HETEROCYCLES, Vol. 82, No. 2, 2011, pp. 1379 - 1409. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd July, 2010, Accepted, 12th August, 2010, Published online, 13th August, 2010
DOI: 10.3987/COM-10-S(E)93

A CYCLIC ACETAL TETHERED INTRAMOLECULAR DIELS-ALDER CYCLOADDITION. STUDIES DIRECTED TOWARD A TOTAL SYNTHESIS OF (±)-FUSIDILACTONE C†

Sunil K. Ghosh, Yonggang Wei, Aleksey I. Gerasyuto, John B. Feltenberger, Jiashi Wang,* and Richard P. Hsung*

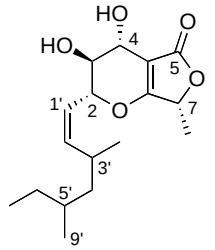
Division of Pharmaceutical Sciences, School of Pharmacy, University of Wisconsin, Madison, WI 53705, U. S. A.
jwang@ptcbio.com, *rhsung@wisc.edu*

Abstract – Efforts toward a synthesis of (±)-fusidilactone C is described here featuring a novel cyclic acetal tethered intramolecular Diels-Alder strategy. This unique and facile IMDA turned out to be highly *endo*-selective [*endo-I* and *endo-II*], as assessed from our mechanistic analyses. When using protic solvents or Lewis acids, the *endo-I* selectivity was greatly enhanced. Thus, it proved to be a real challenge to circumvent this excellent stereochemical outcome, which is undesired for the total synthesis, as an *exo-II* selectivity is desired. Progress was made to use the *endo-II* cycloadduct and to access the desired *trans*-2-oxadecalin motif in (±)-fusidilactone C.

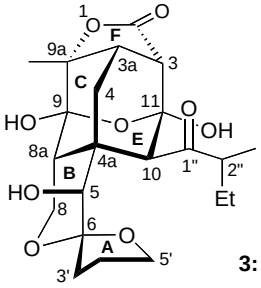
†This paper is dedicated to Professor Albert Eschenmoser with the utmost admiration and deepest respect on the special occasion of his 85th birthday.

INTRODUCTION

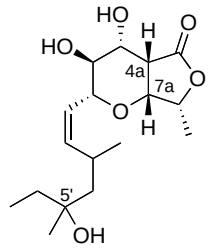
(+)-Fusidilactone C [**3**], a highly-oxygenated polycyclic lactone, along with simpler family members fusidilactones A and B [**1** and **2** in Scheme 1], were isolated from the culture broth of *fusidium* sp.,[1] a fungal endophyte found in the leaves of *Mentha arvensis* in Germany. Organic extracts from this culture broth reveal potent antifungal activities against *Eurotium repens* and *Fusarium oxysporum*, and they also possess moderate antimicrobial activities against *E. coli, Bacillus megaterium* and *Chlorella fus*ca.[1] While fusidilactones A and B contain six-membered oxygen heterocycle fused to a γ-lactone with the only difference being the oxidation state at the ring junction and side chain, what drew our attention was the unique structural motif of fusidilactone C, which poses a tremendous amount of challenge.



1: (+)-fusidilactone A

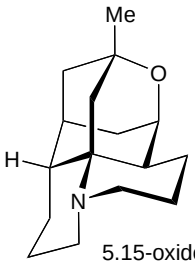


3: (+)-fusidilactone C

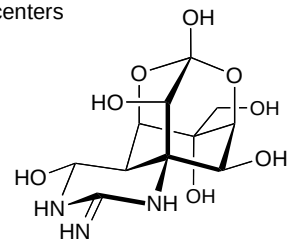


2: (+)-fusidilactone B

***** the CDE-ring is a rare oxoadamantane core
***** the oxo-bridge is a bis-hemiacetal
***** the bridged lactone F-ring
***** highly substituted cyclohexane C-ring
***** trans-fusion at the BC-ring junction
***** the spiroketal moiety at the bottom in AB-ring
***** severe 1,3-diaxial interaction between the axial substituents at C4a and C6
***** 11 stereogenic centers



5.15-oxidolycopodane



tetrodotoxin

Scheme 1. (+)-Fusidilactone C

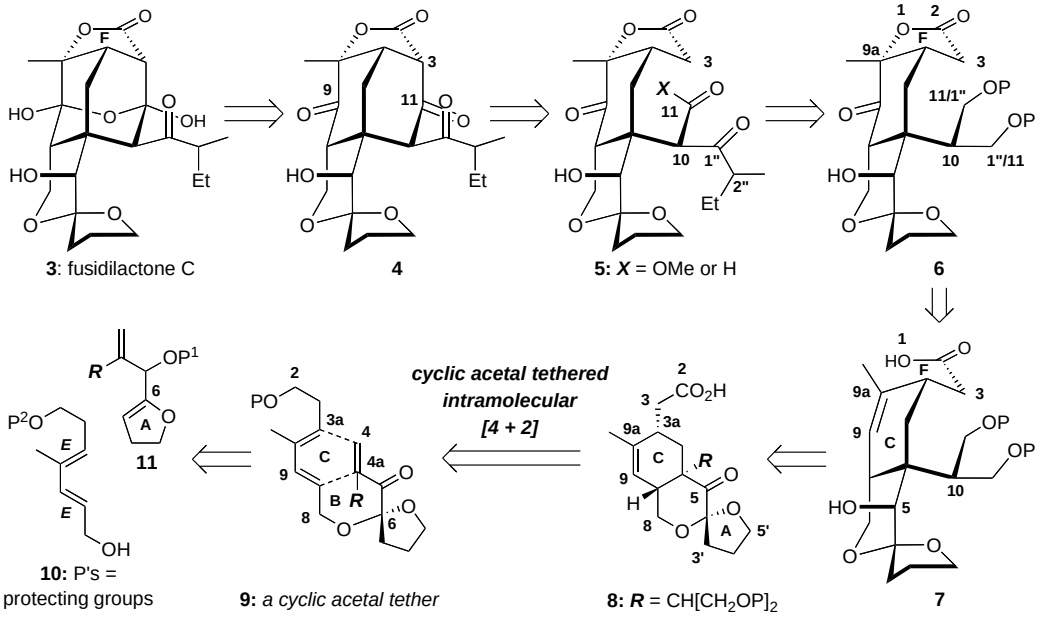
Foremost, (+)-fusidilactone C [**3**] features a rare oxo-adamantane skeleton comprised of an unusual ether-bridged bis-hemiacetal motif.[2] The only other known natural product containing an oxo-adamantane motif is 5,15-oxidolycopodane,[3] although tetrodotoxin possesses a dioxo-admantane core.[4,5] In addition, **3** embodies a bridged γ-lactone F-ring, a highly substituted cyclohexane C-ring, a *trans*-fused 2-oxadecalin as the BC-ring, and a spiroketal as the AB-ring but with severe 1,3-diaxial interaction from axial substituents at C4a and C6. Last, but not the least, (+)-fusidilactone C [**3**] also has 11 stereogenic centers with configuration at C2" remaining unassigned. To date, besides Snider's synthesis of B [see **2**],[6] and our efforts toward **3**,[7] there has not been any other reports in this family of natural products. We report here our progress toward a total synthesis of (±)-fusidilactone C.

RESULTS AND DISCUSSION

1. Retrosynthetic Analysis

Retrosynthetically, the *oxo*-bridge of the bis-hemiacetal in fusidilactone C [**3**] could be derived from hydration of C9,11-diketone **4**, which could be envisioned from tetracyclic lactone **5** via a Dieckmann condensation [X = OMe] or an aldol reaction [X = H] to re-connect C3- and C11 [**Scheme 2**]. These analyses allowed us to simplify the C11-C1" β-diketo motif in **5** to the protected C11-C1" diol **6** because

either C11 or C1" could serve as the precursor for Dieckmann or aldol, and the C10-stereochemistry can be regulated through means of epimerization.



Scheme 2. A Cyclic Acetal Tethered IMDA Approach to (±)-Fusidilactone C

The lactone F-ring in **6** could be constructed in two different ways: Through an esterification route connecting O1-C2, or via an iodolactonization of C9a-C9 olefin using acid **7** to connect O1-C9a, which is shown here as our first option. Acid **7** is just an oxidation state away from tricycle **8** at C5-OH, and tricycle **8**, containing the 2-oxadecalinic BC ring and the spiroketal AB-ring of fusidilactone C [**3**], would represent a key advanced intermediate that we would like to target.

Synthesis of the advanced tricycle **8** would then feature a cyclic acetal tethered intramolecular Diels-Alder cycloaddition [IMDA] preferably in an *exo*-manner using cyclic acetal **9**, leading to an efficient approach for completing the formation of not only both B and C rings of the 2-oxadecalinic motif but also the AB-spiroketal moiety. This cyclic acetal tethered IMDA represents a novel strategy developed in our lab. Cyclic acetal **9** could be accessed from *E*-*E*-diene **10** and dihydrofuran **11** through simple Brønsted acid promoted acetal formation.

2. The Cyclic Acetal Tethered Intramolecular Diels-Alder Cycloaddition

Cyclic acetal-tethered intramolecular Diels-Alder cycloaddition reaction [IMDA][8] should represent a powerful strategy for constructing polycyclic spiroketals. There can be four possibilities as shown in **Figure 1**: ***Type a*** is the most commonly seen with both reactive partners A and B [dienes and a dienophiles] being connected at the acetal carbon C2. However, in these cases, it is clear that the acetal predominately serves as a carbonyl-protecting group. Another common scenario is ***Type b***, and the

distinction here is not as clear whether the acetal is used to protect the diol or to link together A and B, although most belong the former case. Some interesting examples are shown here for ***Type b***. The best examples of ***Type b*** are from Craig's[9] IMDA using acetal **12**.

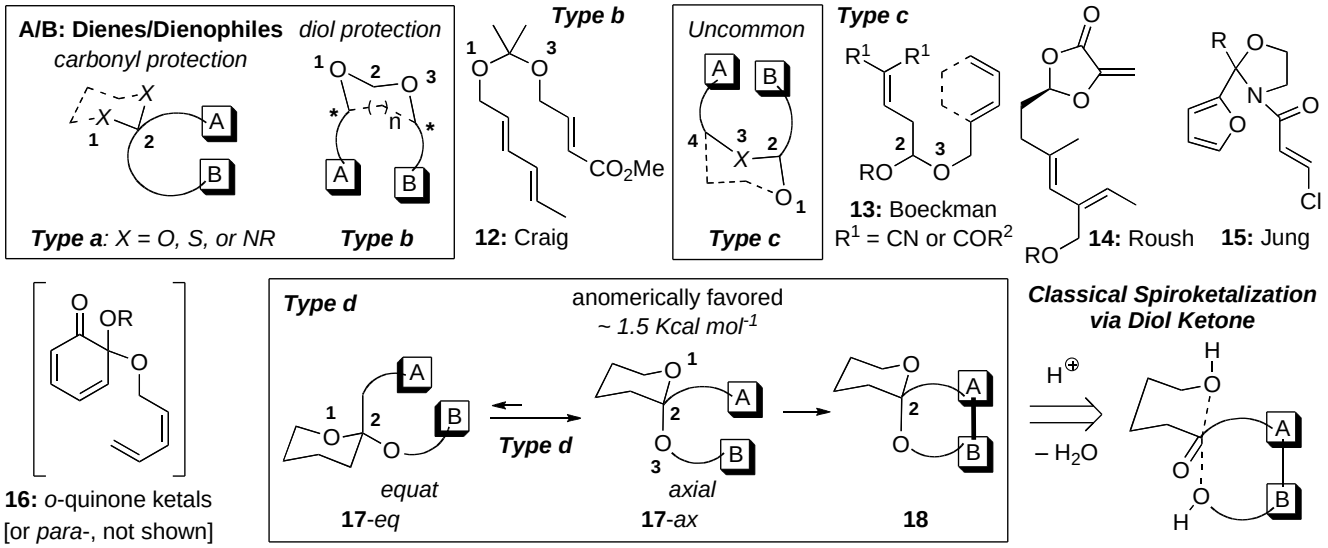


Figure 1. General Classifications of Acetal Tethered IMDA

Thirdly, ***Type c***, although uncommon, represents a more accurate concept of acetal tethered intramolecular reactions. There are only a few precedents for IMDA in this category. Notable examples of ***Type c*** would be Boeckman's acetal tethered IMDA using **13**,[10] Roush's dioxolanone **14**,[11] and Jung's[12] [**15**] aminal tether. Chemistry of *ortho*- [**16**] or *para*-quinone ketals [not shown] is quite well known, but these intermediates are usually generated *in situ*.[13] Finally, ***Type d*** can be classified as cyclic acetal tethered systems, and IMDA reactions between A and B would lead to the construction of spiroketals. Examples in this classification are virtually unknown until our work.

The lack of interest in using acetals as tethers could be due to their overwhelming reputation as protecting groups for carbonyls and alcohols and their perceived instability under hydrolytic conditions. However, we recognized that developing cyclic acetal tethered IMDA in ***Type d*** would allow us to examine the potential influence of the anomeric effect on the conformational preference for **17-*ax*** over **17-*eq*** [**Figure 1**] [~ 1.5 kcal mol^{-1} *per* anomeric effect],[14,15] which could impact on both reactivity and the stereochemical outcome of an IMDA.[7,16,17] In addition, pursuing ***Type d*-IMDA** should prove to be significant in bringing forth a fundamentally different approach to constructing spiroketals **18** or related natural products.[18-20]

3. Possible Stereochemical Outcome of the Cyclic Acetal Tethered IMDA

Given the novelty of this cyclic acetal tethered IMDA strategy, we first analyzed all possible transition states for the cycloaddition. As shown in **Figure 2**, there can be 4 possible *endo*-transition states: TS-**19**^{n1} [TS-*endo-I*: Boat-Boat conformation], TS-**19**^{n2} [TS-*endo-II*: Chair-Boat conformation], TS-**20**^{n1} [TS-*endo-I*: Chair-Boat conformation], and TS-**20**^{n2} [TS-*endo-II*: Chair-Boat conformation]. The major difference between TS-**19** and TS-**20** is the position of the furanyl oxygen atom with respect to the formation of pending 3-pyranone [or the actual B-ring]: *Pseudo*-axial [***ax***] in TS-**19** and *pseudo*-equatorial [***eq***] TS-**20**. Based on an anomeric effect worthy of ~1.5 kcal mol^{-1},[18] and our related work demonstrating a profound anomeric control of transition state conformation,[16] the furanyl oxygen would prefer a pseudo-axial position, leading to TS-**19** being preferred.

