# Asymmetric Synthesis of Sesaminone: Confirmation of Its Structure and Determination of Its Absolute Configuration

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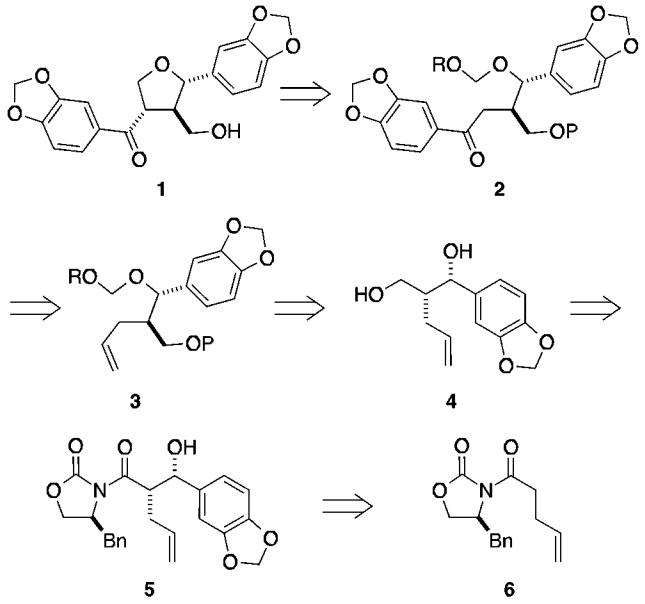
An asymmetric synthesis of the naturally occurring antipode of the tetrahydrofuran lignan sesaminone ((−)-**1**) has been achieved. An X-ray crystal structure of the synthetic material validated the structure proposed in the literature for this lignan. Additionally, the absolute configuration of the natural product was established by correlation of the synthetic tetrahydrofuran with the known absolute configuration of L-Phe. The opening of the synthesis was a diastereoselective Evans aldol reaction between *N*-4-pentenoyloxazolidinone **6** and piperonal. Reduction of the major diastereomer of the aldol product provided enantiomerically pure diol **4**. The primary and secondary hydroxyl groups of **4** were protected in tandem to generate silyl ether-MOM ether **9**. The vinyl group contained in **9** was then elaborated, via a series of four steps, to aryl ketone **10**. This aryl ketone was transformed to a mixture of silyl enol ether stereoisomers (**11a**,**b**); $TiCl_4$-mediated activation of the MOM ethers contained in this mixture of enol ethers yielded tetrahydrofuran **12** as the major product. Treatment of **12** with fluoride provided synthetic (−)-**1**.

The lignan class of natural products comprises a wide variety of structures and has furnished a number of compounds with useful therapeutic profiles.[1] Nakayama *et al.* disclosed in 1994 the isolation, determination of the structure, and antibiotic profile of the previously unknown tetrahydrofuran lignan sesaminone (**1**).[2] Sesaminone (**1**) was isolated from a culture of *Streptomyces* sp. IT-44. The basic structure of **1** was elucidated by a combined spectral analysis and its relative stereochemistry was assigned based on $^1$H NMR NOE experiments. An absolutely unequivocal structure assignment for sesaminone was not possible at that time because the material obtained from the bacterial culture was not crystalline. Screening of **1** against a group of microorganisms revealed micromolar activity against *Enterococcus faecium*. As a result of our interest in the synthesis of biologically active natural products, we selected **1** as a target for asymmetric synthesis seeking additionally to verify its proposed structure and to determine its absolute configuration.

Our retrosynthetic analysis of sesaminone (**1**) is outlined in Scheme 1. The tetrahydrofuran ring of **1** was deconstructed initially to give alkoxymethyl ether **2**; it was our hope that the alkoxymethyl ether in **2** could be activated to generate a methylene oxonium ion, or a functional equivalent thereof, that would be attacked intramolecularly by an enol derivative of the aryl ketone moiety to yield the heterocycle.[3] We expected the relative stereochemistry of the substituents at C-3 and C-4 of the furan produced in this cyclization to be governed ultimately by the thermodynamic preference[4] for a *trans* relationship between vicinal substituents on furans rather than by the configuration of the intermediate enol derivative contained in the starting material for the cyclization. The aryl ketone functional group of **2** was

**Scheme 1**




anticipated to be accessible, via a series of standard transformations, from the vinyl group resident in **3**. Olefin **3** was viewed simply as a differentially protected form of enantiomerically pure diol **4**. Enantiomerically

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(1) (a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207. (b) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (c) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499. (d) Ayres, D. C.; Loike, J. D. *Chemistry and Pharmacology of Natural Products: Lignans; Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990. (d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183.

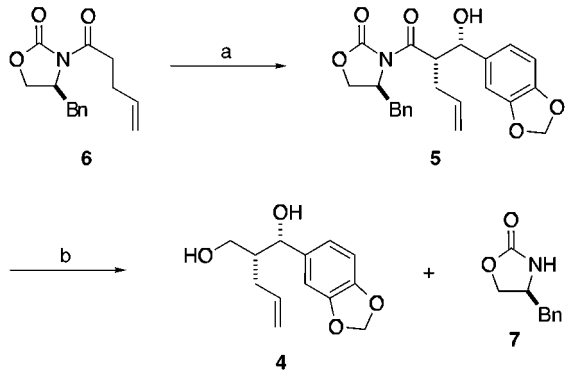
(2) Chiung, Y.-M.; Hayashi, H.; Matsumoto, H.; Otani, T.; Yoshida, K.; Huang, M.-Y.; Chen, R.-X.; Liu, J.-R.; Nakayama, M. *J. Antibiot.* **1994**, *47*, 487.

