Reprinted from the Journal of the American Chemical Society, 1995, *117*.

Total Synthesis of Brevetoxin B. 2. Second Generation Strategies and Construction of the Dioxepane Region [DEFG]

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Received March 2, 1995®

Abstract: The second generation strategy for the total synthesis of brevetoxin B (**1**) is presented. According to this strategy, the heptacyclic [ABCDEFG] phosphonium iodide **4** and the tricyclic [IJK] aldehyde **3** were defined as the precursors for the brevetoxin B skeleton. The Yamaguchi lactonization was successfully applied for the formation of the [EFG] and [DEFG] lactones (**15** → **7**) and (**29** → **6**), respectively. The required appendage on ring [E] was efficiently introduced via a Murai coupling, involving addition of a higher order organocuprate derived from iodide **20** to the lactone-derived enol triflate **16** (**16** → **25**). The minor epimer of the resulting product **6**β was then converted to the desired isomer **6**α via hydrogenation using an Ir(I) catalyst. A number of approaches were considered for further elaboration of lactone **6**. Among them a convienient Cr/Ni-promoted coupling reaction was developed and applied to the introduction of the side chain on ring D. The scope and generality of this reaction was examined with a variety of aldehydes (e.g., **39**, **59**, and **62**). Construction of **38** was thus achieved from vinyl triflate **36** and the ring B aldehyde **39**. However, the projected intramolecular Michael addition (**41** → **42**) and reductive hydroxy ketone cyclization (**47** → **48**) failed to yield ring C. Fetizon cyclization afforded the pentacyclic lactone [CDEFG] (**51** → **52**), which resisted further useful functionalization. Using the more elaborate aldehyde **62**, the Cr/Ni coupling reaction afforded allylic alcohol **64**, which then served as a precursor to the pentacyclic lactol **80**. The latter compound also resisted advancement to more elaborate intermediates, leading to abandonment of this approach and the formulation of a new strategy.

Introduction

In the preceding paper,[1] we discussed first generation strategies toward the total synthesis of brevetoxin B (**1**, Scheme 1) and described the synthesis of several key intermediates required for a projected construction of the target molecule. The successes and failures in that campaign yielded information that led us to design a second generation of strategies toward brevetoxin B (**1**). In this article, we describe these new strategies which led to the successful construction of the DEFG region, containing the dioxepane system of the molecule and to the formulation of the third and final approach to brevetoxin B (**1**).[2]

Second Retrosynthetic Analysis and Strategy

Our original strategy toward brevetoxin B (**1**) postulated an optimally convergent route in which three equally complex fragments[3a−c] were to be constructed, coupled, and elaborated to form the oxocene and dioxepane regions of the molecule.[1] The effectiveness and reliability of the hydroxy dithioketal cyclization in forming the oxocene system coupled with the difficulties associated with the construction of the challenging dioxepane framework forced us to adopt the reverse approach in which the dioxepane region would be secured first. According to this newly evolved strategy, which was based on the retrosynthetic analysis of Scheme 1, the final ring closure would involve *retro* oxocene formation (**1** → **2**) defining hydroxy dithioketal **2** as a key advanced intermediate. The latter compound (**2**) was projected to be derived from aldehyde **3** and phosphonium salt **4** via a Wittig coupling reaction. Attempting to preserve as much convergency as possible in the scheme, intermediate **4** was disconnected as indicated on the structure, revealing fragments **5** (ring system B) and **6** (ring system DEFG) as potential precursors. Both intermediates **5** and **6** were projected to arise from 2-deoxy-D-ribose (**9**). The latter fragment (**6**) would require, according to this plan, the intermediacy of tricycle **7** and bicycle **8**. Both lactones **6** and **7** are disconnected by *retro* lactonization reactions, whereas bicyclic system **8** could be disconnected sequentially by two *retro* hydroxy epoxide cyclizations as shown in Scheme 1. Below, we describe first the construction of the DEFG lactone **6**, and then a number of attempts to elaborate compound **6** further along the path toward brevetoxin B (**1**).

Construction of the DEFG Lactone 6

The plan for the construction of the DEFG lactone **6** required the synthesis and elaboration of the EFG tricyclic lactone **7** (Scheme 1). The latter compound (**7**) was prepared from the previously reported FG ring system **8**[4] as shown in Scheme 2. Thus, Swern oxidation of **8** led to aldehyde **10** (100% yield) which was olefinated with the appropriate ylide (TBSO-

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® Abstract published in *Advance ACS Abstracts,* October 1, 1995.

(1) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227−10238.

(2) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252−10263.

(3) (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6676. (c) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682.

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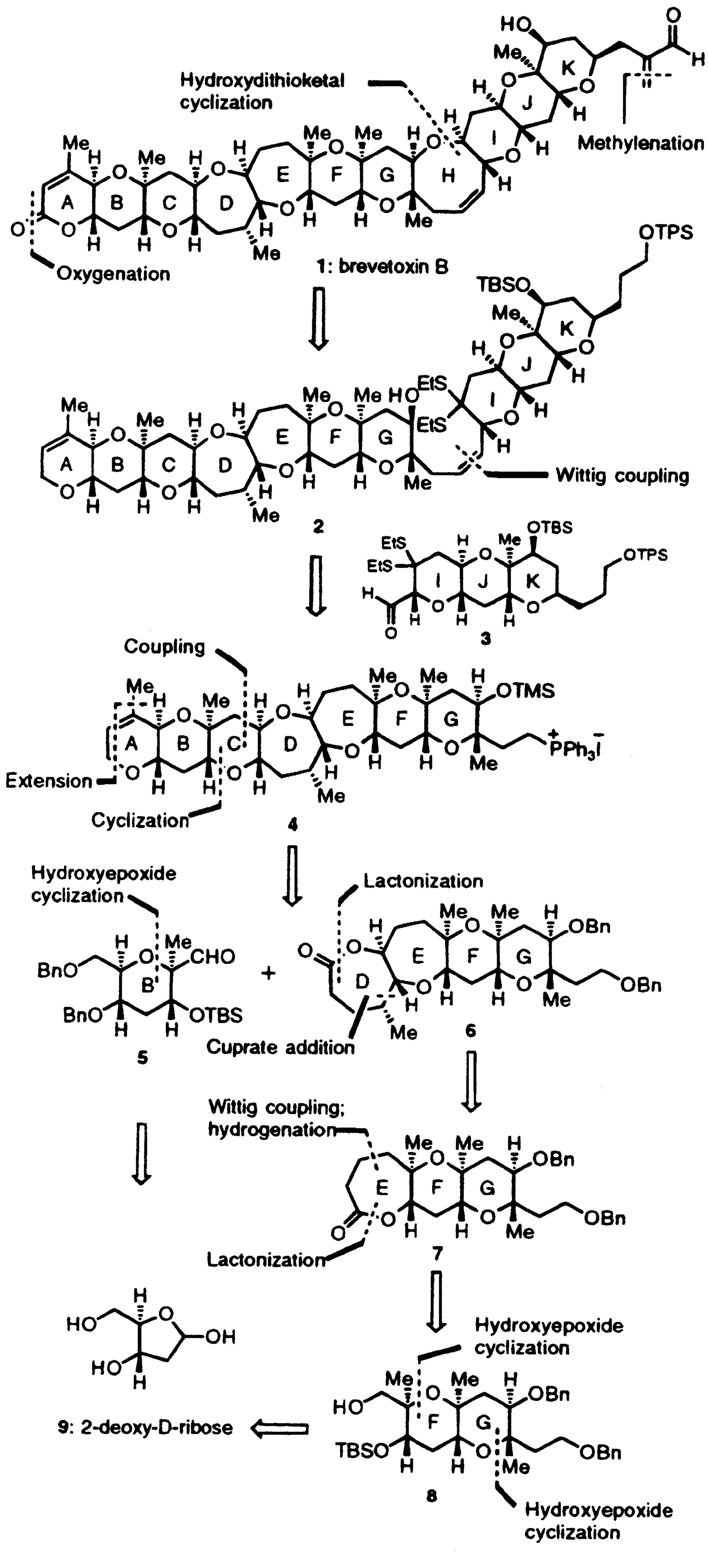
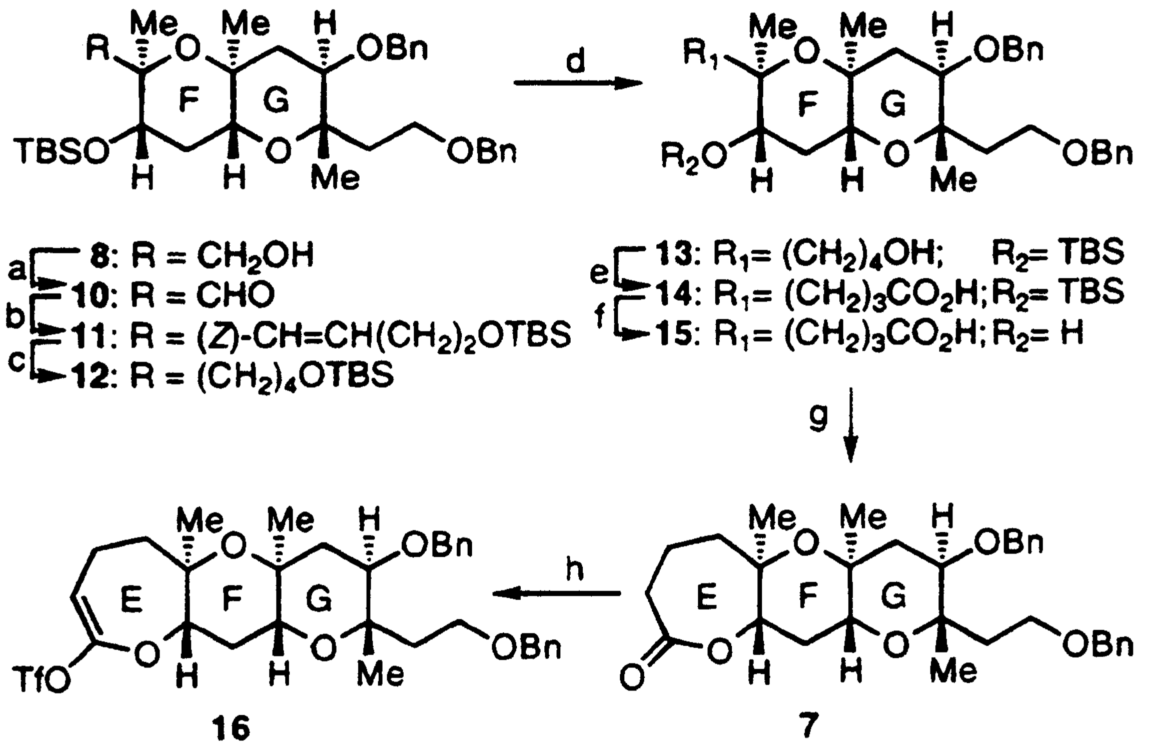
Scheme 1. Retrosynthetic Analysis and Strategic Bond Disconnections of Brevetoxin B (**1**): Second Generation Approach



$(CH_2)_3PPh_3^+I^-$, NaHMDS, Scheme 2) to afford the (*Z*)-olefin **11** in 99% yield. Catalytic hydrogenation of the double bond in **11** using 10% Pd/C and Na_2CO_3 gave the saturated compound **12** in 100% yield, while exposure of the latter compound (**12**) to CSA in $CH_3OH-CH_2Cl_2$ (1:1) at 0 °C allowed selective desilylation of the primary hydroxyl group to afford monosilyl ether **13** in 97% yield. Sequential oxidation of **13** with $COCl_2-DMSO-Et_3N$ and $NaClO_2$ led to the formation of carboxylic acid **14** in 97% overall yield. The secondary alcohol in **14** was then liberated with TBAF in THF at 65 °C to afford hydroxy acid **15** in 91% yield. The latter compound (**15**) was lactonized using the Yamaguchi protocol[5] [2,4,6-$Cl_3C_6H_2COCl$, Et_3N; DMAP, 80 °C] furnishing, in 90% yield, the desired tricyclic lactone **7**. In preparation for the anticipated Murai coupling,[6] lactone **7** was converted to its enol triflate **16** via enolization (LiHMDS) followed by quenching with $PhNTf_2$ (93% yield)[7] (Scheme 2).

Scheme 2[a] Construction of the EFG Ring System **16**



[a] Reagents and conditions: (a) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 5.0 equiv of Et_3N, 30 min, 100%; (b) 2.0 equiv of $TBSO(CH_2)_3PPh_3^+I^-$, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then **8**, 0.5 h, 99%; (c) H_2, 10 wt % of Pd/C (10%), 0.1 equiv of Na_2CO_3, EtOAc, 25 °C, 12 h, 100%; (d) 1.0 equiv of CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 1 h, 97%; (e) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 7.0 equiv of Et_3N, 0.5 h; 1.5 equiv of $NaClO_2$, 2.0 equiv of NaH_2PO_4, 2.0 equiv of 2-methyl-2-butene, *t*-BuOH:H_2O (2:1), 25 °C, 1 h, 97%; (f) 5.0 equiv of TBAF, THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 3 h, 90%; (h) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, −78 °C, 2 h, then 1.5 equiv of $PhNTf_2$, $-78 \rightarrow 25$ °C, 93%.

The next task was to attach an appropriate appendage on ring E in order to allow the formation of the D ring. To this end, iodides **21**[8] and **22**[9] (both racemic, Table 1) were converted to their lithio derivatives by halogen−metal exchange (*t*-BuLi) and thence to the higher order cuprates RLi/Cu(2-thienyl)CNLi[10] which coupled smoothly with the lactone-derived enol triflate **16** to afford extended oxepenes **23** (50% yield, *ca.* 1:1.4 ratio of epimers in favor of the wrong epimer at C*) and **24** (49% yield, *ca.* 1:1.5 ratio of epimers at C*), respectively (see Table 1, entries 1 and 2). In view of the lack of stereoselectivity in these coupling reactions the orthoester iodide **20** (Table 1 and Scheme 3) was prepared[11] and utilized in the hope of improving the stereochemical outcome of the process. The synthesis of **20** proceeded in a straightforward manner from γ-valerolactone **17** as outlined in Scheme 3. Its coupling to enol triflate **16** via the higher order cuprate reagent proved quite superior to the two previous cases, leading to **25** with an 85% total yield and with *ca.* 2.4:1 stereoselectivity in favor of the desired stereoisomer at C* (see Table 1). It should be noted at this point

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(4) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.

(5) Inanaga, J.; Hirata, K.; Saiki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(6) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 131. Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761.

(7) Jarowicki, K.; Kocienski, P.; Marczak, S.; Willson, T. *Tetrahedron Lett.* **1990**, *31*, 3433.

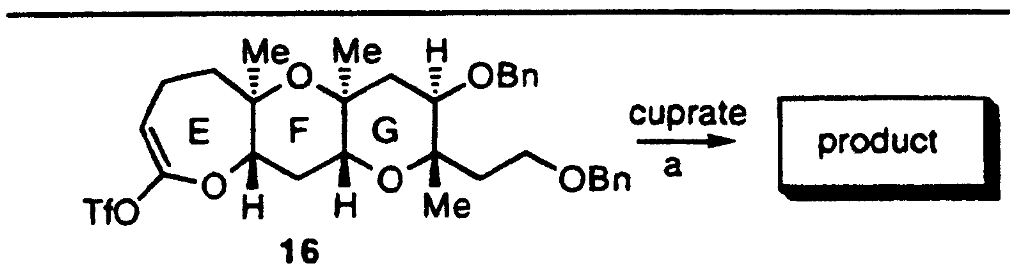
(8) Iodide **21** was prepared from 1,4-butanediol in four steps: (a) 1.0 equiv of NaH, 1.0 equiv of TBSCl, THF, 25 °C; (b) 1.5 equiv of $(ClCO)_2$, 2.0 equiv of DMSO, −78 °C, then Et_3N; (c) 1.2 equiv of MeMgCl, $-78 \rightarrow 25$ °C; (d) 1.4 equiv of I_2, 1.0 equiv of PPh_3, 1.2 equiv of imidazole, benzene, 25 °C (64% overall yield).

(9) Iodide **22** was prepared from 1,4-butanediol in seven steps: (a−d) as for **21** (see ref 8); (e) 1.0 equiv of CSA, CH_2Cl_2/MeOH (1:1), 0 °C; (f) 3.0 equiv of SO_3·pyridine, CH_2Cl_2/DMSO (1:1), 10 equiv of Et_3N, −30 °C; (g) 2.0 equiv of 1,2-ethanediol, TsOH catalyst, benzene, 25 °C (55% over 3 steps).

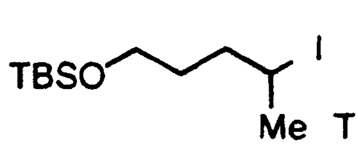
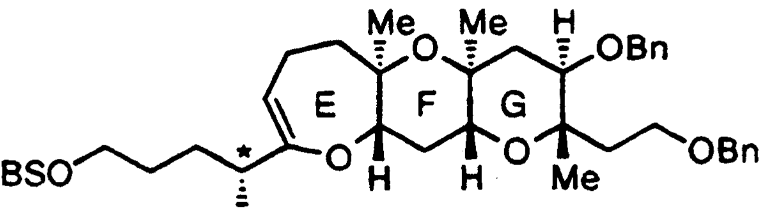
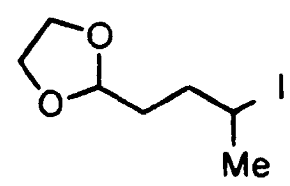
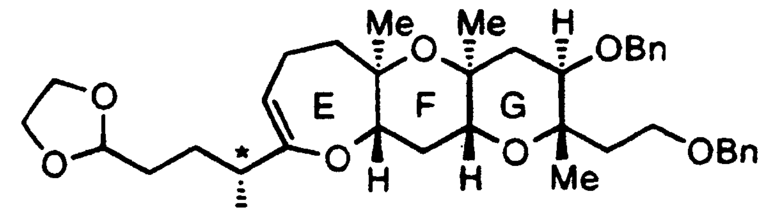
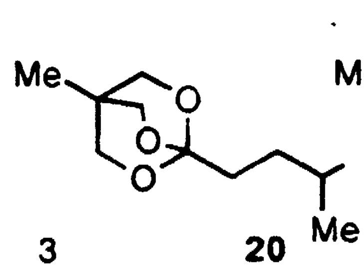
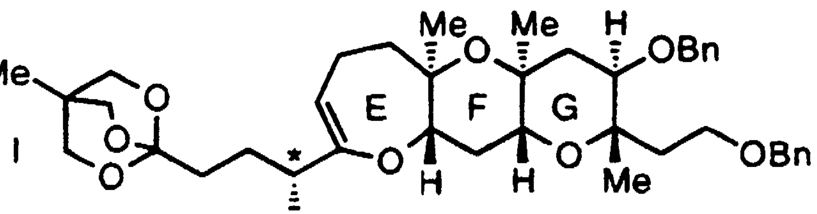
(10) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945. For a review on organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(11) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

Table 1. [a] Synthesis of Extended Oxepenes **23**–**25**

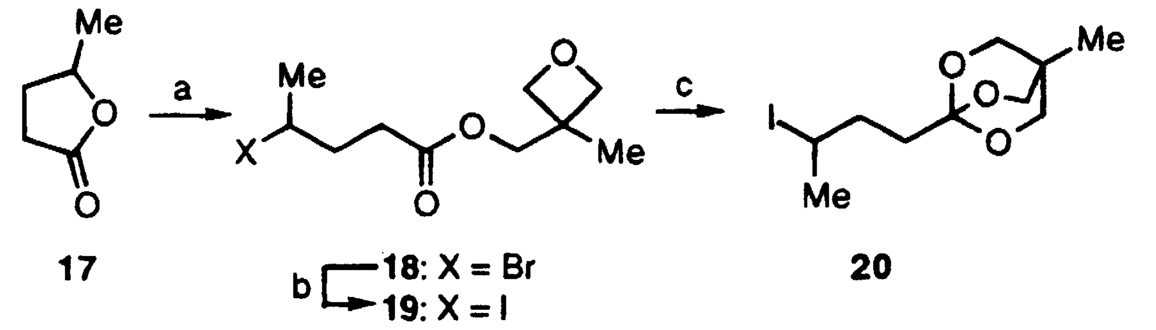


16

entry	iodide	product (yield (%), ratio)
1	 **21**	 **23** (50, ca 1:1.4 at C*)
2	 **22**	 **24** (49, ca 1:1.5 at C*)
3	 **20**	 **25** (85, ca 2.4:1 at C*)

[a] Reagents and conditions: (a) 6.0 equiv of RI, 10.0 equiv of t-BuLi, Et_2O, −120→−78 °C, 0.5 h, then 5.0 equiv of Cu(2-Th)(CN)Li, −78→−30 °C, 0.5 h, Et_2O:THF:HMPA (1:1:1), then **16**, −78→0 °C, 2 h.

