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TETRAHEDRON: *ASYMMETRY*

# Enantioselective synthesis of the PAF antagonist MK-287

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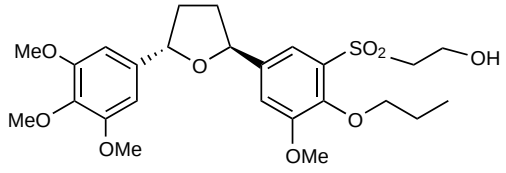
**Abstract**—Following a general method of synthesis of optically active 2,5-disubstituted tetrahydrofurans, an enantioselective synthesis of the PAF antagonist, MK-287 is described. 

## 1. Introduction

Platelet-activating factor (PAF), a highly potent phospholipid, is considered to play a major role in several human diseases.[1] A number of PAF antagonists are known, including non-natural *trans*-2,5-diaryl tetrahydrofurans,[2] which could be good candidates for the treatment of asthma, inflammation, ischemia or acute allergy. Of these compounds, the (–)-(2*S*,5*S*)-diastereomer of MK-287[3] appears to be a very promising therapeutic agent (Fig. 1).



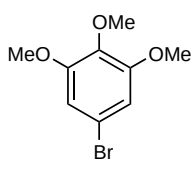

MK-287

**Figure 1.**

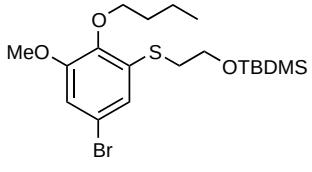
For these reasons, during the last few years, the synthesis of MK-287 and its analogs has attracted much attention.[4] We have recently reported the stereoselective synthesis of *cis*- or *trans*-2,5-diaryl tetrahydrofurans[5] and we describe in this short paper the synthesis of diastereomerically pure (2*S*,5*S*)-MK-287 as an application of this general method.[6]

## 2. Results and discussion

The use of two aryllithium reagents, prepared by reaction of *tert*-butyllithium with 1-bromo-3,4,5-trimethoxy benzene **1** or 1-bromo-3-methoxy-4-propyloxy-5-*tert*-butyldimethylsilyloxy-1′-ethylsulfobenzene **2**, respectively, was necessary to accomplish our synthesis. The aryl bromide **1** could be obtained efficiently from the corresponding aminobenzene by Sandmeyer reaction (Fig. 2).




**1**




**2**

**Figure 2.**

However, poor yields were observed when the same process was tentatively applied to the formation of bromide **2**. These results led us to find a new synthetic route, in which the bromine atom could be introduced by a radical reaction.[7] The key step involves the chemoselective substitution of 2-hydroxyethyl thiol with a compound which is both brominated and iodinated as shown in Scheme 1.

Iodovanilin **3** was treated in DMF with 1.5 equiv. of 1-bromopropane in the presence of cesium carbonate to give the *O*-alkylated aldehyde **4** in excellent yield of 96%. The aldehyde **4** was then oxidized with sodium

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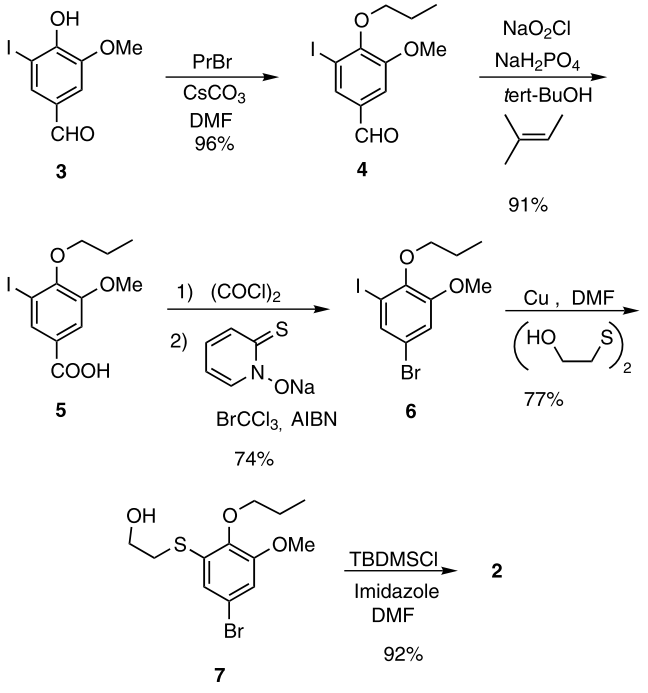
chlorite, following the method of Nilson[8] to afford the acid **5** in 91% yield. Reaction of **5** with oxalyl chloride gave rise to the corresponding acid chloride, which, without purification, was treated under Barton conditions[9] with the sodium salt of mercaptopyridine oxide in bromotrichloromethane in the presence of AIBN radical initiator. The dihalide **6** thus obtained in 74% yield was reacted with copper and 2-hydroxyethyl disulfide in DMF at 100°C for 20 h. Selective substitution of iodide afforded compound **7** in 77% yield, which after protection as its *tert*-butyldimethylsilyl ether led to the desired bromide **2** (Scheme 1).




