Keywords: altohyrtin · antitumor agents · natural products · spongistatin · total synthesis

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[4] Abbreviations: *dr* = diastereomer ratio; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; TMS = trimethylsilyl; DIBALH = diisobutylaluminum hydride; Np = 2-naphthyl; TBAF = tetrabutylammonium fluoride; Tr = trityl = triphenylmethyl; Tf = trifluoromethanesulfonyl; Bn = benzyl; PPTS = pyridinium *p*-toluenesulfonate; CSA = camphorsulfonic acid; LDBB = di-*tert*-butylbiphenyllithium.

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[23] Under these reaction conditions, aldehyde **26** has no preferred diastereoface. Coupling of methyl ketone **25** with the antipode of **26** under the same reaction conditions also gives a 1,5-*anti* product.

[24] The diastereoselectivity for this methyl ketone aldol coupling is 9.6:1 at −78°C. At −110°C, the diastereoselectivity increases to 22:1. a) D. A. Evans, P. J. Coleman, B. Cote, *J. Org. Chem.* **1997**, *62*, 788–789; b) I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585–8588.

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[26] Attempted spiroketalization of **28** in the absence of MeOH led to rapid β-elimination of the C_{21} methyl ether to give an α,β unsaturated ketone.

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[28] Stereochemical assignments were supported by NOE experiments (1D and 2D) and ^{1}H NMR measurements. An NOE enhancement between H_{19} and H_{27} was observed in the axial–equatorial isomer **30**. The NMR signal for H_{25} was illuminating as well: **29**: δ = 3.9 (m, $J(H_{25}, H_{26ax}) = 11$ Hz); **30**: δ = 3.9 ppm (t, $J = 3.2$ Hz).

[29] Due to the sensitivity of spiroketal substrate **29** to acidic media, equilibration experiments were kept short (1–3 h). In dichloromethane/CSA, **29** equilibrated to a 1:1 (29:30) mixture of spiroisomers after 3 h.

[30] Presumably, the C_{25} hydroxyl is assisting in the equilibration to afford **30** by participating in an internal chelate with the metal cation and proximally positioned anomeric oxygen. For related cases see a) D. R. Williams, P. A. Jass, R. D. Gaston, *Tetrahedron Lett.* **1993**, *34*, 3231–3234; b) M. J. Kurth, E. G. Brown, E. Hendra, H. Hope, *J. Org. Chem.* **1985**, *50*, 1115–1117; c) S. L. Schreiber, T. L. Sommer, K. Satake, *Tetrahedron Lett.* **1985**, *26*, 17–20.

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Enantioselective Synthesis of Altohyrtin C (Spongistatin 2): Synthesis of the EF-Bis(pyran) Subunit**

David A. Evans,* B. Wesley Trotter, Bernard Côté, and Paul J. Coleman

Dedicated to Professor Dieter Seebach and Professor Yoshito Kishi on the occasion of their 60th birthdays

Concurrent with the syntheses of the AB- and CD-spiroketal subunits of the altohyrtin skeleton,[1] the synthesis of the altohyrtin C_{29}–C_{51} EF-bis(pyran) fragment was addressed. The principal subunits for this portion of the altohyrtin skeleton are illustrated in Figure 1. The retrosynthetic proposal focuses on the incorporation of the C_{44}–C_{51} side chains (X = H, Cl, Br) as allylmetal nucleophiles into the illustrated F-ring epoxide at a late stage in the synthesis. In turn, this bis(pyran) is assembled through acylation of the illustrated E-ring sulfonyl anion with an F-ring[2] carboxylic

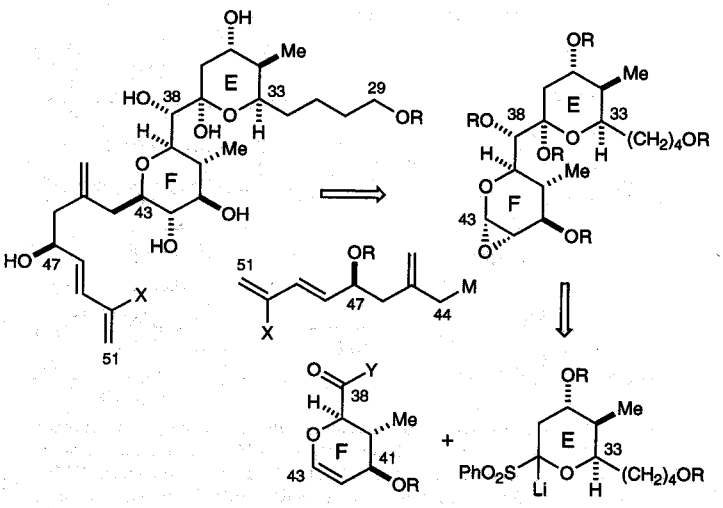

Figure 1. Retrosynthesis of the EF-bis(pyran) subunit.