Scheme 3[a] Construction of Orthoester Iodide **20**

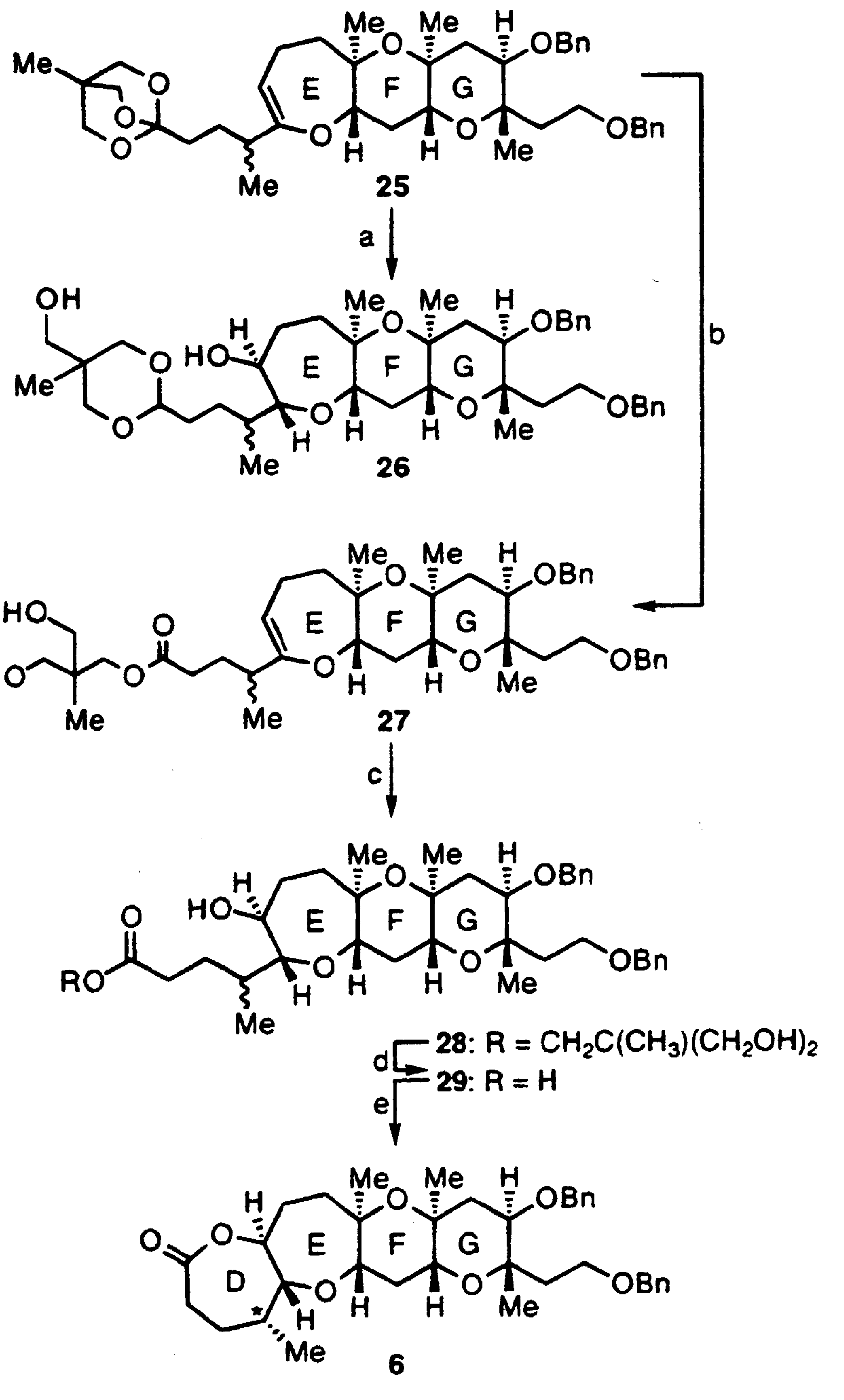


[a] Reagents and conditions: (a) 0.5 equiv of $SOBr_2$, 0.05 equiv of $ZnBr_2$, 55 °C, 42 h, then 1.0 equiv of 3-methyl-3-oxetanemethanol, 2.0 equiv of Et_3N, 0.2 equiv of DMAP, CH_2Cl_2, 25 °C, 5 h, 20%; (b) 5.0 equiv of NaI, 0.1 equiv of 18-crown-6, acetone, 25 °C, 50 h, 90%; (c) 0.25 equiv of BF_3·OEt_2, −30 °C, 12 h, 70%.

that crucial to the observed stereoselectivity was the employment of the solvent system Et_2O:THF:HMPA (1:1:1) in the coupling reaction. The two diastereoisomers so obtained were carried through to a later stage as a mixture, where chromatographic separation and structural assignment became possible (lactone **6**, *vide infra*).

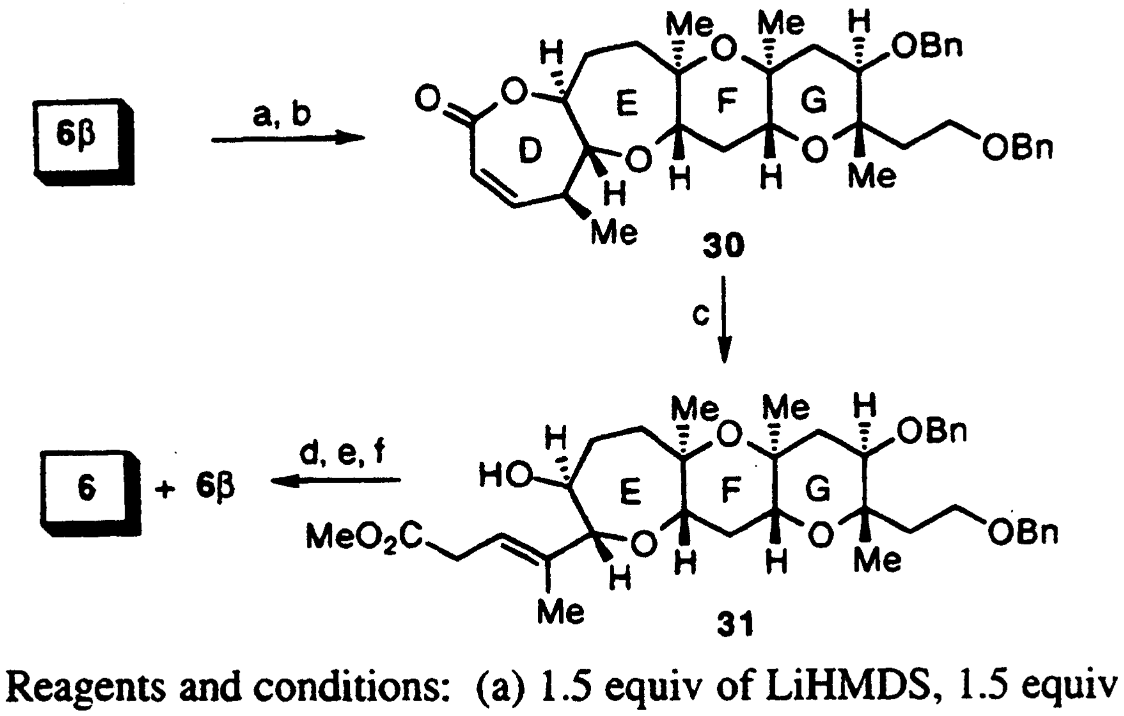
Having attached the required appendage on ring E, the next task was hydroboration of the double bond of the oxepene system and construction of the second lactone comprising ring D. Scheme 4 details how this objective was achieved. Initial attempts to hydroborate compound **25** to the corresponding secondary alcohol were accompanied by considerable amounts of the reduced product **26**, which is presumably formed by initial hydroboration of the double bond, followed by intramolecular hydride delivery onto the adjacent orthoester carbon atom. To circumvent this problem, the orthoester **25** was partially hydrolyzed under mildly acidic conditions (PPTS, DME/H_2O, 25 °C) to the dihydroxyester **27** (100% yield) which now underwent smooth hydroboration to furnish, regio- and stereoselectively, ester triol **28** in 89% yield. Basic hydrolysis of ester **28** then gave hydroxy acid **29** (82% yield) from which lactone **6**, together with its C* stereoisomer (see Scheme 4), was derived via Yamaguchi lactonization[5] (85% total yield). After flash chromatography (silica, 50→70%, ether–petroleum ether), a 60% yield of the desired α-epimer **6** was obtained pure, whereas the minor *β*-epimer was isolated in 25% yield.

Scheme 4[a] Construction of the DEFG Ring System **6**



[a] Reagents and conditions: (a) 5.0 equiv of BH_3·THF, −30 °C, 17 h, then 25 equiv of 3 N NaOH, 50 equiv of 30% H_2O_2, 81%; (b) 0.3 equiv of PPTS, DME:H_2O (1:1), 25 °C, 100%; (c) 6.0 equiv of BH_3·THF, 0 °C, 40 min, then 10 equiv of 3 N NaOH, 20 equiv of 30% H_2O_2, 89%; (d) 2.0 equiv of LiOH, DME:H_2O (1:1), 25 °C, 1 h, 82%; (e) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (*c* = 0.05 mM), 80 °C, 3 h, 60% of **6**, plus 25% of its *β*-epimer **6*β*** (after column chromatography).

Scheme 5[a] Recycling of Epimeric Lactone **6*β*** to Lactone **6**



[a] Reagents and conditions: (a) 1.5 equiv of LiHMDS, 1.5 equiv of HMPA, 2.0 equiv of PhSeBr, THF, −78→−30 °C, 1 h; (b) 2.0 equiv of mCPBA, THF, 25 °C, 91% (2 steps); (c) 2.0 equiv of LiHMDS, 2.0 equiv of HMPA, −78 °C, THF, 30 min; quench with MeOH, 94%; (d) H_2, 0.2 equiv of Ir(COD)(Py)P(Cy)$_3$PF$_6$, CH_2Cl_2, 25 °C, 15 min, 80% of a 1:1 mixture of epimers; (e) 2.0 equiv of LiOH, MeOH:H_2O (4:1), 30 min, 100%; (f) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (*c* = 0.05 mM), 80 °C, 1 h, 90% of a 1:1 mixture of **6** and **6*β*** (separated by chromatography). COD = 1,5-cyclooctadiene, Cy = cyclohexyl.

In order to optimize the yield of the desired α-epimer **6**, a process was developed whereby the *β*-epimer (**6*β***) was converted to the desired α-compound (**6**). Scheme 5 outlines the chemistry used in this sequence. Thus, **6*β*** was converted to its α,*β*-unsaturated counterpart (**30**) via phenylselenenylenation–oxidation–*syn*-elimination (91% overall yield) and thence to the hydroxy methyl ester **31** (in which the double bond has

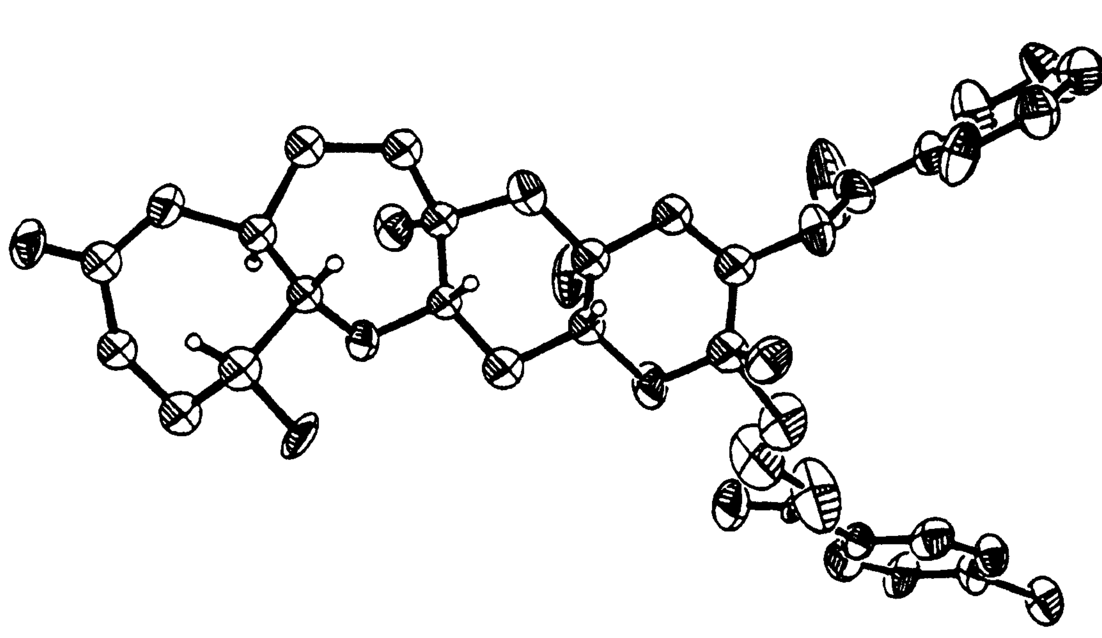
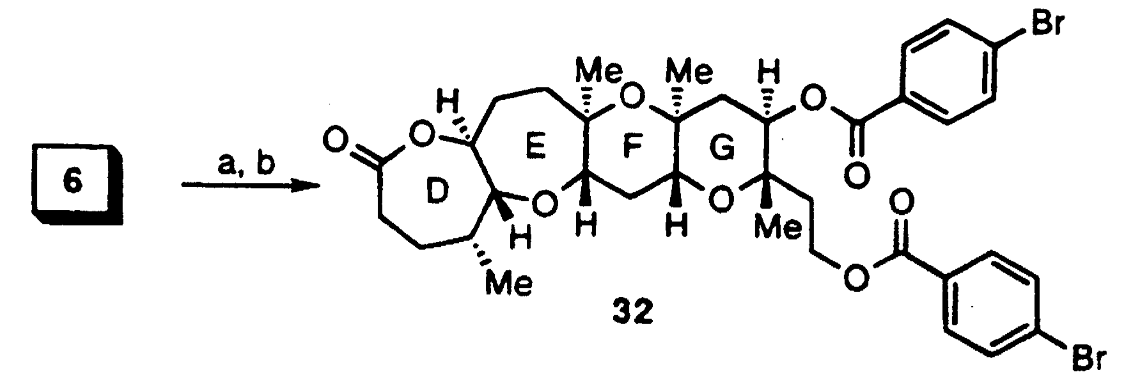


Figure 1. ORTEP drawing of **32**.

Scheme 6[a] Synthesis of DEFG Lactone Derivative **32**



[a] Reagents and conditions: (a) H_2, 20 wt % of 10% $Pd(OH)_2/C$, EtOAc, 25 °C, 48 h, 93%; (b) 3.0 equiv of *p*-bromobenzoyl chloride, 4.5 equiv of DMAP, CH_2Cl_2, 25 °C, 25 min, 72%.

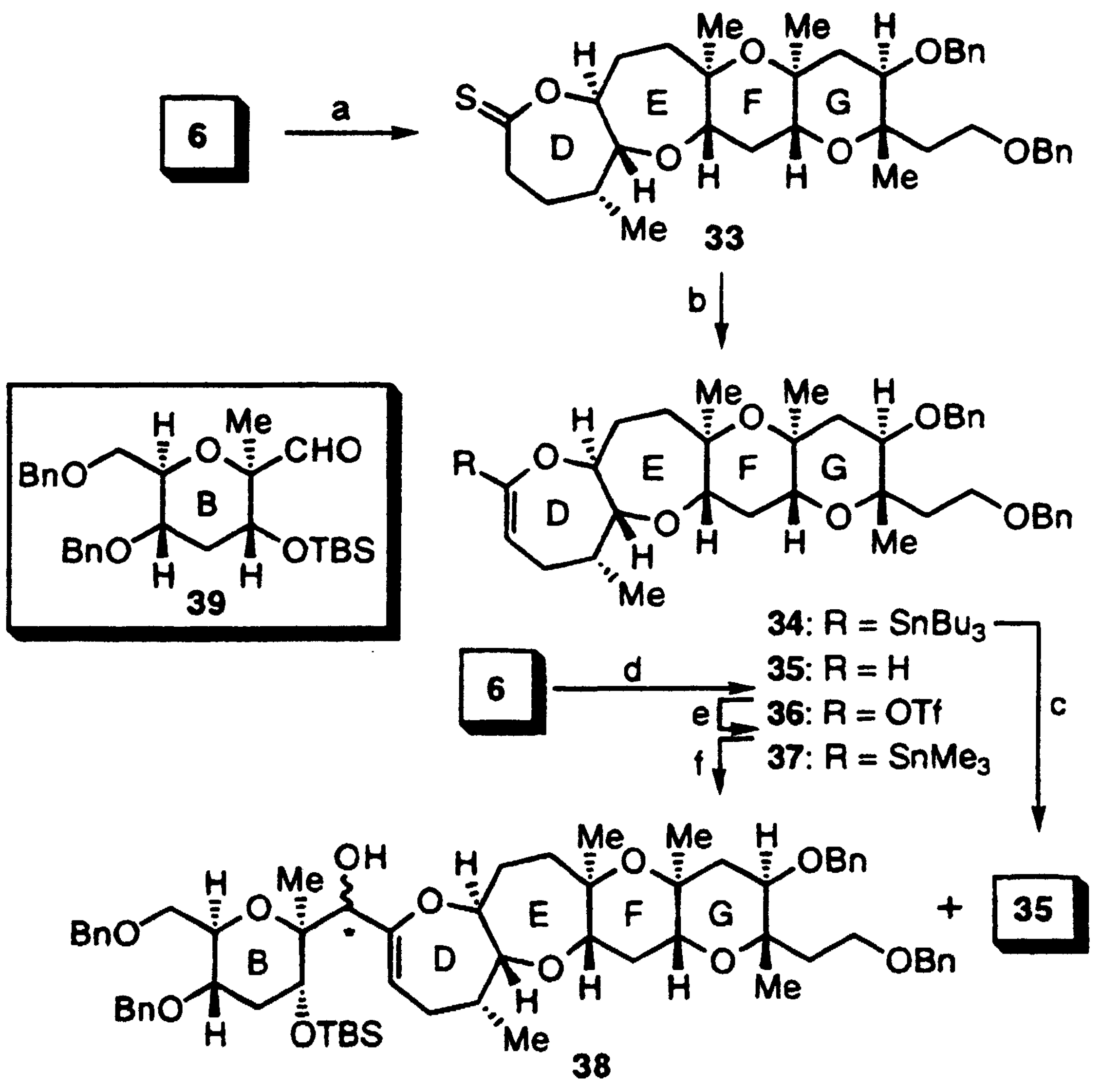
migrated to the β,γ-position) by deconjugation with LiHMDS, followed by methanolic quenching (94% yield). Hydrogenation of ester **31** using $Ir(COD)(py)P(Cy)_3PF_6$[12] (80% yield) followed by saponification furnished a 1:1 mixture (100% yield) of the corresponding hydroxy acids. Finally, lactonization of the latter mixture under the Yamaguchi conditions[5] gave a 1:1 mixture of lactones **6** and **6β** (90% total yield) which was chromatographically separated into its pure components.

The structural assignment of lactone **6** was secured by X-ray crystallographic analysis of its bis(*p*-bromobenzoate) derivative **32** (see ORTEP drawing, Figure 1), prepared as summarized in Scheme 6.

Coupling of B and DEFG Ring Systems and Attempts To Construct the BCDEFG Framework

After securing the DEFG lactone **6**, the plan called for its coupling to ring B aldehyde **39**[13] (Scheme 7). To this end, lactone **6** was converted to the thionolactone **33** (Scheme 7) by treatment with Lawesson's reagent[14] at 180 °C (68% yield) and thence to the vinylstannane **34** via sequential treatment with LDA, n-Bu_3SnH, $I(CH_2)_2I$, and 2,6-lutidine (50% overall yield).[15] Conversion of **34** to the corresponding lithium reagent via tin–lithium exchange (n-BuLi, HMPA, THF, −78 °C) followed by addition of aldehyde **39** resulted in the formation of adduct **38** (40%, *ca.* 6:1 mixture of C* epimers), together with oxepene **35** (20%) derived by protonation of the organometallic species. In an attempt to improve the coupling of the two partners (**39** and **6**), a second sequence was explored according to which lactone **6** was converted to its enol ether **36** (LiHMDS, HMPA, THF, −78 °C, then $PhNTf_2$, 93%) and thence to stannane enol ether **37** [$Me_3SnSnMe_3$, $Pd(PPh_3)_4$ catalyst, LiCl, DMF, 95%][16] before metal exchange (n-BuLi, HMPA, THF, −78 °C) and addition of **39**. Although the overall yield of converting **6** to the stannyl enol ether was significantly higher in the latter case, compounds **38** and **35** were obtained in the same yields (40 and 20%, respectively) as before. The above two methods of coupling were surpassed, however, in both efficiency and convenience, by a third approach, whose discussion will be deferred to a later section (*vide infra*).