(3) For entry into the literature on the formation of carbon−carbon bonds utilizing acetals as a source of electrophilic carbon and the mechanisms of these reactions, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 5. (b) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (c) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (d) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (e) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (f) Denmark, S. E.; Almstead, N. *J. Org. Chem.* **1991**, *56*, 6458. (g) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354. (h) Denmark, S. E.; Almstead, N. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (i) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997. (j) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (k) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.

(4) For examples of this preference in systems where one of the vicinal stereocenters has been equilibrated via an enolate to give the *trans* product as the major diastereomer, see: (a) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707. (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.

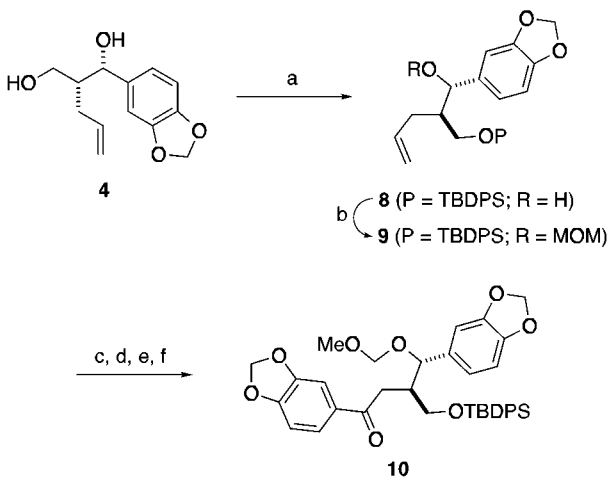
S0022-3263(97)01027-X CCC: $14.00 

**Scheme 2**[a]




[a](a) $Bu_2BOTf$, $CH_2Cl_2$, 0 °C; $Et_3N$, 0 to -78 °C; piperonal; 82%. (b) $LiBH_4$ (1 equiv), $H_2O$ (1 equiv), THF, 0 °C; **4**, 82%; **7**, 73%.

**Scheme 3**[a]




[a](a) TBDPSCl, imidazole, THF; 87%. (b) MOMCl, $Et_3N$, $CH_2Cl_2$; 98%. (c) $OsO_4$, NMO, *t*-BuOH, $H_2O$, THF; 97%. (d) $NaIO_4$, $H_2O$, THF, 0 °C; 86%. (e) 5-Lithio-1,3-benzodioxole, THF, -78 to 0 °C; 85%. (f) $MnO_2$, $CH_2Cl_2$; 90%.

pure diol **4** was certain to be available via Evans' asymmetric aldol technology[5] from *N*-4-pentenoyloxazolidinone[6] **6** and piperonal.

## Results and Discussion

An Evans asymmetric aldol reaction between acyloxazolidinone **6** and piperonal produced a mixture, apparently comprising only two diastereomers, of aldol adducts with greater than 19:1 diastereoselectivity based on $^1$H NMR spectra of the crude reaction mixture; diastereomerically pure **5** was obtained from this crude mixture in 82% yield based on **6** (Scheme 2). Reduction of aldol adduct **5** with lithium borohydride in the presence of stoichiometric water[7] produced enantiomerically pure diol **4** in 82% yield and oxazolidinone **7** in 73% yield.

Diol **4** was then elaborated, in two steps and 85% overall yield, to silyl ether−MOM ether **9** (Scheme 3). The MOM ether contained in **9** was to play the role of protecting group for the next five steps in the synthesis; in the penultimate step of the synthesis, the latent oxonium ion character of the MOM ether would be exploited to construct the furan ring contained in **1**. Silyl ether−MOM ether **9** was converted to aryl ketone **10** in four steps and 64% overall yield.

Aryl ketone **10** was then transformed utilizing conditions developed by Mander[8] to a mixture of silyl enol ethers **11a** and **11b** (**11a**:**11b** = 7:1 based on $^1$H NMR spectra of the mixture; the configurations of the individual enol ether isomers have not been assigned[9]) in 85% yield (Scheme 4). In accord with previous disclosures by Linderman *et al.*,[10] treatment of enol ethers **11a**,**b** with titanium tetrachloride produced the desired *trans*,*trans*-tetrahydrofuran diastereomer **12** (63%) along with unexpected α-tetralone **13** (6%). At this point, our assignment of structure **12** to the tetrahydrofuran product of the Lewis acid-mediated cyclization rested on the known thermodynamic preference[4] for a *trans* relationship between substituents at positions 3 and 4 in the tetrahydrofuran ring system; there was no evidence of the production of additional tetrahydrofuran diastereomers in the cyclization reaction.

α-Tetralone **13** may arise from initial Lewis acid-mediated cleavage of the benzylic carbon-oxygen bond associated with the MOM ether in **11a**,**b** to generate a stabilized benzylic cation, followed by intramolecular Friedel−Crafts alkylation of the distal 1,3-benzodioxole ring via a half-chair transition state (Scheme 5). Direct formation of tetralone **13** from ***Z*-11** is precluded by the strain energy of *trans*-cyclohexenes; tetralone **13** is apparently, therefore, derived from ***E*-11** followed by hydrolysis, upon workup, of the resulting *cis*-cyclohexene enol ether.