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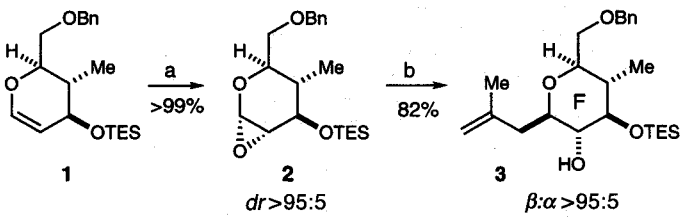
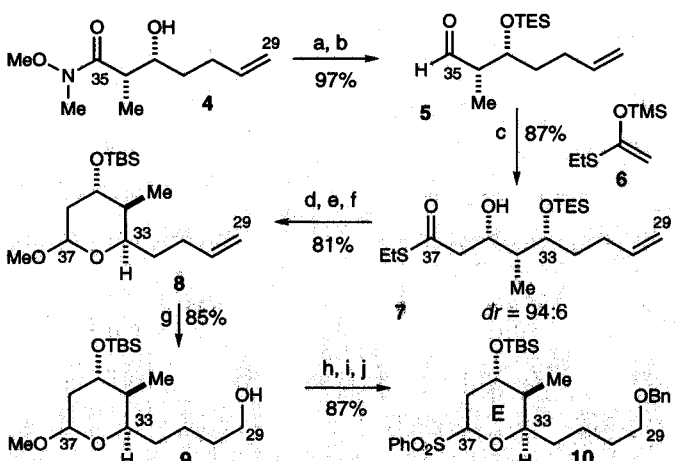
acid derivative. This strategy accommodates the use of either antipode of the E- or F-ring subunits in the event of a stereochemical discrepancy in this portion of the structure.[3]

In conjunction with this plan, a practical solution for β-*C*-glycosidation through the allylstannane-mediated cleavage of glycal epoxides has been developed (Scheme 1).[4] Dihydropyran **1** was found to undergo highly stereoselective epoxidation by dimethyldioxirane in full accord with extensive precedent.[5] The resulting glycal epoxide **2**, when treated with tributylmethallylstannane and tributylstannyl triflate, was transformed to the F-ring analogue **3** with high diastereoselectivity. Tributylstannyl triflate was unique among the surveyed Lewis acid activators in providing exclusively the β isomer; other Lewis acids afforded significant amounts of diastereomeric addition products, presumably through the intervention of an oxocarbenium ion intermediate.



Scheme 1. β-C-glycosylation mediated by tributylstannyl triflate. a) Dimethyldioxirane, acetone, CH_2Cl_2, 0°C; b) 5 equiv of tributylmethallylstannane, 2 equiv of Bu_3SnOTf, CH_2Cl_2, −78°C. (See ref. [4] for abbreviations.)

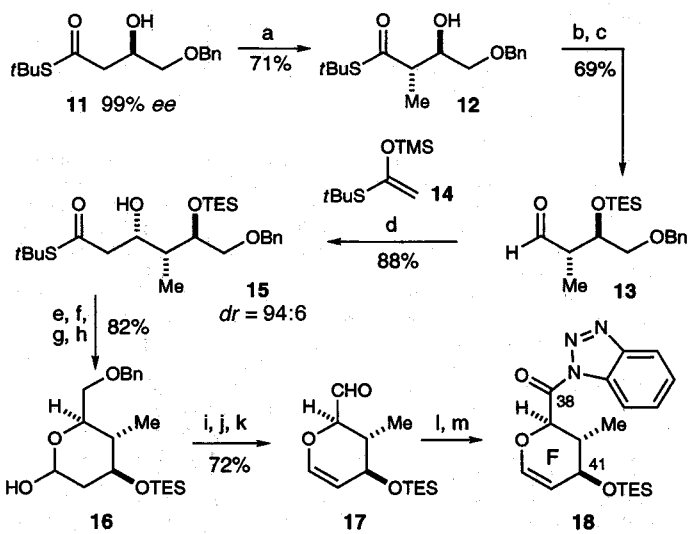
Application of this methodology to a more highly functionalized system was next investigated. Synthesis of the $C_{29}-C_{37}$ E-ring fragment was initiated from the enantiomerically pure boron aldol adduct **4**[6] (Scheme 2). Sequential alcohol protection and amide reduction provided aldehyde **5**, which was subjected to a Felkin-selective Lewis acid catalyzed ($BF_3 \cdot Et_2O$) aldol addition with thioketene acetal **6** to afford thioester **7** (87%; *dr* = 94:6). Fukuyama reduction to the derived aldehyde[7] and acid-catalyzed deprotection–acetalization followed by silyl protection of the remaining secondary alcohol afforded the E-ring methyl ketal **8** (81%, three steps).



