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A Stereoselective Synthesis of the C10–C31 (BCDEF Ring) Portion of Pinnatoxin A

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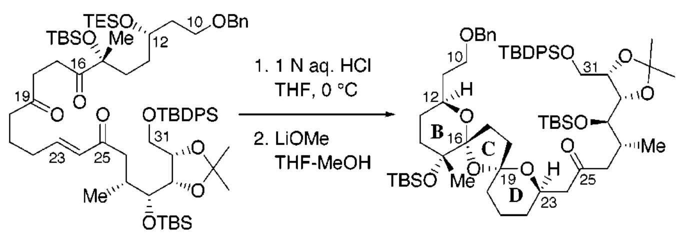
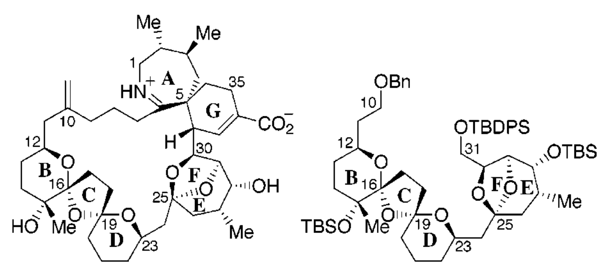
ABSTRACT



An efficient synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A has been achieved. The key step is a highly stereoselective construction of the dispiroketal (BCD ring) system employing an intramolecular hetero-Michael reaction of a reversibly formed hemiketal alkoxide through the use of LiOMe.

Recently, several novel, marine-derived macrocycles containing a spiro-linked cyclic imine moiety have been isolated.[1,2] These natural products have been considered as culprits in shellfish poisoning, and a number of them have also been found to be Ca^{2+} channel activators.[2a,3] Pinnatoxins, the first and most prominent members of this class, were isolated from the shellfish *Pinna muricata* and characterized by Uemura and co-workers in 1995.[1a] Their unprecedented molecular architecture, combined with the associated biological activity and scarcity of natural supply, has prompted a major effort toward the synthesis of pinnatoxins.[4,5] In 1998, Kishi and co-workers accomplished the first total synthesis of (−)-pinnatoxin A utilizing a biomimetic intramolecular Diels−Alder reaction to construct the G ring as well as the macrocycle, establishing the absolute stereochemistry of natural pinnatoxin A, as shown in **1**.[6] As part of a program



Pinnatoxin A (**1**) **2**

directed toward the total synthesis of pinnatoxin A (**1**), we report herein a highly stereoselective synthesis of **2**, corresponding to the C10−C31 (BCDEF ring) portion of this

(1) (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S. Z.; Chen, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 1155. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023.

(2) (a) Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C. *Chem. Commun.* **1995**, 2159. (b) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093. (c) Lu, C.-K.; Lee, G.-H.; Huang, R.; Chou, H.-N. *Tetrahedron Lett.* **2001**, *42*, 1713.

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(4) (a) Sugimoto, T.; Ishihara, J.; Murai, A. *Tetrahedron Lett.* **1997**, *38*, 7379. (b) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1998**, 603. (c) Sugimoto, T.; Ishihara, J.; Murai, A. *Synlett* **1999**, 541. (d) Ishihara, J.; Tojo, S.; Kamikawa, A.; Murai, A. *Chem. Commun.* **2001**, 1392.

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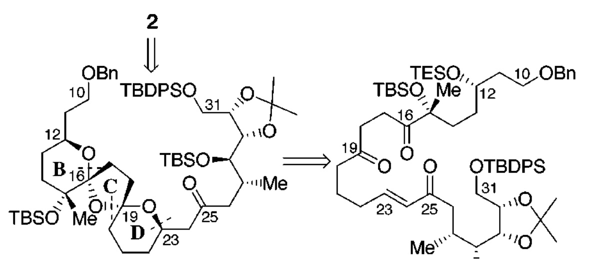
molecule, exploiting an intramolecular hetero-Michael reaction of a reversibly formed hemiketal alkoxide as the key step in creating the BCD ring system.

