Pergamon

Tetrahedron Letters 40 (1999) 3351–3354

TETRAHEDRON LETTERS

Towards the Synthesis of Spongistatin 1: Diastereoselective Synthesis of the C(36)-C(45) Subunit

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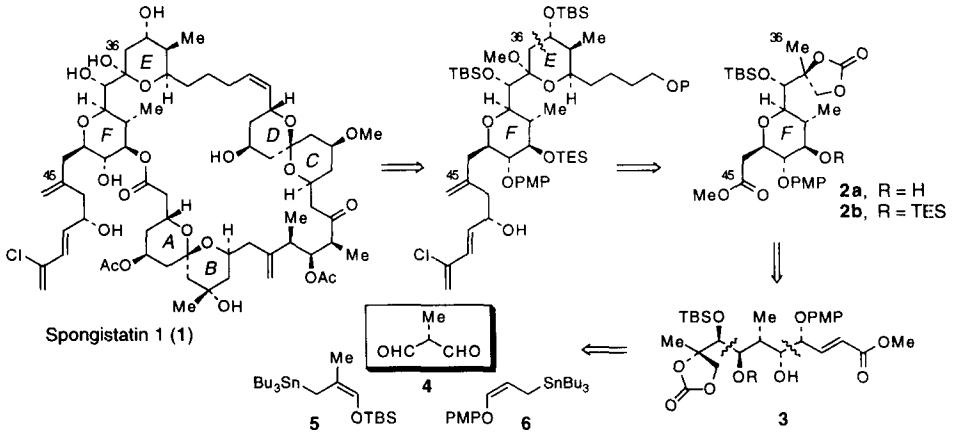
Received 9 February 1999; accepted 17 February 1999

Abstract: An efficient and highly diastereoselective 12 step synthesis of the C(36)-C(45) subunit (**2a**) of spongistatin 1 is described. The synthesis features highly diastereoselective α–alkoxyallylation reactions using the γ-alkoxy substituted allylstannanes **5** and **6**, and a thermodynamically controlled intramolecular Michael addition to close the pyran.

The spongistatins and altohyrtins are a structurally complex class of sponge-derived macrolide polyethers possessing unparalleled inhibitory activity against a subset of chemoresistant tumor types.[2] Spongistatin 1 (**1**, also known as altohyrtin A) is among the most active members of this family.[3] The extremely meager natural supply, novel structural features, and potent biological activities have defined the spongistatins and altohyrtins as interesting targets for total synthesis. Elegant total syntheses of spongistatins 2 and 1 have been reported by the Evans[4] and Kishi[5] groups, and additional studies directed towards the synthesis of this family have appeared.[6] We report herein a very brief and highly diastereoselective synthesis of the spongistatin C(36)-C(45) fragment, represented by the F ring pyran unit **2a**.



Our strategy from the outset called for **2a** to be assembled by the intramolecular Michael cyclization of **3** (R = H), which in turn would be assembled by a series of diastereoselective γ-alkoxyallylstannylations[7] of a suitable synthetic equivalent of methyl malondialdehyde, **4**. During the course of this work we developed the (*Z*)-γ-alkoxymethallylstannane reagent **5**[8] for introduction of the C(38)-C(39) diol unit in a fully differentiated manner. The γ-alkoxyallyl stannane **6**[9] (PMP = *p*-methoxyphenyl) similarly proved useful for introducing the differentiated C(41) and C(42) diol unit of **3**.

Chelate controlled addition of the allylstannane reagent **5** to the readily available aldehyde **7**[10] ($MgBr_2$•Et_2O, CH_2Cl_2, -78 °C) provided the homoallylic alcohol **8a** in 93% yield.[7,11] The diastereoselectivity of this reaction was excellent (≥20 : 1 d.s.). Treatment of **8a** with triethylsilyl triflate (TES-OTf) provided the corresponding TES ether in 92% yield. We initially transformed **8a** into aldehyde **9**, which we imagined

