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Stereoselective Synthesis of 3-Alkyl-2-aryltetrahydrofuran-4-ols: Total Synthesis of (±)-Paulownin

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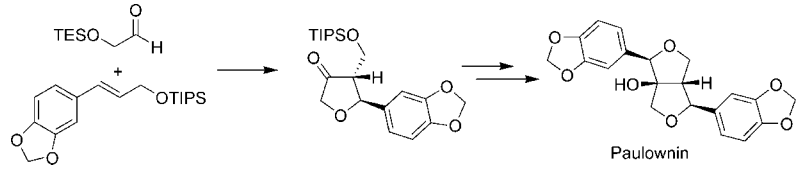

A formal [3 + 2]-cycloaddition involving the Lewis acid mediated reaction of α-silyloxy aldehydes and styrenes to afford 3-alkyl-2-aryltetrahydrofuran-4-ols has been developed. This methodology was applied to the total synthesis of the naturally occurring furofuran lignan (±)-paulownin.

Introduction

There are a number of hetero ring-containing natural products with aryl groups as substituents.[1] Many of these belong to a class of compounds known as lignans, which are found in most plants and exhibit a variety of biological activities.[2] Accordingly, synthetic chemists are interested in lignans as targets for total syntheses.[3] Furofuran lignans (Figure 1) are a series of structurally similar compounds that are potent biologically active targets[4] and might be synthesized using a formal [3 + 2] cycloaddition reaction similar to those studied previously in our laboratory.[5]

A new method for the synthesis of tetrahydrofurans and its application to the total synthesis of (±)-paulownin (Figure 1) is described herein. (±)-Paulownin, isolated from *Paulownia tomentosa* (kiri), was first isolated by Takahashi[6] in 1963. Paulownin and similar compounds are attractive synthetic targets due to their antioxidant properties and other biological activity.[2f,4a,b]

Results and Discussion

The high reactivity of electron-rich styrenes with electrophiles[7] in the presence of Lewis acids stimulated us to examine the stereoselective synthesis of tetrahydrofurans using styrenes and α-siloxy aldehydes. There are two possible products that might be generated via such a formal cycloaddition reaction: an oxetane and a tetrahydrofuran (Scheme 1, **8** and **9**). Activation of aldehyde **6** with a Lewis acid followed by reaction with styrene **5** would afford stabilized cation **7**. This cation could then undergo an intramolecular reaction with an oxygen nucleophile via pathways "a" or "b." Previous studies in our

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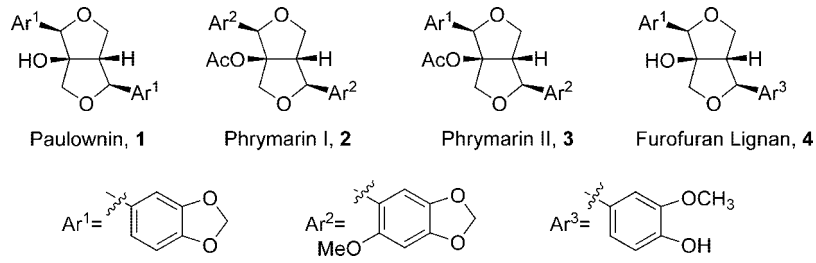
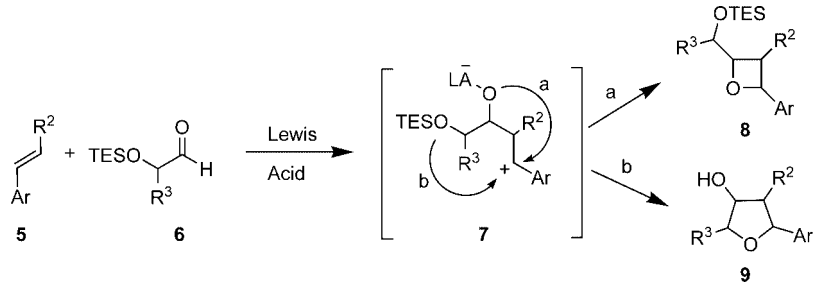


FIGURE 1. Furofuran lignans.

SCHEME 1. Possible Products from Formal Cycloaddition Reaction



laboratory have shown that oxetane **8** was not observed via the formal [3 + 2]-cycloaddition reaction of allylic silanes and α-siloxy aldehydes.[5g,8] Thus, we were optimistic that the sole product of this reaction would be tetrahydrofuran **9** and not oxetane **8**.

Synthesis of THFs. The first attempt of the formal cycloaddition reaction used styrene **10** and α-siloxy aldehyde **11** in the presence of $TiCl_4$ or $BF_3 \cdot OEt_2$ (Table 1, entries 1 and 2). These two reactions failed to afford any isolable THF products; we obtained what appeared to be polymerized styrene and no unreacted aldehyde **11** was observed (^{1}H NMR analysis). Reaction of aldehyde **11** with *trans*-*β*-methylstyrene **12** in the presence of $BF_3 \cdot OEt_2$ afforded THFs **13a/b** in 20% yield and a 4.1:1 ratio. When the more nucleophilic *p*-methoxystyrene **14**[9] was used, only polymerized styrene was observed.

We questioned the stability of aldehyde **11** to the reaction conditions and elected to optimize the reaction conditions using α-phenyl aldehyde **15**[5g] and *trans*-anethole **14** (Table 1, entry 4). We hoped this aldehyde would be more stable to the reaction conditions. Styrene **14** would be sufficiently nucleophilic and yet slower to polymerize than monosubstituted styrene **10**. Three Lewis acids ($SnCl_4$, $TiCl_4$, and $BF_3 \cdot OEt_2$) were examined (Table 1, entries 4−6) using reaction conditions A (reaction time, 3 h at −78 °C remove cold bath and stir 1 h; no additive). The only Lewis acid to afford the desired THF product **16** was $BF_3 \cdot OEt_2$ (entry 6). This reaction afforded two diastereomers in a 1.7:1 ratio.

Employing a longer reaction time of 24 h at −78 °C (Table 1, entry 7, condition B) resulted in a lower yield of THF, and the diasteromer ratio was closer to 1:1. This result led us to question the stability of the product to the reaction conditions. Accordingly, we examined conditions C and D which employed either 0.5 or 0.75 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) as an acid scavenger and a reaction time of 5 min at −78 °C, followed by removal of the cold bath and stirring for 1 h (Table 1, entries 8 and 9). The yield of THF increased markedly (to 59−62%) as did the diastereomer ratio. This result led to the conclusion that the major diastereomer is the kinetic product. Our results are also consistent with the two reactants (styrene and aldehyde) and the THF product being unstable to the reaction conditions and that long reaction times lead to low yields due to their decomposition. An acid scavenger was imperative to maximize the yield and minimize decomposition of the starting materials. These results (Table 1, entries 1−9) were used to develop the general procedure using 2 equiv of styrene, 0.75 equiv of DBMP, 1 equiv of $BF_3 \cdot OEt_2$, and a reaction time of 5 min at −78 °C followed by removal of the cold bath and stirring for 1 h. This procedure (condition D) was used for further investigation of scope and limitations of the formal cycloaddition reaction.

Using the optimized reaction conditions, α-siloxy aldehydes **11** and **15** and optically active **22**[5g] were reacted with styrenes **14**, **17**, and **18** to study the impact of substitution α to the aldehyde and styrene structure on THF yield and diastereomer ratio (Table 1). (*E*)-Isosafrole **18** was selected because a number of lignans[2a,g,h] contain the 3,4-(methylenedioxy)phenyl group as a substituent on the THF skeleton.

Reaction of aldehyde **15** with the *Z*-isomer of **14**, styrene **17**, under the standard conditions, afforded THFs **16a/b** in lower yield, 44%, but slightly higher diastereomer ratio (64:1; Table 1, entry 10) than the *E*-isomer (table 1, entry 9). Thus, the stereochemistry of the THF is independent of the styrene alkene geometry. Reaction of aldehyde **15** with styrene **18** afforded THFs **19a**,**b** in 64% yield (33:1 ratio, Table 1, entry 11).

Using the standard reaction conditions developed above with unsubstituted aldehyde **11** led to mixtures of three THF diastereomers. The *E*- and *Z*-isomers **14** and **17** afforded THFs **20a**,**b**,**c** in 79% and 61% yield, respectively, and identical 8:5:1 diastereomer ratios (Table 1, entries 12 and 13). Styrene **18** gave similar results. The stereochemistry of the formal cycloaddition clearly benefits from an aldehyde possessing a bulky α-substituent.

In an attempt to further explore the stereochemical aspects of the formal cycloaddition, α-methyl aldehyde **22** was reacted with *E*-styrenes **17** and **18** to afford THFs **23** and **24** in 56%

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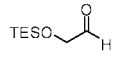
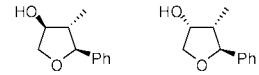
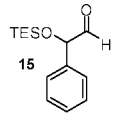
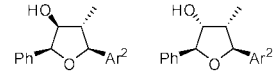
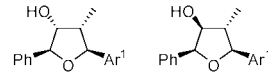
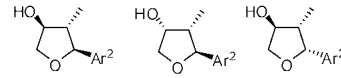
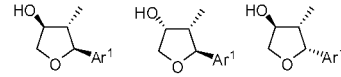
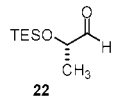
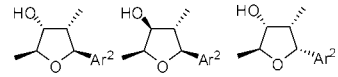
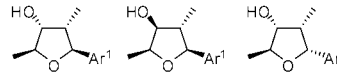
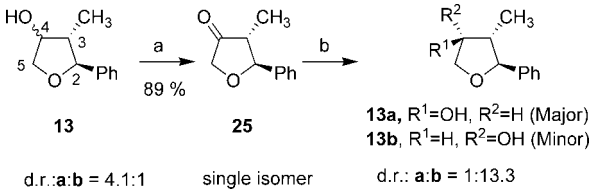
TABLE 1. Summary of THF Formation from Styrenes[a]

