Synthesis of the C(29)−C(45) Bis-pyran Subunit (E−F) of Spongistatin 1 (Altohyrtin A)

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A synthesis of the C(29)−C(45) bis-pyran subunit **2** of spongistatin 1 (**1a**) is described. The synthesis proceeds in 19 steps from the chiral aldehyde *ent*-**7**, and features highly diastereoselective α-alkoxyallylation reactions using the γ-alkoxy substituted allylstannanes **17** and **19**, as well as a thermodynamically controlled intramolecular Michael addition to close the F-ring pyran. The E ring was assembled via the Mukaiyama aldol reaction of F-ring methyl ketone **3** and the 2,3-syn aldehyde **4**.

The spongistatins and altohyrtins, isolated in 1993 and 1994 independently by the Pettit and Kitagawa groups from *Spongia* sp. and *Hyrtios altum*, are members of a class of highly cytotoxic sponge derived macrolide polyethers possessing unparalleled inhibitory activity against a subset of highly chemoresistant tumor types.[1−5] Spongistatin 1 (**1a**) is one of the most active members of the spongipyran family, typically displaying IC_{50} values of 10^{-10} to 10^{-12} M against a number of human cancer cell lines including colon, renal, ovarian, and breast cancer cells.[1,6] Spongistatin 1 (**1a**) is an exquisitely complex macrocyclic structure adorned with six highly oxygenated heterocycles. Specifically, the 51 carbon chain incorporates two spiroketals (AB and CD rings), one hemiketal (E ring), one pyran (F-ring), and 24 asymmetric centers.

The extremely meager natural supply (e.g., 14 mg of **1a** from 400 kg of wet sponge),[1] novel structural features, and potent biological activities have defined the spongistatins as attractive targets for total synthesis. Several groups are actively engaged in efforts to complete total syntheses of members of this class.[7−35] Total syntheses of spongistatin 2 (altohyrtin C, **1b**) and spongistatin 1 (altohyrtin A, **1a**) have been completed by Evans[36−39] and Kishi,[40,41] thereby confirming Kobayashi's and Kitagawa's relative and absolute stereochemical assignments for these compounds.[3−5] We have previously published a highly diastereoselective synthesis of the C(36)−C(45) subunit,[19] and now report the details of our efforts to define a workable strategy for the synthesis of the fully elaborated E−F bis-pyran portion of spongistatin 1 (**1a**), represented by structure **2**.

We anticipated that the C(29)−C(45) subunit **2** could

(1) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302.
(2) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605.
(3) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795.
(4) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243.
(5) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989.
(6) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812.
(7) Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667.
(8) Smith, A. B.; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671.
(9) Smith, A. B.; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675.
(10) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646.
(11) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678.
(12) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267.
(13) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.
(14) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.
(15) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241.
(16) Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727.
(17) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911.
(18) Paterson, I.; Wallace, D. J.; Oballa, R. M. *Tetrahedron Lett.* **1998**, *39*, 8548.
(19) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351.
(20) Paquette, L. A.; Zuev, D. *Tetrahedron Lett.* **1997**, *38*, 5115.
(21) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119.
(22) Hermitage, S. A.; Roberts, S. M. *Tetrahedron Lett.* **1998**, *39*, 3563.
(23) Hermitage, S. A.; Roberts, S. M.; Watson, D. J. *Tetrahedron Lett.* **1998**, *39*, 3567.
(24) Kary, P. D.; Roberts, S. M.; Watson, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 213.
(25) Kary, P. D.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *10*, 217.
(26) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487.
(27) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795.
(28) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345.
(29) Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895.
(30) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991.
(31) Anderson, J. C.; McDermott, B. P. *Tetrahedron Lett.* **1999**, *40*, 7135.
(32) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957.
(33) Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349.
(34) Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 3346.
(35) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649.
(36) Evans, D. A.; Trotter, W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.
(37) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738.
(38) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741.
(39) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744.
(40) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187.
(41) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 192.

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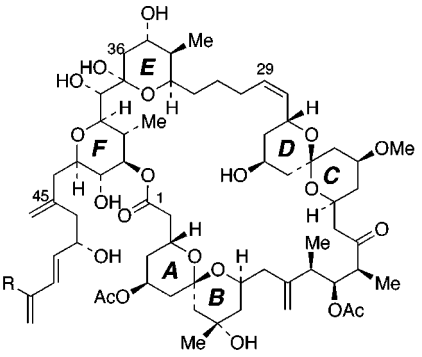
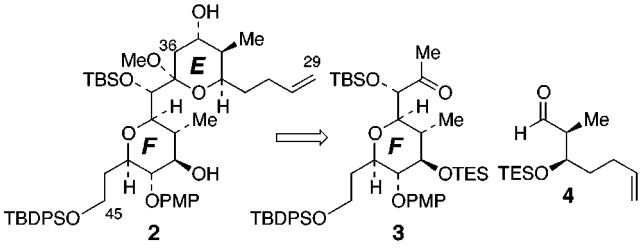
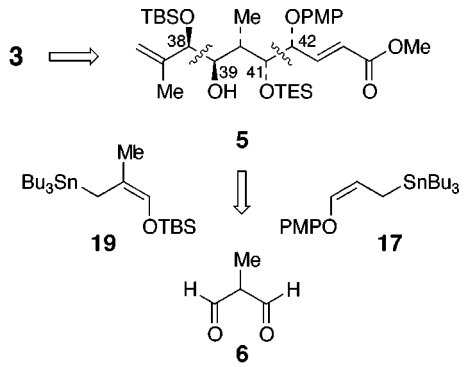