Apart from constructing the 6,7-spiro-linked cyclic imine (AG ring) system, building the 6,5,6-dispiroketal (BCD ring) system presents a major challenge in the synthesis of **1** as mentioned by the Kishi,[6] Murai,[4] and Hirama[5] groups. Although a number of methods have been developed to synthesize bicyclic spiroketal subunits,[7] the formation of tricyclic dispiroketals has been less thoroughly investigated.[8,9] The majority of reported synthetic strategies in either case rely on the acid-catalyzed cyclization of open-chain hydroxyketones. In this context, Kishi and co-workers demonstrated that treatment of an appropriate tetrahydroxy diketone with CSA led to the formation of a 2:3 mixture of C19 epimeric dispiroketals, and the undesired isomer epimerized exclusively to the natural series under silylation conditions.[6] An alternative approach to spiroketals involves the intramolecular hetero-Michael reaction of a hemiketal alkoxide,[10] which has the advantage of generating a chiral center from an enone in the conjugate addition step as well as a chiral spirocenter. This elegant approach, however, has not yet been applied to the synthesis of dispiroketals. It was readily apparent that the strategy based on this approach would not only benefit from the construction of the BCD ring system but also from the direct assembly of the EF ring system (Scheme 1).

Scheme 1. Synthetic Plan for the C10−C31 Fragment **2**

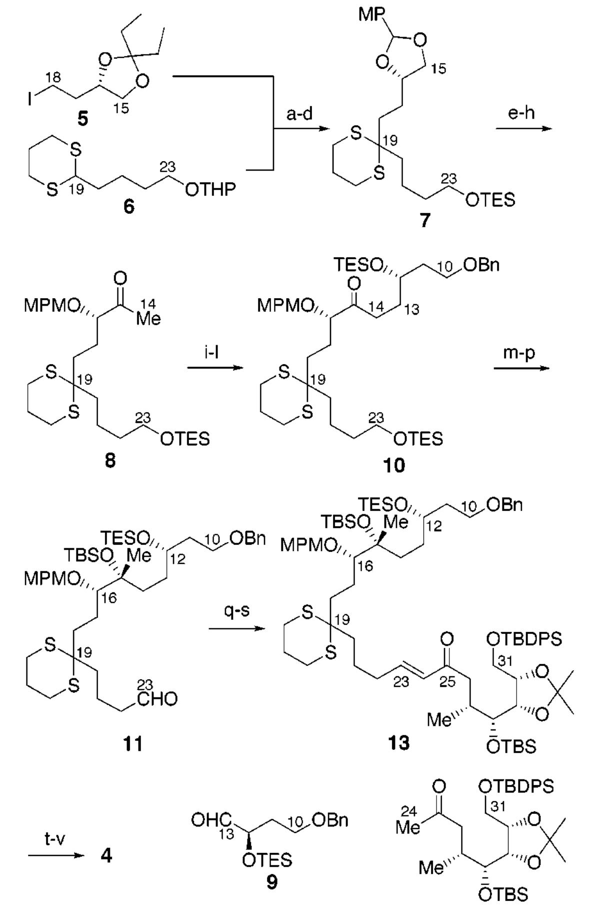


3   4

Focusing primarily on the two anomeric stabilization effects due to the axial-type orientation of the C ring oxygen atom with respect to both the B and D ring pyrans, we were thus intrigued by the feasibility of the tandem hemiketal formation/hetero-Michael reaction initiated by selective desilylation of **4** under thermodynamic conditions.

