C, 60.14; H, 10.09; N, 4.25. Found: C, 60.01; H, 10.15; N, 4.15.

Unsaturated Nitrogen Unit 60. The reaction was carried out according to general procedure C, using TBSOF (0.21 mL, 1.01 mmol) and methyl pyrrolidinose **58** (445 mg, 0.68 mmol). After flash chromatographic purification (hexanes/EtOAc 65:35), pure butenolide **60** (435 mg, 90%) was obtained as a white waxy solid: $[\alpha]^{20}_D$ +74.0 (*c* 0.6, $CHCl_3$); CD (CH_3OH, 1.1 × 10^{-4} M) $[\theta]_{217}$ +11932 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 5.8, 1.3 Hz, 1H), 5.97 (dd, J = 5.7, 1.9 Hz, 1H), 5.65 (dt, J = 3.6, 1.8 Hz, 1H), 4.3−4.4 (m, 2H), 3.6−3.9 (m, 3H), 3.3−3.5 (m, 2H), 1.5−2.2 (m, 8H), 1.47 (s, 9H),

1.42 (s, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 6H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 154.8, 153.8, 153.3, 120.6, 83.1, 80.0, 79.8, 72.1, 64.3, 61.3, 60.9, 60.5, 58.5, 29.6, 28.6 (3C), 28.2 (3C), 27.5, 25.9 (3C), 25.7 (3C), 23.9, 23.7, 18.4, 17.9, −4.3, −4.6, −5.4, −5.6. Anal. Calcd for $C_{36}H_{66}N_2O_8Si_2$: C, 60.81; H, 9.36; N, 3.94. Found: C, 60.87; H, 9.41; N, 3.82.

Unsaturated Nitrogen Unit 61. The reaction was carried out according to general procedure C, using TBSOF (0.14 mL, 0.66 mmol) and methyl pyrrolidinose **59** (290 mg, 0.44 mmol). After flash chromatographic purification (hexanes/EtOAc 65:35), pure butenolide **61** (307 mg, 98%) was obtained as a white waxy solid: $[\alpha]^{20}_D$ −29.0 (*c* 0.7, $CHCl_3$); CD (CH_3OH, 1.0 × 10^{-4} M) $[\theta]_{213}$ −17656 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 1H), 6.03 (m, 1H), 5.66 (m, 1H), 4.2−4.4 (m, 3H), 4.05 (m, 1H), 3.75 (m, 1H), 3.3−3.5 (m, 2H), 1.5−2.1 (m, 8H), 1.44 (s, 18H), 1.84 (s, 18H), 0.05 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 154.3, 153.6, 153.4, 120.9, 83.1, 80.3, 79.4, 72.4, 64.0, 62.6, 60.9 (2C), 58.4, 31.9, 29.2, 28.5 (3C), 28.3 (3C), 25.9 (3C), 25.7 (3C), 24.6, 22.2, 18.3, 17.9, −4.4, −4.8, −5.5, −5.6. Anal. Calcd for $C_{36}H_{66}N_2O_8Si_2$: C, 60.81; H, 9.36; N, 3.94. Found: C, 60.90; H, 9.48; N, 4.01.

Saturated Nitrogen Unit 62. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **60** (400 mg, 0.56 mmol). After flash chromatographic purification (hexanes/EtOAc 55:45), pure lactone **62** (380 mg, 95%) was obtained as a yellow transparent oil: $[\alpha]^{20}_D$ +37.1 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (td, J = 8.0, 4.4 Hz, 1H), 4.2−4.4 (m, 2H), 3.90 (m, 2H), 3.78 (m, 1H), 3.3−3.5 (m, 2H), 2.4−2.5 (m, 2H), 2.0−2.2 (m, 2H), 1.5−2.0 (m, 8H), 1.45 (s, 9H), 1.44 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 154.1, 152.0, 79.8, 79.7, 79.6, 72.3, 64.4, 61.3, 61.2, 60.3, 58.4, 30.1, 28.9, 28.7 (3C), 28.4 (3C), 27.2, 26.0 (3C), 25.8 (3C), 25.2, 23.8, 23.6, 18.0 (2C), −4.2, −4.6, −5.4, −5.5; MS (CI, CH_4) m/z 713 $[M + H]^+$. Anal. Calcd for $C_{36}H_{68}N_2O_8Si_2$: C, 60.63; H, 9.61; N, 3.93. Found: C, 60.51; H, 9.49; N, 3.86.

