Pergamon

SCIENCE DIRECT®

TETRAHEDRON

Tetrahedron 59 (2003) 8963–8974

# Controlling influences in bisspiroketal formation: synthesis of the ABC ring system of azaspiracid

Rich G. Carter,* T. Campbell Bourland,† Xiao-Ti Zhou and Melissa A. Gronemeyer

*Department of Chemistry, Oregon State University, Corvallis, OR 97331, USA*

Received 20 February 2003; accepted 21 March 2003

Dedicated to Dr Lawrence V. Puckett on the occasion of his retirement

**Abstract**—Substitution effects on the stereochemical outcome of bisspiroketalization on the $C_1-C_{17}$ carbon backbone of azaspiracid is presented. A possible explanation is offered to explain the observed stereochemical outcome.


## 1. Introduction

Bisspiroketals have generated a considerable amount of synthetic and biological attention in recent years.[1] One focus area in bisspiroketal chemistry has been understanding the controlling stereochemical factors in bisspirocyclization. In bisspiroketals which possess a pyran ring system, the anomeric effect plays an important governing role in the stereochemical outcome by guiding the relevant oxygen into an axial position.[2] An additional controlling influence that has been proposed involves a minimization of the two dipoles present in the external carbon–oxygen bonds of the bisspiroketals. This dipole minimization argument has been put forth to explain the observed slight (usually less than 1 kcal/mol) thermodynamic preference for the *transoidal* spirocycle, such as **1**, over the corresponding *cisoidal* spirocycle, such as **2** (Fig. 1).[3,4] Despite these important advances in the understanding of bisspirocyclization, more complicated systems (e.g. possessing multiple additional stereocenters and/or functional groups) often fall victim to explanations which may not take into full account several of the controlling influences of the reaction. For example, once an additional stereogenic center is placed on one or more of the rings, accessing a conformer that satisfies the anomeric effect for both the *cisoidal* and the *transoidal* bisspirocycle can become prohibitively high in energy, due to the development of unfavorable 1,3-diaxial interactions in the pyran rings. In such systems where the desired stereochemistry is not thermodynamically favored due to one (or more) of these reasons, a stabilizing interaction (usually via hydrogen bonding or metal-chelation)[1,5] of a neighboring functional group has also been invoked to explain the stabilization of a specific spiroketal stereochemistry.

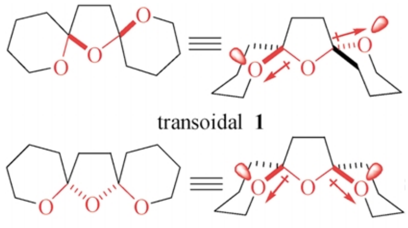



**Figure 1.** *Transoidal* and *cisoidal* bisspiroketals.

Our laboratory became focused on this issue during our synthetic efforts toward the *transoidal* bisspiroketal azaspiracid (**3**) (Fig. 2).[5–7] Based on the solution conformation proposed by Yasumoto and co-workers,[8,9] the $C_{13}$ spiroketal linkage of **3** does not appear to be oriented in the anomeric conformation as depicted in simplified example **1**. Instead, Yasumoto proposed the alternate chair conformation **4** in which the center oxygen is located in an equatorial orientation with respect to the C ring. Furthermore, no neighboring hydrogen bond donors are suitably positioned on the A, B, C or D rings for stabilization and a metal-chelation argument has not been proposed to explain this stereochemical and conformational arrangement. It would appear from these observations that further insight into the controlling influences of bisspiroketalization is necessary. Particularly intriguing is the possible effects of the nature of substitution at $C_{16}$ and $C_{17}$ on the stereochemical outcome of bisspirocyclization. Herein, we

*Keywords*: azaspiracid; bisspiroketal; bisspirocyclization; Julia coupling; substituent effects; anomeric effect.

* Corresponding author. Tel.: +1-541-737-9486; fax: +1-541-737-9496; e-mail: rich.carter@oregonstate.edu

† Present address: Baylor Dental School, 3302 Gaston Ave., Dallas, TX 75246, USA.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.03.003

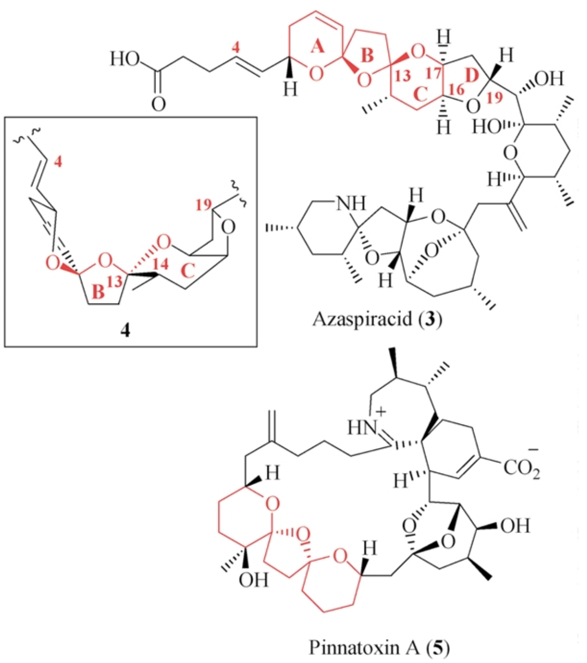


**Figure 2.** Selected bisspiroketals natural products.

disclose the unprecedented effects of C ring substitution on the bisspiroketalization.

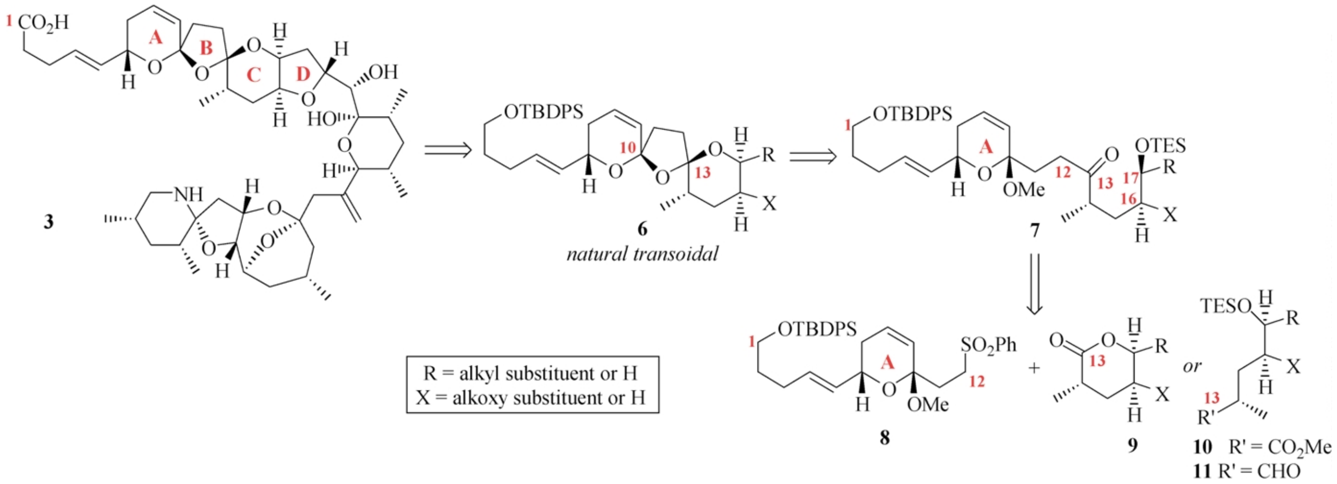
## 2. Background and general strategy

Azaspiracid was first observed in the mid 1990s when several individuals became severely ill from eating mussels harvested from Killary Harbor, Ireland.[10] Yasumoto and co-workers determined the relative configuration of **3** using 2D NMR techniques.[8,9] The toxic effects of azaspiracid have been shown to include serious injury to the digestive tracts, liver, pancreas, thymus and spleen in mice.[11] Subsequent to Yasumoto's original report, several derivatives of azaspiracid have been isolated from Western Ireland[12] and there is growing evidence of the spread of azaspiracid throughout other regions of Europe.[13] Also, recent reports appear to link the presence of azaspiracid to an ubiquitous alga.[14] The significant effect of this toxin on the European shellfish industry[13] and its daunting structure garnered our attention.

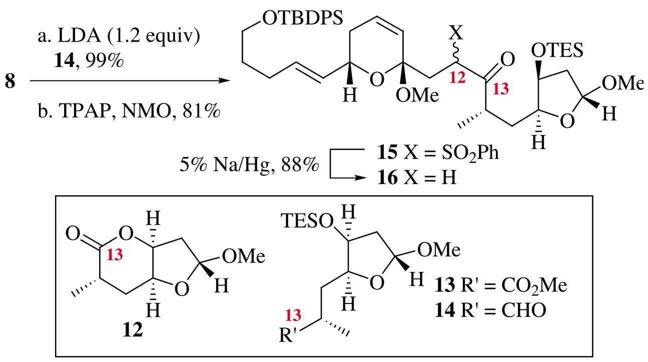
In order to access a variety of substitution patterns on the C ring, our synthetic approach had to be significantly flexible (Scheme 1). The bisspirocyclization precursor **7** was designed to possess the necessary ketone function at $C_{13}$ and a methoxy ketal function at $C_{10}$. This approach allowed for the incorporation of the A ring into the sulfone fragment **8**.[6a] A variety of corresponding electrophiles **9–11** needed to be screened in order to ascertain the ideal coupling partner. Once the coupling strategy had been optimized, it could be applied to systems possessing different degrees of substitution at $C_{16}$ and $C_{17}$.