Entry	Styrene	Aldehyde	Lewis Acid	Conditions*	THF	% Yield
1	 **10**	 **11**	$TiCl_4$	A	-----	no THF
2	**10**	**11**	$BF_3{\cdot}OEt_2$	A	-----	no THF
3	 **12**	**11**	$BF_3{\cdot}OEt_2$	A	 **13a** **13b**	20% (4.1:1)
4	 **14**	 **15**	$SnCl_4$	A	-----	no rxn
5	**14**	**15**	$TiCl_4$	A	-----	no rxn
6	**14**	**15**	$BF_3{\cdot}OEt_2$	A	 **16a** **16b**	26 (1.7:1)
7	**14**	**15**	$BF_3{\cdot}OEt_2$	B	**16a:16b**	14 (1.3:1)
8	**14**	**15**	$BF_3{\cdot}OEt_2$	C	**16a:16b**	59 (30:1)
9	**14**	**15**	$BF_3{\cdot}OEt_2$	D	**16a/16b**	62 (29:1)
10	 **17**	**15**	$BF_3{\cdot}OEt_2$	D	**16a/16b**	44 (64:1)
11	 **18**	**15**	$BF_3{\cdot}OEt_2$	D	 **19a** **19b**	64 (33:1)
12	**14**	**11**	$BF_3{\cdot}OEt_2$	D	 **20a** **20b** **20c**	79 (8:5:1)
13	**17**	**11**	$BF_3{\cdot}OEt_2$	D	**20a/20b/20c**	61 (8:5:1)
14	**18**	**11**	$BF_3{\cdot}OEt_2$	D	 **21a** **21b** **21c**	64 (6.5:5:1)
15	**17**	 **22**	$BF_3{\cdot}OEt_2$	D	 **23a** **23b** **23c**	56 (17.1:9:1)
16	**18**	**22**	$BF_3{\cdot}OEt_2$	D	 **24a** **24b** **24c**	49 (12.5:1)

[a] Conditions: (A) reaction time = 3 h, no additive; (B) reaction time = 24 h, no additive; (C) reaction time = 5 min, DBMP additive, 0.5 equiv; (D) reaction time = 5 min, DBMP additive 0.75 equiv; Ar^1 = 3,4-OCH_2O−C_6H_3; Ar^2 = *p*-$MeOC_6H_4$.

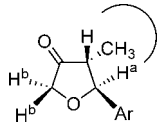
and 49% yield, respectively (Table 1, entries 15 and 16). In both cases, the smaller α-methyl substituent led to a decrease in selectivity relative to α-phenyl aldehyde **15** but higher selectivity than unsubstituted aldehyde **11**. THFs **23** and **24** are optically active, consistent with being derived from optically active aldehyde **15.**

SCHEME 2. Determination of Relative Stereochemistry of THF 13[a]



[a] Key: (a) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt; (b) $NaBH_4$, MeOH, 0 °C to rt.

TABLE 2. Comparison of ^{1}H NMR Data



furanone	H^a	H^b
25	4.64 (d, J = 10.3 Hz)	4.41 (d, J = 17.4) 4.00 (d, J = 17.4)
26	4.57 (d, J = 10.2 Hz)	4.38 (d, J = 17.4) 3.98 (d, J = 17.4)
27	4.54 (d, J = 10.5 Hz)	4.38 (dd, J = 17.4, 0.9) 3.98 (d, J = 17.4)

Determination of Stereochemistry of Trisubstituted THFs. To determine the stereochemistry of THF **13**, we first oxidized the secondary alcohol on the THF ring to a ketone (Scheme 2) using Dess−Martin periodinane to give ketone **25** as a single diastereomer. Reduction with $NaBH_4$ afforded the same two diastereomers with which we started, but in a different, and reverse, ratio (1:13.3). This oxidation−reduction reaction confirmed that THF **13** was a mixture of diastereomers at C4. From our previous study, we were able to determine the stereochemistry of C2 phenyl and C3 methyl group by comparing coupling constants.[10] The relative stereochemistry of diastereomers **13a** and **13b** was determined to have a *trans*-relationship at C2 and C3.[5g]

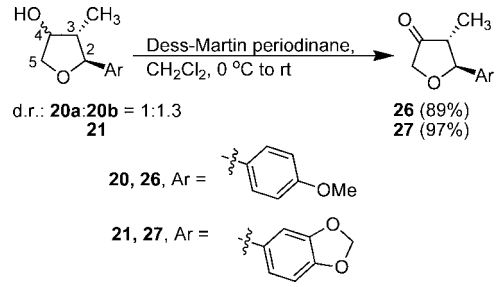
Tetrahydrofurans **20** and **21** were a mixture of three diastereomers (Table 2, entries 13 and 14) and brought new challenges to assign the stereochemistry. Since both **20** and **21** have three stereocenters, at least one of the three diastereomers must have the substituents at C2 and C3 in a *cis*-relationship instead of a *trans*-relationship. It seemed reasonable that the two major diastereomers of **20** (Table 2, entries 2 and 3) might have the same stereochemistry as **13a** and **13b** (Scheme 2). The mixture of the two major diastereomers were separated from the third (minor) diastereomer by HPLC (ratio of diastereomers: **13a**:**13b**:**13c** = 8:5:1 changed to 2.1:1:0). Oxidation of the **13a/13b** mixture gave ketone **26** as a single diastereomer, proving that C4 is the epimeric center for the two diastereomers (Scheme 3). The same technique was applied to THF **21**, and again, a single ketone (**27**) was produced upon oxidation of the alcohol.

To further substantiate our stereochemical findings, we compared ^{1}H NMR data of furanones **25**, **26**, and **27** which should possess similar ^{1}H NMR data for hydrogens on the THF rings (Table 2). The three ketones (Table 2) have nearly identical ^{1}H NMR chemical shifts and coupling constants for H^a and H^b. Coupling constants of H^a's are 10.5−10.2 Hz. Chemical shifts as well as coupling constants of H^b's matched closely (J = 17.4 Hz). This NMR data proved to be helpful in assigning the relative stereochemistry of other tetrahydrofuran diastereomers.

After the stereochemistry of the two major diastereomers was determined, process of elimination determined that the third

(10) See the Supporting Information.

SCHEME 3. Oxidation of 20 and 21



diastereomer must have C2 and C3 in a *cis*-relationship. There are two possible structures for the third diastereomer, **20c** and **20d** (Figure 2), both of which possess a *cis*-relationship on C2 and C3. Based on our investigation, it is not possible to determine the relative stereochemistry of the third diastereomer. However, the major diastereomer **20a** shows the relationship of C3 and C4 is *trans*; thus, THF **20c** is likely to be the minor diastereomer. The same assumption could be applied to the minor diastereomer of THF **21**.

Determination of Stereochemistry of Tetrasubstituted THFs. The stereochemistry of the tetrasubstituted THF products was determined in a similar fashion to those for the trisubstituted THF's discussed above. The formal cycloaddition reaction of α-methyl aldehyde **22** and styrenes **17** and **18** afforded three diastereomers each. The major diastereomer of THF **23** (**23a**) was separated from the other diastereomers by HPLC and analyzed by gNOESY NMR. It was found that there was only one cross peak observed for NOEs between hydrogens the THF ring: H^{a-d} (Figure 3). We did not observe a cross peak between H^{a-c} or between H^{b-d}. The gNOESY NMR is consistent with the stereochemical assignment of **23a**, as shown in Figure 3. An X-ray crystal structure of **23a** further confirmed the stereochemical assignment.[10]

Since the other two diastereomers of THF **23** were inseparable by HPLC, *p*-nitrobenzoyl derivatives of the three diastereomers as a mixture were synthesized (THF **28a**, **28b**, and **28c**), separated by flash chromatography, and subjected to gNOESY analysis. Diastereomer **28a** showed a cross peak between H^a and H^d, which indicated that the methyl on C5 and the aryl group on C2 are in a *cis* orientation (Figure 4). The lack of other cross peaks is consistent with those observed for alcohol **23a** and expected on the basis of the X-ray structure of **23a**.

The gNOESY spectrum of diastereomer **28b** showed two cross peaks in the NOE spectrum between H^a and H^d and H^b

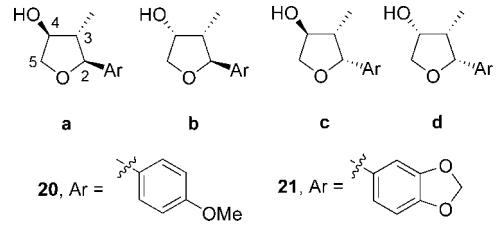
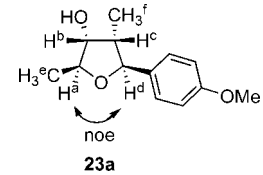


FIGURE 2. Possible diastereomers of **20** and **21**.



23a

FIGURE 3. NOEs for tetrahydrofuran **23a**.

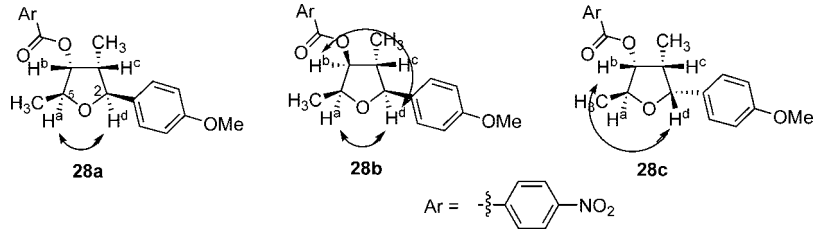
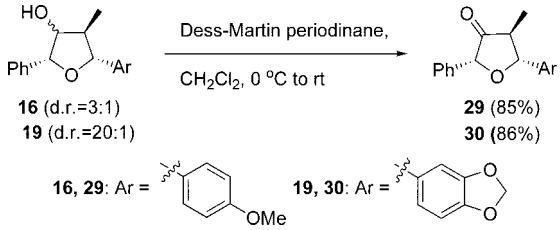
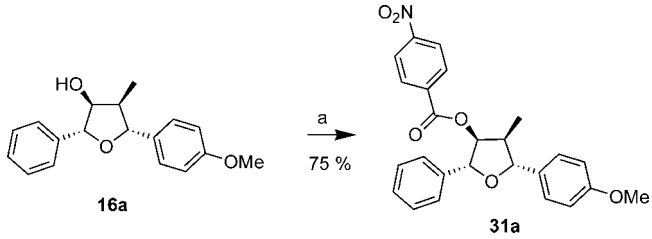


FIGURE 4. NOEs for Three Diastereomers of **28a**−**c**.

