ORGANIC LETTERS

2004
Vol. 6, No. 12
1939−1942

Stereoselective Ketal-Tethered Intramolecular Diels–Alder Cycloadditions. An Approach to the 2-Oxadecalin Spiroketal Core of Antifungal Agent Fusidilactone C

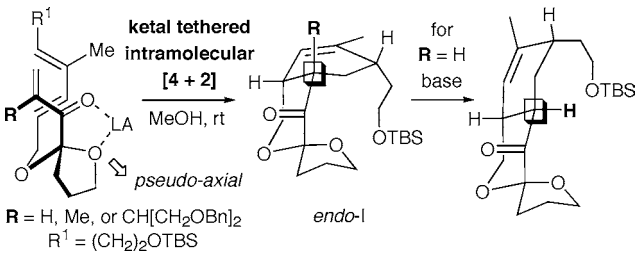
Jiashi Wang, Richard P. Hsung,* and Sunil K. Ghosh

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

hsung@chem.umn.edu

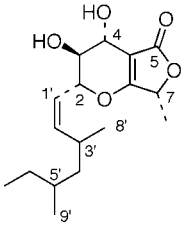
Received March 9, 2004

ABSTRACT

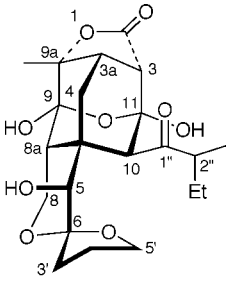


An approach toward the 2-oxadecalin spiroketal core of fusidilactone C via a rare ketal-tethered intramolecular Diels–Alder cycloaddition is described here. This intramolecular Diels–Alder cycloaddition is highly endo-selective and overall depended upon the nature of solvents and Lewis acids. We also observed some remarkable rate acceleration in MeOH.

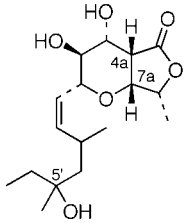
Recently, three new polycyclic lactones, fusidilactones A−C [**1**−**3**], were isolated from the culture broth of *fusidium* sp., along with *cis*-4-hydroxy-6-deoxyscytalone [**4**].[1] *Fusidium* sp. is a fungal endophyte isolated from the leaves of *Mentha arvensis*, which is found in Germany, and ether extracts of its cultures show promising antifungal activities toward *Eurotium repens* and *Fusarium oxysporum*, as well as other moderate antibacterial activities.[1] We became interested first in fusidilactones A and B [**1** and **2**] because of our ongoing program in natural product syntheses employing a tandem Knoevenagel-pericyclic ring-closure[2] or a stepwise formal *oxa*-[3 + 3] cycloaddition strategy.[3−7] However, fusidilactone C [**3**] possesses a structural complexity rivaling that of tetrodotoxin,[8,9] thereby representing a unique challenge. Fusidilactone C [**3**] comprises a rare oxoadamantane structural motif[1,10] and, in addition to its spiroketal, also has an unusual ether-bridged hemiacetal held in place by the rigid frame of oxoadamantane.[11] We report here our initial efforts toward the synthesis of the 2-oxadecalin spiroketal of fusidilactone C featuring a ketal-tethered intramolecular Diels−Alder cycloaddition [IMDA].