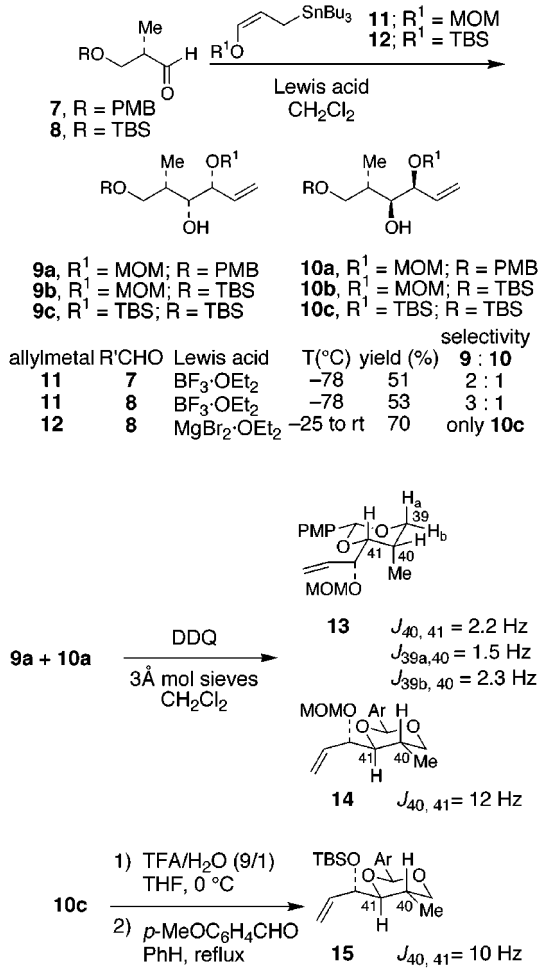
spongistatin 1 (**1a**), R = Cl
spongistatin 2 (**1b**), R = H



be assembled via an aldol reaction between a suitably functionalized F-ring methyl ketone **3** and the 2,3-syn aldehyde **4**. Further, our strategy called for the F-ring pyran **3** to be synthesized by the intramolecular Michael cyclization of an enoate such as **5**, which in turn would be constructed by a series of diastereoselective α-alkoxyallylation[42−46] reactions of a suitable synthetic equivalent of methyl malondialdehyde **6**. Although the allylation reactions could be performed in two distinctly different sequences, we decided to explore the C(41)−C(42) bond construction first, since subsequent allylation of a C(39) aldehyde with reagent **19** would lead directly to the C(39) carbinol needed for the intramolecular Michael cyclization. Therefore, our initial efforts focused on developing a highly diastereoselective synthesis of the C(40)−C(42) syn,syn stereotriad substructure of **5**.



Treatment of aldehyde **7**[47] with γ-alkoxyallylstannane **11**[48,49] in the presence of BF_3·Et_2O at −78 °C furnished a 2:1 mixture of diastereomers **9a** and **10a** in 53% yield. Stereochemistry was assigned to **9a** and **10a** after conversion of the mixture to the *p*-methoxybenzylidene acetals **13** and **14**. The stucture of acetal **13** was assigned based on the three small coupling constants observed for C(40)-H ($J_{40,41}$ = 2.2 Hz, $J_{39a,\ 40}$ = 1.5 Hz, and $J_{39b,\ 40}$ = 2.3 Hz). The structure of acetal **14** was assigned on the basis of the large diaxial coupling observed between the C(40) and C(41) protons ($J_{40,\ 41}$ = 12 Hz). Slightly increased diastereoselectivity was realized in the BF_3·OEt_2-promoted reaction of **11** with the TBS-protected aldehyde **8**, which afforded a 3:1 mixture of isomers **9b** and **10b** in 51% yield. The TBS-protected γ-alkoxyallylstannane **12**[42] was also employed in an allylation reaction with aldehyde **8** ($MgBr_2$·Et_2O, CH_2Cl_2, −25 °C to +23 °C). Surprisingly, this reaction provided **10c**, the product of chelation control, in 70% yield.[50−54] Unfortunately, cyclopropane products predominated when the reaction of **8** and **12** was attempted using BF_3·Et_2O as catalyst.[44,55]

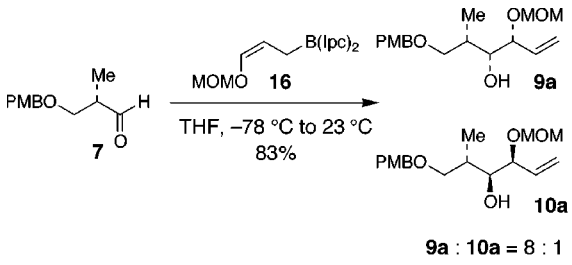


allylmetal	R'CHO	Lewis acid	T(°C)	yield (%)	selectivity **9** : **10**
11	**7**	BF_3·OEt_2	−78	51	2 : 1
11	**8**	BF_3·OEt_2	−78	53	3 : 1
12	**8**	$MgBr_2$·OEt_2	−25 to rt	70	only **10c**