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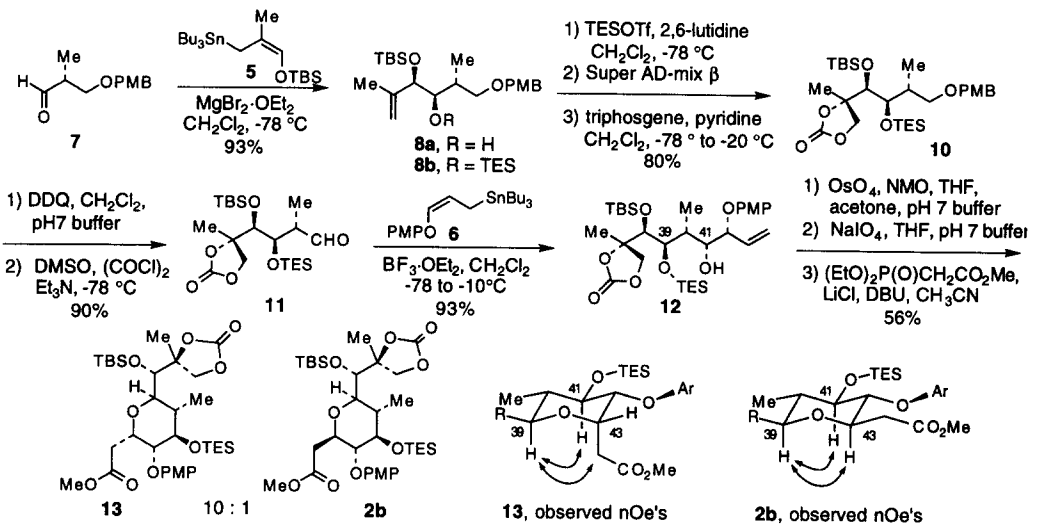
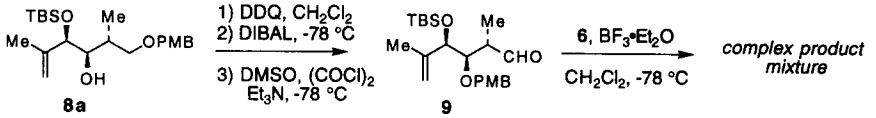


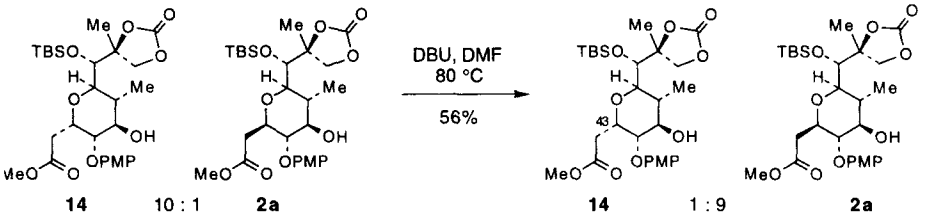
would be a suitable substrate for a Lewis acid promoted α-alkoxyallylation with **6**. However, this reaction gave a complex mixture of products lacking disubstituted olefin units, and we suspected that **9** may have undergone an intramolecular Prins reaction. Accordingly, we decided to chemically differentiate the C(37)-olefin before proceeding with the synthesis. This was accomplished by asymmetric dihydroxylation of TES



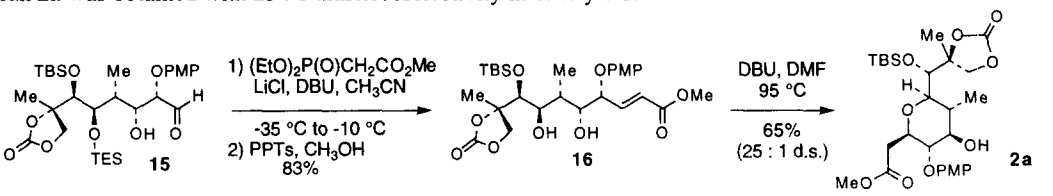
ether **8b**, which provided an 8 : 1 mixture of diastereomeric diols in 88% yield.[12] Treatment of the resulting diol with triphosgene and pyridine in CH_2Cl_2 provided carbonate **10** in 99% yield. The major diastereomer was assigned the stereochemistry shown by application of Sharpless' empirical mnemonic device.[12,13] Removal of the PMB ether by treatment of **10** with DDQ[14] in wet CH_2Cl_2 provided the primary alcohol which was oxidized to the aldehyde using the standard Swern protocol.[15] The resulting 2,3-anti aldehyde **11** was then treated with allylstannane reagent **6** and BF_3•Et_2O in CH_2Cl_2 at -78 °C, which provided the desired alcohol **12** with >20 : 1 diastereoselectivity (93% yield). The terminal olefin was oxidatively cleaved via a two step procedure (OsO_4, NMO followed by $NaIO_4$, 82%). The crude aldehyde was then subjected to a Horner-Wadsworth-Emmons reaction using $(EtO)_2POCH_2CO_2Me$, LiCl and DBU in acetonitrile.[16] When the HWE reaction was performed using excess LiCl at room temperature, the TES group migrated from the C(39) hydroxyl to the C(41) hydroxyl, and the C(39) hydroxyl subsequently underwent 1,4-addition to the newly introduced enoate. This one pot olefination, silyl migration, 1,4-addition reaction sequence furnished the targeted pyran system as a 10 : 1 mixture of diastereomers in 68% yield. The stereochemistry of the diastereomeric pyrans was assigned by ^1H NMR studies, which showed that the major pyran **13** possessed the incorrect (axial) stereochemistry at C(43).