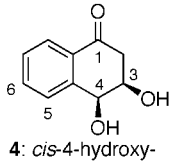
1: fusidilactone A



3: fusidilactone C



2: fusidilactone B



4: *cis*-4-hydroxy-6-deoxyscytalone

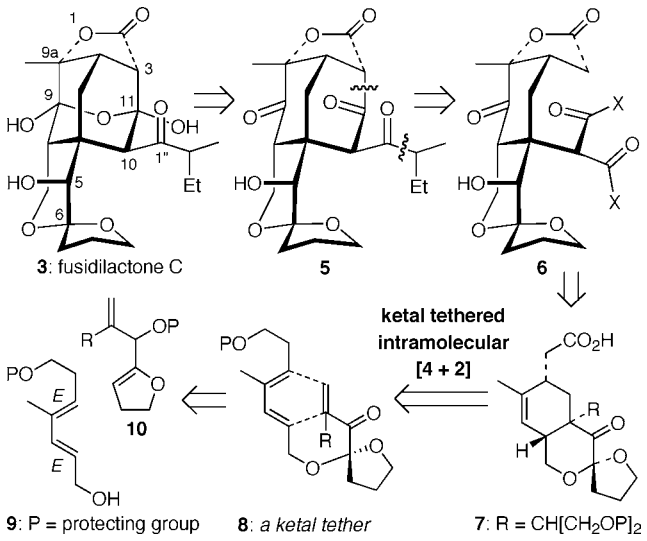
(1) Krohn, K.; Biele, C.; Drogies, K.-H.; Steingröver, K.; Aust, H.-J.; Draeger, S.; Schulz, B. *Eur. J. Org. Chem.* **2002**, 2331.

(2) For reviews, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47.

10.1021/ol0495624 CCC: $27.50
Published on Web 05/11/2004

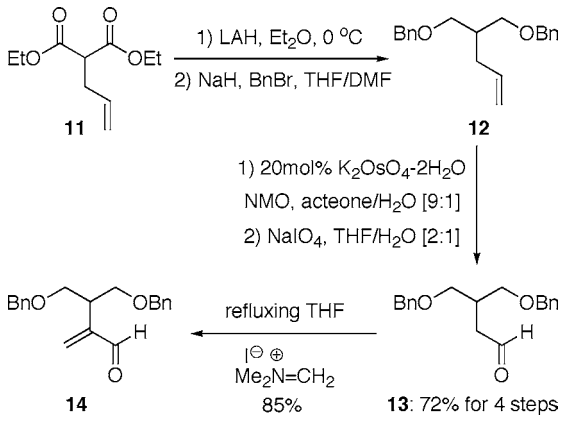
Retrosynthetically, we envisioned that the *oxo*-bridge of the two hemiacetals in fusidilactone C [**3**] could be derived from hydration of diketone **5**, which could be attained from lactone **6** via a Dieckmann-type condensation or an aldol reaction [Scheme 1]. The lactone ring in **6** may be furnished

Scheme 1



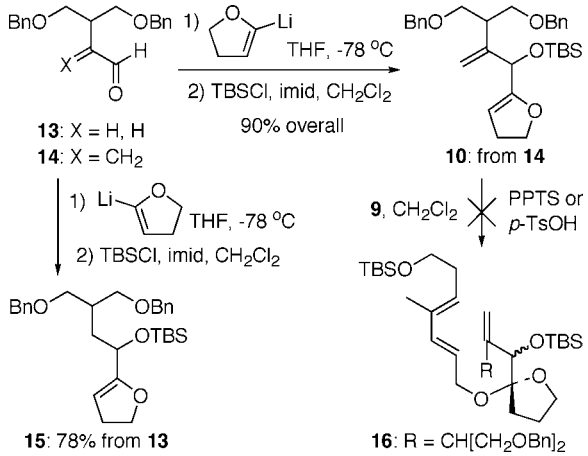
via an iodolactonization of acid **7**, a key advanced intermediate that contains the 2-oxadecalin spiroketal of fusidilactone C [**3**]. Synthesis of **7** would feature a ketal-tethered intramolecular [4 + 2] cycloaddition reaction, preferably in an exo-manner using ketal **8**, which can be accessed from (*E*)-(*E*)-diene **9** and dihydrofuran **10**.

Scheme 2



To construct the ketal precursor **8** for the key Diels−Alder cycloaddition, dihydrofuran **10**[12] was prepared as shown in Schemes 2 and 3. LAH reduction of 2-allyl diethyl malonate **11** followed by protection of the diol intermediate using BnBr led to alkene **12**. Subsequent dihydroxylation followed by periodate cleavage furnished aldehyde **13** in 72% yield over four steps [Scheme 2]. Refluxing aldehyde **13** with Eschenmoser's salt in THF afforded enal **14** in 85% yield.