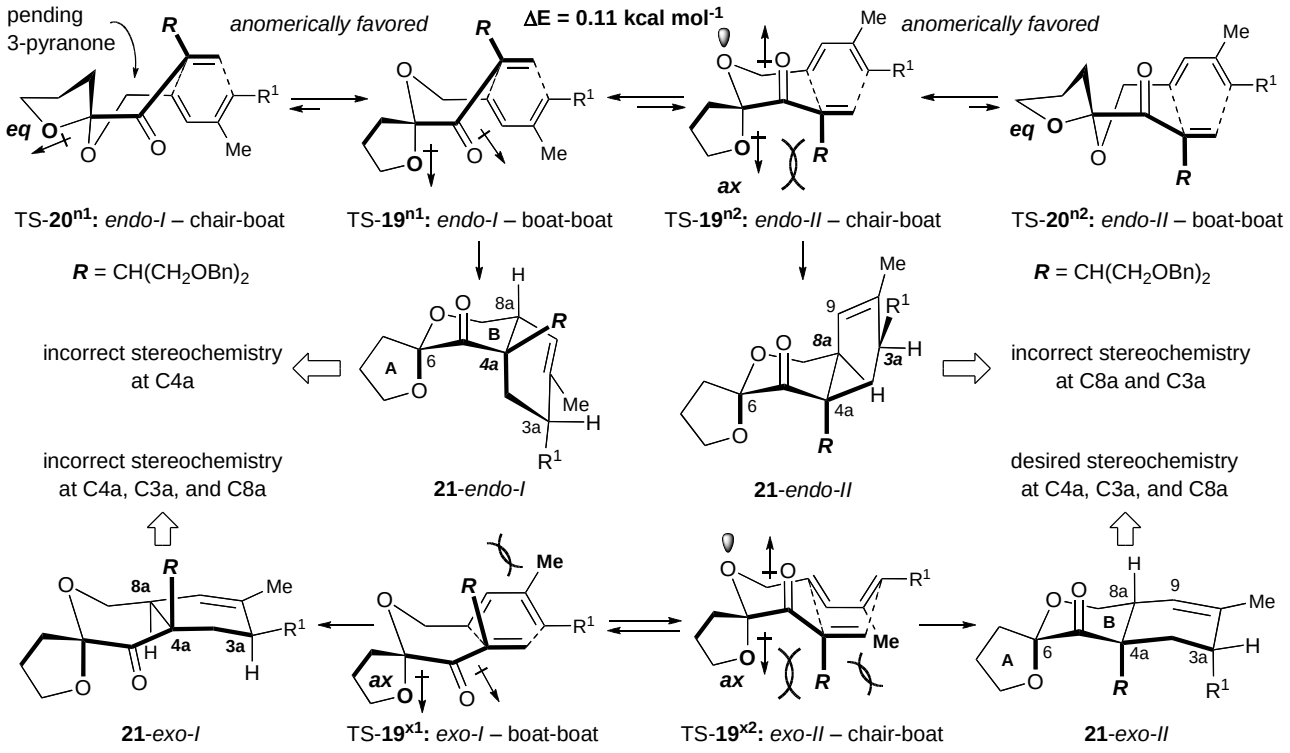


Figure 2. Stereochemical Analysis of the Key Cyclic Acetal Tethered IMDA

Likewise, we focused on analyzing the two *exo*-transition states, TS-**19**^{x1} [TS-*exo-I*: Boat-Boat] and TS-**19**^{x2} [TS-*exo-II*: Chair-Boat], in which furanyl oxygen is pseudo-axial. Calculations [Spartan^{TM}: G-31G*/B3LYP] distinctly revealed that both *endo*-transition states TS-**19**^{n1} and TS-**19**^{n2} [for ***R*** = $CH(CH_2OBn)_2$] are favored over *exo*-transition states TS-**19**^{x1} and TS-**19**^{x2} by ~1.40-1.57 kcal mol^{-1}, while the difference between TS-**19**^{n1} and TS-**19**^{n2} [and that of TS-**19**^{x1} and TS-**19**^{x2}] is very small [~ 0.11 kcal mol^{-1}] in favored TS-**19**^{n1}. These mechanistic assessments were not overtly surprising because one still expects the *endo*-rule to be comparably significant in IMDA reactions as in intermolecular ones, although *exo*-transition state is well known to play a prominent role in IMDAs. In addition, it is

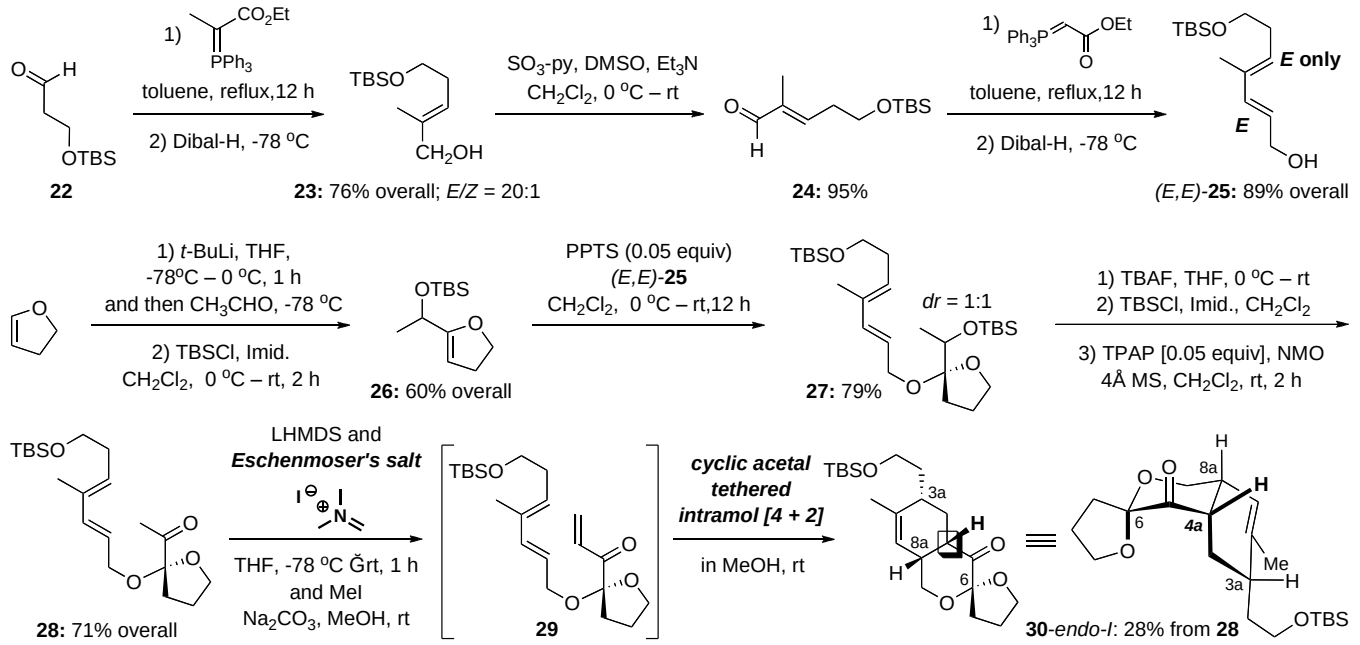
conceivable that both TS-**19**^{n1} and TS-**19**^{n2} have an advantage over TS-**19**^{x1} or TS-**19**^{x2} because of the steric interaction between the diene and the ***R*** group [on the dienophile] in the *exo*-transition state. However, we had gauged TS-**19**^{n1} to be less favorable than TS-**19**^{n2} due to the unfavorable dipole between the carbonyl group and C-O bond in the furan ring, and that TS-**19**^{n2} pertains a Chair-Boat reactive conformation. On the other hand, it is conceivable that the repulsion between the lone-pair electrons on the pending 3-pyanone oxygen atom and the carbonyl oxygen atom, as well as 1,3-diaxial interaction between the ***R*** group and the furan could lead a significant destabilization of TS-**19**^{n2}.

From these analyses, the most desired pathway TS-**19**^{x2} appeared to be far reaching, but that did not deter our efforts toward a total synthesis of fusidilactone C. While the TS-**19**^{x1} pathway would lead to a real dead end in terms of a total synthesis of fusidilactone C, as all three key stereocenters in the cycloadduct **21**-*exo-I* are incorrect, IMDA cycloadducts **21**-*endo-I* and **21**-*endo-II* attained through TS-**19**^{n1} or TS-**19**^{n2}, respectively, could still represent viable entries to the *trans*-2-oxadecalin spiroketal of fusidilactone C [**3**] via appropriate stereochemical adjustments. However, given the preconceived notion that the steric interaction between the diene motif and the ***R*** group [$CH(CH_2OBn)_2$] in the dienophiles is destabilizing the two *exo* transitions states, we first pursued the following model studies using substrates in which ***R*** = H or Me.

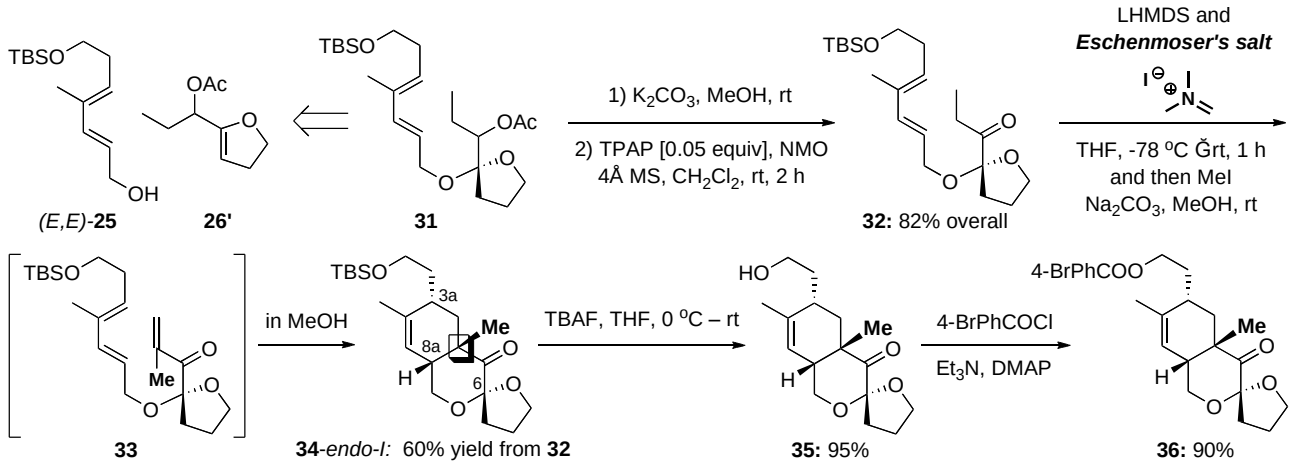
4. Model Studies on the Cyclic Acetal Tethered IMDA

*(E,E)-D*iene **25** that will be employed in model studies as well as in the total synthesis could be readily prepared in 5 steps from known aldehyde **22** in good overall yield and high level stereochemical control with regards to the olefin geometry [**Scheme 3**]. For the first model study, ketone **28** was synthesized from dihydrofuran [DHF] in 34% overall yield in 6 steps, featuring addition of lithiated dihydrofuran [Li-DHF] to acetaldehyde and cyclic acetal formation using PPTS and diene **25** that gave the key cyclic acetal **27** anchored with the diene motif. The minor sidetrack here is that we had to remove both TBS protecting groups and re-protect the resulting primary alcohol.

Befitting with the theme of this special issue of *Heterocycles* dedicated to Professor Albert Eschenmoser, the ensuing enone formation from ketone **28** involved the addition of Eschenmoser's salt[21] to the lithium enolate generated from **28** and subsequent β-elimination in MeOH at rt. The use of Eschenmoser's salt is a key to constructing all the cycloaddition precursors here. Intriguing, the cyclic acetal tethered intramolecular Diels-Alder cycloaddition had already occurred under the alpha-olefination conditions to give **30**-*endo-I* cycloadduct as a single diastereomer in 28% overall yield from **28**. Enone **29** was never isolated, and while not characterized, an equal amount of the side product resulting from the addition of MeOH to **29** was found. It is noteworthy that this novel cyclic acetal tethered IMDA is unusually fast, and such rate enhancement is likely associated with protic solvent.[22,23]



Scheme 3. Cyclic Acetal Tethered IMDA: A Model Study



Scheme 4. Cyclic Acetal Tethered IMDA: Concise Assignment of Endo-I Selectivity

We then quickly assembled ketone **32** in an analogous manner but without the confusion of TBS protecting groups by using the acetyl capped LiDHF addition product **26'** [**Scheme 4**]. The exact same scenario unfolded when ketone **32** was subjected to alpha-methylenation using Eschenmoser's salt: We could not isolate enone **33**, but we obtained the IMDA cycloadduct **34**-*endo-I* as a single isomer in much higher overall yield. Desilylation of **34**-*endo-I* followed by *p*-bromobenzoyl ester formation gave **36**, which afforded a single crystal X-ray structure [**Figure 3**] that allowed us to unambiguously assign the *endo-I* stereochemical outcome. This assessment lent support to the favorable TS-**20** pathway in our

mechanistic analysis, and its manifestation in protic solvent, as proton from MeOH can chelate to both carbonyl and furanyl oxygens.

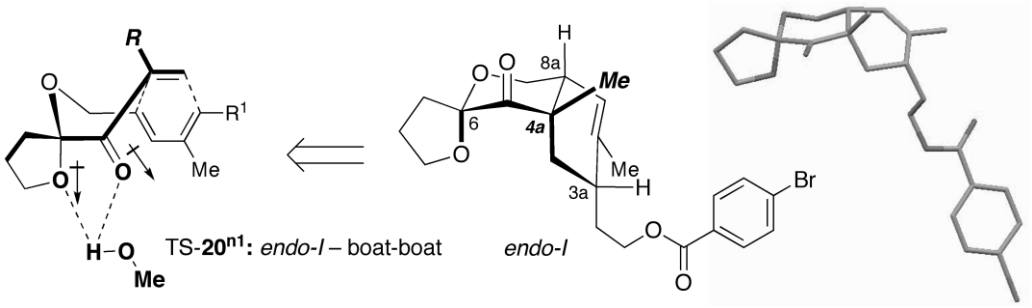
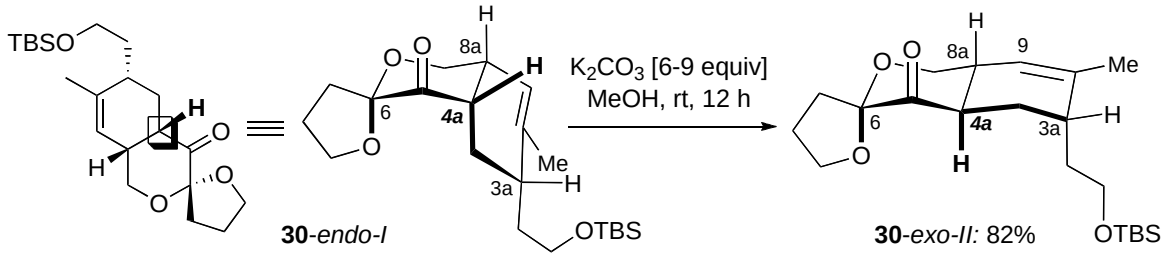


Figure 3. The X-Ray Structure of Ester **36**

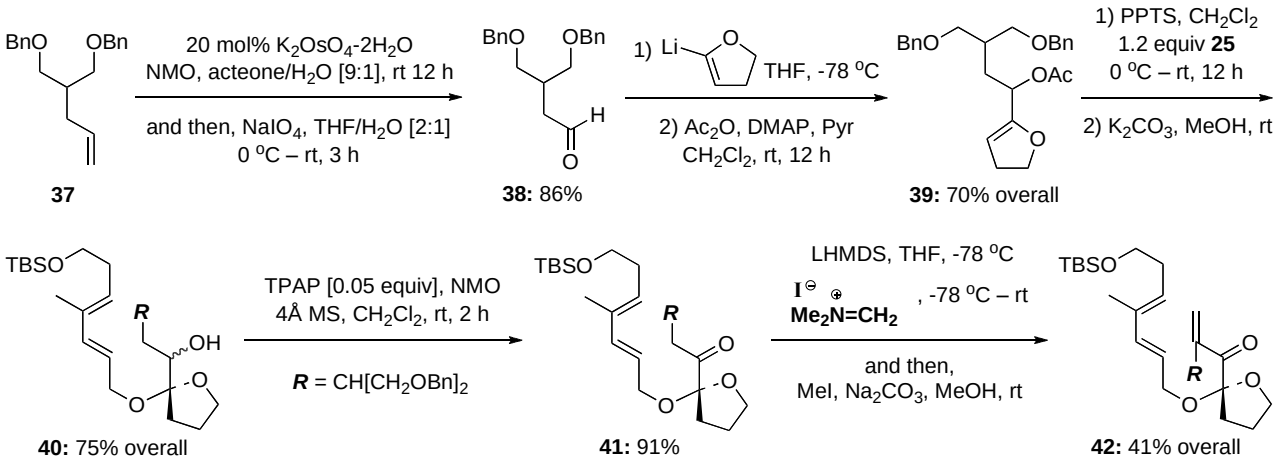
To demonstrate that we could at least access the *trans*-2-oxadecalin spiroketal motif required in fusidilactone C [**3**], epimerization of C4a in **30**-*endo-I* was carried out using K_2CO_3 and MeOH at rt [**Scheme 5**]. Tricycle **30**-*exo-II* was cleanly attained in 82% yield, thereby suggesting that while the respective TS-*exo-II* pathway [see TS-**19**^{x2} in **Figure 2**] may not be a favorable one, the *exo-II* cycloadduct containing the *trans*-2-oxadecalin spiroketal is thermodynamically more stable than that of *endo* cycloadducts. The relative stereochemistry **30**-*exo-II* was assigned using NOE experiments as well as coupling constants.