Scheme 7[a] Coupling of B Ring **39** with the DEFG Ring System



[a] Reagents and conditions: (a) 6.0 equiv of Lawesson's reagent, xylene, 180 °C, 45 min, 68%; (b) 4.0 equiv of LDA, 5.0 equiv of n-Bu_3SnH, −10 °C, THF, 30 min, then add **33**, 30 min, 5.0 equiv of $I(CH_2)_2I$, 10 equiv of 2,6-lutidine, 30 min, 50%; (c) 2.0 equiv of n-BuLi, 5.0 equiv of HMPA, THF, −78 °C, 20 min, then add **39**, −78 °C, 20 min, 40% of **38** (6:1 mixture of isomers) and 20% of **35**; (d) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, −78 °C, 2 h, then 2.0 equiv of $PhNTf_2$, −78→25 °C, 2 h, 93%; (e) 0.05 equiv of $Pd(PPh_3)_4$, 2.0 equiv of $Me_3SnSnMe_3$, 1.0 equiv of LiCl, DMF, 25 °C, 14 h, 95%; (f) 2.0 equiv of n-BuLi, 1.0 equiv of HMPA, THF, −78 °C, 20 min, then add **39**, −78 °C, 20 min, 40% of **38** (6:1 mixture of isomers) and 20% of **35**.

Having secured coupling product **38**, an attempt was made to construct ring C via an intramolecular Michael reaction[17] as shown in Scheme 8. Thus, Dess-Martin oxidation of **38** led smoothly to enone **40** (91%) which was then transformed to the requisite hydroxy enone **41** by desilylation (TBAF, 93%). All attempts, however, to induce ring closure in **41** under basic or acidic conditions failed and, therefore, a second approach was explored.

According to the new alternative, outlined in Scheme 9, hydroxy ketone **45** was to serve as a precursor to the BCDEFG ring system **48** via a reductive cyclization process.[1,18] The sequence leading to **47** involved initial deoxygenation of **38** via the Barton–McCombie two-step protocol[19] [(a) KH–CS_2–MeI (70%); (b) n-Bu_3SnH–AIBN, Δ (75%)] to afford compound **44** via xanthate **43** followed by hydroboration–oxidation of the resulting enol ether (**44**) leading, regio- and stereoselectively, to alcohol **45** (76% yield). Finally, oxidation of the latter

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(12) Crabtree, R. H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *135*, 395.

(13) Aldehyde **39** was prepared in three steps from intermediate **20**, ref 3a: (a) 0.2 equiv of CSA, $MeOH/CH_2Cl_2$ (1:1), 0 °C; (b) 3.0 equiv of $PhCH_2Br$, THF, 45 °C; (c) O_3, CH_2Cl_2 −78 °C, then PPh_3, 25 °C (90% overall yield).

(14) For optimization of thionation conditions, see: Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. K.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.

(15) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K. *J. Am. Chem. Soc.* **1990**, *112*, 3696. Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4988.

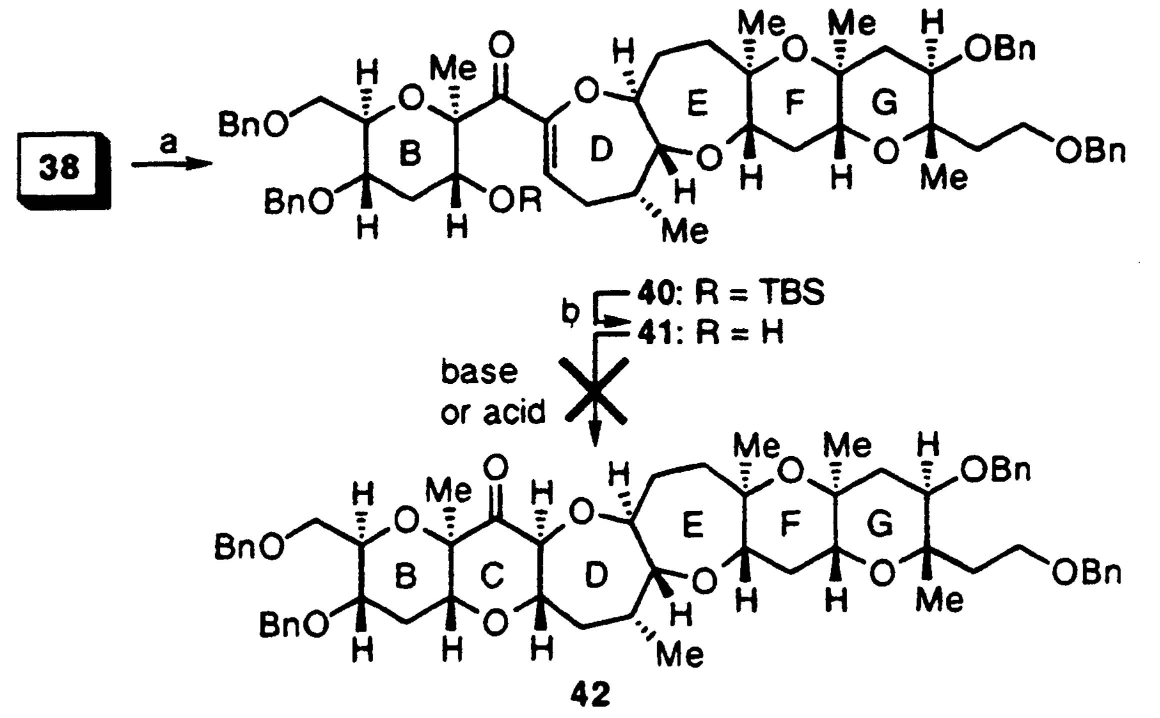
(16) Barber, C.; Jarowicki, K.; Kocieński, P. *Synlett* **1991**, 197.

(17) For a selected number of successful examples, see: Palázon, J. M.; Soler, M. A.; Ramirez, M. A.; Martin, V. S. *Tetrahedron Lett.* **1993**, *34*, 5467. Soler, M. A.; Palázon, J. M.; Martin, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471.

(18) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.

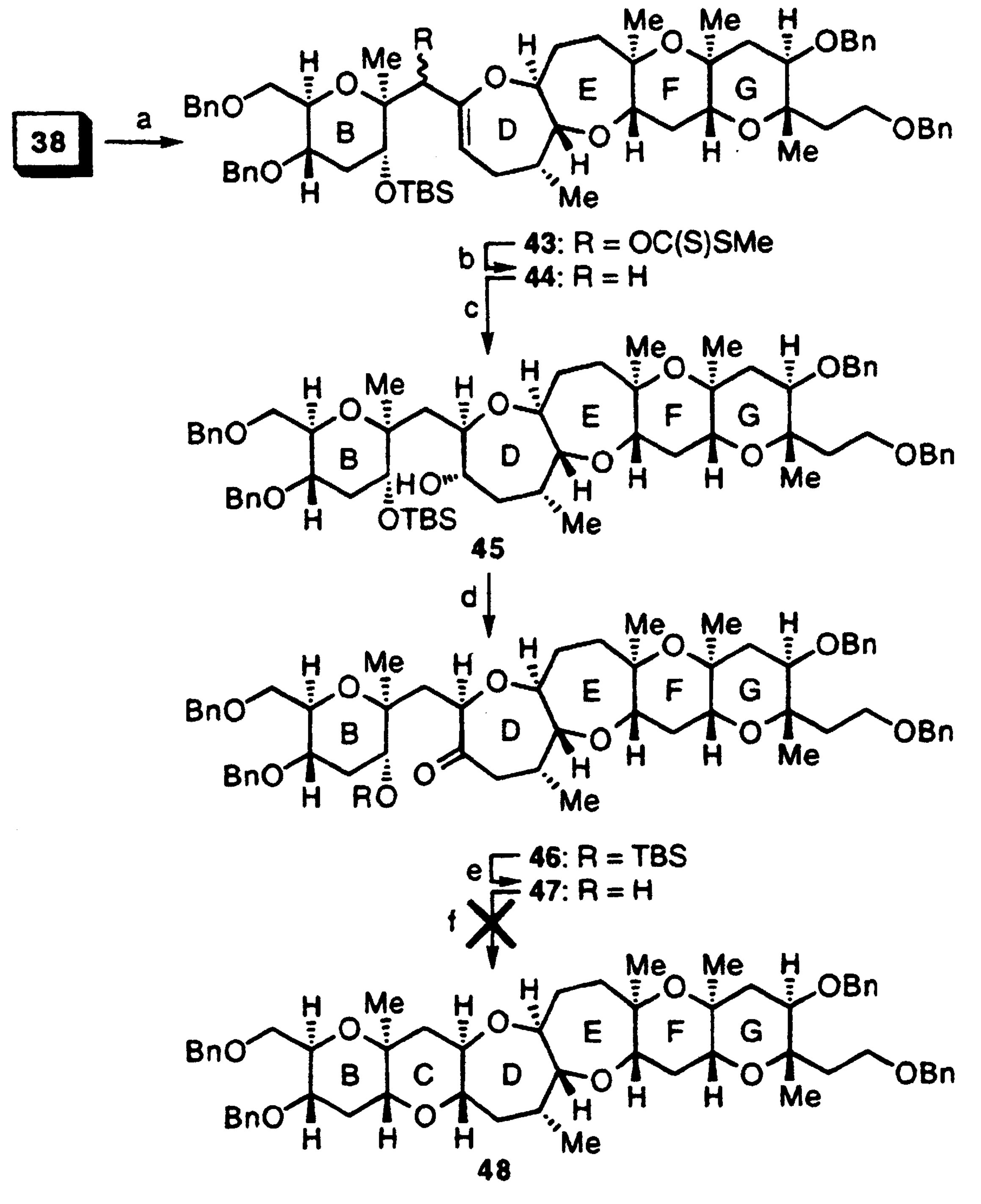
(19) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

Scheme 8[a] Failed Attempts To Construct the C Ring via Conjugate Addition



[a] Reagents and conditions: (a) 4.0 equiv of Dess-Martin periodinane, CH_2Cl_2, 3 h, 25 °C, 91%; (b) 2.0 equiv of TBAF, THF, 25 °C, 3 h, 93%.

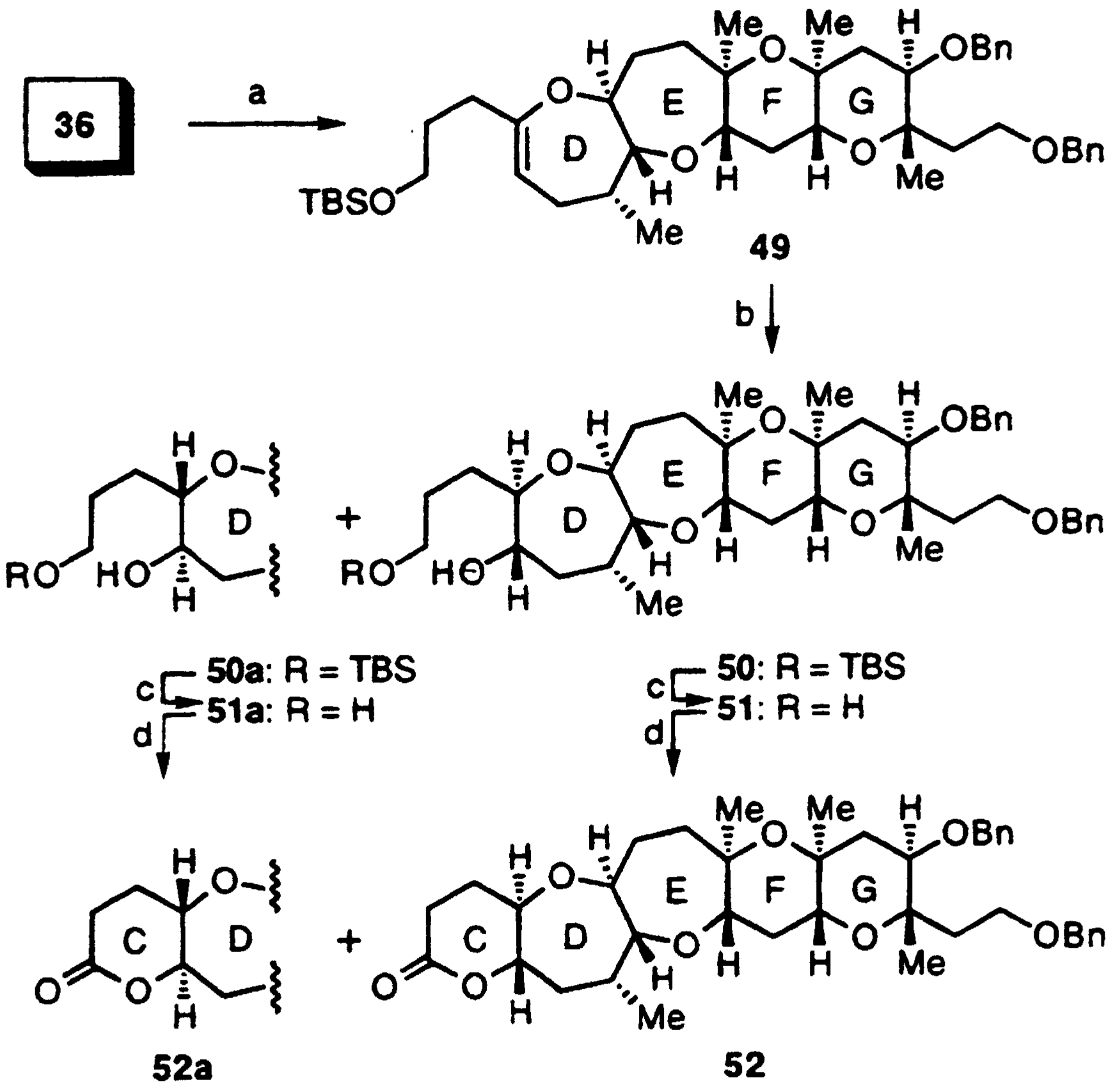
Scheme 9[a] Failed Attempts To Construct the C Ring via Reductive Hydroxy Ketone Cyclization



[a] Reagents and conditions: (a) 10 equiv of KH, 5.0 equiv of CS_2, 25 °C, 2 h, then 20 equiv of MeI, 10 min, 70%; (b) 5.0 equiv of n-Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 1 h, 75%; (c) 5.0 equiv of BH_3·THF, THF, −30 °C, 12 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H_2O_2, 0 °C, 1 h, 76%; (d) 0.1 equiv of TPAP, 2.0 equiv of NMO, CH_3CN, 25 °C, 1 h, 90%; (e) 1.2 equiv of TBAF, THF, 25 °C, 7 h, 95%; (f) 10 equiv of Ph_2MeSiH, 1.2 equiv of TMSOTf, $MeNO_2$, 0 °C, 1 h.

compound (**45**) with *N*-methylmorpholine *N*-oxide (NMO) in the presence of a catalytic amount (10%) of tetra-*n*-propylammonium perruthenate (TPAP)[20] furnished ketone **46** (90%) which was desilylated (TBAF) to give the desired hydroxy ketone **47** in 95% yield. Again, however, all attempts to effect cyclization of **47** to **48** using a number of silanes and a variety of acid conditions proved unsuccessful (Scheme 9).

Scheme 10[a] Preparation of the CDEFG Ring System Lactone **52**



[a] Reagents and conditions: (a) 2.0 equiv of HMPA, 5.0 equiv of $TBSO(CH_2)_3Cu(2\text{-}Th)(CN)Li_2$, THF:$Et_2O$ (1:1), −78→0 °C, 1 h, 82%; (b) 5.0 equiv of BH_3·THF, THF, −30 °C, 14 h, then 10 equiv of 3 N NaOH, 20 equiv of H_2O_2 (30%), 25 °C, 88%, 6:1 mixture of isomers; (c) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 93%; (d) 10 equiv of Ag_2CO_3/Celite, benzene, 80 °C, 2 h, 96%. Th = 2-thienyl.

At this juncture, it was decided that a linear strategy toward the BCDEFG ring system might prove more fruitful and, therefore, a number of approaches involving sequential building of rings C and B were explored. First to be attempted was the sequence shown in Scheme 10 in which the pentacyclic lactone **52** was to be utilized as a precursor for further elaboration. Thus, enol triflate **36** was coupled with the mixed higher order cuprate carrying the appropriate side chain [$TBSO(CH_2)_3Cu(2\text{-}Th)CNLi_2$][21] furnishing oxepene **49** (82%) which was subjected to hydroboration−oxidation to give alcohols **50** and **50a** (88%, *ca.* 6:1 mixture in favor of **50**). Desilylation of the latter mixture of compounds (**50** + **50a**) gave a mixture of diols (**51** and **51a**, 93% total yield) which was subjected to Fetizon oxidation (Ag_2CO_3/Celite, Δ) furnishing a mixture of lactones (**52** and **52a**, 96% total yield).[22] Attempts to elaborate this pentacyclic system gave mixed and discouraging results. For example, the corresponding triflate could only be obtained with difficulty and in low yield, whereas addition reactions to the corresponding thionolactone led to unsatisfactory mixtures of products. In order to circumvent these problems, more elaborate side chains were designed and coupled with the DEFG framework as described below.

Cr−Ni Coupling of the DEFG Lactone-Derived Enol Ether with Aldehydes and Further Attempts To Construct the ABCDEFG Ring System

In light of the difficulties encountered in functionalizing pentacyclic lactone **52** (Scheme 10), the fully functionalized side chain aldehydes **59** and **62** (Scheme 11) were considered as coupling partners. The latter compounds were synthesized by standard methods from D-mannitol (**53**) as summarized in Scheme 11.[23] A number of second generation attempts to construct the ABCDEFG framework of brevetoxin B (**1**) from the DEFG system were then made. A new method of coupling

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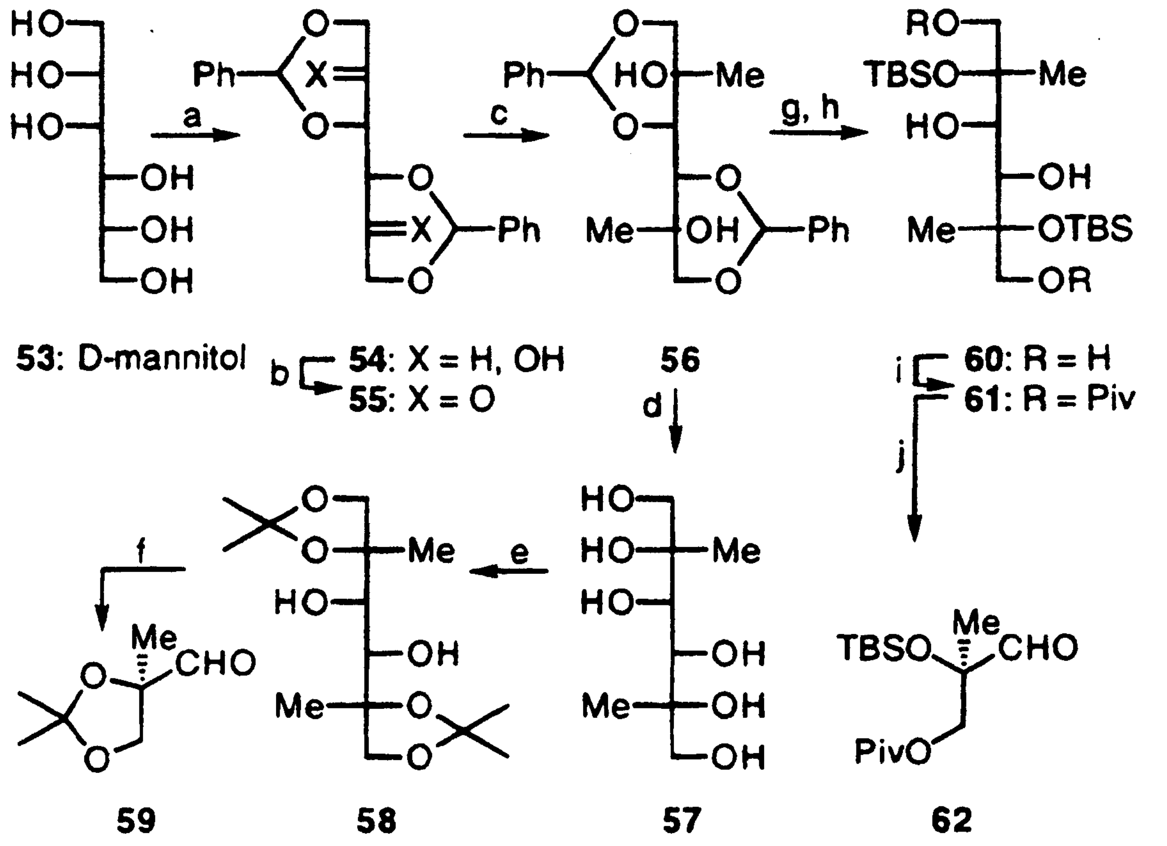
(20) For a review on TPAP oxidations, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(21) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558.