Because the starting material for the above Lewis acid-mediated cyclization was a mixture of enol ether isomers (**11a**:**11b** = 7:1) and because α-tetralone **13** was produced unexpectedly in this reaction, a more thorough study was completed of the fate of **11a**,**b** under these conditions. A series of painstaking chromatographic operations on **11a**,**b** provided reasonable quantities of homogeneous **11a** (the major enol ether isomer with undetermined olefinic configuration) and minute quantities of a mixture enriched in **11b** (**11a**:**11b** = 1:12). Exposure of homogeneous **11a** to the cyclization conditions gave **12** (70%) and **13** (7%) (see Table 1); this result corresponds within experimental error to the outcome of the cyclization beginning with **11a**,**b** (**11a**:**11b** = 7:1), available directly from ketone **10**. Treatment with $TiCl_4$ of the mixture of silyl enol ethers enriched in **11b** (**11a**:**11b** = 1:12), on the other hand, gave **12** (57%), **13** (11%), and a small amount of ketone **10** (6%). Treatment of ketone **10** with $TiCl_4$ under identical conditions produced neither tetrahydrofuran **12** nor tetralone **13**.

As outlined above, only ***E*-11** would be expected to be capable of producing tetralone **13**; because tetralone **13** was produced from enol ethers **11a**,**b**, independent of the initial ratio **11a**:**11b**, enol ethers **11a** and **11b** must interconvert under the reaction conditions (see Scheme 6). On the other hand, **11a**,**b** enriched in **11b** gave a

(5) For a general review and a checked experimental procedure, see: (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

(6) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525.

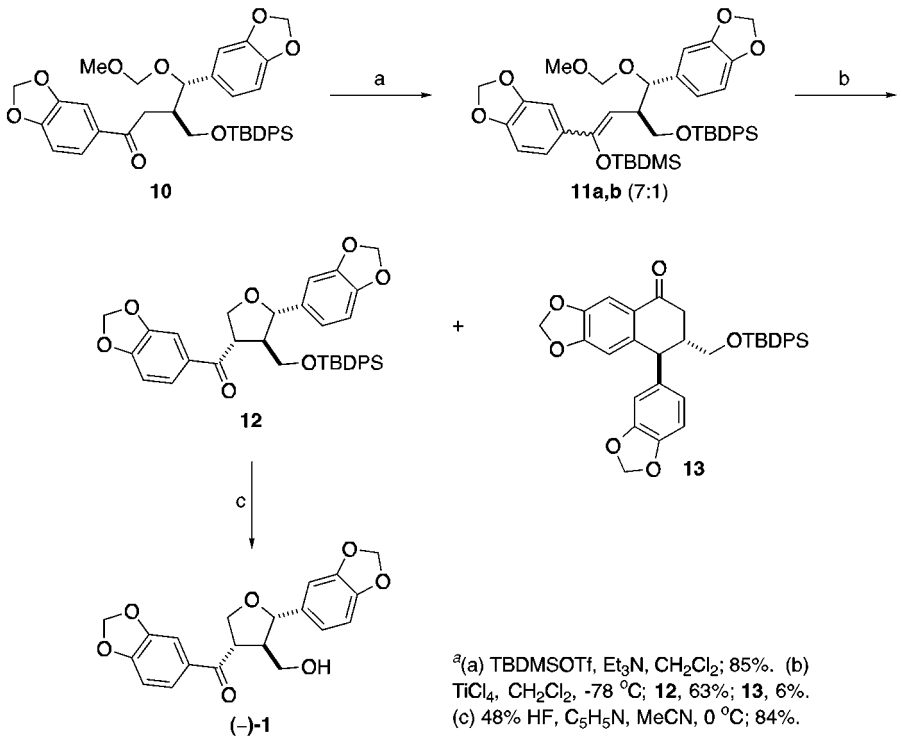
(7) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

(8) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.

(9) Various aryl ketones have been converted under similar reaction conditions to mixtures of TBDMS enol ethers enriched in the *Z* stereoisomer, see: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399.

(10) (a) Linderman, R. J.; Godfrey, A. *J. Am. Chem. Soc.* **1988**, *110*, 6249. (b) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438. (c) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078.

**Scheme 4**[a]




[a](a) TBDMSOTf, $Et_3N$, $CH_2Cl_2$; 85%. (b) $TiCl_4$, $CH_2Cl_2$, -78 °C; **12**, 63%; **13**, 6%. (c) 48% HF, $C_5H_5N$, MeCN, 0 °C; 84%.