Scheme 2. Synthesis of E-ring phenylsulfone **10**. a) TESOTf, 2,6-lutidine; b) DIBALH, −78°C; c) **6**, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78°C; d) Lindlar catalyst, Et_3SiH, 1-hexene, acetone; e) CSA, MeOH; f) TBSCl, imidazole, DMF; g) 9-BBN, then H_2O_2; h) TMSSPh, ZnI_2; i) NaH, BnBr, Bu_4NI; j) *m*-CPBA, $NaHCO_3$. (See ref. [4] for abbreviations.)

Hydroboration of **8** with 9-BBN then afforded alcohol **9** (85%). Preparation of the E-ring phenylsulfone **10** was completed by anomeric sulfide formation (TMSSPh, ZnI_2),[8] C_{29} alcohol benzylation (NaH, BnBr, Bu_4NI, 90% from **9**), and sulfide oxidation (*m*-CPBA, $NaHCO_3$, 97%).

Synthesis of the F-ring dihydropyran began from our previously reported aldol adduct **11** (99% ee, *R* configuration; Scheme 3).[9] Fräter–Seebach alkylation (71% yield; *dr* = 5–8:1)[10] was followed by successive alcohol protection (TESCl, imidazole, 80%) and thioester reduction (DIBALH, 86%) to give aldehyde **13**. A Felkin-selective, 1,3-*anti* aldol reaction[11] with thioketene acetal **14** ($BF_3 \cdot Et_2O$, toluene, −93°C) provided thioester **15** (88%; *dr* = 94:6). Silyl deprotection and Ag(I)-mediated lactonization (88%, two steps) followed by TES protection and DIBALH reduction (93%, two steps) afforded lactol **16**. $POCl_3$-mediated dehydration (81%), removal of the C_{38} benzyl group (LDBB, 99%), and Parikh–Doering oxidation (90%)[12] provided the F-ring dihydropyran aldehyde **17**. Buffered Kraus oxidation[13] of this intermediate provided a carboxylic acid that could be transformed to the activated benzotriazolyl amide **18** through the corresponding acid chloride.[14] In our subsequent sulfonyl carbanion acylation studies (vide infra), it was found that **18** is superior to the analogous acid chloride, which readily undergoes competitive carbanion-initiated proton transfer.



Scheme 3. Synthesis of the activated F-ring amide **18**. a) LDA, HMPA, MeI, THF, −55°C; b) TESCl, imidazole; c) DIBALH, −78°C; d) **14**, $BF_3 \cdot Et_2O$, toluene, −93°C; e) PPTS, MeOH; f) AgO_2CCF_3, benzene; g)TESCl, imidazole; h) DIBALH, −78°C; i) $POCl_3$, pyridine, 80°C; j) LDBB, THF, −78°C; k) $SO_3 \cdot$ pyridine, DMSO, Et_3N; l) $NaClO_2$, 2-methyl-2-butene, ethyl-1-propenyl ether, *t*-BuOH, pH 5.5; m) 1. 1-chloro-*N*,*N*-trimethylpropenylamine; 2. benzotriazole, pyridine, DMAP. (See ref. [4] for abbreviations.)