The synthetic sequence to the envisaged potential dispiroketal precursor **4** is detailed in Scheme 2. Alkylation of the dithiane **6**[11] with the iodide **5**[12] and concurrent removal of the acetal protective groups were followed by reprotection

Scheme 2[a]



[a] Reagents and conditions: (a) BuLi, THF−HMPA (10:1), −78 °C, 1 h, 95%; (b) TsOH, MeOH−H_2O, 35 h, 98%; (c) anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, 6 h, 75%; (d) TESCl, imidazole, CH_2Cl_2, 2 h, 98%; (e) DIBAL-H, CH_2Cl_2, −78 to −20 °C, 1 h, 87%; (f) SO_3·pyridine, Et_3N, DMSO, 1 h, 96%; (g) MeMgI, THF−Et_2O, −78 to −50 °C, 2 h, 92%; (h) SO_3·pyridine, Et_3N, DMSO, 1 h, 93%; (i) LiHMDS, $ZnCl_2$, THF, −78 °C, then **9**, 1.5 h, 98%; (j) Ac_2O, pyridine, DMAP, 20 h; (k) DBU, CH_2Cl_2, 0 °C, 1 h, 96% (two steps); (l) $[(Ph_3P)CuH]_6$, benzene, 10 h, 91%; (m) MeMgI, Et_2O, −78 °C, 1 h, 95%; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 4 h 93%; (o) Bu_4NF (1.05 equiv), THF−AcOH (10:1), 0 °C, 1 h, 88%; (p) SO_3·pyridine, Et_3N, DMSO, 1 h, 94%; (q) **12**, LiHMDS, THF, −78 to −50 °C, 1.5 h, 88%; (r) Ac_2O, pyridine, DMAP, 16 h; (s) DBU, CH_2Cl_2, 1 h, 89% (two steps); (t) DDQ, CH_2Cl_2−H_2O (10:1), 1 h, 93%; (u) Dess−Martin periodinane, CH_2Cl_2−pyridine, 0 °C, 1 h, 84%; (v) NCS, $AgNO_3$, γ-collidine, CH_3CN−H_2O (4:1), 0.5 h, 87%.

(5) (a) Noda, T.; Ishiwata, A.; Uemura, S.; Sakamoto, S.; Hirama, M. *Synlett* **1998**, 298. (b) Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692. (c) Nitta, A.; Ishiwata, A.; Noda, T.; Hirama, M. *Synlett* **1999**, 695.

(6) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(7) For a review on the synthesis of spiroketals, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(8) (a) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. In *Frontiers of Chemistry*; Laidler, K. J., Ed.; Pergamon Press: Oxford, 1982; pp 287−304. (b) Baker, R.; Brimble, M. A. *J. Chem. Soc., Chem. Commun.* **1985**, 78. (c) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2047.

(9) For a review on the synthesis of dispiroketals, see: Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661.

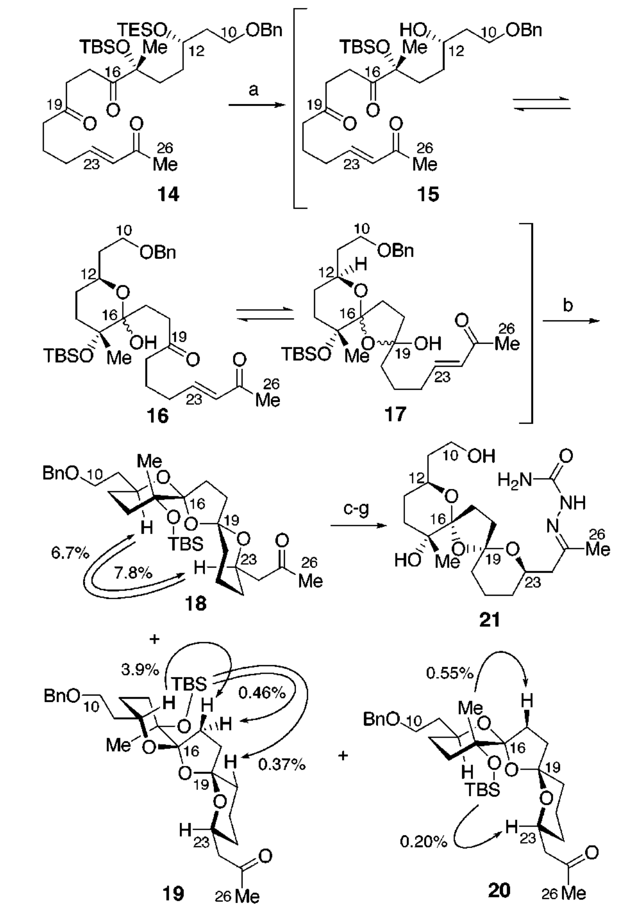
(10) (a) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. (b) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. (c) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063. (d) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (e) Toshima, H.; Aramaki, H.; Furumoto, Y.; Inamura, S.; Ichihara, A. *Tetrahedron* **1998**, *54*, 5531.

