Total Synthesis of (+)-Brefeldin A

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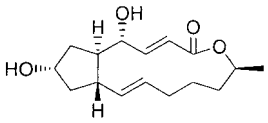
The total synthesis of (+)-brefeldin A has been accomplished via 15 linear steps in a 7.9% overall yield from the known Weinreb amide **6**. The key parts of this approach include the stereoselective construction of the cis-disubstituted hydroxycyclopentane skeleton and the direct introduction of the C1−C3 acrylate moiety using a new variant of a trans-vinylogous acyl anion equivalent.

Introduction

(+)-Brefeldin A (**1**) has been, since its isolation[1] and structural elucidation[2] many years ago, one of the most attractive targets for synthetic chemists due to its wide range of biological activities and well-functionalized macrolide structure. Its biological mode of action has been disclosed by a number of important discoveries.[3] Especially, brefeldin A is known as a disassembler of the Golgi apparatus, because brefeldin A can block protein transport from the rough endoplasmic reticulum (ER) to the Golgi complex and cause a redistribution of the cis, medial, and trans Golgi proteins into the ER in mammalian cells.[4] In addition, the ability of brefeldin A to induce DNA fragmentation associated with apoptosis in cancer cells has stimulated a great deal of recent interest in its preclinical development as an anticancer agent.[5,6] Since Corey's first total synthesis of **1** in 1976,[7] a number of synthetic routes to this macrolide antibiotic have been explored.[8] In particular, the exciting biological activities of brefeldin A, combined with the impracticality of the previously developed syntheses led us to take on the challenge of the total synthesis of **1**.



(+)-Brefeldin A (1)

In planning our approach, we hoped to develop a versatile, practical, and stereocontrolled route that would minimize protecting group manipulations and adapt a platform that leads to a variety of analogues of **1**. This paper fully describes our synthetic studies[9] toward (+)-brefeldin A

Results and Discussion

Synthetic Plan. Our retrosynthetic strategy toward **1** is illustrated in Figure 1. (+)-Brefeldin A (**1**) could be prepared from the seco acid **2** through the regioselective macrolactonization and stereoselective reduction of the C4 (refer to the numbering system of brefeldin A) ketone at the final stage. It might be expected that, to effect the proposed selective macrolactonization, the C15 hydroxy group must be differentiated from the remaining C7 hydroxy group. However, we recognized that such macrolactonization could take place preferentially at the C15 hydroxy group under controlled conditions. Therefore, we

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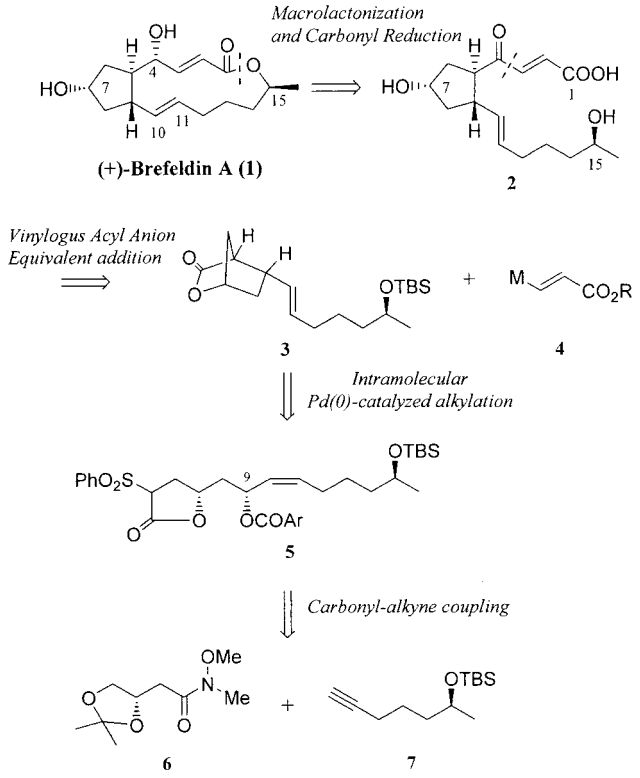
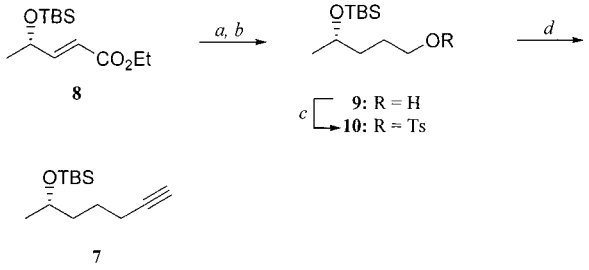


Figure 1. Retrosynthetic analysis of (+)-brefeldin A.

decided to leave the C7 and C15 hydroxy groups undifferentiated for synthetic efficiency. The acrylate moiety of the seco acid **2** is directly introduced by the reaction of a three-carbon synthon such as the trans-vinylogous acyl anion **4**[9c] with the bicyclic lactone **3**. The bicyclic lactone **3**, corresponding to the hydroxycyclopentane skeleton of brefeldin A, is efficiently constructed by the highly stereoselective palladium-catalyzed cyclization of the allylic benzoate **5** we developed[9a,9b] as the key step. The stereochemistry of C9 as well as the olefin geometry of C10−C11 would also be established during this process. The Weinreb amide **6**[10] was considered to be the best starting material, which could be conveniently transformed into the cyclization precursor **5**. This transformation involves the coupling of **6** and **7**, Suzuki's reduction[11] for the installation of the C9 stereocenter, and the formation of the butyrolactone moiety. This strategy would provide the relevant timing of the necessary operations and also minimize protecting group manipulations.

Synthesis of the C10−C16 Fragment. Our synthesis was commenced by the preparation of the requisite **7**,[12] as shown in Scheme 1. The known α,β-unsaturated ester **8**[13] was initially hydrogenated, and the resulting saturated ester was reduced with DIBAL to give the corresponding alcohol **9** in a 98% yield. Tosylation of the alcohol **9**, followed by the addition of lithium acetylide,

Scheme 1[a]

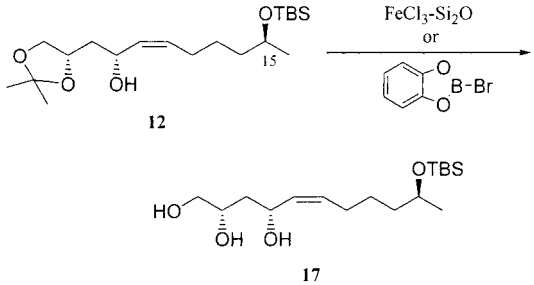


[a] Reagents and conditions: (a) H_2, 10% Pd/C, EtOH; (b) DIBAL, CH_2Cl_2, −78 °C, 98% for two steps; (c) TsCl, Et_3N, 4-DMAP, CH_2Cl_2; (d) lithium acetylide−EDA complex, DMSO, 81% for two steps.

afforded the alkyne **7** as a part of the lower side chain in an 81% two-step yield.

Synthesis of the Cyclization Precursor. The allylic benzoate **5**, bearing the butyrolactone moiety as a Pd(0)-catalyzed cyclization precursor, was synthesized as outlined in Scheme 2.

Starting from the known Weinreb amide **6**,[10] treatment with the lithium anion of **7** in THF at −78 °C provided the ynone intermediate in an 81% yield.[14] The initial partial reduction of the ynone by hydrogenation in the presence of $Pd/BaSO_4$ resulted in a disappointingly low yield of the desired enone **11**. However, partial hydrogenation of the ynone intermediate was efficiently effected using the Lindlar catalyst ($Pd/CaCO_3$, quinoline, H_2, MeOH), which afforded the enone **11** in a 95% yield. The allylic alcohol **12** was also efficiently synthesized as the only stereoisomer in a 95% yield by stereoselective reduction with LAH in the presence of LiI, according to Suzuki's protocol.[11] In particular, the 1,3-syn diol functionality was conveniently installed in a highly diastereoselective fashion by this excellent method. At this stage, the selective removal of the acetonide protecting group was problematic due to the presence of the acid-sensitive C15 TBS group (eq 1). The initial deprotection, using an acid catalyst such as $FeCl_3$−Si_2O[15] or *B*-bromocatecholborane,[16] afforded the triol **17** in 83 and 94% yields, respectively. However, these reactions on a large scale consistently failed to provide mainly the triol **17**.



(1)

This problem was fortunately solved by the acetal exchange conditions.[10,17] The exposure of the acetonide **12** to camphorsulfonic acid (CSA) and the dimethylacetal

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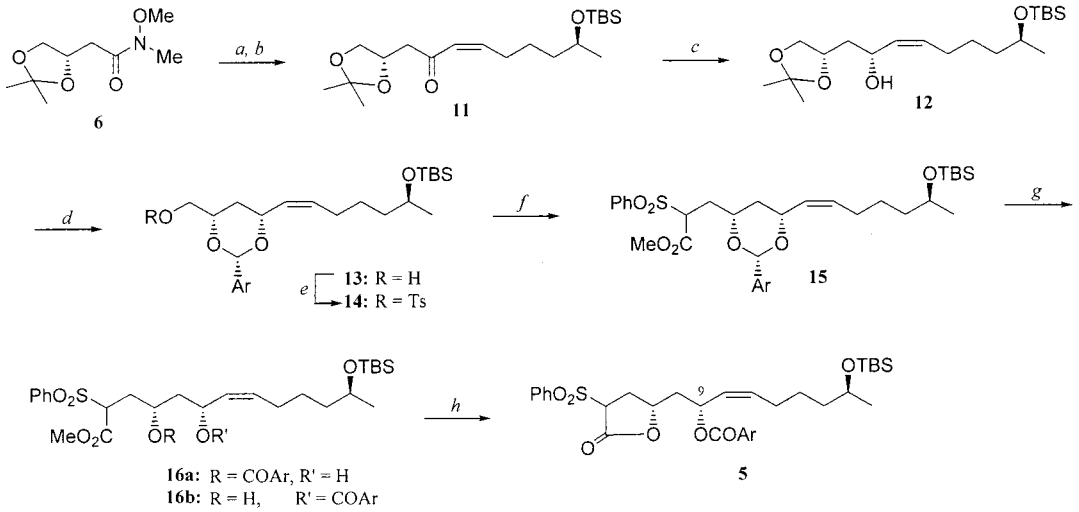
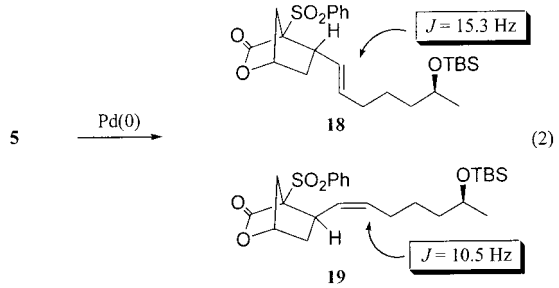
Scheme 2[a]



