Total Synthesis of (−)-Ircinianin and (+)-Wistarin†

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(−)-Ircinianin (**1**), a cyclic furanosesterterpenetetronic acid isolated from a marine sponge (*genus Ircinia*), is synthesized in 17 steps from (*S*)-2-methylpropane-1,3-diol mono THP ether **10** and 3-furfural. The key step involves a $NiCl_2$−$CrCl_2$-mediated coupling reaction of iodotriene **9** with chiral aldehyde **8** in DMSO and subsequent intramolecular Diels−Alder reaction in one pot. Both reactions proceed very smoothly at room temperature and eventually give the cyclic product **30A** possessing the desired cyclic skeleton of **1** in 60% yield. The structure of **30A** is determined by X-ray crystallographic analysis. The stereochemistry of Diels−Alder reactions of **7A** and another acyclic precursor **7B** are discussed. The first total synthesis of (+)-wistarin (**2**) is accomplished in 55% yield by iodoether ring formation of **1** and hydrogenolysis of the iodide **33A**. Based on the coupling constant in the proton NMR spectrum of **33A**, the reported structure **2A** is revised to **2B**.

Introduction

(−)-Ircinianin (**1**) was isolated from the marine sponge, *genus Ircinia*, by Hofheinz et al. in 1977,[1] and its cyclic isomer (+)-wistarin (**2**) was obtained from the marine sponge, *Ircinia wistarii*, by Gregson et al. in 1982.[2] They are both structurally unique cyclic furanosesterterpenetetronic acids, as shown in Figure 1. The relative structure of **1** was determined by X-ray crystallographic analysis, and that of **2** was assumed on the basis of spectroscopic data. Although a number of furanosesterterpenetetronic acids,[3] e.g. fasciculatin (**3**),[4] variabilin (**4**),[5] and ircinic acid (**5**),[6] have been reported, the absolute stereochemistries of this family including **1** and **2** have not been determined except in the case of **3**.[4] Because most furanosesterterpenetetronic acids exist in a linear form, the cyclic structures of **1** and **2** are particularly interesting. Biogenetically, **1** is assumed to be produced enzymatically or thermally by intramolecular Diels−Alder reaction from acyclic 8,11,13,20-tetraene precursor **6** in nature.[7] The thermal transformation of **6** to ircinianin was achieved in racemic form by Yoshii and Takeda.[8] However, a lack of absolute structure determination and not enough biological and chemical studies,[1,9] for both compounds prompted us to synthesize **1** and **2** in optically active forms. In this paper, we report the first enantioselective total synthesis of (−)-ircinianin and (+)-wistarin, including a minor stereochemical revision of the proposed wistarin structure **2A** to **2B**.

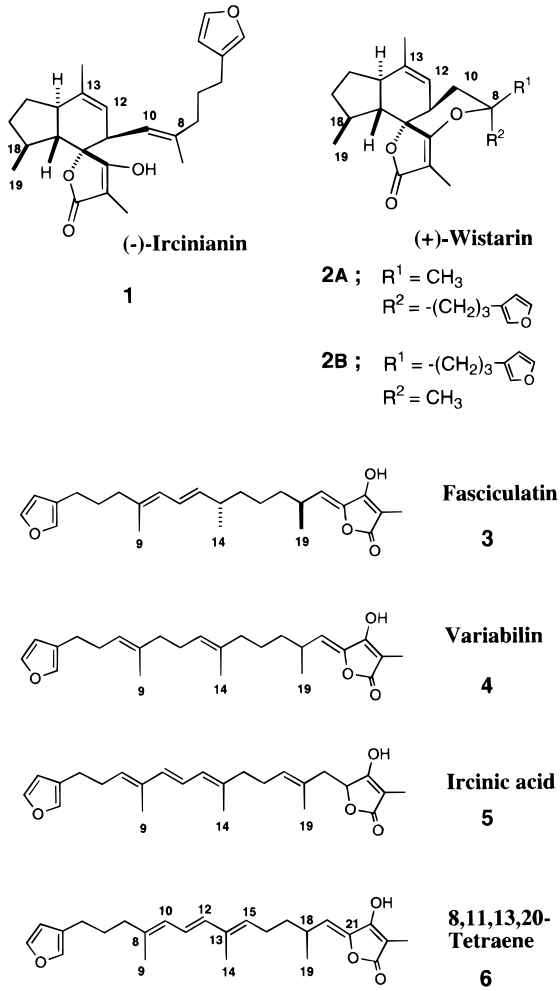

Figure 1. Furanosesterterpenetetronic acids.

Our synthetic plan of **1** and **2** is outlined in Figure 2. The tricyclic ring is constructed by an intramolecular Diels−Alder reaction of tetraene **7**, which may be obtained by a $NiCl_2$−$CrCl_2$-promoted coupling reaction of iodo triene **9** with aldehyde **8**. The (*R*)- or (*S*)-chiral carbogenic center of **8** will be derived from commercially available (*S*)-(+)- or (*R*)-(−)-3-hydroxy-2-methylpropionic

† This paper is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

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(1) Hofheinz, W.; Schönholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367.
(2) Gregson, R. P.; Ouvrier, D. *J. Nat. Prod.* **1982**, *45*, 412.
(3) (a) Krebs, H. C. In *Fortschritte der Chemie Organischer Naturstoffe*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer-Verlag: New York, 1986; Vol. 49, pp 151−363. (b) Crews, P.; Naylor, S. In *Fortschritte der Chemie Organischer Naturstoffe*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer-Verlag: New York, 1985, Vol. 48, pp 203−269.
(4) Cafieri, F.; Fattorusso, E.; Santacroce, C.; Minale, L. *Tetrahedron* **1972**, *28*, 1579.
(5) Faulkner, D. J. *Tetrahedron Lett.* **1973**, 3821.
(6) Manes, L. V.; Crews, P.; Ksebati M. B.; Schmitz, F. J. *J. Nat. Prod.* **1986**, *49*, 787.
(7) Ichihara, A. In *Studies in Natural Products Chemistry*, Stereoselective Synthesis (Part C); Atta-ur-Rahman, Ed.; Elsevier: New York, 1989; Vol. 4, pp 570−624.
(8) The elegant total synthesis of racemic **1** was achieved by Yoshii et al. See Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903.
(9) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Ishihama, M. *Pure Appl. Chem.* **1986**, *58*, 387.

S0022-3263(96)01993-7 CCC: $14.00

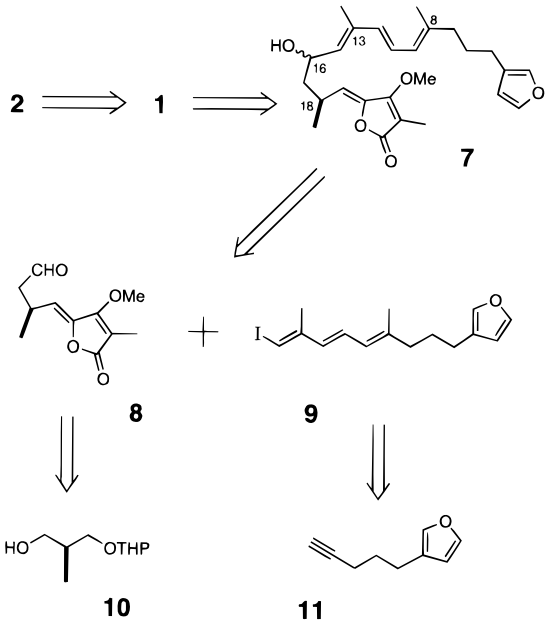
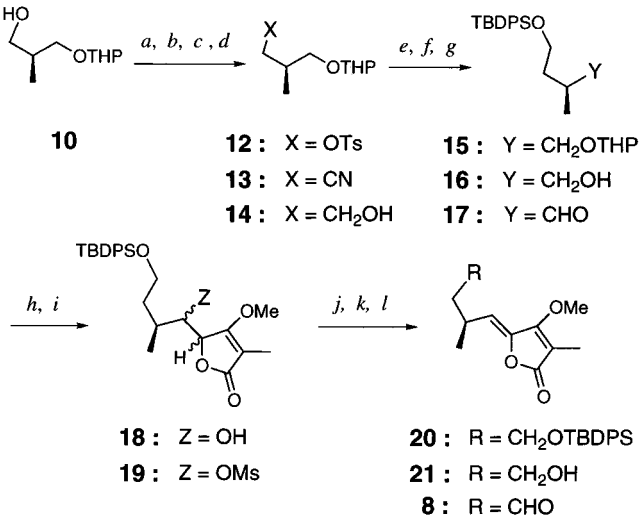


Figure 2. Retrosynthesis of **1** and **2**.

Scheme 1



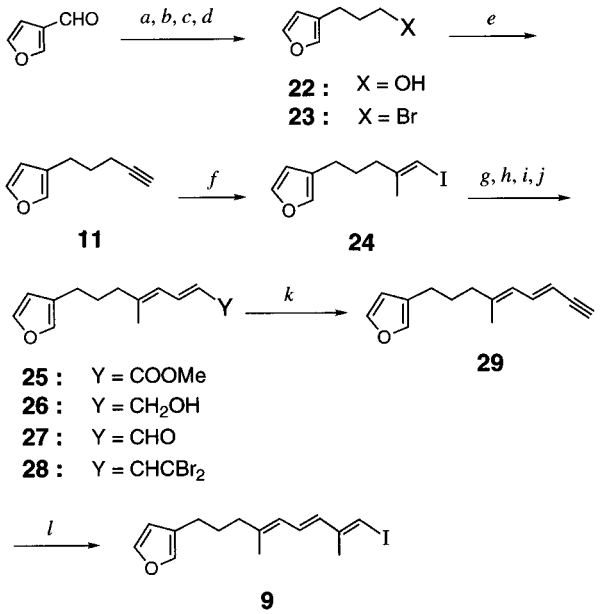
Reagents and conditions ; (*a*) TsCl, pyridine, 0°C, 3 h; (*b*) NaCN, DMSO, 60°C, 30 min; (*c*) DIBAL-H, CH_2Cl_2, -78°C, 5 min; (*d*) $NaBH_4$, Et_2O:MeOH (6:1), rt, 5 min; (*e*) TBDPSCl, DMAP, CH_2Cl_2, rt, 5 min; (*f*) $Bu_2Sn(SMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 5 min; (*g*) Swern oxidation; (*h*) Methyl 2-methyltetronate, LDA, THF:HMPA (4:1), -78°C, 30 min; (*i*) MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 5 min; (*j*) DBU, benzene, rt, <10 min; (*k*) Bu_4NF, THF, rt, 1 h, then separation of geometrical isomers; (*l*) PCC, CH_2Cl_2, rt, 1 h.

acid methyl ester through the optically active alcohol **10**. Iodo triene **9** is prepared from furanopentyne **11**.

