Efficient Conditions for Conversion of 2-Substituted Furans into 4-Oxygenated 2-Enoic Acids and Its Application to Synthesis of (+)-Aspicilin, (+)-Patulolide A, and (−)-Pyrenophorin

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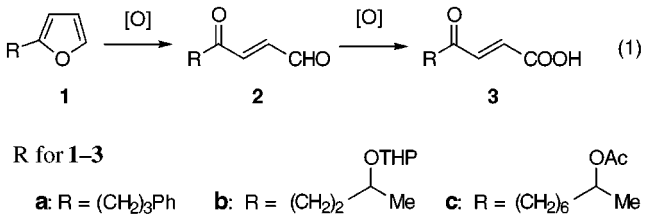
2-Substituted furans **1a**,**b**,**c** were found to be conveniently transformed into trans 4-oxo-2-enals **2a**,**b**,**c** in 62−87% yields by using NBS/pyridine in THF−acetone−H_2O (<−15 °C then rt) or NBS/$NaHCO_3$ in acetone−H_2O (<−15 °C then rt after addition of pyridine). Further oxidation of the enals **2a**−**c** using $NaClO_2$ led to the trans 4-oxo-2-enoic acids **3a**−**c** in good yields. With this transformation in mind, we designed syntheses of (+)-aspicilin, (+)-patulolide, and (−)-pyrenophorin. In the synthesis of (+)-aspicilin as shown in Schemes 1 and 2, the pivotal intermediate **6** was prepared from olefin **7** in which 2-furyl group is attached. The AD reaction of **7** secured the C(5) and C(6) stereochemistry of aspicilin, and the subsequent transformation using the protocol described above afforded the ester **6**. Stereocontrolled reduction of **6** followed by deprotection and the Yamaguchi macrocyclization furnished (+)-aspicilin. For the synthesis of (+)-patulolide (Scheme 3) and (−)-pyrenophorin (Scheme 4), the intermediates are the furans **38** and **44**, which were prepared easily by the classical methods using furyllithium **33**. The furan ring oxidations proceeded as well, furnishing acids **40** and **46** in good yields, acetalization of which afforded the known intermediates **41** and **47**, respectively.

Introduction

Oxidation of 2,5-disubstituted furans into functionally rich trans 2-ene-1,4-diones has been intensively studied.[1,2] Application of this oxidation to 2-substituted furans provides trans 4-oxo-2-enals, which are important intermediates in organic synthesis. To date, Br_2 coupled with subsequent hydrolysis under acidic conditions,[3] PCC,[2i,4] and Jones reagent[5] have been utilized for this transformation. However, these reagents are not compatible with functional groups which are frequently present in synthetic intermediates. Such groups are olefins, acid labile groups or protective groups, and/or distal hydroxyl group(s). Moreover, inadequate or moderate to low yields have been reported for some of the 2-substituted furans. Thus, it is not surprising that only a few applications of this methodology have been successful. Among them, the further oxidation to trans 4-oxo-2-enoic acids published by Hase[3c] is attractive in that the overall transformation (eq 1) constitutes a method for synthesis of the natural products possessing the 4-oxygenated 2-enoic acid structures, some of which are shown in Figure 1.[6]



2-Substituted furans are prepared easily and in large quantity not only by the classical alkylation of furyllithium with alkyl halides,[7] but also by the modern coupling reaction using the appropriate combination of a furyl organometallic or halide and an alkenyl or aryl halide or organometallic under a transition metal catalyst.[8,9] In addition, the furan ring is chemically stable

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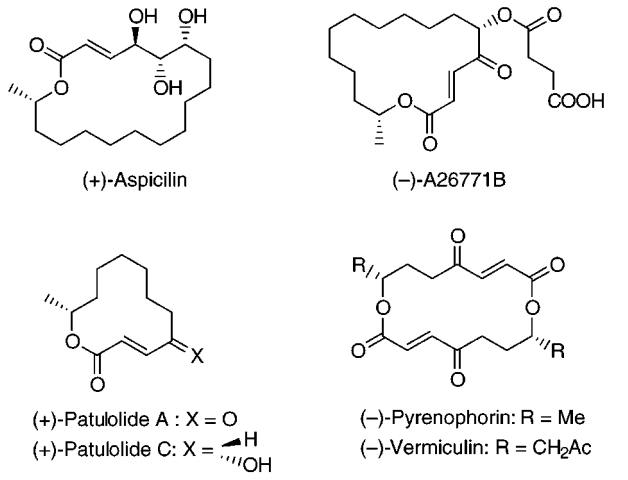
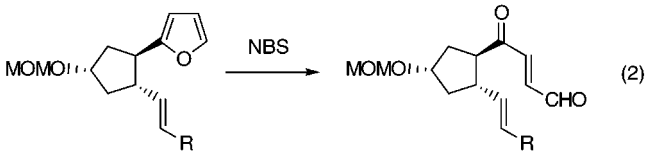


Figure 1. Naturally occurring 4-oxygenated 2-enoic acid derivatives.

under mild oxidative, weakly acidic, and basic conditions. These properties are convenient for transformation of an initially introduced simple substituent to a more complicated one through carbon−carbon bond-forming reactions and/or functional group conversions. Thus, finding a mild reagent and conditions for oxidation of 2-substituted furans **1** into trans 4-oxo-2-enals **2** makes the transformation depicted in eq 1 a more versatile and general method for synthesis of 4-oxo-2-enoic acids **3** and 4-oxygenated 2-enoic acids.[10]

Recently, we had an occasion to study the oxidation of furan **4** in the synthesis of brefeldin A. After our efforts with the literature protocols using PCC in CH_2Cl_2,[2i,4] and Br_2 in aqueous acetone[2c] or aqueous MeCN[2d] proved fruitless, we found that NBS[11] in THF−acetone−H_2O (at −20 °C, then rt) was effective for oxidation of **4** into trans 4-oxo-2-enal **5** (eq 2).[12] Slightly acidic conditions (pH 5−6) and short reaction times (4 h) coupled with easy



(2)

4 **5**

R = $(CH_2)_3CH(OTBDMS)Me$

handling seem to suit the present purpose. Thus, to test the generality of this key oxidation and efficiency of the overall furan-methodology, we have carried out the asymmetric syntheses of (+)-aspicilin,[13] (+)-patulolide A,[3f,14] and (−)-pyrenophorin.[5,10c,14e,15] Herein we describe full results of our experimentation.[16]

Table 1. Oxidation of Furans 1a−c to Aldehydes 2a−c[a]

entry	furan	oxidant	base	yield of **2a−c**[b] (%)
1	**1a**	NBS	pyridine	65
2	**1a**	NBS	−	50
3	**1a**	NBS	$NaHCO_3$[c]	71
4	**1a**	NCS	pyridine	0
5	**1b**	NBS	pyridine	62
6	**1b**	NBS	$NaHCO_3$[c]	69
7	**1c**	NBS	pyridine	87
8	**1c**	NBS	$NaHCO_3$[c]	76

[a] Reactions were carried out below −15 °C until the furan was consumed completely (usually <2 h) and then at room temperature for several hours. [b] Further oxidation to the acids **3a−c**: see the text. [c] After the disappearance of **1** (checked by TLC), pyridine was added to the mixture.

Results and Discussion

Preliminary Results. To obtain more information, the NBS oxidation was applied to furans **1a−c**. As a scavenger of HBr, a weak base[17] such as pyridine and $NaHCO_3$ was examined, and the results are shown in Table 1. Although oxidation was completed within 2 h at <−15 °C, further reaction at room temperature for several hours was indispensable for isomerization of the initially produced cis 4-oxo-2-enals to the trans enals **2a−c**. Since the aldehydes **2a−c** were found to be unstable, especially under alkaline conditions,[17] isolation and purification by column chromatography on silica gel were carried out as fast as possible. With regard to **1a**, oxidation in the presence of pyridine did provide a better yield of the aldehyde **2a** (entries 1 and 2). Almost equal efficiency was also obtained with $NaHCO_3$ (entry 3), where addition of pyridine after the oxidation accelerated isomerization to trans enal **2a**. The oxidation of **1a** with NCS was not successful (entry 4). Similarly, NBS/

(10) Although the method using 2-alkoxyfuran originally published by Takei is efficient, this approach suffers from inadequacy of a side chain-manipulation(s) due to instability of alkoxyfuran: (a) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269−4270. (b) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 4611−4614. (c) Asaoka, M.; Yanagida, N.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061−1064. (d) Gunn, B. P.; Brooks, D. W. *J. Org. Chem.* **1985**, *50*, 4417−4418.

(11) NBS has been used to convert furfuryl alcohols and related compounds into 2*H*-pyran-3(6*H*)-ones: (a) Georgiadis, M. P.; Couladouros, E. A. *J. Org. Chem.* **1986**, *51*, 2725−2727. (b) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2044−2047.

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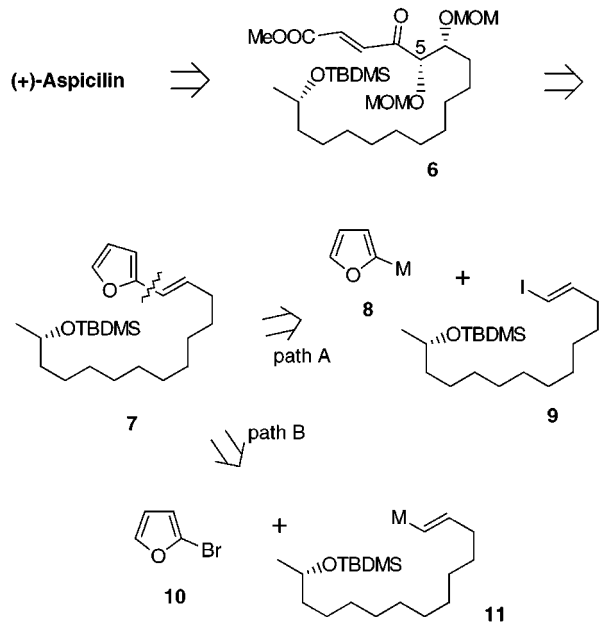
(17) For example, stirring a mixture of an ethereal solution of **2a** and 1 N NaOH (1:1) at room temperature only for 30 min resulted in complete decomposition. To remove pyridine, organic extracts were washed with dilute HCl or dilute $CuSO_4$ solution in some cases.

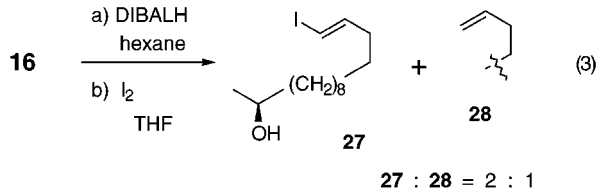
Scheme 1



pyridine and NBS/$NaHCO_3$ oxidation of **1b**,**c** furnished the corresponding aldehydes **2b**,**c** in good yields. The aldehydes **2a**−**c** thus prepared were converted to acids **3a**−**c** with $NaClO_2$[3c,18] in 77%, 78%, and 70% yields, respectively.