[a] Reagents and conditions: (a) **7**, *n*-BuLi, ThF, −78 °C, 81%; (b) Lindlar catalyst, quinoline, H_2, MeOH, 95%; (c) LAH, LiI, Et_2O, −78 °C, 95%; (d) $(MeO)_2CHC_6H_4$(*p*-OMe), CSA, CH_2Cl_2, 84%; (e) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, 99%; (f) $PhO_2SCH_2CO_2Me$, NaH, DMF, 100 °C, 72%; (g) DDQ, CH_2Cl_2/H_2O (18/1); (h) DBU, Ch_3CN, 71% for two steps.

of anisaldehyde led to the concomitant deprotection of acetonide and the formation of benzylidene acetal, thus furnishing the hydroxydioxane **13** in a good yield. Tosylation of **13** followed by benzenesulfonyl acetate displacement of the tosylate **14** provided the alkylated dioxane **15**. Finally, oxidative cleavage of benzylidene **15** and subsequent lactonization of **16** afforded the allylic benzoate **5** as the cyclization precursor. DDQ treatment[18] of **15** initially liberated a 10:1 diastereomeric mixture of hydroxyesters **16a** and **16b**. However, DBU-promoted lactonization of the isomeric mixtures afforded the desired butyrolactone **5** as the only product in a 71% yield for the two steps. The isomer **16a** seems to undergo an initial intramolecular acyl transfer and then lactonization. With the cyclization precursor **5** in hand, the crucial cyclization resulting in perfect chirality transfer was tried next.

Cyclization of the Allylic Benzoate. The cyclization of the allylic benzoate **5** was carried out according to a procedure that was previously established in our laboratory.[9a]



The cyclization of **5** in the presence of 5 mol % $Pd(dppe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in dichloromethane proceeded smoothly to afford the bicyclic lactone **18** along with a small amount of the unexpected stereoisomer **19**, as shown in Table 1 (entry 1). The *trans*- and *cis*-olefin geometries of **18** and **19**, respectively, were

Table 1. Stereoselective Cyclization of Allylic Benzoate 5 (Equation 2)

entry	reaction conditions[a]	yield (%)	ratio (18:19)[b]
1	$Pd(dppe)_2$, BSA, CH_2Cl_2, reflux	73	9:1
2	$Pd(dppe)_2$, DBU, THF, reflux	81	7:1
3	$Pd(PPh_3)_4$, DBU, THF, reflux	88	>99:<1

[a] Reactions were performed at a 0.05 M concentration. [b] Ratio was determined by 300 MHz ^{1}H NMR.

confirmed by the observed coupling constants of their olefinic hydrogens (15.3 and 10.5 Hz, respectively). The formation of the (*Z*)-isomer **19** is likely due to the direct cyclization of a part of the *syn*,*anti*-π-allyl palladium complex[19] initially derived from the (*Z*)-allylic benzoate **5**. The use of a stronger base such as DBU provided lower selectivity (entry 2). In light of the result[20] that the reaction rate for $Pd(PPh_3)_4$ is slower than that for $Pd(dppe)_2$, we attempted the cyclization of **5** in the presence of $Pd(PPh_3)_4$/DBU. To our delight, the cyclization of **5** under these conditions afforded the bicyclic lactone **18** in an excellent yield, with no detection of the (*Z*)-isomer **19**. This result would arise from the greater steric effect of $Pd(PPh_3)_4$ compared to that of $Pd(dppe)_2$, which provides the preferred *syn*,*syn*-π-allyl palladium complex $\mathbf{T_2}$ in the transition state (Figure 2). Having successfully addressed the synthesis of the bicyclic lactone **18**, we investigated the direct introduction of the requisite acrylate moiety to the bicyclic lactone intermediate **18**.

Synthetic Approach by the Three-Carbon Homologation. The sulfonyl group was initially removed by the treatment of **18** with 6% Na−Hg in the presence of $B(OH)_3$,[21] as shown in Scheme 3. The use of $B(OH)_3$ is

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(21) Unpublished results. The details for the desulfonylation procedure under extremely mild conditions will be reported soon. Professor Trost also reported the same conditions for the reductive elimination. See: Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2632.

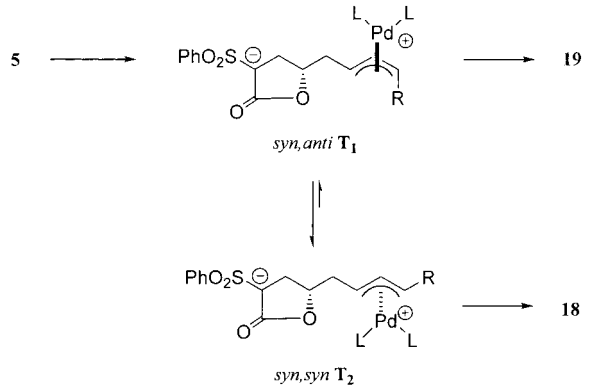
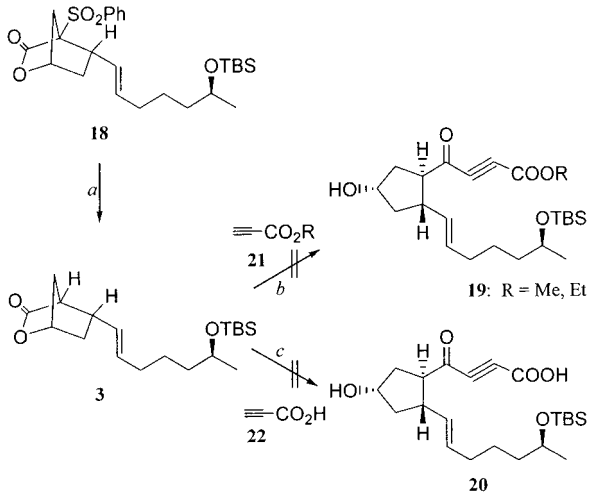


Figure 2. Transition state of Pd(0)-catalyzed cyclization.

Scheme 3[a]



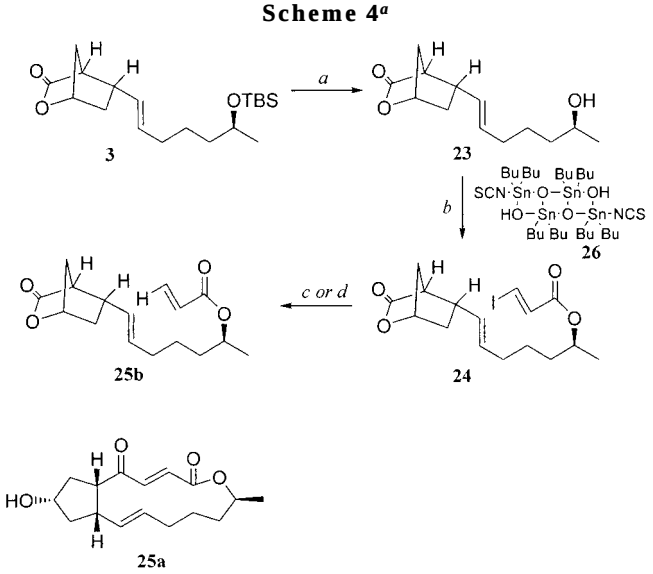
[a] Reagents and conditions: (a) 6% Na−Hg, $B(OH)_3$, MeOH, 87%; (b) **21**, *n*-BuLi or LDA, THF; (c) **22**, *n*-BuLi or LDA, DMPU or HMPA, THF.

quite crucial for the selective desulfonylation without ring opening of the bicyclic lactone.

At this point, the synthetic plan called for the alkylation of the lactone **3** with an appropriately functionalized three-carbon synthon.[22] To this end, we first attempted to utilize a propiolic acid or ester as a nucleophile (Scheme 3). However, the lithium anions of methyl and ethyl propiolate[23] (**21**) were too weakly nucleophilic to add the lactone **3** at a low temperature, despite the high degree of structural strain of the bicyclic lactone **3**. The alkylation at higher temperatures only resulted in decomposition of the reactants. In addition, the propiolic acid (**22**) dianion was not sufficiently nucleophilic to alkylate the bicyclic lactone **3** under a variety of conditions.[24]

Thus, an intramolecular acylation of the acrylate anion generated by halogen−metal exchange was investigated.

Scheme 4[a]



[a] Reagents and conditions: (a) CSA, MeOH, 97%; (b) **26**, methyl 3-iodoacrylate, toluene, reflux, 73%; (c) *n*-BuLi, THF, from −78 °C to room temperature, 77%; (d) *t*-BuLi, THF, from −78 °C to room temperature, 81%.