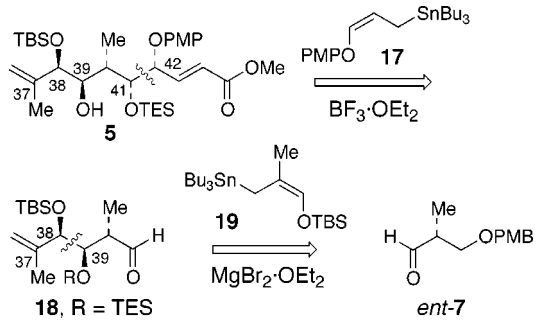
The modest diastereoselectivities observed for the desired syn,syn diastereomer **9** in the reactions of γ-alkoxyallylstannanes **11** and **12** with chiral aldehydes

(42) Keck, G. E.; Abbott, D. E.; Wile,: M. R. *Tetrahedron Lett.* **1987**, *28*, 139.
(43) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143.
(44) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(45) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1980**, *45*, 195.
(46) Koreeda, M.; Tanaka, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 845.
(47) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. P. *Tetrahedron Lett.* **1998**, *39*, 9361.
(48) Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597.
(49) Burgess, K.; Chaplin, D. A. *Tetrahedron Lett.* **1992**, *33*, 6077.
(50) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.
(51) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457.
(52) Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461.
(53) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281.
(54) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279.

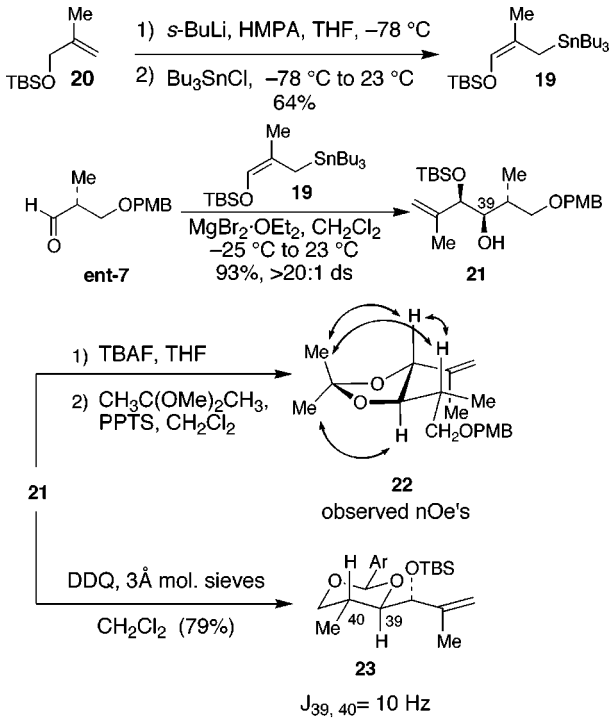
7 and **8** were insufficient for application of these reactions to the projected total synthesis. Consequently we explored use of the chiral γ-alkoxyallylborane technology developed by Brown.[56] Although the asymmetric γ-alkoxyallylboration of achiral aldehydes with **16** has been reported to be highly enantioselective (~90% ee), we found that the α-alkoxyallylation of **7** with **16** provided an 8:1 diastereomeric mixture favoring the desired differentially protected syn,syn diastereomer **9a**. We presume that this reaction is stereochemically mismatched,[57] since reactions of α-methyl branched aldehydes such as **7** with various (*Z*)-substituted allylboron reagents favors production of the diastereomer represented by **10**.[58−60] Although this sequence offered an improvement in diastereoselectivity as compared to substrate-based asymmetric induction utilizing the γ-alkoxyallylstannane **11** or **12**, large-scale production of **9a** was impeded by difficulties associated with diastereomer separation, which was challenging even using HPLC.



The poor to moderate diastereoselection observed in both the single and double asymmetric α-alkoxyallylations of the chiral aldehydes **7** and **8** prompted exploration of an alternative approach to enoate **5** in which the C(38)−C(40) stereotriad was formed first. This would allow for the generation of the C(40)−C(42) all syn stereotriad via Felkin addition of **17** to the 2,3-anti aldehyde **18**. The β-methyl-γ-alkoxyallylstannane **19** was identified for construction of the differentially protected C(38)−C(39) diol unit as well as the introduction of the C(36)−C(37) alkene in **18**, which we anticipated would serve as a suitable precursor to the methyl ketone in the targeted F ring pyran **3**.



Metalation of *tert*-butyldimethylsilyl methallyl ether **20** followed by addition of Bu_3SnCl afforded the β-methyl-γ-alkoxyallylstannane **19** (64%). Chelation controlled addition of **19** to aldehyde *ent*-**7** ($MgBr_2$·Et_2O, CH_2Cl_2, −25 °C to +23 °C) provided the anticipated homoallylic alcohol **21** in 93% yield with greater than 20:1 stereoselectivity.[42] The stereochemistry of the C(38)−C(39) diol was deduced from ^1H NOE studies of the acetonide **22**, prepared by sequential treatment of **21** with TBAF, then dimethoxypropane and PPTS. The relative stereochemistry of the C(39) carbinol and C(40) methyl of **21** was assigned after conversion to the *p*-methoxybenzylidene acetal **23**. The large coupling constant observed between H(39) and H(40) indicated the diequatorial substitution pattern of acetal **23** and hence the anti stereochemical relationship in **21**.