(22) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171. For a relevant example, see: Masamune, S.; Lu, L. D.-L.; Jacobson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523.

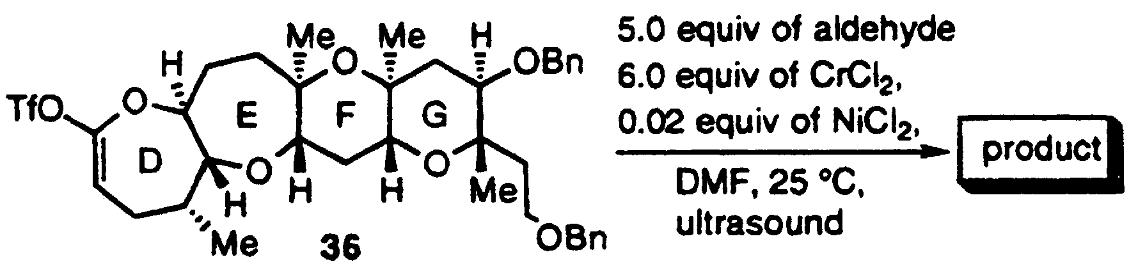
(23) Literature procedures for the preparation of **59** proved less satisfactory: Dung, J.-S.; Armstrong, R. W.; Anderson, O. P.; Williams, R. M. *J. Org. Chem.* **1983**, *48*, 3592. Baggett, N.; Stribblehill, P. *Carbohydr. Res.* **1981**, *96*, 41. Banner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384. Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461.

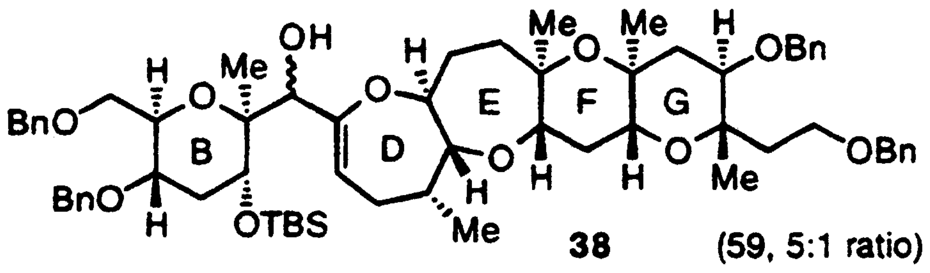
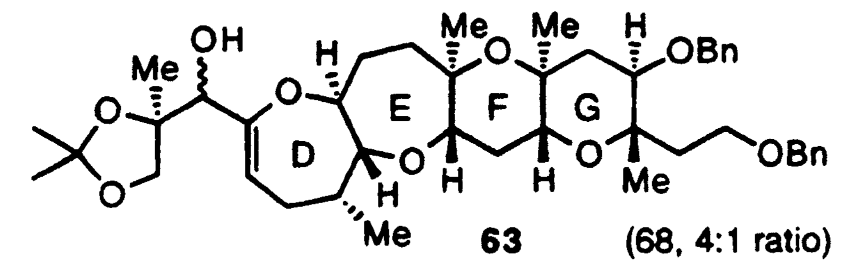
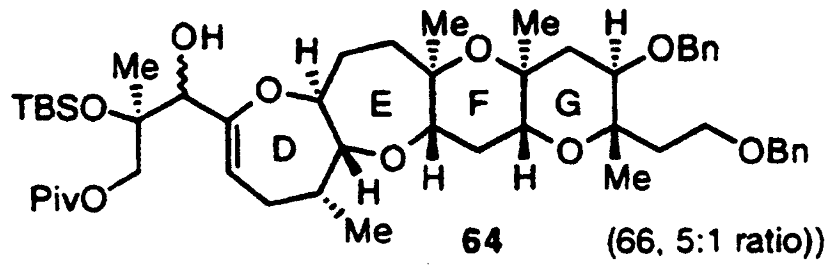
Scheme 11[a] Synthesis of Aldehydes **59** and **62**



[a] Reagents and conditions: (a) 2.1 equiv of PhCHO, 0.7 equiv of H_2SO_4, DMF, 25 °C, 3 days, 35%; (b) 2.3 equiv of Dess-Martin periodinane, CH_2Cl_2, reflux, 12 h, 90%, then toluene, 110 °C, 12 h, Soxhlet condenser, 4Å MS, 90%; (c) 6.0 equiv of MeMgI (3.0 M in THF), 0 °C, 1 h, 92%; (d) H_2, 0.1 equiv of 10% $Pd(OH)_2$, AcOH, 25 °C, 48 h, 94%; (e) 2.5 equiv of $Me_2C(OMe)_2$, 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of $NaIO_4$, THF/H_2O (1:1), 72 h, 90%; (g) 4.0 equiv of TBSOTf, 7.0 equiv of 2,6-lutidine, 0.1 equiv of DMAP, 25 °C, 5 h, 99%; (h) H_2, 0.1 equiv of 10% Pd/C, AcOH, 25 °C, 48 h, 91%; (i) 3.0 equiv of PivCl, 0.2 equiv of DMAP, pyridine, 25 °C, 24 h, 100%; (j) 1.1 equiv of $Pb(OAc)_4$, CH_2Cl_2, 25 °C, 15 min, 91%.

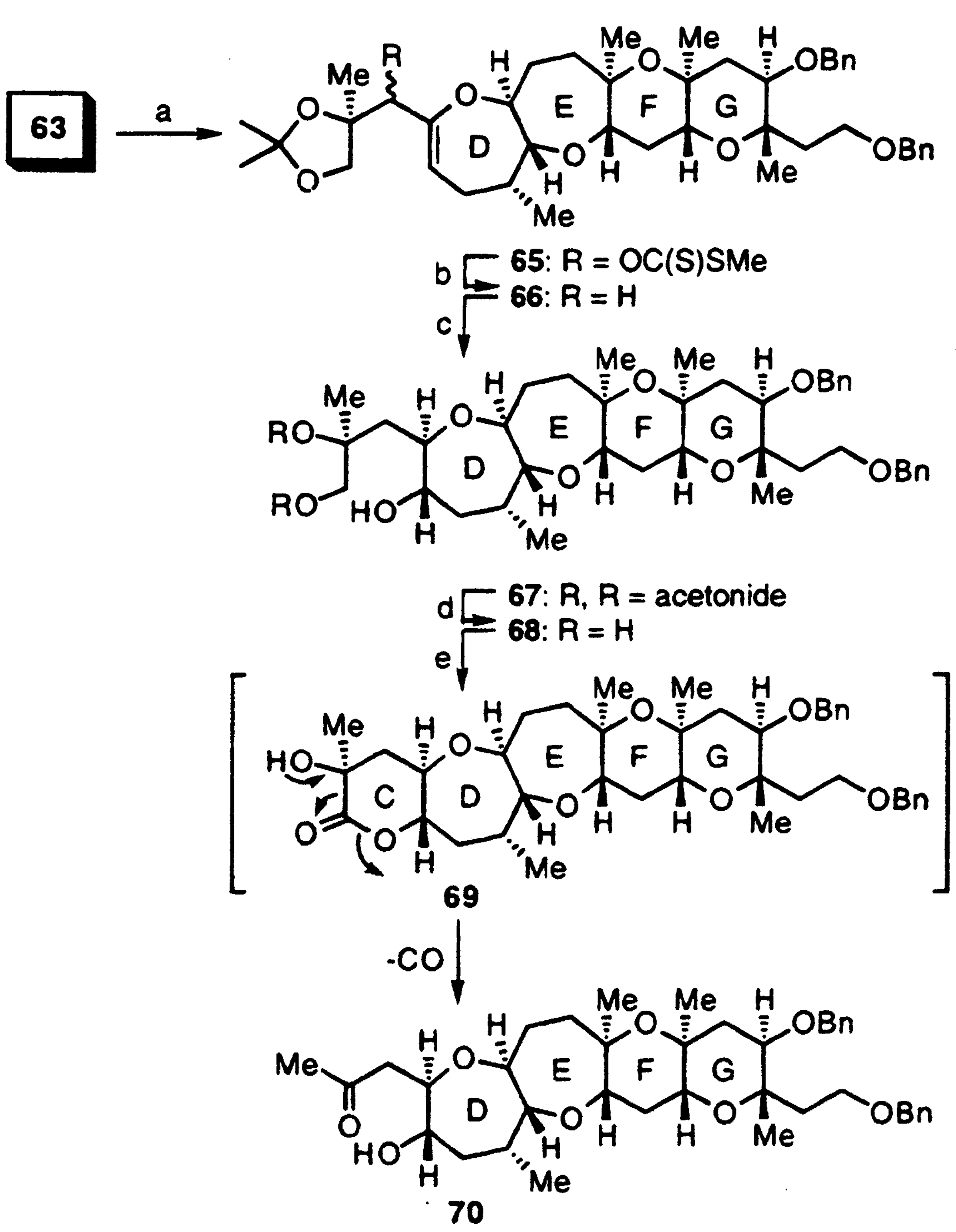
Table 2. Cr/Ni-Mediated Coupling of Aldehydes with Enol Triflate **36**



aldehyde	product	(yield (%))
39	 **38**	(59, 5:1 ratio)
59	 **63**	(68, 4:1 ratio)
62	 **64**	(66, 5:1 ratio))

enol triflate **36** with these aldehydes was developed using the chromium–nickel system[24,25] as a means of activation. As demonstrated in Table 2, aldehydes **39** (ring B, Scheme 7), **59** (Scheme 11), and **62** (Scheme 11) coupled smoothly with enol triflate **36** in the presence of excess $CrCl_2$ and a catalytic amount of $NiCl_2$ in DMF under sonication conditions (59–68% yields, stereoisomeric mixtures). This Cr/Ni-mediated reaction is also the preferred method for the synthesis of **38** (Scheme 7), whose chemistry has already been discussed (*vide supra*). Applications of this facile process in other areas of chemistry are envisioned.

Scheme 12[a] Attempts to Construct the C Ring via Functionalized Lactone Formation



[a] Reagents and conditions: (a) 10 equiv of KH, 5.0 equiv of CS_2, 25 °C, 2 h, then 20 equiv of MeI, 10 min, 90%; (b) 5.0 equiv of *n*-Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 30 min, 60%; (c) 5.0 equiv of BH_3·THF, THF, −30 °C, 16 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H_2O_2, 0 °C, 1 h, 72%; (d) 0.3 equiv of CSA, MeOH, 25 °C, 5 h, 95%; (e) 20 equiv of Ag_2CO_3/Celite, benzene, 80 °C, 3 h, 82%.

The plan for coupling product **63** (Table 2) called for the generation and elaboration of functionalized lactone **69** (Scheme 12) via deoxygenation, hydroboration, and Fetizon oxidation.[22] The Barton deoxygenation[19] **63** → **66** (54% overall yield) proceeded smoothly under the standard conditions via xanthate **65** as shown in Scheme 12. The resulting olefin **66** was then subjected to hydroboration, leading selectively to acetonide alcohol **67** (72% yield), from which the triol **68** was generated upon acid hydrolysis (95% yield). Fetizon oxidation of **68**, however, resulted in the unexpected formation of hydroxy ketone **70**, a compound with one carbon less than the anticipated lactone **69** (Scheme 12). This unusual outcome could be explained by the assumption of the initial intermediacy of **69** and its facile decarbonylation (−CO), under the reaction conditions, as indicated in the structure (Scheme 12). Having failed, once again, to reach our goal by this route, it was then decided to turn our attention to compound **64** (Table 2) and its chemistry.

The deoxygenation of secondary alcohol **64** proved sensitive, in that it was accompanied by two interesting migrations (Scheme 13). First, during xanthate formation, it was observed that upon addition of KH, an immediate migration of the silyl group from the tertiary to the secondary oxygen was taking place, leading to an equilibrium in which the tertiary alcohol **71** (as the alkoxide) was by far the major component (Scheme 13). Fortunately, the low reactivity of the tertiary alkoxide derived from **64** toward CS_2 allowed the latter compound to drive the unfavorable equilibrium in its direction by forming xanthate **72** (89% yield). Second, the *n*-Bu_3SnH–AIBN-induced C–O bond cleavage was accompanied by double bond migration, leading to a mixture of products **73** (30%) and **74** (69%). The unwanted isomer **73** was fortunately convertible to the desired isomer **74** via $Rh(PPh_3)_3Cl$-induced double bond

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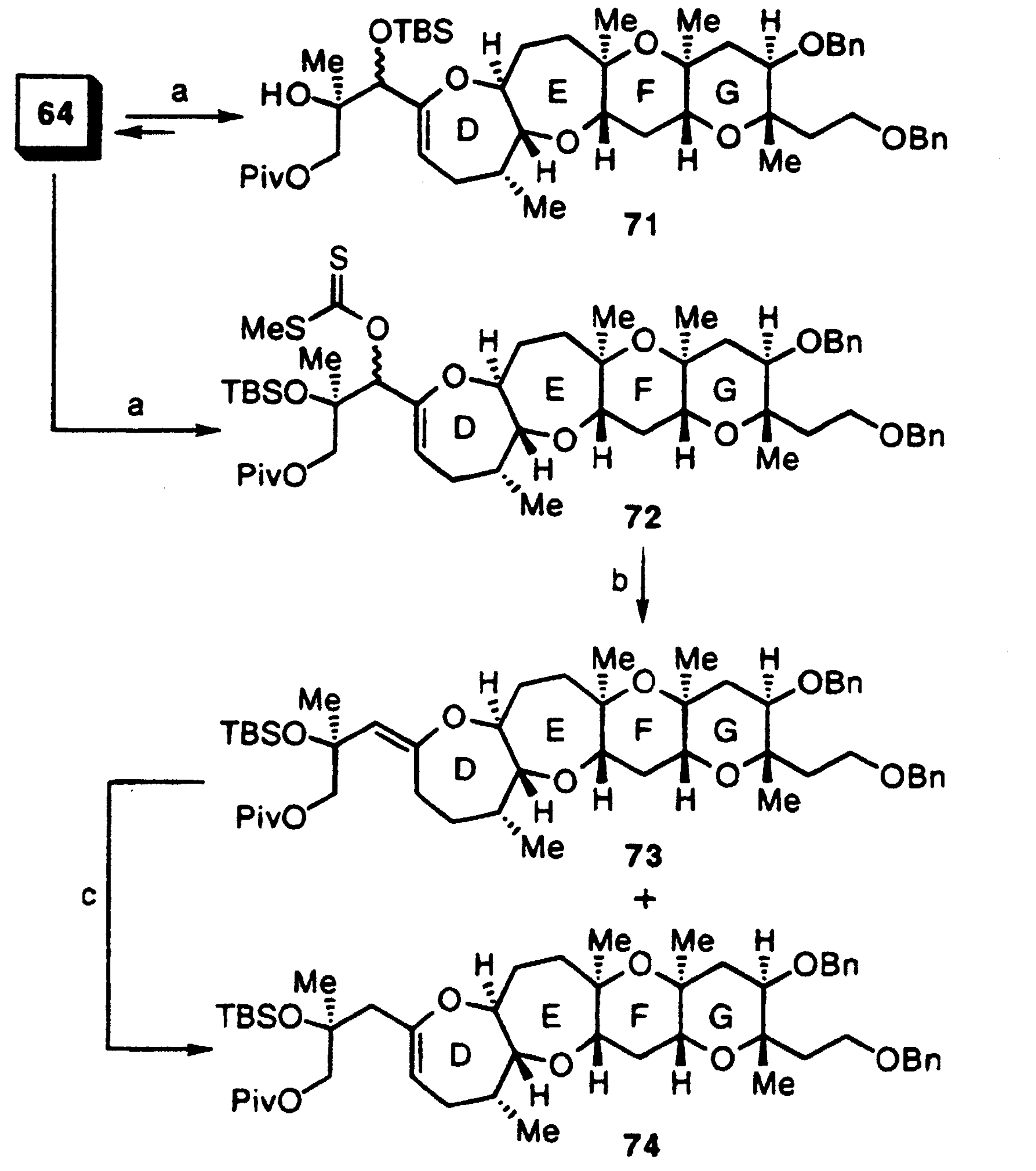
[24] For examples of this coupling reaction involving enol triflates derived from ketones, see: Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

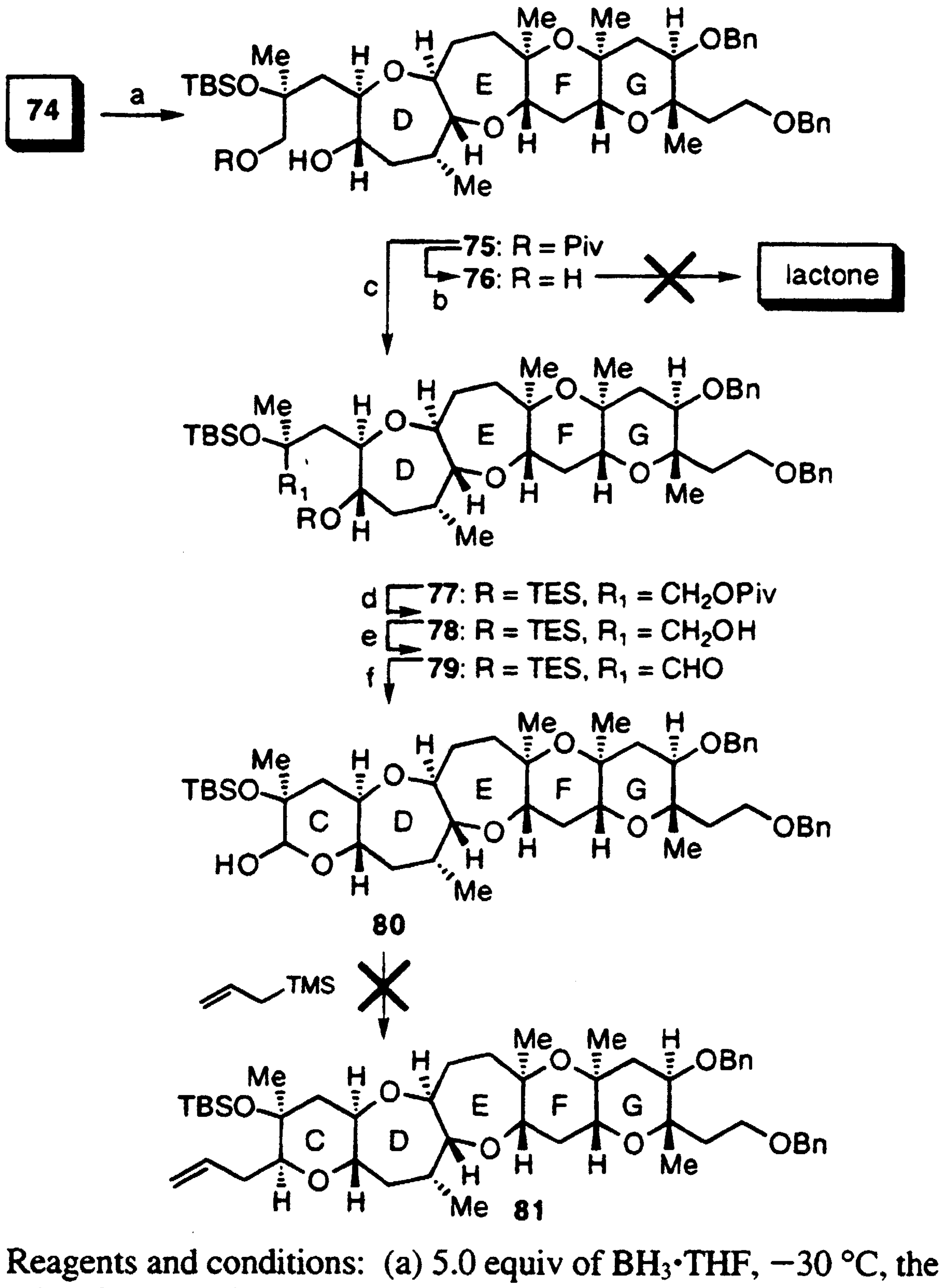
[25] For a review on vinyl triflate chemistry, see: Ritter, K. *Synthesis* **1993**, 735.

Scheme 13[a] Synthesis of Oxepene **74**



[a] Reagents and conditions: (a) 3.0 equiv of CS_2, 50.0 equiv of KH (added over 6 h), Et_2O, then 10.0 equiv of MeI, 25 °C, 89% of **72**; (b) 4.0 equiv of *n*-Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 30% of **73** and 67% of **74**; (c) 0.1 equiv of $Rh(PPh_3)_3Cl$, CH_3CN/H_2O (1:1), 80 °C, 4 h, 40%.