Scheme 3



To attach both the diene and dienophile onto a ketal tether, we first deprotonated dihydrofuran using *t*-BuLi at −78 °C,

(3) For method development, see: (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (b) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509. (c) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*,1729.

(4) For applications in natural product synthesis, see: (a) Cole, K. P.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4843. (b) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (c) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L. L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311. (d) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 8791.

(5) (a) For a review, see: Hsung R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. *Trends Heterocycl. Chem.* **2001**, *7*, 1−24. (b) For a recent review on stepwise [3 + 3] formal cycloadditions leading to bridged carbocycles, pyridines, or pyridones using enamines, enaminones, enol ethers, or β-ketoesters, see: Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27.

(6) For recent related studies in syntheses of oxygen heterocycles, see: (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554. (b) Shen, K.-H.; Lush, S. F.; Chen, T.-L.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 8106. (c) Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, 49.

(7) For a recent report on fusidilactone B, see: Gao, X.; Snider, B. B. *J. Org. Chem.* **2004**, *69*, ASAP.

(8) For isolation and biological activities, see: (a) Kao, C. Y., Levinson, S. R., Eds. *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel;* New York Academy of Sciences: New York, 1986; Vol. 479. (b) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059. (c) Mosher, H. S.; Fuhrman, F. A.; Buchwald, H. D.; Fischer, H. G. *Science* **1964**, *144*, 1100. (d) Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, R.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull.* **1964**, *12*, 1357. (e) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49. (f) Narahashi, T. J. *Toxicol., Toxin Rev.* **2001**, *20*, 67−84.

(9) For total syntheses and synthetic efforts, see: (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (b) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (c) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Pure Appl. Chem.* **2003**, *75*, 251. (d) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217. (e) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219. (f) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619. (g) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323.

(10) For a rare example, see: Ayer, W. A.; Browne, L. M.; Singer, A. W.; Elgersma, P. *Can. J. Chem.* **1990**, *68*, 1300.

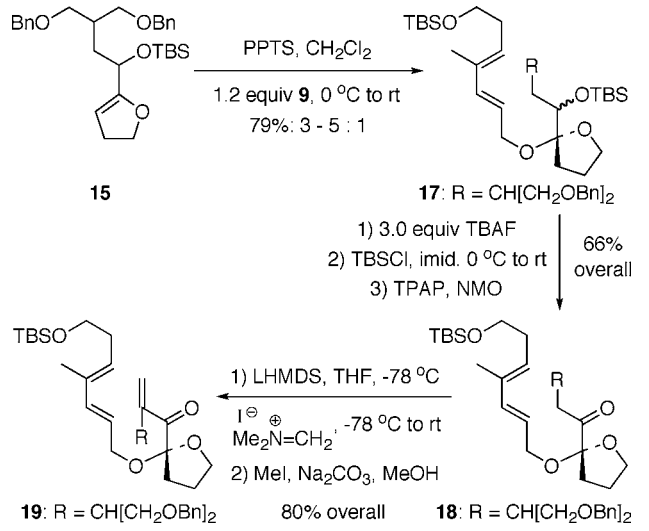
(11) For a rare example, see: Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 3162.

(12) All new compounds are characterized using ^{1}H NMR, ^{13}C NMR, FTIR, and LRMS.

and addition of either aldehyde **13** or enal **14** led to dihydrofurans **15** and **10** in 78 and 90% overall yields, respectively, after protection with TBSCl group [Scheme 3]. The rationale for initially using a large TBS protecting group was the concern over the stability of **10** under acidic conditions. As it turned out, attempts to prepare ketal **16** from dihydrofuran **10** and diene **9**[13] using PPTS or *p*-TsOH were unsuccessful, for **10** decomposed under these acidic conditions presumably due to ionization of the TBS-protected secondary hydroxyl group and formation of a divinyl cation-type intermediate. Thus, dihydrofuran **15** was pursued as an alternative to construct the Diels−Alder cycloaddition precursor.