SCHEME 4. Oxidation Reaction of Alcohols



SCHEME 5. Preparation of a Derivative 31a[a]



[a] Key: (a) *p*-nitrobenzoyl chloride, pyr, DMAP, CH_2Cl_2, 0 °C to rt.

and H^d. The observed NOEs are consistent with the assignment of relative stereochemistry of diastereomer **28b** as shown in Figure 4. Thus, the two major diastereomers of THF **23** are epimeric at C4. Diastereomer **28c** showed a cross peak between H^b and H^d but lacked cross peaks between H^a and H^d and H^a and H^c. The gNOESY data for **28c** is consistent with the substituents at C2 and C3 having a *cis* orientation as shown in Figure 4.

The stereochemistry of the diastereomers of THF **24** was determined by comparing ^{1}H NMR data to those for the diastereomers of THF **23**

Stereochemical determination of THFs derived from α-phenyl aldehyde **15** was relatively easy because each reaction produced only two diastereomers and the oxidation reaction of the mixture of two diastereomers afforded a single ketone **29** and **30** in good yield (Scheme 4).

Purification of **16** by HPLC, followed by the esterification of **16a**, afforded *p*-nitrobenzoyl ester **31a** in 85% yield (Scheme 5). The X-ray crystal structure of **31a**[10] shows the major diastereomer **31a** having identical stereochemistry to **22a**; *trans* (C2 and C3), *cis* (C3 and C4), *trans* (C4 and C5).

TABLE 3. Comparison of ^{1}H NMR Data of 29 and 30

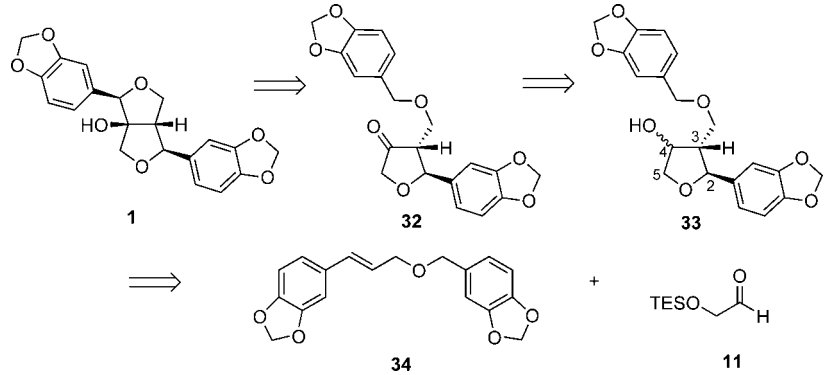
THF	H^a	H^b
29	4.92 (s)	4.71 (d, J = 10.0 Hz)
30	4.91 (s)	4.67 (d, J = 10.0 Hz)

The same approach was applied to the diastereomers of THF **19** as was used for the stereochemical determination of THF **16**. Scheme 6 shows the oxidation of the two mixtures (**19a** and **19b** in 20:1 ratio) afforded single furanone **30** in 86% yield. Chemical shifts and coupling constants of **29** and **30** in ^{1}H NMR data closely matched each other, and the ^{1}H NMR was used to assign the stereochemistry of the third stereocenter (Table 3). The major diastereomer of **19** was determined to have a *trans* relationship of substituents at C2 and C3, the same as **16**. The structures of the two diastereomers of **19** are shown in Table 1.

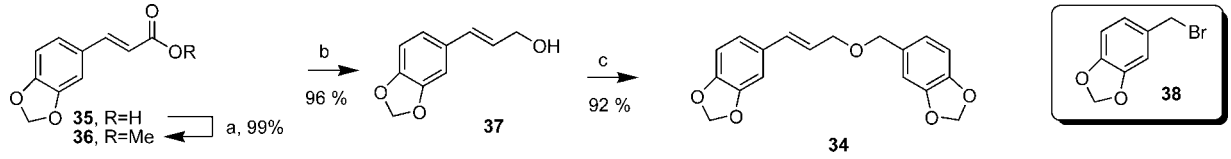
Stereochemistry. The major diastereomers of the THF products in Table 1 have the methyl and aryl stubstituents at C2 and C3 in a *trans* orientation about the ring. This is even true for styrenes **14** and **17** which are *E*/*Z* alkene isomers, and yet they both afford a similar ratio of THF products **16a/b** (Table 1, entries 9 and 10). The result is consistent with the formation of an aryl-stabilized cation under Lewis acid reaction conditions that allows epimerization of the substituents at C2 and C3. The C4 hydroxyl and C3 methyl goups are in a *cis* orientation about the ring in the major diastereomers of the THF products in Table 1. This is consistent with a syn synclinal approach of the styrene to the aldehyde and in agreement with our results using crotylsilanes in formal [3 + 2] and [4 + 2] cycloaddition reactions.[5g,8a]

Synthesis of (±)-Paulownin. Retrosynthetic analysis of (±)-Paulownin shows it might be prepared from ketone **32** (Scheme

SCHEME 6. Retrosynthesis of Paulownin

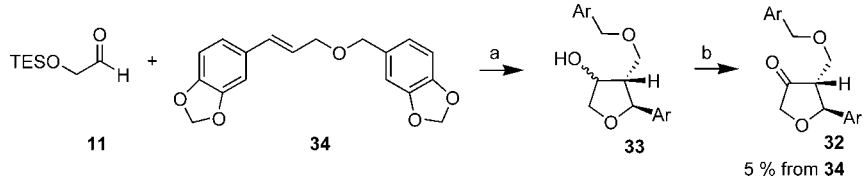


SCHEME 7. Preparation of Benzyl Ether 34[a]



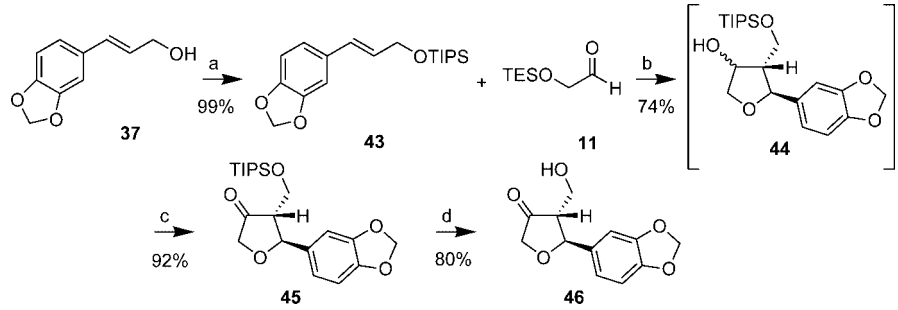
[a] Key: (a) H_2SO_4, MeOH, reflux; (b) DIBAL-H, CH_2Cl_2, 0 °C to rt; (c) NaH, 3,4-(methylenedioxy)phenylmethyl bromide **38**, THF, 0 °C to rt.

SCHEME 8. Formal [3 + 2]-Cycloaddition Reaction[a]



[a] Key: (a) $BF_3 \cdot OEt_2$, DBMP, CH_2Cl_2, −78 °C to rt; (b) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt.

SCHEME 9. Synthesis of β-Hydroxy Ketone 46[a]



[a] Key: (a) TIPSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt; (b) $BF_3 \cdot OEt_2$, DBMP, CH_2Cl_2, −78 °C to rt; (c) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt; (d) HF−Py, THF, 0 °C to rt.

6). This in turn might be derived from alcohol **33**. The *trans*-stereochemistry between the C2 methylene and C3 aryl group is what one would expect from the formal cycloaddition reaction of benzyl ether **34** and aldehyde **11**. The expected mixture of diastereomers at the C4 alcohol would be of no consequence since oxidation of **33** would provide ketone **32** a single diastereomer (Scheme 6). Finally, photochemical cyclization[11] of **32** affords paulownin **1**.

Fisher esterification of commercially available cinnamic acid **35** gave ester **36**, which was then reduced to alcohol **37** in excellent yield (Scheme 7).[12] In order to reduce the number of synthetic steps, we attempted the direct reduction of acid **35** to alcohol **37** using LAH, but the yield of **37** was lower (50%) after purification than the two step process.[13] Reaction of **37** with sodium hydride followed by the addition of benzyl bromide[14] gave the ether **34** in 92% yield (Scheme 7).

The next step was the formal [3 + 2]-cycloaddition reaction of **34** with aldehyde **11** to form tetrahydrofuran **33** (Scheme 8). This reaction afforded a mixture of products, but the desired THF was not separable from the impurities, so the crude product was used without further purification in the Dess−Martin oxidation to give ketone **32** in 5% yield for the two steps. This low yield may be explained by the instability of **33** to the reaction conditions. Two stable cations (**40** and **41**) can be derived from decomposition of the ether **33** in the presence of a Lewis acid (Figure 5).

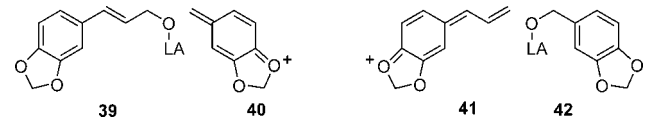
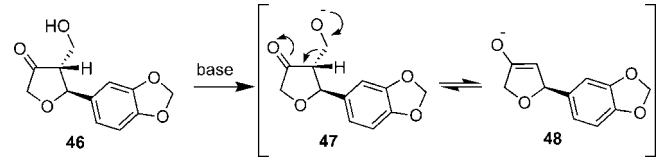


FIGURE 5. Possible carbocations.