Scheme 14[a] Attempts To Construct the C Ring via Functionalized Lactone Formation and *C*-Glycosidation



[a] Reagents and conditions: (a) 5.0 equiv of BH_3·THF, −30 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H_2O_2, 82%; (b) 2.2 equiv of DIBALH, −78 °C, 10 min, 80%; (c) 2.0 equiv of TESOTf, 2.5 equiv of 2,6-lutidine, CH_2Cl_2, −70 °C, 1 h, 96%; (d) 2.5 equiv of DIBALH, CH_2Cl_2, −78 °C, 5 min, 98%; (e) 1.7 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h, 85%; (f) 0.2 equiv of CSA, $MeOH/H_2O$ (4:1), 2 h, 25 °C, 85% (single isomer, unassigned stereochemistry).

migration back into the ring (40% yield), thus increasing the overall yield of the requisite oxepane.

The hydroxylation of compound **74** via the standard hydroboration−oxidation protocol proceeded again regio- and stereoselectively to afford, in 82% yield, pivaloate ester alcohol **75** (Scheme 14). Cleavage of the pivaloate group from the latter compound with DIBALH then furnished diol **76** (80% yield) which, however, resisted Fetizon oxidation to the corresponding lactone. The latter failure is presumably due to steric hindrance provided by the tertiary center adjacent to this reaction site. A second route was then chosen in an attempt to form ring C via a stepwise approach. Thus, protection of the secondary alcohol in **75** as a triethylsilyl (TES) ether followed by DIBALH-induced removal of the pivaloate group and Dess-Martin oxidation gave aldehyde **79** via intermediates **77** and **78** in 80% overall yield (Scheme 14). Finally, treatment of **79** with methanol/H_2O (4:1) containing catalytic amounts of camphorsulfonic acid (CSA) furnished lactol **80** in 85% yield as a single anomer (stereochemistry unassigned). However, all attempts to C-glycosidate the anomeric position of the latter compound (**80**) met with failure. For example, allyltrimethylsilane under a variety of conditions did not lead to the expected derivative **81**. A number of other relatives of **80** (e.g., methyl glycoside, acetate) also resisted functionalization and, therefore, this approach was no longer pursued.

Conclusion

In this paper a number of second generation strategies toward brevetoxin B (**1**) are described. The main themes of these studies were developed around a retrosynthetic analysis which defined suitable ABCDEFG and IJK ring systems as potential advanced intermediates for a convergent strategy and projected the oxocene ring system as the last ring to be closed. A successful synthesis of the DEFG ring framework, a precursor to the larger ABCDEFG ring system, was developed. Several methods for the elaboration of the latter compound to a more advanced intermediate were also explored. Despite the many attempts to fuse additional rings onto the DEFG ring system with suitable functionalities for framework extension, this goal remained elusive. A number of new tactics and strategies were developed, however. Among them, a convergent Cr/Ni-promoted coupling procedure of lactone-derived enol triflates and aldehydes proved quite general and applicable to a potential precursor of the ABCDEFG ring system of brevetoxin B (**1**). In the following article,[2] we detail the successful construction of this advanced intermediate (**4**, Scheme 1) and the final stages of the strategy that led to the completion of the total synthesis of brevetoxin B (**1**).[26,27]

Experimental Section

General Techniques. For a description of general techniques, see the preceding paper in this issue.[1] NMR spectra were recorded on Brucker AMX-500 or AM-300 instruments. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (mp) are uncorrected and were recorded on a Thomas Hoover capillary melting point apparatus.

Olefin 11. A solution of DMSO (13.0 mL, 168 mmol) in CH_2Cl_2 (200 mL) was treated with oxalyl chloride (11.0 mL, 126 mmol) at −78 °C. After stirring at −78 °C for 30 min, a solution of alcohol **8** (49.0 g, 83.8 mmol) in CH_2Cl_2 (100 mL) was added dropwise and the mixture was stirred for an additional 30 min at −78 °C. Triethylamine (58.4 mL, 419 mmol) was added and the reaction mixture was allowed to warm to 0 °C. The mixture was diluted with ether (500 mL), washed

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(26) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171.

(27) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

with saturated aqueous ammonium chloride (300 mL), dried ($MgSO_4$), and concentrated. The crude aldehyde was used for the next step without further purification. A mixture of 3-(*tert*-butyldimethylsilyl)-oxypropyl-1-triphenylphosphonium iodide (83.8 g, 168 mmol) in THF (200 mL) was treated dropwise with sodium bis(trimethylsilyl)amide (126 mL of a 1.0 M solution in THF, 126 mmol) at 0 °C. The resulting orange ylide solution was treated dropwise with a solution of the aldehyde **10** (49.0 g, 83.8 mL) in THF (100 mL) at 0 °C. After stirring at 0 °C for 20 min, the mixture was quenched with acetone (10 mL), diluted with ether (500 mL), washed with brine (200 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 5→20% ether in petroleum ether) gave olefin **11** (61.3 g, 83.0 mmol, 99%). **11**: colorless oil; $R_f = 0.64$ (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2951 (s), 2933 (s), 2887 (m), 2858 (s), 1653 (w), 1464 (m), 1369 (m), 1254 (m), 1097 (s), 837 (s), 766 (m), 736 (m), 696 (m) cm^{-1}; $[\alpha]^{22}_D$ +7.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (m, 10 H, ArH), 5.51 (d, *J* = 11.5 Hz, 1 H, =CH), 5.41−5.37 (m, 1H, CH=), 4.59 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 4.48 (s, 2 H, CH_2Ph), 4.41 (d, *J* =12 Hz, 1 H, C*H*HPh), 3.86 (dd, *J* = 10.2, 5.2 Hz, 1 H, OCH), 3.67−3.61 (m, 5 H, OCH), 2.67−2.59 (m, 2 H, CH_2C=), 2.17 (dd, *J* = 12.7, 5.1 Hz, 2 H, CH), 1.99 (t, *J* = 7.1 Hz, 2 H, CH), 1.81−1.69 (m, 2 H, CH), 1.38 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 0.90 (s, 9 H, *t*-Bu), 0.89 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.08 (s, 6 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 137.8, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 78.7, 77.7, 75.3, 73.1, 73.0, 71.3, 66.0, 63.2, 40.1, 40.0, 32.5, 32.0, 26.0, 25.9, 25.7, 24.2, 19.9, −3.4, −4.5, −4.7; HRMS, calcd for $C_{43}H_{70}O_6Si_2Cs$ (M + Cs^+) 871.3765, found 871.3765.

Disilyl Ether 12. A mixture of the olefin **11** (61.3 g, 82.9 mmol), 10% Pd/C (6.1 g, 10% by weight), and sodium carbonate (900 mg, 8.30 mmol) in ethyl acetate (200 mL) was stirred under a H_2 atmosphere for 12 h at 25 °C. The mixture was filtered through Celite and concentrated to give disilyl ether **12** (61.4 g, 82.9 mmol, 100%). **12**: colorless oil; $R_f = 0.64$ (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2953 (s), 2929 (s), 2884 (m), 2856 (s), 1462 (m), 1454 (m), 1378 (m), 1100 (s), 1089 (s), 836 (s), 775 (m), 734 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −3.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10 H, ArH), 4.56 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* = 12 Hz, 1 H, C*H*HPh), 3.65−3.57 (m, 5 H, OCH), 3.23 (bt, *J* = 8.0 Hz, 1 H, OCH), 2.09 (dd, *J* = 11.0, 5.0 Hz, 2 H, CH), 1.73−1.67 (m, 2 H, CH), 1.49−1.39 (m, 4 H, CH), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 0.90 (s, 9 H, *t*-Bu), 0.86 (s, 9 H, *t*-Bu), 0.07 (s, 3 H, $SiCH_3$), 0.06 (s, 9 H, $SiCH_3$, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 128.8, 128.8, 128.2, 128.1, 128.0, 78.2, 78.2, 77.4, 73.5, 73.2, 73.0, 72.5, 71.4, 66.6, 63.9, 42.2, 40.7, 40.5, 33.9, 32.1, 26.5, 26.2, 24.2, 19.9, 19.7, 17.9, −3.4, −4.5, −4.7; HRMS, calcd for $C_{43}H_{72}O_6Si_2Cs$ (M + Cs^+) 873.3922, found 873.3922.

Alcohol 13. A solution of disilyl ether **12** (61.4 g, 82.9 mmol) and camphorsulfonic acid (19.3 g, 82.9 mmol) in CH_2Cl_2/methanol (1:1, 80 mL) was stirred for 1 h at 0 °C. The reaction was quenched with triethylamine (20 mL) and concentrated. Flash chromatography (silica, 5→30% ether in petroleum ether) gave alcohol **13** (50.4 g, 80.4 mmol, 97%). **13**: colorless foam; $R_f = 0.48$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 3446 (m), 2947 (s), 2859 (m), 1461 (m), 1373 (m), 1254 (m), 1071 (s), 865 (s), 837 (m), 776 (m), 737 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −1.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 10 H, ArH), 4.57 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 3.69−3.57 (m, 7 H, OCH), 3.25 (bt, *J* =5.3 Hz, 1 H, OCH), 2.11 (dd, *J* = 11.5, 5.0 Hz, 1 H, CH), 1.97 (dt, *J* = 1.0, 5.5 Hz, 2 H, CH), 1.75−1.70 (m, 3 H, CH), 1.56−1.50 (m, 2 H, CH), 1.48−1.40 (m, 4 H, CH), 1.28 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 0.87 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 128.3, 128.2, 127.7, 127.5, 127.4, 77.9, 77.6, 76.9, 73.0, 72.9, 72.6, 71.9, 70.9, 66.0, 62.9, 41.3, 40.2, 40.0, 33.0, 31.5, 25.6, 23.4, 19.4, 19.2, 17.8, 17.5, −3.8, −5.0; HRMS, calcd for $C_{37}H_{59}O_6Si$ (M + H^+) 627.4081, found 627.4056.

Carboxylic Acid 14. Oxalyl chloride (14.0 mL, 161 mmol) was added dropwise to a solution of DMSO (17.1 mL, 241 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After 10 min, a solution of alcohol **13** (50.4 g, 80.4 mmol) was added dropwise. Triethylamine (78.4 mL, 563 mmol) was added after stirring at −78 °C for 1 h, and the reaction mixture was allowed to warm to 0 °C. The mixture was diluted with ether (500 mL), washed with aqueous saturated ammonium chloride (300 mL), dried ($MgSO_4$), and concentrated. The crude aldehyde was dissolved in *tert*-butyl alcohol/H_2O (2:1, 150 mL) and treated with 2-methyl-2-butene (80.4 mL of a 2.0 M solution in THF, 161 mmol), $NaH_2PO_4 \cdot H_2O$ (10.9 g, 121 mmol), and sodium chlorite (10.9 g, 121 mmol) at 25 °C. After 1 h, the reaction mixture was diluted with ethyl acetate (200 mL) and washed with 10% aqueous tartaric acid (2 × 100 mL). The water layer was re-extracted with ethyl acetate (2 × 100 mL) and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed (silica, 50→100% ether in petroleum ether) to give carboxylic acid **14** (50.0 g, 78.0 mmol, 97%). **14**: colorless foam; $R_f = 0.48$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 3446 (m), 2950 (s), 2885 (m), 1709 (m), 1461 (m), 1376 (m), 1254 (m), 1078 (s), 865 (s), 837 (m), 776 (m), 737 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −1.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 10 H, ArH), 4.57 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* =11.5 Hz, 1 H, C*H*HPh), 3.69−3.57 (m, 4 H, OCH), 3.25−3.20 (m, 1 H, OCH), 2.35 (dt, *J* = 6.0, 2.1 Hz, 2 H, CH), 2.11 (dd, *J* = 11.5, 5.0 Hz, 1 H, CH), 1.97 (dt, *J* = 1.0, 5.5 Hz, 2 H, CH), 1.75−1.70 (m, 4 H, CH), 1.56−1.50 (m, 2 H, CH), 1.48−1.40 (m, 2 H, CH), 1.28 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 0.87 (s, 9 H, *t*-Bu), 0.09 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 138.5, 138.5, 128.3, 128.2, 127.7, 127.5, 127.4, 77.7, 77.6, 76.9, 73.2, 73.0, 72.6, 71.9, 70.9, 66.0, 41.2, 40.1, 40.0, 34.4, 31.5, 25.6, 23.2, 19.4, 18.4, 17.5, −3.8, −5.0; HRMS, calcd for $C_{37}H_{57}O_7Si$ (M + H^+) 641.3874, found 641.3850.

Hydroxy Acid 15. A mixture of carboxylic acid **14** (50.0 g, 78.0 mmol) and tetra-*n*-butylammonium fluoride (390 mL of a 1.0 M solution in THF, 390 mmol) in THF (100 mL) was stirred at 65 °C for 8 h. The reaction mixture was diluted with ethyl acetate (500 mL) and washed with 2 M hydrochloric acid (300 mL). The water layer was re-extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed (silica, 0→20% methanol in ethyl acetate) to give hydroxy acid **15** (41.1 g, 71.0 mmol, 91%). **15**: colorless foam; $R_f = 0.14$ (silica, ether); IR (film) ν_{max} 3425 (m), 3062 (m), 2946 (s), 2874 (m), 1711 (s), 1456 (m), 1378 (m), 1275 (m), 1209 (m), 1098 (s), 1070 (s), 1028 (s), 894 (s), 738 (m), 698 (m), 608 (m) cm^{-1}; $[\alpha]^{22}_D$ −14.6 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 10 H, ArH), 4.56 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 3.69 (dd, *J* = 11.7, 4.7 Hz, 1 H, OCH), 3.65−3.56 (m, 3 H, OCH), 3.28 (dd, *J* = 12.2, 3.3 Hz, 1 H, OCH), 2.37 (dt, *J* = 7.0, 2.5 Hz, 2 H, CH), 2.10 (dd, *J* = 11.7, 5.2 Hz, 1 H, CH), 2.02−1.91 (m, 2 H, CH), 1.85−1.83 (m, 1 H, CH), 1.78−1.62 (m, 3 H, CH), 1.61−1.57 (m, 1 H, CH), 1.53−1.41 (m, 2 H, CH), 1.24 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 138.3, 128.3, 128.2, 127.6, 127.5, 127.4, 127.4, 77.7, 77.1, 72.9, 72.8, 72.6, 72.4, 70.9, 65.9, 41.2, 40.1, 39.8, 34.0, 30.8, 22.4, 19.3, 18.3, 17.3; HRMS, calcd for $C_{31}H_{42}O_7Cs$ (M + Cs^+) 659.1985, found 659.1997.

Lactone 7. A solution of hydroxy acid **15** (5.02 g, 14.3 mmol) and triethylamine (2.0 mL, 14.3 mmol) in THF (100 mL) was treated dropwise with 2,4,6-trichlorobenzoyl chloride (2.40 g, 10.0 mmol) at 0 °C. After 2 h, the reaction mixture was diluted with benzene (500 mL) and added dropwise over 1 h to a refluxing solution of *N,N*-dimethyl-4-aminopyridine (5.81 g, 47.5 mmol) in benzene (1.5 L). After 3 h, the mixture was concentrated and the residue was diluted with ether (500 mL), washed with aqueous saturated ammonium chloride (200 mL), aqueous saturated sodium bicarbonate (200 mL), and brine (200 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (silica, 50→70% ether in petroleum ether) to give lactone **7** (4.30 g, 8.60 mmol, 90%). **7**: colorless needles, mp 103 °C (ether/hexanes); $R_f = 0.38$ (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2943 (m), 2871 (m), 1739 (s), 1455 (m), 1378 (m), 1273 (m), 1098 (s), 1050 (s), 739 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ −43.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.28 (m, 10 H, Ar), 4.56 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.47 (s, 2 H, CH_2Ph), 4.41 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.31 (dd, *J* = 11.0, 5.5 Hz, 1 H, CHOC(O)), 3.66−3.59 (m, 3 H, C*H*$_2$OCH$_2$Ph and OCH), 3.35 (dd, *J* = 12.0, 3.8 Hz, 1 H, OCH), 2.65−2.62 (m, 2 H, $CH_2C(O)$), 2.13 (dd, *J* = 11.7, 5.1 Hz, 1 H, CH), 2.00−1.87 (m, 6 H, CH), 1.75−1.40 (m, 3 H, CH), 1.26 (s, 6 H, 2 × CH_3), 1.23 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.3, 138.3, 128.2, 127.6, 127.4, 127.4, 79.7, 77.6, 77.1, 75.3, 72.9, 71.4, 71.0, 65.8, 43.6, 40.0, 39.9, 33.5, 28.2, 20.2, 19.7, 19.2, 17.3; HRMS, calcd for $\mathrm{C_{31}H_{40}O_6Na}$ (M + Na$^+$) 509.2903, found 509.2888.

Lactone Derived Enol Triflate 16. A solution of lactone **7** (4.30 g, 8.50 mmol) and HMPA (2.2 mL, 12.8 mmol) in THF (50 mL) was treated with lithium bis(trimethylsilyl)amide (42.5 mL of a 1.0 M solution in THF, 42.5 mmol) at −78 °C. After stirring at −78 °C for 2 h, *N*-phenyl trifluormethanesulfonimide (4.61 g, 12.8 mmol) was added and the mixture was allowed to warm to 25 °C over 1 h. After stirring for 1 h at 25 °C, the reaction was quenched with water (50 mL, containing 1% of triethylamine) and extracted with ether (200 mL). The organic layer was dried ($\mathrm{MgSO_4}$), concentrated, and subjected to flash chromatography (silica, 20→50% ether in petroleum ether containing 1% of triethylamine) to give enol triflate **16** (5.11 g, 7.91 mmol, 93%). **16**: colorless foam; $R_f = 0.81$ (silica, 50% ether in petroleum ether); IR (film) $\nu_{\max}$ 2943 (m), 2872 (m), 1701 (s), 1421 (m), 1241 (s), 1215 (s), 1137 (s), 1094 (s), 1071 (s), 1021 (m), 922 (m), 840 (m), 740 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_{\mathrm{D}}$ −34.9 (*c* 1.0, $\mathrm{CH_2Cl_2}$); ^{1}H NMR (500 MHz, $\mathrm{C_6D_6}$) δ 7.31−7.07 (m, 10 H, ArH), 4.36−4.34 (m, 1 H, =CH), 4.34 (s, 2 H, $\mathrm{CH_2Ph}$), 4.33 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.19 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.75 (dt, *J* = 9.2, 6.8 Hz, 1 H, OCH), 3.64−3.55 (m, 3 H, OCH), 3.29 (dd, *J* = 12.5, 3.3 Hz, 1 H, OCH), 2.13−2.05 (m, 4 H, CH), 1.83 (bq, *J* = 12.0 Hz, 1 H, CH), 1.66−1.57 (m, 2 H, CH), 1.51 (bt, *J* = 11.6 Hz, 1 H, CH), 1.43−1.35 (m, 1 H, CH), 1.30 (s, 3 H, $\mathrm{CH_3}$), 1.20−1.17 (m, 1 H, CH), 1.13 (s, 3 H, $\mathrm{CH_3}$), 1.03 (s, 3 H, $\mathrm{CH_3}$); ^{13}C NMR (125 MHz, $\mathrm{C_6D_6}$) δ 152.6, 138.7, 138.6, 128.2, 127.8, 127.5, 127.3, 118.5 (q, *J* = 320 Hz, $\mathrm{CF_3}$), 95.4, 87.3, 77.9, 77.0, 76.4, 73.0, 72.8, 71.9, 70.9, 65.9, 40.4, 40.3, 40.2, 28.2, 19.4, 18.8, 18.4, 17.2; HRMS, calcd for $\mathrm{C_{32}H_{39}F_3O_8SCs}$ (M + Cs$^+$) 773.1372, found 773.1367.