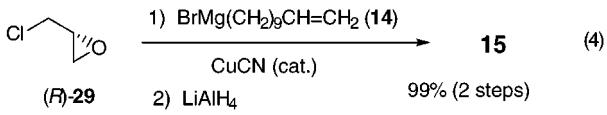
Synthesis of (+)-Aspicilin. Keeping in mind that the furan ring is a chemically stable synthetic equivalent of the 4-oxo-2-butenoic acid structure, we envisioned a synthesis of (+)-aspicilin as shown in Scheme 1. The pivotal intermediates are 4-oxo-2-enoate **6** and the alkenyl furan **7**. Asymmetric dihydroxylation (AD) of **7** using AD-mix-β[19] followed by the oxidative transformation of the furan ring should produce **6**. Stereoselective reduction of **6** and lactonization of the corresponding seco acid would furnish (+)-aspicilin. To accomplish the stereoselective reduction, chelation of a metal cation to the oxygen at C(5) of **6** is a crucial requirement.

For preparation of **7**, two sequences (paths A and B depicted in Scheme 1) are feasible. Initially, path A was examined. Preparation of the required iodide **9** was attempted from the readily available acetylene **16** of Scheme 2 (vide infra). Hydroalumination of **16** with DIBALH (2.2 equiv) in hexane and the subsequent iodination were carried out according to the procedure for simple acetylenes.[20] However, a substantially large quantity of olefin **28** was coproduced with iodide **27** (eq 3). Slow addition of DIBALH to **16** in hexane at lower temperatures or *vice versa* did not improve the situation. These results indicate the reaction of DIBALH with the hydroxyl group was competitive with the hydroalumination on the triple bond followed by proton transfer to give an aluminum alkoxide of **28**. Hydroalumination of the



silyl ether **17** (Scheme 2), on the other hand, hardly proceeded, and **17** was recovered. We then investigated path B, and this approach using 2-bromofuran (**10**) and alkenylborane **11** (M = $B(Sia)_2$) was found to be successful. The sequence to **7** and further transformation to (+)-aspicilin is summarized in Scheme 2.

11-Bromo-1-undecene, prepared from commercially available 10-undecen-1-ol (**12**), was transformed into the corresponding Grignard reagent **14**. Copper-catalyzed epoxide ring-opening of (−)-propylene oxide ((*S*)-**13**)[21] of $[\alpha]^{20}_D = -13$ to -14 (neat) (cf. $[\alpha]^{20}_D = +12$ to $+14$ for (*R*)-isomer of >97% ee) with **14** afforded alcohol **15** in 88% yield. Since accurate enantiomeric purity of (*S*)-**13** was not given, **15** was transformed to the corresponding MTPA ester, and >95% ee was ascertained by ^{1}H NMR spectroscopy. The alcohol **15** was also obtained from (*R*)-**29** of 98.8% ee by the epoxide ring-opening with **14** followed by reductive dechlorination with $LiAlH_4$ quantitatively (eq 4). Compound **15** was transformed into acetylene **17** in excellent yield by the standard method through alcohol **16**. To convert **17** into the key alkenyl-



metal **11** (Scheme 1) and to accomplish the reaction with **10** producing the key intermediate **7**, we selected the Suzuki reaction due to its convenience.[8c,22] Hydroboration of **17** with $(Sia)_2BH$ in THF was carried out as usual to produce alkenylborane **11** (M = $B(Sia)_2$). Subsequently, aqueous NaOH, 2-bromofuran (**10**), and $Pd(PPh_3)_4$ (5 mol %) were added to a THF solution of **11**, and the mixture was stirred for further 5 h under reflux to afford **7** in 92% yield. ^{1}H NMR (500 MHz) spectrum of **7** confirmed the trans olefin geometry ($J_{olefin} = 16$ Hz), and there was no production of the cis isomer or the terminal olefin (deiodination product).

The Sharpless asymmetric dihydroxylation[19] of **7** proceeded efficiently at room temperature overnight. Exclusive production of one diastereoisomer was confirmed by ^{1}H NMR spectroscopy of the derived bis-MTPA ester since the ^{1}H NMR spectra of **18** and its diastereoisomer **32** shown in eq 5 (vide infra) were superimposed. Absolute stereochemistry of the diol was tentatively assigned as **18** based on the well-established empirical rule and was confirmed upon completion of the synthesis. It is worth mentioning that, while the high yield of 91% was obtained with AD-mix-β, the classical osmium-catalyzed dihydroxylation[23] afforded the diol only in moderate yield (50%). These results indicate that competitive oxidation of the furan ring occurred under the

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(21) Purchased from Merck.

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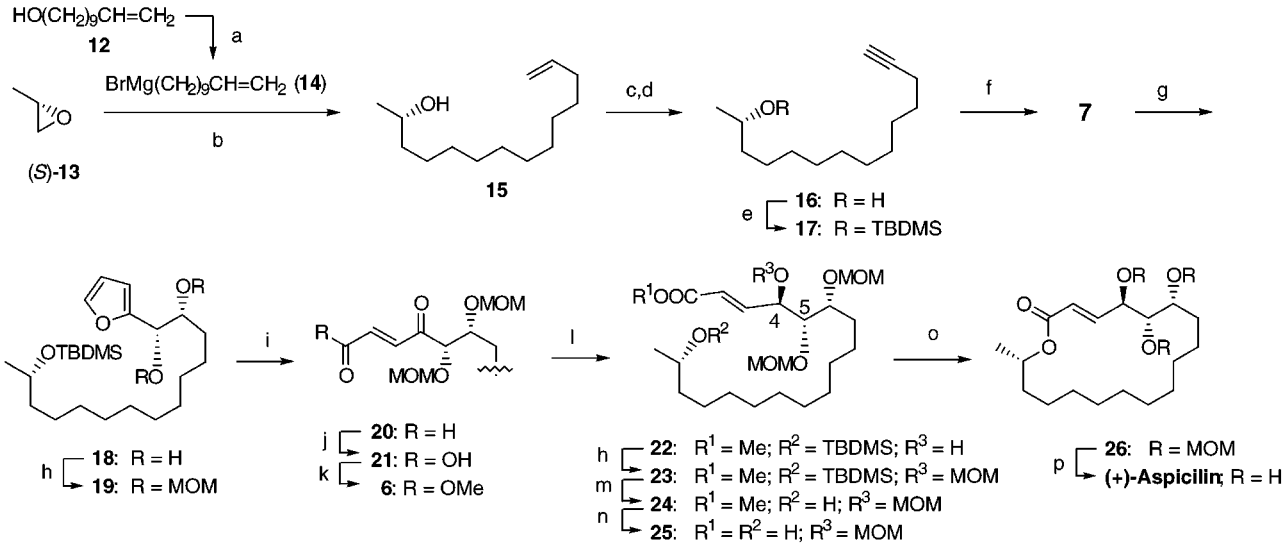
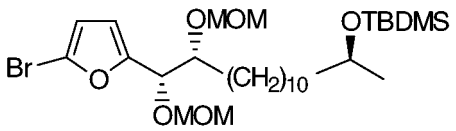
Scheme 2[a]



[a] Reagents and conditions: (a) (1) CBr_4, PPh_3 (100%), (2) Mg, THF; (b) **14**, CuCN (0.05 equiv) (88%); (c) Br_2; (d) $NaNH_2$, NH_3 (96% from **15**); (e) TBDMSCl, imidazole, DMF (100%); (f) Sia_2BH (2 equiv), THF, −10 °C, 1 h then **10** (3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), aq NaOH (1.5 equiv), reflux, 5 h (92%); (g) AD-mix-β, $MeSO_2NH_2$, 0 °C to room temperature (91%); (h) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 30 °C (92% for **19**, 84% for **23**); (i) NBS (1.1 equiv), $NaHCO_3$ (2 equiv), acetone/H_2O (10:1), −15 °C, 15 min then furan (3 equiv), 30 min and C_5H_5N (2 equiv), overnight (71%); (j) $NaClO_2$ (5 equiv), Me_2C=CHMe (15 equiv) (88%); (k) [2-Cl−C_5H_4NMe]I (3 equiv), MeOH (1.2 equiv), NEt_3 (2.4 equiv) (65%); (l) $Zn(BH_4)_2$, −78 °C to −40 °C, Et_2O (90%); (m) NBS (1.1 equiv), DMSO/H_2O (19:1) (79%); (n) LiOH, MeOH−H_2O; (o) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3 then DMAP, toluene, reflux (53% from **24**); (p) $HS(CH_2)_2SH$, BF_3·OEt_2 (56%).

latter conditions as has been suggested.[24] During our investigation, the AD reaction of 2-(1-alkenyl)furans was reported by Ogasawara.[25] The alcohol **18** was protected with MOMCl into the MOM ether **19** in high yield, and the stage was set for the furan ring oxidation.

Oxidation of furan **19** with NBS was carried out under the conditions mentioned above. Unfortunately, NBS/pyridine afforded a mixture of the aldehyde **20** and the bromofuran **30** in a ratio of 7:1.[26] However, NBS/$NaHCO_3$ proceeded successfully to furnish the somewhat



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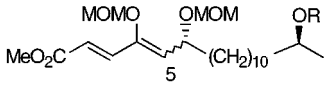
unstable aldehyde **20** in 71% yield. Further oxidation of **20** with $NaClO_2$ furnished the acid **21** and the subsequent esterification by using the Mukaiyama reagent[27] afforded the key intermediate **6** in good yield.

According to the procedure of Nakata,[28] reduction of **6** using excess $Zn(BH_4)_2$ was carried out in Et_2O at −78 °C to produce the alcohol **22** in 90% yield with >15:1 diastereoselectivity (determined by ^1H NMR spectroscopy). The structure of **22** with the C(4)−C(5) anti stereochemistry was tentatively assigned on the basis of literature analogy[2d,29] and was confirmed at the stage of aspicilin. Protection of alcohol **22** afforded the MOM ether **23**, which was transformed in good yield to the seco acid **25** by deprotection of the TBDMS group with NBS[30] followed by hydrolysis. With regard to the deprotection, the use of Bu_4NF in THF resulted in competitive elimination of the MOM group at the C(5) position to furnish **31** (R = H, TBDMS). Finally, macrolactonization by the Yamaguchi method[31] furnished **26** (FAB mass, M^+ + Na



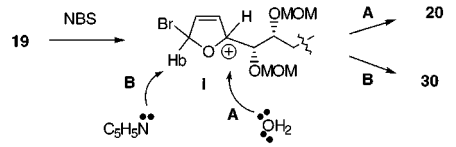
31: R = H, TBDMS

= 483), which upon deprotection of the three MOM groups with BF_3·OEt_2 and $HS(CH_2)_2SH$[13e,f] afforded (+)-aspicilin in 30% yield from **24** after chromatography on silica gel. Physicochemical data of (+)-aspicilin thus obtained were consistent with the reported values: ^1H NMR (300 MHz),[13e,f] optical rotation ($[\alpha]^{22}_D$ = +37.5 (*c* 0.55, $CHCl_3$); lit.[13e] $[\alpha]^{23}_D$ = +37.7 (*c* 0.22, $CHCl_3$), lit.[13f] $[\alpha]_D$ = +38.5 (*c* 1.05, $CHCl_3$)), and mp (152−155 °C (recrystallized from hexane−ethyl acetate); lit. 154−156 °C;[13c,f] 150−152 °C[13e]).

(24) Oxidation of furans: Hartman, R. F.; Rose, S. D. *J. Org. Chem.* **1981**, *46*, 4340−4345.

(25) (a) Taniguchi, T.; Ohnishi, H.; Ogasawara, K. *Chem. Commun.* **1996**, 1477−1478. (b) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synlett* **1996**, 971−972. (c) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509−511.

