Synthesis of the C29−C44 Portion of Spongistatin 1 (Altohyrtin A)

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Two synthetic approaches to the C29−C44 portion of spongistatin 1 (altohyritin A) have been developed. The key step of the first approach relies on the Claisen rearrangement of glucal **18** to provide ester **20a**. This intermediate was advanced to silyl enol ether **30**, which was coupled under Mukaiyama aldol conditions with aldehyde **3**. Cyclization of this aldol adduct completed our first synthesis of the C29−C44 portion of spongistatin 1, requiring 25 total steps and occurring in 2.4% yield over the longest linear sequence (21 steps). We have also developed a second-generation approach based on the C-glycosidation of glucal **43**. Through equilibration of the corresponding C-glycosides **49a/b** and **50a/b** the desired C-glycoside (**50a**) was obtained in good yield. Aldol condensation of this ketone provided cyclization precursor **67**, which undergoes acid-catalyzed ketalization to close the **E**-ring of the spongistatins. An oxidation/reduction protocol was employed to set the C37 stereocenter. Protection of the C37 carbonol and selective unmasking of the C44 carbonol completed our second generation synthesis. This approach requires 27 steps and occurred in 13.2% yield over the longest linear sequence (18 steps).

In 1993 and 1994, isolations of the spongistatins,[1] altohyrtins,[2] and cinachyrolide A[3] were reported. These structurally related macrocyclic lactones show extreme cytotoxicity toward various tumor cell lines, thus making them valuable tools for understanding cancer. Spongistatin 1 has been identified as "probably the best to date in the NCI's evaluation programs,"[4] exhibiting 50% growth inhibition against a range of tumor lines at concentrations in the range of 10^{-10} to 10^{-12} mol/L. Additionally, this material has shown potent activity against a subset of highly chemoresistant tumor types.[4] Spongistatin appears to disrupt microtubule assembly by binding tubulin in the vinca alkaloid binding site.[5] The compound also has potent antifungal properties, inhibiting the growth of many fungi, including strains resistant to amphotericin B, ketoconazole, and flucyosine.[6]

These extremely active marine natural products provide a good example of the power of Nature to point us in the direction of organic structures of potential use in chemotherapy. The problem is that they are available from Nature in only minute amounts and there is currently no practical way to farm sponges to obtain larger quantities of the metabolites. We believe that, even despite their great complexity, conventional organic synthesis can provide multigram quantities of the spongistatins, and it is the goal of the current project to develop an efficient total synthesis to provide several grams of the natural product so that a phase I clinical trial can be carried out.

Because of their complex structures and extreme cytotoxicity, these natural products have attracted the attention of many groups,[7] and two groups have already recorded complete total syntheses. Evans and co-workers reported the first total synthesis of spongistatin 2 and proved it to be identical to altohyrtin C (**2**).[8] Kishi has published the total synthesis of altohyrtin A, which is identical to spongistatin 1 (**1**).[9]

At the beginning of our synthetic efforts, we decided to focus on altohyrtin A (**1**), since it was the only structure whose absolute and relative configuration was supported by adequate data. Our strategy was designed around a macrolactonization as the final key step. Further disconnection of the C28−C29 double bond revealed two similarly complex fragments, which were to be joined using a Wittig reaction. We have previously described our synthesis of the C1−C28 portion of spongistatin 1 (altohyrtin A).[10] The C29−C51 fragment was envisioned

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(2) (a) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243−1246. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795−2798.

(3) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977−3981.

(4) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812−821.

(5) (a) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol.* **1993**, *44*, 757−766. (b) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Proc. Annu. Meet. Am. Assoc. Cancer Res.* **1993**, *34*, 4: A2243. (c) Bai, R.; Taylor, G. F.; Cichaz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettir, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714−9721.

(6) Pettit, G. R. Patent Application WO97-US10200.

(7) For a recent review, see: Pietruszka, J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2629−2636.

(8) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738−2741. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741−2744. (c) Evans, D. A.; Trotter, W. B.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744−2747.

(9) (a) 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*, 187−192. (b) 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*, 192−196.

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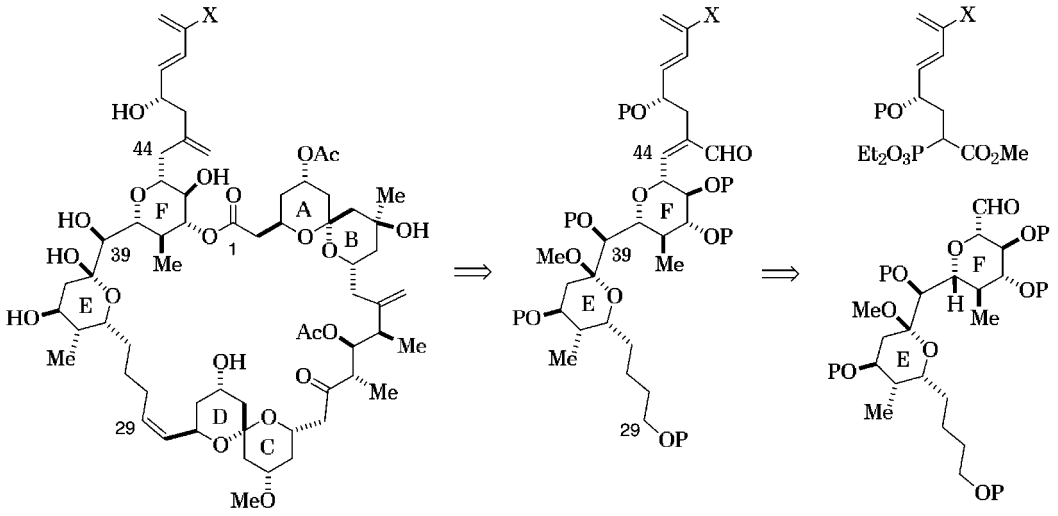
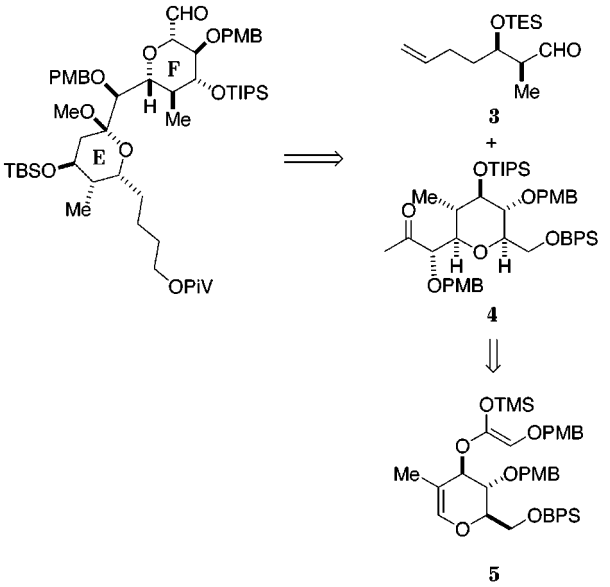