SCHEME 10. Retro-Aldol Reaction of β-Hydroxy Ketone 46

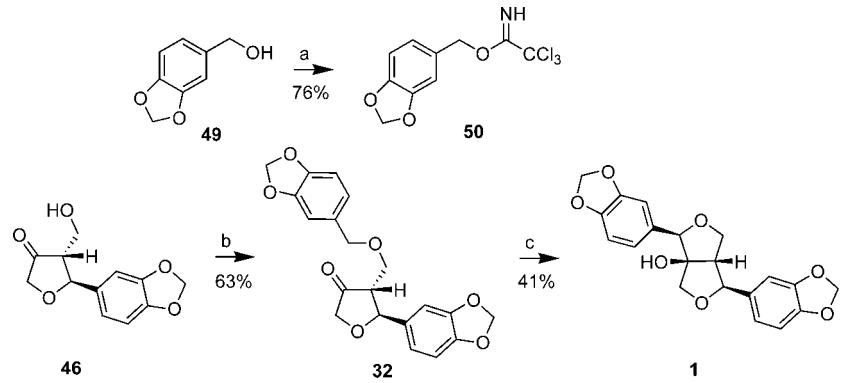


We then examined an alternative approach to increase the overall yield of THF in the formal cycloaddition reaction that focused on reducing the possibility of stabilized carbocation formation in the styrene partner (**40** or **41**). Alcohol **37** was protected as a triisopropylsilyl ether (Scheme 9). Reaction of silyl ether **43** with aldehyde **11** gave THF **44** in 74% yield as a mixture of two diastereomers (3:1 ratio by ^1H NMR). The mixture of diastereomers was used without further separation and underwent oxidation to afford ketone **45** as a single diastereomer in 92% yield. Subsequent desilylation using HF−pyridine provided β-hydroxy ketone **46** in 80% yield.[15]

Attempts to produce benzyl ether **32** under basic conditions were not successful due to the facile retro-aldol reaction of β-hydroxy ketone **46**. This retro-aldol reaction led to a loss of

(11) Kraus, G. A.; Chen, L. *J. Am. Chem. Soc.* **1990**, *112*, 3464–3466.
(12) Belletire, J. L.; Mahmoodi, N. O. *J. Nat. Prod.* **1992**, *55*, 194–206.
(13) Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929–32.
(14) Hirano, H.; Osawa, E.; Yamaoka, Y.; Yokoi, T. *Biol. Pharm. Bull.* **2001**, *24*, 1277–1281.
(15) Jung, J.-C.; Kache, R.; Vines, K. K.; Zheng, Y.-S.; Bijoy, P.; Valluri, M.; Avery, M. A. *J. Org. Chem.* **2004**, *69*, 9269–9284.

SCHEME 11. Synthesis of (±)-Paulownin 1



Key: (a) (i) NaH, ether, rt, (ii) trichloroacetonitrile, THF, 0 °C to rt; (b) imidate **50**, CH_2Cl_2, TMSOTf, rt; (c) *hν*, PhH.

the C3 stereocenter as well as decomposition of the starting *β*-hydroxy ketone **46** (Scheme 10).

The synthesis of (±)-paulownin **1** was accomplished via a known procedure.[11] Imidate **50** was prepared from 3,4-(methylenedioxy)benzyl alcohol **49**.[16] Reaction of THF **46** with imidate **50** in the presence of a catalytic amount of TMSOTf gave ether **32** in 63% yield. Photocyclization reaction with medium-pressure Hanovia lamp[11] gave the target (±)-paulownin **1** in 41% yield (Scheme 11).

Comparison of the NMR data for **1** with literature data[4d,11] showed nearly identical ^{1}H and ^{13}C NMR spectral data, confirming the synthesis of paulownin.[10]

Experimental Section

(+)-Paulownin (1). Following the procedure of Kraus and Chen,[11] a solution of ketone **32** (0.022 g, 0.059 mmol) in benzene (20 mL) was degassed with nitrogen. The mixture was irradiated with a medium-pressure Hanovia lamp for 1 h. After the brown slurry mixture was concentrated, the residue was purified by flash chromatography (4:1 hexanes/ethyl acetate) to give (±)-paulownin, **1** (0.0090 g, 41%), as pale yellow solid: mp = 80−84 °C (lit.[2] mp 82−85 °C); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.97−6.79 (m, 6H), 6.00 (s, 2H), 5.97 (s, 2H), 4.85 (d, *J* = 5.1 Hz, 1H), 4.83 (s, 1H), 4.53 (dd, *J* = 9.2, 8.2 Hz, 1H), 4.06 (d, *J* = 9.8 Hz, 1H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.86 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.06 (m, 1H), 1.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 148.1, 147.9, 147.9, 147.2, 134.6, 129.1, 120.0. 119.7, 108.6, 108.2, 107.4, 106.9, 101.2, 101.1, 91.7, 87.5, 85.8, 74.9, 71.7, 60.5; IR (neat) 3412, 2924, 1503, 1486, 1444, 1246 cm^{-1}; MS (FAB, MeOH/NBA) *m/z* 370 (M^+, 2), 219 (3), 135 (2), 120 (4); HRMS (FAB) *m/z* 370.1069 (370.1053 calcd for $C_{20}H_{18}O_7$, M^+).

General Procedure for Preparation of Tetrahydrofurans. To a solution of aldehyde, styrene (2.0 equiv), and DBMP (0.75 equiv) in CH_2Cl_2 (1 M) was added $BF_3 \cdot OEt_2$ (1.0 equiv) dropwise at −78 °C. After 5 min, the cold bath was removed and the reaction mixture was allowed to warm to rt over 1 h. The reaction mixture was poured into a rapidly stirring solution of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (4:1 or 2:1 hexanes/ethyl acetate) or HPLC (2:1 or 1:2 hexanes/ethyl acetate) after column chromatography was used to separate diastereomers:

(2*S,3*R**,4*S**)- and (2*S**,3*R**,4*R**)-3-Methyl-2-phenyltetrahydrofuran-4-ol (13a and 13b).** Following the general procedure, the cycloaddition reaction of aldehyde **11** (0.040 g, 0.23 mmol) gave tetrahydrofurans **13a** and **13b** (0.0080 g, 20%) as a 4.1:1 mixture of two diastereomers (^{1}H NMR) after flash chromatography (2:1 hexanes/ethyl acetate). Analytical samples of each diastereomer were obtained by using HPLC (2:1 hexanes/ethyl acetate), **13a** t_R = 50 min, **13b** t_R = 56 min. Major diastereomer **13a** (2*S**,3*R**,4*S**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.37−7.29 (m, 5H), 4.56 (d, *J* = 9.6 Hz, 1H), 4.41 (apparent q, *J* = 3.9 Hz, 1H), 4.34 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.96 (dd, *J* = 9.6, 0.9 Hz, 1H), 2.03 (m, 1H), 1.69 (d, *J* = 4.2 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 141.4, 128.4, 127.7, 126.2, 85.2, 76.0, 75.1, 47.9, 9.2; IR (CH_2Cl_2) 3420, 3053, 2962, 1613, 1514, 1265 cm^{-1}; MS (DEI) *m/z* 178 (M^+, 14), 160 (8), 107 (100), 91 (31); HRMS (EI) *m/z* 178.0998 (178.0994 calcd for $C_{11}H_{14}O_2$, M^+). Minor diastereomer **13b** (2*S**,3*R**,4*R**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.42-?m, 5H), 4.38 (d, *J* = 7.8 Hz, 1H), 4.17−4.04 (m, 2H), 3.96 (dd, *J* = 9.3, 3.9 Hz, 1H), 2.07 (m, 1H), 1.80 (d, *J* = 5.7 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 141.3, 128.5, 127.6, 126.1, 87.6, 79.2, 74.3, 51.3, 15.1; IR (CH_2Cl_2) 3420, 2962, 1613, 1514, 1265 cm^{-1}; MS (DEI) *m/z* 178 (M^+, 16), 160 (19), 107 (99), 91 (77), 79 (100); HRMS (EI) *m/z* 178.0988 (178.0994 calcd for $C_{11}H_{14}O_2$, M^+).

(2*R,3*R**,4*S**,5*R**)- and (2*R**,3*R**,4*R**,5*R**)-2-(4-Methoxyphenyl)-3-methyl-5-phenyltetrahydrofuran-4-ol (16a and 16b).** Following the general procedure, the cycloaddition reaction of aldehyde **15** (0.039 g, 0.16 mmol) and (*E*)-anethole **14** (0.047 mL, 0.31 mmol) gave tetrahydrofurans **16a** and **16b** (0.030 g, 62%) as a 29:1 mixture (^{1}H NMR) after flash chromatography (2:1 hexanes/ethyl acetate). Two diastereomers were partially separated by HPLC (2:1 hexanes/ethyl acetate) for analytical purposes, **16a** t_R = 24 min, **16b** t_R = 28 min. Major diastereomer **16a** (2*R**,3*R**,4*S**,5*R**): clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.45-(m, 7H), 6.94 (m, 2H), 4.95 (d, *J* = 2.7 Hz, 1H), 4.68 (d, *J* = 10.2 Hz, 1H), 4.22 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.83 (s, 3H), 2.42 (br. s, 1H), 2.16 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 159.2, 141.0, 131.9, 128.3, 128.0, 127.3, 125.6, 113.8, 87.9, 85.7, 81.1, 55.2, 45.4, 9.1; IR (CH_2Cl_2) 3425, 3060, 2963, 1612, 1514, 1248 cm^{-1}; MS (DCl/NH_3) *m/z* 284 (M^+, 5), 178 (47), 137 (56), 121 (100), 108 (12), 77 (17); HRMS (EI) *m/z* 284.1411 (284.1412 calcd for $C_{18}H_{20}O_3$, M^+). Minor diastereomer **16b** (2*R**,3*R**,4*R**,5*R**): clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.54 (d, *J* = 7.2 Hz, 2H), 7.40 (apparent t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.31 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 5.7 Hz, 1H), 3.85 (apparent t, *J* = 5.7 Hz, 1H), 3.82 (s, 3H), 2.42 (m, 1H), 2.36 (br. s, 1H), 0.63 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 158.6, 140.3, 131.6, 128.4, 127.6, 127.5, 125.6, 113.5, 86.2, 85.0, 82.0, 55.3, 46.6, 13.9; IR (CH_2Cl_2) 3428, 2963, 2931, 2835, 1612, 1514, 1248 cm^{-1};; MS (DEI) *m/z* 284 (M^+, 9), 178 (54), 137 (95), 121 (100), 108 (22), 91 (41); HRMS (EI) *m/z* 284.1417 (284.1412 calcd for $C_{18}H_{20}O_3$, M^+).