Total Synthesis of (−)-Ircinianin

The synthetic route to **8** is described in Scheme 1. The starting optically pure alcohol **10** was derived from (*R*)-(−)-3-hydroxy-2-methylpropionic acid methyl ester[11] in 78% yield with a slight modification of Mori's method[10]. A one-carbon extension of **10** to **14** was performed in 54%

Scheme 2



Reagents and conditions ; (*a*) NaH, $(EtO)_2POCH_2COOEt$, THF, 0°C, 5 min; (*b*) 10% Pd/C, H_2, Et_2O, rt, 5 h; (*c*) $LiAlH_4$, Et_2O, 0°C, <10 min; (*d*) CBr_4:PPh_3 (1:1), CH_2Cl_2, 0°C, <5 min; (*e*) Sodium acetylide, HMPA, 15°C, 2 h; (*f*) *i*, $MeMgSnBu_3$, cat. CuCN, THF, 0 °C, 15 min, *ii*, MeI, 0°C, 20 min, *iii*, Extraction with hexane, *iv*, I_2, CH_2Cl_2, 0°C; (*g*) Methyl acrylate, cat. $Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF, rt, 3 h; (*h*) DIBAL-H, CH_2Cl_2, -78°C, <5 min, (*i*) $BaMnO_4$, CH_2Cl_2, rt, 6 h; (*j*) CBr_4:PPh_3 (2:2), CH_2Cl_2, 0°C, <5 min; (*k*) LDA (2.2 eq), THF, 0°C, <5 min; (*l*) *i*, $MeMgSnBu_3$, cat. CuCN, THF, -20 °C, 15 min, *ii*, MeI, -20°C, 20 min, *iii*, Extraction with hexane, *iv*, I_2, CH_2Cl_2, 0°C.

yield *via* the following steps: (i) tosylation of **10** by *p*-toluenesulfonyl chloride in pyridine; (ii) cyanation with sodium cyanide in 90% yield (over two steps, **10** → **12** → **13**); (iii) reduction of cyanide to the aldehyde by DIBAL-H; (iv) reduction of aldehyde with $NaBH_4$ in 60% yield (over two steps, **13** → CHO → **14**). After protection of the alcohol as a *tert*-butyldiphenylsilyl ether and deprotection of THP ether with $Bu_2Sn(SMe)_2$ in the presence of $BF_3{\cdot}OEt_2$,[12] the primary alcohol was oxidized to chiral aldehyde **17** under the Swern oxidation condition in 86% yield (over three steps, **14** → **15** → **16** → **17**). Treatment of the lithium salt of methyl 2-methyltetronate[13] with **17** gave aldol adducts **18** as three diasteromers. Mesylation of aldol **18** with methanesufonyl chloride followed by elimination of the mesylate with DBU afforded **20** as a 2:1 mixture of *Z* and *E* isomers in 84% yield (over three steps, **17** → **18** → **19** → **20**). After deprotection of the TBDPS group with tetrabutylammonium fluoride, the geometric isomers were separated by silica gel flash chromatography and the desired *Z* isomer **21** was isolated as a major product in 62% yield.[14] This was subject to PCC oxidation to give **8** in 68% yield.

Synthesis of **9** started from 3-furfural *via* **11** in 12 steps as shown in Scheme 2. Compound **11** was prepared by standard carbon chain extension reactions and functionalizations in the following five steps: (i) Wittig−Horner−Emmons reaction of 3-furfural with the sodium salt of

(10) Mori, K. *Tetrahedron* **1983**, *39*, 3107.
(11) The (*R*)-enantiomer was initially taken as a chiral pool, and later it was found that this was a proper choice to build up the correct stereochemistry for **1** and **2**.

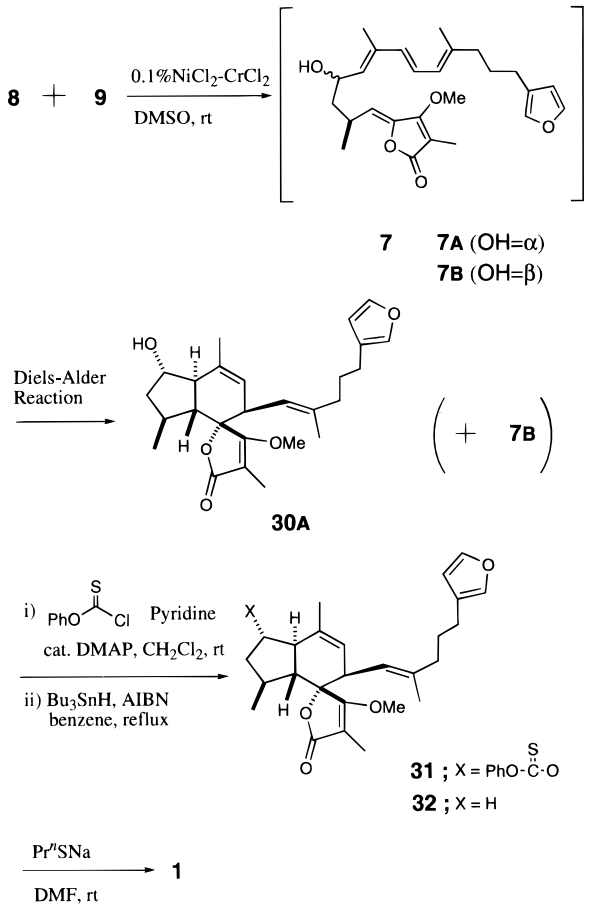
(12) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 4770.
(13) Wengel, A. S.; Reffstrup, T.; Boll, P. M. *Tetrahedron* **1979**, *35*, 2181.
(14) The geometries and stereochemistries were confirmed after leading to the final product **1** ultimately.

triethyl phosphonoacetate, (ii) Pd-catalyzed reduction of the α,β-unsaturated ester under H_2 atmosphere, (iii) $LiAlH_4$ reduction of the ester to primary alcohol **22** in 88% yield (over three steps, 3-furfural→→→**22**), (iv) bromination with carbon tetrabromide and triphenylphosphine in 96% yield (**22** → **23**[15]), (v) coupling reaction with sodium acetylide in 90% yield (**23** → **11**).

A key functional transformation for terminal alkyne **11**, and dienyne **29** at a later stage, to trisubstituted iodoolefin was performed by a regioselective *syn* addition of $MeMgSnBu_3$.[16] Thus, the alkyne **11** was treated with $MeMgSnBu_3$[17] in the presence of a catalytic amount of CuCN followed by methylation with iodomethane to give the 1-(tributylstannyl)-2-methylalkene which was then treated with iodine to afford (*E*)-1-iodo-2-methylalkenyl function of **24** in 62% yield. The improved Heck reaction[18] of **24** with methyl acrylate in the presence of Pd(OAc)$_2$ catalyst provided dienyl acid methyl ester **25** in 95% yield. Manipulation of the ester to the terminal alkyne (**25** → **29**) was carried out by standard procedures in 51% overall yield; thus, (i) DIBAL-H reduction of the ester to alcohol (**25** → **26**) in 88% yield; (ii) $BaMnO_4$ oxidation of alcohol to aldehyde (**26** → **27**) in 95% yield; (iii) dibromoolefin formation by CBr_4 and Ph_3P; (iv) transformation of the dibromoalkene to alkyne by treating with 2.2 equiv of LDA in 61% yield (over two steps, **27** → **28** → **29**). Stereospecific conversion of the terminal acetylene **29** to the (*E*)-1-iodo-2-methylalkene was carried out using by the same procedure described for **11** and afforded **9** in 75% yield.[19,20]

Since Kishi used 0.1% $NiCl_2$−$CrCl_2$-promoted addition of iodoalkenes and iodoalkynes to aldehydes,[21] the reaction has been successfully adopted as an important key coupling reaction in natural product syntheses.[22] Thus, the coupling of **9** with **8** using this method proceeded smoothly in DMSO at room temperature (Scheme 3). This is the first successful case of a $NiCl_2$−$CrCl_2$-promoted coupling reaction of an iodotriene with an aldehyde. The reaction afforded the desired alcohols **7A** and **7B** at the initial stage of the reaction. However, surprisingly, one of the two isomers, presumably **7A**, started to undergo Diels−Alder cyclization during the reaction at *room temperature*, and eventually gave the single cyclized product **30A** among four possible stereoisomers.[23] The other isomer, **7B**, did not cyclize and remained in the reaction mixture. This reaction is discussed later in this paper. After the mixture was allowed to react at room temperature for 18 h, purification of the reaction mixture gave the desired cyclized product **30A** in 60% yield along

Scheme 3



with the uncyclized coupling product **7B** in 20% yield. Phenoxythionoformylation of **30A** with phenyl chlorothionoformate in the presence of DMAP followed by AIBN-catalyzed deoxygenation with Bu_3SnH[24] provided ircinianin methyl ether **32** in 64% overall yield (**30A** → **31** → **32**). Deprotection of the methyl ether with PrSNa[25] completed the total synthesis of **1** in 90% yield. Spectroscopic data for synthetic **1** were identical to those reported in the literature.[1] In particular, the specific rotation, $[\alpha]^{24}_D$ −235° (*c* 0.3, $CHCl_3$) was in accordance with the reported value, $[\alpha]^{25}_D$ −232° (*c* 0.5, $CHCl_3$), confirming the correct absolute structure of **1** including the *S*-configuration at the C-18 chiral center, originally provided from (*R*)-(−)-3-hydroxy-2-methylpropionic acid methyl ester.

Chemical Transformation of (−)-Ircinianin to (+)-Wistarin

Gregson reported that attempts of an acid-promoted transformation of **1** to **2** were unsuccessful.[2] However, as shown in Scheme 4, when **1** was treated with iodine in the presence of K_2CO_3, cyclic iodo ether **33A** was formed very cleanly as a single product in 71% yield. Chemical shifts in ^1H and ^{13}C NMR spectra of **33A** indicated that the cyclization occurred in 6-*endo*-trigonal fashion, in which the methine (C-10) proton appeared at 4.13 ppm, and the corresponding carbon (C-10) and the next quaternary carbon (C-8) appeared at 38.4 and 79.7 ppm, respectively.[26] Hydrogenolysis of the iodide **33A**

(15) Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.
(16) Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1438.
(17) Matsubara, S.; Hibino, J.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163.
(18) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(19) This compound is unstable, and so it is better to be used subsequently.
(20) The use of Negishi's carbometalation reaction by Cp_2ZrCl_2 with Me_3Al also worked well to give the same product in similar yield.
(21) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463. (c) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909.
(22) Recent examples for total syntheses of natural products using this coupling. (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Roush, W. R.; Brown,.B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268. (c) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621.
(23) The stereoisomers are due to the hydroxy center, the ring juncture, and *exo*- and/or *endo*-adducts.
(24) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(25) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

Scheme 4. Chemical Transformations of Ircinianin to Wistarin

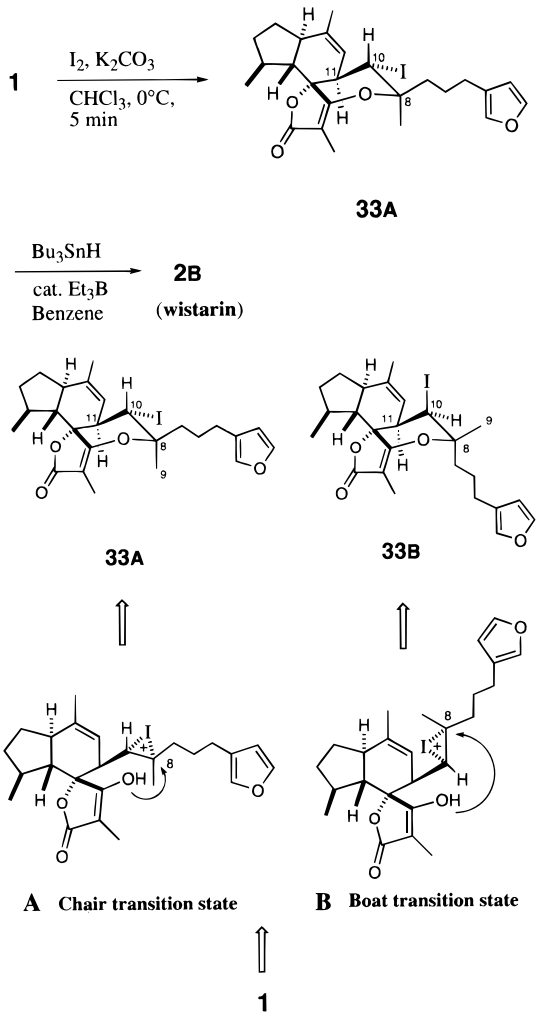


Figure 3. Cyclic iodo ether formation of **1** 6-*endo*-trigonal fashion.

under radical conditions by Bu_3SnH and a catalytic amount of Et_3B proceeded at 7 °C in benzene to give (+)-wistarin **2B** in 77% yield. The specific rotation, $[\alpha]^{27}_D$ +132° (*c* 0.3, CH_2Cl_2) and other spectroscopic data for the synthetic material confirmed the total synthesis of (+)-wistarin, lit. $[\alpha]^{20}_D$ +130° (*c* 0.25, CH_2Cl_2).[2]

In this cyclization, differentiation of the two diastereotopic faces of the trisubstituted olefin is possible, and is shown in Figure 3. In one case, the enol oxygen attacks from the *re*-face of the C-8 olefin plane, in which the iodonium intermediate is located on the α side in **A**. This reaction path goes through a chair transition state leading to **33A**. In the other case, the enol oxygen attacks from the *si*-face of the C-8 olefin plane, in which the iodonium intermediate is located on the α side, shown in the structure **B**. This path affords **33B** *via* a boat transition state. The former can be considered preferred because the chair transition state smoothly proceeds to the end product **33A**. However, in the latter case the resulting boat product requires a ring inversion leading to the stable chair conformation **33B**. Furthermore, based on MM2 calculations, the structure of **33A** was 2.93 kcal/mol more stable than that of **33B**.[27] The C-10 stereocenter of **33A** was confirmed by proton NMR, in which a 11.7 Hz coupling constant between C-10 and C-11 protons was clearly observed as a typical axial−axial coupling. Therefore, the C-9 methyl group is located at an axial position and the 3-furylpropyl group is placed at an equatorial position. Consequently the reported structure **2A** conflicts stereochemically with (*R*)-configuration at the C-8 quaternary center, and therefore, we revise the structure of (+)-wistarin to **2B**.