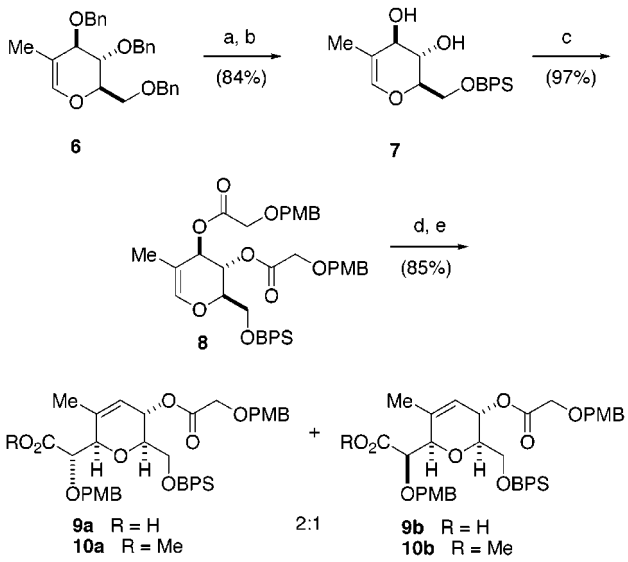
1: X=Cl (spontistatin **1** = altohyrtin A)
2: X=H (spongistatin 2 = altohyrtin C)

Figure 1.

Scheme 1



Scheme 2[a]



[a] Key: (a) Na, NH_3; (b) BPSCl, imid., DMF; (c) (4-methoxy)benzyloxyacetic acid, DCC, DMAP, DMF; (d) LiHMDS, TMSCl, pyr., −78 °C to rt; (e) CH_2N_2.

as arising from an allylic rearrangement where the C45−C58 olefin would originate in the C44−C45 position. Disconnection across the $\alpha-\beta$ unsaturation leads to the C29−C44 fragment of altohyrtin A. In this paper, we describe our first- and second-generation approaches to this key intermediate (Figure 1).

Retrosynthetic analysis of the EF bispyran ring system (Scheme 1) suggested aldehyde **3** and ketone **4** as potential precursors. We planned to use a Claisen rearrangement of glucal **5** as a key step in our synthesis of ketone **4**. This would allow us to simultaneously set the C38 and C39 stereocenters in a single synthetic operation.

As shown in Scheme 2, synthesis of the Claisen rearrangement precursor began with tribenzyl ether **6**, previously described by our laboratory.[11] The benzyl groups of **6** were removed with a dissolving metal reduction, and the resulting triol was protected as the primary *tert*-butyldiphenylsilyl ether in 84% overall yield. Our attempts to esterify the 3-OH of **7** selectively with (4-methoxybenzyloxy)acetic acid[12] were unsuccessful, providing a mixture of products. Instead, we chose to bisesterify diol **7** with an excess of the PMB-protected glycolic acid, providing **8** in 97% yield.

With the Claisen rearrangement precursor in hand we could explore this key step of the synthesis. Treatment of a premixed solution of **8**, pyridine, and TMS-Cl with excess LiHMDS resulted in formation of the bis-silylketene acetal.[13] Upon warming to room temperature, this substrate underwent rapid Claisen rearrange-

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(11) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.***1996**, *291*, 205−208.
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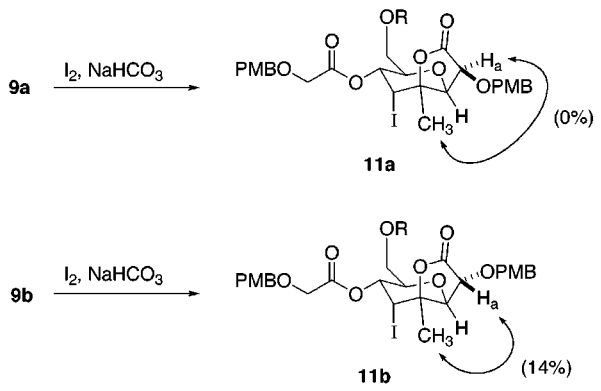
Scheme 3



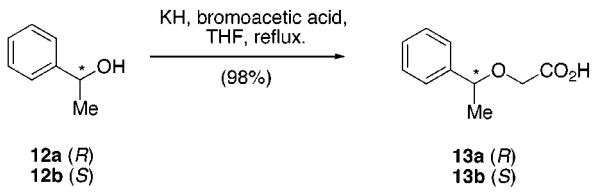
ment.[14,15] The crude reaction mixture was treated with diazomethane to facilitate isolation of the methyl esters **10a** and **10b** in a 85% overall yield, as a 2:1 mixture of diastereomers. If the reaction mixture was allowed to remain at room temperature for more than 15 min, the tandem Claisen product predominated.[16] To elucidate the relative stereochemistry of **10a** and **10b**, they were separated by column chromatography, saponified to the acids, and induced to lactonize with I_2 and $NaHCO_3$.[17] With the structures rigidified as the 6/5 lactones **11a** and **11b**, NOE difference experiments were performed (Scheme 3).[18] Irradiation of the bridgehead methyl group of **11b** produced a 14% enhancement in the signal of the proton labeled H_a that was not observed when the bridgehead methyl group of **11a** was irradiated.