(26) Formation of **30** is explained by considering the cation **i** where the abstraction of Hb by pyridine is competitive with the desired reaction (A) due to the steric hinderence by the MOM-oxy group.



(27) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863−1866.

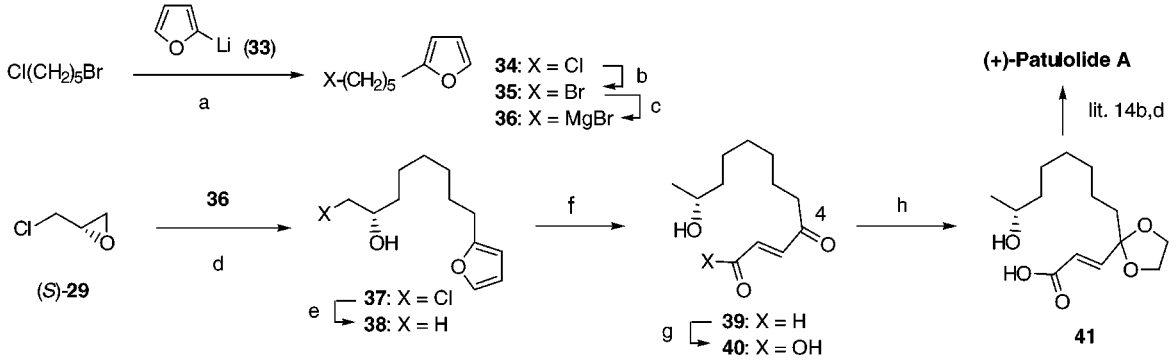
(28) (a) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411−1415. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.

(29) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769−3771 and references therein.

(30) Batten, R. J.; Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *Synthesis* **1980**, 234−236.

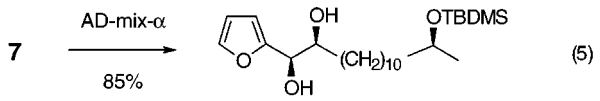
(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

Scheme 3[a]



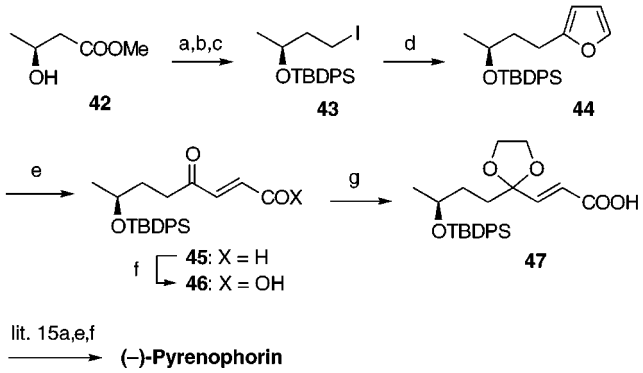
[a] Reagents and conditions: (a) **33**, THF, rt (95%); (b) LiBr, $[(C_8H_{17})_3NMe]Cl$ (cat.), 100 °C (94%); (c) Mg, THF; (d) **36**, CuCN (cat.), THF (90%); (e) $LiAlH_4$, THF, rt (93%); (f) NBS (1.5 equiv), pyridine (2 equiv), THF/acetone/H_2O (5:4:2), −20 °C, 1 h then rt, 4 h (73%); (g) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/phosphate buffer (pH 3.6)/H_2O (2:1:1) (87%); (h) $HO(CH_2)_2OH$, *p*-TsOH (cat.), C_6H_6 then LiOH, MeOH/H_2O (62%).

As mentioned above, we established a highly stereoselective synthesis of (+)-aspicilin. Our route has the advantages of flexibility and simplicity. Consequently, stereoisomers and analogues with methylene chains of different lengths will be synthesized with a similar effort in a predictable way. For example, 17(*R*)-isomer of aspicilin would be prepared simply by switching the starting epoxide (*S*)-**13** to the (*R*)-isomer, while the C(4)−C(6) diastereoisomers by carrying out the AD reaction with AD-mix-α, by preparing the cis isomer of **7** thereby producing the C(5)−C(6) anti diol upon the AD reaction with AD-mix-α or -*β*, and/or by nonchelation controlled reduction of the 4-oxo-2-enoate producing the C(4)−C(5) syn alcohol. In practice, dihydroxylation of **7** using AD-mix-α resulted in exclusive production of **32** in good yield (eq 5). These flexibilities are indispensable for elucidating the biological function of aspicilin.



Synthesis of (+)-Patulolide A. Since (+)-patulolide A is synthesized from acid **41** by macrolactonization followed by deprotection,[14b,d] we planned a synthesis of acid **41** as shown in Scheme 3, where the key intermediate is the furan **38**. Alkylation of 1-bromo-5-chloropentane with 2-furyllithium (**33**) afforded the chloride **34** in 95% yield according to the procedure of Büchi.[7] Since an attempt to prepare the Grignard reagent from **34** failed due to instability of the reagent under the conditions we used (THF, reflux), **34** was converted to bromide **35** with LiBr (2 equiv) in the presence of $[(C_8H_{17})_3NMe]Cl$[32] in 94% yield (97% conversion by ^1H NMR), and the Grignard reagent **36** was prepared successfully. Although the direct precursor of alcohol **38** is apparently (*R*)-propylene oxide[33] on the basis of the above aspicilin synthesis, we opted for (*S*)-epichlorohydrin (**29**) (98.9% ee) due to its easier handling and availability. Thus, reaction of (*S*)-**29** with **36** under the copper catalyst afforded **37** in 90% yield, and reductive dechlorination of **37** with $LiAlH_4$ furnished the key intermediate **38** in excellent yield.

Scheme 4[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF (100%); (b) DIBALH, THF, −50 to −15 °C, 3 h (91%); (c) I_2, PPh_3, C_6H_6 (88%); (d) **33**, THF, rt (94%); (e) NBS (1.2 equiv), pyridine (4 equiv), THF/acetone/H_2O (5:4:2), −20 °C, 1 h then rt, 5 h (64%); (f) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/phosphate buffer (pH 3.6)/H_2O (2:1:1) (83%); (g) $HO(CH_2)_2OH$, *p*-TsOH (cat.), C_6H_6 then LiOH, MeOH/H_2O (8:1) (70%).

Without protection of the hydroxyl group, the NBS/pyridine oxidation was applied to furan **38** under the conditions mentioned above. The reaction proceeded successfully to furnish trans 4-oxo-2-enal **39** in 73% yield. Oxidation of **39** with $NaClO_2$ in the presence of 2-methyl-2-butene[18] furnished acid **40** in 87% yield. During these conversions the hydroxyl group remained untouched. Finally, protection of the carbonyl group at the C(4) position and hydrolysis of the ethyl ester partially formed during ketalization furnished the acid **41**, whose ^1H NMR spectra were in accord with the data reported.[14b]

Synthesis of (−)-Pyrenophorin. Previously, the Mitsunobu reaction has been utilized for synthesis of (−)-pyrenophorin from **47** with inversion of the hydroxyl group at C(7).[15a,e,f] Consequently, the key intermediate is furan **44**, and the target compound is acid **47** as shown in Scheme 4. Iodide **43**[34] was prepared from commercially available **42** (86% ee)[35] in 80% yield. Alkylation of **43** with 2-furyllithium (**33**) afforded the key compound

(32) Loupy, A.; Pardo, C. *Synth. Commun.* **1988**, *18*, 1275−1281.
(33) Koppenhoefer, B.; Schurig, V. *Organic Syntheses*; Wiley: New York, 1993; Coll. Vol. VIII; pp 434−441. This epoxide is available from Merck.
(34) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549−557.
(35) Synthesis of enantiomerically pure **42**: Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

44 in good yield. The NBS oxidation of **44** under the same conditions mentioned above afforded the enal **45** in 64% yield, which upon oxidation with $NaClO_2$ (83% yield) and subsequent ketalization furnished the intermediate **47**, whose ^1H NMR spectrum was in good agreement with the reported data.[15c]

Conclusion

In summary, we have shown the usefulness of the two-step conversion of 2-substituted furans **1** into trans 4-oxo-2-enoic acids **3**. The pivotal NBS oxidation is carried out under mild conditions and consequently, common functional groups should be compatible. Actually, ester, THP, siloxy, phenyl, and free hydroxyl groups were found to be such groups. In addition, this furan methodology has the advantages of easy preparation and chemical stability of furans **1** under various conditions, which are convenient for manipulation of the substituent as is demonstrated in this manuscript. We are confident that when 4-oxygenated 2-enoic acids or their derivatives are required, an efficient method can immediately be devised by taking into consideration the 2-substituted furans as a synthetic equivalent of 4-oxo-2-enoic acids.

Experimental Section

General Methods. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). Unless otherwise noted, ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta = 0$ ppm) and the center line of $CDCl_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). *N*,*N*-Dimethylformamide (DMF) was dried over CaH_2. (*S*)-Propylene oxide (**13**) was purchased from Merck, and (*R*)- and (*S*)-epichlorohydrins (**29**) were kindly offered by Daiso, Japan. The phosphate buffer of pH 3.6 was prepared by mixing $Na_2HPO_4 \cdot 12H_2O$ (2.31 g), citric acid (1.31 g), and H_2O (98.6 g). 2-Bromofuran (**10**) was prepared according to the literature procedure.[36] Routinely, organic extracts were concentrated using a rotary evaporator, and residues were purified by chromatography on silica gel.

2-(3-Phenylpropyl)furan (1a). To an ice-cold solution of furan (4.12 mL, 57 mmol) and bipyridine (ca. 10 mg) in THF (100 mL) was added *n*-BuLi (45 mL, 0.91 M in hexane, 41 mmol) dropwise. After being stirred for 1 h at 0−5 °C, 1-bromo-3-phenylpropane (4.75 mL, 6.27 g, 31.5 mmol) was added to the solution. The brown solution was stirred overnight at room temperature and poured into a mixture of hexane and saturated NH_4Cl with vigorous stirring. Hexane layer was separated, and the aqueous layer was extracted with hexane. The combined hexane solutions were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/ethyl acetate) followed by distillation under reduced pressure to afford **1a** (5.16 g, 88%): bp 113−115 °C (2 Torr); IR (neat) 1599, 1506, 1496, 1454, 731, 700 cm^{-1}; ^1H NMR δ 1.97 (quintet, $J = 7$ Hz, 2 H), 2.62−2.70 (m, 4 H), 5.99 (d, $J = 3$ Hz, 1 H), 6.28 (dd, $J = 3$, 2 Hz, 1 H), 7.15−7.33 (m, 6 H); ^{13}C NMR δ 156.2, 142.1, 141.0, 128.7, 128.5, 126.0, 110.2, 105.0, 35.2, 29.6, 27.4. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.62; H, 7.62.

2-(3-(Tetrahydropyranyloxy)butyl)furan (1b). By using a similar procedure for the preparation of **1a**, furan (0.12 mL, 1.7 mmol), 1-iodo-3-(tetrahydropyranyloxy)butane[37] (160 mg, 0.56 mmol) dissolved in THF (1 mL), *n*-BuLi (0.46 mL, 2.47 M solution in hexane, 1.13 mmol), and THF (3 mL) afforded **1b** (90 mg, 71%) after workup with saturated $NaHCO_3$ followed by extraction with ethyl acetate and purification by chromatography (hexane/Et_2O): IR (neat) 1597, 1508, 729 cm^{-1}; ^1H NMR δ 1.15 and 1.28 (2d, $J = 7$ and 7 Hz, 3 H), 1.46−1.98 (m, 8 H), 2.63−2.89 (m, 2 H), 3.43−3.53 (m, 1 H), 3.70−3.98 (m, 2 H), 4.62 and 4.72 (2m, 1 H), 5.96−6.02 (m, 1 H), 6.26−6.29 (m, 1 H), 7.29 (br s, 1 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.44; H, 9.04.