Saturated Nitrogen Unit 63. The reaction was carried out according to general procedure B, by starting with unsaturated lactone **61** (290 mg, 0.41 mmol). After flash chromatographic purification (hexanes/EtOAc 60:40), pure lactone **63** (256 mg, 88%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (m, 1H), 4.0−4.4 (m, 4H), 3.76 (m, 1H), 3.3−3.5 (m, 2H), 2.48 (m, 2H), 1.5−2.2 (m, 10H), 1.45 (s, 18H), 0.85 (s, 18H), 0.05 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 152.5, 151.9, 81.6, 81.4, 79.5, 72.9, 65.6, 63.1, 61.2, 60.5, 59.6, 30.7, 29.3, 28.5 (3C), 28.2 (3C), 28.0, 26.1 (3C), 25.8 (3C), 25.4, 24.1, 23.4, 18.2, 18.1, −4.5 (2C), −5.2, −5.4; MS (CI, CH_4) m/z 713 $[M + H]^+$. Anal. Calcd for $C_{36}H_{68}N_2O_8Si_2$: C, 60.63; H, 9.61; N, 3.93. Found: C, 60.68; H, 9.54; N, 3.87.

Unsaturated Thiolactone 64. Thiolactone **64** was prepared according to the procedure described for **23**, by employing 2.71 g (12.6 mmol) of TBSOT, 2.13 g (16.4 mmol) of D-glyceraldehyde **22** and 1.55 mL (12.6 mmol) of BF_3 etherate in CH_2Cl_2 (50 mL) at −80 °C for 4 h. After flash chromatographic purification (hexanes/EtOAc 50:50), thiolactone **64** was recovered in 70% yield (2.0 g), accompanied by a minor amount of its C4-epimer. Compound **64**: an oil; $[\alpha]^{20}_D$ +67.0 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, J = 6.1, 2.9 Hz, 1H), 6.31 (dd, J = 6.1, 1.9 Hz, 1H), 4.91 (m, 1H), 3.8−4.2 (m, 4H), 2.74 (bs, 1H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 156.7, 133.4, 110.0, 78.1, 72.9, 67.1, 58.4, 26.7, 24.9. Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13. Found: C, 52.24; H, 6.01.

Thiolactone 65. The above hydrogenation procedure to transform **23** into **24** was adopted, using unsaturated thiolactone **64** (2.0 g, 8.7 mmol), 10% Pd on carbon (200 mg), and NaOAc (70 mg) in dry THF (45 mL). After 24 h, the hydrogen was evacuated and the catalyst was filtered on a Celite pad and thoroughly washed with methanol. The filtrates were concentrated and subjected to flash chromatographic purification (hexanes/EtOAc 50:50) giving a saturated thiolactone intermediate (1.8 g, 90% yield) as white crystals. This intermediate (1.8 g, 7.8 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) and sequentially treated with 2,6-lutidine (1.45 mL, 12.5 mmol) and TBSOTf (2.5 mL, 10.9 mmol) under stirring at room temperature. After 4 h, the reaction mixture was quenched with 5% citric acid, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum, to afford a crude residue that was purified by flash chromatography (hexanes/EtOAc 70:30). Protected thiolactone **65** was obtained (2.16 g, 80%, corresponding to a 72% overall yield from **64**) as a golden oil: $[\alpha]^{20}_D$ −57.3 (*c* 3.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (ddd, J = 9.9, 5.7, 4.8 Hz, 1H), 4.02 (m, 2H), 3.93 (dd, J = 5.4, 4.8 Hz, 1H), 3.84 (m, 1H), 2.61 (m, 2H), 2.29 (m, 1H), 2.09 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 109.2, 77.8, 74.7, 66.4, 54.9, 42.3, 28.5, 26.5, 25.8 (3 C), 25.1, 18.3, −3.6, −3.9. Anal. Calcd for $C_{16}H_{30}O_4SSi$: C, 55.45; H, 8.73. Found: C, 55.39; H, 8.88.