Synthesis of the requisite allylstannane side chain began with the known (2*S*,3*E*)-hexa-3,5-diene-1,2-diol (**19**)[15] (Scheme 4). A three-step sequence provided monosilylated ether **20** in 90% overall yield without intervening purifications. Conversion of **20** into the corresponding alkyl triflate followed by treatment with the lithium enolate of methyl β-dimethylaminopropionate[16] provided **21** (80%). Quaternization and elimination of the dimethylamino group (MeI, Na_2CO_3, 94%) was followed by ester reduction (DIBALH, 95%) to give the corresponding allylic alcohol. In situ mesylation and displacement with tributylstannyllithium[17] gave TES-protected allylstannane **23** in 85% yield. Basic

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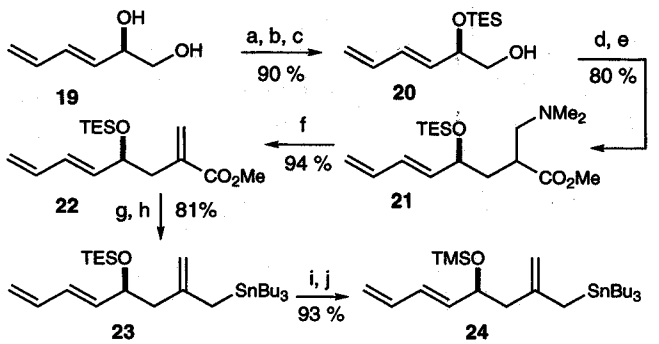


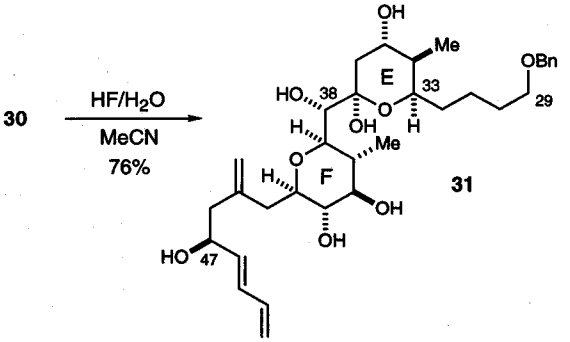
Scheme 4. Synthesis of altohyrtin C side chain **24**. a) AcCl, 2,6-lutidine, CH_2Cl_2, −78°C; b) TESCl, imidazole, CH_2Cl_2; c) DIBALH, toluene, −78°C; d) Tf_2O, pyridine, CH_2Cl_2, −10°C; e) methyl β-dimethylaminopropionate, LDA, THF, −78°C; f) MeI, Na_2CO_3, MeOH; g) DIBALH, CH_2Cl_2, −78°C; h) BuLi, MsCl, THF, −78°C, then Bu_3SnLi; i) NaOH, EtOH; j) *N,O*-bis(trimethylsilyl) acetamide. (See ref. [4] for abbreviations.)

deprotection and resilylation then provided TMS-protected allylstannane **24** in 93% yield.

At this stage, acylation of the E-ring phenylsulfone[18] with the activated F-ring amide was addressed (Scheme 5). While the use of F-ring derivatives including the C_{38} aldehyde **17**, activated esters, and acid chlorides engendered problems ranging from sulfone elimination to unwanted proton transfer, lithiation of 1.1 equivalents of sulfone **10** followed by addition of 1 equivalent of amide **18** provided the EF bis(pyran) **25** in 60% yield (four steps from **17**). Methanolysis of **25** provided ketone **26** isolated in 48% yield.[19] Of the hydride reducing agents surveyed, $KBHEt_3$ proved most effective in securing the desired configuration at C_{38} (90%; $dr > 99{:}1$). At this juncture, a single-crystal X-ray analysis of alcohol **27** unequivocally confirmed the structure of this advanced intermediate.[20]

After silylation of **27**, epoxidation of **28** with dimethyldioxirane again proceeded stereoselectively (100%; $dr > 95{:}5$) to afford **29**. Treatment of this epoxide with allylstannane **24** and tributylstannyl triflate provided the desired adduct **30** in 80% yield as a single diastereomer. The excess allylstannane from this experiment was recovered quantitatively after chromatography. The size of the C_{47} alcohol protecting group appears to play a significant role in this reaction; use of allylstannanes containing larger silyl protecting groups (e.g. **23**) resulted in lower yields of isolated **30** due to competitive decomposition of starting epoxide.