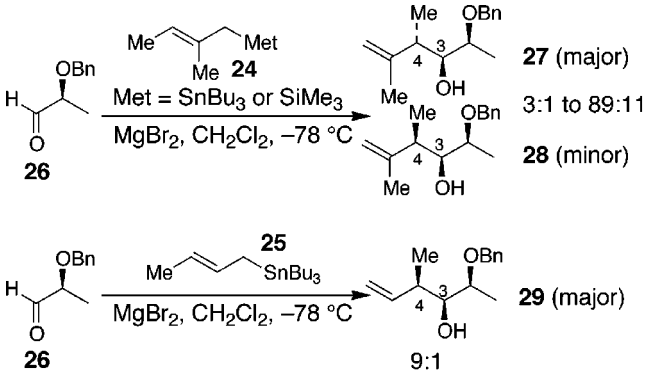


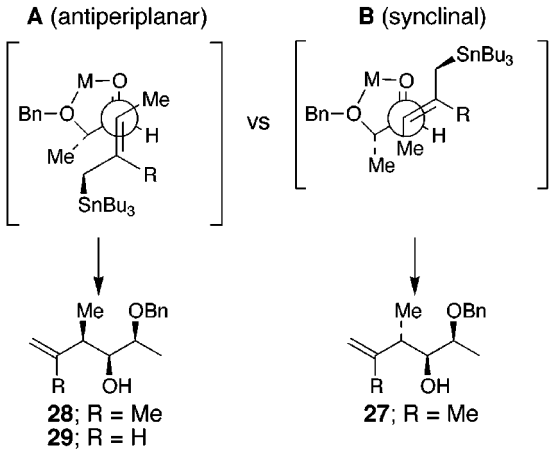
Precedent suggests that chelate-controlled allylation reactions of γ-alkoxyallylstannanes lacking a β-methyl substituent (i.e., **25**) provide the syn-anti stereochemistry present in **21**.[42,43] Therefore our result with **19** does not appear surprising. However in comparison to the crotylstannane literature, where a striking stereodivergence has been observed in chelate controlled allylation reactions between β-methylcrotylstannanes and the parent crotylstannanes,[61] our result is fundamentally interesting.

Mikami has shown that the major product from the chelate controlled addition of β-methyl-(*Z*)-crotylstannane **24** to aldehyde **26** is the 3,4-anti diastereomer **27**, whereas under similar conditions the reaction of **26** and the unsubstituted crotylstannane **25** affords predominantly the 3,4-syn diastereomer **29**.[61] It has been proposed that crotylstannane **25** prefers to adopt an antiperiplanar orientation in transition state **A**, leading to

(55) Marshall, J. A.; Jablonowski, J. A.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 7825.
(56) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.
(57) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(58) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(59) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
(60) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 403.
(61) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161.

the 3,4-syn stereochemistry in **29**.[62] Mikami suggests the β-methylcrotylstannane **24** prefers to adopt a synclinal geometry in transition state **B**, as a result of increased steric demand imparted by the β-methyl substituent in transition state **A**, and therefore that the 3,4-anti stereochemistry in **27** is favored with **24**.