We were pleased that the Claisen rearrangement provided the desired diastereomer as the major product. However, the rather low selectivity deserves further discussion. Literature data suggest that the presence of a vinyl ether accelerates Claisen rearrangements on olefins of this type. In addition, the presence of an oxygen α to the carbonyl group also has an accelerating effect.[13,14,16] No examples could be found where both of these situations were present simultaneously, as in the present case. However, our data suggest that the two accelerating effects are additive, providing a Claisen rearrangement that is very facile, but not very selective.

At this point, we attempted to alter the reaction conditions of the Claisen rearrangement to increase the diastereoselectivity of this reaction. Attempts at prechelation of the glycolic ester with lithium chloride in order to affect the E/Z ratio of the silyl enol ether[13] were unsuccessful, providing esters **10a** and **10b** in the same ratio. Addition of solvent additives such as HMPA, were equally ineffective. Trapping the bisenolate of **8** with either TES-Cl or TBS-Cl led to complex mixtures of products. Returning to the original conditions and running the reaction at −78 °C was unsuccessful, providing the same product ratio observed previously.

From the above results, it was evident that conventional alterations in the reaction protocol were not going to substantially affect the ratio of **9a** and **9b**. At this juncture, we took a purely empirical approach. The idea was to replace the *p*-methoxybenzyl group with a *p*-methoxyphenylethyl group. This change would presumably produce a small but unpredictable effect on the disastereoselectivity of the Claisen rearrangement. If the effect happened to be beneficial, it was hoped that this small beneficial effect would act to amplify the observed 2:1 diastereomeric ratio of **9a** and **9b**. Since we would be introducing a new stereocenter, we thought we might find ourselves with a double diastereoselection situation: with one of the diastereomeric *p*-methoxyphenylethyl derivatives amplifying the 2:1 ratio and the other attenuating it. To investigate the feasibility of this approach, we chose the easily prepared methylbenzyloxy glycolic acids **13a** and **13b**. Coupling of the potassium salt of commercially available (*S*)- and (*R*)-phenethyl alcohols with bromoacetic acid provided the desired acids in high yield (Scheme 4).

Scheme 4



12a (*R*)
12b (*S*)

13a (*R*)
13b (*S*)

Coupling of acids **13a** and **13b** with diol **7** was accomplished with DCC and DMAP, providing the diesters **14a** and **14b** in high yield. The results of the Claisen rearrangements of **8**, **14a**, and **14b** are shown in Scheme 5. The use of (*R*)-methylbenzyloxy ester caused a decrease in the inherent selectivity of the rearrangement, now slightly favoring the undesired ester **15b**. However, use of the (*S*)-methylbenzyloxy ester caused an increase in the ratio to 6:1, favoring the desired diastereomer **16a**. Under the optimized reaction conditions, the desired diastereomer could be isolated in 70% yield.

To explore the later steps of our synthesis, we had to change the *tert*-butyldiphenylsilyl protecting group of **15a** to a protecting group that would withstand the deprotection of the methylbenzyl moiety. This was most conveniently done early in the synthesis (Scheme 6). To this end, glucal **6** was deprotected under dissolving metal conditions and the resulting triol was protected as the TIPS ether to provide **17** in 90% overall yield. The diol was bis-acylated with acid **13b** to provide the bis-ester **18** in 88% yield. Claisen-rearrangement and esterification provided the desired ester **20a** as the major product in 73% isolated yield.

With ester **20a** in hand we were in a position to explore the later steps of our synthesis. Ester **20a** was hydroborated with 9-BBN (Scheme 7). Unfortunately, reduction of the methylbenzyloxyacetate of **20a** occurred in preference to hydroboration of the double bond, providing alcohol **21**. Under more forcing conditions triol **22** was obtained. Other hydroborating reagents were also unsatisfactory, producing complex mixtures of products. This unforseen complication forced us to add unwanted steps to keep the C41 and C42 hydroxyl groups (spongistatin numbering) differentially protected.

Diester **20a** was reduced with DIBAL-H in nearly quantitative yield, providing diol **23** (Scheme 8). Protection of the primary alcohol as the TBS ether provided **24** in 90% yield. Compound **24** represented a convenient

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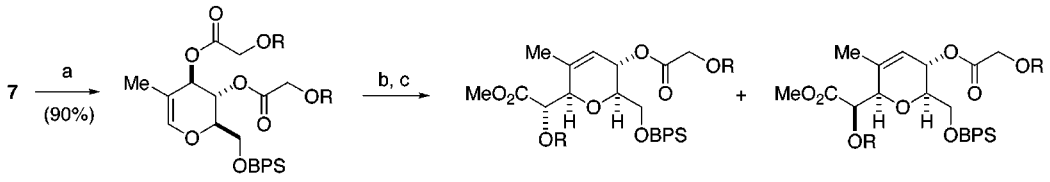
(16) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.***1987**, *171*, 161−191.
(17) (a) Barnett, W. E.; Sohn, W. H. *Tetrahedron Lett.* **1972**, *18*, 1777−1780. (b) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950−3952.
(18) We thank Dr. Anna Mapp for performing these experiments.