7-(2-Furyl)-1-methylheptyl Acetate (1c). A solution of 8-(2-furyl)-2-octanol (**38**) (305 mg, 1.55 mmol) (preparation: see below), Ac_2O (1 mL, 10 mmol), and pyridine (1.4 mL, 17 mmol) was allowed to stand overnight at room temperature, and most of volatile materials were removed by using a vacuum pump. The residue was directly subjected to chromatography (hexane/ethyl acetate) to afford the acetate **1c** (359 mg, 97%): IR (neat) 1736, 1246, 729 cm^{-1}; ^1H NMR δ 1.19 (d, $J = 6$ Hz, 3 H), 1.22−1.70 (m, 10 H), 2.02 (s, 3 H), 2.59 (t, $J = 7$ Hz, 2 H), 4.82−4.94 (m, 1 H), 5.98 (dq, $J = 3$, 1 Hz, 1 H), 6.25 (dd, $J = 3$, 2 Hz, 1 H), 7.28 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 170.9, 156.6, 140.8, 110.2, 104.8, 71.0, 35.9, 29.17, 29.04, 27.96, 27.92, 25.3, 21.3, 19.9.

(2*E*)-7-Phenyl-4-oxo-2-heptenal (2a). (A) NBS/pyridine: To a solution of **1a** (218 mg, 1.17 mmol) and pyridine (0.38 mL, 4.70 mmol) in THF−acetone−H_2O (5:4:1, 6 mL) was added NBS (250 mg, 1.40 mmol) dissolved in THF−acetone−H_2O (5:4:1, 2 mL) at −20 °C. The solution was stirred for 1 h at −20 °C and 6 h at room temperature and then poured into a mixture of ethyl acetate and aqueous $Na_2S_2O_3$ with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford **2a** (153 mg, 65%).

(B) NBS/$NaHCO_3$: To a mixture of **1a** (100 mg, 0.538 mmol) and $NaHCO_3$ (90 mg, 1.08 mmol) in acetone−H_2O (10:1, 2 mL) was added NBS (105 mg, 0.591 mmol) dissolved in acetone−H_2O (10:1, 0.7 mL) at −15 °C. After 40 min at −15 °C, pyridine (0.16 mL, 1.98 mmol) was added, the mixture was stirred further 2 h at room temperature, and ethyl acetate was added. The solution was washed with 1 N HCl, dried over $MgSO_4$, and concentrated to furnish the crude product, which was purified by chromatography (hexane/ethyl acetate) to afford **2a** (77 mg, 71%): IR (neat) 1730, 1695, 1248 cm^{-1}; ^1H NMR δ 2.01 (quintet, $J = 7$ Hz, 2 H), 2.67 (t, $J = 7$ Hz, 2 H), 2.70 (t, $J = 7$ Hz, 2 H), 6.73 (dd, $J = 16$, 7 Hz, 1 H), 6.83 (d, $J = 16$, 1 H), 7.15−7.33 (m, 5 H), 9.76 (d, $J = 7$ Hz, 1 H); ^{13}C NMR δ 200.0, 193.6, 144.9, 141.2, 137.4, 128.60, 128.58, 126.3, 40.2, 34.8, 24.9.

(2*E*)-7-(Tetrahydropyranyloxy)-4-oxo-2-octenal (2b). (A) Furan **1b** (77 mg, 0.34 mmol) was oxidized by using NBS (64 mg, 0.36 mmol) dissolved in THF−acetone−H_2O (5:4:2, 1 mL) and pyridine (0.083 mL, 1.03 mmol) in THF−acetone−H_2O (5:4:2, 3 mL) at −20 °C for 1 h and then rt for 5 h to furnish aldehyde **2b** (51 mg, 62% yield) after a similar workup as described above. (B) A mixture of **1b** (100 mg, 0.45 mmol), NBS (87 mg, 0.49 mmol), and $NaHCO_3$ (75 mg, 0.89 mmol) in acetone−H_2O (10:1, total 2.7 mL) was stirred at −15 °C for 40 min and, after addition of pyridine (0.071 mL, 0.89 mmol), at room temperature for 2.5 h. To this was added 0.5 N $CuSO_4$ (2.5 mL), and the mixture was stirred vigorously for 15 min. After separation of the phases, the organic layer was rinsed again with 0.5 N $CuSO_4$ (1 mL), washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford **2b** (73 mg, 69%): IR (neat) 1692, 1641 cm^{-1}; ^1H NMR δ 1.15 and 1.25 (2d, $J = 6$ and 6 Hz, 3 H), 1.40−1.98 (m, 8 H), 2.72−2.97 (m, 2 H), 3.39−3.52 (m, 1 H), 3.76−3.96 (m, 2 H), 4.53−4.61 (m, 1 H), 6.79 (dt, $J = 16$, 7 Hz, 1 H), 6.89 (dd, $J = 16$, 4 Hz, 1 H), 9.79 (d, $J = 7$ Hz, 1 H).

(2*E*)-11-Acetoxy-4-oxo-2-dodecenal (2c). (A) According to the procedure for the oxidation of **1b**, furan **1c** (30 mg, 0.125 mmol) was converted into **2c** (28 mg, 87% yield) by using NBS (29 mg, 0.16 mmol) dissolved in THF−acetone−H_2O (5:4:2, 0.7 mL), pyridine (0.040 mL, 0.49 mmol), and THF−acetone−H_2O (5:4:2, 2 mL). (B) According to the procedure for the oxidation of **1b**, furan **1c** (50 mg, 0.21 mmol) was converted into **2c** (41

(36) Keegstra, M. A.; Klomp, A. J. A.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3371−3374.

(37) Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221−3225.

mg, 76%) by using NBS (41 mg, 0.23 mmol), $NaHCO_3$ (35 mg, 0.42 mmol), pyridine (0.033 mL, 0.23 mmol), and acetone−H_2O (10:1, total 1.5 mL): ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3 H), 1.22−1.73 (m, 10 H), 2.03 (s, 3 H), 2.68 (t, J = 6 Hz, 2 H), 4.83−4.96 (m, 1 H), 6.78 (dd, J = 16, 7 Hz, 1 H), 6.88 (d, J = 16 Hz, 1 H), 9.79 (d, J = 7 Hz, 1 H); ^{13}C NMR δ 200.3, 193.7, 171.0, 145.1, 137.5, 70.9, 41.1, 35.8, 29.1, 28.9, 25.1, 23.4, 21.3, 19.9.

(2*E*)-7-Phenyl-4-oxo-2-heptenoic Acid (3a). To a solution of the aldehyde **2a** (358 mg, 1.77 mmol) and 2-methyl-2-butene (1.87 mL, 17.7 mmol) in *t*-BuOH (23 mL), and the phosphate buffer (pH 3.6, 11 mL) was added $NaClO_2$ (226 mg, purity 85%, 2.12 mmol) dissolved in H_2O (11 mL), and the resulting mixture was stirred for 2 h at room temperature. Most of the solvents were removed by using a vacuum pump, and ethyl acetate and brine were added to the residue. The aqueous layer was acidified to pH ca. 4 by addition of 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to leave an oil, which was purified by chromatography (benzene/ethyl acetate/MeOH) to give **3a** (297 mg, 77%): IR (Nujol) 1672, 1624 cm^{-1}; ^{1}H NMR δ 1.99 (quintet, J = 7 Hz, 2 H), 2.660 (t, J = 7 Hz, 2 H), 2.661 (t, J = 7 Hz, 2 H), 6.64 (d, J = 16 Hz, 1 H), 7.10 (d, J = 16 Hz, 1 H), 7.14−7.33 (m, 5 H); ^{13}C NMR δ 199.5, 170.5, 141.33, 141.27, 129.7, 128.6, 126.3, 40.8, 34.8, 24.9.

(2*E*)-7-(Tetrahydropyranyloxy)-4-oxo-2-octenoic Acid (3b). According to the above procedure, aldehyde **2b** (29 mg, 0.12 mmol) was converted into acid **3b** (24 mg, 78%) by using $NaClO_2$ (19 mg, purity 85%, 0.18 mmol) dissolved in H_2O (0.3 mL), 2-methyl-2-butene (0.10 mL, 0.94 mmol), *t*-BuOH (1 mL), and the phosphate buffer (pH 3.6, 0.3 mL): IR (CCl_4) 1698, 1640 cm^{-1}; ^{1}H NMR δ 1.15 and 1.26 (2d, J = 6 and 6 Hz, 3 H), 1.44−1.96 (m, 8 H), 2.72 and 2.84 (2t, J = 7 and 7 Hz, 2 H), 3.42−3.55 (m, 1 H), 3.74−3.97 (m, 2 H), 4.58−4.64 (m, 1 H), 6.68 and 6.70 (2d, J = 16 and 16 Hz, 1 H), 7.150 and 7.156 (2d, J = 16 and 16 Hz, 1 H).

(2*E*)-11-Acetoxy-4-oxo-2-dodecenoic Acid (3c). According to the above procedure, aldehyde **2c** (23 mg, 0.090 mmol) was oxidized to acid **3c** (17 mg, 70%) by using $NaClO_2$ (12 mg, purity 85%, 0.11 mmol) dissolved in H_2O (0.5 mL), 2-methyl-2-butene (0.099 mL, 0.93 mmol), *t*-BuOH (1 mL), and the phosphate buffer (pH 3.6, 0.5 mL). The following ^{1}H NMR spectrum (300 MHz) was identical with the reported[3f] data (90 MHz): ^{1}H NMR δ 1.21 (d, J = 6 Hz, 3 H), 1.2−1.7 (m, 10 H), 2.04 (s, 3 H), 2.65 (t, J = 7 Hz, 2 H), 4.83−4.94 (m, 1 H), 6.68 (d, J = 16 Hz, 1 H), 7.13 (d, J = 16 Hz, 1 H).

10-Undecenylmagnesium Bromide (14). To an ice-cold solution of alcohol **12** (14 mL, 70 mmol) and PPh_3 (20.2 g, 77 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (23.2 g, 70 mmol) portionwise. The solution was stirred at the same temperature for 1 h and concentrated to give a white solid. Hexane was added to the solid, and the mixture was filtered through a pad of silica gel with hexane. The filtrate was concentrated, and the residue was distilled to afford 11-bromo-1-undecene (16.0 g, 100%): bp 89−90 °C (3 Torr); IR (neat) 1639, 993, 910 cm^{-1}; ^{1}H NMR δ 1.23−1.51 (m, 12 H), 1.85 (quintet, J = 7 Hz, 2 H), 2.04 (q, J = 7 Hz, 2 H), 3.40 (t, J = 7 Hz, 2 H), 4.93 (d, J = 10 Hz, 1 H), 4.99 (d, J = 17 Hz, 1 H), 5.81 (ddt, J = 17, 10, 7 Hz, 1 H); ^{13}C NMR δ 134.3, 109.2, 29.0, 28.7, 27.8, 24.3, 24.0, 23.8, 23.7, 23.1.