Thiolactone 66. Protected thiolactone **65** (2.0 g, 5.77 mmol) was dissolved in 7 mL of 80% aqueous acetic acid, and the resulting mixture was warmed to 50 °C and allowed to stir for 24 h. The reaction mixture was concentrated under vacuum, furnishing a crude residue, which was purified by flash chromatography eluting with ethyl acetate. A white crystalline diol intermediate was obtained (1.5 g) in 85% isolated yield. To a stirred solution of this pure diol (1.5 g, 4.9 mmol) in CH_2Cl_2 (35 mL) were added chromatography grade SiO_2 (15 g) and a 0.65 M aqueous $NaIO_4$ solution (15 mL, 9.8 mmol). The resulting slurry was vigorously stirred at room temperature for 1 h, after which time the reaction mixture was filtered under suction and the silica thoroughly washed with CH_2Cl_2. The filtrates were evaporated, affording a crude aldehyde intermediate (1.08 g, 80%) as a yellow oil. A stirred solution of this aldehyde (1.08 g, 3.92 mmol) in 95% ethanol (50 mL) under nitrogen atmosphere was cooled to −30 °C and treated with $NaBH_4$ (74 mg, 1.96 mmol). After 1 h, the reaction mixture was quenched by addition of 5% aqueous citric acid solution until neutral. The mixture was extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum, furnishing a crude residue that was purified by flash chromatography (hexanes/EtOAc 60:40). A pure alcohol intermediate was recovered in 88% yield as white crystals: mp 63−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (ddd, J = 9.3, 7.4, 6.0 Hz, 1H), 3.81 (dt, J = 7.2, 3.6 Hz, 1H), 3.63 (m, 2H), 2.62 (ddd, J = 16.9, 8.2, 4.4 Hz, 1H), 2.54 (ddd, J = 17.1, 10.1, 6.7 Hz, 1H), 2.28 (dddd, J = 12.7, 6.8, 5.9, 4.2 Hz, 1H), 2.03 (bs, 1H), 1.91 (dddd, J = 12.7, 10.4, 9.4, 8.2 Hz, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). A stirred solution of the carbinol intermediate (950 mg, 3.44 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled with an ice-bath and sequentially treated with 2,6-lutidine (0.64 mL, 5.5 mmol) and TBSOTf (1.11 mL, 4.82 mmol), under nitrogen atmosphere. After being stirred at 0 °C for 45 min, the reaction mixture was quenched with 5% aqueous citric acid and extracted with CH_2Cl_2. The combined orgainc layers were dried, filtered, and concentrated under vacuum, providing a crude residue that was purified by flash chromatography (hexanes/EtOAc 80:20). Pure thiolactone **66** was obtained (1.29 g) in 96% yield (57% overall yield from **65**) as white crystals: mp 44−45 °C; $[\alpha]^{20}_D$ −60.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (dt, J = 8.2, 5.8 Hz, 1H), 3.80 (dt, J = 6.7, 4.8 Hz, 1H), 3.61 (dd, J = 10.4, 4.3 Hz, 1H), 3.48 (dd, J = 10.3, 6.7 Hz, 1H), 2.61 (ddd, J = 16.9, 7.8, 5.1 Hz, 1H), 2.50 (ddd, J = 16.9, 9.4, 7.5 Hz, 1H), 2.27 (dddd, J = 13.3, 7.3, 6.3, 5.1 Hz, 1H), 2.03 (dddd, J = 12.8, 9.4, 9.4, 8.0 Hz, 1H), 0.85 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 75.6, 65.8, 54.4, 42.2, 28.2, 25.8 (3C), 25.7 (3C), 18.1, 17.9, −4.2, −4.8, −5.6 (2C). Anal. Calcd for $C_{18}H_{38}O_3SSi_2$: C, 55.33; H, 9.80. Found: C, 55.26; H, 9.91.