At this juncture, acidic catalysts were evaluated for the deprotection of the EF bis(pyran) **30**. Prior experience had revealed that ring-E Δ^{36} dihydropyran formation was to be avoided, since rehydration of this intermediate was problematic. Treatment of **30** with aqueous HF resulted in removal of all four silyl protecting groups as well as hydrolysis of the C_{37} methyl ether to the corresponding lactol [Eq. (1)]. This experiment allayed concerns that the unwanted elimination

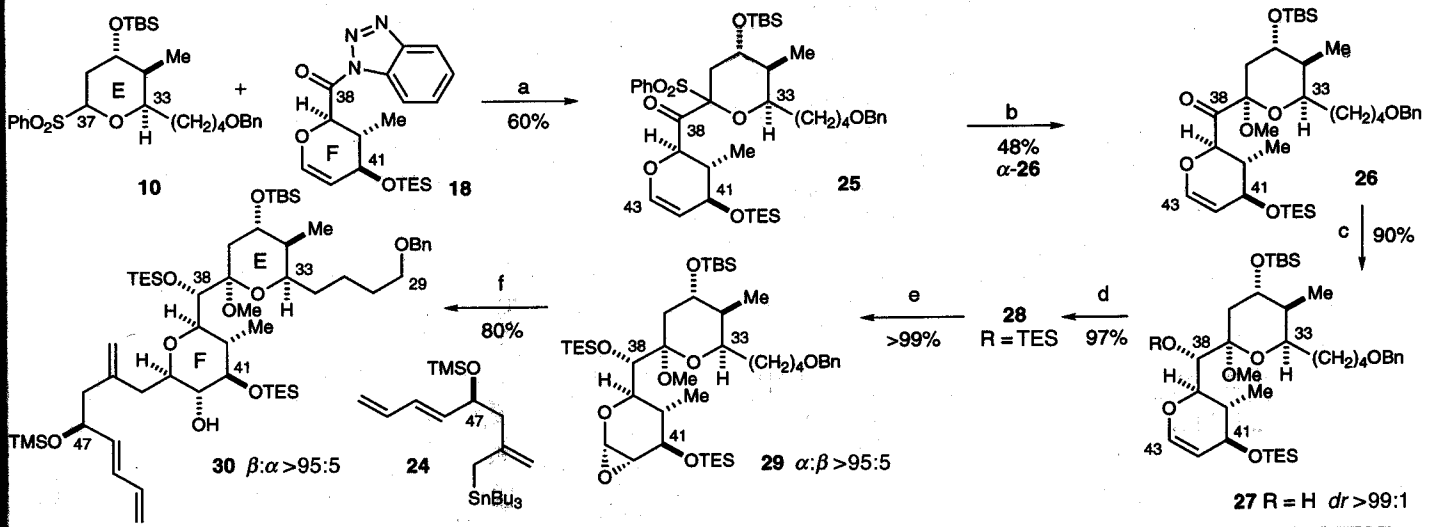


(1)

to the dihydropyran would complicate the projected final deprotection sequence leading to the target structure. In addition, ^1H NMR chemical shifts and coupling constants of **31** correlated very well with those reported for altohyrtin C (Table 1).[21] The union of the EF bis(pyran) **28** with the

Table 1. Chemical shifts (δ), multiplicities, and coupling constants [Hz] in [D6]DMSO.

Proton	Altohyrtin C[21]	**31**
$C_{38}H$	3.28 (d, 8)	3.16 (d, 8.2)
$C_{39}H$	3.60 (d-like, 10)	3.45 (d, 10.6)
$C_{41}H$	4.68 (t-like, 10)	2.91 (dt, 9.3, 5.5)
$C_{42}H$	3.04 (ddd, 10, 10, 6)	2.82 (dt, 8.7, 5.1)
$C_{43}H$	3.36 (t-like, 10)	3.21 (t-like, 9.7)
$C_{48}H$	5.72 (dd, 15, 6)	5.69 (dd, 15.2, 5.9)
$C_{49}H$	6.16 (dd, 15, 10)	6.14 (dd, 15.0, 10.7)
$C_{50}H$	6.30 (ddd, 17, 10, 10)	6.29 (ddd, 17, 10, 10)
$C_{51}H_2$	5.01 (d, 10)	5.00 (d, 10.8)
$C_{51}H_2$	5.14 (d, 17)	5.14 (dd, 17.0, 1.5)



Scheme 5. Synthesis of the EF bicycle **30**. a) LDA, THF, −78°C, then **18**; b) 1. ZnI_2, MeOH; 2. $MgBr_2 \cdot Et_2O$, MeOH; c) $KBHEt_3$, THF, −78 to −40°C; d) TESCl, imidazole, DMF; e) dimethyldioxirane, acetone, CH_2Cl_2, 0°C; f) 16 equiv of **24**, 2 equiv of Bu_3SnOTf, CH_2Cl_2, −78°C. (See ref. [4] for abbreviations.)