Ketal **17** was successfully prepared in 79% yield as a separable isomeric mixture with a ratio of 3−5:1 from dihydrofuran **15** and diene **9** using PPTS [Scheme 4]. The

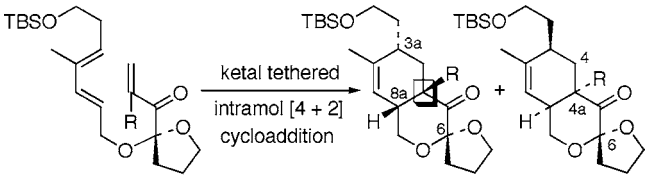
Scheme 4

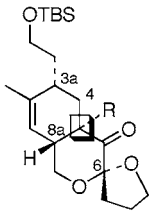


mixture was subjected to double desilylation[14] using 3.0 equiv of TBAF, followed by monoprotection of the primary alcohol, and subsequent TPAP−NMO oxidation of the secondary alcohol afforded ketone **18** in 66% yield over three steps. The final enal formation, furnishing the Diels−Alder cycloaddition precursor **19**, was accomplished in 80% overall yield using Eschenmoser's salt, but the β-elimination of the dimethyl amino group required the use of MeI and Na_2CO_3 in MeOH.

Because it was surprising to find that IMDA employing a ketal tether is rare,[15−19] we examined the reaction of ketal **19** in some detail as shown in Scheme 5. The cycloaddition was found to be not only feasible but also exceptionally fast, especially in MeOH [entry 1], leading to cycloadducts **20a**

Scheme 5





entry	solvent	additive	temp	yield	**20a** : **b**
1	MeOH	none	rt	90%	12 : 1
2	toluene	none	rt	10	1 : 1
3	toluene	none	110 °C	70	1.4 : 1
4	undecane	none	200 °C	80	1 : 1
5	CH_2Cl_2	$ZnCl_2$	-78 °C - rt	85	100 : 0
6	CH_2Cl_2	$ZnOTf_2$	-78 °C - rt	82	100 : 0
7	CH_2Cl_2	$CuOTf_2$	-78 °C - rt	80	100 : 0
8	CH_2Cl_2	$MgBr_2$-Et_2O	-78 °C - rt	80	100 : 0
9	CH_2Cl_2	$AlEt_2Cl$	-78 °C - rt	75	100 : 0
10	CH_2Cl_2	BF_3-Et_2O	-78 °C - rt	decomposition	

and **20b** as a 12:1 mixture. Initial NOE experiments of desilylated **20a** and **20b**[13] suggested that the ring junction [C4a−C8a] of the 2-oxadecalin was cis for both cycloadducts, thereby implying endo-cycloaddition pathways. An unambiguous assignment of **20a** was accomplished using the X-ray structure of a derivative of cycloadduct **22a**[20] [Scheme 5], derived from the simplified ketal precursor **21** [R = Me].[20] These combined assignments rule out the exo-I product **20c**.

On the other hand, in toluene at room temperature, the reaction was very slow [entry 2], although in toluene at 110 °C [entry 3] and in undecane at 200 °C [entry 4], reactions

(13) Details for the preparation of diene **9** can be found in Supporting Information. All NOE experiments and analyses of key coupling constants can also be found in Supporting Information.

(14) After solidifying this as an appropriate route to the cycloaddition ketal precursor, an acetyl protecting group for the secondary hydroxyl group was proven to be useful on related substrates, thereby avoiding this sequence of double-deprotection and reprotection of the primary hydroxyl group.