(2*R,3*R**,4*S**,5*R**)- and (2*R**,3*R**,4*R**,5*R**)-2-(3,4-Methylenedioxyphenyl)-3-methyl-5-phenyltetrahydrofuran-4-ol (19a and 19b).** Following the general procedure, aldehyde **15** (0.092 g, 0.37 mmol) gave tetrahydrofurans **19a** and **19b** (0.071 g, 64%) as

(16) Ishibashi, F.; Hayashita, M.; Okazaki, M.; Shuto, Y. *Biosci. Biotech. Biochem.* **2001**, *65*, 29–34.

a 33:1 mixture (^{1}H NMR) after flash chromatography (2:1 hexanes/ethyl acetate). The characterization of **19b** was not possible due to the small amount isolated. Diastereomer **19a** was partially separated by HPLC (2:1 hexanes/ethyl acetate) for analytical purposes, **19a** t_R = 22 min. Major diastereomer **19a** (2*R**,3*R**,4*S**,5*R**): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.29 (m, 5H), 6.99 (d, J = 1.6 Hz, 1H), 6.91 (dd, J = 7.8, 1.4 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 5.98 (s, 2H), 4.93 (d, J = 2.4 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 4.21 (dd, J = 6.0, 2.4 Hz, 1H), 2.16 (br. s, 1H), 2.12 (m, 1H), 1.00 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.3, 141.0, 134.0, 128.4, 127.5, 125.8, 120.6, 108.1, 107.0, 101.0, 88.0, 86.0, 81.1, 45.7, 9.0; IR (CH_2Cl_2) 3425, 3060, 2966, 2895, 1503, 1444, 1250 cm^{-1}; MS (DEI) *m*/*z* 298 (M^+, 37), 192 (54), 135 (100), 91 (39), 77 (15); HRMS (EI) *m*/*z* 298.1210 (298.1205 calcd for $C_{18}H_{18}O_4$, M^+).

(2*S,3*R**,4*S**)-, (2*S**,3*R**,4*R**)-, and (2*R**,3*R**,4*S**)-2-(4-Methoxyphenyl)-3-methyltetrahydrofuran-4-ol (20a, 20b, and 20c).** Following the general procedure, aldehyde **11** (0.035 g, 0.20 mmol) gave tetrahydrofurans **20a**, **20b**, and **20c** (0.033 g, 79%) as an 8:5:1 mixture of three diastereomers (^{1}H NMR) after flash chromatography (2:1 hexanes/ethyl acetate). Analytical samples of each diastereomer were obtained by using HPLC (1:2 hexanes/ethyl acetate), **20a** t_R = 24 min, **20b** t_R = 26 min, **20c** t_R = 22 min. Major diastereomer **20a** (2*S**,3*R**,4*S**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.31 (d, J = 8.2 Hz, 1H), 4.11 (m, 1H), 4.04 (dd, J = 9.6, 5.7 Hz, 1H), 3.93 (dd, J = 9.2, 4.1 Hz, 1H), 3.81 (s, 3H), 2.04 (m, 1H), 1.95 (d, J = 4.7 Hz, 1H), 1.10 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 133.0, 127.4, 113.8, 87.4, 79.2, 74.1, 55.3, 51.1, 15.0; IR (CH_2Cl_2) 3431, 3054, 2963, 1612, 1514, 1462, 1265 cm^{-1}; MS (40 eV) *m*/*z* 208 (M^+, 20), 137 (100), 121 (27), 109 (29); HRMS (EI) *m*/*z* 208.1106 (208.1099 calcd for $C_{12}H_{16}O_3$, M^+). Diastereomer **20b** (2*S**,3*R**,4*R**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.51 (d, J = 10.3 Hz, 1H), 4.40 (apparent t, J = 4.1 Hz, 1H), 4.32 (dd, J = 10.3, 4.1 Hz, 1H), 3.92 (d, J = 10.3 Hz, 1H), 3.81 (s, 3H), 2.01 (m, 1H), 1.73 (br. s, 1H), 1.03 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 133.1, 127.5, 113.8, 84.9, 75.8, 75.0, 55.3, 47.7, 9.2; IR (CH_2Cl_2) 3417, 2960, 1612, 1586, 1458, 1248 cm^{-1}; MS (40 eV) *m*/*z* 208 (M^+, 21), 137 (100), 121 (31), 109 (29), 77 (23); HRMS (EI) *m*/*z* 208.1096 (208.1099 calcd for $C_{12}H_{16}O_3$, M^+). Diastereomer **20c** (2*R**,3*R**,4*S**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.25 (d, J = 5.6 Hz, 1H), 4.34 (dd, J = 9.8, 4.7 Hz, 1H), 4.25 (br. s, 1H), 3.82 (m, 1H), 3.81 (s, 3H), 2.31 (m, 1H), 1.89 (br. s, 1H), 0.58 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 131.4, 127.0, 113.4, 81.6, 78.8, 74.3, 55.3, 46.9, 12.9; IR (CH_2Cl_2) 3405, 2965, 2934, 1514, 1247 cm^{-1}; MS (40 eV) *m*/*z* 208 (M^+, 26), 137 (100), 121 (24), 109 (24), 77 (16); HRMS (EI) *m*/*z* 208.1098 (208.1099 calcd for $C_{12}H_{16}O_3$, M^+).

(2*S,3*R**,4*S**)-, (2*S**,3*R**,4*R**)-, and (2*R**,3*R**,4*S**)-2-(3,4-Methylendioxyphenyl)-3-methyltetrahydrofuran-4-ol (21a, 21b, and 21c).** Following the general procedure, aldehyde **11** (0.047 g, 0.27 mmol) gave tetrahydrofurans **21a**, **21b**, and **21c** (0.038 g, 64%) as a 6.5:5:1 mixture of three diastereomers (^{1}H NMR) after flash chromatography (2:1 hexanes/ethyl acetate). Analytical samples of each diastereomer were obtained by HPLC (1:2 hexanes/ethyl acetate), **21a** t_R = 21 min, **21b** t_R = 24 min, **21c** t_R = 20 min. Major diastereomer **21a** (2*S**,3*R**,4*S**): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 1.6 Hz, 1H), 6.82 (dd, J = 7.8, 1.4 Hz, 1H), 6.77 (dd, J = 8.0 Hz, 1H), 5.95 (s, 2H), 4.27 (d, J = 8.0 Hz, 1H), 4.10 (m, 1H), 4.03 (dd, J = 9.6, 5.6 Hz, 1H), 3.92 (dd, J = 9.8, 4.2 Hz, 1H), 2.01 (m, 1H), 1.89 (br s, 1H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.1, 135.0, 119.6, 107.9, 106.6, 100.9, 87.5, 79.0, 74.1, 51.1, 15.0; IR (neat) 3403, 2948, 2925, 1514, 1245 cm^{-1}; MS (40 eV) *m*/*z* 222 (M^+, 57), 151 (100), 135 (30), 123 (31), 93 (62), 77 (22); HRMS (EI) *m*/*z* 222.0892 (222.0892 calcd for $C_{12}H_{14}O_4$, M^+). Diastereomer **21b** (2*S**,3*R**,4*R**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.78 (s, 2H), 5.95 (s, 2H), 4.47 (d, J = 10.3 Hz, 1H), 4.38 (br. s, 1H), 4.31 (dd, J = 9.8, 4.1 Hz, 1H), 3.92 (d, J = 10.2 Hz, 1H), 1.97 (m, 1H), 1.73 (br. s, 1H), 1.03 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.1, 135.1, 119.9, 108.0, 106.5, 100.9, 85.1, 75.9, 74.9, 47.8, 9.2; IR (neat) 3406, 2960, 2927, 1613, 1514, 1460, 1246 cm^{-1}; MS (40 eV) *m*/*z* 222 (M^+, 45), 151 (100), 135 (38), 123 (27), 93 (47), 77 (20); HRMS (EI) *m*/*z* 222.0893 (222.0892 calcd for $C_{12}H_{14}O_4$, M^+). Diastereomer **21c** (2*R**,3*R**,4*S**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (m, 3H), 5.95 (s, 2H), 5.22 (d, J = 5.1 Hz, 1H), 4.32 (dd, J = 10.3, 4.6 Hz, 1H), 4.24 (br. s, 1H), 3.82 (dd, J = 9.8, 1.5 Hz, 1H), 2.30 (m, 1H), 1.82 (br. s, 1H), 0.59 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.3, 133.4, 119.0, 107.9, 106.7, 100.8, 81.7, 78.7, 74.3, 47.0, 12.8; IR (neat) 3405, 2959, 2926, 1613, 1514, 1246 cm^{-1}; MS (40 eV) *m*/*z* 222 (M^+, 53), 151 (100), 135 (32), 123 (27), 93 (59), 77 (14); HRMS (EI) *m*/*z* 222.0893 (222.0892 calcd for $C_{12}H_{14}O_4$, M^+).

(2*S,3*S**,4*R**,5*S**)-, (2*S**,3*S**,4*S**,5*S**)-, (2*R**,3*S**,4*R**,5*S**)-3,5-Dimethyl-2-(4-methoxyphenyl)tetrahydrofuran-4-ol (23a, 23b, and 23c).** Following the general procedure, aldehyde **22** (0.041 g, 0.22 mmol) gave a 17.1:9:1 mixture (^{1}H NMR) of tetrahyrdofurans **23a**, **23b**, and **23c** (0.027 g, 56%) which was not separable by flash chromatography (2:1 hexanes/ethyl acetate). An analytical sample of **23a** was obtained by HPLC (1:1 hexanes/ethyl acetate). A 3.3:1 mixture (^{1}H NMR) of **23b/23c**, white solid, was used for analytical purposes (**23a**, t_R = 25 min, a 3.3:1 mixture of **23b** and **23c**, t_R = 22 min). Major diastereomer **23a** (2*S**,3*S**,4*R**,5*S**): white solid; mp = 93−94 °C; $[\alpha]_D$ –0.45 (*c* 0.0088, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.90 (m, 2H), 4.50 (d, J = 10.2 Hz, 1H), 4.07 (dq, J = 2.1, 6.3 Hz, 1H), 3.94 (dd, J = 6.3, 2.1 Hz, 1H), 3.81 (s, 3H), 2.04 (m, 1H), 1.81 (br. s, 1H), 1.37 (d, J = 6.3 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.9, 127.6, 113.7, 85.7, 82.5, 80.0, 55.3, 45.9, 20.4, 9.1; IR (CH_2Cl_2) 3398, 3005, 2959, 1612, 1513, 1460, 1244 cm^{-1}; MS (DEI) *m*/*z* 222 (M^+, 55), 137 (100), 121 (73), 109 (14), 77 (13); HRMS (EI) *m*/*z* 222.1258 (222.1256 calcd for $C_{13}H_{18}O_3$, M^+). Diastereomer **23b** (2*S**,3*S**,4*S**,5*S**) 3.3:1 mixture of **23b/23c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 6.88 (m, 2H), 4.24 (d, J = 7.8 Hz, 1H), 4.07 (m, 1H), 3.88 (apparent t, J = 4.7 Hz, 1H), 3.80 (s, overlaps with diastereomer, 3H), 2.05 (m, 1H), 1.81 (br. s, overlaps with diastereomer, 1H), 1.35 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 133.3, 127.6, 113.8, 86.2, 80.5, 76.9, 55.3, 51.1, 15.6, 14.6. Diastereomer **23c** (2*R**,3*S**,4*R**,5*S**) 3.3:1 mixture of **23b/23c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (m, 2H), 6.88 (m, overlaps with diastereomer, 2H), 5.13 (d, J = 6.9 Hz, 1H), 3.84 (m, overlaps with diastereomer, 1H), 3.80 (s, overlaps with diastereomer, 3H), 3.56 (apparent t, J = 5.1 Hz, 1H), 2.28 (m, 1H), 1.81 (br. s, overlaps with diastereomer, 1H), 1.43 (d, J = 6.3 Hz, 3H), 0.63 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 130.7, 127.5, 113.4, 84.0, 81.7, 80.9, 55.2, 46.7, 19.9, 13.8. Mixture of **23b** and **23c** (3.3:1): IR ($CDCl_3$) 3407, 2961, 2929, 2971, 1613, 1514, 1457, 1247.