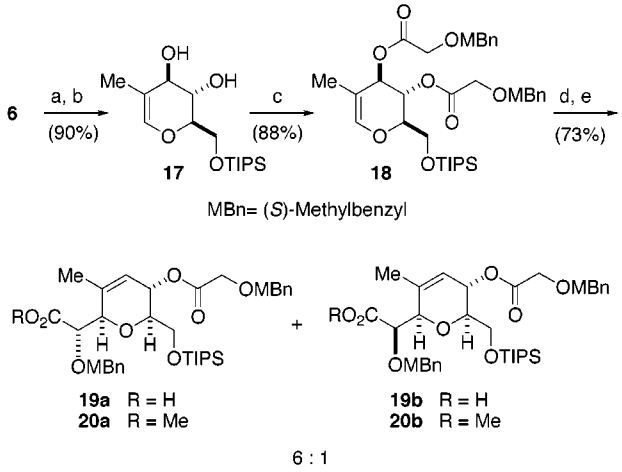
Scheme 5



a. **13a** or **13b**, DCC, DMAP.
b. LiHMDS, TMSCl, Pyr., –78 °C to RT. c. CH_2N_2.

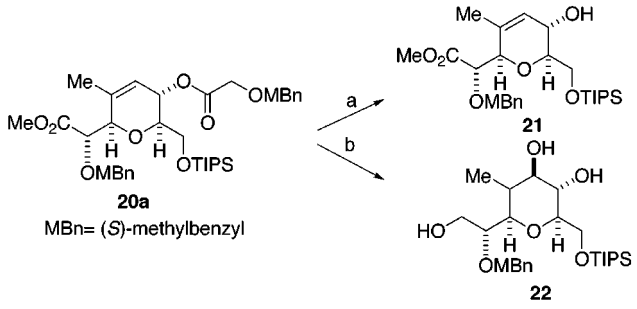
entry	R	esters	ratio
1	PMB	**10a** : **10b**	2.0 : 1.0
2	(*R*)-α-methylbenzyl	**15a** : **15b**	1.0 : 1.3
3	(*S*)-α-methylbenzyl	**16a** : **16b**	6.0 : 1.0

Scheme 6[a]



[a] Key: (a) Na, NH_3; (b) TIPSCl, imid., DMF; (c) **13b**, DCC, DMAP, DMF; (d) LiHMDS, TMSCl, pyr., −78 °C to rt (2−3 min); (e) CH_2N_2.

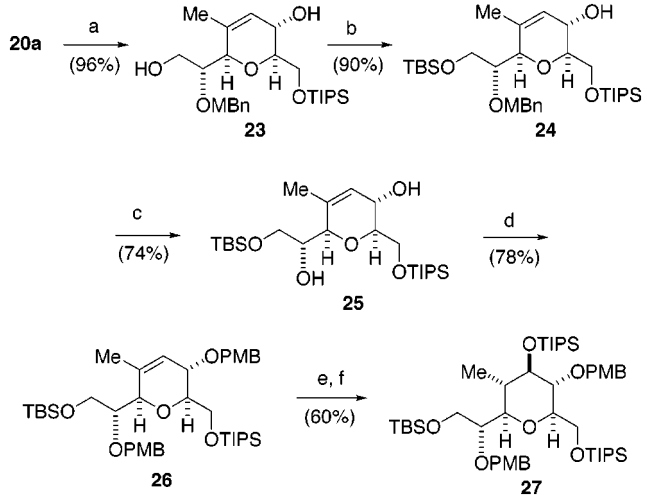
Scheme 7[a]



[a] Key: (a) (i) 9-BBN, 50 °C, 10 h, (ii) [O]; (b) (i) 9-BBN, 80 °C, 48 h, (b) [O].

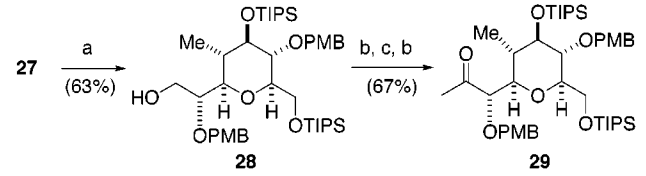
point to remove the (*S*)-methylbenzyl protecting group, which was incompatible with several of the later steps in our synthetic plan. Eventually, we planned to use the *p*-methoxy version of this group, obviating this swap. The methylbenzyl ether of **24** was removed with a dissolving metal reduction in 74% yield, followed by the protection of diol **25** as the bis-PMB ether, **26**. Hydroboration of **26** proceeded to give a single diastereomer, which was predicted by addition of the bulky reagent trans to the allylic ether functionality at C42. Protection of the resultant hydroxyl as the TIPS ether provided **27** in 60% yield for the two-step procedure.

Scheme 8[a]



[a] Key: (a) DIBAL-H; (b) TBSCl, imid.; (c) Na, NH_3; (d) PMBBr, NaH; (e) (i) 9-BBN, (ii) [O]; (f) TIPSOTf, 2,6-lutidene.

Scheme 9[a]

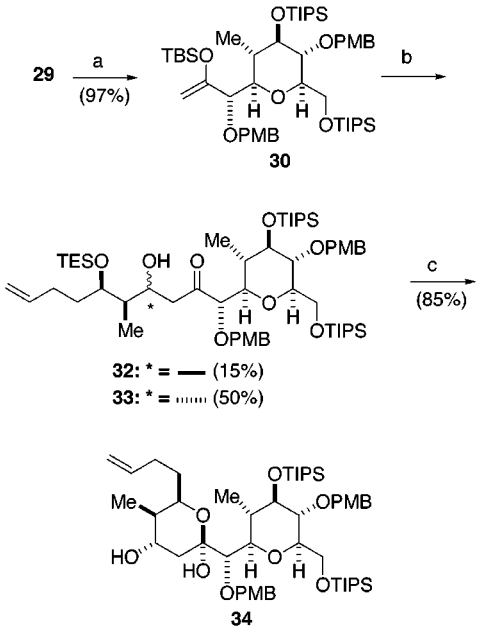


[a] Key: (a) 0.5% H_2SO_4, THF, H_2O, (three iterations); (b) Dess−Martin; (c) MeLi.

