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Syntheses of Combretastatins D-1, D-2, and D-4 via Ring Contraction by Flash Vacuum Pyrolysis

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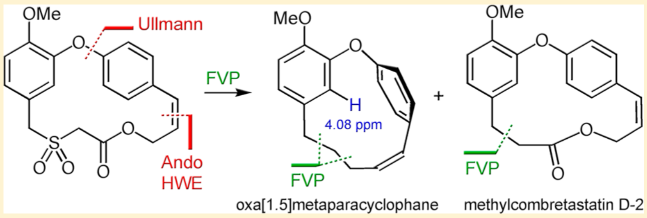
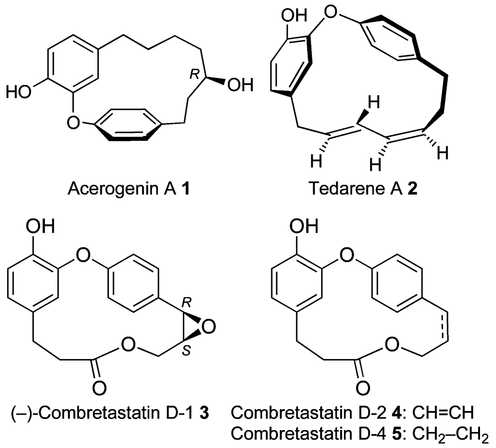
S *Supporting Information*

ABSTRACT: We report the syntheses of combretastatins D-2 and D-4 as well as a formal synthesis of combretastatin D-1 by a conceptually new route harnessing a ring-contracting flash vacuum pyrolytic extrusion of sulfur dioxide from the respective 16-membered sulfone precursors. Via flash vacuum pyrolysis, even metaparacyclophanes as small and strained as the hitherto unknown oxa[1.5]metaparacyclophane could be prepared as a side product en route to combretastatin D-2 by synchronous extrusion of SO_2 and CO_2.



■ INTRODUCTION

Naturally occurring cyclic diaryl ether heptanoids (DAEH)[1] share an oxa[1.7]metaparacyclophane scaffold while differing in the nature and position of additional functional groups on the *n*-heptyl spacer and the phenyl rings. The high incidence of biological activity[2] among these plant metabolites, their challenging structures, and their potential chirality originating from a restricted conformational flexibility[3] attracted the interest of organic chemists. Figure 1 shows typical examples of natural DAEH: the longest known optically active acerogenin A **1**[4] and the optically inactive diene tedarene A **2**.[5] The combretastatins D constitute a particulary interesting subclass of DAEH, both chemically and with respect to their biological activity.[6] They are metabolites of various *Combretaceae* species which feature a lactone group as part of the 7-atom tether. The epoxy macrolide (−)-combretastatin D-1 **3** and its deoxygenated congener combretastatin D-2 **4** were isolated from the South African bushwillow *Combretum caffrum* and were structurally elucidated in the late 1980s by Pettit et al.[7] They were found to interfere with the dynamics of the polymerization of tubulin in cells by stabilizing the microtubules, in contrast to the stilbene-like combretastatins A which stabilize the tubulin heterodimers and inhibit their polymerization.[8] Pettit et al. also reported antiproliferative activities of combretastatin D-2 with single-digit micromolar IC_{50} values against various cancer cell lines.[9] The saturated analogue combretastatin D-4 **5** was isolated from the stem of *Getonia floribunda*(*Combretaceae*), characterized, and found inactive in all biological tests by Vongvanich et al.[10] The same compound was later isolated by Ponnapalli et al. from the Mangrove shrub *Aegeceras corniculatum* (*Aegecerataceae*) and termed corniculatolide A.[11] No specific optical rotations were reported for combretastatins D-2 and D-4. The known synthetic approaches to the combretastatins D differ by the ring closure reaction and by the method and timing of the introduction of the alkene or epoxide, respectively. The first synthesis of combretastatin D-2 **4** by Boger et al.[12] employed an Ullmann coupling for the cyclization and a Still−Gennari olefination to introduce the (*Z*)-alkene. The groups of Deshpande[13] and Couladouros[14] closed the macrocycle by means of a Mitsunobu lactonization under high-dilution conditions which gave high yields only when preceding the introduction of the alkene. Mann et al. used a (*Z*)-selective Wittig olefination to close the ring of **4**.[15] Combretastatin D-1 **3** was synthesized by Rychnovsky et al. and Couladouros et al. by a Mitsunobu macrolactonization followed by introduction of the epoxide either via epoxidation[16] of an alkene with *m*CPBA or enantioselectively with a Jacobsen catalyst or via dehydration[17] of a vicinal diol. The macrocycle of



Acerogenin A **1**
Tedarene A **2**
(−)-Combretastatin D-1 **3**
Combretastatin D-2 **4**: CH=CH
Combretastatin D-4 **5**: CH_2–CH_2

Figure 1. Structures of diaryl ether heptanoids.