To a suspension of Mg (1.26 g, 0.052 g-atom) in THF (14 mL) was added 1,2-dibromoethane (5 drops) to activate Mg, and a solution of the above bromide (8.63 g, 37.1 mmol) in THF (20 mL) was added dropwise with a gentle heating. After the addition, the mixture was refluxed for 30 min, cooled to room temperature, and diluted with THF (74 mL). The resulting supernatant was titrated to be 0.34 M of 10-undecenylmagnesium bromide (**14**).

(2*S*)-13-Tetradecen-2-ol (15) from (*S*)-Propylene Oxide (13).[38] To a mixture of (*S*)-propylene oxide (**13**) (249 mg, 4.29 mmol) of $[\alpha]^{20}_D$ = −13 to −14 (neat) (cf. (*R*)-isomer of >97% ee: $[\alpha]^{20}_D$ = +12 to +14) and CuCN (19 mg, 0.21 mmol) in THF (5 mL) was added the above Grignard reagent **14** (19 mL, 0.34 M in THF, 6.5 mmol) between −55 to −60 °C over 40 min. The resulting mixture was stirred below −30 °C for 1 h, warmed to 0 °C over 1 h, and then poured into a mixture of ethyl acetate and saturated NH_4Cl with vigorous stirring. After separation of the phases, the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography (hexane/ethyl acetate) to afford **15** (803 mg, 88%). Since ee of the starting epoxide was not given, **15** was transformed to the bis-MTPA ester by the standard procedure[39] [(1) (*R*)-(−)-MTPACl, pyridine/$CHCl_3$ (1:1), 0 °C to room temperature; (2) $Me_2N(CH_2)_3NH_2$] and ee was determined to be >95%: $[\alpha]^{23}_D$ = +5.2 (*c* 0.96, $CHCl_3$); bp 120−135 °C (1 Torr); IR (neat) 3338, 1641, 993, 908 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.22−1.52 (m, 19 H), 2.04 (q, J = 7 Hz, 2 H), 3.73−3.88 (m, 1 H), 4.93 (d, J = 10 Hz, 1 H), 5.00 (d, J = 17 Hz, 1 H), 5.82 (ddt, J = 17, 10, 7 Hz, 1 H); ^{13}C NMR δ 139.3, 114.2, 68.0, 39.3, 33.7, 29.60, 29.55, 29.52, 29.42, 29.1, 28.9, 25.7, 23.3. HRMS (CI) *m*/*z* calcd for $C_{14}H_{29}O$ (M + H)$^+$ 213.2218, found 213.2222. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.18; H, 13.13.

(2*S*)-13-Tetradecen-2-ol (15) from (*R*)-Epichlorohydrin (29). To a mixture of (*R*)-epichlorohydrin (**29**) (463 mg, 5.0 mmol, 98.8% ee) and CuCN (22 mg, 0.25 mmol) in THF (5 mL) at −50 °C was added slowly a THF solution of **14** (14 mL, 0.46 M, 6.44 mmol), which had been prepared from Mg (800 mg, 0.033 g-atom), 11-bromo-1-undecene (4.9 g, 21 mmol), 1,2-dibromoethane (4 drops), and THF (total 40 mL) in a similar manner described above. The mixture was stirred between −20 and −30 °C for 1.5 h and poured into a mixture of saturated NH_4Cl and ethyl acetate with vigorous stirring. Extraction and purification as mentioned above afforded (2*R*)-1-chloro-13-tetradecen-2-ol (1.23 g, 100%): IR (neat) 3371, 1641, 993, 910 cm^{-1}; ^{1}H NMR δ 1.15−1.63 (m, 18 H), 2.04 (q, J = 7 Hz, 2 H), 2.30 (d, J = 3 Hz, 1 H), 3.47 (dd, J = 11, 7 Hz, 1 H), 3.63 (dd, J = 11, 3 Hz, 1 H), 3.75−3.85 (m, 1 H), 4.93 (d, J = 10 Hz, 1 H), 5.00 (d, J = 17 Hz, 1 H), 5.81 (ddt, J = 17, 10, 7 Hz, 1 H); ^{13}C NMR δ 139.4, 114.2, 71.5, 50.5, 34.2, 33.8, 29.52, 29.50, 29.46, 29.44, 29.1, 28.9, 25.5.

To an ice-cold solution of the above chloride (1.23 g, 5.0 mmol) in THF (15 mL) was added $LiAlH_4$ (143 mg, 3.77 mmol) portionwise. The mixture was stirred at room temperature overnight and cooled to 0 °C. After sequential addition of ethyl acetate (0.98 mL, 10 mmol), H_2O (0.45 mL, 25 mmol), and NaF (1.05 g, 25 mmol), the resulting mixture was stirred at room temperature for 1 h and filtered through a pad of Celite with ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography (hexane/ethyl acetate) to furnish the title alcohol **15** (1.05 g, 99%), ^{1}H NMR spectrum of which was identical with that obtained from (*S*)-propylene oxide (**13**).

(2*S*)-13-Tetradecyn-2-ol (16). To a solution of olefin **15** (2.12 g, 10 mmol) in $CHCl_3$ (15 mL) was added bromine (0.52 mL, 10 mmol) slowly at −50 °C. After 15 min, the solution was poured into a vigorously stirred aqueous $Na_2S_2O_3$ with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were concentrated to give the bromine-adduct, which was used for the next reaction without further purification.

To a suspension of $NaNH_2$ in liquid NH_3 (ca. 200 mL), which had been prepared from sodium metal (1.6 g, 0.070 g-atom) and a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ in NH_3, was added a solution of the above bromine-adduct in THF (8 mL) slowly. The cooling bath was removed and stirring was continued. After 1 h, a mixture of H_2O−THF (ca. 1:1), saturated NH_4Cl, and Et_2O were added successively, and the resulting mixture was stirred overnight at room temperature. The product was extracted with Et_2O several times, and the combined ethereal solutions were dried over $MgSO_4$ and concentrated. The

(38) Reaction was carried out by T. Okui of our laboratory.

(39) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

residue was purified by chromatography (hexane/ethyl acetate) to afford acetylene **16** (2.01 g, 96% from **15**): $[\alpha]^{22}_D = +6.3$ (*c* 0.94, $CHCl_3$); IR (neat) 3360, 3311, 2117 cm^{-1}; ^1H NMR δ 1.19 (d, $J = 6$ Hz, 3 H), 1.22−1.58 (m, 19 H), 1.94 (t, $J = 3$ Hz, 1 H), 2.18 (dt, $J = 3$, 7 Hz, 2 H), 3.72−3.86 (m, 1 H); ^{13}C NMR δ 84.9, 68.2, 68.1, 39.4, 29.60, 29.54, 29.48, 29.43, 29.1, 28.7, 28.5, 25.7, 23.4, 18.3. HRMS (CI) *m*/*z* calcd for $C_{14}H_{27}O$ $(M + H)^+$ 211.2062, found 211.2059. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.88; H, 12.42.

(13*S*)-13-[(*tert*-Butyldimethylsilyl)oxy]-1-tetradecyne (17). A solution of alcohol **16** (2.01 g, 9.57 mmol), TBDMSCl (1.73 g, 11.5 mmol), and imidazole (0.98 g, 14.4 mmol) in DMF (20 mL) was stirred overnight at room temperature and poured into a mixture of hexane and saturated $NaHCO_3$. After being vigorously stirred at room temperature for 30 min, the layers were separated, and the aqueous layer was extracted with hexane twice. The combined hexane solutions were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/ethyl acetate) to afford the silyl ether **17** (3.12 g, 100%): $[\alpha]^{21}_D = +8.2$ (*c* 0.94, $CHCl_3$); IR (neat) 3313, 2119, 835, 773 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.11 (d, $J = 6$ Hz, 3 H), 1.16−1.60 (m, 18 H), 1.94 (t, $J = 3$ Hz, 1 H), 2.18 (dt, $J = 3$, 7 Hz, 2 H), 3.70−3.82 (m, 1 H); ^{13}C NMR δ 84.9, 68.7, 68.1, 39.8, 29.70, 29.63, 29.55, 29.49, 29.1, 28.8, 28.5, 25.9, 25.8, 23.8, 18.4, 18.2, −4.5, −4.8. HRMS (CI) *m*/*z* calcd for $C_{20}H_{41}OSi$ $(M + H)^+$ 325.2927, found: 325.2918.

(1*E*,13*S*)-2-(13-[(*tert*-Butyldimethylsilyl)oxy]-1-tetradecenyl)furan (7). To a solution of acetylene **17** (2.45 g, 7.56 mmol) in THF (8 mL) at −10 °C was added a solution of Sia_2BH in THF (30 mL), which had been prepared from BH_3 (20 mL, 1 M in THF, 20 mmol) and 2-methyl-2-butene (20 mL, 2 M in THF, 40 mmol) at −10 °C for 2 h. After being stirred at −10 °C for 1 h, 3 N NaOH (4 mL, 12 mmol), 2-bromofuran (**10**) (3.34 g, 22.7 mmol), and $Pd(PPh_3)_4$ (440 mg, 0.38 mmol) were added to the solution. The mixture was stirred under reflux for 5 h. After being cooled to 0 °C, 3 N NaOH (25 mL, 75 mmol) and 35% H_2O_2 (7.5 mL) were added slowly. Vigorous stirring was continued at room temperature for 2 h, and the mixture was poured into saturated NH_4Cl. The product was extracted with hexane several times, and the combined extracts were dried over $MgSO_4$ and concentrated to leave the residue, which was purified by chromatography (hexane/Et_2O) to furnish **7** (2.72 g, 92%): IR (neat) 960, 837, 777, 729 cm^{-1}; ^1H NMR (500 MHz) δ 0.035 (s, 6 H), 0.89 (s, 9 H), 1.11 (d, $J = 6$ Hz, 3 H), 1.17−1.52 (m, 18 H), 2.12−2.21 (m, 2 H), 3.72−3.81 (m, 1 H), 6.12 (d, $J = 3$ Hz, 1 H), 6.16 (dt, $J = 16$, 6 Hz, 1 H), 6.19 (d, $J = 16$ Hz, 1 H), 6.33 (dd, $J = 3$, 2 Hz, 1 H), 7.30 (d, $J = 2$ Hz, 1 H); ^{13}C NMR δ 153.6, 141.3, 136.5, 118.6, 111.2, 105.9, 68.8, 39.8, 32.8, 29.70, 29.65, 29.60, 29.5, 29.3, 29.2, 25.9, 25.8, 23.8, 18.2, −4.5, −4.8. HRMS (CI) *m*/*z* calcd for $C_{24}H_{45}O_2Si$ $(M + H)^+$ 393.3189, found: 393.3195.