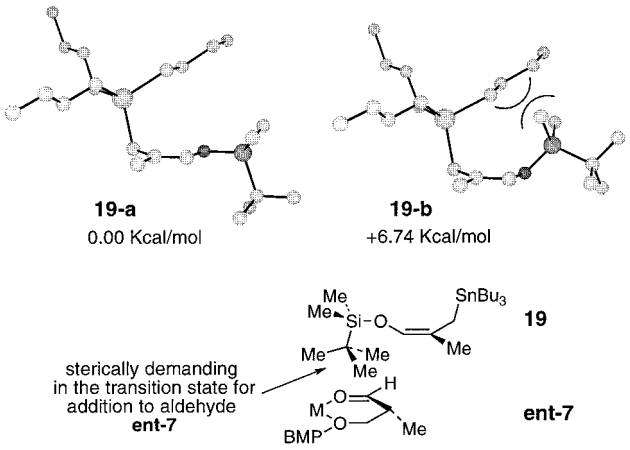




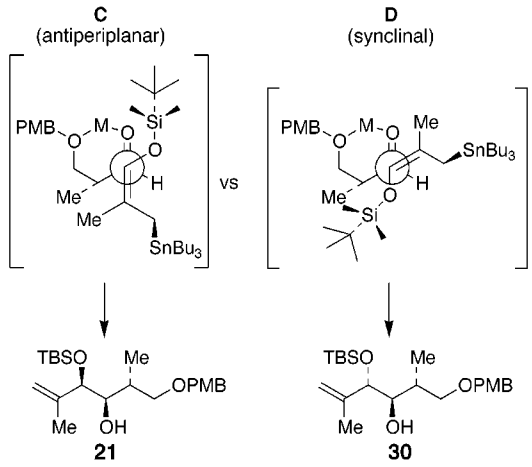
While Mikami's results suggest that the β-methyl substituent of **24** provides an overriding steric component in the chelate controlled reaction with **26**, it appears that the β-substituent of **19** plays a much diminished role in the reaction of *ent*-**7** and **19**, and that a different control element is operational in this case. In accord with an $S_{E'}$ mechanism,[63] the dihedral angle of the Sn–C–C=C unit of **19** should be approximately 90° in the transition state, thereby maximizing overlap between the Sn–C σ bond and the π^* orbital of the double bond. MM2 calculations of **19** indicate that the O–Si bond remains coplanar with the C=C, and that the *t*-Bu substituent is positioned anti to the Bu_3Sn– group as in **19a**. Therefore, the Lewis acid complex of *ent*-**7** must be oriented in the transition state for allylation with **19** in such a way as to minimize interactions with the *t*-Bu of the TBS ether protecting group of **19**.

It is conceivable that the antiperiplanar transition state **C** is preferred in this case compared to the synclinal transition state **D** because it can better accommodate the large *t*-Bu substituent of the γ-alkoxyallylstannane **19**. Inspection of models clearly indicates that the *tert*-butyl group of the TBS ether interacts with the aldehyde C(α) substituents in transition state **D**.

Conversion of the PMP acetal **23** to the C(41) aldehyde **31** was achieved via regioselective reduction of the acetal



with DIBAL[64] followed by Swern oxidation.[65] The γ-alkoxyallylstannane **17** needed for homologation of **31** was generated by alkylation of *p*-methoxyphenol **32** with allylbromide followed by metalation with *s*-BuLi and addition of Bu_3SnCl. Unfortunately, attempted allylation of 2,3-*anti*-aldehyde **31** with γ-alkoxyallylstannane **17** in the presence of $BF_3{\cdot}OEt_2$ gave a complex mixture of products lacking disubstituted olefins. We speculated that **31** may have undergone an intramolecular Prins reaction owing to the nucleophilicity of the C(37) alkene.[66,67]



Due to the sensitivity of enal **31** to Lewis acids, we attempted to use the γ-alkoxyallylaluminate **34**, a reagent that does not require the addition of an external Lewis acid for allylation to occur.[45] However, treatment of **31** with allylaluminate **34** afforded a 1:1 mixture of stereoisomeric homoallylic alcohols tentatively assigned as **35** and **36**.

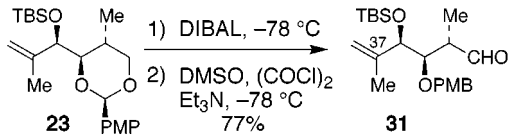
In view of these difficulties, we decided to modify the C(37) olefin of **31** before proceeding with the synthesis. Accordingly, treatment of the homoallylic alcohol **21** with triethylsilyl triflate (TESOTf) followed by asymmetric dihydroxylation[68] provided an 8:1 mixture of diastereomeric diols in a combined 81% yield. The major diastereomer was assigned the stereochemistry shown by application of Sharpless' empirical mnemonic.[68] The major diol was treated with triphosgene and pyridine in

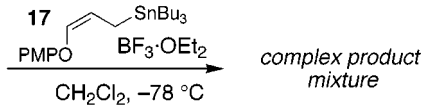
(62) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 9, 7889.

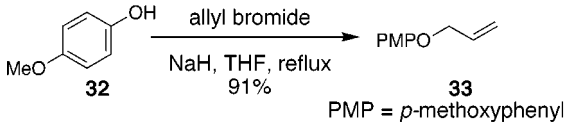
(63) Denmark, S. E.; Hosoi, S. *J. Org. Chem.* **1994**, *59*, 5133.

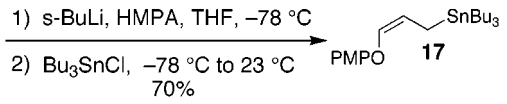
(64) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

(65) Tidwell, T. T. *Synthesis* **1990**, 857.