Initial attempts to equilibrate the mixture of pyran diastereomers were unsuccessful ($BnMe_3N^+$ ^-OMe, MeOH, THF, O °C; KO*t*-Bu, THF, 0 ° to 23 °C; DBU, DMF, 100 °C); in general, pyran **13** was recovered without significant equilibration to **2b**. 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. As long as the C(43) substituent is axial, the C(42) aryl ether then occupies an unhindered quadrant, devoid of any significant gauche interactions.[17] However, if the C(43) side chain is equatorial, then the C(42) aryl ether experiences significant gauche interactions with either with C(44), or with the C(41)-TES ether. Therefore, in order to relieve these interactions, the mixture of **13** and **2b** was treated with PPTs in methanol, which provided the corresponding 10 : 1 mixture of C(41)-alcohols **14** and **2a** (93%). Fortunately, treatment of this mixture with DBU in DMF at 80° C furnished an equilibrated 9 : 1 mixture of the desired pyran **2a** (now major) and the C(43) axial epimer **14** in 56% yield.



Armed with the insight provided by these equilibration studies, the synthesis of **2a** was improved as follows. When the Horner-Wadsworth-Emmons olefination of **15** (generated from **12** as described above) was performed using 3 equiv of $(EtO)_2P(O)CH_2CO_2Me$, 3 equiv of LiCl and 3 equiv of DBU in CH_3CN at -35 ° 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 **16** in 94% yield. Finally, the 1,4-addition was accomplished by treatment of **16** with DBU under thermodynamic conditions (DMF, 95 °C, 22 h), from which the desired pyran **2a** was obtained with 25 : 1 diastereoselectivity in 65% yield.



In summary, we have developed a 12 step synthesis of the C(36) to C(45) subunit (**2a**) of spongistatin 1 that proceeds in 28% yield from the known aldehyde **7**. The synthesis features highly diastereoselective α–alkoxyallylation reactions using the γ-alkoxy substituted allylstannanes **5** and **6**, and a thermodynamically controlled intramolecular Michael addition to close the pyran ring system. Additional progress towards the synthesis of spongistatin 1 will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM 38436) is gratefully acknowledged.

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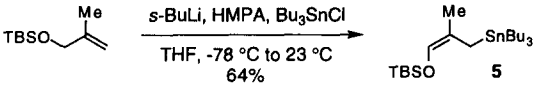
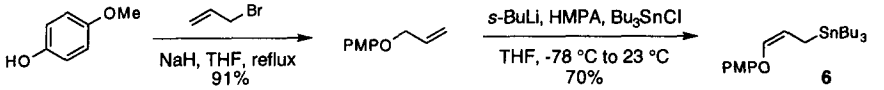
(8) (*Z*)-γ-(*tert*-Butyldimethylsilyloxy)methallyltributylstannane (**5**) was prepared in 64% yield by metallation of *tert*-butyldimethylsilyl methallyl ether followed by addition of Bu_3SnCl.



(9) (*Z*)-γ-Alkoxyallylstannane **6** was prepared via alkylation of *p*-methoxyphenol with allyl bromide followed by metallation with *s*-BuLi and quenching with Bu_3SnCl.



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