To properly functionalize **27**, it was necessary to deprotect the carbinol at C38 and convert the resulting primary alcohol to the methyl ketone (Scheme 9). Deprotection of the primary TBS ether in the presence of the primary TIPS ether[19] was somewhat problematic, with deprotection of the TIPS ether being competitive. To obtain quantities of the primary alcohol **28** we settled on the unoptimized procedure of treating bis-silyl ether **27** with catalytic sulfuric acid in THF/H_2O, stopping the reaction after partial conversion, and resubjecting the recovered starting material. After three iterations, primary alcohol **28** was obtained in 63% yield along with 17% of recovered starting material. Primary alcohol **28** was oxidized to the aldehyde with Dess−Martin perio-

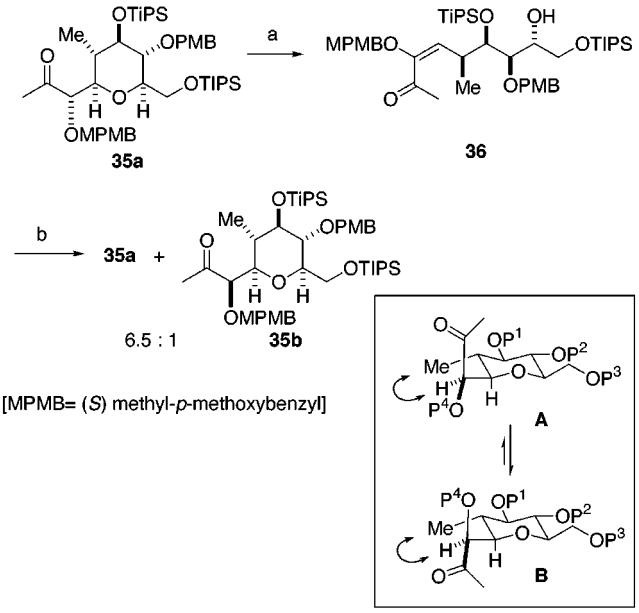
(19) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797−4798.

Scheme 10[a]



[a] Key: (a) (i) LDA; (ii) TBSCl, HMPA; (b) **3**, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (c) 0.5% H_2SO_4, THF, H_2O.

Scheme 11



dinane.[20] The crude aldehyde was treated with methyllithium to provide a diastereomeric mixture of alcohols, which were oxidized a second time with Dess−Martin periodinane to provide the desired ketone in 67% overall yield. With ketone **29** in hand, we were prepared to explore the aldol coupling with a suitably protected aldehyde.

The coupling of ketone **29** and aldehyde **3** (synthesized as described by Evans and co-workers[8a]) and transformation into the E−F ring system of the spongistatins is shown in Scheme 10. Ketone **29** was converted to silyl enol ether **30** by treatment with LiHMDS followed by quenching of the enolate with TBS-Cl in HMPA. The crude silyl enol ether **30** was condensed with aldehyde **3** using $BF_3{\cdot}OEt_2$ as the catalyst to provide the desired Felkin−Ahn product **33** in 50% yield along with the undesired anti-Felkin−Ahn product **32** (15%) and some recovered ketone **29**. The aldol adduct **33** was treated with catalytic acid in THF/H_2O, which removed the TES group and caused spontaneous cyclization to the hemiketal **34**.

Structure **34** represents the successful completion of the C29−C44 portion of the spongistatin structure. The synthesis required 25 total steps, with a 2.4% overall yield for the longest linear sequence (21 steps). Although we were pleased with the success of these efforts, we realized that if our ultimate goal of producing gram-quantities of the natural product were to be met a more efficient synthesis was needed. We now describe a serendipitous discovery that lead to a dramatic simplification of our synthesis and ultimately allowed us to produce gram quantities of the C29−C44 portion of spongistatin.

While generating the lithium enolate of advanced intermediate **35a**,[21] we noticed that fragmentation byproduct **36**, resulting from retro-Michael reaction of the undesired enolate, was produced in small amounts (Scheme 11). When this α,β-unsaturated ketone was treated with K_2CO_3 in MeOH it cyclized to return ketone **35a** with good stereochemical integrity. Upon extended treatment under these conditions the C38 stereocenter of **35a** was equilibrated to a 6.5:1 mixture, favoring the desired C38-(*S*) configuration. At this point, we carried out molecular mechanics calculations of compounds of this general structure and discovered, that, indeed, one stereoisomer is favored over the other three. Of course, the bulky side chain favors the equatorial position, and there is precedent for this in analogous C-glycoside chemistry.[22] However, the C2 methyl group also has an ordering effect, forcing the side chain to orient itself so as to avoid potentially serious *syn*-pentane interactions (inset). Calculations of a simplified model (P^2 and P^4 = Me; P^1 and P^3 = TMS) showed that conformation **B** is favored over conformation **A** by approximately 0.4 kcal mol^{-1}, corresponding to an equilibrium ratio of approximately 2:1. Thus, the alkyloxy group prefers the position anti to the anomeric hydrogen; this may be a simple steric effect or there may be a polar component. This observation suggested that we might be able to introduce the alkyloxyacetone side chain and deal with the C38 and C39 configuration in a very straightforward manner.

To take advantage of this discovery, we altered our synthetic strategy so as to incorporate a C-glycosidation followed by an equilibration to set the C38 and C39 stereocenters. The new approach (Scheme 12) began with commercially available tri-*O*-acetyl glucal, which was converted into glucal **37** using Danishefsky's procedure.[23] Selective protection of the 3-OH of **37** was accomplished with TES-Cl in CH_2Cl_2, providing bis-silyl ether **38** in 81% yield. Cyclopropanation of **38**, directed by the unprotected 4-OH, gave the desired α-isomer in 94% yield.[24,25] Removal of the TES ether was accomplished