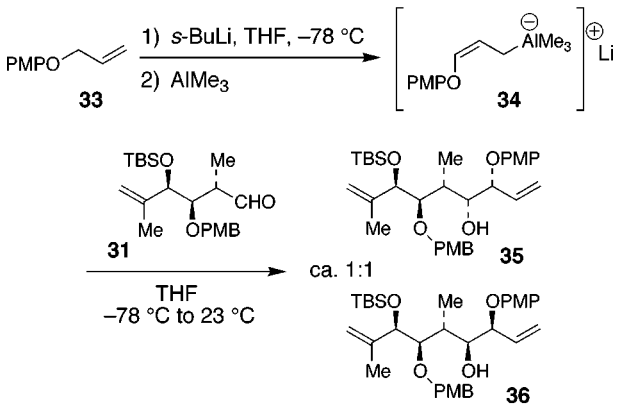




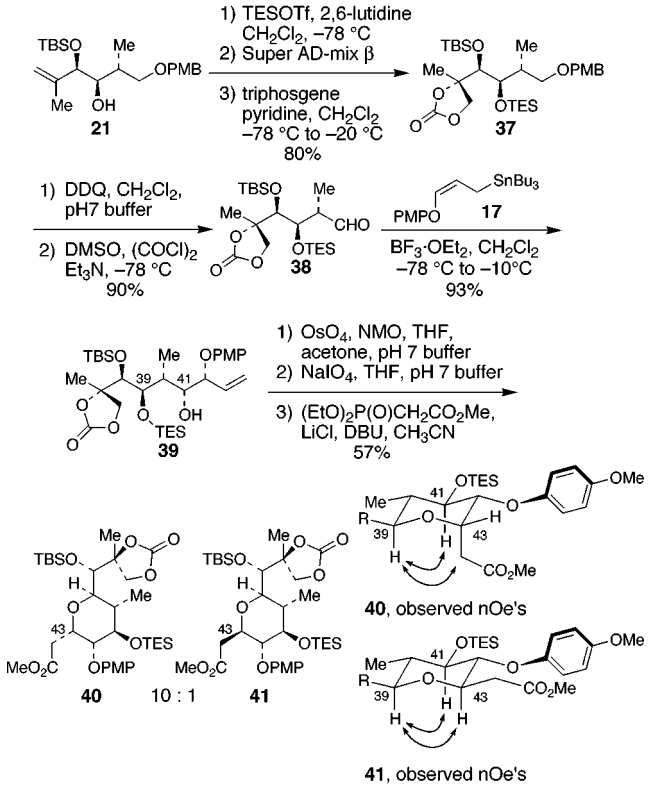




CH_2Cl_2 to give the corresponding carbonate **37** in 99% yield. Removal of the PMB ether by exposure of **37** to DDQ[69] in wet CH_2Cl_2 provided the primary alcohol which was oxidized to the aldehyde **38** using the standard Swern protocol.[65]



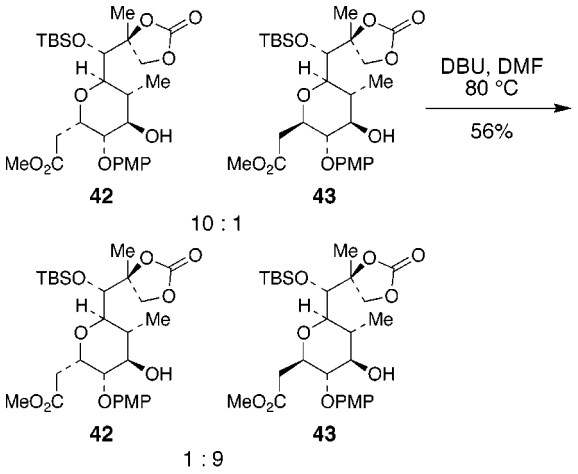
We now were in position to revisit the α-alkoxyallylation of the C(41) aldehyde. Gratifyingly, treatment of aldehyde **38** with allylstannane reagent **17** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C gave the desired alcohol **39** in 93% yield with >20:1 diastereoselectivity. The terminal olefin of **39** was oxidatively cleaved via a two step procedure (OsO_4, NMO[70] followed by $NaIO_4$, 84%), and the resulting crude aldehyde was subjected to a Horner−Wadsworth−Emmons reaction using $(EtO)_2POCH_2CO_2Me$, LiCl, and DBU in acetonitrile.[71] When the Horner-Wadsworth-Emmons reaction was performed in the presence of excess LiCl at room temperature, the TES group migrated from the C(39) hydroxyl to the C(41) hydroxyl, and the newly liberated C(39) alcohol underwent 1,4-addition to the enoate. This one pot olefination, silyl migration, 1,4-addition reaction sequence furnished the targeted pyran system as a 10:1 mixture of diastereomers **40** and **41** in 68% yield. However, ^{1}H NOE studies of the diastereomeric pyrans indicated that the major product **40** possessed the incorrect (axial) stereochemistry at C(43).



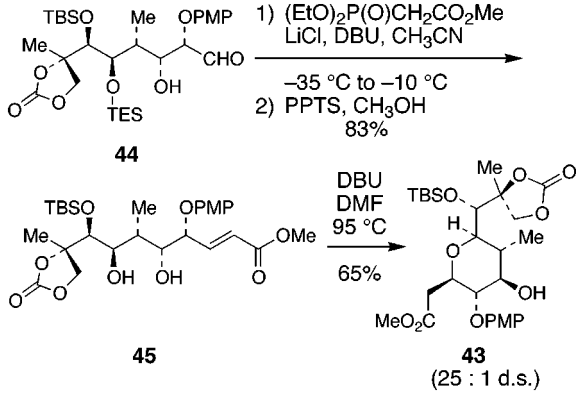
Initial attempts to equilibrate the mixture of diastereomeric pyrans were unsuccessful ($BnMe_3N^+\ ^-OMe$, MeOH, THF, 0 °C; KO*t*-Bu, THF, 0−23 °C; DBU, DMF, 100 °C); in general, pyran **40** was recovered without significant equilibration to **41**. We speculated that the inability to equilibrate this mixture was due to a remote steric effect of the C(41)-triethylsilyl ether, which causes the C(42) *p*-methoxyphenyl ether to adopt a conformation anti to the C(41)−C(42) bond, thereby destabilizing **41** with an equatorial acetate side chain, compared to **40**. However, MM2 calculations suggest that **41** is more stable than **40** by ca. 1 kcal/mol. Therefore, our inability to equilibrate **40** to **41** must reflect a kinetic and not a thermodynamic problem. Nevertheless, removal of the C(41) TES ether (PPTS in methanol, 93%) followed by subjection of the resulting pyranols to basic conditions (DBU, DMF, 80 °C) resulted in an equilibrated 9:1 mixture of the desired pyran **43** (now major) and the C(43) axial epimer **42** in 56% yield.