## 3. Results

As shown in Scheme 2, the formation of the $C_{12,13}$ linkage was explored on an electrophilic fragment with the D ring already incorporated (electrophiles **12–14**[6c]). The ideal coupling partner would be the $C_{13}$ lactone **12** as it possesses the correct oxidation state at $C_{13}$ and the $C_{17}$ hydroxyl is internally protected. While a wealth of examples of sulfone–ester couplings have been disclosed,[15] significantly fewer examples of sulfone–lactone couplings have been reported.[16] Unfortunately, the lactone **12** proved disappointing, even under our optimum protocol [LDA (2.2 equiv.), THF, −78°C, 20%]. A considerable amount of decomposition of the lactone **12** was consistently observed under a variety of conditions. The corresponding methyl ester **13** proved only slightly more encouraging with up to a 40% yield [LDA (1.2 equiv.), **13** (0.5 equiv.), then LDA (0.5 equiv.), **13** (0.6 equiv.)]. The low yield may be attributed to deprotonation of the ester by the lithiated sulfone species; a considerable amount of epimerization was observed in recovered **13**. We were gratified to find that the corresponding aldehyde **14** proved to be an effective coupling partner providing a quantitative yield of the hydroxy sulfone adduct as a mixture of three of the four possible diastereomers. Subsequent Ley oxidation[17] and Na/Hg amalgam reduction yielded the bisspirocyclization precursor **16**. It should be noted that only Ley's TPAP oxidant proved effective in this transformation; both Swern



**Scheme 1.** Retrosynthetic strategy.

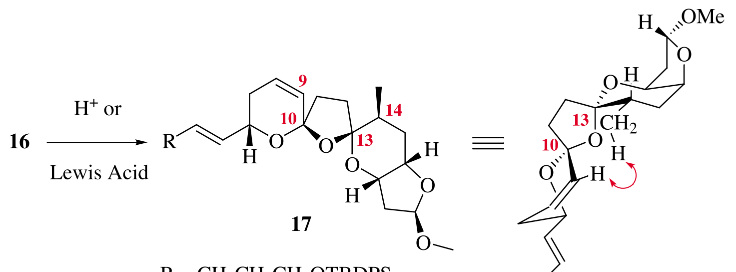



**Scheme 2.** Julia coupling strategy.

oxidation[18] and Dess–Martin periodinane[19] led to complex mixtures of products.

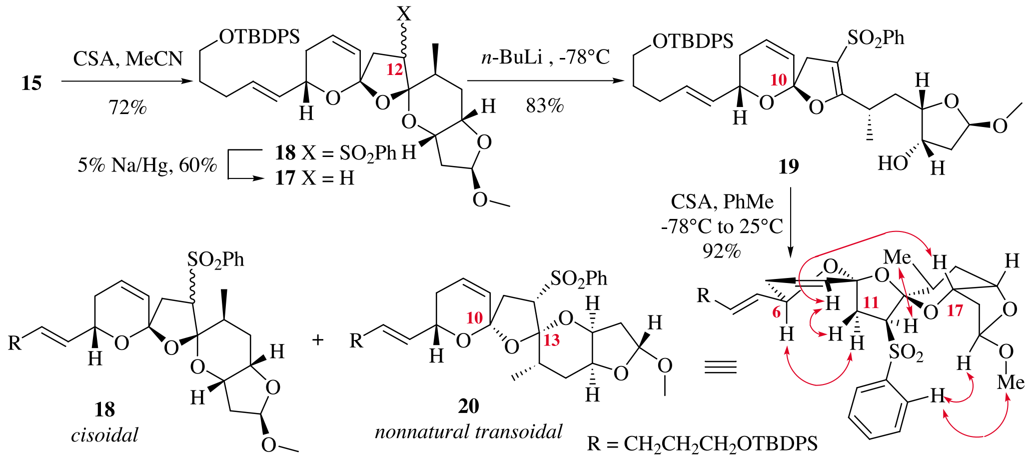
With the ketone **16** in hand, our attention turned to the bisspirocyclization (Scheme 3). Treatment of **16** under a variety of acidic and Lewis acidic conditions resulted in formation of single bisspiroketal **17** which was shown to possess the unwanted *cisoidal* stereochemistry. This result was observed independently and concurrently[6b] by Forsyth and co-workers on a similar D ring containing substrate.[7a] Nicolaou later reported the same stereochemical outcome on their related, D ring functionalized systems.[5] This *cisoidal* arrangement allows for placement of central furan oxygen in the anomeric (or pseudo-anomeric) positions with respect to both pyran rings.

Another possible bisspirocyclization precursor lies in the keto sulfone **15** (Scheme 4). We hoped that the $C_{12}$ sulfone might impart a directing effect on the spiroketalization at $C_{13}$. Treatment of the keto sulfone **15** under acidic conditions (CSA, MeCN) again led to a single bisspiroketal **18** [epimeric (1:1 ratio) at $C_{12}$]. The new spiroketal **18** was correlated with the previously established *cisoidal* species **17** via reductive removal of the sulfone. In addition, both $C_{12}$ stereoisomers of the *cisoidal* sulfone-containing bisspiroketal **18** were verified individually by COSY and NOESY correlations. Interestingly, the use of an alternate solvent (PhH) in the bisspirocyclization of **15** did result in the production of a small amount (5–10%) of an additional bisspiroketal which was later identified as the non-natural[20] *transoidal* bisspiroketal **20** via COSY and ROESY correlations. The yield of this new bisspiroketal **20** could be significantly improved (up to 43%) via elimination of the C ring pyran bridge followed by treatment under acidic conditions (CSA, PhMe, −78°C to rt). The new spiroketal **20** was isolated as a single α-stereochemistry at $C_{12}$. In addition, the *cisoidal* spiroketal **18** was also produced in 49% yield as a 3:1 diastereomeric ratio at $C_{12}$ (3:1 α–β). While resubmission of the *cisoidal* ketal **18** to the same reaction conditions (CSA, PhMe) did not result in the formation of the *transoidal* spiroketal **20**, acid treatment (CSA, PhMe) of the *transoidal* ketal **20** did lead to slow formation of the *cisoidal* product **18** (40% conversion to **18** by $^{1}H$ NMR after 24 h).[21] These results indicate that this transformation is operating under kinetic control in which the sulfone substitution is able to retard the rate of equilibration versus the $C_{12}$ unfunctionalized series. It is



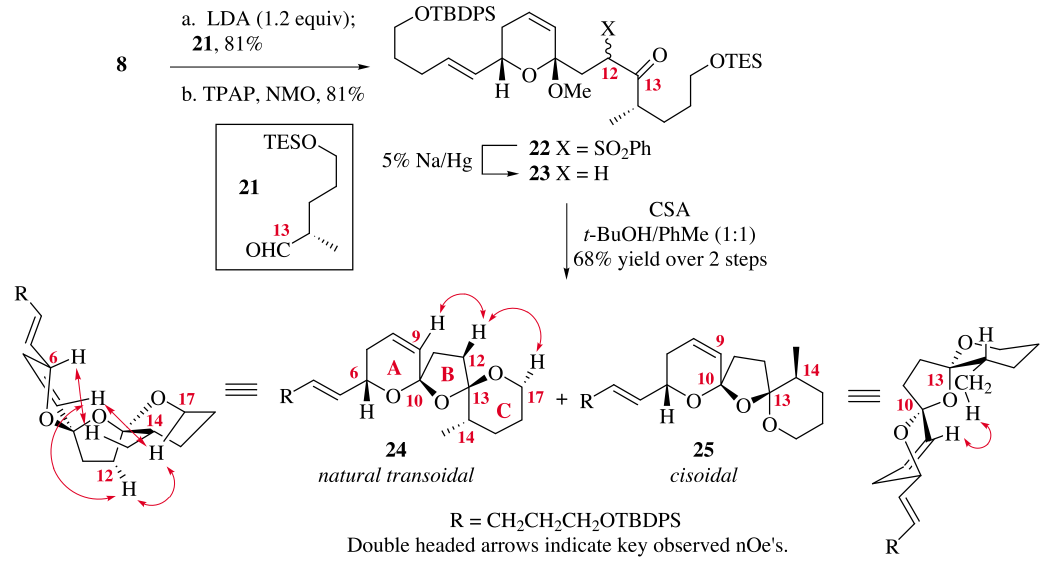

R = $CH_2CH_2CH_2OTBDPS$
Double headed arrows indicate key observed nOe's.

**Scheme 3.** Thermodynamic bisspirocyclization of D ring substrate.




R = $CH_2CH_2CH_2OTBDPS$
Double headed arrows indicate key observed nOe's.

**Scheme 4.** Formation of the non-natural *transoidal* bisspiroketal.



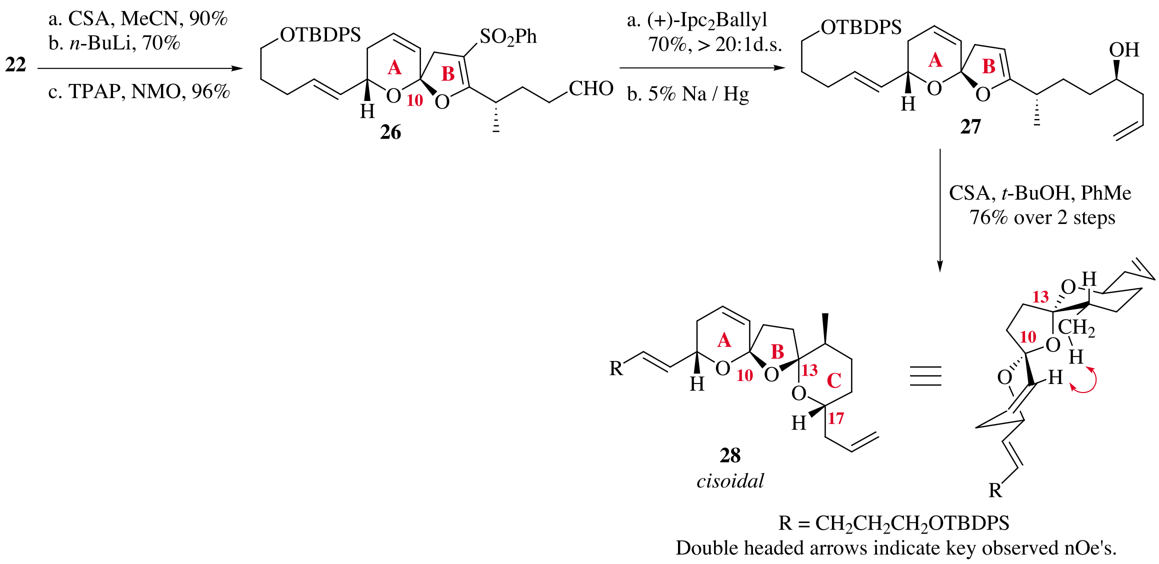

**Scheme 5.** Bisspirocyclization of D ring truncated substrate.

unlikely that the desired natural *transoidal* bisspiroketal will be accessible on the fully functionalized ABCD ring system.