**Scheme 1.**

The synthetic strategy for the synthesis of (2*S*,5*S*)-MK-287 is illustrated in Scheme 2: addition of the triisopropoxytitanium reagent derived from 1-bromo-3,4,5-trimethoxybenzene **1** to the optically active lactol (–)-**8**[10] afforded the unique diol stereoisomer **9** in excellent yield.[11] This diol was oxidized to the lactone **10** by reaction with 4-methoxymorpholine *N*-oxide (NMO) in the presence of tetrapropylammonium perruthenate (TPAP) at room temperature.[12] Addition to the lactone **10** of the organolithium compound arising from the reaction of **2** with *tert*-butyllithium occurred on the face opposite to the trimethoxybenzyl group to give the lactol **11**. The deoxygenation of the hemiketal **11** was carried out with sodium cyanoborohydride in the presence of dichloroacetic acid in trifluoroethanol in high yield and excellent stereoselectivity,[5] leading to the *trans*-tetrahydrofuran **12**. Flash thermolysis of **12** at 450°C gave rise to the dihydrofuran **13**, which was reduced to the tetrahydrofuran **14** under standard conditions. Oxidation of the sulfide moiety to the sulfone **15** followed by deprotection of the *tert*-butyldimethylsilyl ether led to MK-287 **16**. The *trans*-stereoisomer was obtained as the sole product, as shown by $^1$H and $^{13}$C NMR analyses and the (2*S*,5*S*)-absolute configuration and high enantiomeric purity was confirmed by comparison of the specific rotation value of the synthesized material, $[\alpha]_D^{20}$ −72.4 (*c* 1.03, MeOH) with that reported in the literature[2b] $[\alpha]_D^{20}$ −72.8 (*c* 1.0, MeOH).

## 3. Conclusion

In conclusion, we have described in this short paper an alternative and flexible route to enantiomerically pure (2*S*,5*S*)-MK-287 in eight steps from the lactol **8** (10% overall yield), which compares favorably with existing methods for the synthesis of this drug candidate.

## 4. Experimental

### 4.1. General

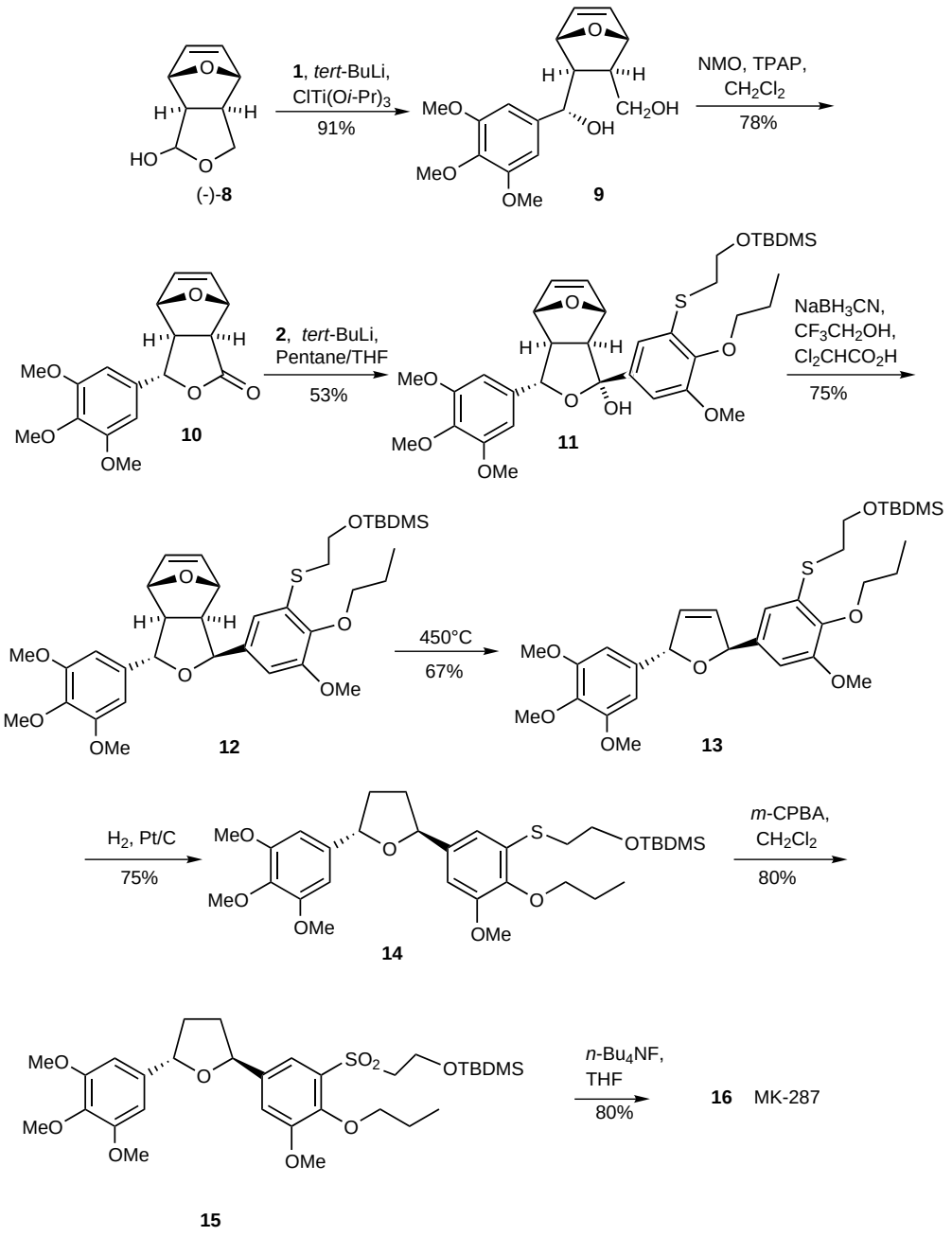
NMR spectra were recorded on a Bruker AM250 or AC200 spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Mass spectra were obtained with a GC–MS R.10-10 or a Finnigan MAT 95S spectrometer. Melting points are reported without correction. Elemental analyses were performed by the analytical center of Gif/Yvette. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silica gel 60F-254 precoated on glass.