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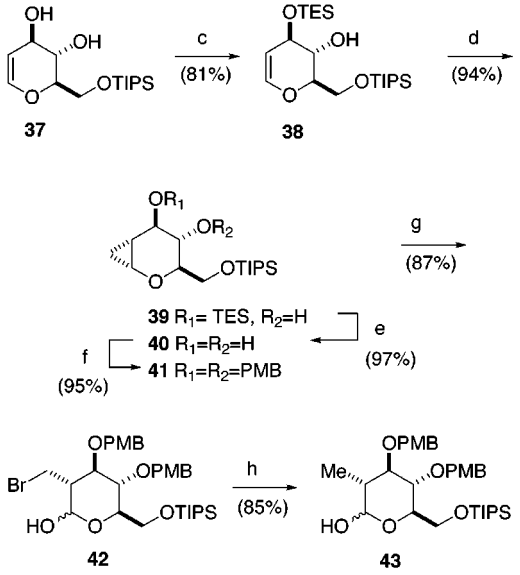
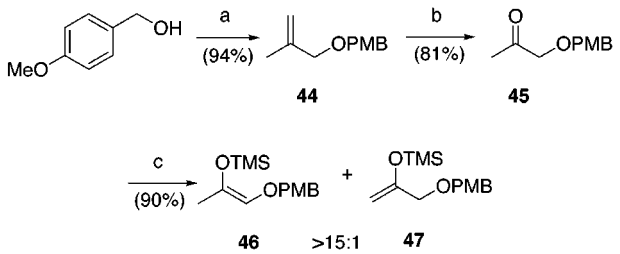
(23) Danishefsky, S. J.; Gordon, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 659−663.

Scheme 12[a]



[a] Key: (a) NaOMe, MeOH; (b) TIPSCl, imid., DMF; (c). TESCl, imid., Et_3N, CH_2Cl_2; (d) Et_2Zn, CH_2I_2, toluene; (e) CSA, H_2O, THF; (f) NaH, PMBCl, DMF; (g) $PyrHBr_3$, pyridine, H_2O, THF; (h) Bu_3SnH, AIBN, toluene, Δ.

Scheme 13[a]



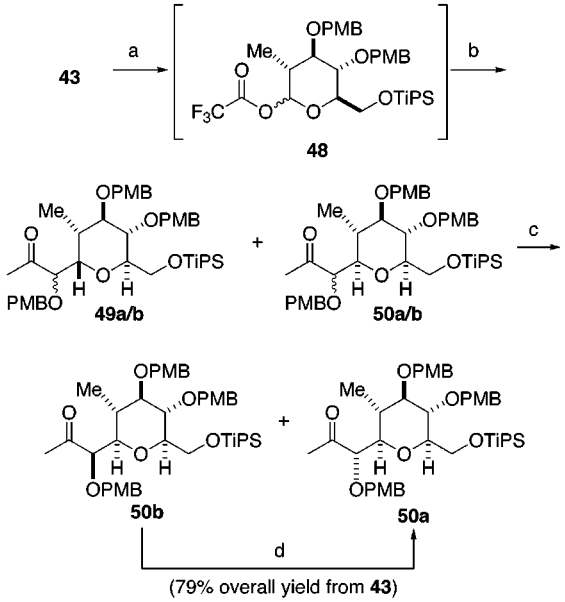
[a] Key: (a) NaH, chloro-2-methyl-2-propene, DMF; (b) OsO_4, $NaIO_4$, H_2O/THF; (c) LiHMDS, TMSCl, THF.

with catalytic acid in THF/H_2O in near-quantitative yield. Diol **40** was then protected as the bis-PMB ether by treatment with NaH and PMBCl in DMF/THF. Treatment of **41** with pyridinium hydrobromide perbromide in THF/H_2O resulted in ring opening to the bromide **42** in 87% yield. Reduction of bromide **42** with Bu_3SnH provided the desired hemiacetal in good yield.

Synthesis of the alkyloxyacetone coupling partner is shown in Scheme 13. *p*-Methoxybenzyl alcohol was alkylated with 3-chloro-2-methylpropene, and the resulting alkene **44**[26] was oxidized to ketone **45** with OsO_4 and $NaIO_4$. Conversion to the desired thermodynamic silyl enol ether was accomplished by treating ketone **45** with LiHMDS in the presence of TMS-Cl.[27]

With 2-methyl glucal **43** and silyl enol ether **46** in hand, we were prepared to explore our C-glycosidation/equilibration strategy (Scheme 14). After considerable experimentation, a one-pot procedure for the anomeric activation and C-glycosidation of **43** was developed. Treatment of glucal **43** with trifluoroacetic anhydride in the presence of pyridine and DMAP resulted in acylation

Scheme 14[a]



[a] Key: (a) TFAA, pyr., DMAP, CH_2Cl_2; (b) **46**, $ZnBr_2$; (c) NaHMDS, THF; (d) KOH, MeOH.

of the anomeric hydroxyl group. Addition of an excess of silyl enol ether **46** and $ZnBr_2$ provided the desired C-glycosides **49a/b** and **50a/b** as a mixture of diastereomers in good overall yield. The crude reaction mixture was treated with NaHMDS to effect the α to *β* equilibration, providing ketones **50a** and **50b** as a 2:1 mixture of diastereomers. Ketones **50a** and **50b** were separated by column chromatography and the undesired isomer **50b** was equilibrated to the desired ketone **50a** with KOH in MeOH. Following three equilibration cycles, the desired ketone **50a** was obtained in 79% overall yield, based on glucal **43**.

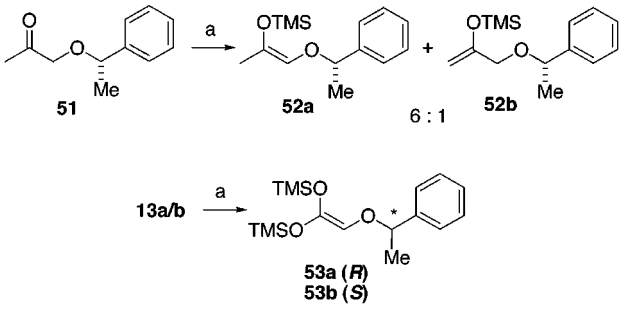
Although we were pleased with the success of this strategy at providing ketone **50a**, we were surprised at the difference in equilibrium ratios of ketones **50a** and **50b** (2:1) compared to those seen with ketones **35a** and **35b** (6.5:1). Because we had changed both the protecting groups on the C38 and C41 carbinols we were unable to determine which change had caused the deterioration in the ratio of **50a** and **50b**. To better understand the factors defining the thermodynamics in this system we decided to synthesize a series of C-glycosides changing the protecting groups on the C38 and C41 carbinols individually.