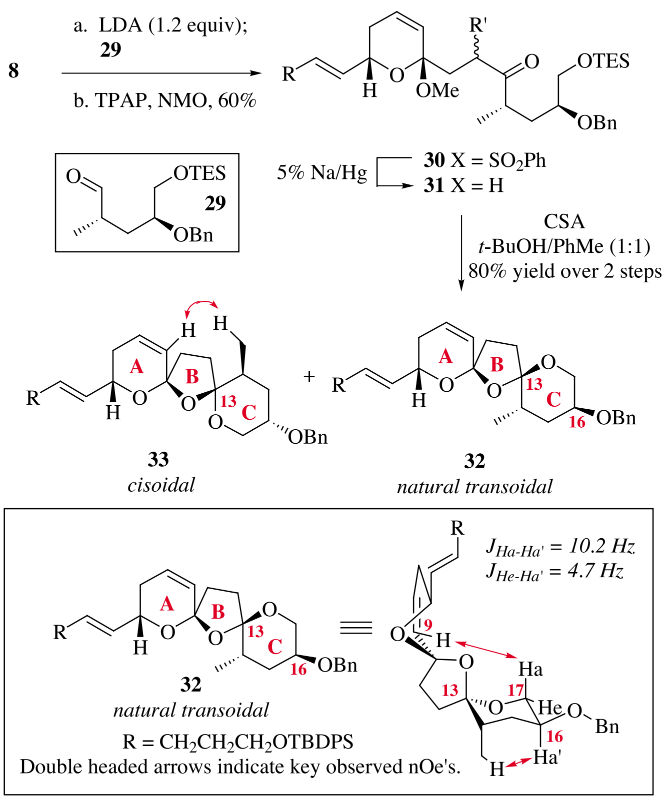
Thwarted by the inherit preference of the fully substituted system to yield the unwanted *cisoidal* isomers **17** and **18**, we were intrigued by the possibility of alternate methods to control the stereochemical outcome. In particular, the degree and nature of substitution on the C ring might play an important role in bisspirocyclization. We surmised that the one (or both) of the substituents at $C_{16}$ and $C_{17}$ might be inhibiting the formation of the desired natural *transoidal* bisspiroketal. This approach, while enticing, was not well precedented.

To test this hypothesis, the bisspirocyclization precursor **23**[6d] possessing no substitution at $C_{16}$ or $C_{17}$ was synthesized in an analogous fashion as described previously (Scheme 5). We were pleased to observe that treatment of the ketone **23** under acidic conditions [0.04 M CSA, *t*-BuOH/PhMe (1/1), 16–20 h] led to formation of two separate bisspiroketals: the desired natural *transoidal* bisspiroketal **24** and unwanted *cisoidal* product **25** in equal amounts. Resubmission of the *cisoidal* isomer **25** to the identical reaction conditions led to the same equilibrium ratio (1:1) of products. It should be pointed out that the 2D NMR studies of spiroketal **24** appeared to indicate that the C ring existed in the chair conformation shown above. This conformation places both the $C_{13}$ furan oxygen and the $C_{14}$ methyl in equatorial positions as is observed in the solution structure of azaspiracid (**3**).

Encouraged by the formation of the *transoidal* bisspiroketal **24**, the synthesis of a bisspirocyclization precursor containing $C_{17}$ substitution was undertaken (Scheme 6). From inspection of the conformation of the *transoidal* bisspiroketal **24** (with both the $C_{13}$ furan oxygen and the $C_{14}$ methyl located in equatorial arrangements on the C ring), substitution at $C_{17}$ should be well-tolerated as the




**Scheme 6.** Bisspirocyclization of $C_{17}$ substrate.




**Scheme 7.** Bisspirocyclization of the $C_{16}$ substrate.

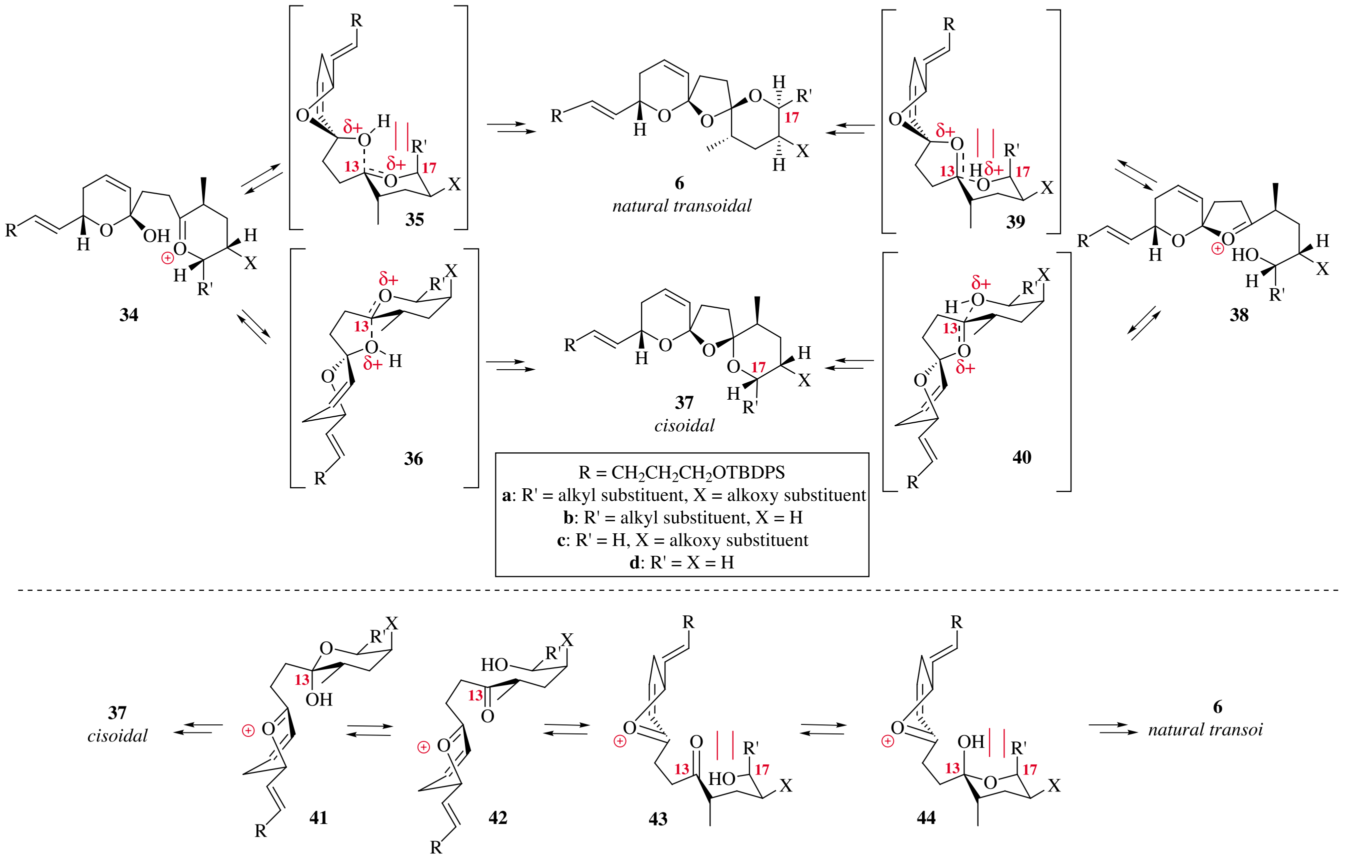
substituent would adopt an equatorial orientation. We chose to explore a linear approach for the synthesis of this series. Starting from the keto sulfone **22**, bisspirocyclization using CSA in MeCN followed by elimination of the pyran bridge and oxidation yielded the aldehyde **26**. This approach allowed for the protection of the $C_{13}$ carbonyl while freeing the $C_{17}$ position. Brown allylation of **26** yielded the desired $C_{17}$ stereocenter as a single diastereoisomer by $^{1}H$ NMR. Removal of the sulfone and submission to the same acidic conditions [0.04 M CSA, *t*-BuOH/PhMe (1/1), 14.5 h] yielded solely the *cisoidal* bisspiroketal **28** in 76% yield.

With the success of the $C_{16}/C_{17}$ unsubstituted series **23** and the disappointment of the $C_{17}$ substituted substrate **27**, the remaining $C_{16}$ series had to be synthesized (Scheme 7). Using a convergent approach and the key Julia coupling, the ketone **31**[6e] was constructed. Treatment of **31** under the standard conditions [0.04 M CSA, *t*-BuOH/PhMe (1/1), 16–20 h] once again yielded two bisspiroketals, the desired natural *transoidal* product **32** and the unwanted *cisoidal* isomer **33**, in a 3:5 ratio (**32**–**33**). The *transoidal* bisspiroketal **32** appears to adopt an alternate C ring chair conformation based on the NMR data versus both azaspiracid (**3**) and the D ring truncated system **24**. The proposed conformation for the *transoidal* bisspiroketal **32** places the $C_{13}$ furan oxygen in an anomeric position while locating the $C_{16}$ benzyloxy substituent in an equatorial arrangement. Miljkovíc and Srivastava independently studied the controlling influence of similar substitution patterns in pyran ring systems. They observed a slight computational preference for placement of the non-glycoside linkage in an equatorial arrangement while locating the acetal in an axial conformation.[22]

Resubmission of the *cisoidal* product **33** to the same reaction conditions [0.04 M CSA, *t*-BuOH/PhMe (1/1), 16–20 h] resulted in the thermodynamic 3:5 ratio of products (**32**–**33**). Interestingly, treatment of ketone **31** at lower temperatures (−10 to 4°C, 21 h) and lower molarity of CSA (0.003 M) under otherwise identical reaction conditions (1:1 *t*-BuOH/PhMe) led to the *cisoidal* bisspirocycle **33** as the predominate product by TLC. Gratifyingly, further warming of the reaction to room temperature for an additional 48 h, resulted in the previously observed (3:5 ratio of **32**–**33**) equilibrium mixture. It would appear from this experiment that the *cisoidal* bisspirocycle **33** is the result of kinetic control while the *transoidal* bisspiroketal **32** is available under equilibrating, thermodynamic conditions.

## 4. Discussion

The bisspiroketalization results clearly show that the degree and nature of substitution at $C_{16}$ and $C_{17}$ has a dramatic impact on the stereochemical outcome of the bisspiro-cyclization. Based on the reported data, a working hypothesis can be put forth: the formation of the desired natural *transoidal* bisspiroketal **6** is blocked by a $C_{17}$ substituent while $C_{16}$ substitution appears to have little impact on the stereochemical outcome of the transformation.[23] One possible explanation for the $C_{17}$ blocking effect may involve the potential transition states shown below in Scheme 8 in which the approaching hydroxyl function should enter in a pseudo-axial fashion during the $C_{13}$ spiroketal formation.[24] Given this requirement, access of the necessary transition states **35a-b** and/or **39a-b** would seem prohibitively high in energy due to the developing $C_{13}$–$C_{17}$




**Scheme 8.** Possible explanation for the observed stereochemical preference.

diaxial interaction. It should be noted that a related explanation is possible involving the oxonium ions **41**–**44**. In this case, a similar argument could be offered for the inability to access oxonium ions **43a-b** and **44a-b**. This kinetic-based argument necessitates that true *cisoidal*/*transoidal* equilibrating conditions are not feasible on systems containing $C_{17}$ substituents under the prescribed reaction conditions. The inability to observe any natural *transoidal* bisspiroketal formation with $C_{17}$ containing compounds **16** and **27** appears to support this model. In addition, the successful construction of the natural *transoidal* bisspiroketals **24** and **32** under thermodynamically equilibrating conditions while observing that the *cisoidal* bisspiroketal **33** is the predominate kinetic product under the non-equilibrating conditions [0.003 M CSA, −10 to 4°C, *t*-BuOH/PhMe (1:1)] provides further beneficial data toward this explanation.