Bromide 18. Thionyl bromide (104 g, 0.501 mol) was added to a mixture of γ-valerolactone (**17**, 100 g, 1.00 mol) and dry zinc bromide (11.3 g, 50.2 mmol) and the mixture was heated at 55 °C for 50 h. The reaction mixture was cooled to 25 °C, diluted with $\mathrm{CH_2Cl_2}$ (300 mL), and added dropwise to a solution of *N*,*N*-dimethyl-4-aminopyridine (24.4 g, 0.200 mol), triethylamine (279 mL, 2.00 mol), and 3-methyl-3-oxetanemethanol (100 g, 1.00 mol) in $\mathrm{CH_2Cl_2}$ at 0 °C. After stirring for 2 h at 25 °C, the mixture was filtered through Celite, diluted with ether (1 L), and washed with brine (500 mL). The organic layer was dried ($\mathrm{MgSO_4}$), concentrated, and subjected to flash chromatography (silica, 10→30% ether in petroleum ether containing 1% of triethylamine) to give bromide **18** (55.7 g, 0.212 mol). **18**: yellow oil; $R_f = 0.32$ (silica, 40% ether in petroleum ether); IR (film) $\nu_{\max}$ 2964 (s), 2930 (m), 2871 (m), 1739 (s), 1458 (m), 1380 (m), 1272 (m), 1163 (s), 982 (s), 833 (m) cm^{-1}; ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ 4.52 (dd, *J* = 4.6, 1.4 Hz, 2 H, oxetane $\mathrm{CH_2}$), 4.37 (d, *J* = 6.0 Hz, 2 H, oxetane $\mathrm{CH_2}$), 4.18 (s, 2 H, $\mathrm{OCH_2C}$), 4.19−4.13 (m, 1 H, BrCH), 2.61−2.54 (m, 2 H, $\mathrm{CH_2C(O)}$), 2.18−2.01 (m, 2 H, $\mathrm{CHBrC}\mathit{H}_2$), 1.73 (d, *J* = 6.7 Hz, 3 H, $\mathrm{CHC}\mathit{H}_3$), 1.32 (s, 3 H, $\mathrm{CCH_3}$); ^{13}C NMR (125 MHz, $\mathrm{C_6D_6}$) δ 173.2, 79.9, 69.2, 50.7, 39.5, 36.2, 32.8, 26.9, 21.5; HRMS, calcd for $\mathrm{C_{10}H_{18}O_3Br}$ (M + H$^+$) 265.0439, found 265.0427.

Iodide 19. A solution of bromide **18** in acetone (1 L, containing 1% of triethylamine) was treated with sodium iodide (165 g, 1.10 mol) and 18-crown-6 (5.0 g). After stirring at 25 °C for 50 h, the reaction mixture was diluted with ether (1.5 L) and washed with aqueous saturated sodium thiosulfate (1 L) and water (1 L). The organic layer was dried ($\mathrm{MgSO_4}$), concentrated, and subjected to flash chromatography (silica, 10→30% ether in petroleum ether containing 1% of triethylamine) to give iodide **19** (62.4 g, 0.20 mol, 20% over 2 steps). Iodide **19**: yellow oil; $R_f = 0.32$ (silica, 40% ether in petroleum ether); IR (film) $\nu_{\max}$ 2962 (s), 2930 (m), 2870 (m), 1738 (s), 1445 (m), 1379 (m), 1268 (m), 1178 (s), 982 (s), 833 (m) cm^{-1}; ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ 4.53 (dd, *J* = 6.0, 1.2 Hz, 2 H, oxetane $\mathrm{CH_2}$), 4.40 (d, *J* = 6.0 Hz, 2 H, oxetane $\mathrm{CH_2}$), 4.25−4.16 (m, 1 H, CHI), 4.19 (s, 2 H, $\mathrm{CH_2C}$), 2.61−2.52 (m, 2 H, $\mathrm{CH_2C(O)}$), 2.12−1.96 (m, 2 H, $\mathrm{CHC}\mathit{H}_2$), 1.96 (d, *J* = 6.5 Hz, 3 H, $\mathrm{CHC}\mathit{H}_3$), 1.35 (s, 3 H, $\mathrm{CCH_3}$); ^{13}C NMR (125 MHz, $\mathrm{C_6D_6}$) δ 173.0, 80.0, 69.2, 39.4, 37.8, 34.8, 29.3, 28.8, 21.6; HRMS, calcd for $\mathrm{C_{10}H_{18}O_3I}$ (M + H$^+$) 313.0301, found 313.0314.

Orthoester 20. A stirred solution of iodide **19** (62.4 g, 0.201 mol) in $\mathrm{CH_2Cl_2}$ (1 L) was treated dropwise with boron trifluoride etherate (6.26 mL, 0.050 mmol) at −30 °C. After stirring for 12 h at −30 °C, the mixture was quenched with triethylamine (10 mL), diluted with ether (1 L), and washed with water (500 mL). The organic layer was dried ($\mathrm{MgSO_4}$), concentrated, and subjected to flash chromatography (silica, 10→20% ether in petroleum ether containing 1% of triethylamine) to give orthoester **20** (43.8 g, 0.14 mol, 70%). **20**: white solid; $R_f = 0.34$ (silica, 30% ether in petroleum ether); IR (film) $\nu_{\max}$ 2928 (m), 2874 (m), 1450 (m), 1396 (m), 1348 (m), 1292 (m), 1228 (m), 1059 (s), 922 (s), 887 (m) cm^{-1}; ^{1}H NMR (500 MHz, $\mathrm{C_6D_6}$) δ 3.94−3.88 (m, 1 H, CH), 3.51 (s, 6 H, $\mathrm{OCH_2}$), 2.27−2.15 (m, 2 H, $\mathrm{CH_2C}$), 2.23−1.91 (m, 2 H, $\mathrm{CHC}\mathit{H}_2$), 1.58 (d, *J* = 6.5 Hz, 3 H, $\mathrm{CHC}\mathit{H}_3$), 0.00 (s, 3 H, $\mathrm{CCH_3}$); ^{13}C NMR (125 MHz, $\mathrm{C_6D_6}$) δ 109.2, 73.1, 72.6, 37.6, 37.5, 30.0, 29.0, 14.1; HRMS, calcd for $\mathrm{C_{10}H_{18}O_3I}$ (M + H$^+$) 313.0301, found 313.0288.

Enol Ether 25. A solution of orthoester **20** (6.14 g, 19.7 mmol) in ether (75 mL) was treated with *tert*-butyllithium (20.7 mL of a 1.7 M solution in pentane, 35.2 mmol) at −120 °C. After stirring at −120 °C for 30 min, the mixture was allowed to warm to −78 °C and lithium 2-thienylcyanocuprate (70.5 mL of a 0.25 M solution in THF, 17.6 mmol) was added. After stirring at −30 °C for 30 min, the mixture was cooled to −78 °C and treated with HMPA (75 mL) and a solution of enol triflate **16** (2.10 g, 3.28 mmol) in THF (25 mL). The mixture was allowed to warm to 0 °C over 2 h, diluted with ether (500 mL), and washed with brine (2 × 400 mL). The organic layer was dried ($\mathrm{MgSO_4}$), filtered, concentrated, and subjected to flash chromatography (silica, 10→50% ether in petroleum ether containing 1% triethylamine) to give enol ether **25** (1.89 g, 2.79 mmol, 85%, 2.4:1 mixture of diastereoisomers). **25**: colorless oil; $R_f = 0.44$ (silica, 50% ether in petroleum ether); IR (film) $\nu_{\max}$ 2932 (m), 2873 (m), 1669 (w), 1485 (m), 1378 (m), 1280 (m), 1199 (m), 1080 (s), 992 (s), 840 (m), 738 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_{\mathrm{D}}$ −45.5 (*c* 1.0, $\mathrm{CH_2Cl_2}$, 2.4 :1 mixture of isomers); ^{1}H NMR (500 MHz, $\mathrm{C_6D_6}$) δ (major isomer) 7.33−7.06 (m, 10 H, ArH), 4.48 (dd, *J* = 8.0, 2.4 Hz, 1 H, =CH), 4.36 (s, 2 H, $\mathrm{CH_2Ph}$), 4.35 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.17 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.83−3.78 (m, 1 H, OCH), 3.68−3.59 (m, 2 H, OCH), 3.58 (s, 6 H, $\mathrm{C(CH_2O)_3}$), 3.51−3.48 (m, 1 H, OCH), 3.44−3.40 (m, 1 H, OCH), 2.20−1.94 (m, 11 H, CH), 1.86−1.76 (m, 2 H, CH), 1.68−1.59 (m, 1 H, CH), 1.49−1.43 (m, 1 H, CH), 1.30 (s, 3 H, $\mathrm{CH_3}$), 1.28 (s, 3 H, $\mathrm{CH_3}$), 1.23 (s, 3 H, $\mathrm{CH_3}$), 1.03 (d, *J* = 6.5 Hz, 3 H, $\mathrm{CH_3}$), −0.02 (s, 3 H, $\mathrm{CH_3}$); ^{13}C NMR (125 MHz, $\mathrm{C_6D_6}$) δ (major isomer) 162.2, 139.4, 139.3, 128.5, 128.3, 127.6, 127.5, 109.5, 102.9, 85.7, 78.7, 78.5, 77.1, 73.1, 72.9, 72.5, 71.1, 66.4, 46.7, 41.6, 41.1, 41.0, 40.6, 35.4, 34.8, 29.3, 28.1, 21.3, 19.7, 19.3, 18.6, 17.4, 13.6, 12.1; HRMS, calcd for $\mathrm{C_{41}H_{57}O_8}$ (M + H$^+$) 677.4053, found 677.4025.

Dihydroxy Ester 27. A solution of enol ether **25** (2.4:1 mixture of diastereoisomers, 1.50 g, 2.22 mmol) in 1,2-dimethoxyethane/$\mathrm{H_2O}$ (5:1, 24 mL) was treated with pyridinium *p*-toluenesulfonate (111 mg, 0.44 mmol) and stirred at 25 °C for 30 min. The mixture was diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (2 × 100 mL), and dried ($\mathrm{MgSO_4}$). Filtration and concentration gave the dihydroxy ester **27** (1.54 g, 2.22 mmol, 100%, 2.4:1 mixture of diastereoisomers). **27**: colorless oil; $R_f = 0.10$ (silica, 50% ether in petroleum ether); IR (film) $\nu_{\max}$ 3459 (w), 2934 (m), 2875 (m), 1732 (m), 1671 (w), 1456 (m), 1380 (m), 1257 (m), 1078 (s), 739 (m), 697 (m) cm^{-1}; ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ (major isomer) 7.33−7.25 (m, 10 H, ArH), 4.62 (dd, *J* = 8.1, 2.7 Hz, 1 H, =CH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, $\mathrm{CH_2Ph}$), 4.38 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.17−4.10 (m, 2 H, OCH), 3.66−3.46 (m, 7 H, OCH), 3.34−3.28 (m, 2 H, OCH), 3.15 (bs, 2 H, OH), 2.33−2.27 (m, 2 H, CH), 2.1−1.86 (m, 8 H, CH), 1.84−1.60 (m, 3 H, CH), 1.46−1.35 (m, 2 H, CH), 1.25 (s, 6 H, 2 × $\mathrm{CH_3}$), 1.24 (s, 3 H, $\mathrm{CH_3}$), 1.02 (d, *J* = 6.9 Hz, 3 H, $\mathrm{CH_3}$), 0.83 (s, 3 H, $\mathrm{CH_3}$); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$) δ (major isomer) 174.6, 160.9, 138.3, 138.3, 128.2, 128.2, 127.6, 127.5, 127.4, 103.9, 85.3, 78.5, 77.7, 76.7, 72.9, 72.1, 70.9, 67.3, 66.2, 65.8, 41.4, 41.2, 40.5, 40.0, 39.7, 32.5, 32.2, 29.6, 29.2, 21.2, 19.6, 19.0, 18.7, 17.3, 16.7, 15.1; HRMS, calcd for $\mathrm{C_{41}H_{58}O_9Cs}$ (M + Cs$^+$) 827.3135, found 827.3103.

Trihydroxy Ester 28. A solution of dihydroxy ester **27** (2.4:1 mixture of diastereoisomers, 550 mg, 0.793 mmol) in THF (8 mL) was treated at 0 °C with $\mathrm{BH_3{\cdot}THF}$ (4.76 mL of a 1.0 M solution in THF, 4.76 mmol) and stirred at 0 °C for 40 min. Sodium hydroxide (5.0 mL, 3 N) and 30% aqueous hydrogen peroxide (4.0 mL) were added at 0 °C and the mixture was stirred for 1 h at 25 °C. The organic layer was washed with brine (20 mL), dried ($\mathrm{MgSO_4}$), filtered, concentrated, and subjected to flash chromatography (silica, 100% ether → 100% ethyl acetate) to give trihydroxy ester **28** (503 mg, 0.71 mmol, 89%, 2.4:1 mixture of diastereoisomers). **28**: colorless foam; R_f = 0.62 (silica, 100% ethyl acetate); IR (film) ν_{max} 3413 (m), 2935 (m), 2875 (m), 1726 (m), 1453 (m), 1381 (m), 1069 (s), 738 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (major isomer) 7.33−7.25 (m, 10 H, ArH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.37 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.22−4.08 (m, 2 H, OCH), 4.05−3.96 (m, 1 H, OCH), 3.64−3.40 (m, 9 H, OCH), 3.33−3.27 (m, 1 H, OCH), 3.04 (bs, 3 H, OH), 2.49−2.32 (m, 2 H, CH), 2.15−2.11 (m, 1 H, CH), 2.00−1.53 (m, 11 H, CH), 1.38 (bt, *J* = 15.5 Hz, 1 H, CH), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 0.93 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.84 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major isomer) 174.6, 138.4, 138.3, 128.2, 128.2, 127.6, 127.5, 127.4, 89.0, 87.8, 83.6, 80.7, 77.9, 72.9, 72.6, 72.2, 70.9, 70.4, 69.4, 66.3, 65.9, 40.3, 40.2, 36.3, 35.9, 31.8, 31.7, 29.3, 29.0, 26.8, 21.4, 19.8, 17.5, 16.8, 15.7, 13.6; HRMS, calcd for $C_{41}H_{60}O_{10}Cs$ (M + Cs^+) 845.3241, found 845.3210.

Hydroxy Acid 29. A solution of trihydroxy ester **28** (2.4:1 mixture of diastereoisomers, 1.52 g, 2.13 mmol) in 1,2-dimethoxyethane/H_2O (25 mL, 4:1) was treated with lithium hydroxide hydrate (447 mg, 10.7 mmol) and stirred at 25 °C for 1 h. The mixture was acidified with 2 N hydrochloric acid to pH 1 and the water layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give hydroxy acid **29** (1.07 g, 1.75 mmol, 82%, 2.4:1 mixture of diastereoisomers) that was used for the next step without further purification. **29**: colorless foam; R_f = 0.10 (silica, 100% ether); IR (film) ν_{max} 3416 (m), 2932 (s), 2874 (s), 1711 (m), 1456 (m), 1377 (m), 1305 (m), 1269 (m), 1211 (m), 1072 (s), 738 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (major isomer) 7.35−7.25 (m, 10 H, ArH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.02 (bd, *J* = 5.5 Hz, 1 H, OCH), 3.65−3.56 (m, 3 H, OCH), 3.52−3.48 (m, 1 H, OCH), 3.42−3.40 (m, 1 H, OCH), 3.33−3.31 (m, 1 H, OCH), 2.47−2.30 (m, 2 H, $CH_2C(O)$), 2.13 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH), 2.02−1.47 (m, 11 H, CH), 1.44 (bt, *J* = 11.3 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 0.93 (d, *J* = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major isomer) 178.8, 138.3, 138.2, 128.2, 128.2, 127.6, 127.5, 127.4, 89.1, 80.6, 77.8, 77.4, 76.7, 73.5, 73.0, 72.6, 70.8, 65.9, 58.0, 40.1, 36.3, 35.9, 31.5, 29.2, 28.4, 28.1, 26.5, 21.3, 19.8, 17.5, 15.7, 13.6; HRMS, calcd for $C_{36}H_{50}O_8Cs$ (M + Cs^+) 743.2560, found 743.2560.

Lactone 6. A solution of hydroxy acid **29** (2.4:1 mixture of diastereoisomers, 1.16 g, 1.90 mmol) and triethylamine (397 μL, 2.85 mmol) in THF (10 mL) was treated dropwise with 2,4,6-trichlorobenzoyl chloride (296 μL, 1.90 mmol) at 0 °C. After 2 h, the reaction mixture was diluted with benzene (600 mL) and added dropwise over 1 h to a refluxing solution of *N*,*N*-dimethyl-4-aminopyridine (1.39 g, 11.4 mmol) in benzene (300 mL). After 3 h, the mixture was concentrated and the residue was diluted with ether (300 mL) washed with aqueous saturated ammonium chloride (100 mL), aqueous saturated sodium bicarbonate (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (silica, 50→70% ether in petroleum ether) to give the desired lactone **6** (676 mg, 1.14 mmol, 60%) and its epimer **6β** (282 mg, 0.475 mmol, 25%). **6**: colorless foam; R_f = 0.75 (silica, 80% ether in petroleum ether); IR (film) ν_{max} 2946 (m), 2874 (m), 1738 (s), 1458 (m), 1379 (m), 1267 (m), 1076 (s), 911 (w), 734 (m), 699 (w) cm^{-1}; $[\alpha]^{22}_D$ −24.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, Ar), 4.56 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.46−4.42 (m, 1 H, CHOC(O)), 4.38 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.65−3.57 (m, 3 H, CH_2OCH_2Ph and OCH), 3.46 (dd, *J* = 8.4, 3.6 Hz, 1 H, OCH), 3.34 (dd, *J* = 11.8, 3.7 Hz, 1 H, OCH), 3.26 (dd, *J* = 11.5, 4.0 Hz, 1 H, OCH), 2.81 (dt, *J* = 14.6, 8.7 Hz, 1 H, C*H*HC(O)), 2.56 (dt, *J* = 14.6, 5.8 Hz, 1 H, C*H*HC(O)), 2.15−1.93 (m, 6 H, CH), 1.83−1.70 (m, 6 H, CH), 1.42 (bt, *J* = 11.4 Hz, 1 H, CH), 1.31 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.02 (d, *J* = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.4, 138.4, 128.3, 128.2, 127.6, 127.5, 127.5, 127.4, 87.7, 86.1, 78.0, 77.5, 77.1, 73.3, 73.0, 71.0, 65.9, 40.3, 40.2, 37.9, 34.1, 30.5, 29.2, 27.8, 24.0, 21.5, 20.4, 17.5, 15.0; HRMS, calcd for $C_{36}H_{48}O_7Cs$ (M + Cs^+) 725.2454, found 725.2461. **6β**: colorless needles, mp 126−127 °C (ether); R_f = 0.33 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2932 (m), 2866 (m), 1738 (s), 1454 (m), 1381 (m), 1248 (s), 1204 (s), 1138 (s), 1076 (s), 1042 (m), 1002 (m), 737 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ −24.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 10 H, ArH), 4.45 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.45−4.42 (m, 1 H, OCHOC(O)), 4.38 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 3.65−3.57 (m, 3 H, OCH), 3.37−3.31 (m, 2 H, OCH), 3.05 (dd, *J* = 10.5, 7.5 Hz, 1 H, OCH), 2.72 (bt, *J* = 14.0 Hz, 1 H, C*H*HC(O)), 2.58 (dd, *J* = 15.5, 13.0 Hz, 1 H, C*H*HC(O)), 2.17 (dd, *J* = 11.5, 11.0 Hz, 1 H, CH), 2.12−2.06 (m, 2 H, CH), 2.02−1.91 (m, 3 H, CH), 1.88-1.72 (m, 4 H, CH), 1.69−1.62 (m, 1 H, CH), 1.51−1.41 (m, 2 H, CH), 1.31 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.07 (d, *J* = 6.5, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 138.0, 128.3, 128.3, 127.7, 127.6, 127.5, 91.3, 90.0, 82.0, 78.1, 73.8, 73.5, 73.1, 71.0, 66.0, 40.5, 40.3, 39.8, 37.8, 33.0, 30.2, 29.0, 28.5, 21.0, 20.1, 19.3, 17.3; HRMS, calcd for $C_{36}H_{48}O_7$ (M + Cs^+) 725.2454, found 725.2486.