Diels−Alder Reactions of the Tetraene Intermediates

As noted in the above total synthesis of **1**, the $NiCl_2$−$CrCl_2$-mediated coupling reaction of **8** and **9**, and successive Diels−Alder cyclization gave a mixture of **30A** and **7B** in a combined yield of 80% after 18 h at room temperature. However, when the reaction was stopped after 1 h, aldehyde **8** was consumed in the reaction, and a mixture of **30A**, **7B**, and another acyclic isomer **7A** was obtained in a total yield of 89% in a 1:2:2 ratio. Based on this ratio, the diastereoface selectivity of the addition was found to be 3:2 (α:*β*). Although the acyclic precursor **7A** underwent the intramolecular Diels−Alder reaction to give **30A** quite smoothly under the coupling conditions,[28] alternative diastereoisomer **7B** did not cyclize easily under the conditions at room temperature, and its decomposition proceeded gradually. Interestingly the Diels−Alder cyclization of **7A** surely took place at room temperature in the presence of $CrCl_2$, however, it did not in the absence of $CrCl_2$. This fact indicated that the $CrCl_2$ certainly mediated the Diels−Alder cyclization by acting as an appropriate Lewis acid. Nevertheless, when **7B** was heated in xylene at 150 °C (bath temperature) for 15 min, the Diels−Alder products **30B**, **30B′**, and **30B″** (Scheme 5) were formed in 27, 18, and 14% yields, respectively.[29] All were cyclic stereoisomers with the same molecular weight (*m*/*z* 426) characterized by mass spectrometry. Deoxygenation of the major isomer **30B** led to **32** confirming that **30B** was a diastereomer of **30A**. Fortunately, **30A** was crystallized from methanol, and the relative stereochemistry was determined by X-ray crystallographic analysis[34] which clearly indicated the (*S*)-configuration of the C-16 chiral center. Therefore, we were able to determine all the structures of **30A**, **30B**, and **32** at this stage. The structure of **32** was also confirmed by proton NMR. The coupling constants of $J_{H^1-H^2}$ and $J_{H^2-H^3}$ in **32** were observed as 11.0 and 11.0 Hz, respectively. These values were nearly equal to the corresponding coupling constants (12.1 and 10.5 Hz), calculated with PM3 (Spartan version 4.1). The compound **32′** was obtained by deoxygenation of **30B′** and was identified as a diastereoisomer of **32** by NMR. The coupling constant between H^1 and H^2 protons was 12.4 Hz, indicating a *trans* relationship in the bicyclo[4.3.0]-nonane system.[30] The coupling constant between H^2 and H^3 was observed as 6.6 Hz. Calculated values of the corresponding protons showing 12.5 and 6.4 Hz, respec-

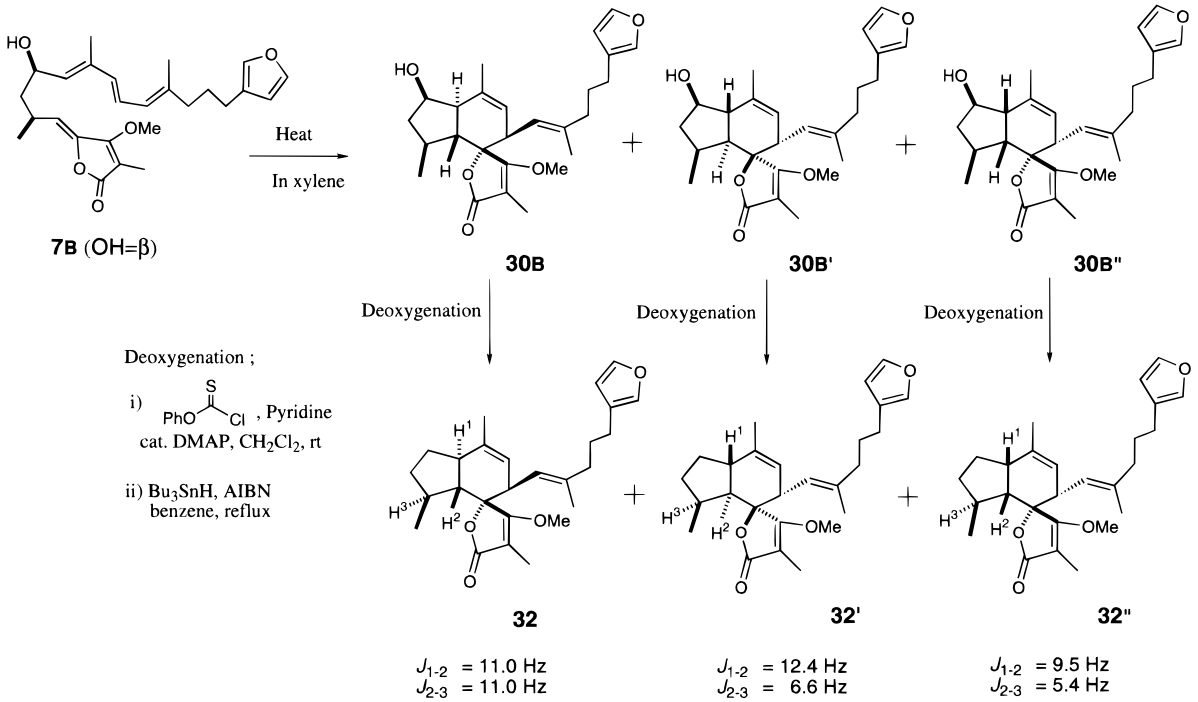
(26) A numbering of carbons is based on the acyclic furanosesterterpenetetronic acid.[3]

(27) The calculations were performed by Macro Model program (version 5.1).

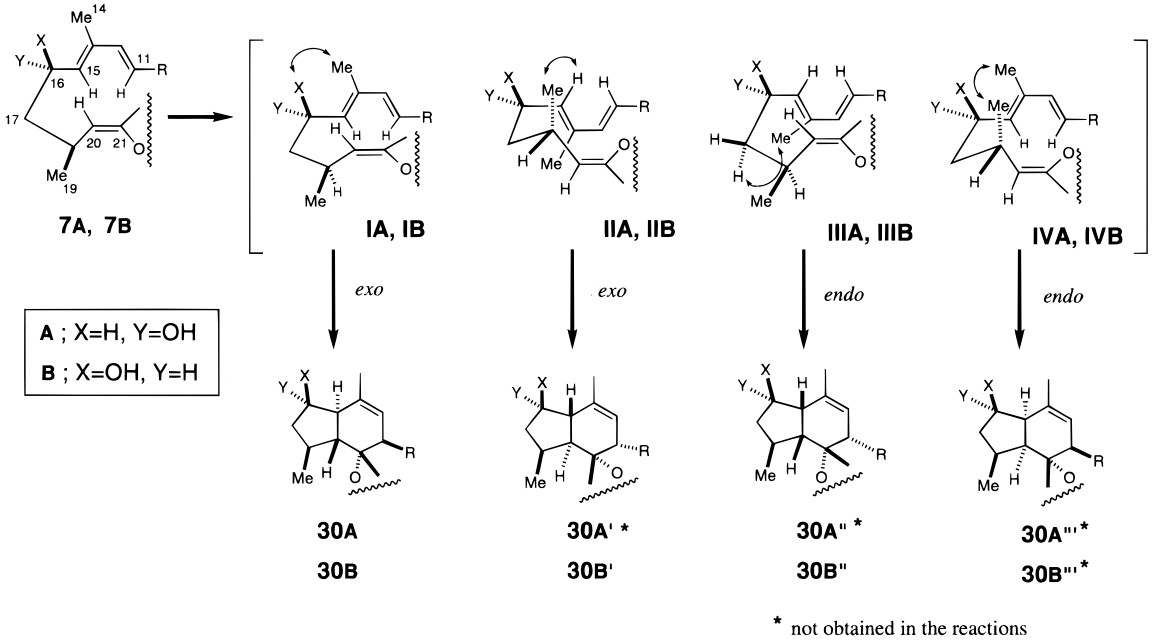
(28) The matching combination of 16*R* and 18*S*[26] chiral centers in **7A** may allow the intramolecular *exo*-Diels−Alder reaction occurring quite smoothly to provide the cyclized product **30A** under the conditions.

(29) Formation of a [4.3.0] ring system by intramolecular Diels−Alder reaction of α-chiral dienes at high temerature was reported by Roush et al. See (a) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. (b) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390.

Scheme 5. Diels−Alder Cyclization of 7B and Deoxygenation of the Cyclized Products



Scheme 6. All Possible Stereoisomers and the Transition States in the Diels−Alder Cyclization



tively, also supported the structure of **32′**. Deoxygenation of **30B″** led to the other isomer **32″**. The coupling constant between H^1 and H^2 was observed as 9.5 Hz, which indicated a *cis*-fused ring system in the bicyclo[4.3.0]nonane. Clear NOE enhancement (9%) between H^2 and C-19 methyl protons suggested that the H^2 and H^3 protons possess a *trans* relationship. All the values obtained here were in good accordance with previous data for bicyclo[4.3.0]nonane systems reported in the literature.[30]

The transition state of the Diels−Alder reaction is considered in Scheme 6. Four possible conformations **I** to **IV**, in two *exo* and two *endo* modes, are possible in the transition state. The experimental results indicate that *trans*-fused products are formed in preference to the corresponding *cis* products. Particularly the reaction of **7A** gave **30A** *via* **IA** exclusively among four possible stereoisomers, **30A** to **30A‴**. On the other hand, the reaction of **7B** provided **30B** *via* **IB** as a major product along with the alternative *trans* ring fused isomer **30B′** *via* **IIB**, and a *cis* isomer **30B″** *via* **IIIB**. The steric effect of an α-oxy group and a 2-bromo or 2-methyldienyl group was previously discussed by Roush.[31] In comparing the transition state **IA** with **IB**, the C-16 OH group com-

(30) (a) Kozikowski, A. P.; Tückmantel, W. *J. Org. Chem.* **1991**, *56*, 2826. (b) Kurth, M. J.; O'Brien, M. J.; Hope, H.; Yanuck, M. *J. Org. Chem.* **1985**, *50*, 2626. (c) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1987**, *52*, 4369.

(31) (a) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.

pletely eclipses the C-14 Me group in **IB**, but not in **IA**. The steric interaction of the OH and Me groups destabilizes the overlap of the C-11 and C-15 carbons in the diene with the C-20 and C-21 carbons in the dienophile. In fact, the Diels−Alder reaction of **7B** required heating at 150 °C to give the major isomer **30B** along with some formation of other stereoisomers **30B′** and **30B″** *via* unfavorable transition states, **IIB** and **IIIB**. In the case of **IA**, the lack of steric interaction between OH and Me groups as well as a perfect overlapping conformation of diene and dienophile accelerate the cyclization of **7A** which occurs very smoothly even at room temperature.[32]

Conclusion

The total syntheses of **1** and **2** were accomplished in optically active forms. The absolute structures were determined by asymmetric synthesis, and the C-8 stereocenter of **2** was revised based on the proton NMR studies and the mechanistic considerations. The methodology for preparation of a trisubstituted iodotriene and its Ni−Cr-promoted addition to an aldehyde was found to be useful for the preparation of Diels−Alder intermediates in the synthesis of complicated natural products. In addition, the availability of synthetic **1** and **2** will permit the further pharmacological studies.