(15) For reviews on IMDA, see: (a) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820. (b) Craig, D. In *Stereoselective Synthesis*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Ed.; Thieme: Stuttgardt, 1996; Vol. E21c, p 2872. (c) Roush, W. R. In *Advances in Cycloaddition*, Curran, D. P., Ed., JAI: Greenwich, CT, 1990; Vol. 2, p91. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (e) Ciganek, E. *Org. React.* **1984**, *32*, 1. (f) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (g) Taber, D. F. *Intramolecular Diels−Alder Reactions and Alder-Ene Reactions*; Springer: Berlin, 1984.

(16) For pioneering work on acetal-tethered IMDAs, see: (a) Boeckman, R, K., Jr.; Flann, C. J. *Tetrahedron Lett.* **1983**, *24*, 1655. (b) Boeckman, R, K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095.

(17) For recent examples of ketal- or aminal-tethered IMDAs, see: (a) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987. (b) Roush, W. R.; Barba, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781. (c) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045. (d) Ainsworth, P. J.; Craig, D.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 8937. (e) Jung, M. E.; Street, L. J. *Heterocycles* **1988**, *27*, 45. (f) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327.

(18) For reviews on *ortho*-quinone ketal-tethered Diels−Alder reactions, see: (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (b) Quideau, S.; Pouységu, L. *Org. Prep. Proc. Int.* **1999**, *31*, 617.

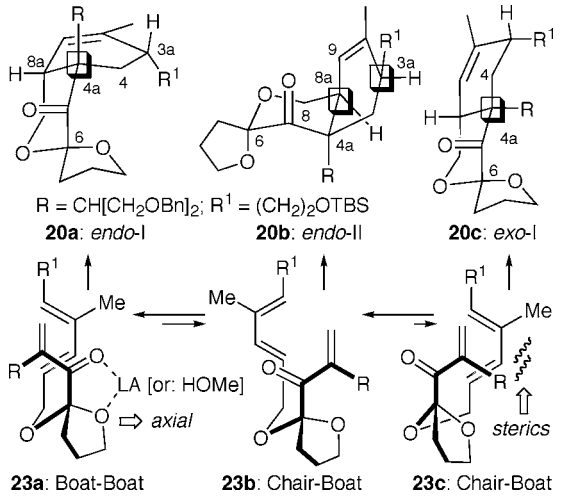
(19) For the use of silyl ketal-tethered IMDAs, see: (a) Stork, G.; Chan, T. Y.; Breault, G. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (b) Gillard, J. A.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. (c) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885. For leading references on silyl ketal-tethered IMDAs from Craig's group, see: (d) Ainsworth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 11601. (e) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 4073 and 6165.

proceeded well and led to the improved formation of endo-II product with the ratio of **20a**:**20b** being 1:1 and 1.4:1, respectively. In comparison with the cycloaddition in MeOH, along with the observation that a substantial amount [10−15%] of **20a** already formed during the preparation of **19** in MeOH at room temperature [for the β-elimination of the dimethyl amino group], there is a pronounced solvent effect on the reactivity and stereoselectivity of this ketal-tethered IMDA with the protic solvent providing a much enhanced reaction rate[21] as well as stereoselectivity.

Finally, the use of various Lewis acids in CH_2Cl_2 favored exclusively the formation of endo-I product **20a** [entries 5−9]. It is noteworthy that with the exception of $BF_3{\cdot}Et_2O$ [entry 10], the ketal motif is very robust under these Lewis acidic conditions.

After the stereochemical assignment of **20a** and **20b** was established, a mechanistic assessment revealed that both endo transitions states [**23a**, endo-I, boat-boat; **23b**, endo-II, chair-boat] likely have an advantage over the exo-pathway [**23c**, exo-I, chair-boat] due to the steric interaction between the diene and the R group in the dienophile [Scheme 6].