(2*S,3*S**,4*R**,5*S**)-, (2*S**,3*S**,4*S**,5*S**)-, and (2*R**,3*S**,4*R**,5*S**)-2-(3,4-Methylendioxyphenyl)-3,5-dimethyltetrahydrofuran-4-ol (24a, 24b, and 24c).** Following the general procedure, aldehyde **22** (0.036 g, 0.19 mmol) gave tetrahydrofurans **24a**, **24b**, and **24c** (0.022 g, 0.093 mmol, 49%) as a 12:5:1 mixture (^{1}H NMR) which was not separable by flash chromatography (2:1 hexanes/ethyl acetate). Diastereomers **24a** and **24b** were separated by HPLC (2:1 hexanes/ethyl acetate) for analytical purposes. Diastereomer **24c** was mixed with other two diastereomers after HPLC, and characterization was not possible, **24a** t_R = 25 min, **24b** t_R = 22 min. Major diastereomer **24a** (2*S**,3*S**,4*R**,5*S**): pale yellow oil; $[\alpha]_D$ +22.3 (*c* 0.0090, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.78 (s, 2H), 5.95 (s, 2H), 4.46 (d, J = 10.0 Hz, 1H), 4.07 (dq, J = 2.4, 6.4 Hz, 1H), 3.94 (dd, J = 5.6, 2.4 Hz, 1H), 2.00 (m, 1H), 1.79 (br. s, 1H), 1.36 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.1, 134.9, 120.2, 108.0, 106.7, 101.9, 85.9, 82.5, 79.9, 45.9, 20.3, 9.0; IR (CH_2Cl_2)

3441, 2969, 2904, 1504, 1489, 1445, 1249 cm^{-1}; MS (DEI) *m/z* 236 (M^+, 40), 162 (18), 151 (100), 135 (44), 93 (18); HRMS (EI) *m/z* 236.1056 (236.1049 calcd for $C_{13}H_{16}O_4$, M^+). Diastereomer **24b** (2*S**,3*S**,4*S**,5*S**): pale yellow oil; $[\alpha]_D$ +17.3 (*c* 0.011, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 1.6 Hz, 1H), 6.82 (dd, J = 8.4, 2.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.94 (s, 2H), 4.20 (d, J = 7.6 Hz, 1H), 4.06 (m, 1H), 3.87 (apparent t, J = 4.6 Hz, 1H), 2.02 (m, 1H), 1.78 (br. s, 1H), 1.34 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.2, 135.3, 119.9, 108.0, 106.8, 101.0, 86.5, 80.5, 77.1, 51.2, 15.7, 14.7; IR (CH_2Cl_2) 3412, 2966, 2901, 1494, 1446, 1247 cm^{-1}; MS (DEI) *m/z* 236 (M^+, 44), 162 (22), 151 (100), 135 (47); HRMS (EI) *m/z* 236.1049 (236.1049 calcd for $C_{13}H_{16}O_4$, M^+).

(2*S,3*R**)-3-Methyl-2-phenyltetrahydrofuran-4-one (25).** To a solution of the 3.5:1 mixture of **13a** and **13b** (0.046 g, 0.26 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (0.13 g, 0.31 mmol) at 0 °C. The mixture was allowed to warm to rt with stirring. After 3 h, a 20% aqueous solution of $Na_2S_2O_3$ (2 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (9:1 hexanes/ethyl acetate) afforded furanone **25** (0.047 g, 89%) as colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.35 (m, 5H), 4.64 (d, J = 10.4 Hz, 1H), 4.41 (dd, J = 17.2, 1.6 Hz, 1H), 4.00 (d, J = 17.2 Hz, 1H), 2.40 (ddq, J = 10.4, 1.6, 7.2 Hz, 1H), 1.14 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 139.2, 128.7, 128.6, 126.2, 86.6, 71.7, 50.3, 9.9; IR ($CDCl_3$) 3032, 2970, 2876, 1761, 1455 cm^{-1}; MS (30 eV) *m/z* 176 (M^+, 80), 118 (100), 91 (33); HRMS (EI) *m/z* 176.0832 (176.0837 calcd for $C_{11}H_{12}O_2$, M^+).

Reduction of Ketone 25. To a solution of furanone **25** (0.012 g, 0.068 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (0.0051 g, 0.14 mmol) at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, MeOH was removed in vacuo. The crude product was combined with a 0.5 N solution of HCl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to afford a 1:13.3 mixture of **13a** and **13b** (0.013 g, quantitative) without further purification.

(2*S,3*R**)-2-(4-Methoxyphenyl)-3-methyltetrahydrofuran-4-one (26).** To a solution of the 1:1.3 mixture of **20a** and **20b** (0.052 g, 0.25 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (0.12 g, 0.28 mmol) at 0 °C. The mixture was allowed to warm to rt with stirring. After 1 h, a 20% aqueous solution of $Na_2S_2O_3$ (2 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded furanone **26** (0.047 g, 89%) as a thick, colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 4.57 (d, J = 10.2 Hz, 1H), 4.38 (d, J = 17.4 Hz, 1H), 3.98 (d, J = 17.4 Hz, 1H), 3.83 (s, 3H), 2.38 (dq, J = 10.2, 7.1 Hz, 1H), 1.10 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.1, 159.7, 131.0, 127.6, 114.0, 86.2, 71.6, 55.3, 50.0, 9.8; IR (CH_2Cl_2) 2967, 2837, 1759, 1613, 1586, 1456, 1250 cm^{-1}; MS (40 eV) *m/z* 206 (M^+, 83), 148 (100), 135 (28); HRMS (EI) *m/z* 206.0950 (206.0943 calcd for $C_{12}H_{14}O_3$, M^+).

(2*S,3*R**)-2-(3,4-Methylendioxyphenyl)-3-methyltetrahydrofuran-4-one (27).** To a solution of the mixture of **21a** and **21b** (0.13 g, 0.59 mmol) in CH_2Cl_2 (6 mL) was added Dess−Martin periodinane (0.27 g, 0.65 mmol) at 0 °C. The mixture was allowed to warm to rt. After the mixture was stirred for 1 h, a 20% aqueous solution of $Na_2S_2O_3$ (5 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded furanone **27** (0.17 g, 97%) as a colorless thick oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 1.0 Hz, 1H), 6.87 (dd, J = 8.2, 1.0 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 5.99 (s, 2H), 4.54 (d, J = 10.3 Hz, 1H), 4.38 (dd, J = 17.4, 0.9 Hz, 1H), 3.98 (d, J = 17.4 Hz, 1H), 2.35 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 147.9, 147.6, 132.9, 120.0, 108.1, 106.4, 101.1, 86.3, 71.5, 50.1, 9.8; IR (neat) 3069, 2973, 1751, 1504, 1452, 1253 cm^{-1}; MS (40 eV) *m/z* 220 (M^+, 86), 162 (100), 149 (41), 104 (23), 77 (24); HRMS (EI) *m/z* 220.0733 (220.0736 calcd for $C_{12}H_{12}O_4$, M^+).

(2*S,3*S**,4*R**,5*S**)-, (2*S**,3*S**,4*S**,5*S**)-, (2*R**,3*S**,4*R**,5*S**)-(4-Nitrobenzoic acid)-3,5-dimethyl-2-(4-methoxyphenyl)tetrahydrofuran-4-yl Ester (28a, 28b, and 28c).** To a solution of the mixture of **23a**, **23b**, and **23c** (0.079 g, 0.36 mmol) in CH_2Cl_2 (3.5 mL) were added Et_3N (0.098 mL, 0.071 mmol) and DMAP (0.022 g, 0.018 mmol) followed by 4-nitrobenzoyl chloride (0.013 g, 0.071 mmol). The reaction mixture was stirred for 2.5 h at rt, and then a 5% aqueous solution of $NaHCO_3$ (4 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) afforded esters **28a** (0.060 g, 46%), **28b** (0.026 g, 20%), and **28c** (0.013 g, 10%). Major diastereomer **28a** (2*S**,3*S**,4*R**,5*S**): pale yellow solid; mp = 118−122 °C; $[\alpha]_D$ +85.3 (*c* 0.0040, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.27 (m, 2H), 7.32 (m, 2H), 6.92 (m, 2H), 5.28 (dd, J = 5.4, 1.6 Hz, 1H), 4.64 (d, J = 10.4 Hz, 1H), 4.27 (dq, J = 1.6, 6.8 Hz, 1H), 3.82 (s, 3H), 2.33 (m, 1H), 1.51 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 159.5, 150.6, 135.4, 131.8, 130.7, 127.7, 123.6, 113.9, 86.2, 83.3, 80.3, 55.2, 44.8, 20.2, 9.2; IR (CH_2Cl_2) 3054, 2973, 2934, 1723, 1609, 1529, 1275 cm^{-1}; MS (DCl/NH_3) *m/z* 389 (MNH_4^+, 7), 372 (MH^+, 16), 342 (19), 205 (100), 187 (71), 161 (52), 135 (33); HRMS (EI) *m/z* 372.1439 (372.1447 calcd for $C_{20}H_{22}NO_6$, MH^+). Diastereomer **28b** (2*S**,3*S**,4*S**,5*S**): yellow thick oil; $[\alpha]_D$ +65.5 (*c* 0.0070, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 2H), 8.22 m, 2H), 7.35 (m, 2H), 6.90 (m, 2H), 5.22 (dd, J = 4.8, 3.2 Hz, 1H), 4.38 (d, J = 7.6 Hz, 1H), 4.30 (m, 1H), 3.81 (s, 3H), 2.34 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.4, 150.6, 135.4, 132.6, 130.7, 127.6, 123.6, 113.9, 86.6, 83.7, 76.9, 55.3, 49.5, 15.6, 14.6; IR (CH_2Cl_2) 3110, 2972, 2934, 1723, 1609, 1529, 1278 cm^{-1}; MS (DCl/NH_3) *m/z* 389 (MNH_4^+, 32), 372 (MH^+, 36), 342 (57), 205 (100), 187 (46), 161 (23), 135 (37); HRMS (EI) *m/z* 372.1450 (372.1447 calcd for $C_{20}H_{22}NO_6$, MH^+). Diastereomer **28c** (2*R**,3*S**,4*R**,5*S**): pale yellow solid; mp = 112−115 °C; $[\alpha]_D$ +30.4 (*c* 0.0024, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.26 (m, 2H), 7.26 (m, 2H), 6.90 (m, 2H), 5.21 (d, J = 5.2 Hz, 1H), 4.90 (dd, J = 4.0, 1.6 Hz, 1H), 4.19 (dq, J = 4.0, 6.8 Hz, 1H), 3.82 (s, 3H), 2.54 (m, 1H), 1.57 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 158.7, 150.6, 135.3, 130.7, 130.3, 127.1, 123.5, 113.5, 87.7, 82.0, 79.6, 55.3, 45.0, 19.9, 13.5; IR (CH_2Cl_2) 3055, 2977, 2936, 1724, 1608, 1530, 1248 cm^{-1}; MS (DCl/NH_3) *m/z* 389 (MNH_4^+, 6), 372 (MH^+, 20), 342 (100), 219 (21), 205 (80), 187 (23), 135 (36); HRMS (EI) *m/z* 372.1450 (372.1447 calcd for $C_{20}H_{22}NO_6$, MH^+).