**Scheme 5**

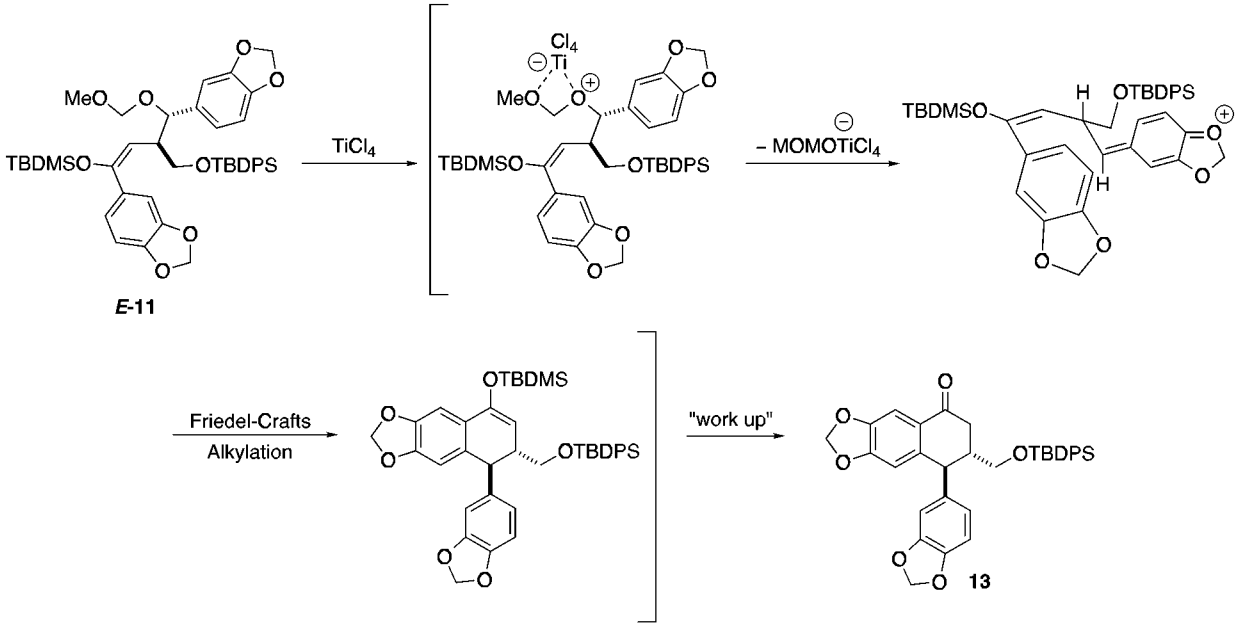


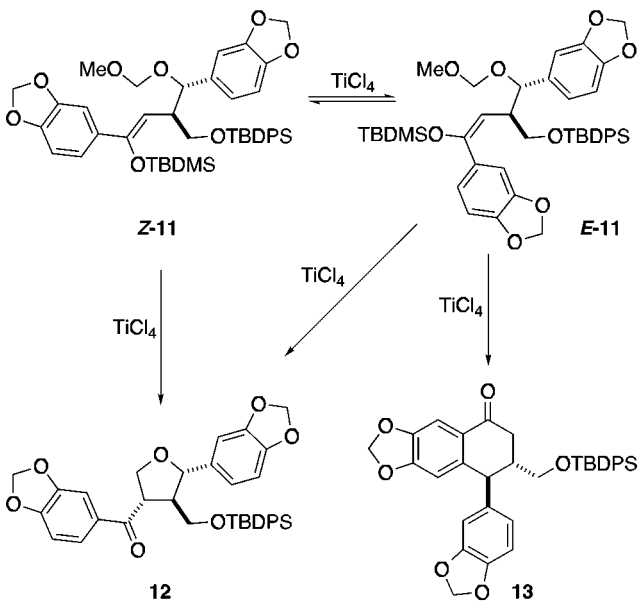

**Table 1. Isolated Yields as a Function of 11a:11b of the Products of Treatment of Enol Ethers 11a,b with $TiCl_4$**

| | % yield | | |
|---|---|---|---|
| **11a:11b** | **10** | **12** | **13** |
| 7:1 | 0 | 63 | 6 |
| 1:0 | 0 | 70 | 7 |
| 1:12 | 6 | 57 | 11 |

greater proportion of **13** (**12**:**13** = 5:1) than was obtained from either **11a**,**b** enriched in **11a** (**12**:**13** = 10:1) or homogeneous **11a** (**12**:**13** = 10:1); the equilibration of ***E*-11** and ***Z*-11** is not sufficiently rapid, therefore, to completely obscure the initial composition of enol ethers **11a**,**b**. On the basis of our results and the precedent of Snider *et al.*,[9] we have tentatively assigned the *Z*-configuration to the major enol ether (**11a**) obtained from exposure of ketone **10** to Mander's conditions.

Treatment of tetrahydrofuran **12** with aqueous fluoride yielded synthetic (−)-sesaminone ((−)-**1**) in 84% yield. Synthetic **(−)-1** displayed optical [$[\alpha]^{21}_D = -25$ (*c* 0.11, MeOH); lit.[2] $[\alpha]^{25}_D = -25.0$ (*c* 0.140, MeOH)] and spectroscopic characteristics identical to those reported for the natural product. Synthetic (−)-sesaminone was a crystalline solid (mp 133−4 °C). After substantial experimentation, a suitable crystal of **(−)-1** was grown and an X-ray crystal structure was obtained that unequivocally confirmed the structure and relative stereochemistry of the lignan.[11] This work constitutes the first synthesis of the novel lignan sesaminone ((−)-**1**), verifies the structure proposed in the literature for this com-

**Scheme 6**




pound, and establishes for the first time the absolute configuration of the natural product.