## 5. Conclusion

The systematic construction of bisspirocyclization precursors has been accomplished possessing the four possible substitution patterns at $C_{16}$ and $C_{17}$ via a Julia coupling strategy. Their subsequent bisspirocyclization led to the observations of the dramatic and unprecedented controlling influence of the $C_{17}$ substituent. A possible working model has been put forth to explain the observed results. Finally, the successful construction of the natural *transoidal* bisspiroketal stereochemistry has been accomplished under equilibrating conditions on a species possessing a $C_{16}$ benzyloxy substituent. The application of this strategy to the total synthesis of azaspiracid will be reported in due course.

## 6. Experimental

### 6.1. General

**6.1.1. Keto sulfone 15.** To a stirred solution of **8**[6a] (224 mg, 0.371 mmol) in THF (1.5 mL) at −78°C was added LDA[25] (420 μL, 0.42 mmol, 1.0 M in THF/hexanes) dropwise. After 20 min, a precooled solution of **14**[6a] (134.4 mg, 0.445 mmol) in THF (0.4 mL) was added via cannula to the yellow sulfone solution. An additional portion of THF (2×100 μL) was added to rinse the aldehyde flask. After 25 min, the reaction removed from the cooling bath. After 2 min, the reaction was quenched with saturated aqueous $NH_4Cl$ (25 mL), allowed to warm to room temperature and extracted with $Et_2O$ (5×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–25% EtOAc/hexanes, to give sequentially the least polar hydroxy sulfone **45a** (64 mg, 0.071 mmol, 19%) followed by the more polar hydroxy sulfones **45b** and **45c** (272 mg, 0.300 mmol, 81%) as a colorless oils.

To a stirred solution of **45b/45c** (39.8 mg, 0.0439 mmol) and powdered 4 Å molecular sieves (200 mg) in $CH_2Cl_2$

(0.7 mL) was added sequentially NMO (8.5 mg, 0.072 mmol) and TPAP (3.8 mg, 0.0108 mmol). An additional portion of TPAP (3.7 mg, 0.0105 mmol) was added during the course of the reaction. After 1 h, the reaction was diluted with 30% EtOAc/hexanes (5 mL), filtered through a small plug of silica gel (30% EtOAc/hexanes rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–30% EtOAc/hexanes, to give **15** as a colorless oil (32.0 mg, 0.0354 mmol, 81%). $[\alpha]_D^{23}=-12.6°$ (*c* 1.65, $CHCl_3$); IR (neat) 3069, 2932, 1719, 1310, 111, 703 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.75–7.82 (m, 2H), 7.65–7.68 (m, 5H), 7.48–7.58 (m, 4H), 7.35–7.45 (m, 6H), 6.03 (m, 1H of 1 diastereomer), 5.93 (m, 1H of 1 diastereomer) 5.36–5.66 (m, 3H), 5.13 (t, *J*=4.4 Hz, 1H of 1 diastereomer), 5.02 (dd, *J*=2.7, 5.3 Hz,1H of 1 diastereomer), 4.68 (t, *J*=6.8 Hz, 1H of 1 diastereomer), 4.61 (d, *J*=10.2 Hz, 1H of 1 diastereomer), 4.33–4.40 (m, 1H), 4.14–4.19 (m, 1H), 3.95–4.01 (m, 1H), 3.65 (dd, *J*=6.2, 11.3 Hz, 2H), 3.36 (s, 3H of 1 diastereomer), 3.33 (s, 3H of 1 diastereomer), 3.20–3.30 (m, 1H), 3.10 (s, 3H of 1 diastereomer), 3.04 (s, 3H of 1 diastereomer), 2.53 (dd, *J*=10.6, 13.5 Hz, 1H of 1 diastereomer), 3.30–3.33 (m, 1.5H), 1.85–2.20 (m, 8H), 1.60–1.66 (m, 3H), 1.30–1.45 (m, 1H), 1.25 (d, *J*=6.6 Hz, 3H of 1 diastereomer), 1.17 (d, *J*=7.2 Hz, 3H of 1 diastereomer), 1.06 (s, 9H of 1 diastereomer), 1.05 (s, 9H of 1 diastereomer), 0.99 (t, *J*=8.0 Hz, 9H of 1 diastereomer), 0.93 (t, *J*=8.0 Hz, 9H of 1 diastereomer), 0.64 (q, *J*=8.0 Hz, 6H of 1 diastereomer), 0.57 (q, *J*=8.0 Hz, 6H of 1 diastereomer); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 205.3, 204.9, 137.2, 136.8, 135.7, 134.22, 134.16, 132.8, 132.6, 130.3, 129.9, 129.81, 129.75, 129.5, 129.1, 127.8, 104.1, 103.7, 97.2, 96.5, 78.4, 78.2, 72.6, 70.0, 69.9, 68.9, 68.7, 63.6, 63.4, 55.3, 55.2, 49.3, 49.2, 45.3, 45.1, 43.8, 35.7, 34.8, 32.3, 32.1, 31.4, 30.6, 30.42, 30.36, 29.9, 28.8, 27.0, 19.4, 16.0, 15.1, 7.1, 7.0, 5.0, 4.9; HRMS (FAB+) calcd for $C_{50}H_{72}O_9SSi_2Li$ (M+Li) 911.4596, found 911.4598.

**6.1.2. Ketone 16.** To a stirred solution of **15** (33 mg, 0.037 mmol) in THF (730 μL) and MeOH at −10°C (2.2 mL) was added sequentially $Na_2HPO_4$ (21 mg) and Na/Hg (500 mg, 5% Na). After 45 min, the reaction was poured directly on a small plug of dry silica gel (40% EtOAc/hexanes rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 7–30% EtOAc/hexanes, to give **16** as a colorless oil (25 mg, 0.033 mmol, 88%). $[\alpha]_D^{23}=-15.3°$ (*c* 1.18, $CHCl_3$); IR (neat) 2952, 1709, 1463, 1427, 1107 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.66 (dd, *J*=1.5, 7.5 Hz, 4H), 7.35–7.45 (m, 6H), 5.95–6.01 (m, 1H), 5.62–5.73 (m, 2H), 5.51 (dd, *J*=6.5, 15.5 Hz, 1H), 5.05 (t, *J*=4.7 Hz, 1H), 4.24–4.37 (m, 2H), 3.91 (dt, *J*=3.8, 10.0 Hz, 1H), 3.67 (t, *J*=6.3 Hz, 2H), 3.32 (s, 3H), 3.25 (s, 3H), 2.68–2.77 (m, 1H), 2.50–2.57 (m, 1H), 1.85–2.24 (m, 6H), 1.60–1.71 (m, 2H), 1.45 (ddd, *J*=3.6, 6.8, 11.5 Hz, 1H), 1.11 (d, *J*=6.9 Hz, 3H) 1.05 (s, 9H), 0.95 (t, *J*=7.9 Hz, 9H), 0.59 (q, *J*=7.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 214.1, 135.8, 134.2, 132.7, 130.3, 129.7, 128.6, 128.4, 128.0, 104.0, 98.2, 78.8, 72.6, 68.9, 63.5, 55.3, 48.4, 43.8, 43.6, 36.1, 32.4, 32.1, 30.6, 29.6, 28.9, 27.1, 19.4, 16.6, 7.0, 4.9; HRMS (FAB+) calcd for $C_{44}H_{68}O_7Si_2Li$ (M+Li) 771.4664, found 771.4682.

**6.1.3. Spiroketal 17.** To a stirred solution of **16** (16.0 mg, 0.0021 mmol) in *t*-BuOH (1.6 mL) at room temperature was added PPTS (6.8 mg, 0.027 mmol). After 5 h, the reaction was quenched with solid $NaHCO_3$ (100 mg), diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with $Et_2O$ (3×50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–20% EtOAc/hexanes, to give **17** as a colorless oil (6.6 mg, 0.011 mmol, 51%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.65–7.68 (m, 4H), 7.36–7.45 (m, 6H), 5.95–5.97 (m, 1H), 5.50–5.75 (m, 3H), 5.17 (dd, *J*=4.2, 5.5 Hz, 1H), 4.35–4.42 (m, 1H), 4.27–4.30 (m, 1H), 3.97 (m, 1H), 3.66 (t, *J*=6.3 Hz, 2H), 3.39 (s, 3H), 1.83–2.30 (m, 11H), 1.59–1.69 (m, 4H), 1.05 (s, 9H), 0.87 (d, *J*=6.6 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.8, 134.3, 132.5, 130.5, 129.7, 128.6, 128.2, 127.8, 109.3, 105.6, 105.4, 75.1, 72.3, 63.5, 55.8, 41.6, 37.5, 32.3, 31.8, 31.1, 30.4, 29.9, 29.0, 27.1, 19.4, 15.9; HRMS (FAB+) calcd for $C_{37}H_{50}O_6SiLi$ (M+Li) 625.3537, found 625.3516.