Experimental Section

General Procedures. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under Ar atmosphere. Solvents were distilled freshly over sodium/benzophenone ketyl for THF, ether, and benzene, over P_2O_5 for CH_2Cl_2, and over CaH_2 for hexane, toluene, DMSO, and DMF under nitrogen atmosphere. Unless otherwise stated, organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure (30−40 mmHg). Thin layer chromatography (TLC) was performed with Merck $60F_{254}$-precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70−230 mesh) for gravity column, silica gel 60 (230−400 mesh) for flash column, and Wako neutral alumina (200 mesh).

(*R*)-(−)-2-Methyl-3-[(2-tetrahydropyranyl)oxy]propyl *p*-Toluenesulfonate (12).[10] A mixture of **10** (9.68 g, 55.6 mmol) and *p*-toluenesulfonyl chloride (15.9 g, 83.3 mmol) was stirred for 3 h in pyridine (90 mL) at 0 °C. The reaction mixture was poured into ice−water and extracted with 20% ether in pentane. The crude product was used for the next reaction without further purification, but for analytical purposes, a part of the product was purified by column chromatography on silica gel eluted with 7.5% EtOAc in hexane to give **12** as a diastereomeric mixture. Colorless oil; R_f = 0.33 (20% EtOAc in hexane); $[\alpha]^{29}_D$ −8.9° (*c* 1.00, Et_2O); IR (neat) 1361, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3/2H, d, *J* = 6.9 Hz) and 0.94 (3/2H, d, *J* = 6.9 Hz), 1.42−1.65 (10/2H, m), 1.66−1.78 (2/2H, m), 2.03−2.14 (2/2H, m), 2.45 (6/2H, s), 3.20 (1/2H, dd, *J* = 9.7 and 7.4 Hz) and 3.58 (1/2H, dd, *J* = 9.8 and 6.9 Hz), 3.26 (1/2H, dd, *J* = 9.8 and 5.0 Hz) and 3.60 (1/2H, dd, *J* = 9.8 and 5.4 Hz), 3.42−3.49 (2/2H, m), 3.70−3.78 (2/2H, m), 3.94 (1/2H, dd, *J* = 9.3 and 5.9 Hz), 3.97−4.04 (2/2H, dm, *J* = 5.5 Hz), 4.07 (1/2H, dd, *J* = 9.3 and 6.0 Hz), 4.42−4.48 (2/2H, dm, *J* = 11.8 Hz), 7.34 (4/2H, d, *J* = 8.2 Hz), 7.79 (4/2H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 and 13.6, 19.2 and 19.4, 21.5 and 21.6, 25.3, 30.4, 33.4 and 33.6, 61.9 and 62.1, 67.9 and 68.4, 72.1 and 72.2, 98.5 and 99.0, 127.9, 129.7, 133.1, 144.5.

(*S*)-(−)-3-Methyl-4-[(2-tetrahydropyranyl)oxy]butyronitrile (13).[10] To a DMSO solution (50 mL) of the crude **12** was added sodium cyanide (5.4 g, 111 mmol) and heated at 60 °C for 30 min. The mixture was quenched with ice−water and extracted with 20% ether in pentane. The crude product was distilled to give **13** (9.16 g) in 90% (two steps). Colorless oil; bp 85−87 °C/1.8 mmHg; R_f = 0.34 (20% EtOAc in hexane); $[\alpha]^{29}_D$ −31.0° (*c* 1.00, Et_2O), lit. $[\alpha]^{21.5}_D$ −27.8° (*c* 1.41, Et_2O)[10]; IR (neat) 2245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3/2H, d, *J* = 6.8 Hz) and 1.10 (3/2H, d, *J* = 6.8 Hz), 1.48−1.62 (8/2H, m), 1.64−1.76 (2/2H, m), 1.76−1.86 (2/2H, m), 2.16 (2/2H, qm, *J* = 6.8 Hz), 2.36 (1/2H, dd, *J* = 16.6 and 7.3 Hz) and 2.39 (1/2H, dd, *J* = 16.6 and 6.9 Hz), 2.49 (1/2H, dd, *J* = 16.6 and 5.2 Hz) and 2.53 (1/2H, dd, *J* = 16.6 and 5.4 Hz), 3.21 (1/2H, dd, *J* = 9.8 and 8.0 Hz) and 3.58 (1/2H, dd, *J* = 9.8 and 7.8 Hz), 3.38 (1/2H, dd, *J* = 9.8 and 4.7 Hz) and 3.75 (1/2H, dd, *J* = 9.8 and 4.8 Hz), 3.48−3.56 (2/2H, m), 3.78−3.88 (2/2H, m), 4.54−4.62 (2/2H, dm, *J* = 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 and 16.2, 19.2 and 19.4, 21.3 and 21.3, 25.3, 30.4 and 30.4, 30.9 and 31.0, 62.0 and 62.3, 70.1 and 70.5, 98.5 and 99.2, 118.5 and 118.6. MS (EI) *m/z* 183 (M^+). HRMS Calcd for $C_{10}H_{17}NO_2$: M^+, 183.1259. Found: *m/z* 183.1249.

(*S*)-(−)-3-Methyl-4-[(2-tetrahydropyranyl)oxy]butanol (14). To a solution of **13** (12.0 g, 65 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added dropwise DIBAL-H (0.93 M in hexane solution; 78 mL). The reaction mixture was stirred for 5 min at the same temperature and quenched with saturated ammonium chloride (200 mL). The mixture was stirred vigorously at room temperature for 30 min and then filtered though a Celite pad. The filtrate was extracted with ether (300 mL), and the extract was condensed to 150 mL of the volume and diluted with methanol (25 mL). $NaBH_4$ (2.5 g, 66 mmol) was added to the extract solution at room temperature. The reaction was completed in 5 min. After an excess of $NaBH_4$ was decomposed with 2 mL of acetone, the mixture was diluted with ether and washed with water. The crude product was purified by flash column chromatography on silica gel eluted with 20% EtOAc in hexane to give **14** (7.44 g) in 60% yield (two steps). Colorless oil; R_f = 0.22 (30% EtOAc in hexane); $[\alpha]^{29}_D$ −12.8° (*c* 1.00, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3/2H, d, *J* = 6.6 Hz) and 0.88 (3/2H, d, *J* = 7.0 Hz), 1.39−1.68 (14/2H, m), 1.68−1.78 (2/2H, m), 1.79−1.88 (2/2H, m), 2.90 (2/2H, br s), 3.16 (1/2H, dd, *J* = 9.5 and 7.0 Hz) and 3.19 (1/2H, dd, *J* = 9.5 and 5.1 Hz), 3.41−3.48 (2/2H, m), 3.50−3.69 (6/2H, m), 3.74−3.83 (2/2H, m), 4.52 (2/2H, dd, *J* = 6.6 and 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 and 17.4, 19.3 and 19.4, 25.3, 30.4 and 30.4, 30.8 and 30.9, 37.5 and 37.5, 60.8, 62.1, 73.0 and 73.1, 98.8 and 98.9; MS (FAB) *m/z* 189 (MH^+). HRMS Calcd for $C_{10}H_{21}O_3$: MH^+, 189.1491. Found: *m/z* 189.1463.

(*S*)-(−)-3-Methyl-4-[(2-tetrahydropyranyl)oxy]butyl *tert*-Butyldiphenylsilyl Ether (15). *tert*-Butylchlorodiphenylsilane (6.6 mL, 25.4 mmol) was dropped into a mixture of **14** (3.97 g, 21.1 mmol) and DMAP (2.58 g, 21.1 mmol) in CH_2Cl_2 (30 mL) at room temperature. The mixture was stirred for 5 min and diluted with ether. The mixture was washed with water. The crude product was chromatographed on silica gel eluted with 1−2% EtOAc in hexane to give **15** (9.0 g) quantitatively. Colorless oil; R_f = 0.31 (5% EtOAc in hexane); $[\alpha]^{28}_D$ −1.8° (*c* 1.00, $CHCl_3$); IR (neat) 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3/2H, d, *J* = 6.2 Hz) and 0.91 (3/2H, d, *J* = 6.4 Hz), 1.04 (18/2H, s), 1.33−1.44 (2/2H, m), 1.46−1.60 (8/2H, m), 1.63−1.86 (6/2H, m), 1.89−1.99 (2/2H, qm, *J* = 6.4 Hz), 3.16 (1/2H, dd, *J* = 9.4 and 6.4 Hz), 3.22 (1/2H, dd, *J* = 9.4 and 5.8 Hz), 3.44−3.53 (3/2H, m), 3.58 (1/2H, dd, *J* = 9.4 and 6.4 Hz), 3.73 (4/2H, t, *J* = 6.4 Hz), 3.79−3.86 (2/2H, br t, *J* = 8.5 Hz), 4.51−4.56 (2/2H, dd, *J* = 3.1 and 3.5 Hz), 7.35−7.45 (6H, m), 7.65−7.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1 and 17.2, 19.2, 19.5 and 19.5, 25.5, 26.8 and 26.9, 30.3 and 30.3, 30.7, 36.6 and 36.6, 62.1, 62.2, 72.9, 98.7 and 98.8, 127.6, 129.5, 134.1, 135.5; MS (EI) *m/z* (rel intensity) 325 (M^+ − 101, 9), 285 (73), 199 (34), 85 (base). HRMS Calcd for $C_{26}H_{38}O_3SiNa$: M^+ + Na, 449.2488. Found: *m/z* 449.2483.

(*S*)-(−)-2-Methyl-4-[(*tert*-butyldiphenylsilyl)oxy]butanol (16). To an ice-cooled CH_2Cl_2 solution (100 mL) of **15** (5.12 g, 12.0 mmol) and $Bu_2Sn(SMe)_2$ (4.71 g, 14.4 mmol) was added a CH_2Cl_2 (5 mL) solution of BF_3·OEt (1.77 mL, 14.4 mmol) dropwise. The reaction was stirred for 5 min at 0 °C, EtOAc

(32) Due to a lack of reliable parameters for the tetronic acid part, we have failed to calculate the transition state for the Diels−Alder reactions using the Macro Model.

(200 mL) and saturated $NaHCO_3$ (100 mL) were added to the mixture, and precipitates were filtered through a Celite pad under reduced pressure. The organic filtrate was isolated and washed with water. The oily product was purified by flash column chromatography on silica gel eluted with 7.5% EtOAc in hexane to give **16** (3.76 g) in 91% yield. Colorless oil; R_f = 0.37 (20% EtOAc in hexane); $[\alpha]^{28}_D$ −7.5° (*c* 1.00, $CHCl_3$); IR (neat) 3360, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.9 Hz), 1.05 (9H, s), 1.48 (1H, m), 1.63 (1H, m), 1.84 (1H, qm, *J* = 6.4 Hz), 2.42 (1H, br s), 3.44−3.56 (2H, br m), 3.66−3.80 (2H, m), 7.36−7.45 (6H, m), 7.66−7.68 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 19.1, 26.8, 33.8, 36.7, 62.5, 68.2, 127.7, 129.7, 133.5, 135.6; MS (FAB) *m*/*z* 343 (MH^+). HRMS Calcd for $C_{21}H_{31}O_2Si$: MH^+, 343.2093. Found: *m*/*z* 343.2097.