## Experimental Section

**Aldol Adduct 5.** Freshly prepared dibutylboron triflate (5.3 mL, 21 mmol) was added dropwise over 10 min to a solution of acyloxazolidinone[6] **6** (4.6 g, 18 mmol) in freshly distilled $CH_2Cl_2$ (40 mL) at 0 °C, followed by dropwise addition of triethylamine (3.2 mL, 23 mmol) over 10 min. After cooling of the solution to −78 °C, a solution of piperonal (3.2 g, 21 mmol) in freshly distilled $CH_2Cl_2$ (12 mL) was added dropwise over 10 min and the resulting mixture was stirred for 20 min at −78 °C. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched at 0 °C by the addition of pH 7 phosphate buffer (19 mL), MeOH (58 mL), and 2:1 MeOH−30% $H_2O_2$ (57 mL) and stirred for 1 h. The organic solvents were removed under reduced pressure, and the resulting slurry was extracted with $CH_2Cl_2$. The combined organic layers were washed with 5% aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by $SiO_2$ flash chromatography (6:1 hexane−EtOAc) to yield aldol adduct **5** (5.9 g, 15 mmol, 82%): $[\alpha]^{22}_D = +70$ (*c* 0.34, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.16−7.35 (m, 5H), 6.93 (d, $J$ = 1.6 Hz, 1H), 6.86 (dd, $J$ = 8.0, 1.7 Hz, 1H), 6.76 (d, $J$ = 8.0 Hz, 1H), 5.94−5.76 (m, 3H), 5.10 (d, $J$ = 17.9 Hz, 1H), 5.03 (d, $J$ = 10.1 Hz, 1H), 4.94 (d, $J$ = 5.6 Hz, 1H), 4.59−4.49 (m, 1H), 4.45−4.39 (m, 1H), 4.08 (dd, $J$ = 9.1, 2.6 Hz, 1H), 4.00−3.95 (m, 1H), 3.25 (dd, $J$ = 13.3, 3.3 Hz, 1H), 2.76 (br s, OH), 2.71−2.58 (m, 3H), 2.54−2.44 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.6, 153.1, 147.6, 147.1, 135.2, 135.2, 129.4, 128.9, 127.3, 119.6, 117.3, 108.0, 107.0, 101.0, 74.0, 65.9, 55.5, 47.2, 38.0, 31.9; IR (neat) 3512, 1779, 1695 cm$^{-1}$.

**1,3-Diol 4.** To a mixture of aldol adduct **5** (5.9 g, 15 mmol), water (0.29 mL, 16 mmol), and diethyl ether (290 mL) at 0 °C was added $LiBH_4$ (8.0 mL, 16 mmol, 2.0 M in THF) over 2 min. After 75 min, the reaction mixture was quenched by the addition of 1 N NaOH (175 mL) at 0 °C and allowed to stir for an additional 20 min. The aqueous layer was separated and extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatography (2:1 hexane−EtOAc) to give oxazolidinone **7** (1.9 g, 11 mmol, 73%) and 1,3-diol **4** (2.8 g, 12 mmol, 82%): $[\alpha]^{24}_D = -28$ (*c* 0.12, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.87 (s, 1H), 6.80 (s, 2H), 5.96 (s, 2H), 5.83−5.67 (m, 1H), 5.09−5.00 (m, 1H), 4.89 (d, $J$ = 4.4 Hz, 1H), 3.71−3.64 (m, 2H), 2.91 (br s, 1H), 2.13−2.08 (m, 2H), 2.00−1.95 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 147.6, 146.7, 136.8, 136.3, 119.4, 116.5, 107.9, 106.8, 100.9, 76.1, 63.5, 46.2, 30.1; IR (neat) 3373, 1640 cm$^{-1}$.

**TBDPS Monoprotected Diol 8.** A solution of 1,3-diol **4** (2.8 g, 12 mmol), imidazole (1.8 g, 26 mmol), and *tert*-butyldiphenylsilyl chloride (3.2 g, 12 mmol), in freshly distilled THF (80 mL), was stirred at room temperature for 5.25 h. After removing the bulk of the THF under reduced pressure, $Et_2O$ (200 mL), $H_2O$ (35 mL), and brine (100 mL) were added to the resulting slurry. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$. All organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatography (25:1 hexane−EtOAc) to give TBDPS monoprotected diol **8** (5.0 g, 10 mmol, 87%): $[\alpha]^{21}_D = +8$ (*c* 0.30, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70−7.64 (m, 4H), 7.47−7.36 (m, 6H), 6.87 (br s, 1H), 6.81−6.73 (m, 2H), 5.93, (s, 2H), 5.65−5.49 (m, 1H), 5.00−4.85 (m, 3H), 3.71−3.70 (m, 2H), 3.70−3.61 (m, 2H), 3.37 (br s, 1H), 2.18−2.13 (m, 2H), 1.95−1.83 (m, 1H), 1.10 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 147.5, 146.4, 136.8, 136.7, 135.6, 135.5, 132.8, 132.7, 129.8, 129.8, 127.7, 127.6, 119.4, 116.3, 107.8, 106.8, 100.8, 75.6, 64.7, 46.8, 29.4, 26.9, 19.1; IR (neat) 3466, 1638 cm$^{-1}$.