After TBS deprotection, the alcohol **23** was transesterified with *β*-iodo acrylate with the assistance of Otera's distannoxane catalyst **26** (Scheme 4).[25] Treatment of the *trans*-iodo acrylate **24** with *n*-BuLi or *t*-BuLi (2 equiv) did not provide the desired alkylation product **25a**. Instead, only the dehalogenated product **25b**, obtained by halogen−metal exchange followed by protonation of the resulting vinyl anion, was observed. This failure prompted us to develop a novel method for the direct introduction of the acrylate moiety to a variety of carbonyl functions including lactone.

Revised Approach Using a Trans-Vinylogous Acyl Anion. Consideration of the weak nucleophilicity of the three-carbon synthon, due to the electron-withdrawing effect of the carboxyl functionality, led us to adapt the 2,6,7-trioxabicyclo[2.2.2]octane system (OBO ortho esters)[26] as an equivalent of the carboxyl group.

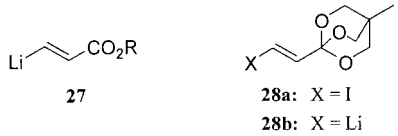


Figure 3. Trans-vinylogous acyl anion equivalent.

In addition, the OBO ortho esters were expected to serve as an excellent carboxyl equivalent, since they are resistant to attacks by strong nucleophiles and readily hydrolyzed under mild conditions.[27] Accordingly, we selected the *trans*-vinyl anion **28b**, generated by halogen−metal exchange of the corresponding (*E*)-1-(2-iodovinyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**28a**), as the best equivalent of the requisite trans-vinylogous ester

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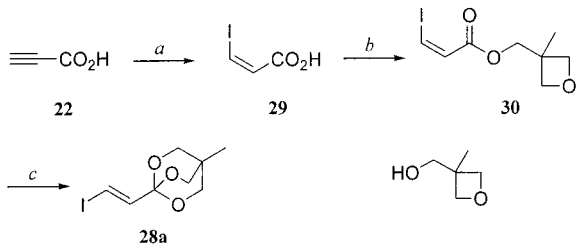
Scheme 5[a]



[a] Reagents and conditions: (a) 57% HI, H_2O, 85 °C, 90%; (b) 3-methyl-3-hydroxymethyloxetane, DCC, 4-DMAP, CH_2Cl_2, room temperature, 95%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −15 °C, 73%.

anion **27**,[28,29] as illustrated in Figure 3. To the best of our knowledge, the trans-vinylogous ester anion equivalent and its synthetic utilization have not been reported yet,[9c] although the β-alkoxy-directed *cis*-vinyl anions have been reported.[29]

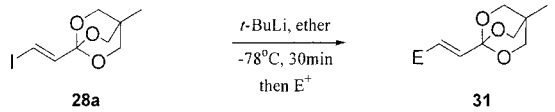
The iodovinyl OBO ortho ester **28a** was conveniently prepared from propiolic acid (**22**) via a three-step sequence. Regioselective hydroiodination[30] of propiolic acid (**22**) with 57% HI, esterfication of the resulting iodoacrylic acid **29** with 3-methyl-3-hydroxymethyloxetane, and then $BF_3{\cdot}OEt_2$-assisted rearrangement[26] of the resulting ester **30** afforded **28a** (Scheme 5).

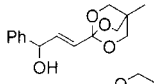
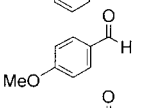
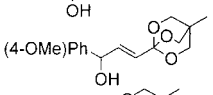
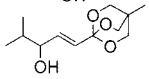
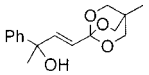
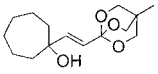
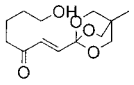
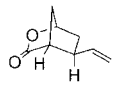
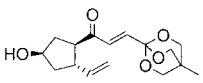
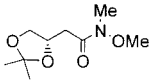
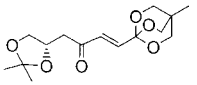
With the iodovinyl OBO ortho ester **28a** in hand, we carried out a survey of the regioselective halogen−metal exchange reaction under varying reaction conditions of base, solvent, and temperature. As expected, the iodo substituent of the vinyl OBO ortho ester **28a** turned out to be crucial for the efficient generation of the requisite *trans*-vinyl anion **28b**, since the bromo-substituted vinyl substrate afforded only the *cis*-halovinyl anion by deprotonation, rather than halogen−metal exchange.[28,29] In particular, the reverse addition of the iodoolefin **28a** to *t*-BuLi in ether provided the best results by the desired halogen−metal exchange.[9c]

Table 2 summarizes the results for the reaction of the lithium anion **28b** with a series of carbonyl compounds. As anticipated, the aldehyde and the ketone (entries 1−5) underwent facile addition reactions to afford the allylic alcohols (**31a**−**e**) in good yields. In the case of the lactones (entries 6 and 7), an extended reaction time at −78 °C and an excess amount of **28b** were necessary in order to ensure a higher yield and to avoid over-addition leading to the tertiary alcohol. It is notable that the Weinreb amide[31] (entry 8) is superior to the lactone (entry 7) for acylation of the vinyl anion **28b** in terms of the yield and the reaction time.

Application of a Trans-Vinylogous Acyl Anion Equivalent. On the basis of the above results, we first reacted the lithium anion **28b** with the bicyclic lactone **3** as shown in Scheme 6. The formation of the lithium anion **28b** (4 equiv) with *t*-BuLi (8 equiv) at −78 °C, followed by the addition of the bicyclic lactone **3** (1 equiv), afforded the enone **32** in a 51% yield as a 1:3 diastereomeric mixture of **32a** and **32b**, along with 23% of the recovered lactone **3**. The *trans*-enone **32b** was presumably produced by epimerization of **32a** due to the strongly basic reaction conditions. Moreover, direct DBU treatment of the diastereomeric mixture afforded the desired enone **32b** in a quantitative yield.

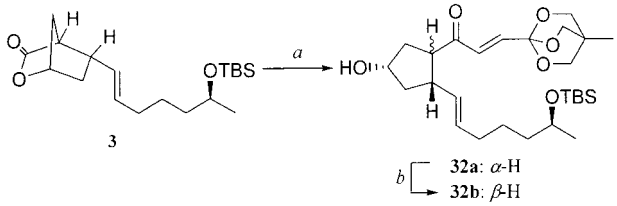
Table 2. Reaction of Trans-Vinylogous Ester Anion Equivalent 28b with Carbonyl Compounds



entry	carbonyl compounds(E^+)	reaction conditions[a]	products		yield (%)[b]
1		A		**31a**	81
2		A		**31b**	90
3		A		**31c**	75
4		A		**31d**	70
5		A		**31e**	80
6		B		**31f**	61
7		B[c]		**31g**	46(72[d])
8		B		**31h**	62

[a] Condition A: 2 equiv of **28a** was used. Condition B: 4 equiv of **28a** were used. [b] Isolated yields. [c] Temperature was maintained at −78 °C. [d] Yield based on recovered starting material.

Scheme 6[a]



[a] Reagents and conditions: (a) **28a**, *t*-BuLi, ether, −78 °C, 30 min, then **3**, −78 °C, 51%; (b) DBU, CH_2Cl_2, reflux, 99%.

Although the alkylation of **3** with **28b** was successful, the long reaction time at −78 °C and the moderate yield prompted us to investigate an alternative method for coupling **3** and **28b**. Thus, according to the Merck procedure,[32] a preliminary experiment was performed on the lactone **33**[9a] as a model compound. Transamidation of the lactone **33** under standard conditions (MeNH(OMe)·HCl, *i*PrMgCl, THF, 0 °C), followed by the addition of the resulting amide to the lithium anion **28b**, provided the hydroxy enone **34** in an excellent yield (eq 3).

Encouraged by these results, we attempted the same reaction with the bicyclic lactone **3**. Alkylation of **3** with

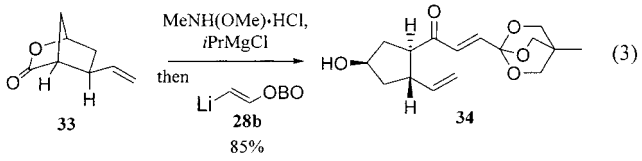
(28) For a recent review, see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2000**, *100*, 1891.

(29) For the halogen−metal exchange reaction in the related systems, see: (a) Richardson, S. K.; Jeganathan, A.; Watt, D. S. *Tetrahedron Lett.* **1987**, *28*, 2335. (b) Meyers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872.

(30) (a) Zoller, T.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 6719. (b) Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchene, A. *Synthesis.* **1996**, 82.

(31) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(32) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, Ulf-H.; Grabowski, J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

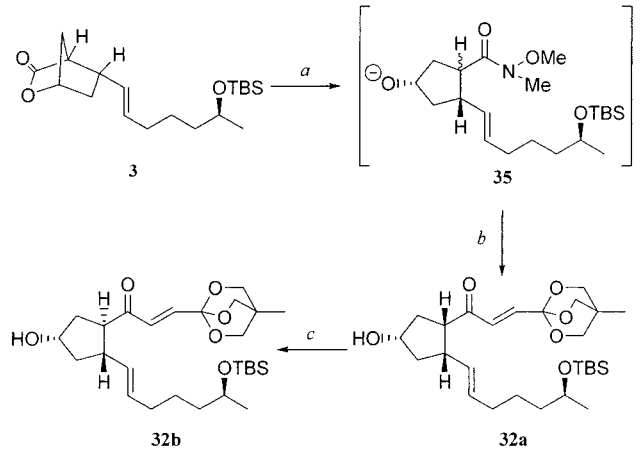


(3)

28b and then epimerization of the resulting *cis*-enone **32a** afforded the *trans*-enone **32b** in an 81% overall yield from **3**. It is notable that this facile alkylation process needs only 3 h for its completion (Scheme 7).