### 4.2. 4-Propyl-5-iodovanilin, 4

To a solution of iodovanilin (2.426 g, 8.72 mmol) in DMF (10 mL) was added in one portion anhydrous cesium carbonate (3.4 g, 10.4 mmol) followed by 1-bromopropane (2 g, 13.1 mmol). The mixture was heated to 50°C and stirred for 2 h. The mixture cooled at room temperature was diluted with water (10 mL). The pH of the mixture was adjusted to 6.0 by dropwise addition of 2 M HCl, carefully controlling the release of carbon dioxide gas. The solution was then extracted with ethyl acetate (3×25 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether, 7/3) to give ether **4** (2.68 g, 96%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 1.03 (t, $J$=7.4 Hz, 3H), 1.81 (m, 2H), 3.84 (s, 3H), 4.01 (t, $J$=6.7 Hz, 2H), 7.35 (d, $J$=1.6 Hz, 1H), 7.81 (d, $J$=1.6 Hz, 1H), 9.78 (s, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 10.7, 23.7, 56.1, 75.3, 92.5, 110.9, 133.7, 134.9, 152.8, 153.7, 189.8; IR (film): 2950, 1680, 1575, 1550, 1405 cm$^{-1}$.

### 4.3. 3-Methoxy-4-propoxy-5-iodo benzoic acid, 5

4-Propyl-5-iodovanilin **4** (2.05 g, 6.4 mmol) and 2-methyl-2-butene (6.4 mL) were dissolved in *tert*-butanol (20 mL), and a solution of 80% sodium chlorite (1.45 g, 12.8 mmol) and monobasic sodium phosphate (1.15 g,




**Scheme 2.**

8.32 mmol) in water (13 mL) was added dropwise. The mixture was stirred for 4 h at room temperature. The solvent was removed in vacuo and the residue was diluted with water (40 mL). The pH of the solution was adjusted to 10 with 1 M aqueous NaOH, the aqueous phase was extracted with ether (2×20 mL). The aqueous layers were acidified to pH 2 by dropwise addition of 3 M aqueous HCl and extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. White crystals of pure acid **5** were obtained (1.97 g, 91%): mp = 139–140°C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 1.09 (t, $J$ = 7.4 Hz, 3H), 1.88 (m, 2H), 3.92 (s, 3H), 4.06 (t, $J$ = 6.7 Hz, 2H), 7.06 (d, $J$ = 1.6 Hz, 1H), 8.16 (d, $J$ = 1.6 Hz, 1H), 10.0–9.0 (s, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 10.6, 23.5, 56.0, 75.1, 92.1, 113.9, 125.9, 133.2, 151.9, 152.9, 170.8; IR (KBr): 3430, 2972, 2935, 2655, 1692, 1589, 1558, 1459, 1422, 1287 cm$^{-1}$; ESMS $m/z$ (relative intensity): 693 [2(M–1)Na$^+$, 10], 671 (2M–1, 6), 335 (M–1, 100). Anal. calcd for $C_{11}H_{13}O_4I$: C, 39.31; H, 3.90. Found: C, 39.35; H, 3.87.