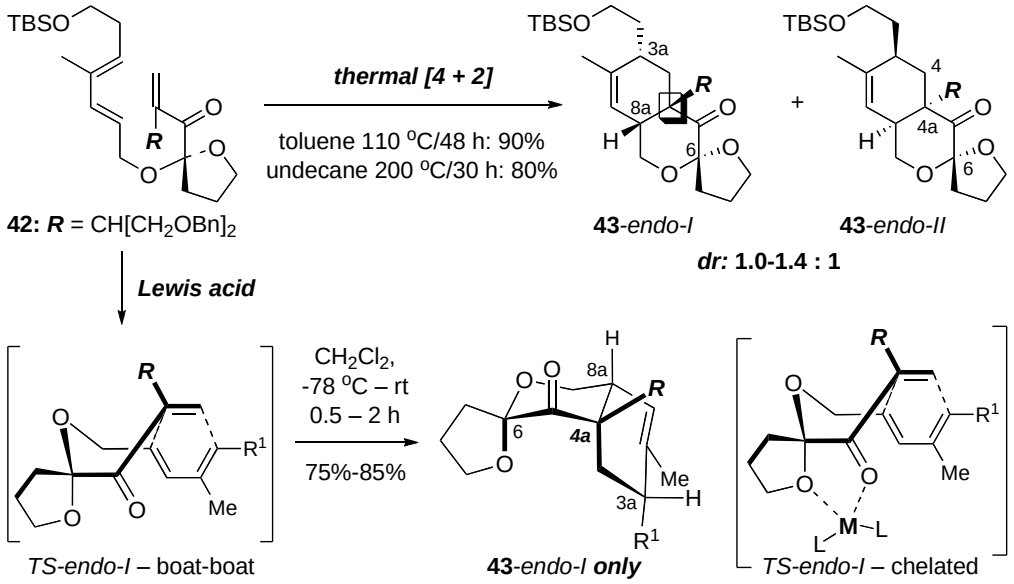
Scheme 5. Epimerization of **30**-Endo-I

5. Progress Toward Fusidilactone C

Continuing to explore this novel IMDA and identify possible pathways en route to the *endo-II* or even *exo* cycloadducts, the key cycloaddition precursor enone **42** was found to be isolable. As shown in **Scheme 6**, the synthesis of enone **42** was achieved in 7 steps commencing from alkene **37**. It is noteworthy that we were able to isolate the cycloaddition precursor for the first time, suggesting a much slower cycloaddition course for enone **42** due to the bulky ***R*** group.



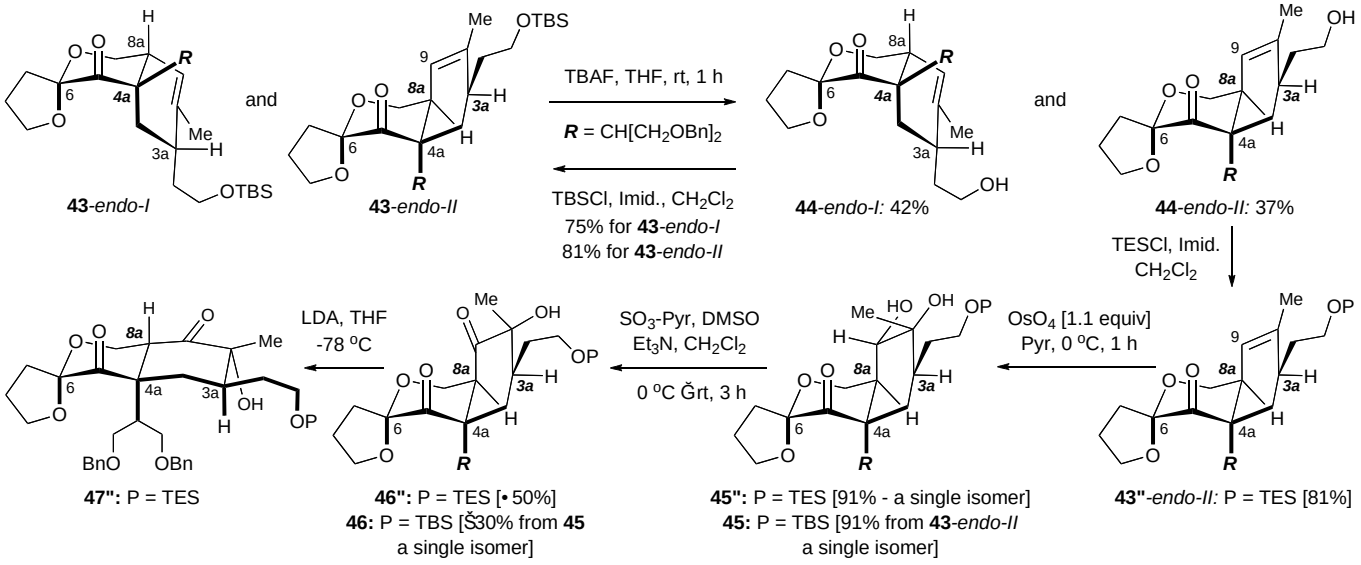
Scheme 6. Synthesis of the Cycloaddition Precursor Enone **42**



Scheme 7. The Key Cyclic Acetal Tethered IMDA of Enone **42**

Isolation of the cycloaddition precursor **42** allowed us to examine this reaction in greater detail. It was quickly found that although the reaction proceeded much slower in toluene even at 110 °C [or in undecane at 200 °C], an improved formation of *endo-II* product was seen with the ratio of **43**-*endo-I* to **43**-*endo-II* being 1.0 to 1.4:1 [**Scheme 7**]. The cycloaddition was again found not only fast in MeOH but also afforded a 12:1 mixture in favor of **43**-*endo-I* with an overall yield of 90%. The use of various Lewis acids [i.e., $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $MgBr_2$-Et_2O, $AlEt_2Cl$, $Sc(OTf)_3$, $Yb(OTF)_3$, $SnCl_2$, $LiClO_4$, $Ti(O\text{-}i\text{-}Pr)_4$, and $RhCl(Ph_3P)_3$/AgOTf or $AgBF_4$] in CH_2Cl_2 led to exclusive formation of **43**-*endo-I* in a facile and high yielding manner at low temperature [-78 °C], thereby suggesting a metal chelation that can further favor TS-*endo-I* in addition to rate enhancement. Only c-hex_2BCl gave **43**-*endo-I* to **43**-*endo-II* in 1:1 ratio.

These findings are consistent with results attained from MeOH and further underscore the significance of TS-*endo-I* in this unique cyclic acetal tethered IMDA. It is also noteworthy that the cyclic acetal tethering is relatively robust under these Lewis acidic conditions.



Scheme 8. An Approach to Fusidilactone C via C8a-Epimerization of **43**-Endo-II

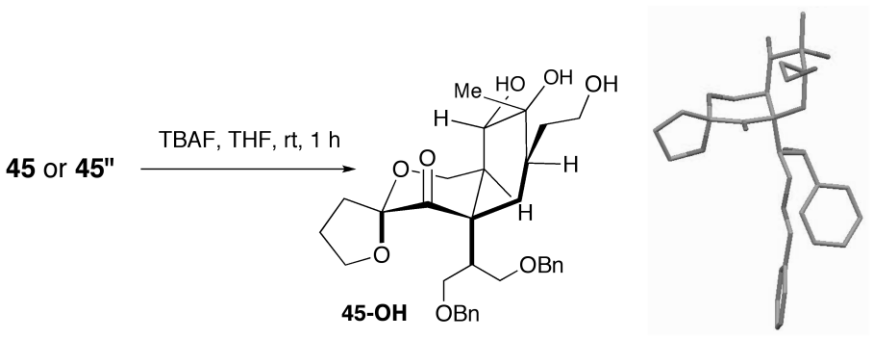


Figure 4. X-Ray Structure of **45-OH**

To continue our total synthesis efforts, we explored the feasibility of converting cycloadduct **43**-*endo-II* to the desired *exo-II* cycloadduct through the epimerization strategy [**Scheme 8**]. Epimerization are required at both C8a and C3a, and we elected to pursue first at C8a. A clean separation **43**-*endo-I* and **43**-*endo-II* required first desilylation, which gave the isomeric mixture of free alcohol **44**. While re-silylation using TBSCl gave **43**-*endo-I* and **43**-*endo-II*, TES-protection of **44**-*endo-II* afforded **43''**-*endo-II*, which was found to be an overall better substrate than **43**-*endo-II* in a later oxidation step. Dihydroxylation of **43''**-*endo-II* employing the stoichiometric amount of OsO_4 produced the desired

1,2-diol **45"** as single diastereomer in excellent yield. The high stereoselectivity probably was the consequence of formation of the osmate from the convex face of the *cis*-oxadecalin. Desilylation of either **45** or **45"** led to **45-OH**, which is a crystalline material for attaining an X-ray structure as shown in **Figure 4**, which unambiguously assigns the relative stereochemical manifold in the *endo-II* cycloadduct. It is noteworthy that compound **45** or **45"** would contain all the carbons in the framework of (±)-fusidilactone C. The subsequent Parikh-Doering oxidation of the secondary alcohol in **45"** in the presence of the adjacent tertiary hydroxyl group provided the desired hydroxy ketone **46"** in 50% yield. Nevertheless, the oxidation yields for **46"** are consistently better than that of **46**.

Attempts to epimerize the tertiary stereocenter α to the carbonyl by exposing hydroxy ketone **46"** to either K_2CO_3 in MeOH, DBU in CH_2Cl_2 at -78 ^oC – 0 ^oC [or in toluene at 110 ^oC], LHMDS in THF at at -78 ^oC failed to provide any desired *trans*-2-oxadecalin **47"**, which indicated the labile nature of the β-alkoxy ketone under basic condition via β-elimination. However, at -78 ^oC in THF, the use of LDA, followed by quenching with MeOH [or D_2O], led to 1:1 mixture of **46"** and **47"** in 45-60% yield, thereby implying the possibility of epimerizing the C8a position, although **47"** was never separable from **46"**, and thus, it could not be vigorously characterized.

CONCLUSION

We have reported here our efforts toward a synthesis fusidilactone C that would feature a novel cyclic acetal tethered intramolecular Diels-Alder strategy. This unique and facile intramolecular Diels-Alder cycloaddition turned out to be highly *endo*-selective, as assessed from our mechanistic analyses. When using protic solvents or Lewis acids, this *endo*-selectivity was even more pronounced. It proved to be a real challenge to circumvent this selectivity, although progress was made to attain *endo-II* cycloadduct and to access the desired *trans*-2-oxadecalin motif through epimerization at C8a.

EXPERIMENTAL

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual $CHCl_3$ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain.

Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported. X-Ray analyses were performed at the X-Ray facility in University of Minnesota.

Preparation of *E,E*-Diene 25.

Wittig Olefination. To a solution of the known aldehyde **22** (55.2 g, 293.1 mmol) in toluene (500 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (112.3 g, 322.4 mmol, 1.1 equiv) in several portions at rt. The resulting mixture was refluxed for 12 h, then cooled down to rt and concentrated *in vacuo*. To the crude product were added hexanes and the precipitated triphenylphosphine oxide was filtered. The filtrate was concentrated in vacuo to afford the crude mixture that was purified using gradient silica gel flash column chromatography (2-15% EtOAc in hexanes) to provide the desired unsaturated ester (70.0 g, 256.9 mmol) as an inseparable 20:1 (*E:Z*) mixture in 88% yield. **The unsaturated ester intermediate:** R_f= 0.72 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 6.78 (tq, 1H, *J* = 1.5, 7.5 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.71 (t, 2H, *J* = 7.0 Hz), 2.41 (dtq, 2H, *J* = 1.0, 7.0, 7.0 Hz), 1.85 (dt, 3H, *J* = 1.0, 1.0 Hz), 1.29 (t, 3H, *J* = 7.5 Hz), 0.90 (s, 9H), 0.06 (s, 6H).

Dibal-H Reduction. To a solution of the aforementioned 20:1 (*E:Z*) mixture of unsaturated ester (34.5 g, 126.6 mmol) in anhyd CH_2Cl_2 (200 mL) was added slowly DIBAL-H (278.6 mL, 1.0 *M* solution in hexanes, 278.6 mmol, 2.2 equiv) at -78 ^{o}C. The reaction was stirred at -78 ^{o}C for 2 h and the TLC analysis indicated the complete conversion from the starting material to the product.

The reaction was quenched with MeOH (50 mL) at -78 ^{o}C carefully, and then, to the resulting mixture was added sat aq sodium potassium tartrate (200 mL) at -78 ^{o}C slowly. The resulting mixture was allowed to warm up to rt and stirred until the organic layer and the aqueous layer were completely separated. The reaction mixture was extracted with ether (3 x 100 mL) and the combined organic layers were washed with sat aq NaCl (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude allylic alcohol was purified using careful gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to provide the desired *E*-allylic alcohol **23** (25.1 g, 108.9 mmol) as colorless oil in 86% yield. **Alcohol 23:** R_f= 0.34 (40% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 5.43 (qt, 1H, *J* = 1.5, 7.5 Hz), 4.02 (d, 2H, *J* = 5.5 Hz), 3.62 (t, 2H, *J* = 7.0 Hz), 2.28 (dq, 2H, *J* = 1.0, 7.0 Hz), 1.69 (s, 3H), 1.31 (dt, -O<u>H</u>, 1H, *J* = 1.5, 6.0 Hz) [long range coupling with one of the allylic methylene protons at 2.28 ppm], 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 136.7, 122.0, 68.7, 62.8, 31.4, 25.9, 18.4, 13.8, -5.3; IR (neat) cm^{-1} 3352brs, 2954s, 2928s, 2857s, 1472s, 1387m, 1256s, 1090s, 1007s, 938ms, 836s, 776s; mass spectrum (GC-MS): m/e (% relative intensity) 173 (10) (M^+-*t*-Bu), 155 (5), 105 (100), 89 (19),

75 (88), 57 (5).