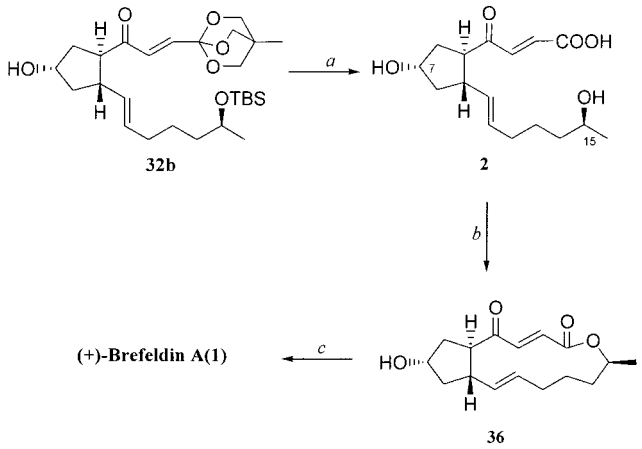
Completion of the Total Synthesis of (+)-Brefeldin A. After successful coupling of the anion **28b** with the bicyclic lactone **3**, the total synthesis of (+)-brefeldin A, shown in Scheme 8, proceeded in a straightforward fashion. Concurrent deprotection of the OBO ortho ester and the C15 TBS group of the enone **32b** with 1 N HCl gave the initial trihydroxy ester intermediate, which was directly subjected to hydrolysis ($LiOH-H_2O$, THF/H_2O) to afford the seco acid **2** in an 85% yield.

Scheme 7[a]



[a] Reagents and conditions: (a) MeNH(OMe)·HCl, ^{i}PrMgCl, THF, from −20 °C to room temperature; (b) **28a**, *t*-BuLi, ether, −78 °C, 30 min, then **35**, from −78 °C to room temperature, 81% from **3**; (c) DBU, CH_2Cl_2, reflux, 99%.

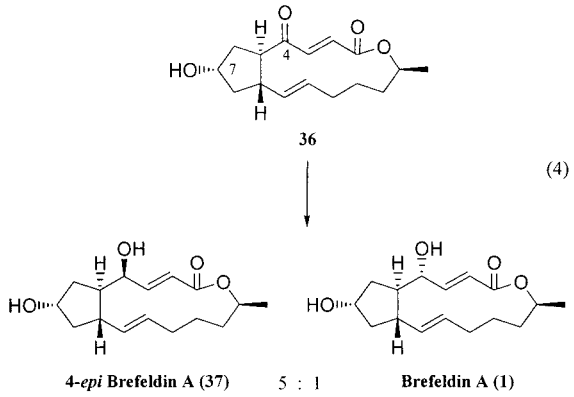
Scheme 8[a]



[a] Reagents and conditions: (a) *aq*, 1 N HCl, H_2O/THF (1/1), then LiOH, 85%; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, room temperature, 2 h, then 4-DMAP, toluene, reflux, 24 h, 51%; (c) $NaBH_4$, −78 °C, 95%.

The selective macrolactonization of the diol acid **2** was attempted in the hope that the conformational and entropic effects might favor cyclization onto the desired C15 hydroxy group, rather than the C7 hydroxy group. As we anticipated, facile macrolactonization occurred selectively at the C15 hydroxy group under the standard Yamaguchi condition[33] in the presence of the C7 hydroxy group to provide the desired 13-membered macrolactone **36** in a 51% yield.[34] The participation of the preferred C15 hydroxy group in the macrolactonization is likely due to the steric and geometric advantages. For the completion of the synthesis, stereoselective reduction of the C4 ketone remained. In previous studies on the reduction of related brefeldin A systems, it has been reported that $NaBH_4$ or K-Selectride reduction of the advanced intermediate **36** possessing the C7-hydroxyl group produces mainly 4-*epi* brefeldin A (**37**),[35] as outlined in eq 4. However, the reduction of **36** with $NaBH_4$ in MeOH at −78 °C surprisingly furnished brefeldin A (**1**) as the sole product. Moreover, the synthetic brefeldin A was identical in all aspects to authentic brefeldin A.[36] Independently, Hori and co-workers have also recently reported the same result.[6b]

Studies on the Reduction of the C4 Carbonyl Group. Thus, we investigated this interesting result in



more detail by the preparation of the intermediate **36** from the natural (+)-brefeldin A, followed by $NaBH_4$ reduction. As outlined in Scheme 9, the natural (+)-brefeldin A was converted to the known intermediate **38** by selective MEM protection of the C7 hydroxy group and PDC oxidation of the C4 hydroxy group. The intermediate **38** was again deprotected by the reported procedure ($TiCl_4$, CH_2Cl_2, 0 °C),[35a] which consistently provided a mixture of two inseparable isomers in the range from 1:2 to 1:5. Accordingly, the mixture was directly reduced with $NaBH_4$ in MeOH to afford a mixture of (+)-brefeldin A (**1**) and the (*Z*)-isomer **40** of brefeldin A, which were separated by flash column chromatography. The (*Z*)-isomer **40** seems to be formed by way of the (*Z*)-isomer **39**,[37] which is produced during MEM deprotection of **38**, along with the (*E*)-isomer **36**, by $TiCl_4$ treatment. Obvi-

(33) Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

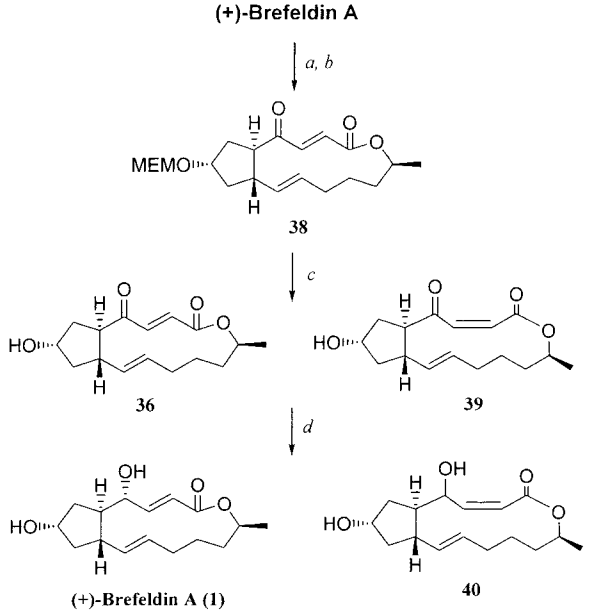
(34) For the regioselective macrolactonization of diol acid, see: (a) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192. (b) Parerson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037

(35) (a) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4701. (b) Bartlett, P. A.; Green, F. R. *J. Am. Chem. Soc.* **1978**, *100*, 4858.

(36) Authentic brefeldin A was purchased from Fluka Co.

(37) Photoinduced isomerizations of α,β-unsaturated carbonyl compound have been reported. See: (a) Smith, A. B.; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648. (b) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027.

Scheme 9[a]



[a] Reagents and conditions: (a) MEMCl, $^{i}Pr_2NEt$, CH_2Cl_2; (b) PDC, 4 Å, MS, CH_2Cl_2; (c) $TiCl_4$, CH_2Cl_2, 0 °C; (d) $NaBH_4$, MeOH, −78 °C.

ously, the major product proved to be the (*Z*)-isomer **40** by careful analysis of the spectral data. Particularly, the ^{1}H NMR spectrum shows an 11.8 Hz coupling constant for the cis olefinic hydrogens of the (*Z*)-isomer **40**.

Conclusion

In conclusion, we have achieved the enantioselective total synthesis of (+)-brefeldin A in 15 linear steps with a 7.9% overall yield. The key features of this synthetic route involve the following: (1) the highly stereoselective construction of the hydroxycyclopentane skeleton of (+)-brefeldin A via Pd(0)-catalyzed allylic cyclization; (2) the efficient preparation of the γ-keto acrylate by the direct introduction of the trans-acrylate moiety to the lactone carbonyl, utilizing a novel vinylogous acyl anion equivalent; (3) the ring-size selective macrolactonization of the diol acid; and (4) the stereoselective reduction of the C4 ketone of an advanced brefeldin A intermediate. These studies provide a timely contribution to the development of a practical synthetic approach to a variety of brefeldin A analogues. With this practical synthesis of (+)-brefeldin A now in hand, the intensive exploration of the promising biological properties of this macrolide will be extended.

Experimental Section

General Procedure. Unless noted otherwise, all starting materials were obtained from commercial suppliers and used without further purification. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230−400 mesh) with indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel F_{254} plates. Optical rotations were measured using sodium light (D line 589.3 nm)

(4*S*)-4-[*tert*-Butyl(dimethyl)silyl]oxy-1-pentanol (9): (i) Hydrogenation. To a solution of **8** (27 g, 0.105 mol) in EtOH (50 mL) was added 10% Pd/C (1.2 g), and the mixture was stirred under an H_2 atmosphere using a balloon at ambient temperature. After stirring for 5 h, the reaction mixture was filtered through a pad of Celite and washed with Et_2O. The filtrate was concentrated (<30 °C bath temperature) and dried on a vacuum pump to give 27 g of crude ester as a colorless oil, which was directly used for the next step: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, 2H, J = 7.1 Hz), 3.74−3.86 (m, 1H), 2.24−2.41 (m, 2H), 1.62−1.71 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.08 (d, 3H, J = 6.0 Hz), 0.83 (s, 9H), 0.00 (s, 6H).

(ii) DIBAL Reduction. To a solution of the above ester (27.0 g, 0.104 mol) in CH_2Cl_2 (100 mL) at −78 °C was added DIBAL (41.0 mL, 0.228 mol) dropwise over 30 min. After the mixture was stirred for 1 h at −40 °C, the reaction was quenched by slow addition of MeOH. A 15% aqueous Rochelle solution was added, and the mixture was stirred at ambient temperature for 2 h. After separation of the organic layers, the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford 22.1 g (98% for two steps) of alcohol **9** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77−3.86 (m, 1H), 3.48−3.61 (m, 2H), 2.32 (bs, 1H), 1.51−1.61 (m, 2H), 1.08 (d, 3H, J = 6.0 Hz), 0.83 (s, 9H), 0.00 (s, 6H); IR (neat) 3360 cm^{-1}.