### 4.4. 1-Bromo-3-methoxy-4-propoxy-5 iodobenzene, 6

To a solution of acid **5** (1.95 g, 5.80 mmol) and three drops of DMF in $CH_2Cl_2$ (50 mL) was added dropwise oxalyl chloride (950 μL, 11.6 mmol) at room temperature. The mixture was stirred for 18 h. The solvent was removed in vacuo and the residue was used directly, without purification.

To a suspension of mercaptopyridine oxide sodium salt in refluxing bromotrichloromethane (30 mL) was added dropwise (2 h) a solution of the acid chloride and AIBN (150 mg) in the same solvent (30 mL), under an inert atmosphere. After heating the mixture for a further period of 5 min, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: petroleum ether/AcOEt, 9/1) to give bromide **6** (1.6 g, 74%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 1.06 (t, $J=7.4$ Hz, 3H), 1.85 (m, 2H), 3.83 (s, 3H), 3.91 (t, $J=6.8$ Hz, 2H), 7.00 (d, $J=2.1$ Hz, 1H), 7.49 (d, $J=2.0$ Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 10.5, 23.3, 55.9, 74.6, 93.0, 115.9, 116.8, 132.0, 147.5, 152.6; IR (film): 3081, 2962, 2936, 2876, 1568, 1463, 1441, 1255, 1033 cm$^{-1}$. Anal. calcd for $C_{10}H_{12}O_2BrI$: C, 32.37; H, 3.26. Found: C, 32.37; H, 3.28%.

### 4.5. 1-Bromo-3-methoxy-4-propoxy-5-(2′-hydroxyethanesulfanyl)benzene, 7

To a solution of iodide **6** (1.5 g, 4.04 mmol) in DMF (10 mL), copper bronze (334 mg, 5.25 mmol) and 2-hydroxyethyldisulfide (334 μL, 2.92 mmol) were added at room temperature. The mixture was heated and stirred at 100°C for 20 h. The mixture was cooled to ambient temperature and ethyl acetate (60 mL) was added. The solution was stirred for 15 min and filtered through a Celite pad. The filter cake was washed with ethyl acetate (25 mL). The combined organic extracts were washed with $NH_4Cl/NH_4OH$ solution (10:1 v/v; pH 9.0, 3×20 mL) followed by water (20 mL), then were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 7/3) to afford **7** (1.0 g, 77%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 1.05 (t, $J=7.4$ Hz, 3H), 1.83 (m, 2H), 2.38 (t, $J=6.4$ Hz, 1H), 3.07 (t, $J=5.8$ Hz, 2H), 3.71 (q, $J=6.0$ Hz, 2H), 3.84 (s, 3H), 3.94 (t, $J=6.8$ Hz, 2H), 6.93 (d, $J=2.1$ Hz, 1H), 7.07 (d, $J=2.2$ Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 10.3, 23.3, 35.6, 55.9, 60.0, 74.8, 114.0, 116.4, 123.6, 131.6, 145.7, 153.2; IR (film): 3413, 3080, 2963, 2936, 2876, 1572, 1461, 1443, 1397, 1047 cm$^{-1}$; ESMS $m/z$ (relative intensity): 345 ($MNa^+$, 100), 343 ($MNa^+$, 98). Anal. calcd for $C_{12}H_{17}O_3SBr$: C, 44.87; H, 5.33; S, 9.98. Found: C, 44.96; H, 5.23; S, 9.76%.