(2*R,3*R**,5*R**)-2-(4-Methoxyphenyl)-3-methyl-2-phenyltetrahydrofuran-4-one (29).** To a solution of the mixture of **16a** and **16b** (0.063 g, 0.22 mmol) in CH_2Cl_2 (2.5 mL) was added Dess−Martin periodinane (0.12 g, 0.27 mmol) at 0 °C. The mixture was allowed to warm to rt. After the mixture was stirred for 3 h, a 20% aqueous solution of $Na_2S_2O_3$ (2.0 mL) and a saturated aqueous solution of $NaHCO_3$ (2.0 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded furanone **29** (0.053 g, 85%): white solid; mp = 106−107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.35 (m, 7H), 7.00 (d, J = 8.4 Hz, 2H), 4.92 (s, 1H), 4.72 (d, J = 10.6 Hz, 1H), 3.83 (s, 3H), 2.53 (dq, J = 10.4, 6.4 Hz, 1H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 159.9, 136.1, 131.1, 128.5, 128.2, 127.9, 126.1, 114.2, 84.1, 82.8, 55.3, 49.6, 9.8; IR (CH_2Cl_2) 3063, 3032, 2971, 1759, 1490, 1445, 1250 cm^{-1}; MS (DCI/NH_3) *m/z* 283 (MH^+,

15), 148 (100), 121 (7), 77 (6); HRMS (EI) *m/z* 283.1342 (283.1334 calcd for $C_{18}H_{19}O_3$, MH^+).

(2*R,3*R**,5*R**)-2-(3,4-Methylenedioxyphenyl)-3-methyl-5-phenyltetrahydrofuran-4-one (30).** To a solution of the mixture of **24a** and **24b** (0.035 g, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added Dess−Martin periodinane (0.060 g, 0.14 mmol) at 0 °C. The mixture was allowed to warm to rt. After the mixture was stirred for 3 h, a 20% aqueous solution of $Na_2S_2O_3$ (2.0 mL) and a saturated aqueous solution of $NaHCO_3$ (2.0 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded furanone **30** (0.030 g, 86%) as a thick oily solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 2H), 7.44−7.32 (m, 3H), 7.08 (s, 1H), 6.99 (dd, J = 8.4, 1.8 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.02 (s, 2H), 4.91 (s, 1H), 4.67(d, J = 10.0 Hz, 1H), 2.48 (dq, J = 10.0, 6.8 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 148.2, 147.9, 135.9, 132.9, 128.6, 128.3, 126.1, 120.5, 108.4, 106.7, 101.3, 84.3, 82.8, 49.8, 9.8; IR (CH_2Cl_2) 2973, 2880, 1760, 1490, 1445, 1251 cm^{-1}; MS (DEI) *m/z* 296 (M^+, 6), 162 (100), 105 (14), 77 (23); HRMS (DEI) *m/z* 296.1054 (296.1049 calcd for $C_{18}H_{16}O_4$, M^+).

(2*R,3*R**,4*S**,5*R**)-(4-Nitrobezoic acid)-2-(4-methoxyphenyl)-3-methyl-5-phenyltetrahydrofuran-4-yl Ester (31a).** To a solution of the **16a** (0.25 g, 0.88 mmol) in CH_2Cl_2 (8.8 mL) were added Et_3N (0.24 mL, 1.76 mmol) and DMAP (0.053 g, 0.44 mmol) followed by 4-nitrobenzoyl chloride (0.033 g, 1.78 mmol). The reaction mixture was stirred for 3 h at rt, and then a 5% aqueous solution of $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) afforded ester **31a** (0.29 g, 75%) as a white solid: mp = 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42−8.30 (m, 4H), 7.64 (d, J = 8.2 Hz, 2H), 7.51−7.33 (m, 5H), 6.99 (d, J = 8.2 Hz, 2H), 5.58 (dd, J = 6.8, 1.2 Hz, 1H), 5.23 (s, 1H), 4.88 (d, J = 10.8 Hz, 1H), 3.86 (s, 3H), 2.48 (m, 1H), 1.04 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.8, 150.8, 140.0, 135.3, 130.9, 130.8, 128.5, 128.3, 127.8, 125.9, 123.7, 114.1, 86.4, 85.5, 84.9, 55.3, 43.7, 9.2; IR (CH_2Cl_2) 3060, 3034, 2970, 2879, 1724, 1611, 1528, 1273 cm^{-1}; MS (electrospray) *m/z* (434, MH^+); HRMS (ESI) *m/z* 434.1618 (434.1604 calcd for $C_{25}H_{24}NO_6$, MH^+).

(2*S,3*R**)-2-(3,4-Methylendioxyphenyl)-3-[(3,4-methylenedioxyphenyl)methoxymethyl]tetrahydrofuran-4-one (32).** To a suspension of NaH (60% in oil, 0.033 g, 0.82 mmol, washed with dry hexanes) in ether (8 mL) was added a solution of piperonyl alcohol **49** (0.50 g, 3.29 mmol) in THF (15 mL) dropwise. After being stirred for 20 min at rt, the reaction mixture was cooled to 0 °C. Trichloroacetonitrile (0.33 mL, 3.29 mmol) was added dropwise. The mixture was stirred for 3 h at rt and concentrated in vacuo. The residue, diluted in a mixture of CH_2Cl_2 (10 mL) and MeOH (0.034 mL), was filtered through a pad of Celite and concentrated to afford (3,4-phenyl)methyl trichloroacetimidate **50** (0.74 g, 76%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br. s, 1H), 6.95−6.80(m, 3H), 5.98 (s, 2H), 5.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 147.7, 147.6, 129.1, 121.8, 108.6, 108.1, 101.1, 91.4, 70.8. To a solution of hydroxy furanone **46** (0.039 g, 0.16 mmol) in CH_2Cl_2 (1 mL) was added a solution of the imidate **50** (0.082 g, 0.28 mmol) in CH_2Cl_2 (0.6 mL). TMSOTf (2 drops from 18 gauge needle) was added into the solution. The reaction mixture was stirred for 2.5 days at rt. The reaction mixture was washed with brine (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried (Na_2SO_4,) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded benzyl ether **32** (0.038 g, 63%) as a clear liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90−6.71 (m, 6H), 5.97 (two s, 4H), 5.12 (d, J = 9.7 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.34 (d, J = 16.9 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 3.99 (d, J = 16.9 Hz, 1H), 3.85 (dd, J = 9.8, 3.4 Hz, 1H), 3.51 (dd, J = 9.8, 3.1 Hz, 1H), 2.42 (apparent dt, J = 9.7, 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 147.9, 147.7, 147.5, 147.1, 133.5, 131.5, 121.2, 119.9, 108.3, 108.2, 108.0, 106.5, 101.1, 101.0, 81.4, 73.3, 72.1, 64.5, 55.7; IR (neat) 3052, 2895, 1722, 1608, 1502, 1488, 1441, 1245 cm^{-1}; MS (DEI) *m/z* 370 (M^+, 13), 235 (44), 218 (16), 205 (100), 149 (8), 135 (24), 77 (2); HRMS (EI) *m/z* 370.1041 (370.1053 calcd for $C_{20}H_{18}O_7$, M^+).

3,4-(Methylenedioxy)cinnamyl 3,4-(Methylenedioxyphenyl)-methyl ether (34). To a suspension of dry NaH (95%, 0.089 g, 3.70 mmol) in THF (9 mL) at 0 °C was added alcohol **35** (0.220 g, 1.23 mmol) diluted in THF (1.5 mL) and 3,4-(methylenedioxy)phenylmethyl bromide **36** (0.330 g, 1.54 mmol) in THF (1.5 mL) via a cannula. The reaction mixture was stirred overnight at rt. Brine (15 mL) was added into the mixture, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded ether **34** (0.35 g, 92%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, J = 15.9, 1.5 Hz, 1H), 6.80 (m, 5H), 6.53 (d, J = 15.9 Hz, 1H), 6.15 (dt, J = 15.7, 6.0 Hz, 1H), 5.94 (s, 4H), 4.46 (s, 2H), 4.13 (dd, J = 6.2, 0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.6, 147.1, 146.9, 132.1, 132.0, 131.0, 124.1, 121.3, 121.0, 108.4, 108.1, 107.9, 105.6, 100.9, 100.8, 71.9, 70.4; IR (neat) 3070, 2891, 2779, 1606, 1502, 1443, 1250 cm^{-1}; MS (FAB,DCM/NBA) *m/z* 312 (M^+, 37), 233 (24), 161 (76), 155 (23), 137 (45), 135 (100); HRMS (FAB) *m/z* 312.0997 (312.0998 calcd for $C_{18}H_{16}O_5$, M^+).