(*S*)-(+)-2-Methyl-4-[(*tert*-butyldiphenylsilyl)oxy]butanal (17). To a solution of oxalyl chloride (0.76 mL, 8.71 mmol) in CH_2Cl_2 (30 mL) was added DMSO (1.24 mL, 17.5 mmol) at −78 °C. The mixture was stirred for 20 min at the same temperature, and then a CH_2Cl_2 solution (10 mL) of **16** (2.0 g, 5.84 mmol) was dropped during 5 min at −78 °C. The stirring was continued for 20 min, and triethylamine (4.1 mL, 29.4 mmol) was dropped. The whole mixture was stirred for 20 min at the same temperature and an additional 30 min on an ice bath. Saturated ammonium chloride (50 mL) was added to the mixture and extracted with EtOAc. The crude aldehyde was purified by column chromatography on silica gel eluted with 1−2.5% EtOAc in hexane to afford pure aldehyde **17** (1.88 g) in 95% yield. Colorless oil; R_f = 0.31 (5% EtOAc in hexane); $[\alpha]^{28}_D$ +8.9° (*c* 1.00, $CHCl_3$); IR (neat) 1715, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.09 (3H, d, *J* = 7.0 Hz), 1.62 (1H, ddt, *J* = 13.9, 6.6 and 5.5 Hz), 2.01 (1H, dtd, *J* = 13.9, 7.0 and 6.6 Hz), 2.58 (1H, qtd, *J* = 7.0, 6.6 and 1.7 Hz), 3.65−3.78 (2H, m), 7.36−7.46 (6H, m), 7.63−7.67 (4H, m), 9.67 (1H, d, *J* = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 19.1, 26.8, 33.4, 43.5, 61.1, 127.6, 129.6, 133.5, 135.5, 204.7; MS (FAB) *m*/*z* 341 (MH^+). HRMS Calcd for $C_{21}H_{28}O_2SiNa$: M^+ + Na, 363.1756. Found: *m*/*z* 363.1746.

Coupling Reaction of 17 with Methyl 2-Methyltetronate and Elimination Reaction. Preparation of 20. Lithium diisopropylamide (8.27 mmol) in THF (12 mL) and HMPA (5 mL) solution was prepared from diisopropylamine (1.23 mL, 9.38 mmol) and BuLi (1.56 M in hexane solution; 5.3 mL) by the standard procedure. To this solution was added methyl 2-methyltetronate (1.06 g, 8.27 mmol) in THF (8 mL) at −78 °C and stirred for 30 min. Aldehyde **17** (1.88 g, 5.52 mmol) dissolved in a mixture of THF (8 mL) and HMPA (2 mL) was dropped to the mixture at −78 °C, and the whole was stirred for 20 min. The bath was removed, and the mixture was quenched with saturated ammonium chloride (20 mL) and extracted with EtOAc. The obtained crude product was purified by flash column chromatography on silica gel eluted with 40% EtOAc in hexane to give oily product **18** as diastereomeric mixtures. This mixture was subjected to the next mesylation. To a mixture of **18**, triethylamine (1.4 mL, 10.0 mmol), and DMAP (406 mg, 3.32 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (0.43 mL, 5.56 mmol) at 0 °C. The reaction mixture was stirred for 5 min at the same temperature to form mesylate **19**, and then DBU (1 mL, 6.69 mmol) was added to the reaction mixture. After stirring for 10 min at room temperature, saturated ammonium chloride (10 mL) was added and the whole mixture was extracted with 20% EtOAc in hexane. The product was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give a 2:1 geometrical mixture of **20** and its *E*-isomer (2.08 g) in 84% yield in three steps. The isomers were separable by HPLC, but for practical purposes, the separation was much easier in the next step. Colorless oil; R_f = 0.28 (15% EtOAc in hexane); $[\alpha]^{29}_D$ −36.2° (*c* 1.00, $CHCl_3$); IR (neat) 1768, 1643, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.6 Hz), 1.03 (9H, s), 1.55−1.74 (2H, m), 2.06 (3H, s), 2.95 (1H, m), 3.65 (2H, td, *J* = 6.2 and 1.8 Hz), 4.08 (3H, s), 5.19 (1H, d, *J* = 10.3 Hz), 7.33−7.44 (6H, m), 7.62−7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 19.0, 21.3, 26.6, 28.1, 40.1, 58.7, 61.7, 99.0, 114.8, 127.5, 129.5, 133.7, 135.4, 142.1, 162.9, 170.5; MS (EI) *m*/*z* (rel intensity) 393 (M^+ − 57, base), 267 (55), 149 (45), 128 (41). HRMS Calcd for $C_{27}H_{35}O_4Si$: MH^+, 451.2305. Found: *m*/*z* 451.2325. 4*E*-Isomer: colorless oil; R_f = 0.28 (15% EtOAc in hexane); $[\alpha]^{22}_D$ +5.4° (*c* 1.00, $CHCl_3$); IR (neat) 1760, 1632, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, *J* = 7.0 Hz), 1.04 (9H, s), 1.50−1.69 (2H, m), 2.07 (3H, s), 3.27 (1H, m), 3.64 (2H, t, *J* = 6.2 Hz), 4.00 (3H, s), 5.38 (1H, d, *J* = 11.0 Hz), 7.33−7.44 (6H, m), 7.61−7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 19.0, 21.3, 26.6, 26.7, 40.1, 58.7, 61.7, 101.2, 120.0, 127.5, 129.5, 133.7, 135.4, 142.1, 162.9, 170.5; MS (EI) *m*/*z* (rel intensity) 393 (M^+ − 57, 27), 285 (50), 212 (46), 167 (base). HRMS Calcd for $C_{27}H_{35}O_4Si$: MH^+, 451.2305. Found: *m*/*z* 451.2314.

Deprotection of TBDPS Group of 20. Preparation of 21. A mixture of **20** (4.0 g, 8.88 mmol) in THF (40 mL) and tetrabutylammonium fluoride (1 M THF solution; 10.6 mL) was stirred for 30 min. The reaction mixture was diluted with EtOAc (150 mL) and washed with brine. The crude product was chromatographed on silica gel eluted with 30% EtOAc in hexane to give **21** (1.16 g) in 62% yield and its *E*-isomer (112 mg) in 6% yield.[33] **21**: Colorless crystals; mp 64.8−65.2 °C (30% Et_2O in hexane); R_f = 0.27 (40% EtOAc in hexane); $[\alpha]^{26}_D$ +5.7° (*c* 1.00, $CHCl_3$); IR (KBr) 3482, 1737, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.8 Hz), 1.54 (1H, m), 1.70 (1H, m), 1.91 (1H, br s), 2.03 (3H, s), 2.88 (1H, m), 3.57 (2H, t, *J* = 6.6 Hz), 4.10 (3H, s), 5.16 (1H, d, *J* = 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5, 20.7, 27.6, 39.7, 58.8, 60.8, 99.0, 114.0, 142.9, 161.9, 170.8; MS (EI) *m*/*z* (rel intensity) 212 (M^+, 66), 167 (78), 151 (74), 78 (base). HRMS Calcd for $C_{11}H_{16}O_4$: M^+, 212.1049. Found: *m*/*z* 212.1031. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.35; H, 7.70. 4*E*-Isomer: Colorless oil; R_f = 0.17 (40% EtOAc in hexane); $[\alpha]^{22}_D$ +41.8° (*c* 0.41, $CHCl_3$); IR (neat) 3432, 1761, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* = 6.7 Hz), 1.46−1.55 (2H, m), 1.71 (1H, m), 2.09 (3H, s), 3.20 (1H, m), 3.54−3.67 (2H, m), 4.15 (3H, s), 5.38 (1H, d, *J* = 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 21.7, 26.7, 40.4, 59.1, 60.8, 102.2, 119.4, 142.5, 162.8, 170.4; MS (EI) *m*/*z* (rel intensity) 212 (M^+, 59), 167 (base), 151 (76). HRMS Calcd for $C_{11}H_{16}O_4$: M^+, 212.1049. Found: *m*/*z* 212.1067.

Preparation of 8. PCC (191 mg, 0.89 mmol) was added to a stirred solution of **21** (126 mg, 0.59 mmol) in CH_2Cl_2 (10 mL), and the reaction was continued at room temperature for 1 h. The mixture was passed through a florisil column eluted with CH_2Cl_2 and condensed. The residue was purified by silica gel flash column chromatography eluted with 20% EtOAc in hexane. Pure aldehyde **8** (85 mg) was obtained in 68% yield. Colorless crystals; mp 59.5−60.0 °C (20% Et_2O in hexane); R_f = 0.27 (30% EtOAc in hexane); $[\alpha]^{28}_D$ −12.9° (*c* 1.00, $CHCl_3$); IR (neat) 1760, 1680, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6.8 Hz), 2.07 (3H, s), 2.52 (2H, dd, *J* = 6.9 and 2.0 Hz), 3.32 (1H, m), 4.12 (3H, s), 5.22 (1H, d, *J* = 9.6 Hz), 9.70 (1H, t, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 20.3, 25.8, 50.0, 58.8, 99.2, 111.6, 142.9, 161.7, 170.4, 201.0; MS (FAB) *m*/*z* 211 (MH^+). HRMS Calcd for $C_{11}H_{15}O_4$: MH^+, 211.0971. Found: *m*/*z* 211.0957. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.84; H, 6.81.

3-(3-Furyl)propanol (22).[15] To a THF solution (300 mL) of sodium triethyl phosphonoacetate (0.25 mol) prepared from triethyl phosphonoacetate (50 mL, 0.25 mol) and sodium hydride (60% dispersion in mineral oil; 10.1 g, 0.25 mol) by the standard method in text was added 3-furfural (22.0 g, 0.23 mol) dropwise during 10 min at room temperature and stirred for 5 min. The reaction mixture was poured into ice−water (100 mL) and extracted with ether. The aqueous layer was reextracted with ether (100 mL × 2). After the combined extracts were washed with water and brine, the mixture was condensed to 300 mL of the volume. To this solution, palladium charcoal (10%, 1.0 g) was added and stirred under hydrogen atmosphere for 5 h. After the removal of palladium

(33) The 4*Z* isomer gave cyclized products by Michael addition during the deprotection with tetrabutylammonium fluoride.

(34) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

charcoal by filtration, the filtrate was dropped to a suspension of $LiAlH_4$ (5 g, 0.13 mol) in ether (100 mL) at 0 °C. The whole was stirred for 30 min, and then the excess of $LiAlH_4$ was decomposed by adding acetone (5 mL) and quenching with water (100 mL). The mixture was diluted with ether and filtered through a Celite pad under reduced pressure. The aqueous layer was reextracted with ether, and the extracts were combined in the organic layer. The crude product was distilled in vacuo to give **22** (25.4 g) in 88% yield. Colorless oil; bp 62−65 °C/2 mmHg; R_f = 0.30 (30% EtOAc in hexane); IR (neat) 3352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (1H, br s), 1.83 (2H, m), 2.53 (2H, t, J = 7.6 Hz), 3.69 (2H, t, J = 6.5 Hz), 6.28 (1H, br s), 7.23 (1H, s), 7.35 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 32.6, 61.6, 110.8, 124.3, 138.7, 142.6; MS (EI) *m/z* (rel intensity) 126 (M^+, 44), 108 (51), 97 (19), 81 (base). HRMS Calcd for $C_7H_{10}O_2$: M^+, 126.0681. Found: *m/z* 126.0676.

3-(3-Furyl)propyl Bromide (23).[15] To a mixture of **22** (9.77 g, 77.5 mmol) and carbon tetrabromide (26.0 g, 78.4 mmol) in CH_2Cl_2 (200 mL) was added Ph_3P (20.6 g, 78.4 mmol) at 0 °C by 20 portions for 20 min. The reaction was completed after the addition, and pentane (2 L) was added to the mixture. Upon cooling, Ph_3PO was formed as a crystal. After removal of the precipitates by filtration, the filtrate was condensed under reduced pressure, and the residue was distilled to give **23** (14.0 g) in 96% yield. Colorless oil; bp 61−62 °C/5 mmHg; R_f = 0.36 (hexane); IR (neat) 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (2H, m), 2.60 (2H, t, J = 7.2 Hz), 3.41 (2H, t, J = 6.6 Hz), 6.27 (1H, br s), 7.26 (1H, s), 7.36 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 32.8, 33.0, 110.8, 123.1, 139.3, 143.0; MS (EI) *m/z* (rel intensity) 190 and 188 (M^+, 16 and 16), 82 (base), 81 (98). HRMS Calcd for C_7H_9OBr: M^+, 189.9816 and 187.9837. Found: *m/z* 189.9835 and 187.9858.