  0570-0833/97/3624-2743 $ 17.50+.50/0

ABCD bis(spiroketal) and the completion of the altohyrtin C synthesis is described in the following communication.[22]

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German version: *Angew. Chem.* **1997**, *109*, 2954–2957

Keywords: altohyrtin · antitumor agents · natural products · spongistatin · total synthesis

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[4] Abbreviations: *dr* = diastereomer ratio; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; TMS = trimethylsilyl; DIBALH = diisobutylaluminum hydride; Tr = trityl = triphenylmethyl; Tf = trifluoromethanesulfonyl; Bn = benzyl; PPTS = pyridinium *p*-toluenesulfonate; CSA = camphorsulfonic acid; LDBB = di-*tert*-butylbiphenyllithium; DMAP = 4-dimethylaminopyridine; 9-BBN = 9-borabicyclo[3.3.1]nonane; *m*-CPBA = *m*-chloroperbenzoic acid; LDA = lithium diisopropylamide HMPA = hexamethylphosphoric triamide.
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Enantioselective Synthesis of Altohyrtin C (Spongistatin 2): Fragment Assembly and Revision of the Spongistatin 2 Stereochemical Assignment**

David A. Evans,* B. Wesley Trotter, Bernard Côté, Paul J. Coleman, Luiz Carlos Dias, and Andrew N. Tyler

Dedicated to Professor Dieter Seebach and Professor Yoshito Kishi on the occasion of their 60th birthdays

With convergent syntheses of the AB,[1] CD,[1] and EF[2] spongipyran fragments in hand, the assembly of these subunits to the altohyrtin C skeleton was addressed (Figure 1). While the $C_{44}-C_{51}$ side chain had been successfully

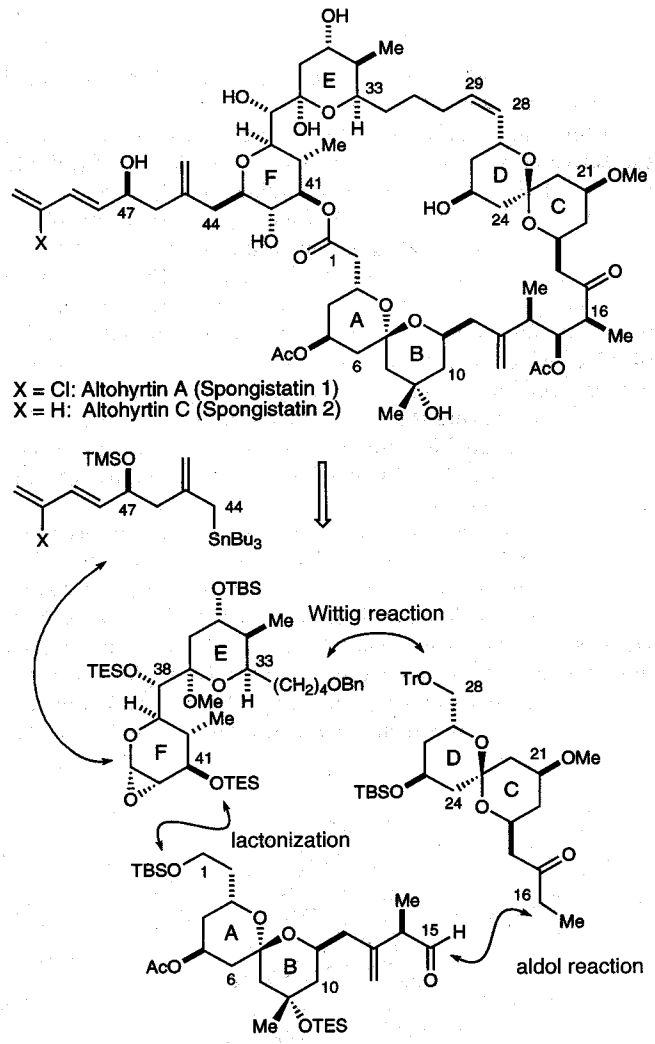

Figure 1. Assembly of the altohyrtin subunits. (See ref. [4] for abbreviations.)

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