Armed with the insight provided by these equilibration studies, the synthesis of **43** was improved as follows. When the HWE olefination of **44** was performed using 3 equiv of $(EtO)_2POCH_2CO_2Me$, 3 equiv of LiCl and 3 equiv of DBU in CH_3CN at −35 °C to −10 °C, the corresponding enoate was isolated in 88% yield. Subsequent deprotection of the TES ether via exposure to PPTS in methanol then gave diol **45** in 94% yield. Finally, the 1,4-addition was accomplished by treatment of **45** with DBU under thermodynamic conditions (DMF, 95 °C, 22 h), from

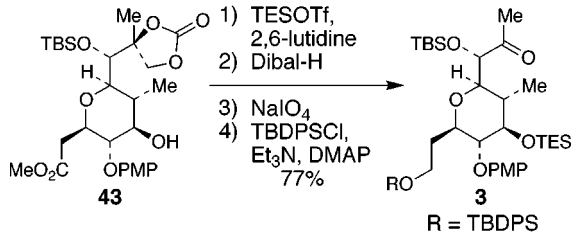
(66) Ziegler, F. E.; Wang, T.-F. *J. Am. Chem. Soc.* **1984**, *106*, 718.
(67) Johnston, M. I.; Kwass, J. A.; Beal, R. B.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 5419.
(68) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(69) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(70) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(71) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.



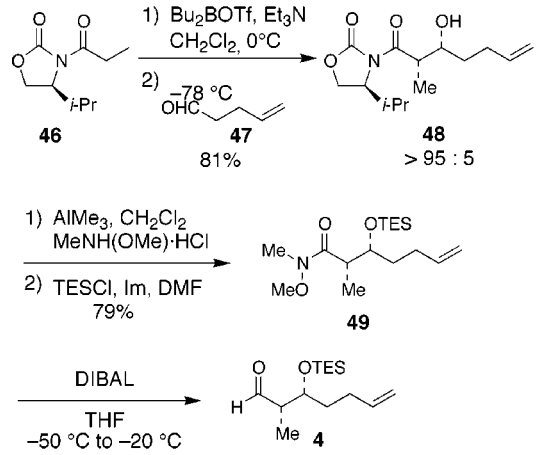
which the desired pyran **43** was obtained in 65% yield with 25:1 diastereoselectivity.



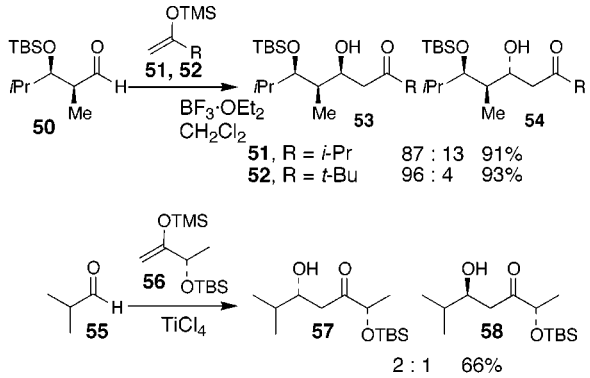
Elaboration of the *cis*-pyran **43** to the targeted methyl ketone **3** was straightforward. Silylation of the C(41) carbinol, followed by simultaneous reduction of the C(45) ester and the carbonate, oxidative cleavage of the resulting diol ($NaIO_4$), and protection of the primary carbinol (TBDPSCl, Et_3N, DMAP) afforded the fully functionalized F-ring methyl ketone **3** in an overall 77% yield.

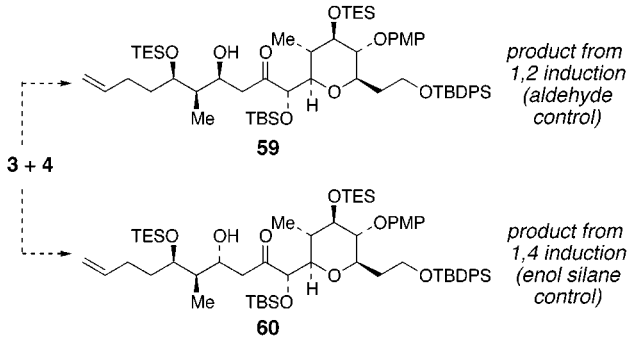


With a route to the C(36)−C(45) methyl ketone fragment **3** secured, we directed our efforts to the synthesis of the 2,3-syn aldehyde **4**.[36] *Syn*-aldol **48** was prepared in 81% yield (>95:5 ds) from the aldol reaction between N-propionyl oxazolidinone **46** and aldehyde **47**.[72,73] Aldol **48** was converted to the Weinreb amide **49** via a two step procedure ($AlMe_3$, MeNH(OMe)·HCl followed by TES−Cl, imidazole) in 79% yield. Reduction of amide **49** with DIBAL afforded the crude aldehyde **4** which was used in subsequent aldol reactions without purification.