(1*S*,2*R*,13*S*)-13-[(*tert*-Butyldimethylsilyl)oxy]-1-(2-furyl)-1,2-tetradecanediol (18).[38] To an ice-cold mixture of olefin **7** (200 mg, 0.509 mmol), *t*-BuOH (2.6 mL), and H_2O (2.6 mL) were added $MeSO_2NH_2$ (48 mg, 0.50 mmol) and AD-mix-β (0.713 g). The mixture was stirred overnight at room temperature and diluted with brine. The product was extracted with ethyl acetate several times. The combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford diol **18** (198 mg, 91%). Since all of the ^1H NMR signals were superimposed with those of the diastereomer **32** of eq 5 (vide infra), diastereomeric purity of **18** was determined by comparison of ^1H NMR signals of the corresponding bis-MTPA esters, and no isomer was detected in each spectrum. Diol **18**: $[\alpha]^{23}_D = +10.8$ (*c* 0.93, MeOH); IR (neat) 3369, 835, 773 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.10 (d, $J = 6$ Hz, 3 H), 1.12−1.52 (m, 20 H), 2.47 (br s, 1 H), 2.78 (br s, 1 H), 3.70−3.82 (m, 1 H), 3.82−3.92 (m, 1 H), 4.46 (t, $J = 6$ Hz, 1 H), 6.31 (ddd, $J = 3.3$, 0.9, 0.6 Hz, 1 H), 6.34 (dd, $J = 3.3$, 1.8 Hz, 1 H), 7.38 (dd, $J = 1.8$, 1.2 Hz, 1 H); ^{13}C NMR δ 154.4, 142.4, 110.5, 107.8, 73.6, 71.2, 68.7, 39.8, 32.9, 29.69, 29.62, 29.57, 29.54, 29.51, 25.9, 25.8, 25.5, 23.8, 18.1, −4.5, −4.8. Anal. Calcd for $C_{24}H_{46}O_4Si$: C, 67.55; H, 10.87. Found: C, 67.50; H, 10.79.

(1*R*,2*S*,13*S*)-13-[(*tert*-Butyldimethylsilyl)oxy]-1-(2-furyl)-1,2-tetradecanediol (32). In a manner similar to the above experiment, olefin **7** (32 mg, 0.080 mmol), AD-mix-α (113 mg), $MeSO_2NH_2$ (8 mg, 0.08 mmol), *t*-BuOH (0.4 mL), and H_2O (0.4 mL) afforded diol **32** (29 mg, 85%), whose ^1H NMR was identical with that of **18**. No contamination of **18** in the product **32** was confirmed by the method described above for **18**.

(1*S*,2*R*,13*S*)-2-(13-[(*tert*-Butyldimethylsilyl)oxy]-1,2-bis(methoxymethoxy)-1-tetradecanyl)furan (19). A solution of alcohol **18** (2.36 g, 5.52 mmol), MOMCl (1.68 mL, 22.1 mmol), and *i*-Pr_2NEt (9.62 mL, 55.2 mmol) in CH_2Cl_2 (18 mL) was stirred overnight between 25 and 30 °C and poured into saturated $NaHCO_3$. After vigorous stirring for 30 min, the mixture was extracted with ethyl acetate twice. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/ethyl acetate) to furnish the MOM ether **19** (2.62 g, 92%): $[\alpha]^{22}_D = -39.3$ (*c* 1.23, $CHCl_3$); IR (neat) 1032, 835, 775 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.10 (d, $J = 6$ Hz, 3 H), 1.10−1.50 (m, 20 H), 3.35 (s, 3 H), 3.36 (s, 3 H), 3.68−3.80 (m, 1 H), 3.83−3.92 (m, 1 H), 4.58 (d, $J = 7$ Hz, 1 H), 4.59 (d, $J = 7$ Hz, 1 H), 4.65 (d, $J = 7$ Hz, 1 H), 4.68 (d, $J = 7$ Hz, 1 H), 4.74 (d, $J = 7$ Hz, 1 H), 6.31 (dd, $J = 3$, 1 Hz, 1 H), 6.33 (dd, $J = 3$, 2 Hz, 1 H), 7.38 (dd, $J = 2$, 1 Hz, 1 H); ^{13}C NMR δ 152.2, 142.5, 110.2, 109.1, 97.2, 94.5, 78.9, 73.9, 68.7, 55.7, 55.6, 39.7, 31.4, 29.65, 29.58, 29.52, 29.49, 29.45, 25.9, 25.7, 25.1, 23.8, 18.1, −4.5, −4.8. Anal. Calcd for $C_{28}H_{54}O_6Si$: C, 65.33; H, 10.57. Found: C, 65.31; H, 10.60.

(2*E*,5*S*,6*R*,17*S*)-17-[(*tert*-Butyldimethylsilyl)oxy]-5,6-bis(methoxymethoxy)-4-oxo-2-octadecenal (20). To a mixture of the MOM ether **19** (793 mg, 1.54 mmol) and $NaHCO_3$ (258 mg, 3.08 mmol) in acetone−H_2O (10:1, 3 mL) was added NBS (304 mg, 1.69 mmol) dissolved in acetone−H_2O (10:1, 1.5 mL) at −15 °C. The mixture was stirred for 40 min, and furan (0.34 mL, 4.7 mmol) was added to quench excess NBS. After 30 min at −15 °C, pyridine (0.24 mL, 3.03 mmol) was added. The mixture was stirred at room temperature overnight and poured into the phosphate buffer (pH 3.6) with ethyl acetate. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated to give the residue, which was purified by chromatography (hexane/ethyl acetate) to furnish aldehyde **20** (584 mg, 71%): IR (neat) 1697, 1032, 835, 775 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.10 (d, $J = 6$ Hz, 3 H), 1.12−1.76 (m, 20 H), 3.26 (s, 3 H), 3.37 (s, 3 H), 3.69−3.81 (m, 1 H), 3.87−3.95 (m, 1 H), 4.27 (d, $J = 3$ Hz, 1 H), 4.57 (d, $J = 7$ Hz, 1 H), 4.64 (d, $J = 7$ Hz, 1 H), 4.70 (d, $J = 7$ Hz, 1 H), 4.72 (d, $J = 7$ Hz, 1 H), 6.88 (dd, $J = 16$, 8 Hz, 1 H), 7.38 (d, $J = 16$ Hz, 1 H), 9.77 (d, $J = 8$ Hz, 1 H). HRMS (CI) *m*/*z* calcd for $C_{24}H_{55}O_7Si$ $(M + H)^+$ 531.3717, found: 531.3718.

Methyl (2*E*,5*S*,6*R*,17*S*)-17-[(*tert*-Butyldimethylsilyl)oxy]-5,6-bis(methoxymethoxy)-4-oxo-2-octadecenoate (6). According to the procedure for the preparation of **3a**, aldehyde **20** (173 mg, 0.326 mmol) was converted into the acid **21** (156 mg, 88%) by using $NaClO_2$ (148 mg, purity 85%, 1.63 mmol) in H_2O (1 mL), 2-methyl-2-butene (0.52 mL, 4.9 mmol), *t*-BuOH (2 mL), and the phosphate buffer (pH 3.6, 1 mL): IR (neat) 1699, 835, 775 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.10 (d, $J = 6$ Hz, 3 H), 1.12−1.72 (m, 20 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 3.67−3.82 (m, 1 H), 3.87−3.97 (m, 1 H), 4.26 (d, $J = 3$ Hz, 1 H), 4.58 (d, $J = 7$ Hz, 1 H), 4.64 (d, $J = 7$ Hz, 1 H), 4.67 (d, $J = 7$ Hz, 1 H), 4.71 (d, $J = 7$ Hz, 1 H), 6.77 (d, $J = 16$ Hz, 1 H), 7.53 (d, $J = 16$ Hz, 1 H), 9.2 (br peak, 1 H).

To a solution of 2-chloro-1-methylpyridinium iodide (363 mg, 1.42 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of acid **21** (259 mg, 0.474 mmol), MeOH (0.023 mL, 0.57 mmol), and NEt_3 (0.16 mL, 1.15 mmol) in CH_2Cl_2 (1.5 mL). The resulting mixture was refluxed for 4 h, cooled to room temperature, and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to furnish the methyl ester **6** (172 mg, 65%): $[\alpha]^{22}_D = -34.1$ (*c* 0.82, $CHCl_3$); IR (neat) 1732, 1703,

835, 775 cm^{-1}; ^1H NMR δ −0.01 (s, 6 H), 0.83 (s, 9 H), 1.06 (d, J = 6 Hz, 3 H), 1.08−1.70 (m, 20 H), 3.23 (s, 3 H), 3.33 (s, 3 H), 3.76 (s, 3 H), 3.65−3.79 (m, 1 H), 3.86 (dt, J = 3, 7 Hz, 1 H), 4.20 (d, J = 3 Hz, 1 H), 4.53 (d, J = 7 Hz, 1 H), 4.59 (d, J = 7 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 6.74 (d, J = 16 Hz, 1 H), 7.46 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 199.5, 166.0, 136.4, 130.6, 97.2, 96.1, 83.3, 78.1, 68.6, 56.5, 55.9, 52.2, 39.7, 30.5, 29.59, 29.52, 29.46, 29.43, 25.8, 25.7, 25.3, 23.7, 18.0, −4.6, −4.9. HRMS (CI) m/z calcd for $C_{29}H_{57}O_8Si$ $(M + H)^+$ 561.3823, found: 561.3817.

Methyl (2*E*,4*R*,5*R*,6*R*,17*S*)-17-[(*tert*-Butyldimethylsilyl)oxy]-5,6-bis(methoxymethoxy)-4-hydroxy-2-octadecenoate (22). To a solution of ketone **6** (123 mg, 0.220 mmol) in Et_2O (1 mL) was added an ethereal solution of $Zn(BH_4)_2$ (4.8 mL, 0.138 M, 0.66 mmol) at −78 °C. The mixture was gradually warmed to −40 °C over 1 h and poured into brine. The resulting mixture was stirred at room temperature for 1 h and then extracted with Et_2O several times. The combined ethereal solutions were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to furnish alcohol **22** (112 mg, 90%), whose diastereomeric selectivity was determined to be >15:1 by ^1H NMR spectroscopy of the crude product: $[\alpha]^{24}_D = +9.6$ (c 1.31, $CHCl_3$); IR (neat) 3473, 1728, 1658, 835, 775 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.10 (d, J = 6 Hz, 3 H), 1.12−1.46 (m, 21 H), 3.41 (s, 6 H), 3.52−3.60 (m, 1 H), 3.74 (s, 3 H), 3.68−3.80 (m, 1 H), 4.02 (d, J = 6 Hz, 1 H), 4.39−4.46 (m, 1 H), 4.66 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.70 (d, J = 7 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 6.19 (dd, J = 16, 2 Hz, 1 H), 7.08 (dd, J = 16, 4 Hz, 1 H); ^{13}C NMR δ 167.0, 147.6, 121.5, 98.1, 97.2, 83.1, 78.7, 70.4, 68.6, 56.3, 56.1, 51.5, 39.7, 30.6, 29.63, 29.60, 29.54, 29.47, 25.8, 25.7, 25.3, 23.7, 18.0, −4.6, −4.9. HRMS (CI) m/z calcd for $C_{29}H_{59}O_8Si$ $(M + H)^+$ 563.3979, found: 563.3979.