The bis TIPS-protected 2-methyl glucal **54**, needed for our study, was synthesized in an analogous fashion to **43**.[28] Likewise, the syntheses of the chiral ketone coupling fragments are analogous to that of ketone **45**. Unfortunately, formation of chiral silyl enol ether **52a** was not as regioselective as the analogous achiral silyl enol ether **46** (Scheme 15). In addition, our inability to readily separate the undesired C-glycosides, resulting from reaction of silyl enol ether **52b**, forced us to adopt an alternative route to the desired C-glycosides. We decided to utilize the chiral bis-silyl ketene acetal **53a** as a surrogate for **52a**. Treatment of acid **13b** with LiHMDS in the presence of TMSCl furnished the desired silylketene acetal **53b** in good yield.

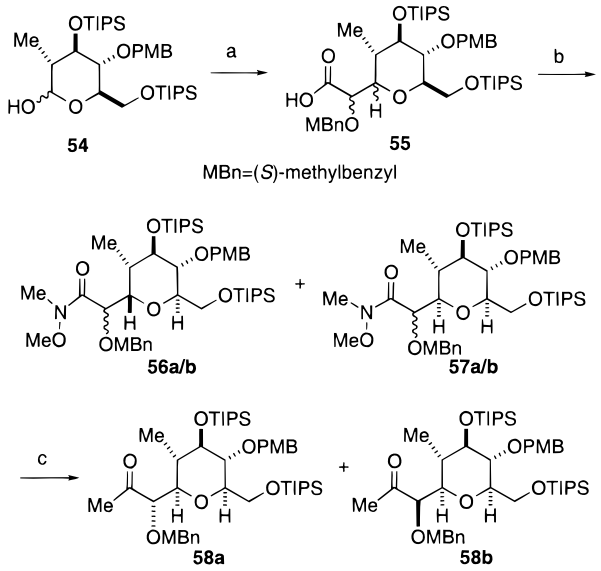
(24) Cope, A. C.; Moon, S.; Park, C. H. *J. Am. Chem. Soc.* **1962**, *84*, 4843−4849.
(25) Charette, A. B.; Cote, B. *J. Org. Chem.* **1993**, *58*, 933−936.
(26) Frejd, T.; Wennerberg, J. *Acta Chem. Scand.***1998**, *52*, 95−99.
(27) The double bond geometry of silyl enol ether **46** was determined through NOE difference experiments performed by Dr. Shannon Chi.

(28) Wallace, G. A. Doctoral Thesis, University of California at Berkeley, 2000.

Scheme 15



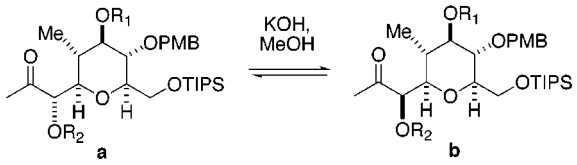
Scheme 16[a]



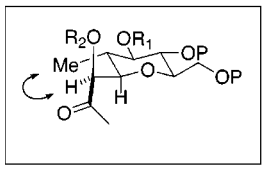
[a] Key: (a) (i) TFAA, pyr., DMAP, CH_2Cl_2; (ii) **59**, $ZnBr_2$; (b) Me(MeO)NH·HCl, DCC, HOAT, Et_3N, DMF; (c) MeMgCl, THF.

Following the C-glycosidation procedure described earlier, glucal **54** and silyl ketene acetal **53** were condensed to furnished acids **55** as a mixture of four diastereomers. The diastereomeric mixture was converted into the corresponding Weinreb amides. At this point, it was convenient to separate the α- and *β*-isomers by column chromatography. Treatment of the mixture of *β*-Weinreb amides, **57a/b**, with MeMgCl provided the desired ketones, **58a** and **58b**.With the desired ketones in hand, the equilibration studies were conducted where each pair of structural isomers was separated and individually equilibrated to the same diastereomeric mixture, as determined by ^{1}H NMR of the crude reaction mixtures. The results of the equilibrations are shown in Scheme 17. From the results, it is clear that both the protecting groups at C41 and C38 have moderate effects on the equilibrium ratio. Comparing entries 1 and 2, an increase in the size of the C41 protecting group accompanied an increase in the ratio of the desired α-(*S*)-isomer. We believe this shift in the equilibrium, although small, arises from a perturbation of the pyranose ring geometry. In addition, changing the C38 protecting group from *p*-methoxybenzyl to (*S*)-methylbenzyl also shows an increase in the ratio of the desired α-(*S*)-isomer (entries 1 and 3). Combined, these two effects are additive, providing a 6.5:1 ratio of the α-(*S*)-isomer (entry 4). However, the effect of the C38 protecting group is sensitive to the absolute configuration of the methylbenzyl group (compare entries 3 and 5). It appears from entry 5 that the effect of the C38 protecting group is the combination of several subtle factors that are not obvious on first inspection.