Methyl 3,4-(Methylenedioxy)cinnamate (36). To a suspension of cinnamic acid **35** (4.06 g, 21.1 mmol) in MeOH (50 mL) at rt was added dropwise concd H_2SO_4 (2.5 mL). After refluxing overnight, the reaction mixture was cooled to rt, and solid $NaHCO_3$ (5.0 g) was added. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and then brine (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded the ester **36** (4.29 g, 99%) as a white solid: mp = 128−130 °C (lit.[12] mp 130−131 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 15.9 Hz, 1H), 7.02 (s, 1H), 6.99 (dd, J = 8.1, 1.5 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.25 (d, J = 15.9 Hz, 1H), 6.00 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 149.4, 148.2, 144.4, 128.7, 124.3, 115.6, 108.4, 106.4, 101.5, 51.6.

3,4-(Methylenedioxy)cinnamyl Alcohol (37). Method A. To a solution of methyl 3,4-(methylenedioxy)cinnamate **36** (0.590 g, 2.86 mmol) in CH_2Cl_2 (28 mL) was added DIBAL-H (1.17 mL, 6.58 mmol) dropwise at 0 °C. The reaction mixture was stirred for 2 h at rt. MeOH (3 mL) and 1 N HCl (30 mL) were added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 →1:1 hexanaes/ethyl acetate) afforded alcohol **37** (0.49 g, 96%) as a white solid. **Method B.** To a solution of cinnamic acid **35** (0.10 g, 0.53 mmol) in THF (5.3 mL) at 0 °C was added LAH (0.080 g, 2.11 mmol). After 3 h at 0 °C, the reaction mixture was allowed to warm to rt and then stirred for an additional 2 h. H_2O (0.08 mL), 15% aqueous NaOH (0.08 mL), and then H_2O (0.24 mL) were added. The mixture was stirred vigorously overnight. The yellow suspension was filtered and then washed with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes/ethyl acetate) afforded alcohol **37** (0.047 g, 50%) as a white solid: mp = 71−72 °C (lit.[12] mp 73−74 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 6.15 (dt, J = 15.9, 5.4 Hz, 1H), 5.92 (s, 2H), 4.24 (d, J = 5.4 Hz, 2H), 2.51 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.0, 131.0, 130.6, 126.6, 120.9, 108.1, 105.6, 100.9, 63.4.

3,4-(Methylenedioxyphenyl)methyl Bromide (38).[14] To a solution of piperonyl alcohol (0.30 g, 1.97 mmol) in CH_2Cl_2 (20 mL) was added PBr_3 (9.85 mL, 1 M in CH_2Cl_2) slowly at 0 °C. The reaction mixture was stirred for 3 h at rt and then poured into H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50

mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded the bromide (0.65 g, 91%) as pale yellow solid: mp = 39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (m, 2H), 6.75 (d, J = 7.8 Hz, 1H), 5.96 (s, 2H), 4.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.6, 131.3, 126.6, 109.3, 108.2, 101.2, 34.2.

3,4-(Methylenedioxy)cinnamyl Triisopropylsilyl Ether (43). To a solution of alcohol **37** (1.00 g, 5.61 mmol) and DMAP (0.340 g, 2.81 mmol) in CH_2Cl_2 (56 mL) were added Et_3N (0.940 mL, 6.73 mmol) and TIPSCl (1.32 mL, 6.17 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stirred overnight. A saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded the silyl ether **43** (1.86 g, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, J = 1.6 Hz, 1H), 6.83 (dd, J = 8.2, 1.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.57 (dm, J = 16.4 Hz, 1H), 6.16 (dt, J = 16.4, 5.2 Hz, 1H), 5.95 (s, 2H), 4.42 (dd, J = 5.2, 1.6 Hz, 2H), 1.13 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.9, 131.7, 128.8, 127.5, 120.8, 108.2, 105.7, 100.9, 63.9, 18.0, 12.1; IR (neat) 2943, 1503, 1490, 1446, 1250 cm^{-1}; MS (DEI) m/z 334 (M^+, 25), 291 (36), 161 (100), 131 (24), 77 (3); HRMS (EI) m/z 334.1955 (334.1964 calcd for $C_{19}H_{30}O_3Si$, M^+).

(2*S,3*R**)-2-(3,4-Methylendioxyphenyl)-3-(triisopropylsiloxy)-methyltetrahydrofuran-4-one (45).** To a solution of aldehyde **11** (0.674 g, 3.87 mmol) and DBMP (0.400 g, 1.93 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added $BF_3 \cdot OEt_2$ (0.490 mL, 3.87 mmol) dropwise. A −78 °C solution of silyl ether **43** (0.650 g, 1.94 mmol) in CH_2Cl_2 (5 mL) was transferred to the reaction mixture via a dry ice wrapped cannula. The combined reaction mixture was allowed to gradually warm to rt in a Dewar flask over 3 h. The reaction mixture was stirred for an additional 1 h at rt and then poured into a saturated aqueous solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) gave 5-(3,4-methylendioxyphenyl)-4-(triisopropylsiloxy)methyltetrahydrofuran-3-ol **44** (0.57 g, 74%) as a 1.2:1 mixture of two diastereomers (^{1}H NMR). The mixture of two inseparable diastereomers was used in the oxidation reaction without characterization. To a solution of the two furanol diastereomers **44** (0.078 g, 0.20 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Dess−Martin periodinane (0.10 g, 0.24 mmol). The reaction mixture was stirred for 3 h at rt, and then a 20% aqueous solution of $Na_2S_2O_3$ (2 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded furanone **45** (0.072 g, 92%) as a white solid: mp = 57−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 1.5 Hz, 1H), 6.90 (dd, J = 8.2, 1.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.98 (s, 2H), 5.27 (d, J = 9.7 Hz, 1H), 4.31 (d, J = 16.9 Hz, 1H), 4.22 (dd, J = 10.3, 3.1 Hz, 1H), 3.92 (d, J = 16.9 Hz, 1H), 3.76 (dd, J = 10.3, 3.1 Hz, 1H), 2.33 (m, 1H), 1.06 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 148.0, 147.6, 133.9, 120.1, 108.2, 106.6, 101.1, 81.1, 72.4, 58.9, 57.5, 18.0, 12.0; IR (neat) 2942, 2867, 1763, 1505, 1447, 1251 cm^{-1}; MS (FAB, ET/NBA) m/z 393 (MH^+, 12), 391 ($M - H^+$, 15), 349 (M − -*i*Pr, 31), 219 (37), 199 (100), 157 (67), 145 (49), 137 (54); HRMS (FAB) m/z 393.2092 (393.2097 calcd for $C_{21}H_{33}O_5Si$, MH^+).

(2*S,3*R**)-3-(Hydroxymethyl)-2-(3,4-methylendioxyphenyl)tetrahydrofuran-4-one (46).** To a solution of silyl ether **45** (0.16 g, 0.41 mmol) in THF (21 mL) at 0 °C was added HF−pyridine dropwise (4.1 mL) over 5 min. The reaction mixture was stirred for 24 h at rt. THF was removed under reduced pressure, and then a saturated aqueous solution of $NaHCO_3$ (10 mL) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) afforded hydroxymethyl furanone **46** (0.077 g, 80%) as a clear liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 1.5 Hz, 1H), 6.89 (dd, J = 8.1, 1.5 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.97 (s, 2H), 5.03 (d, J = 10.2 Hz, 1H), 4.34 (dd, J = 17.4, 1.2 Hz, 1H), 3.99 (dd, J = 11.4, 3.6 Hz, 1H), 3.97 (d, J = 17.4 Hz, 1H), 3.69 (dd, J = 11.7, 4.2 Hz, 1H), 2.45 (m, 1H), 2.41 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 148.0, 147.7, 133.0 120.1, 108.2, 106.5, 101.1, 81.5, 72.0, 57.8, 57.1; IR (neat) 3487, 2925, 1759, 1503, 1448, 1249 cm^{-1}; MS (DEI) m/z 236 (M^+, 100), 218 (42), 206 (61), 160 (35), 148 (63), 157 (67), 135 (53); HRMS (EI) m/z 236.0691 (236.0685 calcd for $C_{12}H_{12}O_5$, M^+).

(3,4-Methylenedioxyphenyl)methyl Trichloroacetimidate (50). To a suspension of NaH (60% in oil, 0.033 g, 0.82 mmol, washed with dry hexanes) in ether (8 mL) was added dropwise a solution of piperonyl alcohol **49** (0.50 g, 3.29 mmol) in THF (15 mL). After being stirred for 20 min at rt, the reaction mixture was cooled to 0 °C. Trichloroacetonitrile (0.33 mL, 3.29 mmol) was added dropwise. The mixture was stirred for 3 h at rt and concentrated in vacuo. The residue was diluted in a mixture of CH_2Cl_2 (10 mL) and MeOH (0.034 mL) and then was filtered through a pad of Celite before being concentrated to afford imidate **50** (0.74 g, 76%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 6.95−6.80(m, 3H), 5.98 (s, 2H), 5.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 147.7, 147.6, 129.1, 121.8, 108.6, 108.1, 101.1, 91.4, 70.8.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **11**, **13a/b**, **15**, **16a**,**b**, **17**, **19a**, **20a**−**c**, **21a**−**c**, **22**, **23a**, **23b**,**c** mixture, **24a**,**b**, **25**−**27**, **28a**−**c**, **29**, **30**, **31a**, **32**, **34**, **36**−**38**, **43**, **45**, **46**, and **50**; general procedures of α-triethylsilyloxy acetaldehydes **11**, **15**, and **22**; procedure for (*Z*)-1-(4-methoxyphenyl)prop-1-ene **17** and 3,4-(methylenedioxy)phenylmethyl bromide **38**; procedures and copies of ^{1}H and ^{13}C NMR spectra for *p*-nitrobenzoyl derivative of **23** and **16a**; X-ray crystal structures of *p*-nitrobenzoyl derivative **23a** and **31a**; procedure and copies of ^{1}H and ^{13}C NMR spectra for oxidation of THF **23**; NMR data comparison of **1** with literature values. This material is available free of charge via the Internet at http://pubs.acs.org.

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