**6.1.4. Spiroketal sulfone 18.** To a stirred solution of **15** (42 mg, 0.046 mmol) in MeCN (5.2 mL) at 0°C was added CSA (5.6 mg, 0.024 mmol). After 1 h, the reaction was allowed to warm to room temperature. After 6.5 h, the reaction was quenched with solid $NaHCO_3$ (500 mg), diluted with saturated aqueous $NaHCO_3$ (25 mL), and extracted with $Et_2O$ (4×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–25% EtOAc/hexanes, to give **18** as a colorless oil (25 mg, 0.032 mmol, 72%). $[\alpha]_D^{23}=-38.8°$ (*c* 1.20, $CHCl_3$); IR (neat) 3068, 2925, 2855, 1463, 1106 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.93 (d, *J*=7.4 Hz, 2H of 1 diastereomer), 7.90 (t, *J*=7.4 Hz, 2H of 1 diastereomer), 7.61–7.68 (m, 5H), 7.54 (t, *J*=7.4 Hz, 2H of 1 diastereomer), 7.50 (t, *J*=7.4 Hz, 2H of 1 diastereomer), 7.35–7.46 (m, 6H), 6.05–6.08 (m, 1H of 1 diastereomer), 5.92–5.97 (m, 1H of 1 diastereomer), 5.40–5.70 (m, 3H), 5.16 (t, *J*=4.8 Hz, 1H of 1 diastereomer), 4.81 (t, *J*=4.8 Hz, 1H of 1 diastereomer), 4.30–4.35 (m, 1H of 1 diastereomer), 4.27 (dd, *J*=7.2, 13.1 Hz, 1H of 1 diastereomer), 4.09–4.16 (m, 1.5H), 3.88 (d, *J*=1.8 Hz, 1H of 1 diastereomer), 3.82 (dd, *J*=8.2, 12.3 Hz, 1H of 1 diastereomer), 3.60 (dd, *J*=6.2, 13.9 Hz, 2H), 3.41 (s, 3H of 1 diastereomer), 3.35 (s, 3H of 1 diastereomer), 2.68 (t=12.3 Hz, 1H of 1 diastereomer), 2.40–2.55 (m, 2H), 2.31 (dd, *J*=7.2, 12.3 Hz, 1H of 1 diastereomer), 1.89–2.19 (m, 7H), 1.56–1.85 (m, 7H), 1.15 (d, *J*=6.4 Hz, 3H of 1 diastereomer), 1.04 (s, 9H), 0.93 (d, *J*=6.7 Hz, 3H of 1 diastereomer); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 140.6, 138.7, 135.7, 134.1, 133.9, 133.7, 133.1, 132.5, 130.8, 130.2, 129.9, 129.7, 129.2, 128.6, 127.8, 127.4, 126.7, 108.8, 106.4, 105.4, 105.2, 102.4, 74.6, 74.0, 73.6, 73.3, 72.3, 70.1, 69.7, 66.4, 66.1, 63.34, 63.30, 60.6, 55.9, 41.3, 40.7, 40.1, 38.5, 32.13, 32.10, 30.9, 30.2, 29.9, 29.8, 29.1, 28.92, 28.87, 28.3, 27.0, 21.3, 19.4, 17.2, 15.6, 15.5, 14.4; HRMS (FAB+) calcd for $C_{43}H_{54}O_8SSiLi$ (M+Li) 765.3469, found 765.3481.

**6.1.5. Enol ether 19.** To a stirred solution of **18** (24.0 mg, 0.0317 mmol) in THF (0.7 mL) at −78°C was added *n*-BuLi (16 μL, 0.040 mmol, 2.5 M in hexanes) dropwise. An additional portion of *n*-BuLi (12 μL, 0.030 mmol, 2.5 M in hexanes) was added during the course of the reaction. After 1.25 h, the reaction was quenched with solid silica gel.

The reaction was allowed to warm to ambient temperature, diluted with saturated aqueous $NH_4Cl$ (25 mL) and extracted with $Et_2O$ (4×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–60% EtOAc/hexanes, to give **19** as a colorless oil (19.9 mg, 0.0263 mmol, 83%). $[\alpha]_D^{23}=+29.1°$ (*c* 0.99, $CHCl_3$); IR (neat) 3518, 3069, 2928, 2859, 1624 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 7.93 (m, 2H), 7.75 −7.78 (m, 4H), 7.22–7.25 (m, 6H), 6.94–6.97 (m, 3H), 5.46–5.68 (m, 3H), 5.18 (dt, *J*=1.1, 9.9 Hz, 1H), 4.44 (dt, *J*=4.2, 11.5 Hz, 1H), 4.34–4.39 (m, 1H), 4.12–4.18 (m, 1H and OH), 3.62 (t, *J*=6.3 Hz, 2H), 3.25 (s, 3H), 3.10 (d, *J*=15.0 Hz, 1H), 2.93 (d, *J*=15.0 Hz, 1H), 1.70–2.30 (m, 10H), 1.48–1.67 (m, 5H), 1.22 (d, *J*=6.9 Hz, 3H), 1.17 (s, 9H); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 170.7, 144.1, 136.7, 135.0, 133.1, 130.7, 130.6, 130.4, 129.9, 129.6, 128.9, 129.6, 127.8, 126.8, 127.8, 126.8, 109.8, 107.3, 105.1, 79.4, 72.5, 71.1, 64.9, 55.9, 44.2, 43.3, 34.2, 32.9, 30.2, 29.6, 29.3, 27.8, 20.1, 19.7; HRMS (FAB+) calcd for $C_{43}H_{54}O_8SSiLi$ (M+Li) 765.3469, found 765.3565.

**6.1.6. Spiroketal 20.** To a stirred solution of **19** (13.0 mg, 0.0172 mmol) in PhMe (2.4 mL) at −78°C was added CSA (36 mg, 0.155 mmol). After 10 min, the reaction was allowed to warm to ambient temperature over a period of 35 min. After an additional 90 min, the reaction was quenched with solid $NaHCO_3$, diluted with 33% EtOAc/hexanes (10 mL), filtered through a small plug of silica gel (33% EtOAc/hexanes rinse) and concentrated in vacuo. The crude oil was purified by chromatography over silica gel, eluting with 5–40% EtOAc/hexanes, to give sequentially **18** (6.3 mg, 0.0083 mmol, 49%) and **20** (5.6 mg, 0.074 mmol, 43%) as colorless oils. **20**: $[\alpha]_D^{23}=-45.5°$ (*c* 0.43, $CHCl_3$); IR (neat) 3070, 2925, 2854, 1460, 1308 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 7.89 (dd, *J*=2.0, 8.0 Hz, 2H), 7.74–7.78 (m, 4H), 7.22–7.25 (m, 6H), 6.86–6.94 (m, 3H), 5.39–5.64 (m, 3H), 5.32 (d, *J*=10.0 Hz, 1H), 5.20 (dd, *J*=4.0, 5.6 Hz, 1H), 4.29 (dd, *J*=6.6, 12.5 Hz, 1H), 4.09 (dd, *J*=2.0, 5.0 Hz, 1H), 3.93–3.96 (m, 1H), 3.80–3.82 (m, 1H), 3.59 (t, *J*=6.3 Hz, 2H), 3.33 (s, 3H), 2.70 (dd, *J*=12.2, 12.5 Hz, 1H), 2.52 (dd, *J*=6.5, 12.2 Hz, 1H), 2.42–2.49 (m, 1H), 1.80–2.14 (m, 8H), 1.52–1.70 (m, 2H), 1.16 (s, 9H), 0.91 (d, *J*=6.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $C_6D_6$) δ 140.9, 136.4, 134.7, 133.6, 131.8, 131.2, 130.4, 130.2, 129.9, 129.3, 128.9, 128.2, 108.1, 105.8, 103.1, 75.6, 73.6, 73.1, 65.9, 63.9, 55.8, 41.5, 38.4, 32.7, 29.2, 28.9, 27.5, 23.5, 19.9, 16.0, 14.8; HRMS (FAB+) calcd for $C_{43}H_{54}O_8SSiLi$ (M+Li) 765.3469, found 765.3466.

**6.1.7. Keto sulfone 22.** To a stirred solution of **8**[6a] (166 mg, 0.275 mmol) in THF (1.5 mL) at −78°C was added LDA[24] (310 μL, 0.31 mmol, 1 M in THF/hexanes) dropwise via a syringe. After 20 min, a precooled solution of the aldehyde **21**[6d] (75 mg, 0.344 mmol) in THF (0.3 mL) was added rapidly via cannula to the yellow sulfone solution. After 25 min, the reaction was removed from the cooling bath. After an additional 2 min, the reaction was quenched with sat. aq. $NH_4Cl$ (25 mL) and extracted with EtOAc (4×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–28% EtOAc/hexanes, to give the hydroxy sulfone **46** (182 mg, 0.0.22 mmol, 81%) as a colorless oil.

To a stirred solution of **46** (40.0 mg, 0.0487 mmol) in $CH_2Cl_2$ (0.8 mL) with powdered 4 Å mol. sieves (≈200 mg) was sequentially added NMO (13 mg, 0.11 mmol) and TPAP (6.8 mg, 0.019 mmol) at room temperature An additional portion of TPAP (6 mg, 0.017 mmol) was added during the course of the reaction. After 1.5 h, the reaction was diluted with 30% EtOAc/hexanes (10 mL), filtered through a small plug of silica gel (30% EtOAc/hexanes rinse), and concentrated in vacuo. The resultant oil was purified by chromatography over silica gel, eluting with 5–20% EtOAc/hexanes, to give **22** (29 mg, 0.035 mmol, 73%) as a colorless oil: $[\alpha]_D^{23}=+17.3°$ (*c* 3.45, $CHCl_3$); IR (neat) 3070, 2952, 17.16, 1310, 1111 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 7.76 (d, *J*=7.5 Hz, 2H), 7.65–7.68 (m, 5H), 7.51–7.59 (m, 2H), 7.36–7.46 (m, 6H), 6.01–6.08 (m, 1H of a diastereomer), 5.01–5.96 (m, 1H of a diastereomer), 5.31–5.64 (m, 3H), 4.61 (dd, *J*=3.4, 3.4 Hz, 1H of a diastereomer), 4.47 (d, *J*=9.0 Hz, 1H of a diastereomer), 4.12–4.22 (m, 1H) 3.57–3.68 (m, 4H), 3.11 (s, 3H of a diastereomer), 3.06 (s, 3H of a diastereomer), 2.92–3.03 (m, 1H), 2.60 (dd, *J*=10.0, 13.8 Hz, 1H of a diastereomer), 2.27–2.38 (m, 1H of a diastereomer), 2.25 (d, *J*=6.2 Hz, 1H), 1.80–2.20 (m, 7H), 1.50–1.68 (m, 3H), 1.17 (d, *J*=6.7 Hz, 3H of a diastereomer), 1.11 (d, *J*=7.2 Hz, 3H of a diastereomer), 1.06 (s, 9H of a diastereomer), 1.05 (s, 9H of a diastereomer), 0.93–0.98 (m, 9H), 0.55–0.65 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 204.8, 204.6, 136.7, 135.8, 134.4, 134.3, 132.8, 132.3, 130.3, 129.8, 139.6, 129.2, 129.1, 127.9, 127.8, 127.7, 97.4, 96.5, 69.8, 69.3, 69.1, 68.8, 63.4, 63.0, 62.8, 49.4, 48.0, 47.6, 34.7, 34.2, 32.2, 32.1, 30.8, 30.5, 30.3, 29.9, 28.9, 28.8, 28.7, 27.1, 19.4, 16.4, 14.9, 7.1, 4.6.