5-(3-Furyl)pentyne (11). Sodium acetylide (purchased from Aldrich Co. in mineral oil; 8.0 g, 166.6 mmol) was washed with hexane (10 mL × 2) and suspended in HMPA (50 mL). To the suspension was added an HMPA (10 mL) solution of **23** (10.5 g, 55.54 mmol) at 15 °C, and it was stirred for 2 h at the same temperature. The mixture was poured into ice−water (100 mL), acidified with 20% HCl, and extracted with pentane. The crude product was roughly purified by column chromatography on silica gel eluted with 5% ether in pentane and distilled in vacuo to give **11** (6.71 g) in 90% yield. Colorless oil; bp 55 °C/7 mmHg; R_f = 0.28 (hexane); IR (neat) 3290, 2110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (2H, m), 1.97 (1H, t, J = 2.6 Hz), 2.21 (2H, td, J = 7.1 and 2.6 Hz), 2.55 (2H, t, J = 7.5 Hz), 6.27 (1H, br s), 7.23 (1H, br s), 7.35 (1H, t, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 23.6, 28.7, 68.6, 84.0, 110.9, 124.0, 139.1, 142.8; MS (EI) *m/z* (rel intensity) 134 (M^+, 68), 105 (40), 91 (54), 82 (base). HRMS Calcd for $C_9H_{10}O$: M^+, 134.0732. Found: *m/z* 134.0710.

***(E)*-5-(3-Furyl)-1-iodo-2-methylpentene (24).** To a suspension of anhydrous $SnCl_2$ (2.1 g, 11.1 mmol) in THF (30 mL) was added BuLi (1.56 M solution in hexane; 21 mL, 33.3 mmol) dropwise at 0 °C and stirred for 20 min. To this solution was dropped methylmagnesium bromide (1.02 M solution in THF; 11 mL, 11.1 mmol) during 10 min, and it was stirred for an additional 15 min. Cuprous cyanide (40 mg, 0.4 mmol) was added, and **11** (500 mg, 3.7 mmol) in THF (5 mL) was dropped slowly. After stirring for 15 min, methyl iodide (3.2 mL, 51.4 mmol) was dropped and stirred for 20 min. To the reaction mixture, anhydrous hexane (300 mL) was added and stirred vigorously for 15 min. After the mixture separated into two layers, the upper layer was transferred *via* cannula to an ice-cooled flask to which iodine in CH_2Cl_2 solution (iodine (20 g) and anhydrous Na_2CO_3 (10 g) in 200 mL of CH_2Cl_2) was dropped carefully by monitoring with TLC. Up to this stage, all the reactions were handled at 0 °C. Then, the ice bath was removed, and the mixture was diluted with ether (200 mL) and washed with sodium thiosulfate (30 mL), water, and brine. The organic extract was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on alumina eluted with 1% ether in pentane to give **24** (630 mg) in 62% yield. Colorless oil; R_f = 0.43 (hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (2H, m), 1.83 (3H, d, J = 0.6 Hz), 2.24 (2H, t, J = 7.6 Hz), 2.39 (2H, t, J = 7.5 Hz), 5.88 (1H, d, J = 0.8 Hz), 6.25 (1H, br s), 7.20 (1H, br s), 7.35 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.0, 27.8, 38.9, 74.8, 110.8, 124.4, 138.8, 142.7, 147.5; MS (EI) *m/z* (rel intensity) 276 (M^+, 16), 149 (M^+ − 127, base). HRMS Calcd for $C_{10}H_{13}OI$: M^+, 276.0011. Found: *m/z* 276.0021.

Methyl (2*E*,4*E*)-8-(3-Furyl)-5-methyl-2,4-octadienate (25). To a mixture of **24** (6.27 g, 22.71 mmol) and methyl acrylate (3.91 g, 45.42 mmol), in anhydrous degassed DMF (40 mL) were added successively tetrabutylammonium chloride (6.31 g, 22.71 mmol), anhydrous K_2CO_3 (7.85 g, 56.78 mmol), and $Pd(OAc)_2$ (255 mg, 1.14 mmol), and the whole was stirred for 3 h under an argon atmosphere. Water (20 mL) was added, and the mixture was extracted with 20% EtOAc in hexane. The crude product was chromatographed on silica gel eluted with 5% EtOAc in hexane to give **25** (5.04 g) in 95% yield. Colorless oil; R_f = 0.33 (10% EtOAc in hexane); IR (neat) 1725, 1630, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73 (2H, m), 1.89 (3H, s), 2.17 (2H, t, J = 7.6 Hz), 2.41 (2H, t, J = 7.6 Hz), 3.74 (3H, s), 5.79 (1H, d, J = 15.2 Hz), 5.99 (1H, d, J = 11.6 Hz), 6.26 (1H, br s), 7.21 (1H, br s), 7.35 (1H, br s), 7.58 (1H, dd, J = 15.2 and 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 24.3, 27.8, 39.6, 51.3, 110.8, 118.6, 123.4, 124.5, 138.9, 141.0, 142.8, 149.5, 168.0; MS(EI) *m/z* (rel intensity) 234 (M^+, 26), 219 (34), 135 (55), 93 (48), 82 (base); MS (FAB) *m/z* 235 (MH^+). HRMS Calcd for $C_{14}H_{19}O_3$: MH^+, 235.1334. Found: *m/z* 235.1325.

(2*E*,4*E*)-8-(3-Furyl)-5-methyl-2,4-octadien-1-ol (26). To a CH_2Cl_2 (40 mL) solution of **25** (2.60 g, 11.1 mmol) was dropped DIBAL-H (0.93 M hexane solution; 24 mL) at −78 °C during 20 min. After the addition, the reaction was completed. Saturated ammonium chloride (100 mL) was added to the mixture, which was then stirred vigorously for 10 min. The precipitate was filtered through a Celite pad, and the filtrate was extracted with EtOAc. The crude product was purified by flash column chromatography on silica gel eluted with 15% EtOAc in hexane to give **26** (2.01 g) in 88% yield. A pale yellow oil; R_f = 0.23 (20% EtOAc in hexane); IR (neat) 3300, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (1H, br s), 1.70 (2H, m), 1.76 (3H, s), 2.10 (2H, t, J = 7.7 Hz), 2.40 (2H, t, J = 7.6 Hz), 4.19 (2H, br s), 5.74 (1H, dt, J = 15.1 and 6.1 Hz), 5.85 (1H, d, J = 11.0 Hz), 6.26 (1H, br s), 6.48 (1H, ddt, J = 15.1, 11.0 and 1.3 Hz), 7.21 (1H, br s), 7.35 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 24.2, 28.0, 39.2, 63.6, 110.9, 124.1, 124.8, 128.1, 129.5, 138.8, 139.3, 142.6; MS (EI) *m/z* (rel intensity) 206 (M^+, 54), 191 (74), 149 (53), 94 (76), 81 (base). HRMS Calcd for $C_{13}H_{18}O_2$: M^+, 206.1307. Found: *m/z* 206.1328.

(2*E*,4*E*)-8-(3-Furyl)-5-methyl-2,4-octadienal (27). A mixture of **26** (1.85 g, 8.97 mmol) and $BaMnO_4$ (6.9 g, 26.93 mmol) was stirred in CH_2Cl_2 (25 mL) for 6 h at room temperature. The mixture was filtered through a Celite pad under reduced pressure, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give **27** (1.74 g) in 95% yield. A pale yellow oil; R_f = 0.37 (15% EtOAc in hexane); IR (neat) 1680, 1665, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (2H, quint, J = 7.5 Hz), 1.94 (3H, d, J = 0.6 Hz), 2.22 (2H, t, J = 7.5 Hz), 2.43 (2H, t, J = 7.5 Hz), 6.08 (1H, dd, J = 15.1 and 8.0 Hz), 6.14 (1H, d, J = 11.4 Hz), 6.26 (1H, br s), 7.22 (1H, br s), 7.35 (1H, t, J = 1.5 Hz), 7.39 (1H, dd, J = 15.1 and 11.4 Hz), 9.57 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 24.2, 27.8, 39.8, 110.8, 123.8, 124.4, 130.0, 138.8, 142.8, 148.3, 152.5, 193.9; MS (EI) *m/z* (rel intensity) 163 (M^+ − 41, 3), 149 (M^+ − 55, base), 81 (36); MS(FAB) *m/z* 205 (MH^+). HRMS Calcd for $C_{13}H_{17}O_2$: MH^+, 205.1229. Found: *m/z* 205.1246.

(3*E*,5*E*)-9-(3-Furyl)-6-methyl-3,5-nonadien-1-yne (29). To a mixture of dienal **27** (1.60 g, 7.83 mmol) and carbon tetrabromide (5.20 g, 15.66 mmol) in CH_2Cl_2 (30 mL) was added PPh_3 (4.11 g, 15.66 mmol) by 10 portions during a 10 min at 0 °C. The reaction completed soon after the addition, and the mixture was diluted with hexane (200 mL). The mixture was then subjected to silica gel flash chromatography, quickly eluted with hexane. Evaporation of the fractions in

vacuo gave pure dibromotriene **28** as a pale yellow oil, which was not very stable and subjected to the next reaction successively. R_f = 0.42 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (2H, m), 1.76 (3H, s), 2.10 (2H, t, J = 7.7 Hz), 2.39 (2H, t, J = 7.5 Hz), 5.91 (1H, d, J = 11.3 Hz), 6.11 (1H, dd, J = 14.9 and 10.5 Hz), 6.24 (1H, br s), 6.58 (1H, dd, J = 14.9 and 11.3 Hz), 6.96 (1H, d, J = 10.5 Hz), 7.19 (1H, br s), 7.33 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 24.3, 27.9, 39.6, 89.3, 110.9, 124.7, 124.9, 126.6, 132.5, 137.5, 138.8, 142.7, 143.1. To a THF (20 mL) solution of **28** was dropped freshly prepared LDA (0.7 M THF solution; 22.4 mL) at 0 °C during 30 min. After the addition, the mixture was diluted with hexane (200 mL) and quenched with water (20 mL). After the general workup, the crude product was purified by column chromatography on silica gel eluted with hexane to give **29** (949 mg) in 61% yield in the two steps. A pale yellow oil; R_f = 0.20 (hexane); IR (neat) 3280, 2070, 1620 cm^{-1}; UV (hexane) λ_{max} 282 (ϵ 25300, sh), 268 (35500), 258 (27700, sh), 207 (9200), 205 (9300), 201 nm (8800). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (2H, m), 1.79 (3H, s), 2.12 (2H, t, J = 7.7 Hz), 2.39 (2H, t, J = 7.3 Hz), 3.00 (1H, d, J = 2.2 Hz), 5.46 (1H, dd, J = 15.5 and 2.2 Hz), 5.89 (1H, d, J = 11.3 Hz), 6.25 (1H, br s), 6.93 (1H, dd, J = 15.5 and 11.3 Hz), 7.20 (1H, br s), 7.35 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 24.2, 27.9, 39.4, 78.6, 83.7, 107.3, 110.9, 124.3, 124.7, 138.8, 140.0, 142.7, 143.1; MS (EI) m/z (rel intensity) 200 (M^+, 10), 149 (M^+ − 51, 52), 81 (29), 44 (base). HRMS Calcd for $C_{14}H_{16}O$: M^+, 200.1201. Found: m/z 200.1181.