(4*S*)-4-[*tert*-Butyl(dimethyl)silyl]oxypentyl 4-Methylbenzenesulfonate (10). To a solution of the alcohol **9** (22.0 g, 0.101 mol) and Et_3N (15.0 mL, 0.151 mol) in CH_2Cl_2 (100 mL) at 0 °C were added *p*-toluenesulfonyl chloride (18.0 g, 0.096 mol) and DMAP (1.20 g, 10.1 mmol). After stirring for 3 h at ambient temperature, the mixture was diluted with CH_2Cl_2 and saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (5% EtOAc/hexanes) to afford 34.0 g (91%) of tosylate **10** as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 2H, J = 6.0 Hz), 7.32 (d, 2H, J = 6.0 Hz), 4.01 (t, 2H, J = 6.3 Hz), 3.67−3.77 (m, 1H), 2.43 (s, 3H), 1.55−1.80 (m, 2H), 1.31−1.42 (m, 2H), 1.06 (d, 3H, J = 6.0 Hz), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 133.2, 129.7, 127.8, 70.8, 67.6, 35.1, 25.7, 25.1, 23.6, 21.5, 17.9, −4.4, −4.8; IR (neat) 2928, 1540, 1255 cm^{-1}.

(6*S*)-6-(*tert*-Butyldimethylsilyl)oxy-1-heptyne (7). To a solution of the tosylate **10** (9.5 g, 25.5 mmol) in DMSO (20 mL) at ambient temperature was added lithium acetylide ethylenediamine (3.13 g, 30.6 mol). After the mixture was stirred for 2 h, the reaction was quenched by a slow addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (5% EtOAc/hexanes) to afford 5.12 g (89%) of heptyne **7** as a colorless oil: $[\alpha]^{17}_D$ +14.2 (*c* 3.7, CH_2Cl_2) [lit.[38] $[\alpha]^{20}_D$ +14.5 (*c* 7.0, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72−3.81 (m, 1H), 2.11−2.17 (m, 2H), 1.89 (t, 1H, J = 2.4 Hz), 1.42−1.64 (m, 4H), 1.08 (d, 3H, J = 6.0 Hz), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 84.6, 68.2, 68.1, 38.6, 25.9, 24.7, 23.7, 18.4, 18.1, −4.4, −4.8; IR (neat) 2857, 2116 cm^{-1}.

(*Z*,8*S*)-8-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-nonen-2-one (11): (i) Alkylation of the Weinreb Amide 6. To a solution of the silyloxyheptyne **7** (1.29 g, 5.75 mmol) in THF (10 mL) at −78 °C was slowly added *n*-BuLi (1.5 M solution in *n*-hexane, 3.80 mL, 5.70 mmol). After stirring for 10 min at −78 °C and for 20 min at −20 °C, the solution was added dropwise via cannula to a solution of **6** (0.970 g, 4.78 mmol) in THF (10 mL) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by an addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 1.43 g (81%) of ynone as a colorless oil: $[\alpha]^{17}_D$ +15.5 (*c* 5.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.46−4.54 (m, 1H), 4.13

(38) Drian, C. L.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473.

(dd, 1H, J = 8.2, 5.8 Hz), 3.72−3.82 (m, 1H), 3.55 (dd, 1H, J = 8.2, 6.3 Hz), 2.96 (dd, 1H, J = 16.8, 6.3 Hz), 2.69 (dd, 1H, J = 16.8, 7.1 Hz), 2.34 (t, 2H, J = 6.8 Hz), 1.42−2.36 (m, 4H), 1.37 (s, 3H), 1.31 (s, 3H), 1.09 (d, 3H, J = 6.0 Hz), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.6, 109.0, 95.2, 80.8, 71.4, 69.1, 67.8, 49.8, 38.5, 26.8, 25.8, 25.4, 23.8, 23.7, 19.0, 18.0, −4.4, −4.8; IR (neat) 2930, 2212, 1672 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{37}O_4Si_1$ (M^+ + H) 369.2461, found 369.2458.

(ii) Partial Hydrogenation. To a solution of the above ynone (590 mg, 1.60 mmol) in MeOH (20 mL) was added 5% Pd on $CaCO_3$ (47.6 mg) and quinoline (120 μL, 1.02 mmol), and the reaction mixture was stirred under an H_2 atmosphere using a balloon. After stirring for 2 h, the reaction mixture was filtered through a pad of Celite, which was then rinsed with Et_2O. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 563 mg (95%) of enone **11** as a colorless oil: $[\alpha]^{16}_D$ +16.2 (c 6.80, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.11 (d, 1H, J = 11.2 Hz), 6.05 (dd, 1H, J = 11.2, 6.0 Hz), 4.40−4.48 (m, 1H), 4.17 (dd, 1H, J = 8.2, 5.8 Hz), 3.71−3.77 (m, 1H), 3.52 (dd, 1H, J = 8.2, 6.8 Hz), 2.92 (dd, 1H, J = 16.8, 5.6 Hz), 2.59 (dd, 1H, J = 16.8, 7.6 Hz), 2.54−2.59 (m, 2H), 1.34−1.54 (m, 4H), 1.37 (s, 3H), 1.32 (s, 3H), 1.07 (d, 3H, J = 6.0 Hz), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.4, 149.6, 126.3, 108.5, 71.7, 69.4, 68.1, 48.2, 39.1, 29.3, 26.7, 25.8, 25.3, 25.1, 23.7, 18.0, −4.5, −4.9; IR (neat) 2930, 1693, 1616 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{39}O_4Si_1$ (M^+ + H) 371.2618, found 371.2624.

(2*R*,3*Z*,8*S*)-8-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-nonen-2-ol (12). To a solution of the enone **11** (200 mg, 0.54 mmol) in Et_2O (10 mL) at −40 °C was added LiI (723 mg, 5.40 mmol). After the mixture was stirred for 10 min at −40 °C, LAH (100 mg, 2.64 mmol) was added in one portion at −78 °C. The reaction mixture was stirred at −78 °C for 30 min before the reaction was quenched by the addition of MeOH. A 15% aqueous Rochelle solution and EtOAc were added, and the mixture was stirred at ambient temperature for 1 h. Separation of the layers was followed by extraction of the aqueous phase with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 198 mg (99%) of allylic alcohol **12** as a colorless oil: $[\alpha]^{13}_D$ +13.7 (c 9.75, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.32−5.48 (m, 2H), 4.63 (dt, 1H, J = 8.0, 4.4 Hz), 4.14−4.23 (m, 1H), 4.04 (dt, 1H, J = 8.0, 6.0 Hz), 3.68−3.76 (m, 1H), 3.51 (t, 1H, J = 7.5 Hz), 2.63 (bs, 1H), 2.00−2.07 (m, 2H), 1.28−1.84 (m, 6H), 1.28 (s, 3H), 1.22 (s, 3H), 1.07 (d, 3H, J = 6.0 Hz), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.0, 131.7, 109.0, 74.5, 69.5, 68.3, 66.3, 40.7, 39.2, 27.6, 26.8, 25.8, 25.7, 23.7, 18.0, −4.5, −4.8; IR (neat) 3418, 2930 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{41}O_4Si_1$ (M^+ + H) 373.2774, found 373.2764.

(2*S*,4*S*,6*R*)-6-((*Z*,6*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy-1-heptenyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-methanol (13). To a solution of the allylic alcohol **12** (76 mg, 0.20 mmol) and CSA (4.7 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) at ambient temperature was added *p*-anisaldehyde dimethylacetal (104 μL, 0.61 mmol). After the mixture was stirred for 4 h, the reaction was quenched by an addition of saturated aqueous $NaHCO_3$ and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford 77 mg (84%) of benzylidene alcohol **13** as a colorless oil: $[\alpha]^{15}_D$ −40.5 (c 7.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, 2H, J = 6.8 Hz), 6.84 (d, 2H, J = 6.8 Hz), 5.54 (s, 1H), 5.40−5.52 (m, 2H), 4.58−4.65 (m, 1H), 3.95−4.01 (m, 1H), 3.75 (s, 3H), 3.61−3.75 (m, 3H), 2.03−2.10 (m, 2H), 1.32−1.67 (m, 6H), 1.07 (d, 3H, J = 6.0 Hz), 0.84 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.9, 132.9, 130.9, 129.3, 127.5, 113.5, 100.6, 76.9, 72.8, 68.4, 65.4, 55.1, 39.2, 32.5, 27.9, 25.8, 25.7, 23.8, 18.0, −4.5, −4.8; IR (neat) 3436, 2929 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{43}O_5Si_1$ (M^+ + H) 451.2880, found 451.2878.

(2*S*,4*S*,6*R*)-6-((*Z*,6*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy-1-heptenyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-methyl-4-methyl-benzenesulfonate (14). To a solution of the alcohol **13** (450 mg, 0.998 mmol), Et_3N (280 μL, 2.01 mmol), and 4-DMAP (13.0 mg, 0.106 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (229 mg, 1.20 mmol). The mixture was stirred for 30 min at 0 °C and warmed to ambient temperature. After stirring for an additional 5 h, the reaction mixture was extracted with EtOAc and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (15% EtOAc/hexanes) to afford 589 mg (99%) of tosylate **14** as a colorless oil: $[\alpha]^{13}_D$ −18.3 (c 6.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (dd, 2H, J = 6.6, 1.7 Hz), 7.21−7.31 (m, 4H), 6.80 (d, 2H, J = 6.8 Hz), 5.44 (s, 1H), 5.35−5.51 (m, 2H), 4.51−4.58 (m, 1H), 3.98−4.11 (m, 3H), 3.75 (s, 3H), 3.69−3.75 (m, 1H), 2.38 (s, 3H), 2.01−2.08 (m, 2H), 1.31−1.54 (m, 6H), 1.07 (d, 3H, J = 6.0 Hz), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 144.7, 133.2, 132.7, 130.4, 129.7, 128.8, 127.9, 127.4, 113.3, 100.4, 73.5, 72.5, 71.4, 68.3, 55.2, 39.2, 32.7, 27.9, 25.8, 25.6, 23.8, 21.5, 18.0, −4.4, −4.8; IR (neat) 2929 cm^{-1}; LRMS (CI) m/z 603 (M^+ − H).