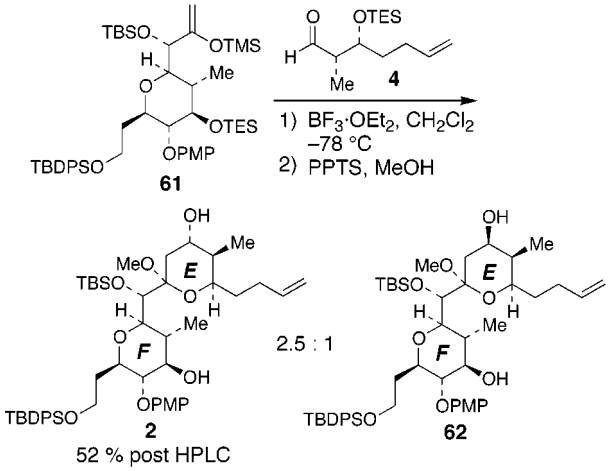
In planning the coupling of **3** and **4**, we were aware of a report by Ley that an analogous aldol reaction using the lithium enolate provided the anti-Felkin aldol preferentially.[30,74] As a means to access the desired Felkin diastereomer, Ley ultimately employed chiral boron enolate (Ipc_2BCl) technology which provided the desired compound as a single diastereomer, but in low yield. We were also aware of reports by Evans that 2,3-syn aldehydes **50** exhibit high Felkin diastereoselectivity in Mukaiyama aldol reactions[75] with sterically demanding enol silanes **51** and **52**, leading to the preferential formation of the *syn, syn* stereotriad in **53**.[74] In addition, Trost has demonstrated that the Mukaiyama aldol reaction of α-silyloxy enol silanes **56** with isobutyraldehyde, affords predominantly the 1,4-syn adduct **57** (2:1 ds).[76] These data suggested that the Mukaiyama aldol coupling of **3** and **4** would be stereochemically mismatched.[57] Nevertheless, we anticipated that the facial bias of the 2,3-syn aldehyde **4** would dominate that of the enol silane generated from **3** in the aldol reaction, thereby providing diastereoselective access to the desired aldol **59**.





(72) Montgomery, L. K.; Matt, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 6556.
(73) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Toward this end methyl ketone **3** was treated with TMSCl, Et_3N and LiHMDS to afford the TMS enol ether **61** as a chromatographically stable oil in 83% yield.[77] A solution of enol silane **61** and aldehyde **4** was then treated with $BF_3{\cdot}Et_2O$ at −78 °C. The mixture of crude aldol products was treated with PPTS in methanol resulting in deprotection of the C(35) and C(41) triethylsilyl ethers and formation of the methyl hemiketal. This sequence provided a mixture of diastereomeric pyrans **2** and **62** (2.5:1 d.s.), which after chromatographic separation afforded the desired diastereomer **2** in 52% yield. After our studies of this reaction were complete, Heathcock reported an analogous Mukaiyama aldol coupling in his synthesis of the spongistatin E−F bis pyran unit.[13]



Increased Felkin diastereoselectivity has been observed in the reactions of 2,3-*syn*-aldehydes and enol silanes using trityl salts as the promoter.[74,78−80] However, application of $(C_6H_5)_3C^+SnCl_5^-$ to the present case merely led to extensive decomposition of both the highly functionalized enol silane **61** and aldehyde **4**. Similarly, attempted use of other Lewis acids ($TiCl_4$, $SnCl_4$, $MeAlCl_2$, TMSOTf, TBSOTf) commonly employed in the Mukaiyama aldol reaction of less functionalized partners were also ineffective.

In final analysis, it is clear that the stereoselectivity of the aldol reaction of **61** and **4** leading to **59** suffers from the dissonant stereochemical pairing of the two components.[57] While it should be possible to utilize the minor aldol adduct (**60**) in the synthesis by epimerization of the C(35) center,[13] alternative strategies for control of this center will be explored in future studies. Despite this one blemish in stereochemical control, the present synthesis of the E−F bis-pyran unit **2** is accomplished in 19 steps and 10.1% overall yield. The use of the γ-alkoxyallylstannane reagents **17** and **19** in highly stereoselective α-alkoxyallylation reactions is noteworthy, as is the insight gained in the development of a thermodynamically controlled intramolecular Michael addition to close the F-ring pyran. Additional progress on the synthesis of the spongistatins will be reported in due course.

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Supporting Information Available: Complete experimental details and copies of ^1H NMR spectra of compounds **2**, **3**, **17**, **19**, **31**, **38**−**44**, **61**, **62**, **68**, **70**, and **71**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(74) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(75) Nelson, S. G. *Tetrahedron*: *Asymmetry* **1998**, *9*, 357.
(76) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982.
(77) Paterson, I.; Watson, C.; Yeung, K.-S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452.
(78) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535.
(79) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759.
(80) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447.