### 4.6. 1-Bromo-3-methoxy-4-propoxy-5-(2′-*tert*-butyldimethylsilyloxyethanesulfanyl)benzene, 2

To a solution of the alcohol **7** (725 mg, 2.26 mmol) and imidazole (384 mg, 5.64 mmol) in DMF (5 mL) was added dropwise *tert*-butyldimethylsilyl chloride (381 mg, 2.49 mmol) in DMF (2 mL). The mixture was stirred at room temperature. After completion of the reaction, the mixture was diluted with ether (10 mL) and water (5 mL). The aqueous layer was extracted with ether (2×10 mL). The organic extracts were washed with brine, dried over $MgSO_4$, concentrated in vacuo. The residue was chromatographed on silica gel (eluent: petroleum ether/ether, 9/1) to give **2** (904 mg, 92%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 0.07 (s, 6H), 0.90 (s, 9H), 1.04 (t, $J=7.4$ Hz, 3H), 1.81 (m, 2H), 3.04 (t, $J=6.9$ Hz, 2H), 3.82 (t, $J=6.9$ Hz, 2H), 3.83 (s, 3H), 3.91 (t, $J=6.7$ Hz, 2H), 6.85 (d, $J=2.0$ Hz, 1H), 6.97 (d, $J=2.1$ Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: −5.4, 10.4, 18.2, 23.4, 25.8, 33.8, 56.0, 62.0, 74.3, 113.0, 116.4, 121.3, 133.7, 144.6, 153.2; IR (film): 2957, 2930, 2878, 2856, 1572, 1462, 1397, 1050 cm$^{-1}$; ESMS $m/z$ (relative intensity): 459 ($MNa^+$, 100), 457 ($MNa^+$, 96); HRESMS calcd for $C_{31}H_{31}BrSSiO_3Na^+$: 457.0845. Found: 457.0844.

### 4.7. (1*R*,2*R*,3*S*,4*S*,1′*R*)-2-Hydroxymethyl-3-hydroxymethyl[1′-(3″,4″,5″)-trimethoxyphenyl]-7-oxabicyclo-[2.2.1]hept-5-ene, 9

A solution of 1-bromo-3,4,5-trimethoxybenzene **1** (2.02 g, 10.1 mmol) in anhydrous ether (40 mL) at −78°C was treated dropwise with a solution of *tert*-butyllithium in pentane (1 M, 20.3 mL, 20.3 mmol) and the resulting mixture was stirred for 1 h at this temperature. The reaction mixture was allowed to warm to −40°C and treated dropwise with a solution of chlorotitanium triisopropoxide in hexane (1 M, 10.1 mL, 10.1 mmol). After warming to 0°C the mixture was treated dropwise with a solution of lactol **8** (0.39 g, 2.53 mmol) in anhydrous THF (25 mL). The mixture was stirred at 0°C for 30 min and at room temperature for 4 h. The mixture was then cooled again to 0°C and diluted with an aqueous solution of aqueous HCl (10% 35 mL), then stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3×30 mL). The organic extracts were combined and dried over $MgSO_4$, then concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: $CH_2Cl_2$/MeOH, 92/8). compound **9** was obtained as a white solid (0.74 g, 91%): mp 52–53°C; $[\alpha]_D^{20}=-32.7$ (*c* 1.0, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 2.07–2.10 (m, 2H), 3.62 (bs, 2H), 3.89 (s, 9H), 3.96 (d, $J=12.1$ Hz, 1H), 4.10 (d, $J=9.9$ Hz, 1H), 4.32 (s, 1H), 4.69 (s, 1H), 4.77 (d, $J=9.9$ Hz, 1H), 6.27 (dd, $J=1.5$ Hz, 5.8 Hz, 1H), 6.42 (dd, $J=1.5$ Hz, 5.8 Hz, 1H), 6.64 (s, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 42,9, 47.9, 55.4, 60.1, 62.6, 65.3, 74.0, 80.8, 81.5, 103.2, 135.3, 136.5, 138.8, 152.6; ESMS $m/z$ (relative intensity): 667 ($2MNa^+$, 100), 345 ($MNa^+$, 92).

### 4.8. (1*R*,2*S*,5*R*,6*R*,7*S*)-5-[(3′,4′,5′)-Trimethoxyphenyl]-4,10-dioxatricyclo[5.2.1.0$^{2,6}$]dec-8-en-3-one, 10

To a solution of the diol **9** (540 mg, 1.67 mmol) in anhydrous $CH_2Cl_2$ (15 mL) was added 4 Å molecular sieves (0.8 g) and NMO (590 mg, 5.01 mmol). After stirring for 10 min, TPAP (17 mg, 0.05 mmol) was added and the mixture was stirred at room temperature for 5 h. The reaction mixture was filtered through a short column of silica gel and washed with AcOMe (200 mL). The filtrate was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 3/7) to give a white solid (0.416 g, yield 78%): mp 127–130°C; $[\alpha]_D^{20}=-95.0$ (*c* 1.0, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 2.67 (dd, $J=3.6$ Hz, 7.7 Hz, 1H), 3.02 (d, $J=7.7$ Hz, 1H), 3.82 (s, 3H), 3.90 (s,

6H), 5.21 (d, $J=1.3$ Hz, 1H), 5.28 (d, $J=3.6$ Hz, 1H), 5.39 (s, 1H), 6.45 (dd, $J=1.6$ Hz, 5.6 Hz, 1H), 6.50 (s, 2H), 6.52 (dd, $J=1.0$ Hz, 5.9 Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: 48.2, 50.3, 55.9, 60.5, 81.7, 83.5, 84.2, 101.9, 135.9, 136.1, 136.4, 137.6, 153.3, 174.9; IR (KBr): 3076, 2968, 1764, 1593 cm$^{-1}$; ESMS $m/z$ (relative intensity): 659 (2MNa$^+$, 100), 341 (MNa$^+$, 51). Anal. calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.95; H, 5.61%.