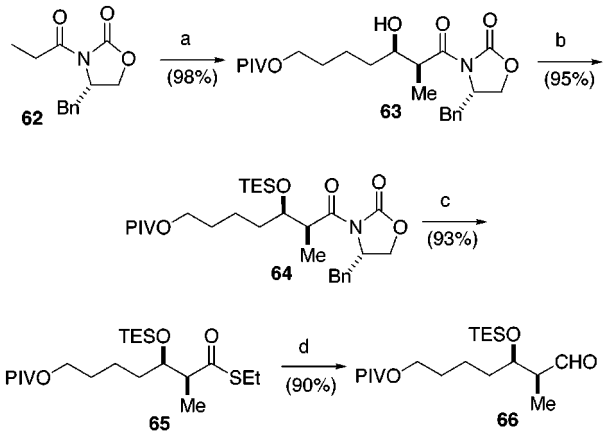
Scheme 17



entry	R_1	R_2	ketones	ratio
1	PMB	PMB	**50a:50b**	2.3:1.0
2	TIPS	PMB	**59a:59b**	2.8:1.0
3	PMB	(*S*)methylbenzyl	**60a:60b**	4.5:1.0
4	TIPS	(*S*)methylbenzyl	**58a:58b**	6.5:1.0
5	PMB	(*R*)methylbenzyl	**61a:61b**	1.0:1.1



Scheme 18[a]

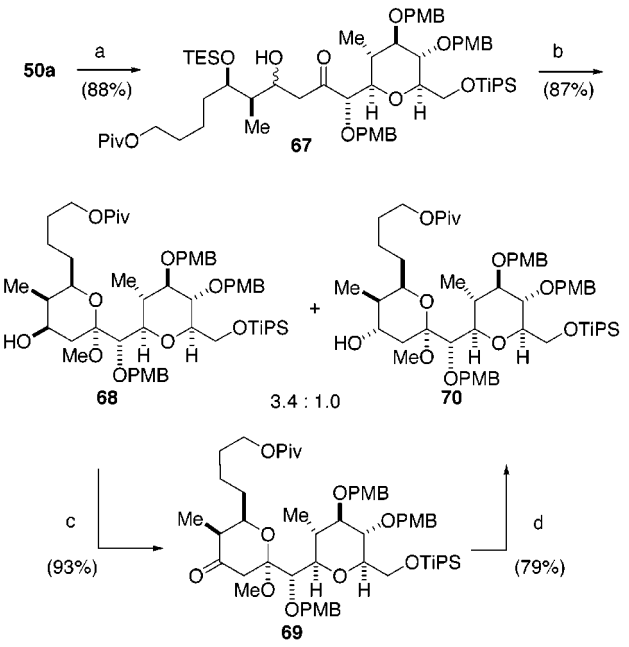


[a] Key: (a) (i) Bu_3BOTf, $(iPr)_2EtN$, (ii) 5-trimethylacetoxypentanal, (iii) H_2O_2; (b) TESCl, imid., DMF; (c) LiSEt, THF; (d) Et_3SiH, Pd/C, CH_2Cl_2.

Due to the added steps needed to prepare ketones such as **58a** and our overall protecting group strategy we decided to continue with the synthesis of the C29−C44 portion of spongistatin with ketone **50a**. To increase the convergency of the later part of our synthesis, we altered our synthesis of the C29−C35 aldehyde. The synthesis of the required aldehyde is shown in Scheme 18. Using Evans' oxazolidinone chemistry, 5-trimethylacetoxy-pentanal was condensed with acylated oxazolidinone **62**. Protection of the secondary alcohol of **63** as the TES ether occurred in 95% yield. Removal of the Evan's auxiliary was accomplished with lithium ethylthiolate, providing thioester **65** in 93% yield. Reduction to desired aldehyde was accomplished with Et_3SiH and Pd/C, providing the desired aldehyde **66** in high yield.

Coupling of aldehyde **66** and ketone **50a** is shown in Scheme 19. Although the Mukaiyama aldol reaction had

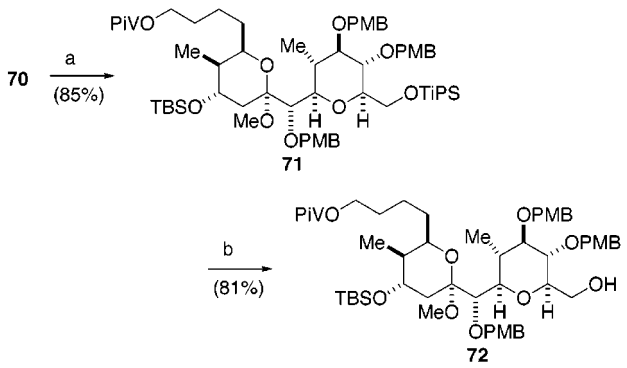
Scheme 19[a]



[a] Key: (a) (i) LiHMDS, THF, (ii) **66**, (iii) K_2CO_3; (b) Ph_3PHBr, MeOH/THF; (c) Dess−Martin periodinane, pyr., CH_2Cl_2; (d) L-Selectride, THF.

provided the desired diastereomer as the major product, our inability to increase the selectivity of this reaction lead us to explore an alternate approach to set the C35 stereocenter. Under carefully optimized conditions, the lithium enolate of ketone **50a** was condensed with aldehyde **60** to provide a diastereomeric mixture of aldol adducts **67**, in 88% yield. Removal of the TES silyl ether and cyclization was accomplished with catalytic Ph_3PHBr in THF/MeOH, providing alcohols **68** and **70** in 87% yield as a 3.4:1.0 ratio. At this point, it was possible to separate the two diastereomers by column chromatography. The undesired diastereomer **68** was oxidized with Dess−Martin periodinane to the ketone **69** in high yield. Reduction of the ketone from the less hindered face with L-selectride provided the desired alcohol **70** (79% yield) along with a small amount of the undesired alcohol **68** (19% yield), which could be recycled through the above procedure.

Scheme 20[a]



[a] Key: (a) TBSCl, KHMDS, THF; (b) TBAF, THF.

Having developed an efficient method to set the C35 stereocenter, we protected the axial alcohol of **70** as the TBS ether in good yield (Scheme 20). Removal of the primary silyl ether was accomplished with TBAF, providing alcohol **72** in 81% yield. Bispyran **72** represents our second generation synthesis of the C29−C44 portion of spongistatin. This route requires 27 total steps and occurs in a much improved 13.2% yield over the longest linear sequence (18 steps). Through our efforts we have been able to produce gram-quantities of alcohol **72**. Investigations on appending the C45−C51 side chain and the completion of the total synthesis of spongistatin 1 are under way and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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