Parikh-Doering Oxidation. To a solution of the above pure *E*-allylic alcohol **23** (21.6 g, 93.8 mmol) in anhyd CH_2Cl_2 (200 mL) were added anhyd DMSO (72.5 mL, 1.02 mol, 10.9 equiv) and anhyd Et_3N (64.8 mL, 464.9 mmol, 5.0 equiv) sequentially at rt. The reaction mixture was cooled down to 0 ^oC before SO_3·Py complex (29.8 g, 187.3 mmol, 2.0 equiv) was added in several portions. The reaction was stirred at 0 ^oC for 1 h, allowed to warm up to rt, and stirred for an additional 1h. TLC analysis indicated the disappearance of the starting material and the reaction was quenched with water (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with water (2 x 100 mL) and sat aq NaCl (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude α,β-unsaturated aldehyde was purified using gradient silica gel flash column chromatography (5-20% EtOAc in hexanes) to afford the desired *E*-enal **24** (20.4 g, 89.3 mmol) as colorless oil in 95% yield. ***E*-Enal 24:** R_f = 0.70 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.56 (qt, 1H, *J* = 1.5, 7.0 Hz), 3.78 (t, 2H, *J* = 6.0 Hz), 2.58 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.77 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Wittig Olefination. To a solution of the pure *E*-enal **24** (20.4 g, 89.3 mmol) in toluene (200 mL) was added (carbethoxymethylene)triphenylphosphorane (36.0 g, 103.3 mmol, 1.2 equiv) at rt. The reaction was refluxed for 12 h before it was cooled down and concentrated *in vacuo*. The residue was dissolved in hexanes and the precipitated triphenylphosphine oxide was filtered off. The filtrate was concentrated *in vacuo* to afford the crude (*E,E*)-dienoate that was purified using gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to provide desired (*E,E*)-dienoate (25.6 g, 85.8 mmol) as colorless oil in 96% yield. R_f = 0.72 (10% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.33 (d, 1H, *J* = 15.5 Hz), 5.92 (t, 1H, *J* = 7.5 Hz), 5.81 (d, 1H, *J* = 15.5 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 3.68 (t, 2H, *J* = 7.0 Hz), 2.43 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.79 (s, 3H), 1.30 (t, 3H, *J* = 7.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H).

Dibal-H Reduction. To a solution of the above (*E,E*)-dienoate (25.6 g, 85.8 mmol) in anhyd CH_2Cl_2 (200 mL) was added DIBAL-H (188.8 mL, 1.0 *M* solution in hexanes, 188.8 mmol, 2.2 equiv) at -78 ^oC slowly. The reaction was stirred at -78 ^oC for 1 h and the TLC analysis indicated the complete conversion from the starting material to the product. The reaction was quenched with MeOH (40 mL) at -78 ^oC carefully then to the reaction was added sat aq sodium potassium tartrate (150 mL) at -78 ^oC slowly. The resulting mixture was allowed to warm up to rt and stirred until the organic layer and aqueous layer were completely separated.

The reaction mixture was extracted with Et_2O (3 x 100 mL) and the combined organic layers were washed with sat aq NaCl (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (5-30% EtOAc in hexanes) to afford desired (*E,E*)-diene **25** (20.4 g, 79.5 mmol) as colorless oil in 93% yield. ***(E,E)*-Diene 25:** R_f = 0.25

(30% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 6.27 (dd, 1H, *J* = 1.0, 15.5 Hz), 5.75 (td, 1H, *J* = 6.0, 15.5 Hz), 5.51 (t, 1H, *J* = 7.0 Hz), 4.21 (dd, 2H, *J* = 1.0, 6.0 Hz), 3.64 (t, 2H, *J* = 7.0 Hz), 2.38 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.77 (d, 3H, *J* = 1.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 136.1, 134.6, 128.8, 125.7, 63.5, 62.6, 32.1, 25.9, 18.3, 12.5, -5.3; IR (neat) cm^{-1} 3369brs, 3020m, 2958s, 2860s, 1472s, 1388m, 1361s, 1253s, 1088s, 992s, 966s, 938s, 841s, 813s, 776s, 664m; mass spectrum (GC-MS): m/e (% relative intensity) 199 (46) (M^+-*t*-Bu), 181 (3), 105 (100), 89 (48), 75 (70), 57 (3); m/e calcd for $C_{14}H_{28}NaO_2Si$ 279.1756, found 279.1755.

Preparation of Ketone 28.

Lithiated 2,3-DHF Addition. To a solution of 2,3-dihydrofuran (4.54 mL, 60.0 mmol) in THF (30 mL) was added a solution of *t*-BuLi (1.7 *M* in pentane, 35.3 mL, 60.0 mmol) at -78 °C dropwise. The resulting bright yellow solution was allowed to warm up to 0 °C slowly and stirred at 0 °C for an additional 1 h. The reaction mixture was re-cooled down to -78 °C, before a solution of acetaldehyde (3.70 mL, 65.9 mmol, 1.09 equiv) in THF (30 mL) was added via a cannula at -78 °C. After 1 h, TLC analysis indicated the disappearance of the starting material. The reaction was quenched by water at -78 °C dropwise then allowed to warm up to room temperature and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo* to afford the corresponding alcohol, which was used in the next step without further purification: R_f = 0.30 (40% EtOAc in hexanes); ^{1}H NMR (300MHz, $CDCl_3$) δ 4.86 (dt, 1H, *J* = 1.2, 2.4 Hz), 4.40 (t, 2H, *J* = 9.6 Hz), 4.43-4.34 (m, 1H), 2.67 (ddt, 2H, *J* = 1.5, 2.4, 9.6 Hz), 1.39 (d, 3H, *J* = 6.6 Hz).

TBS-Protection: To a solution of the above alcohol in CH_2Cl_2 (100 mL) were added imidazole (8.17 g, 120.0 mmol, 2.0 equiv) and TBSCl (9.04 g, 60.0 mmol, 1.0 equiv) sequentially at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for an additional 3 h. TLC analysis indicated the disappearance of the starting material. The reaction mixture was quenched by water and extracted with CH_2Cl_2 (3x60 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-10% EtOAc in hexanes) to afford desired dihydro-furan **26:** (8.21 g, 36.0 mmol) as colorless oil in 60% yield over two steps. R_f = 0.68 (10% EtOAc in hexanes); ^{1}H NMR (300MHz, $CDCl_3$) δ 4.81 (dt, 1H, *J* = 1.2, 2.4 Hz), 4.36 (t, 2H, *J* = 9.3 Hz), 4.38-4.30 (m, 1H), 2.63 (ddt, 2H, *J* = 1.5, 2.4, 9.3 Hz), 1.32 (d, 3H, *J* = 6.3 Hz).

Cyclic Acetal Formation. To a solution of dihydrofuran **26** (510.2 mg, 2.24 mmol) and diene **25** (686.2 mg, 2.68 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added PPTS (28.2 mg, 0.112 mmol, 0.05 equiv) at 0 °C. The resulting solution was allowed to warm up to room temperature slowly and stirred for 12 h. The reaction was quenched by sat aq $NaHCO_3$ and extracted with CH_2Cl_2 (3x30 mL). The combined

organic layers were washed by sat aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2%-10% EtOAc in hexanes) to afford desired cyclic acetal **27** (858.2 mg, 1.77 mmol) as a 1:1 inseparable mixture in 79% yield: R_f= 0.70 (10% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 6.23 (d, 1H, *J* = 15.5 Hz), 5.68-5.59 (m, 1H), 5.47-5.42 (m, 1H), 4.15-4.09 (m, 1H), 4.00-3.94 (m, 3H), 3.90-3.84 (m, 1H), 3.62 (t, 1H, *J* = 7.0 Hz), 2.36 (q, 2H, *J* = 7.0 Hz), 2.17 (ddd, 1H, *J* = 9.0, 9.0, 12.5 Hz), 2.02-1.93 (m, 2H), 1.89-1.80 (m, 1H), 1.75 (s, 3H), 1.17-1.15 (m, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 12H).

Desilylation-Silylation-Oxidation Sequence. To a solution of cyclic acetal **27** (858.2 mg, 1.77 mmol) in THF (10 mL) was added a solution of TBAF (1.0 *M* in THF, 5.3 mmol, 3.0 equiv) at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for 48 h. The reaction mixture was partitioned between water and Et_2O (3 x 60 mL). The combined organic layers were washed by saturated NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (10-60% EtOAc in hexanes) to afford desired diol (389.2 mg, 1.52 mmol) as a 1:1 inseparable mixture in 86% yield.

To a solution of above diol (389.2 mg, 1.52 mmol) in CH_2Cl_2 (5 mL) was added imidazole (217.1 mg, 3.19 mmol, 2.1 equiv) and TBSCl (240.0 mg, 1.59 mmol, 1.05 equiv) sequentially at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After TLC analysis indicated the disappearance of the starting material, the reaction was quenched by water and extracted with CH_2Cl_2 (3x40 mL). The combined organic layers were washed by sat aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (5-30% EtOAc in hexanes) to afford desired mono-TBS protected alcohol (502.3 mg, 1.36 mmol) as a 1:1 inseparable mixture in 89% yield.

To a solution of aforementioned mono-TBS protected alcohol (652.2 mg, 1.76 mmol) in CH_2Cl_2 (8 mL) was added powdered 4Å molecular sieves (0.80 g), NMO (309.5 mg, 2.60 mmol, 1.5 equiv), and TPAP (89.6 mg, 0.093 mmol, 0.05 equiv) sequentially at room temperature. The resulting mixture was stirred for 2 h and TLC showed the complete conversion from the alcohol to the corresponding ketone. The reaction mixture was filtered through a pad of silica gel to remove the molecular sieves and the inorganic salt. The filtrate was concentrated *in vacuo* to afford the crude product, which was purified using gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to afford the desired ketone **28** (601.2 mg, 1.63 mmol) as colorless oil in 93% yield.

Ketone 28: R_f= 0.62 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 6.25 (d, 1H, *J* = 15.5 Hz), 5.64 (dt, 1H, *J* = 6.0, 15.5 Hz), 5.49 (t, 1H, *J* = 7.5 Hz), 4.10-4.04 (m, 3H), 3.89 (ddd, 1H, *J* = 1.0, 6.5, 12.0 Hz), 3.62 (t, 2H, *J* = 7.0 Hz), 2.36 (q, 2H, *J* = 7.5 Hz), 2.25 (s, 3H), 2.15-2.08 (m, 2H), 2.01-1.93 (m, 2H), 1.75 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 205.5, 137.5, 134.4, 129.2,

122.7, 109.0, 69.0, 64.3, 62.5, 34.4, 32.0, 25.9, 25.6, 24.2, 18.2, 12.4, -5.3; IR (neat) cm^{-1} 3034w, 2953s, 2929s, 2886s, 2857s, 1730s, 1471m, 1463m, 1386m, 1335m, 1225s, 1186m, 1099s, 966m, 939m, 835s, 777s; mass spectrum (ESI): m/e (% relative intensity) 391.2 (100) $(M+Na)^+$; m/e calcd for $C_{20}H_{36}NaO_4Si$ 391.2281, found 391.2288.

The Use of Eschenmoser's Salt in Alpha-Methylenation and Cyclic Acetal Tethered IMDA.

Eschenmoser's Alpha-Methylenation. To a solution of ketone **28** (140.0 mg, 0.38 mmol) in THF (3 mL) was added a solution of LiHMDS (1.0 *M* in THF, 0.53 mL, 0.53 mmol, 1.4 equiv) at -78 ^oC. The resulting mixture was warmed up to 0 ^oC and stirred for 1 h. The reaction mixture was re-cooled down to -78 ^oC before a suspension of Eschenmoser's salt (84.4 mg, 0.46 mmol, 1.2 equiv) in THF (3 mL) was added via a cannula. The reaction was allowed to warm up to room temperature slowly and stirred for an additional 1 h. After TLC analysis indicated that the reaction was complete, the reaction was quenched with sat aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (5x10 mL). The combined organic layers were washed with sat aq NaCl (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (5-80% MeOH in EtOAc) to afford the desired β-dimethylamino ketone intermediate (98.7 mg, 0.23 mmol) in 61% yield.

To a solution of the above β-dimethylamino ketone (30.0 mg, 0.070 mmol) in MeOH (3 mL) were added Na_2CO_3 (37.0 mg, 0.35 mmol, 5.0 equiv) and MeI (0.040 mL, 0.70 mmol, 10.0 equiv) sequentially at room temperature. The reaction was stirred for 12 h and TLC indicated the disappearance of the starting material. The reaction was quenched by water (5 mL) and extracted with CH_2Cl_2 (5x5 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (0-5% EtOAc in hexanes) to afford the Diels-Alder cycloadduct **30**-*endo-I* (12.0 mg, 0.032 mmol) as colorless oil in 45% yield overall. **30**-*endo-I*: R_f= 0.71 (10% EtOAc in hexanes); ^1H NMR (500MHz, $CDCl_3$) δ 5.26 (ddd, 1H, *J* = 1.5, 1.5, 5.0 Hz), 4.01 (ddd, 1H, *J* = 6.0, 8.0, 8.0 Hz), 3.96-3.91 (m, 2H), 3.69 (ddd, 1H, *J* = 5.0, 8.0, 10.0 Hz), 3.64 (ddd, 1H, *J* = 7.0, 7.0, 10.0 Hz), 3.55 (ddd, 1H, *J* = 1.0, 5.0, 12.0 Hz), 2.85-2.79 (m, 1H), 2.64 (ddd, 1H, *J* = 5.0, 5.0, 13.5 Hz), 2.60 (ddd, 1H, *J* = 9.0, 9.0, 13.0 Hz), 2.28-2.20 (m, 1H), 2.04-1.90 (m, 4H), 1.81-1.73 (m, 2H), 1.70 (s, 3H), 1.36 (dddd, 1H, *J* = 5.0, 7.0, 10.0, 17.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 205.5, 140.5, 119.9, 107.0, 69.6, 61.5, 60.8, 46.8, 38.2, 36.4, 35.8, 32.8, 28.5, 26.0, 24.4, 21.6, 18.3, -5.2, -5.3; IR (neat) cm^{-1} 2952s, 2884s, 2857s, 1723s, 1255m, 1151m, 1093s, 1027s, 837s, 776s; mass spectrum (ESI): m/e (% relative intensity) 403.2 (100) $(M+Na)^+$; m/e calcd for $C_{21}H_{36}NaO_4Si$ 403.2281, found 403.2280.

*The experimental details for the reaction sequence leading to cyclic acetal **31** and ketone **32** are the same*

*as those described for **40** and **41** below and the Eschenmoser's alpha-methylenation of ketone **32** and the ensuing facile IMDA in MeOH are the same as described above for ketone **28**.*

Cyclic Acetal 31: R_f = 0.41 (30 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.02-1.05 (m, 3H), 1.32-1.44 (m, 2H), 1.74 (s, 3H), 1.77-2.08 (m, 4H), 2.35 (q, 2H, *J* = 6.5 Hz), 3.61 (t, 2H, *J* = 7.0 Hz), 3.69 (dddd, 1H, *J* = 3.0, 3.0, 10.0, 14.0 Hz) 3.89-3.99 (m, 3H), 4.09-4.15 (m, 1H), 5.46 (t, 1H, *J* = 6.5 Hz), 5.56-5.66 (m, 1H), 6.24 (t, 1H, *J* = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.13, 11.2, 12.6, 18.45, 24.3, 24.5, 24.9, 30.3, 31.9, 32.1, 62.2, 62.7, 68.7, 68.9, 72.6, 74.8, 110.6, 111.1, 123.6, 123.7, 128.7, 128.8, 134.6, 136.6, 137.7; IR (neat) cm^{-1} 3488br, 2956s, 2932s, 2859s, 1463m, 1101s.