Sulfur Precursor 67. $NaBH_4$ (61 mg, 1.61 mmol) was added to a stirred solution of thiolactone **66** (1.25 g, 3.21 mmol) in methanol (50 mL) cooled at −15 °C. After being stirred at the same temperature under nitrogen atmosphere for 1 h, five additional portions of $NaBH_4$ (5 × 61 mg, 5 × 1.61 mmol) were added over a period of 6 h. The reaction mixture was quenched at −15 °C with 5% aqueous citric acid and water until neutral pH was reached, and a spatula tip of sodium and potassium tartrate was added. Once warmed to room temperature, the

mixture was extracted with CH_2Cl_2. The organic layers were dried and concentrated, providing a yellow crude residue that was subjected to flash chromatographic purification (hexanes/EtOAc 85:15). A pure thiolactol intermediate was obtained (904 mg, 2.31 mmol, 72%), which was readily dissolved in dry CH_2Cl_2 (40 mL) under argon atmosphere, and sequentially treated with pyridine (0.4 mL, 4.62 mmol), acetic anhydride (0.65 mL, 6.93 mmol), and DMAP (14 mg, 0.12 mmol) at room temperature. After being stirred for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The yellowish crude extract was purified by flash chromatography (hexanes/EtOAc 85:15) to provide acetyl thiolactol **67** (985 mg, 98%) as a golden yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 6.13 (dd, J = 4.6, 2.2 Hz, 0.5H), 6.06 (d, J = 3.2 Hz, 0.5H), 4.17 (dt, J = 8.3, 6.0 Hz, 0.5H), 3.81 (dt, J = 6.7, 5.2 Hz, 0.5H), 3.6−3.8 (m, 1H), 3.59 (dd, J = 10.4, 4.5 Hz, 0.5H), 3.45−3.55 (m, 3 × 0.5H), 2.61 (ddd, J = 16.9, 9.1, 5.1 Hz, 0.5H), 2.52 (ddd, J = 16.9, 9.4, 7.5 Hz, 0.5H), 1.8−2.3 (m, 3H), 0.87 (s, 9 × 0.5H), 0.86 (s, 9 × 0.5H), 0.85 (s, 9 × 0.5H), 0.84 (s, 9 × 0.5H), 0.08 (s, 3 × 0.5H), 0.07 (s, 3 × 0.5H), 0.06 (s, 3 × 0.5H), 0.05 (s, 3 × 0.5H), 0.04 (s, 3 × 0.5H), 0.03 (s, 3 × 0.5H), 0.02 (s, 3 × 0.5H), 0.01 (s, 3 × 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 170.2, 82.9, 75.5 and 75.3, 66.6 and 65.9, 54.6 and 53.1, 42.3 and 41.7, 30.2 and 28.4, 25.9 (3C), 25.7 (3C), 21.3, 19.1, 18.2, −4.1, −4.4, −4.7, −5.4. Anal. Calcd for $C_{20}H_{42}O_4SSi_2$: C, 55.25; H, 9.74. Found: C, 55.38; H, 9.82.

Unsaturated Thiolactones 68 and 69. The reaction was carried out according to general procedure A, using acetyl lactol **67** (985 mg, 2.27 mmol) and TBSOT (583 mg, 2.72 mmol). After flash chromatographic purification (hexanes/EtOAc/Et_2O 75:10:15), pure thiobutenolides **68** (350 mg, 27%) and **69** (685 mg, 53%) were obtained.

68: an oil; CD (CH_3OH, 1.0×10^{-4} M) $[\theta]_{214}$ +4350 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 6.2, 2.6 Hz, 1H), 6.32 (dd, J = 6.2, 1.9 Hz, 1H), 4.65 (dt, J = 6.2, 2.1 Hz, 1H), 3.6−3.8 (m, 3H), 3.5−3.6 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), 1.6−1.9 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 155.7, 133.8, 76.3, 66.7, 59.1, 54.5, 50.5, 33.8, 33.2, 25.9 (3C), 25.6 (3C), 18.3, 18.1, −3.6, −4.0, −4.6, −5.5. Anal. Calcd for $C_{22}H_{42}O_3S_2Si_2$: C, 55.65; H, 8.92. Found: C, 55.50; H, 8.99.

69: an oil; CD (CH_3OH, 1.0×10^{-4} M) $[\theta]_{230}$ −4275 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 6.1, 2.6 Hz, 1H), 6.27 (dd, J = 6.0, 1.8 Hz, 1H), 4.45 (dt, J = 9.3, 2.3 Hz, 1H), 3.77 (m, 1H), 3.65 (m, 2H), 3.4−3.6 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), 1.6−1.9 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 158.0, 132.9, 76.3, 66.6, 60.6, 54.6, 51.6, 36.9, 32.5, 25.9 (3C), 25.7 (3C), 18.2, 18.1, −4.0, −4.6, −5.4, −5.5. Anal. Calcd for $C_{22}H_{42}O_3S_2Si_2$: C, 55.65; H, 8.92. Found: C, 55.70; H, 9.03.