Scheme 6

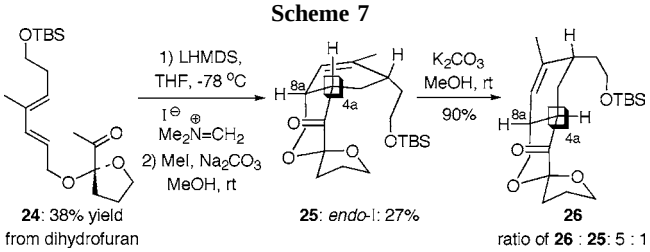


Calculations [Spartan: G-31G*/B3LYP] showed that **23a** is favored by ∼1.57 kcal mol^{-1} over **23c**, while **23a** is favored over **23b** by a much smaller difference of ∼0.11 kcal mol^{-1}.

These three transition states were chosen also on the basis of the assumption that the furan oxygen would prefer a pseudoaxial position given an anomeric effect of ∼1.5 kcal mol^{-1}.[22] This assessment also supports the observation that the formation of **20a** was completely favored using Lewis acids [or a proton from MeOH] that could chelate to the carbonyl oxygen and the furan oxygen, which is the stronger coordinating of the two ketal oxygen atoms.

Unsuccessful preparation of the exo-cycloadduct **20c** does not deter our effort toward a total synthesis of fusidilactone C [**3**] because both endo-cycloadducts **20a** and **20b** are viable entries to the *trans*-2-oxadecalin spiroketal of fusidilactone C [**3**] via appropriate stereochemical adjustments. To demonstrate that we could access the *trans*-2-oxadecalin spiroketal motif in **3**, ketone **24** was prepared from dihydrofuran and diene **9** in 38% overall yield in five steps.[20] During the subsequent enone formation via addition of Eschenmoser's salt to the anion generated from **24** and β-elimination in MeOH at room temperature, Diels−Alder cycloaddition already occurred to give the endo-I product **25** as a single diastereomer in an unoptimized 27% overall yield from **24**. An equal amount of the product resulting from the addition of MeOH to the enone intermediate was also found. Epimerization of C4a in **25** using K_2CO_3 and MeOH afforded **26** in 90% yield as a mixture with a ratio of 5:1 in favor of **26** that contains the *trans*-2-oxadecalin spiroketal. The relative stereochemistry in both **25** and **26** was assigned using NOE experiments as well as coupling constants.[13]

Scheme 7



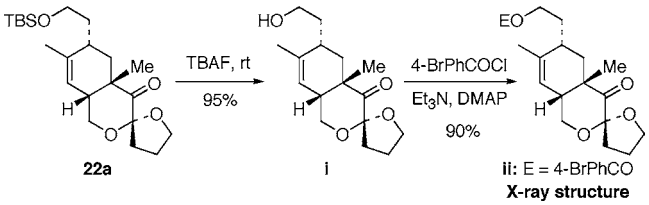
We have communicated here an approach toward the 2-oxadecalin spiroketal frame of fusidilactone C via an intramolecular Diels−Alder cycloaddition, featuring a chiral ketal tether, with a remarkable solvent effect on the rate and stereoselectivity of this cycloaddition. Efforts in completing a total synthesis of fusidilactone C, and in developing ketal-tethered IMDA reactions, are currently underway.

Acknowledgment. R.P.H. thanks The Camille Dreyfus Foundations for financial support, and J.W. thanks UMN for a prestigious Lester C. and Joan Krogh Graduate Dissertation Fellowship. We thank Mr. Aleksey I. Gerasyuto for providing calculations.

Supporting Information Available: Experimental as well as ^{1}H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0495624

(20) Preparations of **21** and **24** are described in Supporting Information. The X-ray structure was obtained after desilylation of cycloadduct **22a** and acylation of **i** with 4-bromobenzoyl chloride that gave crystalline *para*-bromobenzoic ester **ii**. Details are in Supporting Information.



(21) For a recent example on hydrogen bonding-promoted hetero-Diels−Alder cycloadditions, see: (a) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. For some earlier examples on the effect of aqueous or protic solvents on Diels−Alder cycloadditions, see: (b) Grieco, P. A.; Garner, P.; He, Z.-M. *Tetrahedron Lett.* **1983**, *24*, 1897. (c) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901.

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