**MOM Ether 9.** A solution of TBDPS monoprotected diol **8** (4.8 g, 10 mmol), methoxymethyl chloride (2.3 mL, 30 mmol), and diisopropylethylamine (5.0 mL, 30 mmol) in $CH_2Cl_2$ (51 mL) was stirred at room temperature for 21 h. To this solution was added 10% aqueous citric acid (200 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatography (10:1 hexane−EtOAc) to give MOM ether **9** (5.1 g, 9.8 mmol, 98%): $[\alpha]^{21}_D = -99$ (*c* 0.37, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.61−7.297 (m, 10H), 6.74 (s, 1H), 6.68 (s, 2H), 5.92 (s, 2H), 5.70−5.56 (m, 1H), 4.95−4.86 (m, 2H), 4.69 (d, $J$ = 7.6 Hz, 1H), 4.49 (ABq, $J$ = 6.6 Hz, 2H), 3.54 (dd, $J$ = 10.4, 5.0 Hz, 1H) 3.40−3.34 (m, 4H), 2.52−2.39 (m, 1H), 2.32−2.21 (m, 1H), 1.86−1.70 (m, 1H), 1.05 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 147.6, 146.8, 137.1, 135.6, 135.6, 134.4, 133.5, 129.5, 129.4, 127.5, 127.4, 121.3, 116.0, 107.7, 107.5, 100.8, 94.2, 77.5, 62.1, 55.8, 47.6, 30.9, 26.9, 19.2; IR (neat) 1640, 1112, 1034 cm$^{-1}$.

**1,2-Diol 14.** A solution of MOM ether **9** (5.1 g, 9.8 mmol), *N*-methylmorpholine *N*-oxide (1.4 g, 12 mmol), $OsO_4$ (0.88 mmol in 13 mL *t*-BuOH), THF (20 mL), *t*-BuOH (50 mL), and $H_2O$ (4.5 mL) was stirred at room temperature for 5.5 h, after which it was diluted with 0.2 M aqueous $NaHSO_3$ (300 mL) at 0 °C. The mixture was extracted with $CH_2Cl_2$, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatoghaphy (5:1 hexane−EtOAc) to give 1,2-diol **14** (5.1 g, 9.5 mmol, 97%) as an inseparable mixture (∼1:1) of two diastereomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.62−7.31 (m, 10H), 6.58−6.74 (m, 3H), 5.92 (s, 2H), 4.56−4.42 (m, 3H), 3.75−3.28 (m, 9H), 2.3 (br s, 1H), 2.09−1.50 (m, 3H), 1.06 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 147.8, 147.7, 147.1, 147.0, 135.6, 135.5, 133.8, 133.7, 133.1, 133.0, 132.9, 132.8, 129.8, 129.7, 127.7, 127.6, 121.4, 120.9, 107.9, 107.8, 107.3, 107.1, 100.9, 94.1, 93.8, 78.5, 78.4, 70.9, 70.5, 67.2, 66.8, 65.5, 64.2, 56.0, 56.0, 45.4, 44.5, 32.4, 31.9, 26.9, 26.8, 19.2, 19.1; IR (neat) 3425, 1113, 1038 cm$^{-1}$.

**Aldehyde 15.** To a solution of 1,2-diol **14** (5.9 g, 11 mmol) in 2:1 THF−$H_2O$ (91 mL) at 0 °C was added $NaIO_4$ (3.1 g, 14 mmol) and the mixture was allowed to stir for 6.5 h under $N_2$. The reaction was diluted with $H_2O$ (50 mL) and washed with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatography (4:1 hexane−EtOAc) to give aldehyde **15** (4.8 g,

(11) The authors have deposited atomic coordinates for structure **1** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, U. K.

9.2 mmol, 86%): $[\alpha]^{21}_D = -99$ (*c* 0.73, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.69 (m, 1H), 7.61−7.29 (m, 10H), 6.72 (s, 1H), 6.66 (s, 2H), 4.58 (d, $J$ = 8.3 Hz, 1H), 4.42 (ABq, $J$ = 6.6 Hz, 2H), 3.51 (dd, $J$ = 10.2, 4.2 Hz, 1H), 3.40 (dd, $J$ = 10.2, 5.6 Hz, 1H), 3.30 (s, 3H), 2.71 (ddd, $J$ = 16.7, 6.6, 2.6 Hz, 1H), 2.59 (ddd, $J$ = 16.7, 6.2, 1.7 Hz, 1H), 2.53−2.41 (m, 1H), 1.04 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 201.9, 147.9, 147.2, 135.5, 133.4, 133.1, 133.0, 129.7, 127.6, 121.3, 107.9, 107.2, 101.0, 93.8, 77.4, 63.1, 55.9, 43.6, 43.3, 26.8, 19.8; IR (neat) 2824, 2724, 1724 $cm^{-1}$.