Methyl (2*E*,4*R*,5*S*,6*R*,17*S*)-17-[(*tert*-Butyldimethylsilyl)oxy]-4,5,6-tris(methoxymethoxy)-2-octadecenoate (23). According to the procedure for the preparation of **19**, alcohol **22** (58 mg, 0.102 mmol) was converted into **23** (52 mg, 84%) by using MOMCl (0.025 mL, 0.33 mmol), i-Pr_2NEt (0.090 mL, 0.51 mmol), and CH_2Cl_2 (1 mL): $[\alpha]^{23}_D = -7.1$ (c 0.80, $CHCl_3$); IR (neat) 1730, 1660, 835, 775 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.10 (d, J = 6 Hz, 3 H), 1.12−1.70 (m, 20 H), 3.37 (s, 3 H), 3.38 (s, 3 H), 3.40 (s, 3 H), 3.61−3.70 (m, 1 H), 3.74 (s, 3 H), 3.70−3.80 (m, 2 H), 4.36−4.41 (m, 1 H), 4.61 (d, J = 7 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.66 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.73 (d, J = 7 Hz, 2 H), 6.07 (dd, J = 16, 1 Hz, 1 H), 6.97 (dd, J = 16, 7 Hz, 1 H); ^{13}C NMR δ 166.4, 145.3, 123.2, 97.5, 97.0, 94.9, 80.2, 78.0, 75.7, 68.6, 55.98, 55.79, 55.76, 51.5, 39.6, 31.3, 29.58, 29.51, 29.45, 25.8, 25.6, 25.3, 23.7, 18.0, −4.6, −4.9. HRMS (CI) m/z calcd for $C_{27}H_{53}O_9Si$ $(M - C_4H_9)^+$ 549.3459, found: 549.3464.

Methyl (2*E*,4*R*,5*S*,6*R*,17*S*)-4,5,6-Tris(methoxymethoxy)-17-hydroxy-2-octadecenoate (24). A solution of the silyl ether **23** (100 mg, 0.165 mmol) and NBS (30 mg, 0.17 mmol) in DMSO−H_2O (19:1, 1.6 mL) was stirred at room temperature overnight and poured into the phosphate buffer (pH 3.6). The mixture was extracted with Et_2O three times. The combined ethereal solutions were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (benzene/ethyl acetate) to afford alcohol **24** (64 mg, 79%): $[\alpha]^{21}_D = -6.0$ (c 0.64, $CHCl_3$); IR (neat) 3481, 1724, 1660, 1032 cm^{-1}; ^1H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.2−1.7 (m, 21 H), 3.37 (s, 3 H), 3.38 (s, 3 H), 3.40 (s, 3 H), 3.62−3.70 (m, 1 H), 3.74 (s, 3 H), 3.72−3.82 (m, 2 H), 4.35−4.42 (m, 1 H), 4.62 (d, J = 7 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.66 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.73 (d, J = 7 Hz, 2 H), 6.06 (d, J = 16 Hz, 1 H), 6.98 (dd, J = 16, 7 Hz, 1 H); ^{13}C NMR δ 166.6, 145.3, 123.3, 97.6, 97.1, 94.9, 80.2, 78.1, 75.8, 68.2, 56.10, 55.91, 55.88, 51.6, 39.3, 31.3, 29.64, 29.58, 29.53, 29.48, 25.7, 25.3, 23.4. HRMS (CI) m/z calcd for $C_{25}H_{49}O_9$ $(M + H)^+$ 493.3377, found: 493.3376.

(+)-Aspicilin. A mixture of ester **24** (56 mg, 0.114 mmol) and $LiOH·H_2O$ (36 mg, 0.86 mmol) in MeOH and H_2O (6:1, 1.1 mL) was stirred at 40 °C overnight and diluted with the phosphate buffer (pH 3.6). The product was extracted with ethyl acetate several times. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish acid **25**, which was used for the next reaction without further purification: IR (neat) 1716, 1658, 1032 cm^{-1}; ^1H NMR δ 1.19 (d, J = 6 Hz, 3 H), 1.1−1.7 (m, 20 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.61−3.70 (m, 1 H), 3.72−3.89 (m, 2 H), 4.40−4.48 (m, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.74 (d, J = 7 Hz, 2 H), 6.07 (dd, J = 16, 1 Hz, 1 H), 7.07 (dd, J = 16, 6 Hz, 1 H).

A solution of the above acid **25** and NEt_3 (0.09 mL, 0.65 mmol) in THF (1 mL) was stirred at room temperature for 20 min, and then 2,4,6-trichlorobenzoyl chloride (0.05 mL, 0.19 mmol) in THF (0.5 mL) was added. Stirring was continued at room temperature further 2 h, and the solution was diluted with toluene (ca. 20 mL). The resultant white solid (triethylamine hydrochloride) was removed by filtration through a pad of Celite, and the filtrate was diluted further with toluene (total 50 mL). The toluene solution thus obtained was added over 3 h to a refluxing solution of DMAP (78 mg, 0.64 mmol) dissolved in toluene (10 mL). After the addition, the solution was cooled to room temperature, diluted with Et_2O, washed with 1 N HCl and saturated $NaHCO_3$, and dried over $MgSO_4$. Concentration and purification by chromatography (hexane/ethyl acetate) afforded lactone **26** (31 mg, 53% from **24**): IR (neat) 1720, 1657, 920 cm^{-1}; ^1H NMR δ 1.0−1.6 (m, 23 H), 3.35 (s, 3 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.46−3.56 (m, 1 H), 3.86 (dd, J = 7, 1.5 Hz, 1 H), 4.43 (d, J = 8 Hz, 1H), 4.58 (d, J = 7 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.74 (d, J = 7 Hz, 1 H), 4.78 (d, J = 7 Hz, 1 H), 4.82 (d, J = 7 Hz, 1 H), 4.90−5.10 (m, 1 H), 6.01 (d, J = 16 Hz, 1 H), 6.95 (dd, J = 16, 8 Hz, 1 H); ^{13}C NMR δ 165.7, 143.4, 125.4, 97.7, 97.4, 93.9, 81.1, 77.8, 74.8, 70.8, 55.94, 55.87, 55.5, 35.3, 31.1, 28.11, 28.06, 27.4, 26.9, 26.6, 26.2, 25.4, 23.5, 20.4; FAB mass, $M^+ + Na$ = 483.

To an ice-cold solution of the MOM ether **26** (31 mg, 0.067 mmol) and 1,2-ethanedithiol (0.045 mL, 0.61 mmol) in CH_2Cl_2 (1 mL) was added $BF_3·OEt_2$ (0.051 mL, 0.41 mmol), and the solution was stirred at room temperature for 3 h. Saturated $NaHCO_3$ and ethyl acetate were added to the solution, and the mixture was stirred for 10 min. The layers were separated, and aqueous layer was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel with a mixture of benzene and EtOH as an eluent to afford (+)-aspicilin (12.3 mg, 56%): $[\alpha]^{22}_D = +37.5$ (c 0.55, $CHCl_3$) (lit.[13e] $[\alpha]^{23}_D = +37.7$ (c 0.22, $CHCl_3$); lit.[13f] $[\alpha]_D = +38.5$ (c 1.05, $CHCl_3$)); mp 152−155 °C (recrystallized from hexane/ethyl acetate) (lit.[13c,f] 154−156 °C; lit.[13e] 150−152 °C). The following ^1H and ^{13}C NMR spectra were identical with the reported[13e,f] data: ^1H NMR ($CDCl_3 + D_2O$) δ 1.08−1.60 (m, 23 H), 3.57 (t, J = 3 Hz, 1 H), 3.74 (dt, J = 3, 7 Hz, 1 H), 4.52−4.60 (m, 1 H), 5.04 (sextet, J = 6 Hz, 1 H), 6.12 (dd, J = 16, 2 Hz, 1 H), 6.90 (dd, J = 16, 5 Hz, 1 H); ^{13}C NMR δ 165.9, 145.0, 123.2, 74.7, 73.5, 71.3, 70.0, 35.7, 31.9, 28.3, 27.7, 27.5, 27.2, 27.1, 26.3, 24.3, 23.5, 20.4.

2-(5-Bromopentyl)furan (35). To an ice-cold solution of furan (1.38 mL, 14 mmol) and bipyridine (ca. 10 mg) in THF (20 mL) was added n-BuLi (8.44 mL, 1.35 M in hexane, 11.4 mmol) dropwise, and the brown solution was stirred at 0−5 °C for 1 h to generate 2-furyllithium (**33**). 1-Bromo-5-chloropentane (0.50 mL, 704 mg, 3.80 mmol) was added to the solution. After 14 h at room temperature, the solution was poured into a mixture of hexane and saturated NH_4Cl with vigorous stirring. Hexane layer was separated, and the aqueous layer was extracted with hexane. The combined hexane solutions were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/Et_2O) to afford **34** (621 mg, 95%): bp 95−100 °C (3 Torr); IR (neat) 1597, 1508, 732 cm^{-1}; ^1H NMR δ 1.42−1.55 (m, 2 H), 1.62−1.73 (m, 2 H), 1.73−1.88 (m, 2 H), 2.63 (t, J = 7 Hz, 2 H), 3.55 (t, J = 6.5 Hz, 2 H), 5.99 (d, J = 3.5 Hz, 1 H), 6.28 (dd, J = 3.5, 2 Hz,1 H), 7.31 (d, J = 2, 1 H); ^{13}C NMR δ 155.8, 140.6, 109.9, 104.7, 44.7, 32.2, 27.7, 27.2, 26.3.

A mixture of **34** (5.45 g, 31.6 mmol), LiBr (5.48 g, 63.1 mmol), and trioctylmethylammonium chloride (640 mg, 1.6 mmol) was stirred at 100 °C for 2 days, cooled to room

temperature, and filtered through a pad of silica gel with hexane. The filtrate was concentrated to give the bromide **35** (6.46 g, 97% conversion by ^{1}H NMR, 94% yield), which was distilled for the next reaction: bp 80−90 °C (1 Torr); IR (neat) 1600, 1510, 734 cm^{-1}; ^{1}H NMR δ 1.42−1.57 (m, 2 H), 1.59−1.73 (m, 2 H), 1.82−1.97 (m, 2 H), 2.64 (t, J = 7 Hz, 2 H), 3.41 (t, J = 7 Hz, 2 H), 5.98 (d, J = 3 Hz, 1 H), 6.28 (dd, J = 3, 2 Hz, 1 H), 7.29 (d, J = 2 Hz, 1 H).

(2*R*)-8-(2-Furyl)-2-octanol (38). To a mixture of Mg (1.34 g, 0.055 g-atom) and THF (7 mL) was added 1,2-dibromoethane (5 drops) to activate Mg, and a solution of **35** (4.0 g, 18.4 mmol) in THF (10 mL) was added slowly to prepare the Grignard reagent **36**. After the addition, the solution was diluted with THF (20 mL). The Grignard reagent **36** thus prepared was used for the next reaction immediately.

According to the procedure for the preparation of **15**, (*S*)-(+)-epichlorohydrin (**29**) (2.17 mL, 27.7 mmol) of 98.9% ee, the above Grignard reagent **36**, CuCN (164 mg, 1.83 mmol), and THF (36 mL) afforded **37** (3.83 g, 90%): IR (neat) 3390, 1597, 1508, 725 cm^{-1}; ^{1}H NMR δ 1.24−1.70 (m, 10 H), 2.14 (d, J = 5 Hz, 1 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.47 (dd, J = 11, 7 Hz, 1 H), 3.64 (dd, J = 11, 3 Hz, 1 H), 3.74−3.85 (m, 1 H), 5.97 (m, 1 H), 6.28 (m, 1 H), 7.29 (m, 1 H); ^{13}C NMR δ 156.5, 140.7, 110.1, 104.7, 71.5, 50.6, 34.3, 29.3, 29.1, 28.0, 25.5.