**6.1.8. Ketone 23.** To a stirred solution of **22** (86 mg, 0.103 mmol) in THF (0.6 mL) and MeOH (1.8 mL) at −10°C was added $Na_2HPO_4$ (70.6 mg, 0.493 mmol) followed by Na/Hg (330 mg, 0.712 mmol, 5% Na). After 75 min, the reaction was diluted with 35% EtOAc/hexanes (10 mL), filtered through a small plug of silica gel (35% EtOAc/hexanes rinse), and concentrated in vacuo to give crude **23** (0.103 mmol) as a colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J*=0.9, 6.2 Hz, 4H), 7.36–7.45 (m, 6H), 5.96–6.02 (m, 1H), 5.69 (dt, *J*=6.5, 15.5 Hz, 1H), 5. 63 (d, *J*=9.9 Hz, 1H), 5.52 (dd, *J*=6.6, 15.5 Hz, 1H), 4.22–4.29 (m, 1H), 3.67 (t, *J*=6.2 Hz, 2H), 3.58 (t, *J*=5.8 Hz, 2H), 2.40–2.60 (m, 2H), 1.80–2.15 (m, 6H), 1.52–1.70 (m, 5H), 1.30–1.50 (m, 2H), 1.05–1.08 (m, 12H), 0.95 (t, *J*=7.9 Hz, 9H), 0.58 (q, *J*=7.9 Hz, 6H); HRMS (FAB+) calcd for $C_{40}H_{61}O_4Si_2$ ($M^+$−MeOH) 661.4108, found 661.4124.

**6.1.9. Spirocycles 24 and 25.** To a stirred solution of crude **23** (0.103 mmol) in PhMe (7 mL) and *t*-BuOH (7 mL) was added CSA (123 mg, 0.529 mmol). After 19 h, the reaction was quenched with solid $NaHCO_3$ (500 mg). After 10 min, the solution was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with $Et_2O$ (4×100 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 3–12% EtOAc/hexanes, to give more polar *transoidal* **24** and less polar *cisoidal* **25** (38 mg, 0.070 mmol, 68% over the 2 steps) as colorless oils. *transoidal* **24**: $[\alpha]_D^{23}=-13.0°$ (*c* 0.185, $CHCl_3$); IR (neat) 2931, 2858, 1428, 1111, 702 $cm^{-1}$; $^1H$

NMR (300 MHz, $CDCl_3$) 7.65–7.68 (m, 4H), 7.34–7.43 (m, 6H), 5.94–6.0 (m, 1H), 5.62–5.72 (m, 2H), 5.50 (dd, $J$=6.0, 15.4 Hz, 1H), 4.36–4.43 (m, 1H), 3.92 (ddd, $J$=3.0, 11.6, 11.6 Hz, 1H), 3.66 (t, $J$=6.4 Hz, 2H), 3.57 (dt, $J$=4.3, 11.2 Hz, 1H), 1.83–2.20 (m, 10H), 1.56–1.79 (m, 5H), 1.04 (s, 9H), 1.01 (d, $J$=7.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.8, 134.2, 132.3, 130.7, 129.7, 128.2, 127.8, 110.0, 104.4, 69.0, 63.4, 62.8, 37.1, 36.5, 32.6, 32.1, 30.3, 28.9, 27.5, 27.0, 21.5, 19.4, 15.6; HRMS (FAB+) calcd for $C_{34}H_{47}O_4Si$ (M+H) 547.3244, found 547.3228. *cisoidal* **25**: $[\alpha]_D^{23}$=−65.3° ($c$ 0.19, $CHCl_3$); IR (neat) 2960, 2930, 2855, 1467, 1110 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 7.64–7.68 (m, 4H), 7.34–7.45 (m, 6H), 5.94–6.00 (m, 1H), 5.53–5.75 (m, 3H), 4.42–4.49 (m, 1H), 3.84 (ddd, $J$=2.2, 11.1, 11.1 Hz, 1H), 3.60–3.67 (m, 1H), 3.66 (t, $J$=6.2 Hz, 2H), 1.83–2.26 (m, 10H), 1.47–1.72 (m, 5H), 1.04 (s, 9H), 0.87 (d, $J$=6.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.8, 134.2, 132.4, 130.6, 129.7, 128.8, 128.0, 127.8, 109.6, 105.3, 70.1, 63.5, 62.0, 37.8, 37.5, 35.5, 32.1, 30.2, 28.9, 28.6, 27.0, 19.4, 16.8; HRMS (FAB+) calcd for $C_{34}H_{47}O_4Si$ (M+H) 547.3244, found 547.3252.

**6.1.10. Sulfone spirocycle 47.** To a stirred solution of **22** (68 mg, 0.083 mmol) in MeCN (9 mL) at room temperature was added CSA (8.8 mg, 0.038 mmol). After 2 h, the reaction was quenched with solid $NaHCO_3$ (250 mg). The mixture was diluted with 35% EtOAc/hexanes (50 mL), filtered through a small plug of silica gel (35% EtOAc/hexanes rinse), and concentrated in vacuo. The resultant oil was purified by chromatography over silica gel, eluting with 6–40% EtOAc/hexanes, to give **47** (52 mg, 0.076 mmol, 91%) as a colorless oil: IR (neat) 3069, 3046, 2930, 2857, 1471, 1446, 1427, 1307, 1150, 1111 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.88–7.93 (m, 2H), 7.59–7.67 (m, 5H), 7.48–7.55 (m, 2H), 7.32–7.44 (m, 6H), 6.03–6.09 (m, 1H of a diastereomer), 5.88–5.93 (m, 1H of a diastereomer), 5.41–5.70 (m, 3H), 4.33–4.47 (m, 1H), 4.15 (dd, $J$=7.0, 13.2 Hz, 1H of a diastereomer), 3.35–3.82 (m, 2H and 1H of a diastereomer), 2.70 (dd, $J$=12.4, 12.4 Hz, 1H of a diastereomer), 2.52–2.60 (m 1H of a diastereomer), 2.3–2.43 (m, 1H), 1.90–2.20 (m, 5H), 1.40–1.80 (m, 7H), 1.14 (d, $J$=5.9 Hz, 3H of a diastereomer), 1.04 (s, 9H of a diastereomer), 1.03 (s, 9H of a diastereomer), 0.90 (d, $J$=6.7 Hz, 3H of a diastereomer); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 141.0, 139.3, 135.7, 134.2, 133.9, 133.8, 133.2, 132.1, 130.8, 130.1, 130.0, 129.8, 129.4, 128.4, 128.2, 127.8, 127.3, 126.8, 109.9, 107.3, 102.53, 102.46, 73.8, 70.8, 69.3, 66.6, 63.5, 63.4, 61.3, 41.2, 38.7, 35.4, 34.8, 32.1, 32.0, 30.1, 29.9, 29.4, 28.9, 28.8, 28.5, 27.1, 26.0, 25.3, 19.4, 18.2, 16.4, 15.5; HRMS (FAB+) calcd for $C_{40}H_{51}O_6SSi$ (M+H) 687.3176, found 687.3154.

**6.1.11. Sulfone enol ether 48.** To a stirred solution of **47** (51 mg, 0.75 mmol) in THF (2.3 mL) at −78°C was added dropwise $n$-BuLi (35 μL, 0.0875 mmol, 2.5 M in hexanes). An additional portion of $n$-BuLi (6 μL, 0.015 mmol, 2.5 M in hexanes) was added during the course of the reaction. After 70 min, the reaction was quenched with solid silica gel (500 mg). After 5 min, the mixture was diluted with sat. aq. $NH_4Cl$ (20 mL) and extracted with $Et_2O$ (4×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6–50% EtOAc/hexanes, to give **48** (35.8 mg, 0.0.22 mmol, 70%) followed by $C_{10}$-*epi* **48** (5.0 mg, 0.0.073, 10%) as colorless oils. $[\alpha]_D^{23}$=+62.4° ($c$ 180, $CHCl_3$); IR (neat) 3444, 2929, 2856, 1624, 1109 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.87 (d, $J$=7.6 Hz, 2H), 7.66 (d, $J$=6.7 Hz, 4H) 7.49–7.60 (m, 3H), 7.36–7.41 (m, 6H), 6.06–6.12 (m, 1H), 5.69 (d, $J$=10.9 Hz, 1H), 5.65 (dt, $J$=6.6, 15.7 Hz, 1H), 5.46 (dd, $J$=6.0, 15.7 Hz, 1H), 4.35–4.43 (m, 1H), 3.65 (t, $J$=6.2 Hz, 2H), 3.55 (t, $J$=5.7 Hz, 2H), 2.91 (d, $J$=15.1 Hz, 1H), 2.83 (d, $J$=15.1 Hz, 1H), 2.00–2.17 (m, 4H), 1.49–1.67 (m, 7H), 1.14 (d, $J$=6.9 Hz, 3H), 1.05 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 170.3, 142.5, 135.8, 134.2, 133.1, 133.0, 130.4, 129.8, 129.4, 129.3, 127.8, 127.0, 126.0, 108.7, 106.4, 70.6, 63.4, 62.9, 42.1, 32.0, 31.4, 30.6, 30.4, 28.8, 27.0, 19.4, 18.6, 15.5; HRMS (FAB+) calcd for $C_{40}H_{51}O_6SSi$ (M+H) 687.3176, found 687.3158.

**6.1.12. Aldehyde 26.** To a stirred solution of **48** (21.6 mg, 0.0320 mmol) in $CH_2Cl_2$ (1.0 mL) with powdered 4 Å mol. sieves (250 mg) was sequentially added TPAP (2.5 mg, 6.3 μmol) and NMO (9.0 mg, 0.077 mmol) at room temperature After 30 min, the reaction was diluted with 33% EtOAc/hexanes (10 mL), filtered through a small plug of silica gel (33% EtOAc/hexanes rinse), and concentrated in vacuo to give **26** (21.0 mg, 0.031 mmol, 97%) as a colorless oil: $[\alpha]_D^{23}$=+52.4° ($c$ 1.03, $CHCl_3$); IR (neat) 2928, 28.55, 1724, 1627, 1110, 599 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 7.87 (d, $J$=6.8 Hz, 2H), 7.65 (dd, $J$=1.5, 6.0 Hz, 4H), 7.50–7.65 (m, 3H), 7.35–7.43 (m, 6H), 6.07–6.13 (m 1H), 5.68 (d, $J$=10.5 Hz, 1H), 5.60 (dt, $J$=6.5, 15.7 Hz, 1H), 5.41, (dd, $J$=6.5, 15.7 Hz, 1H), 4.29–4.36 (m, 1H), 3.64 (t, $J$=6.2 Hz, 2H), 3.51–3.59 (m, 1H), 2.84 (s, 2H), 2.32–2.43 (m, 2H), 1.95–2.15 (m, 4H), 1.73–1.83 (m, 2H), 1.58–1.68 (m, 4H), 1.15 (d, $J$=6.8 Hz, 3H), 1.05 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 201.8, 170.0, 135.8, 134.1, 133.2, 130.7, 129.8, 129.4, 129.2, 127.8, 127.0, 125.7, 109.9, 106.6, 70.9, 63.4, 42.0, 41.0, 41.7, 32.0, 30.0, 29.9, 28.8, 27.1, 26.3, 19.4, 18.5; HRMS (FAB+) calcd for $C_{40}H_{49}O_6SSi$ (M+H) 685.3019, found 685.3020.