Saturated Thiolactone 70. The reaction was carried out according to general procedure B, by starting with thiobutenolide **68** (350 mg, 0.73 mmol). After flash chromatographic purification (hexanes/EtOAc/Et_2O 80:10:10), pure thiolactone **70** was obtained (286 mg, 82%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (td, J = 8.1, 5.8 Hz, 1H), 3.55−3.70 (m, 3H), 3.45−3.55 (m, 2H), 2.58 (m, 1H), 2.30 (m, 1H), 1.8−2.2 (m, 3H), 1.5−1.8 (m, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 76.4, 66.8, 56.5, 54.0, 53.0, 41.2, 35.6, 32.9, 32.5, 25.9 (3C), 25.6 (3C), 18.3, 18.1, −4.0, −4.3, −4.6, −5.4. Anal. Calcd for $C_{22}H_{44}O_3S_2Si_2$: C, 55.41; H, 9.30. Found: C, 55.37; H, 9.42.

Saturated Thiolactone 71. The reaction was carried out according to general procedure B, by starting with thiobutenolide **69** (685 mg, 1.44 mmol). After flash chromatographic purification (hexanes/EtOAc/Et_2O 80:10:10), pure thiolactone **71** was obtained (535 mg, 78%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (ddd, J = 9.9, 8.0, 5.7 Hz, 1H), 3.72 (m, 1H), 3.63 (m, 1H), 3.4−3.6 (m, 3H), 2.57 (m, 1H), 2.28 (m, 1H), 1.9−2.2 (m, 3H), 1.6−1.8 (m, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 76.4, 66.7, 56.9, 54.2, 53.3, 41.7, 37.3, 32.8, 32.0, 25.9 (3C), 25.5 (3C), 18.3, 18.1, −4.0, −4.6, −5.0, −5.5. Anal. Calcd for $C_{22}H_{44}O_3S_2Si_2$: C, 55.41; H, 9.30. Found: C, 55.29; H, 9.21.

Sulfur Subunit 72. Acetyl thiolactol **72** was prepared according to the two-step procedure utilized to transform **66** into **67**, by starting with thiolactone **70** (286 mg, 0.6 mmol). After flash chromatographic purification (hexanes/EtOAc 85:15), acetyl thiolactol **72** was obtained (205 mg, 66%, two steps) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 6.14 (dd, J = 4.7, 2.2 Hz, 0.5H), 6.08 (bd, J = 4.0 Hz, 0.5H), 3.61 (m, 3H), 3.50 (m, 3H), 2.22 (m, 2H), 1.9−2.1 (m, 2H), 2.01 (s, 3H), 1.6−1.8 (m, 2H), 1.5−1.6 (m, 2H), 0.87 (s, 18H), 0.08 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 170.2, 82.8, 76.1 and 75.9, 66.7 and 66.0, 56.4 and 56.2, 54.2 and 54.0, 53.1 and 52.8, 41.0 and 39.7, 34.8 and 33.9, 32.8 and 31.7, 32.5 and 31.0, 25.8 (3C), 25.7 (3C), 21.2, 18.3, 18.2, −4.2, −4.4, −4.7, −5.3. Anal. Calcd for $C_{24}H_{48}O_4S_2Si_2$: C, 55.34; H, 9.29. Found: C, 55.27; H, 9.21.

Sulfur Subunit 73. Acetyl thiolactol **73** was prepared according to the two-step procedure utilized to transform **66** into **67**, by starting with thiolactone **71** (535 mg, 1.12 mmol). After flash chromatographic purification (hexanes/EtOAc 85:15), acetyl thiolactol **73** was obtained (409 mg, 70%, two steps) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 6.11 (m, 1H), 3.6−3.9 (m, 3H), 3.3−3.6 (m, 3H), 2.29 (m, 2H), 1.9−2.2 (m, 2H), 2.03 (s, 3H), 1.5−1.9 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 anomeric mixture) δ 170.3, 83.0, 76.3 and 76.1, 66.6 and 65.9, 56.8 and 56.5, 54.4 and 54.0, 53.3 and 53.1, 41.9 and 41.5, 36.9 and 35.4, 32.8 and 32.1, 32.0 and 29.4, 25.9 (3C), 25.7 (3C), 21.4, 18.3, 18.1, −4.0, −4.6, −5.0, −5.5. Anal. Calcd for $C_{24}H_{48}O_4S_2Si_2$: C, 55.34; H, 9.29. Found: C, 55.20; H, 9.39.