Methyl 3-[(2*R*,4*S*,6*R*)-6-((*Z*,6*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-heptenyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-2-(phenylsulfonyl)propanoate (15). To a suspension of NaH (60% in mineral oil, 87.6 mg, 2.19 mmol) in DMF (3 mL) at 0 °C was added dropwise a solution of methyl benzenesulfonyl acetate (469 mg, 2.19 mmol) in DMF (8 mL). After stirring for 30 min, a solution of the tosylate **14** (530 mg, 0.876 mmol) in DMF (10 mL) was added. The solution was warmed to 100 °C and stirred for 7 h. The reaction was quenched by an addition of saturated aqueous NH_4Cl, and the reaction mixture was diluted with EtOAc. The reaction mixture was extracted with EtOAc and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford 408 mg (72%) of **15** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H, J = 7.8 Hz), 7.64−7.66 (m, 1H), 7.54 (dt, 2H, J = 7.8, 1.5 Hz), 7.26−7.31 (m, 2H), 6.78−6.85 (m, 2H), 5.40, 5.42 (s, 1H), 5.37−5.54 (m, 2H), 4.52−4.61 (m, 1H), 4.33−4.38, 4.01−4.15 (m, 1H), 3.96−4.03, 3.78−3.83 (m, 1H), 3.77, 3.75 (s, 3H), 3.69−3.75 (m, 1H), 3.61, 3.37 (s, 3H), 2.17−2.39 (m, 2H), 2.00−2.13 (m, 2H), 1.21−1.55 (m, 6H), 1.10, 1.08 (d, 3H, J = 6.0 Hz), 0.86, 0.85 (s, 9H), 0.02 (s, 6H); IR (neat) 1746, 1615 cm^{-1}; LRMS (EI) m/z 589 (M^+ − tC$_4$H$_9$).

(1*R*,2*Z*,7*S*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-[(2*S*)-5-oxo-4-(phenylsulfonyl)tetrahydro-2-furanyl]methyl-2-octenyl 4-Methoxybenzoate (5): (i) Oxidative Cleavage of the PMB Group. To a solution of **15** (242 mg, 0.374 mmol) in CH_2Cl_2/water (18:1, 5 mL) at ambient temperature was added DDQ (262 mg, 1.15 mmol). The reaction mixture was stirred for 2 h and additional DDQ (281 mg, 1.24 mmol) was added. After stirring for 24 h, the reaction mixture was diluted with CH_2Cl_2, filtered through silica gel, and concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexanes) to afford 240 mg of a mixture of **16a** and **16b** (10:1) as a colorless oil. Major isomer **16b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80−7.90 (m, 4H), 7.62−7.66 (m, 1H), 7.52−7.56 (m, 2H), 6.64−6.90 (m, 2H), 5.29−5.45 (m, 2H), 5.11−5.19 (m, 1H), 4.52−4.58 (m, 1H), 4.05−4.14 (m, 1H), 3.84, 3.82 (s, 3H), 3.64−3.71 (m, 1H), 3.51, 3.23 (s, 3H), 2.35−2.60 (m, 2H), 1.74−2.21 (m, 4H), 1.19−1.47 (m, 4H), 1.05, 1.04 (d, 3H, J = 6.0 Hz), 0.85, 0.84 (s, 9H), 0.00 (s, 6H)

(ii) Lactonization of Hydroxy Esters 16a and 16b. To a solution of a mixture (240 mg) of **16a** and **16b** in CH_3CN (5 mL) at ambient temperature was added DBU (65 μL, 0.43 mmol). After stirring for 18 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford 152 mg (71% for two steps) of lactone **5** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88−7.96 (m, 4H), 7.65−7.68 (m, 1H),

7.53−7.59 (m, 2H), 6.87−6.91 (m, 2H), 5.85−5.92 (m, 1H), 5.58−5.69 (m, 1H), 5.38−5.45 (m, 1H), 4.70−4.77, 4.49−4.54 (m, 1H), 4.14−4.20, 4.00−4.04 (m, 1H), 3.83 (s, 3H), 3.70−3.77 (m, 1H), 1.85−3.19 (m, 5H), 1.32−1.45 (m, 5H), 1.08, 1.05 (d, 3H, J = 6.0 Hz), 0.83 (s, 9H), 0.00 (s, 6H); IR (neat) 2929, 1779, 1714 cm^{-1}; LRMS (EI) 573 ($M^+ - tC_4H_9$).

5-((*E*,6*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-heptenyl)-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-3-one (18). To a solution of the allylic benzoate **5** (70 mg, 0.11 mmol) and DBU (26 μL, 0.17 mmol) in THF (5 mL) heated at reflux was added a solution of $Pd(PPh_3)_4$ (6.4 mg, 5.5 μmol) in THF (1 mL). After stirring for 3 h, the reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexanes) to afford 46.7 mg (88%) of bicyclic lactone **18** as a colorless oil: $[\alpha]^{11}_D$ −35.2 (*c* 1.45, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, 2H, J = 7.2 Hz), 7.61 (t, 1H, J = 7.2 Hz), 7.50 (t, 2H, J = 7.2 Hz), 5.45 (dt, 1H, J = 15.3, 6.6 Hz), 5.01 (dd, 1H, J = 15.3, 9.0 Hz), 4.81 (bs, 1H), 3.64−3.74 (m, 1H), 3.40−3.53 (m, 1H), 2.54 (dt, 1H, J = 10.2, 2.7 Hz), 2.42 (ddd, 1H, J = 13.4, 10.7, 2.0 Hz), 2.27 (d, 1H, J = 10.2 Hz), 1.71−1.82 (m, 3H), 1.15−1.39 (m, 4H), 1.05 (d, 3H, J = 6.0 Hz), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 136.9, 135.4, 130.5, 128.7, 126.0, 77.5, 74.9, 68.4, 43.7, 41.4, 39.1, 38.2, 32.2, 25.9, 24.8, 23.7, 18.2, −4.4, −4.7; IR (neat) 1788 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{29}O_5S_1Si_1$ ($M^+ - tC_4H_9$) 421.1505, found 421.1505.

5-((*E*,6*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-heptenyl)-2-oxabicyclo[2.2.1]heptan-3-one (3). To a solution of the bicyclic lactone **18** (10 mg, 0.021 mmol) and boric acid (13 mg, 0.21 mmol) in MeOH (1 mL) was added 6% Na/Hg (48 mg, 0.13 mmol) in one portion. After stirring for 1 h, the reaction was quenched by an addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexanes) to afford 6.1 mg (87%) of lactone **3** as a colorless oil: $[\alpha]^{11}_D$ −19.4 (*c* 0.22, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.52 (dt, 1H, J = 15.0, 6.6 Hz), 5.25 (dd, 1H, J = 15.0, 8.5 Hz), 4.82 (bs, 1H), 3.69−3.75 (m, 1H), 2.83−2.92 (m, 1H), 2.78 (d, 1H, J = 2.4 Hz), 2.19 (ddd, 1H, J = 10.5, 4.0, 2.4 Hz), 2.09 (ddd, 1H, J = 13.4, 10.2, 2.0 Hz), 1.90−1.98 (m, 2H), 1.68 (d, 1H, J = 10.5 Hz), 1.59 (ddd, 1H, J = 13.4, 4.8, 2.4 Hz), 1.21−1.41 (m, 4H), 1.06 (d, 3H, J = 6.0 Hz), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3, 133.2, 129.3, 80.6, 68.4, 48.3, 40.8, 39.6, 39.1, 35.1, 32.4, 25.9, 25.4, 23.8, 18.1, −4.4, −4.7; IR (neat) 1789 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{25}O_3Si_1$ ($M^+ - tC_4H_9$) 281.1573, found 281.1573.

(*Z*)-3-Iodo-propenoic Acid (29). To a solution of the propiolic acid **22** (6.2 g, 88 mmol) in water (13 mL) was added 57% HI (17.6 mL). The mixture was stirred for 24 h at 85 °C and then cooled to ambient temperature. The reaction mixture was diluted with 1 N aqueous HCl and Et_2O and extracted with Et_2O. The combined organic layers were washed with 10% sodium thiosulfate and brine, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization of the residue from hot hexanes afforded 15.8 g (91%) of acid **29** as a white solid. The acid **29** thus obtained displayed NMR spectra and mp identical to literature data:[30] mp 65−67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, 1H, J = 9.0 Hz), 6.96 (d, 1H, J = 9.0 Hz).

(3-Methyl-3-oxetanyl)methyl (*Z*)-3-Iodo-2-propenoate (30). To a solution of the acid **29** (5.2 g, 26 mmol) in CH_2Cl_2 (30 mL) at ambient temperature was added oxetane **31** (2.8 g, 27 mmol), DMAP (1.0 g, 8.0 mmol), and then DCC (5.8 g, 28 mmol). After stirring for 1 h, the reaction mixture was diluted with *n*-hexane, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash column chromatography (33% EtOAc/hexanes) to afford 6.9 g (95%) of ester **30** as a white solid: mp 144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, 1H, J = 14.9 Hz), 6.86 (d, 1H, J = 14.9 Hz), 4.46 (d, 2H, J = 13.9 Hz), 4.34 (d, 2H, J = 6.1 Hz), 4.17 (s, 2H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3, 129.5, 95.4, 79.3, 68.8, 38.8, 21.1; IR (neat) 3439, 1725 cm^{-1}; LRMS (EI) *m*/*z* 282 (M^+); HRMS (EI) calcd for $C_8H_{11}O_3I$ (M^+) 281.9753, found 281.9760.