### 4.9. (1*R*,2*S*,3*R*,5*S*,6*R*,7*S*)-4,10-Dioxa-3-[3″-methoxy-5″-(2‴-*t*-butyldimethylsilyloxyethanesulfanyl)-4″-propoxy]-5-(3′,4′,5′-trimethoxyphenyl)-tricyclo(5.2.1.0$^{2,6}$]dec-8-en-3-ol, 11

To a solution of bromide **2** (620 mg, 1.42 mmol) in pentane (4 mL) at −78°C was added dropwise a solution of *tert*-butyllithium 1.4 M (1.5 mL, 2.135 mmol). The mixture was stirred for 30 min then treated dropwise with a solution of lactone **10** (318 mg, 1 mmol) in THF anhydrous (4 mL). The mixture was stirred for 30 min at −78°C then quenched with saturated aqueous $NH_4Cl$ solution (10 mL) and allowed to warm to room temperature. After extraction with ether (3×20 mL, the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 6/4) to give lactol **11** (357 mg, 53%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 0.04 (s, 6H), 0.86 (s, 9H), 1.06 (t, $J=7.4$ Hz, 3H), 1.84 (m, 2H), 2.70 (dd, $J=7.8$, 8.5 Hz, 1H), 2.87 (d, $J=8.8$ Hz, 1H), 3.10 (t, $J=7.1$ Hz, 2H), 3.82 (t, $J=7.0$ Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.91 (s, 6H), 3.96 (t, $J=6.8$ Hz, 2H), 4.80 (d, $J=7.6$ Hz, 1H), 4.94 (s, 1H), 5.14 (s, 1H), 5.15 (s, 1H), 6.38 (m, 1H), 6.41 (m, 1H), 6.72 (s, 2H), 7.16 (d, $J=1.7$ Hz, 1H), 7.28 (d, $J=1.6$ Hz, 1H); IR (film): 3453, 3084, 2958, 2936, 2881, 2857, 2250, 1737, 1593, 1463, 1129 cm$^{-1}$; ESMS $m/z$ (relative intensity): 698 (MHNa$^+$, 45), 697 (MNa$^+$, 100); HRESMS calcd for $C_{35}H_{50}O_9SSiNa^+$: 697.2842. Found: 697.2842.

### 4.10. (1*R*,2*S*,3*S*,5*S*,6*R*,7*S*)-4,10-Dioxa-3-[3″-methoxy-5″-(2-*t*-butyldimethylsilyloxyethanesulfanyl)-4″-propoxy]-5-(3′,4′,5′-trimethoxyphenyl)-tricyclo[5.2.1.O$^{2,6}$]dec-8-ene, 12

To a solution of lactol **11** (355 mg, 0.526 mmol) and $NaBH_3CN$ (99 mg, 1.58 mmol) in anhydrous 2,2,2-trifluoroethanol (9 mL) was added dropwise dichloroacetic acid (130 μL, 1.58 mmol) at −25°C. The mixture was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$ solution (10 mL), extracted with ether (4×20 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 70/30) to give '*trans*' compound **12** (258 mg, 75%) and '*cis*' compound **12′** (14 mg, 4%) both as colorless oils.

**12**: $[\alpha]_D^{20}=-53$ ($c$ 0.75, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 0.06 (s, 6H), 0.89 (s, 9H), 1.06 (t, $J=7.4$ Hz, 3H), 1.85 (m, 2H), 2.57 (dd, $J=7.0$, 7.1 Hz, 1H), 2.73 (dd, $J=2.1$, 7.1 Hz, 1H), 3.07 (t, $J=7.1$ Hz, 2H), 3.82 (t, $J=7.0$ Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.97 (t, $J=6.8$ Hz, 2H), 4.40 (s, 1H), 5.14 (s, 1H), 5.19 (d, $J=6.1$ Hz, 1H), 5.20 (s, 1H), 6.33 (dd, $J=1.6$, 5.8 Hz, 1H), 6.50 (dd, $J=1.5$, 5.8 Hz, 1H), 6.62 (s, 2H), 6.87 (d, $J=1.5$ Hz, 1H), 6.99 (d, $J=1.5$ Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: −5.3, 10.5, 18.3, 23.5, 25.9, 34.2, 51.7, 53.8, 56.0, 56.3, 60.8, 62.2, 74.5, 79.2, 80.7, 83.1, 83.3, 102.5, 108.7, 117.9, 130.9, 135.0, 137.1, 137.5, 138.8, 145.3, 152.8, 153.4; IR (film): 3075, 2956, 2934, 2878, 2856, 1590, 1462, 1129 cm$^{-1}$; ESMS $m/z$ (relative intensity): 682 (MHNa$^+$, 46), 681 (MNa$^+$, 100): HRESMS calcd for $C_{35}H_{50}O_8SSiNa^+$: 681.2893. Found: 681.2893.