**Secondary Alcohol 16.** To a solution of 4-bromo-1,2-(methylenedioxy)benzene (1.0 mL, 8.5 mmol) in freshly distilled THF (85 mL) at −78 °C was added *tert*-butyllithium (1.7 M in pentane, 10 mL, 17 mmol) dropwise over a 2 min period and the resulting mixture was allowed to stir for 20 min. A solution of aldehyde **15** (4.4 g, 8.4 mmol) in THF (85 mL) was added via cannula over 30 min. After being stirred for 1 h at −78 °C, the reaction mixture was allowed to stir at room temperature for 2.5 h, and was then quenched by the addition of saturated aqueous $NH_4Cl$ (30 mL). After removing the bulk of the THF under reduced pressure, the resulting slurry was extracted with $CH_2Cl_2$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by $SiO_2$ flash chromatography (10:1 hexane−EtOAc) to give secondary alcohol **16** (4.6 g, 7.2 mmol, 85%) as an inseparable mixture (∼1:1) of two diastereomers: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.66−7.30 (m, 10H), 6.78−6.55 (m, 4H), 5.96−5.91 (m, 4H) 4.65−4.48 (m, 4H), 3.56−3.10 (m, 6H), 2.14−1.92 (m, 2H), 1.90−1.78 (m, 1H), 1.10−0.98 (m, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 147.7, 147.6, 147.5, 147.1, 146.9, 146.4, 139.4, 138.7, 135.6, 135.6, 134.1, 133.8, 133.2, 133.1, 129.7, 129.6, 127.6, 127.6, 121.3, 120.9, 119.2, 107.8, 107.8, 107.3, 107.2, 106.3, 106.3, 100.8, 94.2, 93.9, 78.5, 78.1, 72.9, 72.6, 64.9, 64.4, 56.0, 45.0, 44.9, 38.5, 37.3, 26.9, 19.2; IR (neat) 3433, 1609, 1111, 1038 $cm^{-1}$.

**Ketone 10.** $MnO_2$ (25 g, 288 mmol) was added to a solution of secondary alcohol **16** (4.6 g, 7.2 mmol) in $CH_2Cl_2$ (90 mL) at room temperature and the resulting slurry was stirred for 19 h. The mixture was then filtered through a plug of Celite using $CH_2Cl_2$ as eluant. The filtrate was concentrated under reduced pressure to give an oil that was purified by $SiO_2$ flash chromatography (5:1 hexane−EtOAc) to give ketone **10** (4.2 g, 6.5 mmol, 90%): $[\alpha]^{25}_D = -74$ (*c* 0.61, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.57−7.20 (m, 12H), 6.80 (d, $J$ = 1.5 Hz, 1H), 6.79 (d, $J$ = 8.0 Hz, 1H), 6.73 (dd, $J$ = 8.0, 1.5 Hz, 1H), 6.68 (d, $J$ = 8.0 Hz, 1H), 6.02 (m, 2H), 5.93 (m, 2H), 4.78 (d, $J$ = 7.8 Hz, 1H), 4.48 (ABq, $J$ = 6.6 Hz, 2H), 3.62 (dd, $J$ = 10.3, 4.6 Hz, 1H), 3.44 (dd, $J$ = 10.3, 4.2 Hz, 1H), 3.31 (s, 3H), 3.22 (dd, $J$ = 17.0, 4.6 Hz, 1H), 3.13 (dd, $J$ = 17.0, 8.1 Hz, 1H), 2.68−2.56 (m, 1H), 1.04 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.4, 151.3, 148.0, 147.8, 147.0, 135.5, 134.1, 133.3, 132.2, 129.5, 127.5, 124.1, 121.4, 108.0, 107.8, 107.7, 107.5, 101.7, 100.9, 94.3, 77.5, 63.0, 55.9, 44.0, 35.9, 26.9, 19.2; IR (neat) 1677, 1605 $cm^{-1}$.

**Silyl Enol Ethers 11a,b.** To a solution of ketone **10** (557 mg, 868 $\mu$mol) and triethylamine (1.2 mL, 8.7 mmol) in $CH_2Cl_2$ (4.4 mL) was added *tert*-butyldimethylsilyl triflate (300 $\mu$L, 1.3 mmol) at room temperature. After being stirred for 2.5 h, the reaction mixture was diluted with diethyl ether (50 mL) and washed with 5% $NaHCO_3$ and $H_2O$. The organic extracts were concentrated under reduced pressure to give an oil which was purified by $SiO_2$ flash chromatography (70:1 hexane−EtOAc) to give silyl enol ethers **11a**,**b** (558 mg, 738 $\mu$mol, 85%) as a mixture of double bond isomers (7:1 by $^1H$ NMR). **11a** (major enol ether isomer): $[\alpha]^{22}_D = -106$ (*c* 0.31, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.68−7.58 (m, 5H), 7.41−7.26 (m, 6H), 6.86−6.55 (m, 5H), 5.94−5.91 (m 4H), 5.03 (d, $J$ = 10.1 Hz, 1H), 4.98 (d, $J$ = 4.6 Hz, 1H), 4.50 (ABq, $J$ = 6.6 Hz, 2H), 3.73 (dd, = 9.7, 7.2 Hz, 1H), 3.52 (dd, $J$ = 9.7, 4.9 Hz, 1H), 3.26 (s, 3H), 3.23−2.96 (m, 1H), 1.07 (s, 9H), 0.86 (s, 9H), −0.25 (s, 3H), −0.30 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 151.2, 147.5, 147.1, 147.0, 146.7, 135.7, 135.6, 135.5, 134.5, 134.5, 129.5, 127.5, 127.5, 121.0, 120.7, 120.1, 107.8, 107.7, 107.6, 107.5, 100.9, 100.8, 94.5, 77.3, 64.2, 55.7, 46.1, 26.9, 25.8, 18.1; IR (neat) 1650, 1608 $cm^{-1}$.