Enol Triflate 36. A solution of lactone **6** (3.87 g, 6.53 mmol) and HMPA (2.3 mL, 13.1 mmol) in THF (100 mL) was treated with lithium bis(trimethylsilyl)amide (32.6 mL of a 1.0 M solution in THF, 32.6 mmol) at −78 °C. After stirring at −78 °C for 2 h, *N*-phenyl trifluoromethanesulfonimide (3.50 g, 9.80 mmol) was added and the mixture was allowed to warm to 25 °C over 1 h. After further stirring at 25 °C for 1 h, the reaction was quenched with water (50 mL, containing 1% of triethylamine) and extracted with ether (200 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (silica, 10% ether in petroleum ether containing 1% triethylamine) to give the enol triflate **36** (4.40 g, 6.07 mmol, 93%). **36**: colorless foam, R_f = 0.83 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2952 (m), 2875 (m), 1699 (m), 1421 (m), 1214 (m), 1139 (m), 1072 (s), 836 (m), 739 (m), 699 (m), 607 (m) cm^{-1}; $[\alpha]^{22}_D$ −12.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.27−7.07 (m, 10 H, ArH), 4.36 (dd, *J* = 7.1, 2.3 Hz, 1 H, =CH), 4.34 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.30 (s, 2 H CH_2Ph), 4.21−4.19 (m, 1 H, OCH), 4.17 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.72 (dt, *J* = 9.2, 6.8 Hz, 1 H, OCH), 3.62 (dd, *J* = 11.5, 5.3 Hz, 1 H, OCH), 3.57 (dt, *J* = 9.2, 6.5 Hz, 1 H, OCH), 3.36 (dd, *J* = 12.2, 3.3 Hz, 1 H, OCH), 3.00 (dd, *J* = 9.5, 3.9 Hz, 1 H, OCH), 2.88 (dd, *J* = 11.7, 3.8 Hz, 1 H, OCH), 2.12−1.98 (m, 5 H, CH), 1.92−1.74 (m, 4 H, CH), 1.62−1.49 (m, 3 H, CH), 1.30 (s, 3 H, CH_3), 1.25−1.20 (m, 1 H, CH), 1.14 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 0.75 (d, *J* = 6.9 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ 153.4, 139.1, 139.0, 128.5, 128.2, 128.0, 127.7, 119.1 (q, *J* = 320 Hz, CF_3), 96.1, 87.2, 87.1, 85.0, 78.5, 77.6, 77.3, 73.8, 73.5, 73.1, 71.2, 66.3, 40.9, 40.8, 38.2, 34.4, 29.4, 27.8, 25.2, 22.2, 20.2, 17.8, 17.4; HRMS calcd for $C_{37}H_{47}F_3O_9SCs$ (M + Cs^+) 857.1948, found 857.1933.

Diketone 55. A solution of **54** (15.0 g, 41.9 mmol) and Dess-Martin periodinane (40.0 g, 94.3 mmol) in CH_2Cl_2 (200 mL) was heated at 40 °C for 12 h. The mixture was diluted with ethyl acetate (300 mL) and washed with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1, 300 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (silica, 20→50% of ethyl acetate in petroleum ether) to give **55** as its hydrate, which was azeotropically dried with toluene (300 mL) using a Soxhlet condenser containing 4Å molecular sieves. After heating at 110 °C for 12 h, the solution was cooled to 0 °C and the crystalline diketone **55** was filtered off (14.0 g, 37.7 mmol, 90%). **55**: white solid, mp 184−186 °C (toluene); R_f = 0.51 (silica, 50% ethyl acetate in petroleum ether); IR (film) ν_{max} 2930 (m), 1724 (s), 1458 (m), 1382 (s), 1226 (m), 1213 (s), 1062 (s), 862 (m) cm^{-1}; $[\alpha]^{22}_D$ −73.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 4 H, ArH), 7.34−7.32 (m, 6 H, ArH), 5.94 (s, 2 H, 2 × CHAr), 5.08 (s, 2 H, 2 × OCH), 4.48 (d, *J* = 18.0 Hz, 2 H, 2 × C*H*H), 4.38 (d, *J* = 18.0 Hz, 2 H, 2 × C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 138.2, 129.4, 128.4, 126.3, 99.2, 81.3, 72.4; HRMS, calcd for $C_{20}H_{19}O_6$ (M + H^+): 355.1182, found 355.1173.

Diol 56. To a solution of methylmagnesium iodide (68.0 mL of a 3.0 M solution in ether, 256 mmol) was added diketone **55** in four portions at 0 °C. The reaction was quenched with MeOH (10 mL), diluted with EtOAc (250 mL), and washed with aqueous saturated ammonium chloride (200 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (20→50% ethyl acetate in petroleum ether) to give diol **56** (12.0 g, 31.2 mmol, 92%). **56**: colorless crystals, mp 112−114 °C (ether); R_f = 0.37 (silica, 50% ethyl acetate in petroleum ether); IR (film) ν_{max} 3253 (m), 2933 (m), 2886 (m), 1455 (m), 1396 (m), 1096 (s), 1020 (s), 963 (m), 915 (m), 761 (m) cm $^{-1}$; $[\alpha]^{22}_D$ −53.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz,

$CDCl_3$) δ 7.53−7.51 (m, 4 H, ArH), 7.37−7.35 (m, 6 H, ArH), 5.57 (s, 2 H, 2 × CHAr), 3.97 (s, 2 H, 2 × OCH), 3.94 (d, $J = 10.5$ Hz, 2 H, 2 × C*H*H), 3.73 (d, $J = 11.0$ Hz, 2 H, 2 × C*H*H), 2.99 (bs, 2 H, 2 × OH), 1.58 (s, 6 H, 2 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 128.6, 128.0, 125.8, 101.2, 81.5, 77.3, 66.7, 21.0; HRMS, calcd for $C_{22}H_{26}O_6Cs$ (M + Cs^+) 519.0784, found 519.0799.

Tetraol 60. A solution of **56** (5.01 g, 12.9 mmol), 2,6-lutidine (10.6 mL, 90.3 mmol), and *N*,*N*-dimethyl-4-aminopyridine (0.16 g, 1.3 mmol) in CH_2Cl_2 (30 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (11.9 mL, 51.6 mmol) at 0 °C. After stirring for 5 h at 25 °C, the mixture was diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (100 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 5→10% ether in petroleum ether) gave the corresponding disilyl ether (7.80 g, 12.7 mmol, 99%): colorless oil; $R_f = 0.45$ (silica, 10% ether in petroleum ether); IR (film) ν_{max} 2954 (m), 2928 (m), 2856 (m), 1462 (m), 1407 (m), 1385 (m), 1257 (s), 1154 (s), 1104 (s), 1029 (s), 837 (m), 778 (m) cm^{-1}; $[\alpha]^{22}_D$ −11.2 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.56−7.51 (m, 4 H, ArH), 7.40−7.36 (m, 6 H, ArH), 5.55 (s, 2 H, 2 × CHAr), 4.07 (s, 2 H, 2 × OCH), 3.96 (d, $J = 10.2$ Hz, 2 H, 2 × C*H*H), 3.73 (d, $J = 10.2$ Hz, 2 H, 2 × C*H*H), 1.60 (s, 6 H, 2 × CH_3), 0.94 (s, 18 H, 2 × *t*-Bu), 0.19 (s, 6 H, $Si(CH_3)_2$), 0.13 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 129.1, 128.1, 126.0, 101.7, 79.9, 79.2, 68.9, 25.7, 21.9, 18.0, −1.3; HRMS, calcd for $C_{34}H_{55}O_6Si_2$ (M + H^+) 615.3537, found 615.3516. A mixture of the disilyl ether (7.8 g, 12.7 mmol) and Pd/C (800 mg, 10%) in acetic acid (20 mL) was stirred under a H_2 atmosphere for 48 h at 25 °C. Filtration of the mixture through Celite and concentration afforded tetraol **60** (5.10 g, 11.6 mmol, 91%). **60**: white solid, mp 83.5−84.5 °C (benzene); $R_f = 0.36$ (silica, 70% ether in petroleum ether); IR (film) ν_{max} 3413 (m), 2953 (m), 2930 (m), 2858 (m), 1471 (m), 1469 (m), 1386 (m), 1257 (s), 1135 (s), 1058 (s), 1004 (s), 836 (m), 774 (m) cm^{-1}; $[\alpha]^{22}_D$ −12.4 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 2 H, 2 × C*H*OH), 3.62 (d, $J = 11.5$ Hz, 2 H, 2 × C*H*H), 3.45 (d, $J = 11.5$ Hz, 2 H, 2 × C*H*H), 3.30 (bs, 2 H, 2 × CHO*H*), 3.05 (bs, 2 H, 2 × CH_2O*H*), 1.31 (s, 6 H, 2 × CH_3), 0.89 (s, 18 H, 2 × *t*-Bu), 0.16 (s, 12 H, 2 × $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.6, 72.5, 67.0, 25.7, 20.5, 18.1, −2.3; HRMS, calcd for $C_{20}H_{47}O_6Si_2$ (M + H^+) 439.2911, found 439.2895.

Dipivaloate 61. A solution of tetraol **60** (5.10 g, 11.6 mmol), *N*,*N*-dimethyl-4-aminopyridine (0.28 g, 2.3 mmol), and pivaloyl chloride (4.30 mL, 34.8 mmol) in pyridine (15 mL) was stirred at 25 °C for 24 h. The reaction mixture was diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (200 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 30→50% ether in petroleum ether) gave dipivaloate **61** (6.70 g, 11.6 mmol, 100%). **61**: colorless oil; $R_f = 0.33$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 3528 (m), 2958 (s), 2930 (s), 2858 (m), 1732 (s), 14621 (m), 1397 (m), 1284 (m), 1257 (m), 1152 (s), 1037 (m), 836 (s), 775 (m) cm^{-1}; $[\alpha]^{22}_D$ −3.4 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (d, $J = 12.0$ Hz, 2 H, 2 × C*H*H), 4.02 (d, $J = 12.0$ Hz, 2 H, 2 × C*H*H), 3.73 (d, $J = 4.5$ Hz, 2 H, 2 × C*H*OH), 3.11 (d, $J = 4.5$ Hz, 1 H, 2 × CHO*H*), 1.27 (s, 6 H, 2 × CH_3), 1.21 (s, 18 H, 2 × *t*-Bu), 0.88 (s, 18 H, 2 × *t*-Bu), 0.16 (s, 6 H, 2 × $SiCH_3$), 0.15 (s, 6 H, 2 × $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 71.2, 68.3, 38.7, 27.2, 26.9, 25.6, 20.6, 18.1, −2.2, −2.4; HRMS, calcd for $C_{30}H_{62}O_8Si_2Cs$ (M + Cs^+) 739.3038, found 739.3049.

Aldehyde 62. A solution of dipivaloate **61** (6.7 g, 11.7 mmol) in CH_2Cl_2 (25 mL) was treated with lead tetraacetate (5.7 g, 12.9 mmol) and stirred at 25 °C for 15 min. The mixture was diluted with ether (100 mL), washed with aqueous saturated sodium bicarbonate (100 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 10% ether in petroleum ether) gave the aldehyde **62** (6.40 g, 21.2 mmol, 91%). **62**: colorless oil; $R_f = 0.29$ (silica, 10% ether in petroleum ether); IR (film) ν_{max} 2958 (m), 2932 (m), 2858 (m), 1739 (s), 1480 (m), 1447 (m), 1362 (m), 1282 (m), 1148 (s), 1042 (m), 838 (m), 778 (m) cm^{-1}; $[\alpha]^{22}_D$ +12.0 (c 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1 H, CHO), 4.10 (d, $J = 11.5$ Hz, 1 H, C*H*H), 3.99 (d, $J = 11.5$ Hz, 1 H, C*H*H), 1.25 (s, 3 H, CH_3), 1.11 (s, 9 H, *t*-Bu), 0.84 (s, 9 H, *t*-Bu), 0.07 (s, 6 H $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 177.6, 78.9, 67.8, 38.5, 26.9, 25.4, 20.1, 17.9, −2.7; HRMS, calcd for $C_{15}H_{31}O_4Si$ (M + H^+) 303.1992, found 303.1985.

Coupling Product 64. A mixture of enol triflate **36** (435 mg, 0.734 mmol), aldehyde **62** (1.11 g, 3.67 mmol), chromium(II) chloride (360 mg, 2.94 mmol), and nickel(II) chloride (2 mg, 0.015 mmol) in DMF (1 mL) was stirred at 25 °C for 30 min in an ultrasound bath. The resulting dark green suspension was diluted with ether (100 mL), filtered through Celite, washed with brine (2 × 50 mL), dried ($MgSO_4$), and filtered. Concentration and flash chromatography (silica, 10→30% ether in petroleum ether containing 1% triethylamine) gave the addition product **64** (425 mg, 0.484 mmol, 66%, 5:1 mixture of isomers). **64** (major isomer): colorless foam; $R_f = 0.31$ (silica, 10% ethyl acetate in benzene); IR (film) ν_{max} 3546 (w), 2930 (m), 2856 (m), 1730 (m), 1670 (w), 1462 (m), 1253 (m), 1073 (s), 836 (m), 776 (m), 735 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −15.3 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.30−7.07 (m, 10 H, ArH), 5.16 (dd, $J = 7.5, 1.5$ Hz, 1 H, =CH), 4.37 (d, $J = 11.5$ Hz, 1 H, C*H*HPh), 4.35 (d, $J = 11.5$ Hz, 1 H, C*H*HOPiv), 4.33 (s, 2 H, CH_2Ph), 4.29 (d, $J = 11.6$ Hz, 1 H, C*H*HOPiv), 4.19 (d, $J = 11.5$ Hz, 1 H, C*H*HPh), 4.17−4.13 (m, 1 H, OCH), 4.13 (s, 1 H, C*H*OH), 3.80−3.76 (m, 1 H, OCH), 3.67 (dd, $J = 11.5, 5.5$ Hz, 1 H, OCH), 3.65−3.61 (m, 1 H, OCH), 3.45 (dd, $J = 12.0, 2.5$ Hz, 1 H, OCH), 3.22 (dd, $J = 9.0, 4.0$ Hz, 1 H, OCH), 3.06 (dd, $J = 11.5, 4.0$ Hz, 1 H, OCH), 2.52−2.47 (m, 1 H, CH), 2.28−2.21 (m, 1 H, CH), 2.17 (dd, $J = 12.0, 5.5$ Hz, 1 H, CH), 2.12 (t, $J = 6.5$ Hz, 2 H, CH), 2.03−1.73 (m, 8 H, CH), 1.64−1.57 (m, 2 H, CH), 1.35 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.21 (s, 9 H, *t*-Bu), 0.96 (d, $J = 7.0$ Hz, 3 H, CH_3), 0.93 (s, 9 H, *t*-Bu), 0.14 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 177.0, 157.1, 139.3, 139.2, 128.5, 128.2, 127.6, 127.5, 107.2, 87.3, 87.0, 84.1, 78.8, 77.9, 77.5, 76.9, 75.6, 73.9, 73.8, 73.0, 72.8, 71.0, 69.3, 66.3, 41.0, 39.1, 36.2, 30.3, 29.7, 29.5, 28.3, 27.4, 26.0, 22.3, 20.6, 20.2, 18.5, 18.2, −2.4, −2.8; HRMS, calcd for $C_{51}H_{78}O_{10}SiCs$ (M + Cs^+) 1011.4419, found 1011.4462.

Hydroxy Ketone 70. A mixture of triol **68** (7 mg, 10 μmol) and Ag_2CO_3/Celite (50 mg) in benzene (2 mL) was heated at 80 °C under azeotropic removal of water for 3 h. The resulting black suspension was filtered through Celite, concentrated, and subjected to preparative TLC (silica, 100% ether) to give hydroxy ketone **70** (5 mg, 8.2 μmol, 82%). **70**: colorless foam; $R_f = 0.55$ (silica, 100% ether); IR (film) ν_{max} 3449 (m), 2934 (m), 2872 (m), 1714 (m), 1455 (m), 1378 (m), 1071 (s), 737 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ −15.6 (c 0.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 10 H, ArH), 4.55 (d, $J = 11.7$ Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, $J = 11.7$ Hz, 1 H, C*H*HPh), 3.65−3.54 (m, 5 H, OCH), 3.36−3.27 (m, 3 H, OCH), 3.07 (dd, $J = 11.7, 3.8$ Hz, 1 H, OCH), 2.81 (dd, $J = 16.1, 3.0$ Hz, 1 H, C*H*HC(O)), 2.63 (dd, $J = 16.0, 9.0$ Hz, 1 H, C*H*HC(O)), 2.18 (s, 3 H, $C(O)CH_3$), 2.10 (dd, $J = 11.6, 5.2$ Hz, 1 H, CH), 2.01−1.90 (m, 4 H, CH), 1.85−1.79 (m, 2 H, CH), 1.72 (q, $J = 11.8$ Hz, 1 H, CH), 1.67−1.50 (m, 4 H, CH), 1.39 (t, $J = 11.4$ Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.04 (d, $J = 7.0$ Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 138.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 87.5, 86.6, 85.0, 83.0, 78.1, 75.2, 73.4, 73.3, 73.0, 71.0, 66.0, 48.4, 40.3, 40.2, 38.1, 38.0, 31.6, 31.2, 28.8, 28.7, 21.8, 20.1, 18.6, 17.5; HRMS, calcd for $C_{39}H_{54}O_8Cs$ (M + Cs^+) 783.2873, found 783.2849.

Tertiary Alcohol 71. A solution of alcohol **64** (20 mg, 23 μmol) in ether (200 μL) was treated with potassium hydride (5 mg of a 35% suspension in mineral oil) and stirred at 25 °C for 5 min. The mixture was diluted with ether (20 mL) and poured into aqueous saturated ammonium chloride (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to preparative TLC (silica, 30% ether in petroleum ether) to give alcohol **71** (20 mg, 23 μmol, 100%). **71**: colorless foam; $R_f = 0.34$ (silica, 10% ethyl acetate in benzene); IR (film) ν_{max} 3510 (w), 2956 (s), 2855 (s), 1733 (s), 1670 (w), 1461 (m), 1381 (m), 1281 (m), 1153 (s), 1075 (s), 838 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ −11.4 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.30−7.07 (m, 10 H, ArH), 4.76 (dd, $J = 6.0, 1.2$ Hz, 1 H, OCH), 4.41 (d, $J = 10.9$ Hz, 1 H, C*H*HOPiv), 4.36 (d, $J = 11.5$ Hz, 1 H, C*H*HPh), 4.33 (s, 2 H, CH_2Ph), 4.27 (d, $J = 10.7$ Hz, 1 H, C*H*HOPiv), 4.18 (d, $J = 11.5$ Hz, 1 H, C*H*HPh), 4.17−4.12 (m, 1 H, OCH), 3.98 (s, 1 H, CHOSi), 3.79 (dd, $J = 15.8, 6.9$ Hz, 1 H, OCH), 3.68−3.60 (m, 2 H, OCH), 3.47 (dd, $J = 12.0, 3.5$ Hz, 1 H, OCH), 3.19 (dd, $J = 9.0, 4.0$ Hz, 1 H, OCH), 3.02 (dd, $J = 11.6, 3.8$ Hz, 1 H, OCH), 2.92 (bs, 1 H, OH), 2.49−2.40 (m, 1 H, CH), 2.36−2.31 (m, 1 H, CH), 2.27−2.12 (m, 3 H, CH), 2.07−1.85 (m, 3 H, CH), 1.74−1.50 (m, 5 H, CH), 1.35

(s, 6 H, 2 × CH$_3$), 1.32 (s, 3 H, CH$_3$), 1.22 (s, 9 H, *t*-Bu), 1.21 (s, 3 H, CH$_3$), 0.98 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 0.96 (s, 9 H, *t*-Bu), 0.14 (s, 3 H, SiCH$_3$), 0.11 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 177.5, 157.6, 139.3, 139.2, 128.5, 128.3, 127.7, 127.6, 118.7, 86.4, 84.2, 78.6, 78.4, 77.9, 77.3, 74.7, 74.0, 73.5, 73.1, 71.2, 68.3, 66.4, 47.3, 41.0, 41.0, 38.8, 35.5, 29.6, 28.6, 27.4, 26.0, 22.5, 21.8, 20.4, 18.0, 17.8, 15.8, −4.3, −5.0; HRMS, calcd for $C_{51}H_{78}O_{10}SiCs$ (M + Cs$^+$) 1011.4419, found 1011.4464.

Xanthate 72. A solution of alcohol **64** (630 mg, 0.717 mmol) and carbon disulfide (129 μL, 2.15 mmol) in ether (2 mL) was stirred at 25 °C with potassium hydride (1.43 g, 35.9 mmol, after washing with ether) for 6 h. The resulting orange suspension was diluted with ether (50 mL) and decanted and the ether layer was washed with aqueous saturated ammonium chloride (2 × 20 mL). The organic layer was dried (MgSO$_4$), filtered, concentrated, and subjected to flash chromatography (silica, 10% ether in petroleum ether containing 1% of triethylamine) to give the xanthate **72** (619 mg, 0.638 mmol, 89%, 5:1 mixture of isomers). **72** (major isomer): colorless foam, R_f = 0.68 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2955 (m), 2857 (m), 1732 (m), 1672 (w), 1462 (m), 1147 (m), 1069 (s), 836 (m), 775 (m) 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −1.6 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.30−7.07 (m, 10 H, ArH), 6.09 (s, 1 H, CHOC(S)), 5.06 (dd, *J* = 1.9, 7.3 Hz, 1 H, =CH), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.35 (d, *J* = 11.3 Hz, 1 H, C*H*HOPiv), 4.32 (s, 2 H, CH$_2$Ph), 4.27 (d, *J* = 11.2 Hz, 1 H, C*H*HOPiv), 4.26−4.23 (m, 1 H, OCH), 4.18 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.79 (dt, *J* = 9.1, 6.9 Hz, 1 H, OCH), 3.67 −3.59 (m, 2 H, OCH), 3.45 (dd, *J* = 12.2, 3.2 Hz, 1 H, OCH), 3.22 (dd, *J* = 9.2, 3.8 Hz, 1 H, OCH), 3.05 (dd, *J* = 11.6, 3.8 Hz, 1 H, OCH), 2.43−2.40 (m, 3 H, CH), 2.18−2.11 (m, 2 H, CH), 2.12 (s, 3 H, CH$_3$), 2.04−1.99 (m, 2 H, CH), 1.89−1.74 (m, 3 H, CH), 1.63−1.55 (m, 2 H, CH), 1.44 (s, 3 H, CH$_3$), 1.34 (s, 3 H, CH$_3$), 1.32 (s, 3 H, CH$_3$), 1.25 (s, 9 H, *t*-Bu), 1.19 (s, 3 H, CH$_3$), 1.01 (s, 9 H, *t*-Bu), 0.90 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 0.20 (s, 3 H, SiCH$_3$), 0.19 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 215.5, 177.6, 154.2, 139.2, 139.1, 128.5, 128.2, 128.0, 127.6, 115.5, 87.0, 86.8, 86.5, 84.5, 78.7, 78.0, 77.3, 76.8, 74.0, 73.7, 73.1, 71.2, 68.5, 66.4, 41.0, 40.9, 38.9, 35.5, 29.7, 29.6, 29.0, 27.5, 26.0, 22.6, 21.3, 20.3, 19.0, 17.9, 17.8, −2.0; HRMS calcd for $C_{53}H_{80}O_{10}S_2SiCs$ (M + Cs$^+$) 1101.4017, found 1101.4050.