1-[(*E*)-2-Iodoethenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (28a). To a solution of the ester **30** (550 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) at −15 °C was added boron trifluoride etherate (60 μL, 0.50 mmol). After the mixture was stirred for 24 h at the same temperature, the reaction was quenched by an addition of triethylamine (60 μL, 0.60 mmol). The reaction mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes with 2% Et_3N) to afford 480 mg (87%) of OBO ortho ester **28a** as a white solid: mp 97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.81 (d, 1H, J = 14.6 Hz), 6.43 (d, 1H, J = 14.6 Hz), 3.89 (s, 6H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 75M Hz) δ 140.1, 106.5, 84.5, 72.9, 30.5, 14.4; IR (neat) 2936, 2874, 1625, 1469, 1396, 1348, 1315, 1176, 1046, 996, 883, 772, 656 cm^{-1}; LRMS (EI) *m*/*z* 282 (M^+); HRMS (EI) calcd for $C_8H_{11}O_3I$ (M^+) 281.9753, found 281.9759.

Standard Procedure for an Addition of the *trans*-Vinyl Anion 28b to a Carbonyl Compound: (*E*)-3-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-phenyl-2-propen-1-ol (31a). To a solution of *t*-BuLi (1.7 M solution in pentane, 0.63 mL, 1.1 mmol) at −78 °C was added a solution of the iodovinyl OBO ortho ester **28a** (150 mg, 0.53 mmol) in anhydrous ether (2 mL). After the mixture was stirred for 30 min at the same temperature, a solution of benzaldehyde (28 mg, 0.26 mmol) in anhydrous ether (1 mL) was added dropwise using a cannula. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with water, and then the mixture was diluted with Et_2O. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexanes with 1% (v/v) triethylamine) to afford 73 mg (81%) of **31a** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.25−7.35 (m, 5H), 6.17 (dd, 1H, J = 15.6, 5.8 Hz), 5.65 (dd, 1H, J = 15.6, 1.4 Hz), 3.93 (s, 6H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 136.4, 127.9, 127.1, 126.1, 125.0, 106.0, 72.9, 72.4, 29.9, 12.9; IR (neat) 3437 cm^{-1}; LRMS (EI) *m*/*z* 262 (M^+), 233, 161; HRMS (EI) calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1205.

(*E*)-1-(4-Methoxyphenyl)-3-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]oct-1-yl)-2-propen-1-ol (31b): ^{1}H NMR (300 MHz, CD_3OD) δ 7.23 (d, 2H, J = 9.5 Hz), 6.86 (d, 2H, J = 9.5 Hz), 6.14 (dd, 1H, J = 15.6, 5.9 Hz), 5.61 (d, 1H, J = 15.6 Hz), 5.07 (d, 1H, J = 5.9 Hz), 4.85 (d, 1H, J = 3.0 Hz), 3.90 (s, 6H), 3.75 (s, 3H), 0.77 (d, 3H, J = 3.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 159.2, 136.6, 134.7, 127.5, 124.8, 113.4, 106.0, 72.5, 72.4, 54.3, 29.9, 12.9; IR (neat) 3440 cm^{-1}; LRMS (EI) *m*/*z* 292 (M^+); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1311.

(*E*)-4-Methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-penten-3-ol (31c). Compound **31c** was decomposed to the corresponding diol ester in $CDCl_3$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, 1H, J = 15.6, 4.9 Hz), 6.07 (dd, 1H, J = 15.6, 1.7 Hz), 4.24 (s, 2H), 3.53 (m, 5H), 2.25 (bs, 3H), 1.80 (m, 1H), 0.93 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.8 Hz), 0.84 (s, 3H)

(*E*)-4-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-phenylbut-3-en-2-ol (31d): ^{1}H NMR (300 MHz, CD_3OD) δ 7.40−7.44 (m, 2H), 7.17−7.31 (m, 3H), 6.28 (dd, 1H, J = 15.8, 1.0 Hz), 5.57 (d, 1H, J = 15.6 Hz), 3.91 (s, 6H), 3.29−3.31 (m, 1H), 1.56 (s, 3H), 0.79 (d, 3H, J = 1.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 146.4, 140.8, 127.6, 126.4, 125.0, 122.8, 106.2, 73.0, 72.4, 29.9, 28.2, 12.9; IR (neat) 3455 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_4$ 276.1362, found 276.1369.

(*E*)-1-[2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-vinyl]-cycloheptanol (31e): ^{1}H NMR (400 MHz, CD_3OD) δ 6.16 (d, 1H, J = 15.7 Hz), 5.54 (d, 1H, J = 15.7 Hz), 3.95 (s, 6H), 1.67−1.39 (m, 12H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 142.1, 121.3, 106.3, 74.2, 72.4, 40.4, 29.8, 29.3, 21.7, 12.9; IR (neat) 3463 cm^{-1}; LRMS (EI) *m*/*z* 268 (M^+); HRMS (EI) calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1680.

(*E*)-7-Hydroxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-hept-1-en-3-one (31f): ^{1}H NMR (300 MHz, CD_3OD) δ 6.44 (d, 1H, J = 15.8 Hz), 6.40 (d, 1H, J = 15.8 Hz), 3.97 (s,

6H), 3.54 (t, 2H, J = 6.3 Hz), 2.65 (t, 2H, J = 6.8 Hz), 1.69−1.81 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 203.5, 140.0, 133.0, 107.8, 74.8, 63.4, 41.9, 33.7, 32.4, 22.1, 15.0; IR (neat) 3443, 1682, 1652 cm^{-1}; LRMS (EI) m/z 56 (M^+); HRMS (EI) calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1323.

(*E*)-1-[(1*R*,2*S*,4*R*)-4-Hydroxy-2-vinylcyclopentyl]-3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-propen-1-one (31g): ^{1}H NMR (300 MHz, CD_3OD) δ 6.57 (d, 1H, J = 15.9 Hz), 6.49 (d, 1H, J = 15.9 Hz), 5.76 (ddd, 1H, J = 17.3, 10.2, 7.8 Hz), 5.02 (d, 1H, J = 15.6 Hz), 4.98 (d, 1H, J = 7.6 Hz), 4.31 (bs, 1H), 3.96 (s, 6H), 3.03 (m, 2H), 2.65 (d, 1H, J = 6.8 Hz), 2.15−1.84 (m, 3H), 1.61 (m, 1H), 0.83 (s, 3H).

(*E*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-3-buten-2-one (31h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 2H), 4.42 (m, 1H), 4.12 (dd, 1H, J = 8.3, 6.6 Hz), 3.92 (s, 6H), 3.46 (dd, 1H, J = 8.3, 6.6 Hz), 3.03 (dd, 1H, J = 17.3, 8.0 Hz), 2.65 (dd, 1H, J = 17.3, 8.0 Hz), 1.03 (s, 3H), 0.80 (s, 3H).

Preparation of the Enone 32b: (i) Alkylation of the Lactone 3. To a solution of *t*-BuLi (1.7 M solution in pentane, 700 μL, 1.18 mmol) in Et_2O (1 mL) at −78 °C was added a solution of the iodovinyl OBO ortho ester **28a** (167 mg, 0.59 mmol) in Et_2O (1 mL). After the mixture was stirred for 30 min at the same temperature, a solution of the bicyclic lactone **3** (40 mg, 0.12 mmol) in Et_2O (1 mL) was added dropwise. The mixture was stirred for 12 h at −78 °C, and the reaction was quenched with water. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexanes with 1% (v/v) triethylamine) to afford 30 mg (51%) of enone **32** as a colorless oil. Careful analysis of ^{1}H NMR spectrum revealed a 3:1 **32a**:**32b** diastereomeric mixture.

(ii) Epimerization of the Diastereomeric Mixture of 32a and 32b. To a solution of the above mixture (30 mg, 0.061 mmol) in CH_2Cl_2 (2 mL) was added DBU (5 mg, 0.03 mmol). After heating at reflux for 2 h, the reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexanes with 1% (v/v) triethylamine) to afford 30 mg (99%) of *trans*-enone **32b** as a colorless oil: $[\alpha]^{11}_D$ −29.0 (*c* 0.14, CH_3OH); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.51 (dd, 1H, J = 15.8, 1.2 Hz), 6.43 (dd, 1H, J = 15.8, 1.2 Hz), 5.36 (m, 2H), 4.33 (bs, 1H), 3.93 (s, 6H), 3.71 (m, 1H), 3.14 (q, 1H, J = 8.3 Hz), 2.71 (m, 1H), 2.20 (ddd, 1H, J = 13.9, 9.0, 6.1 Hz), 1.83−2.03 (m, 4H), 1.21−1.49 (m, 4H), 1.06 (dd, 3H, J = 6.1, 1.0 Hz), 0.84 (s, 9H), 0.80 (s, 3H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3, 137.5, 132.7, 131.3, 130.9, 105.8, 72.9, 72.8, 68.5, 53.7, 44.3, 42.4, 39.2, 39.1, 32.3, 30.6, 25.9, 25.4, 23.7, 18.1, 14.4, −4.5, −4.7; IR (neat) 3441, 1651 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{46}O_6Si_1$ 494.3064, found 494.3064.

Preparation of 32b through Weinreb Amide: (i) Preparation of the Weinreb Amide 35. To a slurry of the bicyclic lactone **3** (24 mg, 0.07 mmol) and *N*,*O*-dimethylhydroxyamine hydrochloride (28 mg, 0.29 mmol) in THF (1 mL) at −20 °C was added *i*PrMgCl (2.0 M solution in ether, 0.28 mL, 0.56 mmol) over 10 min. The mixture was warmed to room temperature and stirred for 1 h.