Dechlorination of **37** (427 mg, 1.85 mmol) was carried out using $LiAlH_4$ (70 mg, 1.85 mmol) in THF (10 mL) at room temperature overnight to afford the furan **38** (337 mg, 93%): bp 100 °C (1 Torr); $[\alpha]^{23}_D$ = −6.1 (*c* 0.94, $CHCl_3$); IR (neat) 3400, 1632, 1539, 753 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.25−1.53 (m, 9 H), 1.57−1.71 (m, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.72−3.84 (m, 1 H), 5.97 (d, J = 3 Hz, 1 H), 6.27 (dd, J = 3, 2 Hz, 1 H), 7.29 (d, J = 2 Hz, 1 H); ^{13}C NMR δ 156.6, 140.7, 110.1, 104.6, 68.2, 39.4, 29.4, 29.2, 28.06, 28.02, 25.7, 23.6. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.26. Found: C, 73.10; H, 10.45.

(2*E*,11*R*)-11-Hydroxy-4-oxo-2-dodecenoic Acid (40). To a solution of the furan **38** (190 mg, 0.968 mmol) and pyridine (0.16 mL, 1.93 mmol) in THF−acetone−H_2O (5:4:2, 7 mL) was added NBS (259 mg, 1.46 mmol) dissolved in THF−acetone−H_2O (5:4:2, 3 mL) at −20 °C. After being stirred at −20 °C for 1 h and then at room temperature for 4 h, the solution was poured into a mixture of ethyl acetate and aqueous $Na_2S_2O_3$ with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to give aldehyde **39** (150 mg, 73%): IR (neat) 3450, 1720 cm^{-1}; ^{1}H NMR δ 1.19 (d, J = 6 Hz, 3 H), 1.26−1.74 (m, 11 H), 2.70 (t, J = 7 Hz, 2 H), 3.74−3.86 (m, 1 H), 6.78 (dd, J = 16, 7 Hz, 1 H), 6.88 (d, J = 16 Hz, 1 H), 9.79 (d, J = 7 Hz, 1 H).

According to the procedure for preparation of **3a**, a mixture of **39** (299 mg, 1.41 mmol), $NaClO_2$ (225 mg, purity 85%, 2.49 mmol), and 2-methyl-2-butene (1.5 mL, 14 mmol) in *t*-BuOH (10 mL), the phosphate buffer (pH 3.6, 5 mL), and H_2O (5 mL) was stirred at room temperature for 1.5 h to furnish acid **40** (281 mg, 87%). IR and the following ^{1}H NMR spectra of **40** were identical with the reported[14h] data: ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3 H), 1.2−1.7 (m, 10 H), 2.65 (t, J = 7 Hz, 2 H), 3.75−3.90 (m, 1 H), 6.42 (br s, 2 H), 6.67 (d, J = 16 Hz, 1 H), 7.14 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 199.8, 169.1, 140.6, 130.1, 68.4, 41.5, 39.0, 29.2, 29.0, 25.4, 23.5, 23.2.

Ethylene Ketal of (2*E*,11*R*)-11-Hydroxy-4-oxo-2-dodecenoic Acid (41). A solution of acid **40** (29 mg, 0.13 mmol), HC(OEt)$_3$ (67 mg, 0.63 mmol), ethylene glycol (78 mg, 1.26 mmol), and *p*-TsOH·H_2O (3 mg, 0.02 mmol) in benzene (1.5 mL) was stirred at 35 °C overnight and then poured into a mixture of ethyl acetate and brine. The ethyl acetate layer was separated, and the aqueous layer was extracted with ethyl acetate repeatedly. The combined organic layers were dried over $MgSO_4$ and concentrated to give a mixture of **41** and its ethyl ester which, without separation, was treated with 2 N LiOH (0.63 mL, 1.26 mmol) in MeOH (6 mL) at room temperature overnight. The solution was acidified to pH 4 with 1 N HCl and poured into brine with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (benzene/ethyl acetate) to furnish the ketal acid **41** (20 mg, 62%): $[\alpha]^{26}_D$ = −2.2 (*c* 0.6, $CHCl_3$). The following ^{1}H NMR spectra of **41** were in good agreement with the reported[14b] data: ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.2−1.8 (m, 11 H), 3.75−3.84 (m, 1 H), 3.84−4.02 (m, 4 H), 6.08 (d, J = 16 Hz, 1 H), 6.83 (d, J = 16 Hz, 1 H).

(3*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-iodobutane (43). A solution of alcohol **42** (536 mg, 4.54 mmol, 86% ee determined by ^{1}H NMR spectroscopy of the corresponding MTPA ester), TBDPSCl (1.42 mL, 5.46 mmol), and imidazole (927 mg, 13.6 mmol) in DMF (7 mL) was stirred for 18 h at 53 °C, cooled to room temperature, and poured into saturated $NaHCO_3$ with hexane. After 30 min of vigorous stirring, the organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford methyl (3*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]butanoate (1.62 g, 100%): ^{1}H NMR δ 1.04 (s, 9 H), 1.12 (d, J = 6 Hz, 3 H), 2.39 (dd, J = 15, 7 Hz, 1 H), 2.57 (dd, J = 15, 7 Hz, 1 H), 3.59 (s, 3 H), 4.23−4.37 (m, 1 H), 7.32−7.48 (m, 6 H), 7.60−7.75 (m, 4 H).

To a solution of the above product (1.30 g, 3.64 mmol) in THF (15 mL) was added DIBALH (9.1 mL, 1 M in hexane, 9.1 mmol) at −70 °C dropwise. The solution was gradually warmed to −15 °C over 3 h and, after being cooled again to −40 °C, EtOH (2.14 mL, 36.4 mmol) was added slowly to destroy excess hydride. After 15 min, the cooling bath was removed, and the solution was poured into an ice-cold mixture of hexane and 1 N HCl with vigorous stirring. The phases were separated, and the aqueous phase was extracted with hexane twice. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford (3*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-1-butanol (1.08 g, 91%), whose ^{1}H and ^{13}C NMR data were identical with those reported.[34]

To a solution of the above alcohol (291 mg, 0.886 mmol), imidazole (147 mg, 2.16 mmol), and PPh_3 (341 mg, 1.30 mmol) in benzene (10 mL) was added iodine (440 mg, 1.73 mmol). The resulting red brown solution was stirred at room temperature for 1 h and poured into a mixture of aqueous $Na_2S_2O_3$ and hexane with vigorous stirring. The hexane layer was separated, and the aqueous layer was washed with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was dissolved in THF (40 mL), and aqueous 35% H_2O_2 (8.4 mL) was added to destroy PPh_3 recovered. After being stirred at room temperature for 30 min, brine and hexane were added to the mixture. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish the crude product, which was purified by chromatography (hexane/Et_2O) to give iodide **43** (337 mg, 88%), whose IR and ^{1}H NMR data were identical with those reported.[34]

(3*S*)-2-(3-[(*tert*-Butyldiphenylsilyl)oxy]butyl)furan (44). According to the procedure for preparation of **34**, iodide **43** (2.02 g, 4.59 mmol), furan (1.00 mL, 13.7 mmol), *n*-BuLi (6.19 mL, 1.48 M in hexane, 9.16 mmol), bipyridine (ca. 10 mg), and THF (35 mL) afforded **44** (1.62 g, 94%): bp 135 °C (1 Torr); IR (neat) 1596, 1509, 1430, 707 cm^{-1}; ^{1}H NMR δ 1.06 (s, 9 H), 1.08 (d, J = 6 Hz, 3 H), 1.69−1.90 (m, 2 H), 2.57−2.75 (m, 2 H), 3.85−3.97 (m, 1 H), 5.85 (br s, 1 H), 6.24 (br s, 1 H), 7.32−7.47 (m, 7 H), 7.62−7.75 (m, 4 H); ^{13}C NMR δ 156.3, 140.7, 135.99, 135.95, 134.9, 134.5, 129.6, 129.5, 127.6, 127.5, 110.1, 104.6, 69.0, 37.6, 27.2, 23.9, 23.2, 19.4. Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found: C, 76.22; H, 8.25.

(2*E*,7*S*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-4-oxo-2-octenoic Acid (46). To a solution of the furan **44** (676 mg, 1.79 mmol) and pyridine (0.58 mL, 7.2 mmol) in THF−acetone−H_2O (5:4:2, 8 mL) was added NBS (383 mg, 2.15 mmol) dissolved in THF−acetone−H_2O (5:4:2, 2 mL) at −20 °C. The solution was stirred for 1 h at −20 °C and then at room

temperature for 5 h and poured into a mixture of ethyl acetate and aqueous $Na_2S_2O_3$ with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/ethyl acetate) to afford aldehyde **45** (450 mg, 64%): IR (neat) 1695, 1112, 707 cm^{-1}; ^1H NMR δ 1.05 (s, 9 H), 1.11 (d, J = 6 Hz, 3 H), 1.65−1.89 (m, 2 H), 2.59−2.80 (m, 2 H), 3.88−4.01 (m, 1 H), 6.64 (dd, J = 16, 7 Hz, 1 H), 6.74 (d, J = 16 Hz, 1 H), 7.31−7.47 (m, 6 H), 7.61−7.70 (m, 4 H), 9.73 (d, J = 7 Hz, 1 H).

According to the procedure for preparation of **3a**, a mixture of **45** (342 mg, 0.867 mmol), $NaClO_2$ (139 mg, purity 85%, 1.31 mmol), 2-methyl-2-butene (0.74 mL, 7.0 mmol) in *t*-BuOH (8 mL), the phosphate buffer (pH 3.6, 4 mL), and H_2O (4 mL) was stirred at room temperature for 1 h to give acid **46** (296 mg, 83%) after purification by chromatography (hexane/ethyl acetate): IR (neat) 1701, 1111, 702 cm^{-1}; ^1H NMR δ 1.06 (s, 9 H), 1.10 (d, J = 6 Hz, 3 H), 1.66−1.88 (m, 2 H), 2.55−2.78 (m, 2 H), 3.88−3.99 (m, 1 H), 6.57 (d, J = 16 Hz, 1 H), 7.04 (d, J = 16 Hz, 1 H), 7.34−7.48 (m, 6 H), 7.63−7.72 (m, 4 H).

Ethylene Ketal of (2*E*,7*S*)-7-[(*tert*-Butyldiphenylsilyl)-oxy]-4-oxo-2-octenoic Acid (47). According to the procedure for preparation of **41**, a solution of **46** (84 mg, 0.20 mmol), $HC(OEt)_3$ (113 mL, 1.03 mmol), *p*-TsOH·H_2O (5 mg, 0.03 mmol), and ethylene glycol (128 mg, 2.06 mmol) in benzene (3.5 mL) was stirred at 35 °C overnight to afford a mixture of **47** and its ethyl ester, which, without further purification, was treated with 2 N LiOH (1.05 mL, 2.1 mmol) in MeOH (8 mL) at room temperature overnight to furnish **47** (64 mg, 70%), whose ^1H NMR data was in good agreement with the reported[15c] data: ^1H NMR δ 1.04 (s, 9 H), 1.06 (d, J = 6 Hz, 3 H), 1.41−1.60 (m, 2 H), 1.62−1.90 (m, 2 H), 3.79−3.98 (m, 5 H), 6.04 (d, J = 16 Hz, 1 H), 6.79 (d, J = 16 Hz, 1 H), 7.33−7.45 (m, 6 H), 7.64−7.70 (m, 4 H).

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Supporting Information Available: ^1H NMR spectra of compounds lacking elemental analyses (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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