Ketone 32: R_f = 0.62 (30 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.85 (s, 9H), 1.02-1.05 (m, 3H), 1.71 (s, 3H), 1.89-1.93 (m, 2H), 2.07-2.10 (m, 2H), 2.32 (q, 2H, *J* = 7.0 Hz), 2.56-2.61 (m, 2H), 3.59 (t, 2H, *J* = 7.5 Hz), 3.84 (dd, 1H, *J* = 7.0, 12.5 Hz), 3.99-4.03 (m, 3H), 5.45 (t, 1H, *J* = 7.5 Hz), 5.60 (td, 1H, *J* = 6.5, 15.5 Hz), 6.20 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, 7.4, 12.4, 18.0, 24.1, 25.9, 31.0, 31.1, 34.8, 62.6, 64.4, 69.0, 109.1, 122.8, 129.1, 134.5, 137.4, 208.4; IR (neat) cm^{-1} 2932s, 2858s, 1730s, 1462m, 1254m.

Diels-Alder Cycloadduct 34-*Endo-I*: R_f = 0.30 (20 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.08 (s, 9H), 1.08 (s, 3H), 1.32-1.38 (m, 2H), 1.66 (s, 3H), 1.72 (ddd, 1H, *J* = 5.0, 8.5, 17.5 Hz), 1.83-1.96 (m, 3H), 2.07 (t, 1H, *J* = 12.5 Hz), 2.15-2.25 (m, 1H), 2.42-2.45 (m, 1H), 2.55 (dt, 1H, *J* = 9.5, 12.5 Hz), 3.54 (ddd, 1H, *J* = 1.0, 5.0, 12.0 Hz), 3.57-3.67 (m, 2H), 3.86-3.99 (m, 3H), 5.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.2, 20.1, 22.6, 25.9, 32.6, 33.1, 33.6, 35.5, 44.1, 45.4, 60.5, 62.5, 69.5, 107.0, 119.4, 138.6, 207.3; IR (neat) cm^{-1} 2954s, 2936s, 2883s, 2859s, 1720s, 1459m, 1254m; mass spectrum (LCMS) for $C_{22}H_{38}O_4Si$: m/e (% relative intensity) 395 (100) $(M+H)^+$, 377 (61), 263 (26); m/e calcd for $C_{22}H_{38}NaO_4Si$ 417.2437, found 417.2430.

Desilylation of Cycloadduct 34-*Endo-I*: *It was carried using TBAF according to the procedure described for cyclic acetal **27**.* **Free Alcohol 35:** R_f = 0.40 (50 % EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.32 (ddd, 1H, *J* = 1.0, 5.5, 13.0 Hz), 1.37-1.44 (m, 1H), 1.66 (s, 3H), 1.70 (ddd, 1H, *J* = 5.0, 8.5, 18 Hz), 1.86-2.21 (m, 5H), 2.41- 2.45 (m, 1H), 2.53 (dt, 1H, *J* = 8.5, 13.0 Hz), 3.54 (dd, 1H, *J* = 5.0, 12.0 Hz), 3.58-3.68 (m, 2H), 3.84-3.97 (m, 3H), 5.21-5.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 21.4, 24.3, 32.7, 33.1, 33.6, 35.3, 44.0, 45.4, 60.2, 62.5, 69.6, 107.0, 119.7, 138.3, 207.4; IR (neat) cm^{-1} 3418br, 2943s, 2882s, 1718s, 1454m, 1156m, 1096m, 1034s; mass spectrum (LCMS) for $C_{16}H_{24}O_4$: m/e (% relative intensity) 281 (10) $(M+H)^+$, 263 (100), 245 (6).

Para-Bromobenzoyl Ester 36 Formation: *This was accomplished using standard acylation procedures.* **Ester 36:** R_f = 0.42 (20 % EtOAc in hexanes); mp: 105-107 ^{0}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.40-1.43 (m, 1H), 1.71 (s, 3H), 1.67-1.76 (m, 2H), 1.86-2.05 (m, 2H), 2.16-2.25 (m, 3H), 2.47-2.49 (m, 1H), 2.54-2.61 (m, 1H), 3.58 (dd, 1H, *J* = 4.5, 12.0 Hz), 3.84-3.96 (m, 3H), 4.28-4.33 (m, 1H), 4.36-4.41 (m, 1H), 5.29 (dd, 1H, *J* = 1.5, 3.0 Hz), 7.54-7.57 (m, 2H), 7.86-7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 21.4, 24.3, 31.2, 33.0, 33.3, 33.6, 44.1, 45.3, 62.4, 63.0, 69.6, 107.0, 120.5, 128.0, 129.1, 131.1, 131.6, 137.4, 165.7, 206.9; IR (neat) cm^{-1} 2963s, 2928m, 2884m, 1721s, 1591m, 1271s; mass spectrum (LCMS) for $C_{23}H_{27}BrO_5$: m/e (% relative intensity) 464 (24) (M^+/Br^{81}), 462 (24) (M^+/Br^{79}), 445 (23), 263 (100); m/e calcd for $C_{23}H_{27}BrNaO_5$ 485.0940, found 485.0945.

Epimerization of Diels-Alder Cycloadduct 30-*Endo-I*.

To a solution of the Diels-Alder cycloadduct **30**-*Endo-I* (12.0 mg, 0.032 mmol) in MeOH (2 mL) was added K_2CO_3 (36.3 mg, 0.26 mmol, 8.2 equiv) at rt. The reaction mixture was stirred at rt for 12 h. The reaction was diluted with water (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (0-5% EtOAc in hexanes) to afford **30**-*Exo-II* with *trans*-ring junction (10.0 mg, 0.026 mmol) as colorless oil in 82% yield.

30-*Exo-II*: R_f= 0.71 (10% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 5.16 (sextet, 1H, *J* = 1.5 Hz), 4.03 (ddd, 1H, *J* = 6.5, 8.0, 8.0 Hz), 3.95-3.90 (m, 1H), 3.86 (dd, 1H, *J* = 11.0, 12.0 Hz), 3.68 (dd, 1H, *J* = 4.0, 11.0 Hz), 3.68-3.60 (m, 2H), 2.75 (ddd, 1H, *J* = 2.0, 12.0, 12.0 Hz), 2.60 (ddd, 1H, *J* = 8.0, 9.0, 13.0 Hz), 2.51 (dddq, 1H, *J* = 2.0, 4.0, 12.0, 12.0 Hz), 2.22-2.17 (m, 1H), 2.08-1.86 (m, 3H), 1.83-1.76 (m, 1H), 1.75 (ddd, 1H, *J* = 5.5, 8.0, 13.5 Hz), 1.70 (s, 3H), 1.50 (dddd, 1H, *J* = 1.0, 6.0, 12.0, 13.5 Hz), 1.35 (dddd, 1H, *J* = 4.0, 5.5, 10.0, 14.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H); mass spectrum (ESI): m/e (% relative intensity) 403 (100) $(M+Na)^+$; m/e calcd for $C_{21}H_{36}NaO_4Si$ 403.2281, found 403.2275.

*Preparation of **37** From Diethyl Allyl Malonate. (i) LAH Reduction*. To a solution of LAH (10.0 g, 263.5 mmol, 2.1 equiv) in anhyd Et_2O (250 mL) was added via a cannula a solution of known diethyl allylmalonate (25.0 mL, 126.8 mmol) in anhyd Et_2O (150 mL) at 0 ^{o}C. The reaction was allowed to warm up to rt and stirred for 12 h. TLC analysis indicated the disappearance of the starting material and the reaction was quenched with dropwise addition of water. The precipitated white aluminum salt was filtered off and the aluminum salt was washed thoroughly with Et_2O (3 x 150 mL). The filtrate was washed with sat aq NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (10-80% EtOAc in hexanes) to afford desired 1,3-diol (12.3 g, 105.9 mmol) as colorless oil in 84% yield.

1,3-Diol Intermediate: R_f = 0.18 (60% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 7.0, 10.0, 17.0 Hz), 5.08 (ddt, 1H, *J* = 1.5, 1.5, 17.0 Hz), 5.06-5.03 (m, 1H), 3.82 (ddd, 2H, *J* = 4.0, 5.5, 10.5 Hz), 3.68 (ddd, 2H, *J* = 5.0, 7.0, 11.0 Hz), 2.22-2.17 (m, 2H), 2.08 (dddd, 2H, *J* = 1.0, 1.0, 7.0, 7.0 Hz), 1.92-1.84 (m, 1H).

(ii) Di-Benzylation. To a solution of the above 1,3-diol (16.3 g, 140.3 mmol) in anhyd THF (300 mL) and DMF (60 mL) was added the NaH (12.0 g, 60% suspension in mineral oil, 300.0 mmol, 2.1 equiv) in several portions at 0 °C. The resulting white suspension was allowed to warm up to rt and stirred for 45 min. The resulting mixture was cooled back down to 0 °C before a solution of benzyl bromide (51.0 g, 298.2 mmol, 2.1 equiv) in anhyd THF (100 mL) was added via a cannula. The reaction was allowed to warm up to rt and stirred for 12 h. The reaction was quenched with water (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with sat aq NaCl (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to afford desired alkene **37** (41.6 g, 140.3 mmol) as colorless oil in quantitative yield.

Alkene 37: R_f = 0.73 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 5.79 (ddt, 1H, *J* = 7.0, 10.0, 17.0 Hz), 5.03 (ddt, 1H, *J* = 2.0, 2.0, 17.0 Hz), 5.00 (m, 1H), 4.50 (s, 4H), 3.51 (dd, 2H, *J* = 6.0, 9.0 Hz), 3.48 (dd, 2H, *J* = 5.0, 9.0 Hz), 2.21 (dd, 2H, *J* = 7.0, 7.0 Hz), 2.04 (septet, 1H, *J* = 6.0 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 138.8, 136.7, 128.4, 127.6, 127.5, 116.4, 73.2, 70.6, 39.4, 33.3; IR (neat) cm^{-1} 3064m, 3030m, 2902s, 2857s, 1495m, 1453s, 1364s, 1099s, 1028m, 996m, 913m, 736s, 698s; mass spectrum (GC-MS): m/e (% relative intensity) 205 (66) (M^+-Bn), 91 (100), 81 (4), 63 (2).

Dihydroxylation. To a solution of alkene **37** (41.6 g, 140.3 mmol) in acetone (270 mL) and water (30 mL) were added *N*-methyl morpholine *N*-oxide (16.4 g, 140.3 mmol, 1.0 equiv) and $K_2OsO_4{\cdot}2H_2O$ (103.4 mg, 0.28 mmol, 0.5mol%) sequentially at rt. The reaction was stirred at rt for 12 h and TLC analysis indicated the disappearance of the starting material. The reaction was quenched with sat aq sodium metabisulfite (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat aq NaCl (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (5-100% EtOAc in hexanes) to afford desired 1,2-diol (44.5 g, 134.7 mmol) as colorless oil in 96% yield.

1,2-Diol Intermediate: R_f = 0.20 (EtOAc); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H), 4.52 (s, 2H), 4.50 (s, 2H), 3.78 (ddd, 1H, *J* = 3.5, 7.0, 13.0 Hz), 3.60-3.56 (m, 2H), 3.51 (dd, 1H, *J* = 5.5, 9.5 Hz), 3.47-3.43 (m, 3H), 2.21 (septet, 1H, *J* = 6.0 Hz), 1.59 (ddd, 1H, *J* = 2.5, 6.5, 14.0 Hz), 1.52 (ddd, 1H, *J* = 6.0, 9.0, 14.0 Hz).

$NaIO_4$-Oxidative Cleavage. To a solution of the above 1,2-diol intermediate (44.5 g, 134.7 mmol) in

THF (180 mL) and water (90 mL) was added the $NaIO_4$ (30.0 g, 140.3 mmol, 1.0 equiv) at 0 ^oC. The resulting mixture was allowed to warm up to rt and stirred for 3h. After TLC analysis showed that the reaction was complete, the reaction was diluted with water (200 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with sat aq NaCl (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-30% EtOAc in hexanes) to afford desired aldehyde **38** (36.2 g, 121.3 mmol) as colorless oil in 90% yield.

Aldehyde 38: R_f= 0.65 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 9.77 (t, 1H, J = 2.0 Hz), 7.37-7.26 (m, 10H), 4.48 (s, 4H), 3.55 (dd, 2H, J = 5.0, 9.0 Hz), 3.45 (dd, 2H, J = 6.0, 9.0 Hz), 2.63 (septet, 1H, J = 6.0 Hz), 2.54 (dd, 2H, J = 2.0, 6.0 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 201.9, 138.4, 128.5, 128.4, 127.7, 127.6, 73.2, 70.7, 44.0, 35.1; IR (neat) cm^{-1} 3087m, 3063m, 3029s, 2858s, 2725m, 1720s, 1495s, 1478m, 1453s, 1408m, 1389m, 1364s, 1205s, 1099s, 1028s, 741s, 699s; mass spectrum (ESI): m/e (% relative intensity) 353.2 (100) $(M+MeOH+Na)^+$, 321.2 (18) $(M+Na)^+$; m/e calcd for $C_{20}H_{26}NaO_4$ 353.1729, found 353.1720.

Preparation of Alcohol 40.

Lithiated 2,3-DHF Addition. To a solution of 2,3-dihydrofuran (4.11 mL, 54.3 mmol, 1.2 equiv) in anhyd THF (30 mL) was added *t*-BuLi (32.0 mL, 1.7 *M* in Pentane, 54.4 mmol, 1.2 equiv) at -78 ^oC dropwise. The resulting bright yellow solution was allowed to warm up to 0 ^oC slowly and stirred at 0 ^oC for an additional 1 h. The reaction mixture was re-cooled down to -78 ^oC, and a solution of aldehyde **38** (13.5 g, 45.3 mmol, 1.0 equiv) in anhyd THF (30 mL) was added via a cannula at -78 ^0C. After 1 h, TLC analysis indicated the disappearance of the starting material. The reaction was quenched with water (12 mL) at -78 ^oC dropwise, allowed to warm up to rt, and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude furanyl alcohol (16.7 g, 45.3 mmol) was sufficiently pure judging by ^{1}H NMR and used the next step without further purification. The hydroxyl group of the above furanyl alcohol was capped using Ac_2O, DMAP, and pyridine in CH_2Cl_2 at rt for 12 h following standard conditions to afford dihydrofuran **39** in 70% yield over two steps from **38**.

Furanyl alcohol: R_f= 0.33 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 4.85 (t, 1H, J = 2.5 Hz), 4.51 (s, 4H), 4.34 (ddd, 2H, J = 2.5, 9.0, 9.0 Hz), 4.31-4.27 (m, 1H), 3.57-3.53 (m, 3H), 3.46 (dd, 2H, J = 6.0, 9.0 Hz), 2.62 (dddd, 2H, J = 2.0, 2.0, 9.5, 9.5 Hz), 2.24-2.18 (m, 1H), 1.83 (ddd, 1H, J = 4.0, 7.0, 14.5 Hz), 1.75 (ddd, 1H, J = 6.0, 8.5, 14.5 Hz).