(ii) Alkylation of the Weinreb Amide 35. To a solution of *t*-BuLi (1.7 M solution in pentane, 0.33 mL, 0.56 mmol) in Et_2O (0.5 mL) at −78 °C under argon was added a solution of the iodovinyl OBO ortho ester **28a** (80 mg, 0.28 mmol) in Et_2O (1 mL). After the mixture was stirred for 30 min at the same temperature, the above Weinreb amide was added dropwise using a cannula. After the mixture was stirred for 3 h, the reaction was quenched with water. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (30% EtOAc/hexanes with 1% (v/v) triethylamine) of the residue afforded 28 mg (81%) of enone **32a** as a colorless oil.

(iii) Epimerization of the Enone 32a. To a solution of **32a** (28 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (5 mg, 0.03 mmol). The reaction mixture was heated at reflux for 2 h and concentrated in vacuo. The residue was purified by flash column chromatography (30% EtOAc/hexanes with 1% (v/v) triethylamine) to afford 28 mg (99%) of *trans*-enone **32b** as a colorless oil.

Preparation of the Dihydroxy Acid 2. To a solution of **32b** (15 mg, 0.03 mmol) in a mixture of THF and water (1:1, 1 mL) was added 1 N HCl (0.1 mL). The reaction mixture was stirred for 2 h, and lithium hydroxide monohydrate (8 mg, 0.19 mmol) was added. After stirring for an additional 2 h, the reaction mixture was acidified with 1 N HCl (pH < 3) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification via flash column chromatography of the residue with a mixture of benzene, THF, and formic acid (15:5:1) afforded 7.5 mg (85%) of dihydroxy acid **2** as a colorless oil: $[\alpha]^{11}_D$ −31.3 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.04 (d, 1H, J = 15.9 Hz), 6.62 (d, 1H, J = 15.9 Hz), 5.49 (dd, 1H, J = 15.2, 8.4 Hz), 5.40 (dt, 1H, J = 15.2, 6.4 Hz), 4.26 (m, 1H), 3.68 (m, 1H), 3.27 (q, 1H, J = 8.8 Hz), 2.64 (quintet, 1H, J = 8.6 Hz), 2.22 (m, 1H), 1.98−2.06 (m, 3H), 1.85 (m, 1H), 1.36−1.51 (m, 6H), 1.12 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 201.7, 167.1, 139.2, 133.0, 131.4, 130.8, 71.5, 67.0, 53.9, 48.4, 45.2, 42.2, 38.2, 37.9, 32.0, 25.3, 22.0; IR (KBr) 3418, 1696 cm^{-1}; LRMS (EI) m/z 278 ($M^+ - H_2O$).

Preparation of the 4-Oxo-brefeldin 36. To a solution of the dihydroxy acid **2** (5.0 mg, 0.017 mmol) in THF (0.5 mL) was added triethylamine (12 μL, 0.080 mmol) and trichlorobenzoyl chloride (3.2 μL, 0.020 mmol). The reaction mixture was stirred for 2 h and diluted with anhydrous toluene (10 mL). The toluene solution was added dropwise (3 mL/h) to a toluene solution (2 mL) of 4-DMAP (12 mg, 0.10 mmol) heated at reflux. After continued heating for 24 h, the reaction mixture was diluted with EtOAc, washed with aqueous HCl and 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexanes) to afford 2.3 mg (51%) of macrolactone **36** as a colorless oil: $[\alpha]^{25}_D$ −39.3 (*c* 0.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, 1H, J = 15.8 Hz), 6.38 (d, 1H, J = 15.8 Hz), 5.79 (ddd, 1H, J = 14.9, 10.7, 4.1 Hz), 5.49 (dd, 1H, J = 14.9, 10.7 Hz), 4.59 (m, 1H), 4.26 (bs, 1H), 2.92 (dd, 1H, J = 18.4, 9.0 Hz), 2.54 (m, 1H), 1.72−2.25 (m, 8H), 1.56 (m, 2H), 1.24 (d, 3H, J = 9.0 Hz), 1.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.6, 166.4, 140.2, 135.9, 128.3, 73.7, 72.2, 56.2, 45.4, 42.6, 35.6, 34.2, 32.2, 25.6, 20.2; IR (neat) 3733, 3647, 3441, 1716, 1697 cm^{-1}; LRMS (EI) m/z 278 (M^+); HRMS (EI) calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1515.

(+)-Brefeldin A (1). To a solution of **36** (2.3 mg, 0.008 mmol) in MeOH (0.5 mL) at −78 °C was added sodium borohydride (1.2 mg, 0.031 mmol). After the mixture was stirred for 1 h at the same temperature, the reaction was quenched by an addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Mg_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc only) affording 2.2 mg (95%) of **1** as a white solid. Recrystallization of the crude **1** from EtOAc provided analytically pure (+)-brefeldin A: mp 203−204 °C; $[\alpha]^{25}_D$ +92.5 (*c* 0.20, CH_3OH); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 7.32 (dd, 1H, J = 15.6, 3.1 Hz), 5.80 (ddd, 1H, J = 15.6, 1.5, 0.5 Hz), 5.63 (ddd, 1H, J = 14.9, 10.0, 4.8 Hz), 5.20 (dd, 1H, J = 14.9, 9.2 Hz), 4.76 (qdd, 1H, J = 10.7, 6.2, 1.6 Hz), 4.19 (m, 1H), 3.96 (td, 1H, J = 9.1, 2.0 Hz), 2.35−0.77 (m, 12H), 1.19 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.8, 136.8, 129.7, 117.1, 75.3, 71.8, 71.3, 51.8, 44.2, 43.2, 41.0, 33.9, 31.7, 26.6, 20.8; IR (neat) 3733, 3646, 3362, 1715, 1645 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1663.

Preparation of the Enone (38): (i) MEM Protection. To a solution of (+)-brefeldin A (10 mg, 0.036 mmol) and *i*Pr_2NEt (20 μL, 0.11 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added MEMCl (10 μL, 0.088 mmol). After stirring for 12 h at ambient temperature, the mixture was diluted with CH_2Cl_2 and saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford 10.3 mg (76%) of MEM ether as a

clear and colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (dd, 1H, J = 15.6, 2.9 Hz), 7.29 (dd, 1H, J = 15.6, 2.0 Hz), 5.67 (m, 1H), 5.22 (dd, 2H, J = 15.0, 9.5 Hz), 4.86−4.76 (m, 1H), 4.71 (s, 2H), 4.16−4.06 (m, 2H), 3.74−3.53 (m, 3H), 3.38 (s, 3H), 2.30−2.14 (m, 3H), 2.02−1.69 (m, 7H), 1.23 (d, 3H, J = 6.3 Hz), 0.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 151.6, 136.4, 130.5, 117.6, 94.4, 77.6, 77.2, 75.9, 71.9, 66.9, 59.0, 52.0, 44.0, 40.7, 38.5, 34.1, 31.8, 26.7, 20.9; IR (KBr) 3444, 1713, 1644 cm^{-1}; LRMS (EI) m/z 368 (M^+).

(ii) Oxidation. To a solution of the above MEM ether (7.6 mg, 0.021 mmol) and 4 Å molecular sieves (3 mg) in CH_2Cl_2 (1.5 mL) at ambient temperature was added PDC (78 mg, 0.21 mmol). After stirring for 3 h at ambient temperature, the mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by flash column chromatography (33% EtOAc/hexanes) to afford 7.0 mg (98%) of enone **38** as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H, J = 15.8 Hz), 6.37 (d, 1H, J = 15.8 Hz), 5.79 (ddd, 1H, J = 4.1, 10.7, 14.9 Hz), 5.44 (dd, 1H, J = 10.7, 14.9 Hz), 4.65 (s, 2H), 4.59 (m, 1H), 4.08 (m, 1H), 3.63 (m, 2H), 3.48 (m, 2H), 3.32 (s, 3H), 2.81 (q, 1H, J = 9.1 Hz), 2.50 (quintet, 1H, J = 9.0 Hz), 2.24−1.68 (m, 7H), 1.26 (d, 3H, J = 6.0 Hz); IR (KBr) 1724, 1697, 1629 cm^{-1}; LRMS (EI) m/z 366 (M^+).

Deprotection of 38. To a solution of the enone **38** (7.0 mg, 0.019 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 57 μL, 0.057 mmol). After stirring for 30 min at 0 °C, the mixture was diluted with CH_2Cl_2 and saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford 5.0 mg (95%) of the inseparable mixture of **36** and **39**, which proved to be (^{1}H NMR) a 72/28 mixture of (*Z*)-isomer **39** and (*E*)-isomer **36**, as a clear and colorless oil: (*Z*)-isomer; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29 (d, 1H, J = 12.6 Hz), 6.04 (d, 1H, J = 12.6 Hz), 5.35 (dd, 1H, J = 14.8, 10.5 Hz), 5.19 (m, 1H), 4.87 (m, 1H), 4.23 (m, 1H), 3.45 (q, 1H, J = 7.8 Hz), 2.61 (m, 1H), 2.18−1.65 (m, 8H), 1.21 (d, 3H, J = 9.0 Hz).

Reduction of the 4-Oxo-brefeldin A (36) and Its Isomer (39). To a solution of the mixture of **36** and **39** (5 mg, 0.018 mmol) in MeOH (1.0 mL) at −78 °C was added sodium borohydride (1.3 mg, 0.036 mmol). After the mixture was stirred for 1 h at the same temperature, the reaction was quenched by an addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Mg_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc only) to afford 3.4 mg (68%) of (*Z*)-isomer **40** and 1.3 mg (27%) of (+)-brefeldin A (**1**) as a white solid. (*Z*)-Isomer of brefeldin A (**40**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15 (dd, 1H, J = 11.8, 9.3 Hz), 5.63 (d, 1H, 11.1 Hz), 5.58 (m, 1H), 5.53 (m, 2H), 4.93 (m, 1H), 4.35 (m, 1H), 2.43−2.26 (m, 2H), 2.00−1.63 (m, 9H), 1.47 (m, 3H), 1.23 (d, 3H, J = 7.2 Hz).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of key synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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