Unsaturated Sulfur Units 74 and 75. The reaction was carried out according to general procedure A, using TBSOF (96 μL, 0.46 mmol), acetyl thiolactol **72** (200 mg, 0.38 mmol), and TBSOTf (53 μL, 0.23 mmol) and BF_3 etherate (30 μL, 0.23 mmol) as the Lewis acid promoter mixture. After flash chromatographic purification (hexanes/EtOAc 75:25), pure butenolides **74** (54 mg, 26%) and **75** (80 mg 39%) were obtained.

74: an oil; CD (CH_3OH, 0.5×10^{-4} M) $[\theta]_{211}$ +9170 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 5.7, 1.6 Hz, 1H), 6.17 (dd, J = 5.8, 1.9 Hz, 1H), 5.10 (dt, J = 6.0, 1.9 Hz, 1H), 3.5−3.9 (m, 7H), 1.6−2.3 (m, 8H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 155.8, 133.5, 84.6, 76.3, 66.4, 54.5, 54.1, 54.0, 53.9, 32.7, 32.0, 29.4, 28.7, 26.0 (6C), 18.2, 18.0, −4.2, −4.4, −4.7, −5.3; HRMS (CI, CH_4) m/z 545.2594 (MH, 545.2611 calcd for $C_{26}H_{49}O_4S_2Si_2$).

75: an oil; CD (CH_3OH, 2.0×10^{-4} M) $[\theta]_{239}$ −7002 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 5.7, 1.6 Hz, 1H), 6.11 (dd, J = 5.8, 2.0 Hz, 1H), 4.80 (dt, J = 9.8, 1.9 Hz, 1H), 3.4−3.8 (m, 7H), 1.6−2.4 (m, 8H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 157.8, 133.0, 85.2, 76.1, 66.6, 54.6, 53.9 (2C), 53.7, 32.8, 32.1, 29.7, 28.5, 26.2 (3C), 25.9 (3C), 18.2, 18.1, −4.3, −4.6, −5.4 (2C); HRMS (CI, CH_4) m/z 545.2599 (MH, 545.2611 calcd for $C_{26}H_{49}O_4S_2Si_2$).

Unsaturated Sulfur Units 76 and 77. The reaction was carried out according to general procedure A, using TBSOF (190 μL, 0.92 mmol), acetyl thiolactol **73** (400 mg, 0.77 mmol), and TBSOTf (105 μL, 0.46 mmol) and BF_3 etherate (60 μL, 0.46 mmol) as the Lewis acid promoter mixture. After flash chromatographic purification (hexanes/EtOAc 75:25), pure butenolides **76** (113 mg, 27%) and **77** (172 mg, 41%) were obtained.

76: an oil; CD (CH_3OH, 0.5×10^{-5} M) $[\theta]_{240}$ −750 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 5.9, 1.6 Hz, 1H), 6.17 (dd, J = 5.7, 1.7 Hz, 1H), 5.10 (dt, J = 5.2, 1.7 Hz, 1H), 3.4−3.8 (m, 7H), 2.1−2.4 (m, 2H), 1.9−2.1 (m, 3H), 1.4−1.7 (m, 3H), 0.88 (s, 18H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 155.7, 133.7, 84.7, 76.3, 66.1, 54.5, 54.0, 53.8, 53.6, 32.9, 29.9, 29.0, 28.2, 26.1

(3C), 26.0 (3C), 18.2, 18.1, −4.5, −4.6, −5.3, −5.4; HRMS (CI, CH_4) *m*/*z* 545.2632 (MH, 545.2611 calcd for $C_{26}H_{49}O_4S_2Si_2$).