(11) McGarvey, G. J.; Stepanian, M. W. *Tetrahedron Lett.* **1996**, *37*, 5461.

of the vicinal diol as its 4-methoxybenzylidene (MP) acetal and that of the C23 hydroxyl group as its TES ether to give the advanced dithiane **7** in 68% yield. Reductive cleavage of the MP acetal group with DIBAL-H was followed by sequential Parikh−Doering oxidation,[13] addition of MeMgI, and reoxidation, affording the methyl ketone **8** in 71% yield. Aldol fragment coupling of the C14−C23 ketone **8** with the C10−C13 aldehyde **9**[14] using LiHMDS−$ZnCl_2$ followed by successive acetylation, elimination, and conjugate reduction[16] produced ketone **10** in 86% yield. Chelation-controlled alkylation of **10** with MeMgI and protection of the resulting hydroxyl group as its TBS ether were followed by selective removal of the primary TES ether and subsequent oxidation to furnish aldehyde **11** in 73% yield. At this juncture, installation of the C24−C31 fragment **12**[17] was accomplished by aldol coupling of **11** with **12** and dehydration to give the C10−C31 enone **13** in 78% yield. Deprotection of the MPM ether with DDQ followed by Dess−Martin oxidation and removal of the dithiane protective group afforded the targeted triketone **4** in 68% yield.

With a viable route to the dispiroketal precursor **4** secured, the stage was now set for the hemiketal formation/intramolecular hetero-Michael addition sequence. Prior to experimentation in the actual system with **4**, we explored the reaction of triketone **14**,[19] which is devoid of the C27− C31 subunit, to simplify structure determination of the products (Scheme 3). Initial attempts at a direct conversion of **14** to dispiroketals triggered by desilylation with Bu_4NF met with failure. Thus, we examined a stepwise procedure as follows. Upon exposure of **14** to 1 N aqueous HCl in THF, selective liberation of the C12 hydroxyl group provided an equilibrium mixture of hydroxytriketone **15** and stereoisomers of hemiketals **16** and **17**.[20] After considerable experimentation, we were gratified to find that treatment of this mixture with LiOMe (1.0 equiv) in THF−MeOH (10:1) at room temperature for 4 h afforded the desired dispiroketal **18** as the major product out of the eight possible stereoisomers in 72% yield from **14**, together with 13% combined yield of some undesired stereoisomers. Monitoring of this reaction by TLC analysis showed that the intramolecular hetero-Michael addition took place immediately to predominantly form the undesired stereoisomer **19**, which was then slowly consumed to give the desired isomer **18** as a major product. Since all the stereochemistry of the newly formed chiral centers in **19** were opposite to those in **18**, the isomerization was presumed to proceed via the reaction sequence of retro-Michael reaction, dissociation to **15**, double hemiketalization, and hetero-Michael reaction. However, no explanation for the significant kinetic preference for the formation of **19** can be offered at present. Use of NaOMe or KOMe in place of LiOMe also gave **18** as a major product via a similar process within 5 min, which was gradually isomerized to the C19, C23 epimeric dispiroketal **20** via a retro-Michael−Michael reaction process until the **18**:**20** ratio[21] of 52:48 and 54:46, respectively, was established (3−5 h). Molecular mechanics calculations using MacroModel MM2* indicate that the (16*R*,19*S*,23*S*)-isomer **20**, which is stabilized by two anomeric effects as well as by relief from the dipole−dipole

Scheme 3[a]



[a] Reagents and conditions: (a) 1 N aqueous HCl−THF (1:10), 0 °C, 1 h; (b) LiOMe (1.0 equiv), THF−MeOH (10:1), 4 h, 72%; (c) $NaBH_4$, MeOH, 0 °C, 2 h, 93%; (d) Bu_4NF, THF, reflux, 12 h, 91%; (e) SO_3·pyridine, Et_3N, DMSO, 2 h, 90%; (f) H_2, 20% $Pd(OH)_2$/C, AcOEt, 13 h, 85%; (g) $H_2NNHCONH_2$·HCl, NaOAc, EtOH, 8 h, 98% (*syn*:*anti* = 1:1.6).