Dihydrofuran 39: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 10H), 5.54 (t, 1H, *J* = 6.5 Hz), 4.90 (t, 1H, *J* = 2.5 Hz), 4.50 (d, 4H, *J* = 4.5 Hz), 4.34 (t, 2H, *J* = 9.5 Hz), 3.52 (m, 4H), 2.61 (td, 2H, *J* = 2.5, 9.5 Hz), 2.06 (s, 3H), 2.02 (sept, 1H, *J* = 6.5 Hz), 1.91 (ddd, 1H, *J* = 6.5, 6.5, 13.5 Hz), 1.86 (ddd, 1H, *J* = 6.5, 6.5, 13.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.7, 138.6, 138.6, 128.4, 128.3, 128.3, 127.6, 127.6, 127.5, 127.5, 97.9, 73.2, 73.1, 70.8, 70.3, 70.1, 67.6, 36.0, 31.0, 29.8, 21.2, 14.2; IR (neat) cm^{-1} 3030m, 2860s, 1740s, 1668w, 1453m, 1368m, 1237s, 1094m; mass spectrum (APCI): m/e (% relative intensity) 351.2 (100) (M^++OAc), 243.1 (30).

Cyclic Acetal Formation. To a solution of dihydrofuran **39** (10.6 g, 25.9 mmol) and *(E,E)*-Diene **25** (7.96 g, 31.0 mmol, 1.2 equiv) in anhyd CH_2Cl_2 (100 mL) was added the pyridinium *p*-toluenesulfonate (325.0 mg, 1.29 mmol, 5 mol%) at 0 °C. The resulting solution was allowed to warm up to rt slowly and stirred for 12 h. After TLC analysis indicated the disappearance of the starting material, the reaction was quenched with sat aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with sat aq NaCl (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2%-10% EtOAc in hexanes) to afford the acylated cyclic acetal intermediate (13.6 g, 20.4 mmol) as a 1.5:1 mixture in 79% yield. The pure major isomer was isolated after a second gradient flash chromatography for characterization.

Acylated Cyclic Acetal Intermediate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 10H), 6.29 (d, 1H, *J* = 16.0 Hz), 6.15 (d, 1H, *J* = 16.0 Hz), 5.62 (dt, 1H, *J* = 6.0, 16.0 Hz), 5.58 (dt, 1H, *J* = 6.0, 16.0 Hz), 5.52 (d, 1H, *J* = 12.0 Hz), 5.46 (d, 1H, *J* = 7.0 Hz), 5.42 (t, 1H, *J* = 7.0 Hz), 5.37 (dd, 1H, *J* = 2.0, 10.0 Hz), 4.51 (m, 4H), 4.18 (m, 1H), 4.09 (d, 1H, *J* = 6.5 Hz), 3.95 (m, 2H), 3.93 (m, 1H), 3.50-3.62 (m, 6H), 3.48 (m, 1H), 2.38 (p, 2H, *J* = 6.5 Hz), 2.06 (s, 3H), 2.05 (s, 3H), 1.92-2.00 (m, 3H), 1.80-1.90 (m, 2H), 1.78 (s, 3H), 1.73 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.4, 138.8, 138.7, 138.6, 136.7, 136.6, 134.8, 134.7, 128.7, 128.6, 128.4, 128.3, 128.3, 128.3, 127.6, 127.6, 127.5, 127.5, 127.5, 127.4, 126.7, 123.9, 123.6, 112.1, 109.5, 108.9, 81.2, 71.8, 71.6, 71.4, 69.9, 69.3, 69.1, 68.7, 63.0, 62.7, 62.7, 62.5, 62.2, 36.1, 36.1, 34.7, 33.3, 32.2, 31.7, 31.6, 31.3, 28.9, 28.8, 26.0, 25.3, 24.5, 24.2, 22.7, 21.2, 21.1, 20.6, 18.4, 14.2, 12.6, 12.5, -5.2; IR (neat) cm^{-1} 2953s, 2859s, 1745s, 1455m, 1368m, 1239s, 1098s; mass spectrum (APCI): m/e (% relative intensity) 411.2 (35) (M^+-diene), 351.2 (100), 303.1 (30), 261.2 (40), 243.1 (15).

The above acylated cyclic acetal intermediate was deacylated using K_2CO_3 in MeOH at rt following standard conditions to afford alcohol **40** in 75% yield over two steps from **39**.

Alcohol 40 [major isomer]: R_f = 0.35 (40% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 6.15 (d, 1H, *J* = 16.0 Hz), 5.55 (dt, 1H, *J* = 6.0, 16.0 Hz), 5.42 (t, 1H, *J* = 7.0 Hz), 4.52 (s, 2H),

4.49 (s, 2H), 4.10 (dd, 1H, *J* = 6.5, 12.0 Hz), 4.00 (ddd, 1H, *J* = 2.0, 2.0, 11.0 Hz), 3.98-3.90 (m, 3H), 3.61 (t, 2H, *J* = 7.0 Hz), 3.60-3.53 (m, 3H), 3.50 (dd, 1H, *J* = 6.0, 9.0 Hz), 2.62 (d, 1H, *J* = 1.0 Hz), 2.35 (q, 2H, *J* = 7.0 Hz), 2.28-2.23 (m, 1H), 2.12-2.01 (m, 2H), 1.93-1.76 (m, 3H), 1.72 (s, 3H), 1.42 (ddd, 1H, *J* = 5.0, 10.5, 14.0 Hz), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 138.5, 136.6, 134.7, 128.6, 128.3, 127.6, 127.5, 127.4, 123.8, 111.1, 73.2, 73.1, 71.9, 70.7, 69.3, 68.6, 62.7, 62.1, 36.8, 32.2, 31.3, 30.3, 26.0, 24.5, 18.4, 12.5, -5.2; IR (neat) cm^{-1} 3463brs, 3030m, 2952s, 2927s, 2856s, 1470m, 1362m, 1253m, 1098s, 1026s, 965m, 835s, 777m, 735m, 698m; mass spectrum (ESI): m/e (% relative intensity) 1271.8 (16) ($2xM^+$+Na^+), 647.4 (100) $(M+Na)^+$; m/e calcd for $C_{37}H_{56}NaO_6Si$ 647.3744, found 647.3748.

Preparation of Ketone 41.

To a solution of alcohol **40** (3.20 g, 5.10 mmol) in anhyd CH_2Cl_2 (25 mL) was added the molecular sieves (2.50 g), *N*-methyl morpholine *N*-oxide (0.90 g, 7.60 mmol, 1.5 equiv), and tetra-*n*-propyl ammonium perruthenate (89.6 mg, 0.26 mmol, 0.05 equiv) sequentially at rt. The resulting mixture was stirred for 2 h at rt and TLC showed the complete conversion from the alcohol to the corresponding ketone. The reaction mixture was filtered through a pad of silica gel to remove the molecular sieves and the inorganic salt. The filtrate was concentrated *in vacuo* to afford the crude product that was purified using gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to afford desired ketone **41** (2.90 g, 4.60 mmol) as colorless oil in 91% yield.

Ketone 41: R_f = 0.75 (40% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.24 (m, 10H), 6.21 (d, 1H, *J* = 16.0 Hz), 5.61 (dt, 1H, *J* = 6.5, 16.0 Hz), 5.45 (t, 1H, *J* = 7.0 Hz), 4.47 (s, 2H), 4.46 (s, 2H), 4.07-4.00 (m, 3H), 3.84 (dd, 1H, *J* = 6.0, 12.0 Hz), 3.61 (t, 2H, *J* = 7.0 Hz), 3.53 (dd, 1H, *J* = 5.0, 9.0 Hz), 3.52 (dd, 1H, *J* = 4.5, 9.0 Hz), 3.48 (dd, 2H, *J* = 5.5, 9.0 Hz), 2.76 (dd, 1H, *J* = 7.0, 18.5 Hz), 2.71 (dd, 1H, *J* = 6.0, 18.5 Hz), 2.67-2.61 (m, 1H), 2.35 (q, 2H, *J* = 7.0 Hz), 2.10-2.00 (m, 2H), 1.95-1.84 (m, 2H), 1.73 (d, 3H, *J* = 1.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 206.8, 138.5, 137.5, 134.6, 129.1, 128.3, 127.6, 127.5, 123.0, 109.2, 73.0, 70.6, 70.3, 69.1, 64.5, 62.7, 37.0, 34.9, 34.6, 32.2, 26.0, 24.2, 18.4, 12.6, -5.2; IR (neat) cm^{-1} 3032w, 2953s, 2929s, 2857s, 1727s, 1455m, 1362m, 1254m, 1098s, 1036s, 966m, 835s, 777m, 736m, 698m; mass spectrum (ESI): m/e (% relative intensity) 645.4 (100) $(M+Na)^+$, 1267.8 (10) ($2xM^+$+Na); m/e calcd for $C_{37}H_{54}NaO_6Si$ 645.3587, found 645.3587.

Eschenmoser's Salt in Alpha-Methylenation.

To a solution of ketone **41** (140.0 mg, 0.22 mmol) in anhyd THF (2 mL) was added lithium bis-(trimethylsilyl) amide (0.30 mL, 1.0 *M* solution in THF, 0.30 mmol, 1.4 equiv) at -78 ^{o}C dropwise. The resulting mixture was warmed up to 0 ^{o}C and stirred for 1 h. The reaction mixture was re-cooled

down to -78 °C before a suspension of Eschenmoser's salt (50.0 mg, 0.27 mmol, 1.2 equiv) in anhyd THF (2 mL) was added via a cannula. The reaction was allowed to warm up to rt slowly and stirred at rt for an additional 1 h. After TLC analysis indicated that the reaction was complete, the reaction was quenched with sat aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with sat aq NaCl (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (5-100% EtOAc in hexanes) to afford desired major β-dimethylaminoketone (69.0 mg, 0.10 mmol) and minor β-dimethylaminoketone (31.0 mg, 0.046 mmol) in 46% and 21% yields, respectively.

Major Isomer: R_f= 0.15 (EtOAc); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.25 (m, 10H), 6.23 (d, 1H, *J* = 16.0 Hz), 5.66 (dt, 1H, *J* = 6.5, 16.0 Hz), 5.45 (t, 1H, *J* = 7.5 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.47 (s, 2H), 4.45 (d, 1H, *J* = 12.0 Hz), 4.05 (dd, 1H, *J* = 5.5, 7.5 Hz), 4.04-4.02 (m, 1H), 4.00-3.95 (m, 2H), 3.65-3.53 (m, 5H), 3.62 (t, 2H, *J* = 7.0 Hz), 2.60 (dd, 1H, *J* = 8.0, 12.0 Hz), 2.42 (quintet, 1H, *J* = 6.0 Hz), 2.36 (q, 2H, *J* = 7.5 Hz), 2.32 (dd, 1H, *J* = 6.0, 12.0 Hz), 2.16 (s, 6H), 2.20-1.96 (m, 3H), 1.86-1.78 (m, 1H), 1.74 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 209.8, 138.7, 138.6, 137.1, 134.8, 128.7, 128.3, 128.2, 127.6, 127.5, 127.4, 123.5, 109.6, 73.0, 72.8, 69.3, 69.1, 68.6, 64.3, 62.7, 58.6, 45.8, 43.2, 40.1, 34.0, 32.1, 26.0, 24.3, 18.4, 12.5, -5.2; mass spectrum (ESI): m/e (% relative intensity) 680.5 (100) $(M+H)^+$.

Minor Isomer: R_f= 0.12 (EtOAc); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.25 (m, 10H), 6.20 (d, 1H, *J* = 15.5 Hz), 5.64 (dt, 1H, *J* = 6.0, 15.5 Hz), 5.45 (t, 1H, *J* = 7.5 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.05-3.95 (m, 3H), 3.91 (dd, 1H, *J* = 6.5, 12.0 Hz), 3.65 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.62 (t, 2H, *J* = 7.0 Hz), 3.60 (dd, 1H, *J* = 5.0, 9.0 Hz), 3.59 (dd, 1H, *J* = 7.0, 9.5 Hz), 3.47 (ddd, 1H, *J* = 4.0, 4.0, 10.0 Hz), 3.44 (dd, 1H, *J* = 6.5, 9.5 Hz), 2.72 (dd, 1H, *J* = 10.0, 12.0 Hz), 2.47-2.41 (m, 1H), 2.36 (q, 2H, *J* = 7.0 Hz), 2.27-2.21 (m, 2H), 2.13 (s, 6H), 2.16-2.04 (m, 1H), 1.97 (ddd, 1H, *J* = 4.5, 8.5, 13.0 Hz), 1.92-1.84 (m, 1H), 1.74 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 209.2, 138.7, 138.6, 137.1, 134.8, 128.6, 128.3, 127.5, 127.4, 123.5, 109.9, 73.0, 72.7, 69.4, 69.3, 68.0, 64.4, 62.7, 58.1, 45.9, 43.4, 39.2, 34.3, 32.1, 26.0, 24.6, 18.4, 12.5, -5.2; mass spectrum (ESI): m/e (% relative intensity) 680.4 (100) $(M+H)^+$.

To a solution of the above β-dimethylaminoketone (91.0 mg, 0.13 mmol) in MeOH (3 mL) was added Na_2CO_3 (74.0 mg, 0.70 mmol, 5.4 equiv) and MeI (0.080 mL, 1.30 mmol, 10.0 equiv) sequentially at rt. The reaction was stirred for 12 h and TLC indicated the disappearance of the starting material. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with sat aq NaCl (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-20% EtOAc in hexanes) to afford the Diels-Alder *endo* adducts **43** (13.0 mg, 0.020 mmol) as a 12:1 mixture in favoring

43-*endo-I*, and the desired cycloaddition precursor **42** (50.0 mg, 0.079 mmol) as colorless oils in 15% and 61% yields, respectively.

Cycloaddition Precursor 42: R_f = 0.69 (20% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.33-7.26 (m, 10H), 6.69 (s, 1H), 6.17 (d, 1H, *J* = 16.0 Hz), 6.02 (s, 1H), 5.56 (dt, 1H, *J* = 6.5, 16.0 Hz), 5.43 (t, 1H, *J* = 7.5 Hz), 4.48 (s, 4H), 4.08 (dd, 1H, *J* = 6.0, 12.0 Hz), 4.04-4.00 (m, 2H), 3.81 (dd, 1H, *J* = 7.0, 13.0 Hz), 3.66-3.59 (m, 4H), 3.61 (t, 2H, *J* = 7.0 Hz), 3.44-3.40 (m, 1H), 2.35 (q, 2H, *J* = 7.0 Hz), 2.19-2.16 (m, 1H), 2.11-2.04 (m, 2H), 1.89-1.82 (m, 1H), 1.72 (d, 3H, *J* = 1.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 197.4, 143.8, 138.4, 137.5, 134.6, 129.1, 128.7, 128.3, 127.6, 127.5, 127.4, 122.7, 109.4, 73.0, 70.4, 70.2, 68.2, 64.6, 62.7, 40.8, 36.8, 32.2, 26.0, 24.2, 18.4, 12.5, -5.2; IR (neat) cm^{-1} 3030w, 2953s, 2929s, 2859s, 1727m, 1687s, 1455s, 1362s, 1255s, 1100s, 1029s, 966s, 835s, 777m, 736m, 698m; mass spectrum (ESI): m/e (% relative intensity) 657.4 (100) $(M+Na)^+$; m/e calcd for $C_{38}H_{54}NaO_6Si$ 657.3587, found 657.3676.