**12′**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 0.05 (s, 6H), 0.89 (s, 9H), 1.06 (t, $J=7.4$ Hz, 3H), 1.83 (m, 2H), 2.58 (m, 2H), 3.08 (t, $J=7.1$ Hz, 2H), 3.82 (t, $J=7.1$ Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 3.95 (t, $J=6.8$ Hz, 2H), 4.67 (m, 2H), 4.93 (s, 2H), 6.39 (s, 2H), 6.72 (s, 2H), 6.90 (d, $J=1.3$ Hz, 1H), 6.99 (d, $J=1.4$ Hz, 1H).

### 4.11. (2*S*,5*S*)-2-(3′,4′,5′-Trimethoxyphenyl)-5-[3″-methoxy-5″-(2″-*t*-butyldimethylsilyloxyethanesulfanyl)-4″-propoxyphenyl]-2,5-dihydrofuran, 13

The tricyclic compound **12** (250 mg, 0.379 mmol) was evaporated through a horizontal mullite tube (450°C, $10^{-3}$ torr) and the thermolysate was collected on a finger cooled with liquid nitrogen. After warming to room temperature, the finger was washed with ether and the resulting solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 80/20) to give dihydrofurane **13** as a colorless oil (150 mg, 67%): $[\alpha]_D^{20}=-189$ ($c$ 1.07, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$: 0.06 (s, 6H), 0.90 (s, 9H), 1.05 (t, $J=7.4$ Hz, 3H), 1.83 (m, 2H), 3.07 (t, $J=7.2$ Hz, 2H), 3.81 (t, $J=7.2$ Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 6H), 3.94 (t, $J=6.7$ Hz, 2H), 5.97 (s, 2H), 6.09 (s, 2H), 6.61 (s, 2H), 6.76 (d, $J=1.4$ Hz, 1H), 6.87 (d, $J=1.5$ Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$: −5.3, 10.5, 18.3, 23.5, 25.9, 34.2, 55.9, 56.1, 60.8, 62.2, 74.5, 88.0, 88.2, 103.5, 108.5, 118.0, 130.3, 130.4, 131.5, 136.8, 137.0, 137.7, 145.9, 153.0, 153.4; IR (film): 3075, 2956, 2937, 2879, 2856, 1591, 1463, 1129 cm$^{-1}$; ESMS $m/z$ (relative intensity): 614 (MHNa$^+$, 42), 613 (MNa$^+$, 100); HRESMS calcd for $C_{31}H_{46}O_7SSiNa^+$: 613.2631. Found: 613.2631.

### 4.12. (2*S*,5*S*)-2-(3′,4′,5′-Trimethoxyphenyl)-5-[3″-methoxy-5″-(2″-*t*-butyldimethylsilyloxyethanesulfanyl)-4″-propoxyphenyl]tetrahydrofuran, 14

A solution of dihydrofuran **13** (240 mg, 0.406 mmol) in ethyl acetate (4 mL) was hydrogenated over 5% Pt/C (50 mg) at atmospheric pressure. After filtration, the catalyst was washed with ethylacetate (2×5 mL) and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent:

petroleum ether/AcOEt, 75/25) to give 180 mg (75%) of tetrahydrofuran **14** as a colorless oil.

$[\alpha]_D^{20} = -51$ (*c* 1.01, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$: 0.06 (s, 6H), 0.89 (s, 9H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.83 (m, 2H), 2.00 (m, 2H), 2.47 (m, 2H), 3.08 (t, $J = 7.2$ Hz, 2H), 3.81 (t, $J = 7.3$ Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (s, 6H), 3.94 (t, $J = 6.8$ Hz, 2H), 5.20 (m, 2H), 6.64 (s, 2H), 6.83 (d, $J = 1.5$ Hz, 1H), 6.89 (d, $J = 1.5$ Hz, 1H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$: −5.3, 10.4, 18.3, 23.5, 25.8, 34.2, 35.5, 55.9, 56.1, 60.8, 62.2, 81.1, 81.3, 102.3, 107.5, 117.0, 131.0, 137.0, 139.2, 139.4, 145.2, 152.8, 153.2; IR (film): 2956, 2935, 2873, 2856, 1591, 1462, 1129 $cm^{-1}$; ESMS *m*/*z* (relative intensity): 616 ($MHNa^+$, 42), 615 ($MNa^+$, 100); HRESMS calcd for $C_{31}H_{48}O_7SSiNa^+$: 615.2788. Found: 615.2788.