(12) Toshima, H.; Ichihara, A. *Biosci*., *Biotechnol*., *Biochem*. **1995**, *59*, 497.

(13) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc*. **1967**, *89*, 5505.

(14) Compound **9** was prepared from (4*R*)-4-benzyl-3-(4-benzyloxy-1-oxobutyl)-2-oxazolidinone[15] by the following sequence: (1) NaHMDS, 2-benzenesulfonyl-3-phenyloxaziridine, THF, −90 °C, 81%; (2) TESCl, imidazole, CH_2Cl_2, 86%; (3) $LiBH_4$, H_2O, THF, 83%; (4) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 93%.

(15) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6029.

(16) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc*. **1988**, *110*, 291.

(17) Compound **12** was prepared from (3a*S*,6*S*,7*S*,7a*S*)-6-benzyloxy-2,2-dimethyl-7-hydroxytetrahydro-1,3-dioxolo[4,5-*c*]pyran[18] by the following sequence: (1) TBSCl, imidazole, DMF, 97%; (2) H_2, 20% $Pd(OH)_2$/C, AcOEt; (3) Ph_3P=CHCON(Me)OMe, benzene, reflux, 83% (two steps); (4) TBDPSCl, imidazole, DMF, 94%; (5) MeMgI, Et_2O, 0 °C, 94%; (6) MeCu(CN)Li (4 equiv), BF_3·OEt_2, THF-Et_2O, −78 °C, 80%.

(18) Schmidt, R. R.; Gohl, A. *Chem. Ber*. **1979**, *112*, 1689.

(19) Compound **14** was prepared from **11** by the following sequence: (1) Ph_3P=CHCOMe, benzene, reflux, 98%; (2) DDQ, CH_2Cl_2−H_2O (10:1), 94%; (3) Dess−Martin periodinane, CH_2Cl_2−pyridine, 0 °C, 96%; (4) NCS, $AgNO_3$, γ-collidine, CH_3CN−H_2O (4:1), 93%.

(20) In the infrared spectrum of the mixture, absorbance at 1713 cm^{-1} indicated the existence of a nonconjugated ketone carbonyl.

(21) The ratio of isomers was determined by HPLC analysis (column, Zorbax Sil, 4.6 × 250 mm; eluent, 9% AcOEt in hexane; flow rate, 1.0 mL/min).

repulsion, but experiences the severe steric interaction between the C15 TBS ether and the C23 side chain, is 0.27 kcal/mol lower in energy than the desired (16*R*,19*R*,23*R*)-isomer **18**.[22−24] Thus, it is of interest to note that only small amounts of **20** were observed with the use of LiOMe even after prolonged reaction times.[25] The origin of the sluggish isomerization of **18** to **20** under this condition is currently unclear. Stereochemical assignments of **18**, **19**, and **20** were obtained from ^{1}H NOE experiments. The stereochemistry of **18** was further established from the X-ray crystal structure of the derived semicarbazone **21** as shown in Figure 1.