Cyclic Acetal Tethered IMDA Using 42 and De-Silylation.

A solution of **42** (27.0 mg, 0.042 mmol) in anhyd toluene (10 mL) was cannulated into a sealed tube and was refluxed for 48 h. The TLC analysis indicated the disappearance of the starting material. The reaction mixture was concentrated *in vacuo* to afford the crude product that was purified using gradient silica gel flash column chromatography (2-10% EtOAc in hexanes) to afford the inseparable Diels-Alder *endo* adducts **43**-*endo-I* and **43**-*endo-II* (24.0 mg, 0.038 mmol) as a 1:1 inseparable mixture in 90% yield.

To a solution of 1:1 mixture of the Diels-Alder *endo* adducts (24.0 mg, 0.038 mmol) in THF (1 mL) was added TBAF (0.10 mL, 1.0 *M* solution in THF, 0.1 mmol, 2.6 equiv) at rt. The reaction was stirred for 1 h at rt before it was diluted with water (1 mL) and extracted with CH_2Cl_2 (5 x 5 mL).

The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using careful gradient silica gel flash column chromatography (5-30% EtOAc in hexanes) to afford pure **44**-*endo-I* adduct (8.3 mg, 0.016 mmol) and **44**-*endo-II* adduct (7.3 mg, 0.014 mmol) in 42% yield and 37% yields, respectively.

44-*endo-I*: R_f= 0.20 (30% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 5.21 (ddd, 1H, *J* = 2.0, 2.0, 5.5 Hz), 4.51 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.43 (s, 2H), 3.98-3.84 (m, 5H), 3.63 (ddd, 1H, *J* = 5.0, 8.0, 10.5 Hz), 3.60 (dd, 1H, *J* = 5.0, 12.0 Hz), 3.57 (ddd, 1H, *J* = 7.0, 7.0, 10.5 Hz), 3.54-3.48 (m, 2H), 3.05-2.99 (m, 1H), 2.35 (ddd, 1H, *J* = 8.0, 9.0, 13.0 Hz), 2.32-2.25 (m, 1H), 2.10 (dddd, 1H, *J* = 4.0, 4.0, 4.0, 8.0 Hz), 2.01-1.86 (m, 3H), 1.83 (dd, 1H, *J* = 11.0, 14.0 Hz), 1.75 (ddd, 1H, *J* = 1.5, 6.0, 14.0 Hz), 1.67 (ddd, 1H, *J* = 5.0, 8.0, 13.0 Hz), 1.67 (s, 3H), 1.35 (dddd, 1H, *J* = 5.0, 7.0, 9.5, 17.0 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 208.4, 138.8, 138.6, 138.2, 128.4,

128.3, 127.9, 127.8, 127.6, 119.5, 107.4, 73.3, 73.0, 70.1, 69.6, 69.0, 62.5, 60.2, 49.0, 42.8, 39.4, 35.3, 35.1, 32.7, 31.3, 25.0, 21.2; IR (neat) cm^{-1} 3466brs, 3029w, 2945s, 2916s, 2879s, 1714s, 1453s, 1363m, 1094s, 1073s, 1028s, 738s, 699s; mass spectrum (ESI): m/e (% relative intensity) 543.3 (100) $(M+Na)^+$; m/e calcd for $C_{32}H_{40}NaO_6$ 543.2723, found 543.2730.

44-*endo-II:* R_f = 0.23 (30% EtOAc in hexanes); ^1H NMR (500MHz, $CDCl_3$) δ 7.35-7.24 (m, 10H), 5.34-5.31 (m, 1H), 4.51 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.24 (dd, 1H, *J* = 5.0, 12.0 Hz), 4.01 (ddd, 1H, *J* = 6.0, 8.0, 8.0 Hz), 3.88 (dd, 1H, *J* = 5.0, 10.0 Hz), 3.84 (dd, 1H, *J* = 7.0, 15.0 Hz), 3.73 (dd, 1H, *J* = 5.5, 10.0 Hz), 3.73-3.62 (m, 2H), 3.56 (dd, 1H, *J* = 4.0, 10.0 Hz), 3.52 (dd, 1H, *J* = 6.0, 11.5 Hz), 3.42 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.12-3.07 (m, 1H), 2.51 (dq, 1H, *J* = 4.0, 6.0 Hz), 2.40 (td, 1H, *J* = 8.5, 13.0 Hz), 2.32-2.25 (m, 1H), 2.02-1.84 (m, 3H), 1.90 (dd, 1H, *J* = 7.0, 14.0 Hz), 1.83 (dd, 1H, *J* = 7.0, 14.0 Hz), 1.78 (ddd, 1H, *J* = 5.0, 8.0, 13.0 Hz), 1.70 (s, 3H), 1.32-1.24 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 207.4, 138.7, 138.6, 138.5, 128.3, 128.2, 127.7, 127.5, 127.3, 122.9, 106.9, 72.9, 72.8, 69.6, 69.2, 68.9, 64.5, 60.9, 49.3, 42.3, 37.3, 35.1, 34.0, 33.2, 29.6, 24.6, 21.7; IR (neat) cm^{-1} 3452brs, 3029w, 2941s, 2878s, 1718s, 1495m, 1476m, 1453s, 1364m, 1093s, 1028s, 737s, 699s; mass spectrum (ESI): m/e (% relative intensity) 543.3 (100) $(M+Na)^+$; m/e calcd for $C_{32}H_{40}NaO_6$ 543.2723, found 543.2715.

Re-Silylations of 44-*endo-I* and 44-*endo-II*, and Characterization 43-*endo-I* and 43-*endo-II*.

To a solution of the pure **44**-*endo-I* (8.3 mg, 0.016 mmol) in anhyd CH_2Cl_2 (1 mL) was added imidazole (3.00 mg, 0.044 mmol, 2.8 equiv) and TBSCl (5.0 mg, 0.033 mmol, 2.1 equiv) sequentially at 0 ^oC. The resulting mixture was allowed to warm up to rt and stirred for an additional 1 h. After completion as indicated by TLC analysis, the reaction mixture was quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-10% EtOAc in hexanes) to afford **43**-*endo-I* (7.50 mg, 0.012 mmol) as colorless oil in 75% yield.

DA Cycloadduct 43-*endo-I*: R_f = 0.76 (10% EtOAc in hexanes); ^1H NMR (500MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 5.21 (ddd, 1H, *J* = 1.5, 1.5, 5.5 Hz), 4.50 (d, 1H, *J* = 11.5 Hz), 4.44 (d, 1H, *J* = 11.5 Hz), 4.42 (s, 2H), 3.96 (ddd, 1H, *J* = 6.5, 8.0, 8.0 Hz), 3.94-3.90 (m, 3H), 3.87 (dd, 1H, *J* = 11.5, 11.5 Hz), 3.65-3.55 (m, 4H), 3.54 (dd, 1H, *J* = 3.0, 10.0 Hz), 3.06-2.99 (m, 1H), 2.35 (ddd, 1H, *J* = 8.0, 9.0, 13.0 Hz), 2.31-2.23 (m, 1H), 2.14-2.09 (m, 1H), 1.99-1.86 (m, 3H), 1.84 (dd, 1H, *J* = 11.0, 14.0 Hz), 1.75 (ddd, 1H, *J* = 1.5, 6.0, 14.0 Hz), 1.67 (ddd, 1H, *J* = 5.0, 8.0, 13.0 Hz), 1.66 (s, 3H), 1.32 (dddd, 1H, *J* = 5.0, 7.0, 9.5, 17.0 Hz), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 208.5, 139.1, 138.7,

138.3, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 119.2, 107.5, 73.3, 73.1, 70.0, 69.5, 68.8, 62.6, 60.7, 49.0, 42.6, 39.2, 35.9, 35.2, 33.0, 31.4, 26.0, 25.0, 21.3, 18.3, -5.2; IR (neat) cm^{-1} 3027w, 2953s, 2930s, 2882s, 2858s, 1716s, 1454s, 1362m, 1255s, 1095s, 1029s, 837s, 777s, 737s, 698s; mass spectrum (ESI): m/e (% relative intensity) 657.4 (100) $(M+Na)^+$; m/e calcd for $C_{38}H_{54}NaO_6Si$ 657.3587, found 657.3576.

To a solution of the pure **44**-*endo-II* (7.3 mg, 0.014 mmol) in anhyd CH_2Cl_2 (1 mL) was added imidazole (2.40 mg, 0.035 mmol, 2.5 equiv) and TBSCl (4.40 mg, 0.029 mmol, 2.1 equiv) sequentially at 0 °C. The resulting mixture was allowed to warm up to rt and stirred for an additional 1 h. After completion as indicated using TLC analysis, the reaction mixture was quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified using gradient silica gel flash column chromatography (2-10% EtOAc in hexanes) to afford desired **43**-*endo-II* (7.20 mg, 0.011 mmol) as colorless oil in 81% yield.

DA Cycloadduct 43-*endo-II***.** R_f = 0.76 (10% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 5.33-5.31 (m, 1H), 4.51 (d, 1H, *J* = 12.0 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.24 (dd, 1H, *J* = 5.0, 11.5 Hz), 4.02 (dt, 1H, *J* = 6.0, 8.0 Hz), 3.86-3.81 (m, 2H), 3.78 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.72-3.61 (m, 2H), 3.58 (dd, 1H, *J* = 4.0, 10.0 Hz), 3.53 (dd, 1H, *J* = 7.0, 11.5 Hz), 3.48 (dd, 1H, *J* = 5.0, 10.0 Hz), 3.18-3.13 (m, 1H), 2.53-2.48 (m, 1H), 2.41 (td, 1H, *J* = 8.5, 12.5 Hz), 2.31-2.24 (m, 1H), 1.97 (tdd, 1H, *J* = 8.0, 12.0, 15.0 Hz), 1.89-1.78 (m, 4H), 1.77 (ddd, 1H, *J* = 5.0, 8.0, 13.0 Hz), 1.70 (s, 3H), 1.32-1.24 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 206.9, 138.8, 138.6, 128.3, 128.2, 127.6, 127.5, 127.4, 127.2, 122.6, 112.3, 106.9, 73.0, 72.7, 69.7, 69.1, 68.8, 64.6, 61.0, 49.2, 42.1, 36.8, 35.5, 33.8, 33.2, 29.7, 26.0, 24.6, 21.8, 18.3, -5.2, -5.3; IR (neat) cm^{-1} 3027w, 2949s, 2928s, 2855s, 1719s, 1453s, 1362m, 1252s, 1096s, 1028s, 835s, 776s, 735s, 697s; mass spectrum (ESI): m/e (% relative intensity) 657.4 (100) $(M+Na)^+$; m/e calcd for $C_{38}H_{54}NaO_6Si$ 657.3587, found 657.3625.

Preparation of Hydroxy Ketone 46.

Dihydroxylation. To a solution of **43**-*endo-II* (86.7 mg, 0.137 mmol) in pyridine (8 mL) was added OsO_4 (42.0 mg, 0.164 mmol, 1.2 equiv) at -10 °C and the resulting solution turned dark brown slowly. After 1 h, the reaction was quenched by sat aq sodium metabisulfite then allowed to warm up to room temperature and stirred for an additional 1 h. The heterogeneous mixture was partitioned between EtOAc and H_2O. The combined organic layers were washed by sat aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product which was purified by gradient flash column chromatography (10%-40% EtOAc in hexanes) to provide desired diol **45** (83.7 mg, 0.125 mmol) as colorless oil in 91% yield as single diastereomer.

Diol 45 [For P = TBS]: R_f= 0.35 (50% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.24 (m, 10H), 4.51 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.43 (dd, 1H, *J* = 2.0, 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.02 (dt, 1H, *J* = 5.5, 8.0 Hz), 3.99 (dd, 1H, *J* = 2.0, 11.0 Hz), 3.89 (dd, 1H, *J* = 7.0, 15.0 Hz), 3.83 (dd, 1H, *J* = 5.0, 10.0 Hz), 3.78 (dd, 1H, *J* = 3.0, 10.0 Hz), 3.72-3.68 (m, 1H), 3.52 (dt, 1H, *J* = 4.5, 9.5 Hz), 3.40 (dd, 1H, *J* = 8.0, 11.0 Hz), 3.35 (dd, 1H, *J* = 8.0, 10.0 Hz), 3.32 (dd, 1H, *J* = 4.0, 10.0 Hz), 3.06-3.01 (m, 1H), 2.92 (brs, 1H), 2.54 (dt, 1H, *J* = 8.5, 13.0 Hz), 2.45-2.41 (m, 1H), 2.43 (brs, 1H), 2.04-1.95 (m, 1H), 1.93-1.85 (m, 2H), 1.84-1.79 (m, 1H), 1.79 (ddd, 1H, *J* = 4.5, 8.0, 13.0 Hz), 1.70 (dd, 1H, *J* = 4.5, 14.5 Hz), 1.56 (dddd, 1H, *J* = 5.5, 5.5, 8.5, 14.0 Hz), 1.20 (s, 3H), 1.01 (dddd, 1H, *J* = 4.5, 4.5, 9.0, 14.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 205.8, 138.6, 138.2, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 107.6, 73.3, 73.0, 72.7, 71.4, 69.8, 68.4, 67.7, 62.2, 57.4, 51.7, 42.5, 41.2, 40.8, 33.9, 32.3, 26.0, 24.3, 23.7, 18.3, -5.3, -5.4; mass spectrum (ESI): m/e (% relative intensity) 691 (100) $(M+Na)^+$; m/e calcd for $C_{38}H_{56}NaO_8Si$ 691.3642, found 691.3650.

Parikh-Doering Oxidation. To a solution of diol **45** (34.7 mg, 0.052 mmol) in CH_2Cl_2 (1.5 mL) was added DMSO (0.1 mL) and Et_3N (0.1 mL) sequentially at rt. The reaction mixture was cooled down to 0 ^oC before SO_3·Py complex (41.3 mg, 0.259 mmol, 5.0 equiv) was added in one portion. The reaction was stirred at 0 ^oC for 1 h then allowed to warm up to rt. After 5 h, additional SO_3-Py (41.3 mg, 0.259 mmol, 5.0 equiv) was added and the solution was stirred overnight. The reaction was quenched by H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed by sat aq NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product which was purified by gradient flash column chromatography (10-30% EtOAc in hexanes) to afford the desired hydroxy ketone **46** (10.4 mg, 0.0156 mmol) as colorless oil in 30% yield.

Hydroxy Ketone 46 [For P = TBS]: R_f= 0.51 (50% EtOAc in hexanes); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 4.47 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.38 (s, 2H), 4.35 (dd, 1H, *J* = 5.0, 12.5 Hz), 4.03 (dd, 1H, *J* = 2.0, 12.0 Hz), 3.99 (dd, 1H, *J* = 2.5, 8.0 Hz), 3.99-3.72 (m, 1H), 3.75 (dd, 1H, *J* = 5.5, 10.0 Hz), 3.71 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.62 (t, 2H, *J* = 6.5 Hz), 3.48 (dd, 1H, *J* = 2.0, 5.0 Hz), 3.46 (dd, 1H, *J* = 6.5, 10.0 Hz), 3.42 (s, 1H), 3.40 (dd, 1H, *J* = 3.5, 10.0 Hz), 2.92-2.87 (m, 1H), 2.40 (dt, 1H, *J* = 9.0, 13.0 Hz), 2.10-1.83 (m, 7H), 1.28-1.21 (m, 1H), 1.16 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); mass spectrum (ESI): m/e (% relative intensity) 689.3 (100) $(M+Na)^+$; m/e calcd for $C_{38}H_{54}NaO_8Si$ 689.3486, found 689.3486.