**6.1.13. Homoallylic alcohol 49.** To a stirred solution of **26** (20.0 mg, 0.0292 mmol) in $Et_2O$ (1.1 mL) at −100°C was added dropwise precooled $(Ipc)_2$Ballyl[26] (140 μL, 0.035 mmol, 0.25 M in pentane) via syringe. After 30 min, the reaction was quenched with MeOH (50 μL) and warmed to room temperature The solution was further quenched with aq. phosphate buffer (800 μL, pH 7) and $H_2O_2$ (200 μL, 30% in $H_2O$). After 30 min, the solution was diluted with sat. aq. NaCl (25 mL) and extracted with $Et_2O$ (4×25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 7–40% EtOAc/hexanes, to give **49** (15.0 mg, 0.021 mmol, 71%) as a colorless oil. $[\alpha]_D^{23}$=+14.1° ($c$ 0.68, $CHCl_3$); IR (neat) 3566, 2928, 2855, 2625, 1427, 1110 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.85–7.90 (m, 2H), 7.65 (dd, $J$=1.4, 7.4 Hz, 4H) 7.47–7.61 (m, 3H), 7.34–7.45 (m, 6H), 6.06–6.12 (m, 1H), 5.70–5.82 (m, 1H), 5.69 (d, $J$=9.5 Hz, 1H), 5.66 (dt, $J$=6.1, 15.7 Hz, 1H), 5.45 (dd, $J$=5.4, 15.7 Hz, 1H), 5.04–5.10 (m, 2H), 4.37–4.45 (m, 1H), 3.64 (t, $J$=6.3 Hz, 2H), 3.52–3.62 (m, 1H), 2.92 (d, $J$=15.2 Hz, 1H), 2.84 (d, $J$=15.2 Hz, 1H), 2.00–2.19 (m, 6H), 1.30–1.67 (m, 9H), 1.15 (d, $J$=7.0 Hz, 3H), 1.05 (s, 9H); (75 MHz, $CDCl_3$) $\delta$ 170.3, 142.6, 135.8, 135.0, 134.1, 132.9, 132.7, 130.3, 129.8, 129.5, 129.3, 127.8, 126.9, 126.0, 118.2, 108.6, 106.4, 70.6, 70.4, 63.4, 42.2, 42.1, 34.5, 32.0, 31.4, 30.2, 30.0, 28.8, 27.0, 19.4, 18.9; HRMS (FAB+) calcd for $C_{43}H_{55}O_6SSi$ (M+H) 727.3489, found 727.3504.

**6.1.14. Desulfonylated enol ether 27.** To a stirred solution of **49** (12.5 mg, 0.0175 mmol) in THF (0.3 mL) and MeOH (0.6 mL) at −10°C was sequentially added $Na_2HPO_4$ (36 mg) and Na/Hg (224 mg, 5% in Hg). After 20 min, the reaction was warmed to 0°C. After 1 h, the reaction was diluted with $Et_2O$, filtered through a small pad of Celite® ($Et_2O$ rinse) and concentrated in vacuo. The crude product **27** was used immediately in subsequent manipulations.

**6.1.15. $C_{17}$ Spirocycle 28.** To a stirred solution of crude **27** (0.0175 mmol) in PhMe (1.0 mL) and *t*-BuOH (1.0 mL) was added CSA (17.1 mg, 0.0737 mmol) at room temperature After 14.5 h, the reaction was quenched with solid $NaHCO_3$ (250 mg). After 10 min, the solution was diluted with 25% EtOAc/hexanes (25 mL), filtered through a small plug of silica gel (25% EtOAc/hexanes rinse), and concentrated in vacuo. The resultant oil was purified using preparative thin layer chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give **28** (7.6 mg, 0.013 mmol, 76% over 2 steps) as a colorless oil: $[\alpha]_D^{23}=-50.0°$ (*c* 0.38, $CHCl_3$); IR (neat) 3037, 2928, 2865, 1461, 1110 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.65–7.68 (m, 4H), 7.34–7.42 (m, 6H), 5.93–6.97 (m, 1H), 5.59–5.93 (m, 4H), 4.94–5.04 (m, 2H), 4.38–4.43 (m, 1H), 3.80–3.86 (m, 1H), 3.66 (t, *J*=6.2 Hz, 2H), 1.99–2.25 (m, 12H), 1.5–1.78 (m, 5H), 1.04 (s, 9H), 0.87 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 136.0, 134.4, 132.0, 131.0, 129.9, 129.0, 128.2, 128.0, 116.5, 110.1, 105.4, 70.9, 70.0, 63.8, 41.1, 37.9, 36.0, 32.4, 31.5, 30.6, 30.1, 29.2, 28.9, 27.3, 19.6, 16.7; HRMS (FAB+) calcd for $C_{37}H_{49}O_4Si$ (M+H) 585.3400, found 585.3397.

**6.1.16. Keto sulfone 30.** To a stirred solution of sulfone **8**[6a] (76.0 mg, 0.126 mmol) in THF (0.8 mL) at −78°C was added LDA[25] (140 μL, 1.0 M in THF) dropwise. After 25 min, a solution of the aldehyde **29**[6e] (53.9 mg, 0.160 mmol) in precooled THF (0.2 mL) was added via cannula to the orange sulfone solution. After 25 min, the reaction was removed from the cooling bath. After 2 min, the reaction was quenched with sat. aq. $NH_4Cl$ (25 mL) and extracted with $Et_2O$ (4×30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give the crude **50** (125 mg) as a colorless oil. The crude hydroxy sulfone **50** was used immediately; chromatography of the crude mixture resulted in spirocyclization at $C_{10}$ to a complex mixture of isomers.

To a stirred solution of crude **50** (0.126 mmol) in $CH_2Cl_2$ (1.0 mL) with powdered 4 Å mol. sieves (100 mg) was sequentially added NMO (19.0 mg, 0.162 mmol) and TPAP (18.0 mg, 0.0512 mmol). An additional portion of TPAP (17.8 mg, 0.0506 mmol) was added during the course of the reaction. After 3.25 h, the reaction was diluted with 25% EtOAc/hexanes (5 mL), filtered through a small plug of silica gel (25% EtOAc/hexanes rinse) and concentrated in vacuo and purified by chromatography over silica gel, eluting with 7–40% EtOAc/hexanes (with 0.5% $Et_3N$), to give **30** (70.4 mg, 0.0751 mmol, 60% over 2 steps) as a colorless oil: IR (neat) 2931, 1721, 1448, 1310, 1110 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.74–7.78 (m, 2H), 7.60–7.70 (m, 5H), 7.45–7.53 (m, 2H), 7.27–7.43 (m, 11H), 5.86–5.96 (m, 1H), 5.33–5.63 (m, 3H), 4.80–4.86 (m, 1H), 4.47–4.66 (m, 2H), 4.13–4.18 (m, 1H), 3.50–3.85 (m, 6H), 3.16–3.23 (m, 1H of a diastereomer), 3.10 (s, 3H of a diastereomer), 3.07 (s, 3H of a diastereomer), 3.00–3.10 (m, 1H of a diastereomer), 2.65 (dd, *J*=10.0, 13.8 Hz, 1H of a diastereomer), 1.72–2.32 (m, 7H), 1.55–1.70 (m, 3H), 1.3–1.52 (m, 4H), 1.09 (s, 9H of a diastereomer), 1.07 (s, 9H of a diastereomer), 1.05–1.10 (m, 3H), 0.99 (t, *J*=9.4 Hz, 6H of 1 diastereomer), 0.97 (t, *J*=9.4 Hz, 6H of 1 diastereomer), 0.58–0.72 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 205.3, 204.7, 139.2, 139.0, 137.1, 136.9, 135.7, 134.24, 134.17, 132.9, 132.3, 130.5, 129.8, 129.6, 129.5, 129.14, 129.06, 128.53, 128.48, 128.3, 128.1, 127.8, 127.7, 127.6, 97.5, 96.5, 73.0, 72.3, 69.8, 69.3, 69.1, 68.7, 66.5, 66.2, 63.51, 63.47, 49.4, 49.0, 44.6, 44.5, 35.3, 34.7, 34.4, 33.6, 32.2, 32.1, 30.1, 28.9, 28.8, 27.1, 19.4, 15.6, 14.5, 7.04, 7.02, 4.6; HRMS (FAB+) calcd for $C_{53}H_{71}O_7SSi_2$ (M−MeOH) 907.4459, found 907.4452.

**6.1.17. Ketone 31.** To a stirred solution of **30** (16.0 mg, 0.017 mmol) in THF (0.3 mL) and MeOH (1.0 mL) at −10°C was added $Na_2HPO_4$ (16 mg, 0.112 mmol). After 5 min, Na/Hg amalgam (118 mg, 0.257 mmol, 5% in Hg) was added. After 2 h, the reaction was diluted with 20% EtOAc/hexanes, filtered through a small plug of silica gel (20% EtOAc/hexanes rinse) and concentrated in vacuo to yield crude **31** (0.017 mmol) which was used without any further purification. $[\alpha]_D^{23}=-0.5°$ (*c* 2.55, $CHCl_3$); IR (neat) 2931, 1714, 1393, 1109 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.65–7.70 (m, 4H), 7.20–7.45 (m, 11H), 5.93–6.00 (m, 1H), 5.63–6.81 (dt, *J*=6.4, 15.5 Hz, 1H), 5.48–5.60 (m, 2H), 4.73 (d, *J*=11.7 Hz, 1H), 4.52 (d, *J*=11.7 Hz, 1H), 4.21–4.28 (m, 1H), 3.65–3.75 (m, 3H), 3.58 (dd, *J*=5.2, 10.3 Hz, 1H), 3.44–3.51 (m, 1H), 3.21 (s, 3H), 2.64–2.80 (m, 1H), 2.43–2.55 (m, 2H), 1.65–2.20 (m, 9H), 1.47–1.55 (m, 1H), 1.27 (s, 9H), 1.00 (d, *J*=6.8 Hz, 3H), 0.98 (t, *J*=7.8 Hz, 9H), 0.62 (q, *J*=7.8 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 214.0, 138.9, 135.8, 134.2, 132.7, 130.3, 129.8, 128.5, 128.4, 128.2, 127.8, 98.2, 77.8, 72.5, 68.9, 65.9, 63.5, 48.4, 43.2, 35.7, 35.4, 32.1, 30.6, 29.5, 28.9, 27.1, 19.4, 16.5, 7.0, 4.6; HRMS (FAB+) calcd for $C_{47}H_{67}O_5Si_2$ (M−MeOH) 767.4527, found 767.4512.