### 4.13. (2*S*,5*S*)-2-(3′,4′,5′-Trimethoxyphenyl)-5-[3″-methoxy-5″-(2‴-*tert*-butyldimethylsilyloxyethanesulfonyl)-4″-propoxyphenyl]tetrahydrofuran, 15

A solution of sulfur **14** (163 mg, 0.275 mmol) in $CH_2Cl_2$ (5 mL) was treated with *m*-chloroperbenzoic acid 50% (280 mg, 0.814 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was filtered. The filtrate was washed with a solution of $Na_2S_2O_3$, then with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 7/3) to give sulfone **15** as a yellowish oil (163 mg, 80%). $[\alpha]_D^{20} = -58.3$ (*c* 0.865, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$: −0.04 (s, 6H), 0.78 (s, 9H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.89 (m, 2H), 2.00 (m, 2H), 2.49 (m, 2H), 3.68 (m, 2H), 3.85 (s, 3H), 3.89 (s, 6H), 3.92 (s, 3H), 3.98 (t, $J = 6.4$ Hz, 2H), 4.12 (t, $J = 6.8$ Hz, 2H), 5.20 (t, $J = 7.4$ Hz, 1H), 5.25 (t, $J = 7.4$ Hz, 1H), 6.63 (s, 2H), 7.26 (d, $J = 1.8$ Hz, 1H), 7.48 (d, $J = 1.8$ Hz, 1H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$: −5.7, 10.3, 18.0, 23.1, 25.6, 35.5, 56.0, 56.2, 57.0, 57.4, 60.8, 75.9, 80.6, 81.5, 102.2, 114.6, 117.3, 133.8, 136.9, 138.8, 139.5, 145.7, 153.2, 153.5; IR (film): 2936, 2883, 2856, 1592, 1464, 1128 $cm^{-1}$; ESMS *m*/*z* (relative intensity): 648 ($MHNa^+$, 48), 647 ($MNa^+$, 100); HRESMS calcd for $C_{31}H_{48}O_9SSiNa^+$: 647.2686. Found: 647.2686.

### 4.14. (2*S*,5*S*)-2-{3-Methoxy-2-propoxy-5-[5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-yl]phenylsulfonyl}ethanol MK 287, 16

To a solution of ether **15** (125 mg, 0.20 mmol) in THF (1 mL) was added dropwise a solution of *n*-$Bu_4NF$ in THF (1 M, 400 μL, 0.40 mmol). The mixture was stirred for 2 h at 0°C, then diluted with water (2 mL), then extracted with ether (3×10 mL). The combined organic phase were dried over $MgSO_4$, concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: petroleum ether/AcOEt, 4/6) to give 87 mg of MK 287 (yield 85%): mp = 109–110°C; $[\alpha]_D^{20} = -72.4$ (*c* 1.03, MeOH); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$: 1.05 (t, $J = 7.4$ Hz, 3H), 1.88 (m, 2H), 2.01 (m, 2H), 2.51 (m, 2H), 2.87 (t, $J = 6.6$ Hz, 1H), 3.66 (m, 2H), 3.85 (s, 3H), 3.90 (s, 6H), 3.94 (s, 3H), 3.98 (m, 2H), 4.12 (t, $J = 6.9$ Hz, 2H), 5.22 (t, $J = 7.6$ Hz, 1H), 5.27 (t, $J = 7.5$ Hz, 1H), 6.63 (s, 2H), 7.30 (d, $J = 1.8$ Hz, 1H), 7.52 (d, $J = 1.8$ Hz, 1H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$: 10.2, 23.1, 35.6, 56.1, 56.2, 56.4, 57.4, 60.8, 76.3, 80.5, 81.7, 102.3, 115.0, 117.4, 132.4, 137.0, 138.6, 140.0, 145.6, 153.2, 153.7; IR (KBr): 3448, 3030, 2960, 2938, 2875, 2841, 1594, 1465, 1311, 1279, 1234, 1126 $cm^{-1}$; ESMS *m*/*z* (relative intensity): 533 ($MNa^+$, 100), 534 ($MHNa^+$, 30); HRESMS calcd for $C_{25}H_{34}O_9SSiNa^+$: 533.1821. Found: 533.1821. Anal. calcd for $C_{25}H_{34}O_9S$: C, 58.81; H, 6.71; S, 6.28. Found: C, 58.74; H, 6.71; C, 6.18%.

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