Preparation of Diol 45" from 43". Same as that described for **45** from **43.**

Diol 45" [For P = TES]: R_f= 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.33

(m, 10H), 4.52 (d, 1H, *J* = 5.0 Hz), 4.49 (d, 1H, *J* = 5.0 Hz), 4.44 (d, 2H, *J* = 11.5 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.02 (m, 2H), 3.90 (q, 1H, *J* = 7.0 Hz), 3.83 (dd, 1H, *J* = 1.0, 5.5 Hz), 3.78 (dd, 1H, *J* = 1.0, 6.5 Hz), 3.72 (p, 1H, *J* = 5.0 Hz), 3.51 (sextet, 1H, 5.0 Hz), 3.40 (m, 1H), 3.33 (m, 2H), 3.05 (m, 1H), 2.64 (brs, 1H), 2.55 (dt, 1H, *J* = 8.5, 12.5 Hz), 2.45 (d, 1H, *J* = 11.5 Hz), 2.00 (m, 1H), 1.75-1.95 (m, 4H), 1.70 (dd, 1H, *J* = 4.0, 14.0 Hz), 1.59 (td, 1H, *J* = 6.0, 14.0 Hz), 1.18 (s, 3H), 1.02 (m, 1H), 0.95 (t, 9H, *J* = 7.5 Hz), 0.60 (q, 6H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 138.6, 138.2, 128.3, 128.3, 127.8, 127.6, 127.6, 127.4, 107.6, 73.2, 73.0, 72.7, 71.3, 69.8, 68.5, 67.7, 61.8, 57.4, 51.8, 42.5, 41.2, 40.8, 33.9, 32.4, 24.8, 24.3, 24.2, 23.7, 6.8, 4.6, 4.3, 4.2, 4.1; IR (neat) cm^{-1} 3343brs, 3065w, 2955s, 2876s, 1715s, 1455s, 1366w, 1239w, 1095s; mass spectrum (APCI): m/e (% relative intensity) 668.0 (35) (M^+), 650.9 (10), 560.9 (90), 542.9 (100), 524.9 (10), 428.9 (25); m/e calcd for $C_{38}H_{56}O_8Si$ 668.3745, found 668.3746.

Preparation of Hydroxy Ketone 46". Same as that described for **46** from **45.**

Hydroxy Ketone 46" [For P = TES]: R_f = 0.45 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.35 (m, 10H), 4.45 (m, 2H), 4.38 (s, 2H), 4.34 (dd, 1H, *J* = 5.0, 12.5 Hz), 4.00 (dd, 2H, *J* = 1.5, 12.0 Hz), 3.98 (dd, 1H, *J* = 6.0, 7.5 Hz), 3.93 (q, 1H, *J* = 7.5 Hz), 3.72 (ddd, 2H, *J* = 5.5, 10.5, 15.5 Hz), 3.62 (dd, 2H, *J* = 6.0, 6.5 Hz), 3.45-3.49 (m, 2H), 3.39 (dd, 1H, *J* = 3.5, 10.0 Hz), 2.92 (m, 1H), 2.38 (dt, 1H, *J* = 9.0, 12.5 Hz), 1.84-2.12 (m, 7H), 1.60 (s, 1H), 1.25 (m, 1H), 1.16 (s, 3H), 0.94 (t, 9H, *J* = 7.5 Hz), 0.58 (q, 6H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 205.3, 164.8, 138.1, 138.0, 128.4, 128.3, 127.8, 127.7, 127.7, 127.6, 117.2, 107.0, 80.4, 76.6, 73.1, 73.0, 69.7, 69.0, 68.1, 61.3, 58.8, 51.0, 49.4, 43.6, 38.9, 35.5, 32.6, 30.2, 24.4, 19.1, 6.9, 4.4; mass spectrum (APCI): m/e (% relative intensity) 666.0 (10) (M^+), 650.2 (10), 541.0 (100), 523.3 (20), 427.0 (35); m/e calcd for $C_{38}H_{54}O_8Si$ 666.3588, found 666.3578.

Hydroxy Ketone 47'': A fresh solution of LDA was added dropwise to a solution of 46'' in THF at -78 °C to afford an inseperable 1:1 mixture of 46'' and 47''. Characterization of 47'' proved difficult, with many of the ^{1}H NMR signals overlapping slightly with 46''; however, the clean doubling of signal at 2.38 (dt, 1H, *J* = 9.0, 12.5 Hz) with a second signal at 2.30 (dt, 1H, *J* = 9.0, 12.5 Hz), as well as doubling of singlet at 1.16 (s, 3H) with a singlet at 1.18 (s, 3H) provided some direct evidence, in addition to ^{13}C NMR showing doubling of most signals. ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 212.0, 205.3, 164.8, 138.2, 138.1, 138.0, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 117.2, 107.2, 107.0, 104.8, 80.4, 76.8, 76.6, 76.6, 73.9, 73.1, 73.1, 72.9, 69.9, 69.7, 69.0, 69.0, 68.1, 67.8, 61.5, 61.3, 59.0, 58.8, 52.6, 51.0, 50.7, 49.4, 45.3, 43.6, 40.0, 38.9, 35.5, 35.4, 32.8, 32.6, 30.3, 30.1, 24.4, 24.0, 20.5, 19.1, 6.8, 4.4.

ACKNOWLEDGEMENTS

RPH thanks University of Wisconsin for financial support, and JW thanks University of Minnesota for a prestigious Lester C. and Joan Krogh Graduate Dissertation Fellowship. We thank Dr. William W. Brennessel and Dr. Victor G. Young, Jr. of University of Minnesota for providing X-ray structural analysis.

REFERENCE

1. K. Krohn, C. Biele, K.-H. Drogies, K. Steingröver, H.-J. Aust, S. Draeger, and B. Schulz, *Eur. J. Org. Chem.*, 2002, 2331.
2. For another rare example, see: R. B. Woodward, T. Fukunaga, and R. C. Kelly, *J. Am. Chem. Soc.*, 1964, **86**, 3162.
3. W. A. Ayer, L. M. Browne, A. W. Singer, and P. Elgersma, *Can. J. Chem.*, 1990, **68**, 1300.
4. For isolation and biological activities, see: (a) C. Y. Kao and S. R. Levinson, Eds. '*Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel.*' New York Academy of Sciences: New York, 1986; Vol. 479. (b) T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, 1965, **21**, 2059. (c) H. S. Mosher, F. A. Fuhrman, H. D. Buchwald, and H. G. Fischer, *Science*, 1964, **144**, 1100. (d) K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamura, and O. Amakasu, *Chem. Pharm. Bull.*, 1964, **12**, 1357. (d) R. B. Woodward, *Pure Appl. Chem.*, 1964**, 9**, 49. (e) T. Narahashi, *J. Toxicol., Toxin Rev.*, 2001, **20**, 67.
5. For total syntheses and synthetic efforts, see: (a) S. Akai, H. Seki, N. Sugita, T. Kogure, N. Nishizawa, K. Suzuki, Y. Nakamura, Y. Kajihara, J. Yoshimura, and K.-I. Sato, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 279. (b) D. Urabe, T. Nishikawa, and M. Isobe, *Chem. Asian J.*, 2006, **1**, 125. (c) T. Umezawa, T. Hayashi, H. Sakai, H. Teramoto, T. Yoshikawa, M. Izumida, Y. Tamatani, T. Hirose, Y. Ohfune, and T. Shinada, *Org. Lett.*, 2006, **8**, 4971. (d) T. Nishikawa, D. Urabe, and M. Isobe, *Angew. Chem. Int. Ed.*, 2004, **43**, 4782. (e) A. Hinman and J. Du Bois, *J. Am. Chem. Soc.*, 2003, **125**, 11510. (f) N. Ohyabu, T. Nishikawa, and M. Isobe, *J. Am. Chem. Soc.*, 2003, **125**, 8798. (g) T. Nishikawa, D. Urabe, K. Yoshida, T. Iwabuchi, M. Asai, and M. Isobe, *Pure Appl. Chem.*, 2003, **75**, 251. (h) Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.*, 1972, **94**, 9217. (i) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.*, 1972, **94**, 9219. (j) T. Itoh, M. Watanabe, and T. Fukuyama, *Synlett*, 2002, 1323. (k) K. Sato, S. Akai, N. Sugita, T. Ohsawa, T. Kogure, H. Shoji, and J. Yoshimura, *J. Org. Chem.*, 2005, **70**, 7496. (l) K. Sato, S. Akai, H. Shoji, N. Sugita, S. Yoshida, Y. Nagai, K. Suzuki, Y. Nakamura, Y. Kajihara, M. Funabashi, and J. Yoshimura, *J. Org. Chem.*, 2008, **73**, 1234.
6. X. Gao and B. S. Snider, *J. Org. Chem.*, 2004, **69**, 5517.

7. J. Wang, R. P. Hsung, and S. K. Ghosh, *Org. Lett.*, 2004, **6**, 1939.
8. For reviews, see: (a) B. R. Bear, S. M. Sparks, and K. J. Shea, *Angew. Chem. Int. Ed.*, 2001, **40**, 820. (b) D. Craig, '*Stereoselective Synthesis*' Vol. E21c ed. by G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schaumann, Thieme: Stuttgardt, 1996, pp. 2872-2904. (c) W. R. Roush, in '*Advances in Cycloaddition*,' Vol. 2 ed. by D. P. Curran, JAI: Greenwich, CT, 1990, pp. 91-146. (d) W. R. Roush, in '*Comprehensive Organic Synthesis'* Vol. 5 ed. by B. M. Trost, JAI: Pergamon, Oxford, 1991, pp. 513-550. (e) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187. (f) E. Ciganek, *Org. React.,* 1984, **32**, 1. (g) A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 183. (h) D. F. Taber, in '*Intramolecular Diels-Alder Reactions and Alder-Ene Reactions'* Springer: Berlin, 1984.
9. P. J. Ainsworth, D. Craig, A. J. P. White, and D. J. Williams, *Tetrahedron,* 1996, **52**, 8937.
10. (a) R. K. Boeckman, Jr. and C. J. Flann, *Tetrahedron Lett.,* 1983, **24**, 1655. (b) R. K. Boeckman, Jr., K. G. Estep, S. G. Nelson, and M. A. Walters, *Tetrahedron Lett.,* 1991, **32**, 4095.
11. W. R. Roush and D. A. Barba, *Tetrahedron Lett.,* 1997, **38**, 8781.
12. (a) M. E. Jung and L. J. Street, *J. Am. Chem. Soc.*, 1984, **106**, 8327. (b) M. E. Jung and L. J. Street, *Heterocycles,* 1988, **27**, 45.
13. For reviews, see: (a) C.-C. Liao and R. K. Peddinti, *Acc. Chem. Res.*, 2002, **35**, 856. (b) S. Quideau and L. Pouységu, *Org. Prep Proc. Int.,* 1999, **31**, 617.
14. For reviews, see: (a) M. H. D. Postema, *Tetrahedron,* 1992, **48**, 8545. (b) K. A. Parker, *Pure Appl. Chem.*, 1994, **66**, 2135. (c) D. E. Levy and C. Tang, '*The Chemistry of C-Glycosides*.' Vol. 13 Pergamon Press: 1995. (d) For an example, see: A. Hosomi, Y. Sakata, and H. Sakurai, *Carbohydr. Res.*, 1987, **171**, 223.
15. (a) S. R. Shenoy, D. M. Smith, and K. A. Woerpel, *J. Am. Chem. Soc.*, 2006, **128**, 8671. (b) D. M. Smith and K. A. Woerpel, *Org. Lett.*, 2004, **6**, 2063. (c) J. A. C. Romero, S. A. Tabacco, and K. A. Woerpel, *J. Am. Chem. Soc.*, 2000, **122**, 168. (d) H. Matsutani, S. Ichikawa, J. Yaruva, T. Kusumoto, and T. Hiyama, *J. Am. Chem. Soc.*, 1997, **119**, 4541. (e) S. Hosokawa, B. Kirschbaum, and M. Isobe, *Tetrahedron Lett.*, 1998, **39**, 1917.
16. S. K. Ghosh, R. P. Hsung, and J. Liu, *J. Am. Chem. Soc.*, 2005, **127**, 8260.
17. (a) J. Liu and R. P. Hsung, *Org. Lett.*, 2005, **7**, 2273. (b) J. Yang, J. Liu, and R. P. Hsung, *Org. Lett.*, 2008, **10**, 2525.
18. For a review on chemistry of spiroketals, see: (a) J. E. Aho, P. M. Pihko, and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406. (b) K. T. Mead and B. N. Brewer, *Curr. Org. Chem.*, 2003, **7**, 227. (c) M. A. Brimble and F. A. Fares, *Tetrahedron,* 1999, **55**, 7661. (d) M. T. Fletcher and W. Kitching, *Chem. Rev.*, 1995, **95**, 789. (e) F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617.
19. R. Figueroa, R. P. Hsung, and C. C. Guevarra, *Org. Lett.*, 2007, **9**, 4857.

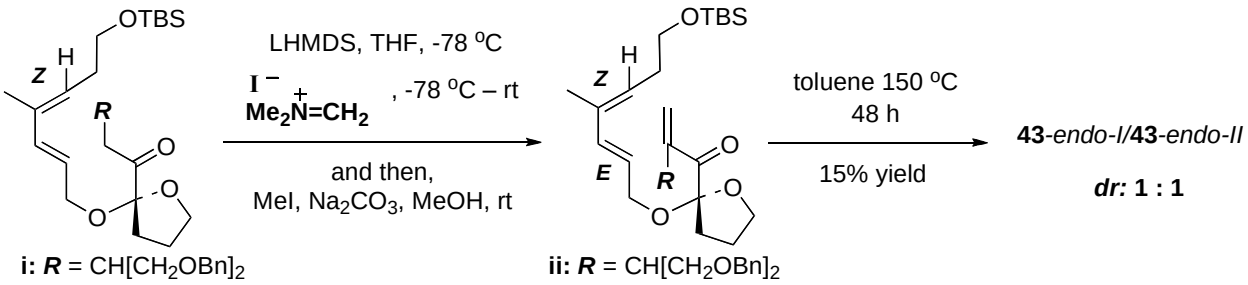
20. S. K. Ghosh, C. Ko, J. Liu, J. Wang, and R. P. Hsung, *Tetrahedron,* 2006, **62**, 10485.

21. J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.,* 1971, **10**, 330.

22. For a leading reference on hydrogen bonding promoted hetero Diels-Alder cycloadditions, see: Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.*, 2002, **124**, 9662.

23. For some earlier examples on effect of aqueous or protic solvents on Diels-Alder cycloadditions, see: (a) P. A. Grieco, P. Garner, and Z.-M. He, *Tetrahedron Lett.*, 1983, **24**, 1897. (b) R. Breslow, U. Maitra, and D. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901.

24. Intriguingly, we also examined *Z,E*-diene **ii** [prepared from **39** and *(Z,E)*-**25**] but the Diels-Alder cycloaddition was not only *endo*-selective but also gave **43** with an *endo-I* to *endo-II* ratio of 1:1, thereby implying isomerization of the olefin geometry took place under the reaction conditions. The use of Lewis acid was not useful in this example.



i: ***R*** = $CH[CH_2OBn]_2$ **ii:** ***R*** = $CH[CH_2OBn]_2$