(1*E*,3*E*,5*E*)-9-(3-Furyl)-1-iodo-2,6-dimethyl-1,3,5-nonatriene (9). To a suspension of anhydrous $SnCl_2$ (682 mg, 3.60 mmol) in THF (8 mL) was added BuLi (1.56 M solution in hexane; 6.9 mL, 10.8 mmol) dropwise at −20 °C, and it was stirred for 20 min. To this solution was dropped methylmagnesium bromide (0.99 M solution in THF; 3.64 mL, 3.60 mmol) during 10 min, and it was stirred for an additional 15 min. Cuprous cyanide (16 mg, 0.18 mmol) was added, and **29** (120 mg, 0.60 mmol) in THF (4 mL) was dropped slowly. After stirring for 15 min, methyl iodide (0.75 mL, 12.0 mmol) was dropped and stirred for 20 min. To the reaction mixture, anhydrous hexane (40 mL) was added and stirred vigorously for 15 min. After the mixture separated to two layers, the upper layer was transferred *via* cannula to the ice-cooled flask, to which iodine solution in CH_2Cl_2 (iodine (2 g) and anhydrous Na_2CO_3 in 20 mL of CH_2Cl_2) was dropped carefully by monitoring on TLC. Up to this stage, all the reactions were carried out at −20 °C. The ice bath was then removed, and the mixture was diluted with hexane (30 mL) containing Et_3N in 5% of the volume and washed with sodium thiosulfate (2 mL), water, and brine. The organic extract was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on alumina eluted with 5% Et_3N in hexane to give **9** (153 mg) in 75% yield. A pale yellow oil; R_f = 0.33 (hexane); UV (hexane) λ_{max} 341 (ϵ 180, sh), 302 (34600), 289 (43300), 279 (38400), 267 (24000, sh), 208 (10800), 196 nm (7800). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (2H, quint, J = 7.5 Hz), 1.78 (3H, s), 2.00 (3H, s), 2.10 (2H, t, J = 7.5 Hz), 2.40 (2H, t, J = 7.5 Hz), 5.85 (1H, d, J = 10.9 Hz), 6.22 (1H, d, J = 15.1 Hz), 6.27 (2H, br s), 6.51 (1H, dd, J = 15.1 and 10.9 Hz), 7.21 (1H, br s), 7.35 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 20.1, 24.3, 28.0, 39.6, 82.1, 110.9, 124.8, 125.0, 125.9, 131.2, 138.8, 140.9, 142.7, 145.6; MS (EI) m/z (rel intensity) 342 (M^+, 53), 328 (28), 215 (M^+ − 127, 34), 133 (83), 120 (64), 105 (base), 81 (73). HRMS Calcd for $C_{15}H_{19}OI$: M^+, 342.0481. Found: m/z 342.0507.

Coupling Reaction of Iodotriene 9 with Aldehyde 8. To a degassed DMSO solution (30 mL) of **8** (600 mg, 2.85 mmol) and **9** (1.67 g, 4.89 mmol) was added $CrCl_2$ containing 0.1% $NiCl_2$ (1.3 g, 10.6 mmol), and the whole mixture was stirred for 18 h at room temperature. Water (10 mL) was then added, and the mixture was extracted with EtOAc. Purification of the crude mixture by silica gel flash chromatography gave cyclized product **30A** (737 mg) in 60% yield and β-alcohol **7B** (244 mg) in 20% yield. **30A**: Colorless crystals; mp 128.0−129.8 °C (methanol); R_f = 0.18 (30% EtOAc in hexane); IR (KBr) 3460, 1734, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 6.5 Hz), 1.58 (3H, d, J = 1.3 Hz), 1.54−1.72 (4H, m), 1.72−1.89 (2H, m), 1.85 (3H, d, J = 1.3 Hz), 1.90−2.07 (3H, m), 1.98 (3H, s), 2.40 (2H, t, J = 7.6 Hz), 2.49 (1H, br m), 3.06 (1H, dm, J = 10.3 Hz), 3.93 (3H, s), 4.07 (1H, m), 4.96−5.04 (2H, dm, J = 10.3 Hz), 6.26 (1H, d, J = 0.8 Hz), 7.21 (1H, br s), 7.35 (1H, t, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7, 16.1, 19.7, 20.4, 24.4, 28.4, 29.7, 39.3, 43.7, 47.5, 47.7, 51.5, 57.9, 72.8, 84.6, 97.3, 110.9, 123.2, 123.6, 124.9, 134.3, 134.4, 138.8, 142.7, 174.2, 175.1; MS (FAB) m/z 427 (MH^+). HRMS Calcd for $C_{26}H_{35}O_5$: MH^+, 427.2485. Found: m/z 427.2494. Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.33; H, 8.12. **7B**: Colorless oil; R_f = 0.28 (30% EtOAc in hexane); IR (KBr) 3437, 1760, 1638 cm^{-1}; UV (EtOH) λ_{max} 292 (ϵ 11600, sh), 278 (18700, sh), 269 (22100), 258 (16400, sh), 200 nm (5500); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 7.0 Hz), 1.47 (1H, ddd, J = 13.9, 9.5, and 5.5 Hz), 1.64−1.82 (4H, m), 1.79 (3H, s), 1.80 (3H, d, J = 1.1 Hz), 2.05 (3H, s), 2.11 (2H, t, J = 7.7 Hz), 2.39 (2H, t, J = 7.7 Hz), 2.95 (1H, m), 4.11 (3H, s), 4.46 (1H, ddd, J = 13.9, 8.8 and 5.5 Hz), 5.17 (1H, d, J = 10.3 Hz), 5.40 (1H, d, J = 8.8 Hz), 5.89 (1H, d, J = 10.6 Hz), 6.12 (1H, d, J = 15.4 Hz), 6.26 (1H, br d, J = 1.1 Hz), 6.41 (1H, dd, J = 15.4 and 10.6 Hz), 7.21 (1H, br d, J = 0.7 Hz), 7.35 (1H, t, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 12.9, 16.7, 21.1, 24.3, 27.8, 28.1, 39.5, 44.6, 58.8, 66.9, 99.1, 110.9, 114.1, 124.9, 124.9, 125.4, 133.2, 134.7, 135.7, 138.8, 139.0, 142.7, 143.0, 161.8, 170.7; MS (EI) m/z (rel intensity) 426 (M^+, 3), 279 (52), 181 (46), 167 (base), 149 (94). HRMS Calcd for $C_{26}H_{34}O_5$: M^+, 426.2401. Found: m/z 426.2385.

Synthesis of Ircinianin Methyl Ether (32). To a mixture of **30A** (260 mg, 0.61 mmol), DMAP (37 mg, 0.3 mmol), and pyridine (0.15 mL, 1.83 mmol) in CH_2Cl_2 (6 mL) was added phenyl chlorothionoformate (0.13 mL, 0.92 mmol) at room temperature, and then it was stirred for 1 h. The mixture was diluted with ether and washed with water and brine. The crude extract was roughly purified by column chromatography on silica gel eluted with 30% EtOAc in hexane to give thionoformate **31** (295 mg) in 89% yield. Colorless oil; R_f = 0.41 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 5.6 Hz), 1.59 (3H, d, J = 0.9 Hz), 1.62−1.80 (3H, m), 1.75 (3H, d, J = 1.2 Hz), 1.96−2.10 (5H, m), 1.99 (3H, s), 2.41 (2H, t, J = 7.6 Hz), 2.98 (1H, br t, J = 11.3 Hz), 3.08 (1H, dm, J = 10.3 Hz), 3.94 (3H, s), 5.00 (1H, dd, J = 10.3 and 0.8 Hz), 5.05 (1H, m), 5.43 (1H, m), 6.26 (1H, br s), 7.08 (2H, d, J = 7.7 Hz), 7.21 (1H, br s), 7.29 (1H, d, J = 7.4 Hz), 7.36 (1H, t, J = 1.5 Hz), 7.41 (2H, dd, J = 7.7 and 7.4 Hz). A mixture of **31** (295 mg, 0.52 mmol), Bu_3SnH (0.21 mL, 0.78 mmol), and AIBN (15 mg, 0.09 mmol) was dissolved in benzene (6 mL) and degassed. The mixture was heated at refluxing temperature for 30 min. After cooling, the mixture was diluted with ether (60 mL) and washed with saturated sodium bicarbonate (1 mL), water, and brine. The crude extract was purified by column chromatography on alumina eluted with 10% EtOAc in hexane to give **32** (155 mg) in 72% yield. Colorless crystals, mp 50−52 °C (hexane); R_f = 0.23 (15% EtOAc in hexane); $[\alpha]^{24}_D$ −167.7° (c 0.47, $CHCl_3$); IR (neat) 1747, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.6 Hz), 1.21−1.37 (2H, m), 1.51 (1H, t, J = 11.0 Hz), 1.58 (3H, d, J = 1.2 Hz), 1.62−1.78 (3H, m), 1.68 (3H, d, J = 1.2 Hz), 1.85 (1H, m), 1.92−2.06 (3H, m), 1.98 (3H, s), 2.40 (2H, t, J = 7.6 Hz), 2.45 (1H, br m), 3.06 (1H, dm, J = 10.3 Hz), 3.94 (3H, s), 4.98 (1H, m), 5.04 (1H, dd, J = 10.3 and 0.8 Hz), 6.27 (1H, br s), 7.21 (1H, br s), 7.35 (1H, t, J = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7, 16.1, 20.2, 20.4, 24.4, 26.1, 28.4, 31.5, 32.3, 39.4, 44.6, 47.8, 50.5, 57.9, 84.9, 96.1, 110.9, 121.9, 124.2, 125.0, 134.0, 135.9, 138.8, 142.7, 174.4, 175.7; MS (FAB) m/z 411 (MH^+). HRMS Calcd for $C_{26}H_{35}O_4$: MH^+, 411.2536. Found: m/z 411.2508.

Synthesis of (−)-Ircinianin (1). To a DMF (5 mL) solution of **32** (120 mg, 0.29 mmol) was added sodium salt of propanethiol (1.1 M DMF solution; 1.33 mL, 1.46 mmol) (sodium salt of propanethiol was prepared as follows: propanethiol (0.2 mL, 2.21 mmol) was added dropwise slowly to a suspension of NaH (60% dispersion in mineral oil, 88 mg, 2.21 mmol) in DMF (1.8 mL) at room temperature, resulting in a clear solution and was used for the next reaction

successively), and then the mixture was stirred for 40 min at room temperature. Aqueous sodium hydroxide (1 M solution, 0.1 mL) was added and diluted with EtOAc (50 mL). The organic layer was taken and washed with water and brine. The solvent was removed under reduced pressure (20 mmHg and then 5 mmHg), and the residue was chromatographed on silica gel eluted with 30% EtOAc in hexane to give **1** (104 mg) in 90% yield. Colorless crystals; mp 153−156 °C; R_f = 0.27 (40% EtOAc in hexane); $[\alpha]^{24}_D$ −235° (*c* 0.28, $CHCl_3$), lit. $[\alpha]^{25}_D$ −232° (*c* 0.5, $CHCl_3$);[1] IR (KBr) 3437, 1720, 1652, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.6 Hz), 1.20−1.38 (2H, m), 1.45 (1H, t, *J* = 11.0 Hz), 1.65 (3H, d, *J* = 0.7 Hz), 1.70 (3H, d, *J* = 1.2 Hz), 1.52−1.74 (3H, m), 1.71 (3H, s), 1.90 (1H, m), 2.00 (1H, m), 2.06−2.19 (2H, m), 2.43 (2H, t, *J* = 7.5 Hz), 2.54 (1H, br m), 3.16 (1H, dm, *J* = 10.2 Hz), 5.04 (1H, m), 5.09 (1H, dd, *J* = 10.2 and 0.8 Hz), 6.06 (1H, br s), 6.28 (1H, br s), 7.23 (1H, br s), 7.37 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.8, 16.7, 20.0, 20.5, 24.4, 26.2, 28.3, 31.4, 32.0, 39.4, 45.1, 46.0, 50.7, 84.0, 100.0, 110.9, 121.1, 122.3, 124.5, 136.6, 138.9, 142.8, 143.3, 174.1, 174.5; MS (EI) *m/z* (rel intensity) 396 (M^+, 27), 287 (52), 135 (base); MS (FAB) *m/z* 397 (MH^+). HRMS Calcd for $C_{25}H_{33}O_4$: MH^+, 397.2379. Found: *m/z* 397.2402.