Enol Ether 74. A solution of xanthate **72** (620 mg, 0.640 mmol), 2,2′-azobis(isobutyronitrile) (6 mg) and tri-*n*-butyltin hydride (690 μL, 2.56 mmol) in benzene (5 mL) was heated at 80 °C for 3 h. The mixture was concentrated and subjected to flash chromatography (silica, 0→30% ether in petroleum ether containing 1% triethylamine) to give the desired enol ether **74** (370 mg, 0.43 mmol, 67%) and the exocyclic enol ether **73** (166 mg, 0.192 mmol, 30%). **74**: colorless oil; R_f = 0.60 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2955 (s), 2857 (s), 1730 (s), 1670 (w), 1460 (m), 1380 (m), 1254 (m), 1149 (s), 1077 (s), 836 (m), 773 (m), 735 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ −10.1 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31−7.13 (m, 10 H, ArH), 4.56 (dd, *J* = 7.8, 1.7 Hz, 1 H, =CH), 4.37 (d, *J* = 11.7 Hz, 1 H, C*H*HPh), 4.33 (s, 2 H, CH$_2$Ph), 4.23 (d, *J* = 11.0 Hz, 1 H, C*H*HOPiv), 4.19 (d, *J* = 11.0 Hz, 1 H, C*H*HOPiv), 4.18 (d, *J* = 11.7 Hz, 1 H, C*H*HPh), 4.18−4.15 (m, 1 H, =CHOC*H*), 3.82−3.77 (m, 1 H, OCH), 3.68−3.61 (m, 2 H, OCH), 3.46 (dd, *J* = 12.1, 3.3 Hz, 1 H, OCH), 3.22 (dd, *J* = 9.2, 4.1 Hz, 1 H, OCH), 3.05 (dd, *J* = 11.7, 3.9 Hz, 1 H, OCH), 2.52−2.46 (m, 1 H, CH), 2.42 (d, *J* = 13.6 Hz, 1 H, =CC*H*H), 2.29 (d, *J* = 13.6 Hz, 1 H, =CC*H*H), 2.20 (m, 4 H, CH), 2.04−1.74 (m, 5 H, CH), 1.64−1.47 (m, 3 H, CH), 1.35 (s, 3 H, CH$_3$), 1.30 (s, 3 H, CH$_3$), 1.27 (s, 3 H, CH$_3$), 1.24 (s, 9 H, *t*-Bu), 1.22 (s, 3 H, CH$_3$), 1.01 (s, 9 H, *t*-Bu), 0.97 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 0.14 (s, 3 H, SiCH$_3$), 0.13 (s, 3 H, SiCH$_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 177.5, 156.2, 139.4, 139.2, 128.6, 128.5, 127.6, 127.5, 107.4, 86.9, 86.7, 83.0, 78.7, 78.0, 77.2, 74.8, 74.0, 73.4, 73.1, 71.2, 71.0, 66.4, 47.0, 41.0, 40.9, 39.0, 36.0, 29.6, 29.5, 28.8, 27.5, 26.0, 22.6, 20.4, 18.4, 18.1, 17.8, −1.9, −2.0; HRMS, calcd for $C_{51}H_{78}O_9SiCs$ (M + Cs) 995.4469, found 995.4489. **73**: colorless foam; R_f = 0.57 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2953 (s), 2860 (s), 1727 (s), 1662 (w), 1460 (m), 1378 (m), 1283 (m), 1252 (m), 1151 (s), 1074 (s), 836 (m), 774 (m), 738 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ +1.6 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.30−7.07 (m, 10 H, ArH), 4.58 (d, *J* = 10.8 Hz, 1 H, C*H*HOPiv), 4.42 (d, *J* = 10.7 Hz, 1 H, C*H*HOPiv), 4.37 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.33 (s, 1 H, =CH), 4.31 (s, 2 H, CH$_2$Ph), 4.19 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.07−4.02 (m, 1 H, OCH), 3.79 (bq, *J* = 7.1 Hz, 1 H, OCH), 3.68 (dd, *J* = 11.4, 5.3 Hz, 1 H, OCH), 3.64−3.56 (m, 2 H, OCH), 3.27 (dd, *J* = 11.8, 3.8 Hz, 1 H, OCH), 3.19 (dd, *J* = 7.9, 3.6 Hz, 1 H, OCH), 2.23−2.16 (m, 2 H, CH), 2.14−2.12 (m, 4 H, CH), 2.07-1.98 (m, 2 H, CH), 1.96−1.85 (m, 3 H, CH), 1.77−1.74 (m, 1 H, CH), 1.67 (bt, *J* = 10.8 Hz, 1 H, CH), 1.40 (s, 3 H, CH$_3$), 1.35−1.30 (m, 1 H, CH), 1.29 (s, 3 H, CH$_3$), 1.26 (s, 9 H, *t*-Bu), 1.25 (s, 3 H, CH$_3$), 1.06 (s, 9 H, *t*-Bu), 0.85 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 0.23 (s, 6 H, 2 × SiCH$_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 175.4, 154.7, 139.4, 139.2, 128.5, 128.2, 127.6, 127.5, 108.1, 88.3, 88.1, 78.7, 77.5, 77.3, 75.7, 74.2, 74.1, 73.4, 73.1, 71.1, 70.9, 66.4, 40.9, 40.8, 33.9, 30.1, 29.7, 28.6, 28.4, 27.5, 27.4, 26.6, 26.1, 26.0, 21.6, 20.8, 17.9, 14.8, −1.9, −2.3; HRMS, calcd for $C_{51}H_{78}O_9SiCs$ (M + Cs$^+$) 995.4469, found 995.4499.

Alcohol 75. A solution of enol ether **74** (100 mg, 0.115 mmol) in THF (0.5 mL) was treated with BH$_3$·THF (0.58 mL of a 1.0 M solution in THF, 0.58 mmol) at −30 °C and stirred at −30 °C for 14 h. The resulting mixture was treated with 3 N sodium hydroxide (1.5 mL) and 30% hydrogen peroxide (1.0 mL) at 0 °C and stirred for 1 h at 25 °C. The mixture was diluted with ether (100 mL) and the organic layer was washed with brine (2 × 50 mL), dried (MgSO$_4$), filtered and concentrated. Flash chromatography (silica, 20→40% ether in petroleum ether) gave the alcohol **75** (82 mg, 0.093 mmol, 82%). **75**: colorless foam; R_f = 0.55 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3510 (w), 2955 (s), 2930 (s), 2857 (s), 1727 (s), 1664 (w), 1458 (s), 1380 (m), 1282 (m), 1253 (m), 1068 (s), 835 (m), 774 (m), 734 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ +13.2 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32−7.24 (m, 10 H, ArH), 4.54 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH$_2$Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.04 (d, *J* = 10.9 Hz, 1 H, C*H*HOPiv), 3.96 (d, *J* = 10.9 Hz, 1 H, C*H*HOPiv), 3.64−3.49 (m, 5 H, OCH), 3.33−3.20 (m, 4 H, OCH), 3.05 (dd, *J* = 11.6, 3.7 Hz, 1 H, OCH), 2.17−2.08 (m, 2 H, CH), 2.03−1.79 (m, 7 H, CH), 1.74−1.58 (m, 4 H, CH), 1.50−1.47 (m, 1 H, CH), 1.39 (bt, *J* = 11.4 Hz, 1 H, CH), 1.28 (s, 3 H, CH$_3$), 1.26 (s, 3 H, CH$_3$), 1.24 (s, 3 H, CH$_3$), 1.20 (s, 9 H, *t*-Bu), 1.17 (s, 3 H, CH$_3$), 1.00 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 0.86 (s, 9 H, *t*-Bu), 0.11 (s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.3, 138.5, 138.5, 128.3, 128.2, 127.7, 127.5, 127.4, 87.5, 86.7, 85.3, 82.7, 78.1, 78.0, 75.4, 74.0, 73.4, 73.2, 73.0, 70.9, 70.3, 66.0, 44.7, 40.3, 40.2, 38.8, 38.2, 38.0, 31.3, 29.7, 29.1, 28.8, 27.2, 26.8, 25.8, 21.5, 20.1, 18.6, 18.1, 17.5, −1.9, −2.1; HRMS, calcd for $C_{51}H_{80}O_{10}SiCs$ (M + Cs$^+$) 1013.4575, found 1013.4534.

Disilyl Ether 77. A solution of alcohol **75** (1.03 g, 1.16 mmol) and 2,6-lutidine (338 μL, 2.90 mmol) in CH$_2$Cl$_2$ (10 mL) was treated dropwise at 0 °C with triethylsilyl trifluoromethanesulfonate (787 μL, 3.48 mmol). After stirring at 0 °C for 30 min, the mixture was diluted with ether (250 mL), washed with aqueous saturated ammonium chloride (2 × 100 mL), and dried (MgSO$_4$). Filtration, concentration, and flash chromatography (silica, 10→30% ether in petroleum ether) gave disilyl ether **77** (1.11 g, 1.12 mmol, 96%). **77**: colorless oil; R_f = 0.72 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2955 (s), 2876 (s), 1729 (s), 1459 (s), 1364 (m), 1253 (m), 1071 (m), 835 (m), 733 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ +23.6 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33−7.25 (m, 10 H, ArH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH$_2$Ph), 4.37 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.00 (s, 2 H, C*H*$_2$OPiv), 3.65−3.53 (m, 4 H, OCH), 3.40 (bt, *J* = 9.9 Hz, 1 H, OCH), 3.32 (dd, *J* = 12.0, 3.5 Hz, 1 H, OCH), 3.28−3.20 (m, 2 H, OCH), 3.05 (dd, *J* = 11.7, 7.9 Hz, 1 H, OCH), 2.18−2.15 (m, 1 H, CH), 2.11 (dd, *J* = 11.7, 5.1 Hz, 1 H, CH), 2.03−1.79 (m, 7 H, CH), 1.76−1.58 (m, 4 H, CH), 1.54, (dd, *J* = 14.5, 10.0 Hz, 1 H, CH), 1.40 (bt, *J* = 12.2 Hz, 1 H, CH), 1.28 (s, 3 H, CH$_3$), 1.26 (s, 3 H, CH$_3$), 1.23 (s, 3 H, CH$_3$), 1.22 (s, 9 H, *t*-Bu), 1.18 (s, 3 H, CH$_3$), 1.00 (bd, *J* = 6.5 Hz, 3 H, CH$_3$), 0.95 (t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$, 0.87 (s, 9 H, *t*-Bu), 0.58 (q, *J* = 7.8 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_2$), 0.11 (s, 6 H, 2 × SiCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.4, 138.5, 138.5, 128.3, 128.2, 127.7, 127.5, 127.4, 87.6, 86.9, 85.8, 82.7, 78.1, 78.1, 76.3, 73.8, 73.5, 73.2, 73.0, 70.9, 66.0, 44.2, 40.3, 40.2, 38.3, 38.2, 31.2, 29.0, 28.8, 27.3, 27.0, 25.8, 21.4, 20.1, 18.9, 17.5, 6.9, 5.2, −1.9, −2.1; HRMS, calcd for $C_{57}H_{94}O_{10}Si_2Cs$ (M + Cs$^+$) 1127.5440, found 1127.5465.

Primary Alcohol 78. A solution of disilyl ether **77** (1.11 g, 1.12 mmol) in CH$_2$Cl$_2$ (10 mL) was treated with diisobutylaluminum hydride (4.48 mL of a 1.0 M solution in CH$_2$Cl$_2$, 4.48 mmol) at −78 °C. After stirring for 2 min at −78 °C the reaction was quenched with MeOH (2 mL). The mixture was diluted with EtOAc (300 mL), washed with aqueous saturated sodium potassium tartrate (100 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 20 → 40% ether in petroleum ether) afforded the alcohol **78** (965 mg, 1.06 mmol, 95%). **78**: colorless oil; $R_f = 0.21$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 3504 (w), 2953 (m), 2876 (m), 1458 (m), 1380 (m), 1254 (m), 1070 (s), 834 (m), 733 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ +19.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.24 (m, 10 H, ArH), 4.54 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.36 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 3.65−3.56 (m, 4 H, OCH), 3.55−3.45 (m, 1 H, OCH), 3.42 (bt, $J = 9.2$ Hz, 1 H, OCH), 3.33−3.22 (m, 4 H, OCH), 3.05 (dd, $J = 12.0$, 3.6 Hz, 1 H, OCH), 2.75−2.70 (m, 1 H, OH), 2.27−2.17 (m, 1 H, CH), 2.10 (dd, $J = 11.6$, 5.2 Hz, 1 H, CH), 2.01−1.89 (m, 4 H, CH), 1.85−1.80 (m, 2 H, CH), 1.75−1.65 (m, 4 H, CH), 1.54 (dd, $J = 14.8$, 9.6 Hz, 1 H, CH), 1.43−1.37 (m, 2 H, CH), 1.26 (s, 6 H, 2 × CH_3), 1.24 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.00 (d, $J = 6.3$ Hz, 3 H, CH_3), 0.94 (t, $J = 7.9$ Hz, 9 H, $\mathrm{Si(CH_2C}\mathit{H}_3\mathrm{)_3}$), 0.85 (s, 9 H, *t*-Bu), 0.57 (q, $J = 7.9$ Hz, 6 H, $\mathrm{Si(C}\mathit{H}_2\mathrm{CH_3)_2}$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 127.5, 87.6, 86.7, 86.0, 83.0, 78.1, 77.9, 75.8, 75.1, 73.4, 73.3, 73.0, 71.0, 69.6, 66.0, 43.0, 40.3, 40.2, 38.1, 38.0, 31.1, 29.3, 29.1, 27.8, 25.8, 21.4, 20.2, 18.9, 18.1, 17.5, 7.4, 5.1, −1.9, −3.3; HRMS, calcd for $C_{52}H_{86}O_9SiCs$ ($M + Cs^+$) 1043.4865, found 1043.4814.

Aldehyde 79. A solution of alcohol **78** (955 mg, 1.05 mmol) in CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (1.78 g, 4.20 mmol) at 25 °C for 3 h. The mixture was diluted with ether (25 mL) and washed with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1, 20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (silica, 5→20% ether in petroleum ether) to give the aldehyde **79** (822 mg, 0.904 mmol, 86%). **79**: colorless foam, $R_f = 0.58$ (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2955 (m), 2877 (m), 1732 (m), 1462 (m), 1380 (m), 1250 (m), 1071 (s), 854 (m), 735 (m) cm^{-1}; $[\alpha]^{22}_D$ +25.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1 H, CHO), 7.32−7.23 (m, 10 H, ArH), 4.54 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.35 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 3.64−3.56 (m, 3 H, OCH), 3.50 (bq, $J = 8.9$ Hz, 1 H, OCH), 3.42 (bt, $J = 9.1$ Hz, 1 H, OCH), 3.30 (dd, $J = 11.9$, 3.5 Hz, 1 H, OCH), 3.27−3.22 (m, 2 H, OCH), 3.03 (dd, $J = 11.7$, 3.8 Hz, 1 H, OCH), 2.11−2.03 (m, 3 H, CH), 2.0−1.87 (m, 4 H, CH), 1.82−1.76 (m, 3 H, CH), 1.71 (t, $J = 11.8$ Hz, 1 H, CH), 1.68−1.50 (m, 2 H, CH), 1.41−1.33 (m, 2 H, CH), 1.26 (s, 3 H, CH_3), 1.23 (s, 6 H, 2 × CH_3), 1.16 (s, 3 H, CH_3), 0.97 (d, $J = 6.5$ Hz, 3 H, CH_3), 0.93 (t, $J = 8.0$ Hz, 9 H, $\mathrm{Si(CH_2C}\mathit{H}_3\mathrm{)_3}$), 0.92 (s, 9 H, *t*-Bu), 0.55 (2 × q, $J = 8.0$ Hz, 6 H, $\mathrm{Si(C}\mathit{H}_2\mathrm{CH_3)_3}$), 0.14 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 138.5, 138.5, 128.3, 128.2, 127.6, 127.5, 87.5, 86.8, 84.5, 83.1, 78.8, 78.2, 78.0, 75.6, 73.4, 73.3, 73.0, 71.0, 66.0, 46.4, 40.3, 40.2, 38.2, 38.0, 31.0, 30.9, 29.0, 28.8, 25.9, 25.3, 21.3, 20.2, 18.9, 18.3, 17.5, 6.9, 5.1, −2.2, −2.4; HRMS calcd for $C_{52}H_{84}O_9Si_2Cs$ ($M + Cs^+$) 1041.4708, found 1041.4749.

Lactol 80. A mixture of silyl ether **79** (5 mg, 6 μmol) and camphorsulfonic acid (0.4 mg, 1 μmol) in MeOH/H_2O (100 μL, 4:1) was stirred at 25 °C for 2 h. The reaction was quenched with triethylamine (10 μL), concentrated, and subjected to preparative TLC (silica, 50% ether in petroleum ether) to give the lactol **80** (4 mg, 5 μmol, 85%, single isomer). **80**: colorless oil; $R_f = 0.45$ (silica, 50% ether in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 10 H, ArH), 4.73 (bs, 1 H, C*H*OH), 4.55 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, $J = 11.6$ Hz, 1 H, C*H*HPh), 3.69−3.55 (m, 5 H, OCH), 3.45−3.32 (m, 2 H, OCH), 3.24−3.21 (m, 1 H, OCH), 3.08 (dd, $J = 11.8$, 3.6 Hz, 1 H, OCH), 2.84 (bs, 1 H, OH), 2.10−1.92 (m, 2 H, CH), 1.82−1.64 (m, 10 H, CH), 1.47−1.37 (m, 3 H, CH), 1.32 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.03 (d, $J = 7.0$ Hz, 3 H, CH_3), 0.89 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); HRMS, calcd for $C_{46}H_{70}O_9SiCs$ ($M + Cs^+$) 928.0563, found 928.0520.

Acknowledgment. We thank Drs. Dee H. Huang (TRSI), Gary Siuzdak (TSRI), Raj Chadha (TSRI), George Furst (University of Pennsylvania), John Dykins (University of Pennsylvania), and Pat Carroll (University of Pennsylvania) for their superb NMR (D.H.H.; G.F.), mass spectroscopic (G.S.; J.D.), and X-ray crystallographic (R.C.; P.C.) assistance. This work was carried out at the University of Pennsylvania, the University of California, San Diego, and The Scripps Research Institute. Financial support was provided by The National Institutes of Health, USA, and by fellowships from The Netherlands Organization for Scientific Research (NWO) (F.P.J.T.R.), the Deutsche Forschungsgemeinschaft (J.T.), and the Agricultural University of Athens (E.A.C.), and grants from the following companies (in alphabetical order): Dainippon Pharmaceutical Co., Ltd. (Japan), Glaxo, Inc. (USA), Hoffmann-La Roche (USA), Merck Sharp & Dohme (USA), Pfizer, Inc. (USA), Rhone-Poulenc Rorer (USA), Schering Plough (USA), Smith Kline Beecham (USA), Unitika, Ltd. (JAPAN).

Supporting Information Available: Selected data for compounds **21−24**, **26**, **30−34**, **37−41**, **43−47**, **49**, **51−52**, **54**, **57−59**, **63**, **65−68**, and **76** are provided as well as X-ray crystallographic data for compound **32**, tables of anisotropic displacement coefficients and H atom coordinates, unit cell packing diagrams, stereoviews, and torsion angles and mean plane equations (45 pages); listing of structure factors (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA950691C