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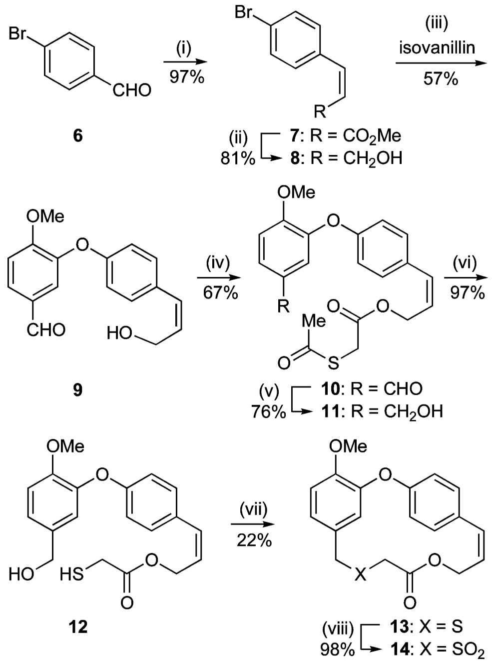
combretastatin D-4 **5** was closed in previous syntheses by the groups of Imoto,[18] Reddy,[19] and Pettit[9] either via Mitsunobu lactonization or Ullmann coupling.

Because of our interest in antimitotic agents and the combretastatins in particular, we now developed a conceptually new approach to the combretastatins D that generates the 15-membered ring via contraction of a macrocyclic sulfone precursor by flash vacuum pyrolysis (FVP).

RESULTS AND DISCUSSION

Initially, we intended to contract 16-membered sulfone derivatives of the respective combretastatins D by extrusion of sulfur dioxide according to the Ramberg−Baecklund protocol.[20] Although all attempts to initiate this reaction failed, the sulfone precursors turned out to undergo the desired ring contraction when submitted to a FVP under carefully adjusted conditions. Scheme 1 shows the synthesis of sulfone **14**, the precursor leading up to combretastatin D-2 **4**. 4-Bromobenzaldehyde **6** was converted to the (*Z*)-bromocinnamate **7** by a Horner−Wadsworth−Emmons reaction with the anion of an Ando ester phosphonate in near quantitative yield.[21] Reduction of this ester with DIBAL-H afforded the (*Z*)-bromocinnamyl alcohol **8** which was submitted to a copper-mediated Ullmann coupling[22] to give the corresponding diphenyl ether **9** in 57% yield. Steglich−Hassner esterification[23] of the alcohol **9** with *S*-acetylthioacetic acid furnished aldehyde **10** which was reduced to the benzyl alcohol **11** with sodium borohydride.[24] Deacetylation[25] of **11** with hydrazine liberated the thiol **12** which underwent an intramolecular thioetherification to give macrolide **13** when treated with sulfuric acid in acetonitrile. Quantitative oxidation with *m*CPBA eventually afforded sulfone **14**.[26]

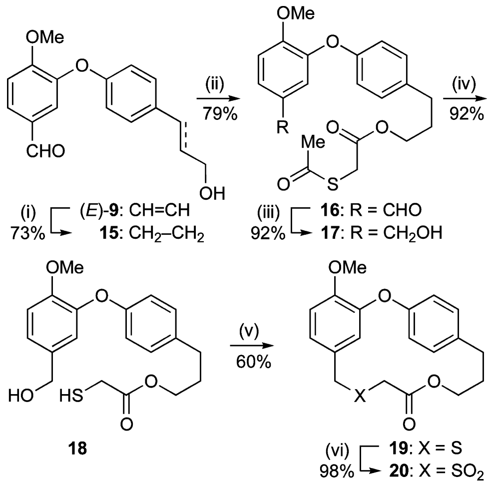
Scheme 1. Synthesis of Sulfone 14, a Precursor to Combretastatin D-2[a]



[a]Reagents and conditions: (i) $(PhO)_2P(O)CH_2CO_2Me$, KO*t*Bu, THF, − 78 °C, 2 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (iii) isovanillin, CuI, Cs_2CO_3, *N*,*N*-dimethylglycine, 1,4-dioxane, reflux, 24 h; (iv) *S*-acetylthioacetic acid, EDC, DMAP, CH_2Cl_2, rt, 3 h; (v) $NaBH_4$, 20% MeOH/THF (1:1), rt, 5 min; (vi) H_2NNH_2, MeCN, rt, 2 h; (vii) H_2SO_4, MeCN, 0 °C, 30 min; (viii) *m*CPBA, CH_2Cl_2, 0 °C → rt, 2 h.