Iodo Ether Formation Reaction of 1. Synthesis of 33A. To an ice-cooled mixture of **1** (18.9 mg, 0.05 mmol) and anhydrous K_2CO_3 (41.5 mg, 0.3 mmol) in $CHCl_3$ (1 mL) was added a $CHCl_3$ (0.5 mL) solution of iodine (13.3 mg, 0.05 mmol). After being stirred for 30 min at the same temperature, the whole mixture was directly purified by silica gel column chromatography and eluted with 10% EtOAc in hexane to give **33A** (17.7 mg) in 71% yield. Colorless oil; R_f = 0.26 (10% EtOAc in hexane); $[\alpha]^{29}_D$ +44.9° (*c* 1.00, $CHCl_3$); IR (neat) 1768, 1695, 1275, 1167, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 6.5 Hz), 1.22−1.38 (2H, m), 1.48 (1H, dd, *J* = 11.0 Hz), 1.53 (3H, s), 1.63 (1H, m), 1.73 (3H, s), 1.74 (3H, d, *J* = 1.0 Hz), 1.70−1.80 (2H, m), 1.89 (1H, m), 1.94−2.04 (2H, m), 2.11 (1H, m), 2.44−2.58 (3H, m), 2.67 (1H, dm, *J* = 11.7 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 5.55 (1H, br m), 6.29 (1H, br d, *J* = 0.7 Hz), 7.26 (1H, br s), 7.37 (1H, br m); ^{13}C NMR (100 MHz, $CDCl_3$); δ 6.2, 20.7, 20.8, 22.1, 22.6, 24.5, 26.5, 30.6, 32.0, 38.4, 40.3, 45.6, 47.9, 52.1, 79.7, 88.5, 108.3, 110.8, 122.0, 124.4, 138.9, 140.6, 142.9, 173.3, 173.4; MS (FAB) *m/z* 523 (MH^+). HRMS Calcd for $C_{25}H_{32}O_4I$: MH^+, 523.1346. Found: *m/z* 523.1328.

Synthesis of (+)-Wistarin (2B). A freshly prepared benzene solution of Bu_3SnH (0.9 M, 277 μL, 249 μmol) containing a catalytic amount of Et_3B (Bu_3SnH (0.37 mmol) and Et_3B (0.124 mmol) in 3 mL of benzene) was added to a benzene (0.3 mL) solution of **33A** (13 mg, 24.9 μmol) at 10 °C. After being stirred for 20 min, the whole mixture was directly purified by column chomatography on silica gel eluted with 20% EtOAc in hexane to give (+)-wistarin (7.6 mg) in 77% yield. Colorless oil; R_f = 0.27 (15% EtOAc in hexane); $[\alpha]^{28}_D$ +132° (*c* 0.34, CH_2Cl_2), lit. $[\alpha]^{20}_D$ +130° (*c* 0.25, CH_2Cl_2);[2] IR (neat) 1757, 1693, 1275, 1171, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 6.4 Hz), 1.21 (3H, s), 1.21−1.36 (2H, m), 1.56 (1H, dd, *J* = 11.0 Hz), 1.65 (1H, m), 1.68 (3H, d, *J* = 1.0 Hz), 1.72 (3H, s), 1.70−1.80 (6H, m), 1.87 (1H, m), 1.97 (1H, m), 2.44−2.59 (4H, m), 5.12 (1H, br m), 6.28 (1H, br s), 7.23 (1H, br s), 7.37 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.2, 20.6, 20.7, 23.4, 23.8, 24.9, 26.7, 30.4, 32.0, 39.9, 40.8, 42.0, 44.8, 51.3, 80.7, 86.2, 107.1, 110.8, 121.2, 124.5, 138.5, 138.9, 142.9, 174.1, 175.1; MS (EI) *m/z* 396 (M^+, 73), 246 (18), 135 (base); MS (FAB) *m/z* 397 (MH^+). HRMS Calcd for $C_{25}H_{33}O_4$: MH^+, 397.2379. Found: *m/z* 397.2395.

Diels−Alder Reaction of 7B. A xylene (4 mL) solution of **7B** (77 mg, 0.18 mmol) was heated at the refluxing temperature for 15 min. After being cooled to room temperature, the mixture was chromatographed directly on silica gel and carefully eluted with 20% EtOAc in hexane to give three stereoisomers. The first fraction gave **30B** (20.8 mg) in 27% yield, the second portion gave **30B″** (10.8 mg) in 14% yield, and **30B′** (13.9 mg) was obtained in 18% yield from the last portion. **30B**: Colorless oil; R_f = 0.28 (30% EtOAc in hexane); IR (KBr) 3469, 1745, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.7 Hz), 1.22−1.30 (2H, ddm, *J* = 14.6 and 6.4 Hz), 1.58 (3H, d, *J* = 1.1 Hz), 1.61−1.74 (3H, m), 1.79 (3H, d, *J* = 1.3 Hz), 1.98−2.08 (2H, m), 1.99 (3H, s), 2.19 (1H, dd, *J* = 12.3 and 10.4 Hz), 2.32−2.42 (4H, m), 3.05 (1H, dm, *J* = 10.3 Hz), 3.95 (3H, s), 4.36 (1H, t, *J* = 4.5 Hz), 5.09 (1H, dd, *J* = 10.3 and 1.0 Hz), 5.15 (1H, m), 6.26 (1H, br s), 7.21 (1H, br s), 7.35 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7, 16.1, 19.9, 20.6, 24.5, 28.5, 30.4, 39.4, 43.8, 45.1, 47.8, 50.6, 58.0, 70.3, 85.0, 97.2, 110.9, 123.8, 124.9, 125.5, 131.7, 134.2, 138.8, 142.7, 174.3, 175.5; MS (EI) *m/z* (rel intensity) 426 (M^+, 34), 408 (15), 241 (27), 167 (35), 135 (77), 44 (base). HRMS Calcd for $C_{26}H_{34}O_5$: M^+, 426.2407. Found: *m/z* 426.2390. **30B′**: Colorless oil; R_f = 0.17 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 7.1 Hz), 1.19 (1H, dm, *J* = 14.1 Hz), 1.58 (3H, d, *J* = 1.2 Hz), 1.50−1.72 (3H, m), 1.87 (3H, s), 1.94−2.10 (4H, m), 1.98 (3H, s), 2.40 (2H, t, *J* = 7.7 Hz), 2.51 (1H, dt, *J* = 14.1 and 9.0 Hz), 2.67 (1H, br t, *J* = 10.7 Hz), 2.95 (1H, m), 3.97 (3H, s), 4.00 (1H, m), 4.95 (1H, d, *J* = 10.2 Hz), 5.03 (1H, br s), 6.26 (1H, br s), 7.21 (1H, br s), 7.35 (1H, t, *J* = 1.5 Hz); MS (EI) *m/z* (rel intensity) 426 (M^+, 4), 408 (6), 241 (19), 167 (27), 149 (base). HRMS Calcd for $C_{26}H_{34}O_5$: M^+, 426.2407. Found: *m/z* 426.2403. **30B″**: Colorless oil; R_f = 0.19 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 7.0 Hz), 1.17 (1H, dt, *J* = 12.3 and 9.2 Hz), 1.58 (3H, d, *J* = 1.0 Hz), 1.45−1.75 (3H, m), 1.87 (3H, s), 1.95 (3H, d, *J* = 1.6 Hz), 1.98 (2H, t, *J* = 7.1 Hz), 2.18−2.26 (2H, m), 2.32 (2H, t, *J* = 7.7 Hz), 2.35−2.50 (2H, m), 3.32 (1H, dm, *J* = 10.1 Hz), 4.02 (3H, s), 4.18 (1H, br m), 4.90 (1H, d, *J* = 10.1 Hz), 5.06 (1H, br s), 6.25 (1H, br s), 7.20 (1H, br s), 7.34 (1H, br s); MS (EI) *m/z* (rel intensity) 426 (M^+, 24), 408 (12), 241 (39), 167 (42), 135 (base), 91 (42). HRMS Calcd for $C_{26}H_{34}O_5$: M^+, 426.2407. Found: *m/z* 426.2413.

Deoxygenation of 30B, 30B′, and 30B″. These deoxygenation reactions were performed using an identical procedure as described for ircinianin methyl ether **32** from **30A**. **30B** gave **32** in 65% yield. The physical and spectroscopic data was noted in the experiment for **32**. **30B′** afforded **32′** in 67% yield. **32′**: Colorless oil; R_f = 0.20 (15% EtOAc in hexane); $[\alpha]^{21}_D$ +124° (*c* 0.27, $CHCl_3$); IR (KBr) 1749, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 7.1 Hz), 1.11−1.34 (2H, m), 1.58 (3H, d, *J* = 1.0 Hz), 1.66 (2H, m), 1.70 (3H, d, *J* = 0.9 Hz), 1.86 (1H, dd, *J* = 12.4 and 6.6 Hz), 1.92−2.06 (4H, m), 1.98 (3H, s), 2.14 (1H, m), 2.39 (2H, t, *J* = 7.3 Hz), 2.60 (1H, br m), 2.94 (1H, dm, *J* = 10.3 Hz), 3.97 (3H, s), 5.00 (1H, dm, *J* = 10.3 Hz), 5.01 (1H, br s), 6.26 (1H, br s), 7.21 (1H, br s), 7.35 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 16.2, 18.1, 20.9, 24.4, 26.8, 28.4, 31.8, 32.6, 39.4, 39.8, 45.3, 50.0, 58.5, 85.7, 97.9, 110.9, 121.8, 124.0, 125.0, 134.6, 136.2, 138.8, 142.7, 174.2, 175.9; MS (FAB) *m/z* 411 (MH^+). HRMS Calcd for $C_{26}H_{35}O_4$: MH^+, 411.2536. Found: *m/z* 411.2534. **32″** was obtained form **30B″** in 60% yield. **32″**; Colorless oil; R_f = 0.30 (15% EtOAc in hexane); $[\alpha]^{21}_D$ +45° (*c* 0.15, $CHCl_3$); IR (KBr) 1748, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.9 Hz), 1.06 (1H, m), 1.42−1.62 (4H, m),1.59 (3H, d, *J* = 1.3 Hz), 1.72 (3H, s), 1.85−1.93 (2H, m), 1.96 (3H, s), 1.98 (2H, t, *J* = 7.5 Hz), 2.08 (1H, dd, *J* = 9.5 and 5.4 Hz), 2.32 (2H, t, *J* = 7.6 Hz), 2.48 (1H, br m), 3.33 (1H, dm, *J* = 10.2 Hz), 4.02 (3H, s), 4.92 (1H, dd, *J* = 10.2 and 0.9 Hz), 5.00 (1H, br d, *J* = 1.5 Hz), 6.24 (1H, br s), 7.19 (1H, br s), 7.33 (1H, t, *J* = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5, 16.0, 21.9 (2C), 24.0, 28.4, 31.8, 33.1, 35.0, 39.2, 40.2, 44.7, 48.3, 58.3, 84.6, 98.8, 110.9, 121.2, 122.5, 124.9, 136.4, 137.6, 138.8, 142.7, 173.9, 174.9; MS (FAB) *m/z* 411 (MH^+). HRMS Calcd for $C_{26}H_{35}O_4$: MH^+, 411.2536. Found: *m/z* 411.2536.

Alternative Addition Reaction of Iodotriene 9 to Aldehyde 8. The reaction of aldehyde **8** (70 mg, 0.33 mmol) and iodotriene **9** (333 mg, 0.97 mmol) was carried out under the same condition described for the precedent synthesis for **30A** and **7B** except for reaction time. The reaction was stopped after 1 h, when the starting aldehyde **8** was consumed. After the same workup, the crude mixture was roughly purified by flash column chromatography on silica gel eluted with 25% EtOAc in hexane to give a mixture of three isomers (126 mg) in 89% yield. This mixture contained **7A**, **7B**, and **30A** in a 2:2:1 ratio determined by ^1H NMR. They were unseparable by chromatography. **7A** was particularly un-

stable and decomposed within a day. ^{1}H NMR of **7A** was assigned from the chart consisting of the mixtures. **7A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 7.0 Hz), 1.47 (1H, m), 1.64−1.82 (4H, m), 1.79 (3H, s), 1.80 (3H, s), 2.05 (3H, s), 2.11 (2H, t, J = 7.7 Hz), 2.39 (2H, t, J = 7.7 Hz), 2.82 (1H, m), 4.12 (3H, s), 4.46 (1H, m), 5.24 (1H, d, J = 10.1 Hz), 5.37 (1H, d, J = 8.9 Hz), 5.89 (1H, d, J = 10.9 Hz), 6.13 (1H, d, J = 15.2 Hz), 6.26 (1H, br s), 6.45 (1H, dd, J = 15.2 and 10.9 Hz), 7.21 (1H, br s), 7.35 (1H, m).

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Supporting Information Available: Copies of ^{13}C-NMR spectra for the 26 new compounds and the ORTEP drawing for **30A** (29 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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