**TBDPS-Protected Sesaminone 12 and α-Tetralone 13.** To a solution of silyl enol ethers **11a**,**b** (193 mg, 255 $\mu$mol) in $CH_2Cl_2$ (2 mL) at −78 °C was added $TiCl_4$ (85 $\mu$L, 760 $\mu$mol). After being stirred for 2.5 h, the reaction was quenched by the addition of MeOH (2 mL), followed by saturated aqueous $NaHCO_3$ (2 mL) at −78 °C and was then stirred until the mixture reached room temperature. The solution was then diluted with $Et_2O$ (60 mL) and washed with $H_2O$. The combined aqueous layers were washed with $Et_2O$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil that was purified by $SiO_2$ flash chromatography (40:1 hexane−EtOAc) to give two compounds, protected sesaminone **12** (98 mg, 161 $\mu$mol, 63%) and α-tetralone **13** (8.5 mg, 14 $\mu$mol, 6%). Protected sesaminone **12**: $[\alpha]^{24}_D = +17$ (*c* 0.16, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.63−7.26 (m, 12H), 6.84−6.82 (m, 2H), 6.69 (d, $J$ = 8.1 Hz, 1H), 6.63 (dd, $J$ = 8.1, 1.5 Hz, 1H), 6.07 (m, 2H), 5.93 (s, 2H), 4.77 (d, $J$ = 8.8 Hz, 1H), 4.25−4.18 (m, 3H), 3.77 (dd, $J$ = 10.7, 3.9 Hz, 1H), 3.68 (dd, $J$ = 10.7, 3.9 Hz, 1H), 2.80−2.70 (m, 1H), 1.07 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.1, 152.0, 148.4, 147.8, 147.2, 135.7, 135.5, 134.6, 133.1, 133.0, 131.6, 129.9, 129.8, 127.8, 127.7, 124.8, 120.3, 108.3, 107.9, 107.9, 107.2, 101.9, 100.9, 100.9, 83.3, 71.0, 61.3, 52.9, 48.9, 26.8, 19.3; IR (neat) 1674, 1604 $cm^{-1}$. α-Tetralone **13**: $[\alpha]^{21}_D = +23$ (*c* 0.26, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.59−7.25 (m, 11H), 6.72 (d, $J$ = 7.8 Hz, 1H), 6.58 (dd, $J$ = 7.8, 1.6 Hz, 1H), 6.50 (d, $J$ = 1.6 Hz, 1H), 6.31 (s, 1H), 5.98−5.90 (m, 4H), 4.22 (d, $J$ = 8.8 Hz, 1H), 3.52 (dd, $J$ = 10.3, 4.4 Hz, 1H), 3.46 (dd, $J$ = 10.3, 6.1 Hz, 1H), 2.80−2.71 (m, 2H), 2.44−2.31 (m, 1H), 1.04 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 196.4, 152.3, 148.0, 147.0, 146.5, 143.1, 136.3, 135.5, 133.2, 133.0, 129.7, 129.6, 127.7, 127.6, 127.4, 122.7, 109.3, 108.9, 108.2, 105.6, 101.7, 101.0, 64.6, 46.9, 44.9, 40.3, 26.9, 19.3; IR (neat) 1673, 1617 $cm^{-1}$.

**(−)-Sesaminone ((−)-1).** 48% aqueous HF (1.2 mL) was added dropwise to a stirred solution of protected sesaminone **12** (49.0 mg, 80.0 $\mu$mol) and pyridine (1.1 mL) in $CH_3CN$ (9 mL) at 0 °C. The mixture was allowed to warm to ambient temperature overnight and stirred for a total of 24 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (12 mL). After gas evolution ceased, the mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give an oil which was purified by $SiO_2$ flash chromatography (15:1 to 2:1 petroleum ether−EtOAc) to give (−)-sesaminone **(−)-1** (25.1 mg, 67 $\mu$mol, 84%): mp 133−134 °C; $[\alpha]^{21}_D = -25$ (*c* 0.11, MeOH) [lit.[2] $[\alpha]^{25}_D = -25.0$ (*c* 0.140, MeOH)]; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.58 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.47 (d, $J$ = 1.7 Hz, 1H), 6.97 (d, $J$ = 1.6 Hz, 1H), 6.88 (d, $J$ = 8.1 Hz, 1H), 6.85 (dd, $J$ = 8.0, 1.6 Hz, 1H), 6.77 (d, $J$ = 8.0 Hz, 1H), 6.06 (s, 2H), 5.95 (s, 2H), 4.67 (d, $J$ = 9.0 Hz, 1H), 4.28 (m, 1H), 4.14 (m, 1H), 4.11 (m, 1H), 3.77 (dd, $J$ = 10.8, 4.5 Hz, 1H), 3.66 (dd, $J$ = 10.8, 5.6 Hz, 1H), 2.80−2.91 (m, 1H), 1.75 (br s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.3, 152.1, 148.3, 147.9, 147.4, 134.4, 131.3, 124.9, 120.3, 108.2, 108.0, 108.0, 107.0, 102.0, 101.0, 83.6, 70.8, 61.1, 52.3, 49.8; IR (KBr) 3452, 1669, 1613 $cm^{-1}$.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR spectra for all new compounds and an ORTEP-style drawing for structure **1** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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