**6.1.18. $C_{16}$ Spirocycles 32 and 33.** To a stirred solution of crude **31** (0.017 mmol) in PhMe (1.1 mL) and *t*-BuOH (1.1 mL) was added CSA (19 mg, 0.0818 mmol). After 17 h, the reaction was quenched with solid $NaHCO_3$ (200 mg). After 5 min, the solution was diluted with 40% EtOAc/hexanes, filtered through a small plug of silica gel (40% EtOAc/hexanes rinse) and concentrated in vacuo. The crude oil was purified by preparative TLC (15% EtOAc/hexanes) to give the less polar *transoidal* spiroketal **32** (3.3 mg, 0.0051 mmol, 30%) and more polar *cisoidal* spiroketal **33** (5.5 mg, 0.0084 mmol, 50%) as colorless oils. *transoidal* **32**: $[\alpha]_D^{23}=-34.7°$ (*c* 0.265, $CHCl_3$); IR (neat) 2960, 2926, 2853, 1427, 1110, 702 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J*=6.1 Hz, 4H), 7.26–7.43 (m, 11H), 5.93–5.97 (m, 1H), 5.61–5.69 (m, 2H), 5.50 (dd, *J*=6.0, 15.8 Hz, 1H), 4.51–4.55 (m, 2H), 4.35–4.39 (m, 1H), 3.68–3.83 (m, 3H), 3.66 (t, *J*=6.2 Hz, 2H), 1.59–2.17 (m, 13H), 1.05 (s, 9H), 1.03 (d, *J*=7.1 Hz, 3H); $^{13}C$ NMR

(75 MHz, $CDCl_3$) δ 138.9, 135.8, 134.2, 132.3, 130.7, 129.74, 129.66, 128.6, 128.0, 127.81, 127.76, 108.9, 104.7, 70.7, 69.5, 69.2, 64.2, 63.4, 36.5, 33.6, 33.14, 33.08, 32.1, 30.3, 28.9, 27.0, 19.4, 16.3; HRMS (FAB+) calcd for $C_{41}H_{53}O_5Si$ (M+H) 653.3662, found 653.3658. *cisoidal* **33**: $[\alpha]_D^{23}=-58.0°$ (*c* 0.40, $CHCl_3$); IR (neat) 3069, 3032, 2961, 2921, 2851, 1467, 1111 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J*=1.7, 7.5 Hz, 4H), 7.26–7.45 (m, 11H), 5.94–6.00 (m, 1H), 5.52–5.82 (m, 3H), 4.61 (d, *J*=12.4 Hz, 1H), 4.52 (d, *J*=12.4 Hz, 1H), 4.36–4.42 (m, 1H), 3.79–3.90 (m, 2H), 3.66 (t, *J*=6.2 Hz, 2H), 3.41–3.43 (m, 1H), 1.60–2.24 (m, 13H), 1.04 (s 9H), 0.87 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 139.0, 135.8, 134.2, 132.2, 130.5, 129.7, 128.7, 128.5, 127.9, 127.8, 127.6, 109.5, 105.3, 77.4, 72.0, 70.1, 63.5, 63.2, 37.4, 35.1, 32.6, 32.2, 32.0, 30.2, 28.9, 27.0, 19.4, 16.4; HRMS (FAB+) calcd for $C_{41}H_{53}O_5Si$ (M+H) 653.3662, found 653.3672.

## Acknowledgements

National Institutes of Health (GM63723) is gratefully acknowledged for support of this work. The authors would also like to thank Professor Max Deinzer (Oregon State University) and Dr Jeff Morré (Oregon State University) for mass spectra data, Professor David E. Graves (University of Alabama-Birmingham) and Roger Kohnert (Oregon State University) for NMR assistance as well as Dr Roger Hanselmann (Rib-X Pharmaceuticals) for his helpful discussions.

## References

1. For a recent review of bisspiroketals: (a) Brimble, M. A.; Farés, F. A. *Tetrahedron* **1999**, *55*, 7661–7706. For other synthetic work towards bisspiroketals not included in the review: (b) Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2002**, *4*, 3655–3658. (c) Nakamura, S.; Inagaki, J.; Kudo, M.; Sugimoto, T.; Obara, K.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2002**, *58*, 10353–10374. (d) Caprio, V.; Brimble, M. A.; Furkert, D. P. *Tetrahedron* **2001**, *57*, 4023–4034. (e) Allen, P. R.; Brimble, M. A.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 379–389.
2. For a recent review of the anomeric effect: Graczyk, P. P.; Mikolajczyk, M. *Top. Stereochem.* **1994**, *21*, 159–349.
3. (a) McGarvey, G. J.; Stepanian, M. W. *Tetrahedron Lett.* **1996**, *37*, 5461–5464. (b) McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Ellena, J. F. *Tetrahedron Lett.* **1996**, *37*, 5465–5468. (c) Brimble, M. A.; Rush, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 497–500.
4. The terms *transoidal* and *cisoidal* refer to the relationship of the two pyran oxygens to one another.
5. For a recent hydrogen-bonding example: Nicolaou, K. C.; Qian, W.; Bernal, F.; Uesaka, N.; Pihko, P. M.; Hinrichs, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4068–4071.
6. (a) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913–3916. (b) Carter, R. G.; Weldon, D. J.; Bourland, T. C. 221st National ACS Meeting, San Diego, ORGN-479. (c) Carter, R. G.; Graves, D. E. *Tetrahedron Lett.* **2001**, *42*, 6035–6039. (d) Carter, R. G.; Bourland, T. C.; Graves, D. E. *Org. Lett.* **2002**, *4*, 2177–2179. (e) Carter, R. G.; Graves, D. E.; Gronemeyer, M. A.; Tschumper, G. S. *Org. Lett.* **2002**, *4*, 2181–2184.
7. For synthetic efforts by other laboratories toward azaspiracid, see: (a) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 975–978. (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979–982. (c) Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817–820. (d) Hao, J.; Aiguade, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 821–824. (e) Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 1262–1265. (f) Buszek, K. R. 221st National ACS Meeting, San Diego, ORGN-570. (g) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3663–3667. (h) Sasaki, M.; Iwamuro, Y.; Nemoto, J.; Oikawa, M. *Tetrahedron Lett.* **2003**, *44*, 6199–6207.
8. Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967–9968.
9. After the submission of this manuscript, the total synthesis of the proposed structure of azaspiracid was reported. (a) Nicolaou, K. C.; Li, Y.; Uesaka, N.; Koftis, T. V.; Vyskocil, S.; Ling, T.; Govindasamy, M.; Qian, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3643–3648. (b) Nicolaou, K. C.; Chen, D. Y.-K.; Li, Y.; Qian, W.; Ling, T.; Vyskocil, S.; Koftis, T. V.; Govindasamy, M.; Uesaka, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 3649–3653.
10. MacMahon, T.; Silke, J. *Harmful Algae News* **1996**, *14*, 2.
11. Ito, E.; Satake, M.; Ofuji, K.; Kurita, N.; McMahon, T.; James, K.; Yasumoto, T. *Toxicon* **2000**, *38*, 917–930.
12. (a) James, K. J.; Sierra, M. D.; Lehane, M.; Brana Magdalena, A.; Furey, A. *Toxicon* **2003**, *41*, 277–283. (b) Ofuji, K.; Satake, M.; McMahon, T.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 740–742. (c) Ofuji, K.; Satake, M.; McMahon, T.; Silke, J.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1999**, *7*, 99–102.
13. James, K. J.; Furey, A.; Lehane, M.; Ramstad, H.; Aune, T.; Hovgaard, P.; Morris, S.; Higman, W.; Satake, M.; Yasumoto, T. *Toxicon* **2002**, *40*, 909–915.
14. James, K. J.; Moroney, C.; Roden, C.; Satake, M.; Yasumoto, T.; Lehane, M.; Furey, A. *Toxicon* **2003**, *41*, 145–151.
15. (a) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049–1057. (b) Solladíe, G.; Almario, A.; Colobert, F. *Synlett* **1992**, 167–168. (c) Smith, A. B.; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037–1040. (d) O'Connor, S. J.; Williard, P. G. *Tetrahedron Lett.* **1989**, *30*, 4637–4640. (e) Beau, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6193–6196. (f) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284–291.
16. (a) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119–126. (b) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 835–847. (c) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759–4766.
17. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
18. Tidwell, T. T. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; Burke, B. D., Danheiser, R. L., Eds.; Wiley: New York, 1999; pp 154–156.
19. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
20. The terms natural and nonnatural refer to relationship of the stereochemistry at $C_{10}$ and $C_{13}$ to the proposed stereochemistry

of azaspiracid as shown in compound **3**. A natural transoidal bisspiroketal possesses the same stereochemical relationship as **3** whereas a nonnatural transoidal spiroketal would possess the opposite $C_{10}$, $C_{13}$ stereochemistry to **3**. These terms are used instead of the traditional Cahn–Ingold–Prelog *R*/*S* nomenclature as the priority rankings change due to the presence of the $C_{12}$ sulfone.

21. It should be noted that decomposition of the bisspirocycles **18** and **20** was a competitive process upon extended reaction times.
22. (a) Miljkovíc, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597–7604. (b) Srivastava, R. M.; Pavão, A. C.; Seabra, G. M.; Brown, R. K. *J. Mol. Struct.* **1997**, *412*, 51–58.
23. This hypothesis assumes that no additional stabilizing functions are present (e.g. Nicolaou and co-workers use of a $C_9$ hydroxyl function). See Ref 5.
24. (a) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC: Boca Raton, FL, 1995. (b) For an alternate explanation involving the Principle of Least Molecular Deformation: Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113–204.
25. The 1.0 M LDA solution was prepared fresh immediately prior to use: to a stirred solution of *N*,*N*-diispropyl amine (404 mg, 560 μL, 4.0 mmol) in THF (1.84 mL) at −78°C was added *n*-BuLi (1.6 mL, 4.0 mmol, 2.5 M in hexanes) dropwise. After 5 min, the white suspension was warmed to −10°C. After 30 min, the solution was employed in the relevant reaction.
26. The $(Ipc)_2$Ballyl was prepared as a stock solution in pentane from the commercially available (−)-$Ipc_2$BOMe and allylMgBr in accord with the low salt protocol developed by Brown and co-workers Racherla, U. S.; Brown, H. C. J. *J. Org. Chem.* **1991**, *56*, 401–404.