77: an oil; CD (CH_3OH, 1.1×10^{-4} M) $[\theta]_{220}$ +3520 deg cm^2 dmol^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J = 5.5, 1.5 Hz, 1H), 6.12 (dd, J = 5.6, 2.1 Hz, 1H), 4.81 (dt, J = 9.6, 2.0 Hz, 1H), 3.4−3.8 (m, 7H), 2.1−2.4 (m, 2H), 1.95−2.10 (m, 3H), 1.6−1.9 (m, 3H), 0.90 (s, 18H), 0.08 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 157.6, 132.9, 85.1, 76.0, 66.5, 54.7, 53.8, 53.7, 53.4, 32.7, 29.8, 29.2, 28.4, 25.9 (3C), 25.8 (3C), 18.3, 18.1, −4.2, −4.5, −5.1, −5.2; HRMS (CI, CH_4) *m*/*z* 545.2587 (MH, 545.2611 calcd for $C_{26}H_{49}O_4S_2Si_2$).

Saturated Sulfur Unit 78. The reaction was carried out according to general procedure B, by starting with **74** (50 mg, 0.09 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactone **78** (34 mg, 68%) was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (m, 1H), 3.6−3.9 (m, 7H), 2.2−2.8 (m, 4H), 1.6−2.2 (m, 8H), 0.86 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 81.5, 75.9, 66.0, 54.3, 54.2 (2C), 54.1, 37.0, 34.1, 31.0, 29.7, 28.5, 28.2, 26.0 (6C), 18.2, 18.0, −4.5 (2C), −5.0, −5.2; MS (CI, CH_4) *m*/*z* 547 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_4S_2Si_2$: C, 57.09; H, 9.21. Found: C, 56.94; H, 9.33.

Saturated Sulfur Unit 79. The reaction was carried out according to general procedure B, by starting with **75** (80 mg, 0.15 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactone **79** (58 mg, 72%) was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (td, J = 7.0, 2.1 Hz, 1H), 3.61 (m, 2H), 3.3−3.5 (m, 5H), 2.1−2.5 (m, 2H), 1.9−2.1 (m, 2H), 1.5−2.0 (m, 8H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 81.5, 76.0, 66.3, 54.6, 53.9, 53.6, 52.9, 37.9, 34.1, 32.5, 32.2, 30.1, 28.6, 26.2 (3C), 26.0 (3C), 18.2, 18.1, −4.1, −4.6 (2C), −5.0; MS (CI, CH_4) *m*/*z* 547 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_4S_2Si_2$: C, 57.09; H, 9.21. Found: C, 57.13; H, 9.15.

Saturated Sulfur Unit 80. The reaction was carried out according to general procedure B, by starting with **76** (100 mg, 0.18 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactone **80** (65 mg, 65%) was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (m, 1H), 3.5−3.9 (m, 7H), 2.1−2.7 (m, 4H), 1.5−2.1 (m, 8H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 82.0, 76.0, 66.1, 54.5, 54.3, 54.2, 53.4, 37.1, 34.5, 31.9, 31.7, 28.6, 28.3, 26.0 (3C), 25.9 (3C), 18.2, 18.1, −4.3, −4.6, −5.0, −5.3; MS (CI, CH_4) *m*/*z* 547 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_4S_2Si_2$: C, 57.09; H, 9.21. Found: C, 57.00; H, 9.17.

Saturated Sulfur Unit 81. The reaction was carried out according to general procedure B, by starting with **77** (150 mg, 0.27 mmol). After flash chromatographic purification (hexanes/EtOAc 75:25), pure lactone **81** (105 mg, 70%) was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (td, J = 6.7, 1.8 Hz, 1H), 3.64 (m, 2H), 3.49 (m, 3H), 3.36 (m, 2H), 2.2−2.4 (m, 2H), 1.9−2.1 (m, 2H), 1.4−1.9 (m, 8H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 81.0, 75.4, 67.0, 54.4, 54.3, 54.1, 53.6, 37.3, 34.0, 32.7, 31.9, 29.2, 28.4, 25.9 (3C), 25.8 (3C), 18.3, 18.1, −4.2, −4.5, −5.1, −5.2; MS (CI, CH_4) *m*/*z* 547 [M + H]$^+$. Anal. Calcd for $C_{26}H_{50}O_4S_2Si_2$: C, 57.09; H, 9.21. Found: C, 57.18; H, 9.18.

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Supporting Information Available: General experimental details and materials, as well as complete experimental procedures and characterization data for compounds **1**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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