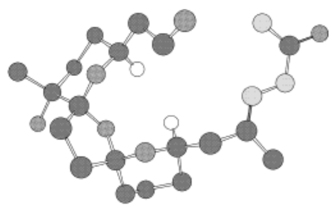
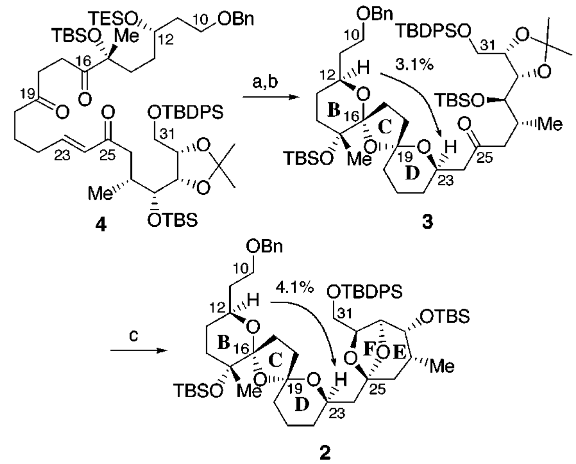


Figure 1. X-ray crystal structure of **21**, rendered in Chem3D. For the purpose of clarity, only protons attached to stereogenic centers are shown.

Encouraged by the success of the crucial spirocyclization in a model system, we then proceeded to complete the BCDEF ring system. Removal of the TES group in **4** followed by the intramolecular hetero-Michael reaction using LiOMe as a base furnished the desired dispiroketal **3** in 73% overall yield as expected from the model studies (Scheme 4). Finally, internal ketalization of **3** with CSA in CH_2Cl_2 gave the bicycloketal **2** in 68% yield.[26] The stereochemistries of **3**[27] and **2** were verified by the diagnostic ^{1}H NOE correlation between C12−H and C23−H.

In summary, we have achieved a highly stereoselective synthesis of the C10−C31 portion of pinnatoxin A. The key step, generating the 6,5,6-dispiroketal (BCD ring) system, is based on an intramolecular hetero-Michael reaction of a reversibly formed hemiketal alkoxide through the use of LiOMe. This novel process should be useful in the construction of other dispiroketals. Further efforts toward a total synthesis of pinnatoxin A are currently underway.

Scheme 4[a]



[a] Reagents and conditions: (a) 1 N aqueous HCl−THF (1:10), 0 °C, 1 h; (b) LiOMe, THF−MeOH (10:1), 5 h, 73% (two steps); (c) CSA (1.0 equiv), CH_2Cl_2, 5 h, 68%.

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Supporting Information Available: Characterization data for the compounds **2**−**4**, **7**−**14**, and **18**−**21** and an X-ray crystallographic file (CIF) for **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Molecular mechanics calculations indicate that the (16*S*,19*S*,23*S*)-isomer **19** is 2.0 kcal/mol higher in energy than **18**.

(23) The other five stereoisomers were estimated to be 3.0−7.6 kcal/mol higher in energy than **18**.

(24) In the case of 1,7,9-trioxadispiro[5.1.5.3]hexadecane, the *cis*-isomer, wherein both O1 and O9 are axially disposed about the central ring, is reported to be less stable by 0.3−0.7 kcal/mol than the *trans*-isomer without the destabilizing dipole repulsion: McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Ellena, J. F. *Tetrahedron Lett*. **1996**, *37*, 5465.

(25) The ratios of **18**, **19**, **20**, and another unidentified isomer after 4 and 48 h were 85:8:3:4 and 82:8:6:4, respectively.

(26) The isomerization of **2** to its C19 epimer, if any, could not be found under the ketalization conditions (CSA in CH_2Cl_2). In this respect, Murai and co-workers reported that the C19 epimer of the closely related dispiroketal compound isomerized under similar conditions to give a 4.3:1 mixture of C19 epimeric dispiroketals, with the undesired configuration favored.[4c] However, they did not mention the result of epimerization of the desired isomer.

(27) The stereochemistry of **3** was further confirmed by comparison of the ^{1}H NMR spectrum with the sample obtained from **18** by the following sequence: (1) LiHMDS, THF, −78 °C, then C27−C31 aldehyde; (2) Ac_2O, pyridine, CH_2Cl_2; (3) DBU, CH_2Cl_2, 0 °C, 20% (three steps); (4) MeCu(CN)Li (4 equiv), $BF_3{\cdot}OEt_2$, THF−Et_2O, −78 °C, 73%.