Sulfone **20**, the saturated congener of **14** and precursor to combretastatin D-4 **5**, was obtained analogously starting with the PtO_2-catalyzed hydrogenation of the more readily available (*E*)-isomer of **9** (cf., the Supporting Information) (Scheme 2).

Scheme 2. Synthesis of Sulfone 20, a Precursor to Combretastatin D-4[a]



[a]Reagents and conditions: (i) PtO_2, MeOH, H_2 (1 bar), rt, 15 min; (ii) *S*-acetylthioacetic acid, EDC, DMAP, CH_2Cl_2, rt, 3 h; (iii) $NaBH_4$, 20% MeOH/THF (1:1), rt, 5 min; (iv) H_2NNH_2, MeCN, rt, 2 h; (v) H_2SO_4, MeCN, 0 °C, 30 min; (vi) *m*CPBA, CH_2Cl_2, 0 °C → rt, 2 h, 98%.

A formal synthesis of combretastatin D-1 **3** was achieved by first establishing the macrolide by extrusion of SO_2 from a cyclic sulfone precursor containing a protected, appropriately configured *syn*-diol (Scheme 3). The diol was obtained by first protecting[27] the alcohol (*E*)-**9** as the pivalate **21**, which was dihydroxylated according to Sharpless[28] with ADmix-*β* to afford pure *syn*-diol **22** in almost 60% yield and >99% ee as to chiral HPLC. The hydroxy groups were protected[29] as TIPS ethers to give ester **23**, which was reduced to the diol **24** with DIBAL-H. Selective oxidation with MnO_2[30] afforded the hydroxyaldehyde **25**, which was esterified with *S*-acetylthioacetic acid to give aldehyde **26**. The latter was reduced quantitatively to the benzyl alcohol **27**, which was deacetylated with hydrazine to leave the thiol **28** in 94% yield. Finally, a new mild macrocyclization protocol employing SO_3·pyridine[31] instead of sulfuric acid afforded the thioether **29**, which was oxidized to the cyclic sulfone **30** with *m*CPBA.

The cyclic sulfones **14**, **20**, and **30** were then subjected to various modifications of the Ramberg−Baecklund reaction, however, to no avail. In contrast, their FVP[32,33] under carefully adjusted conditions led to the extrusion of SO_2 with formation of the 15-membered combretastatin D skeleton. Extrusion of SO_2 using FVP has been widely used in classic synthetic approaches to cyclophanes,[34] but the targets in these studies were typically hydrocarbons with no sensitive functional groups present. For all three compounds **14**, **20**, and **30**, 600 °C was found to be the optimum temperature, with 550 °C and lower temperatures giving partly unchanged starting material, and values of 625 °C and higher leading to increased decomposition

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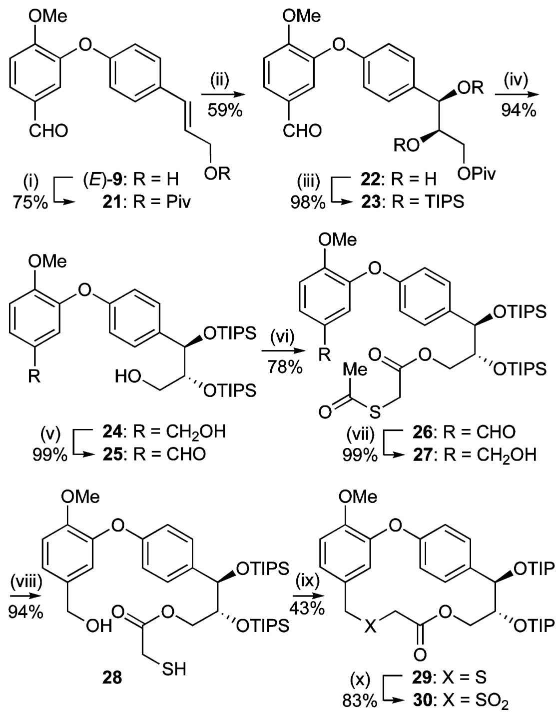
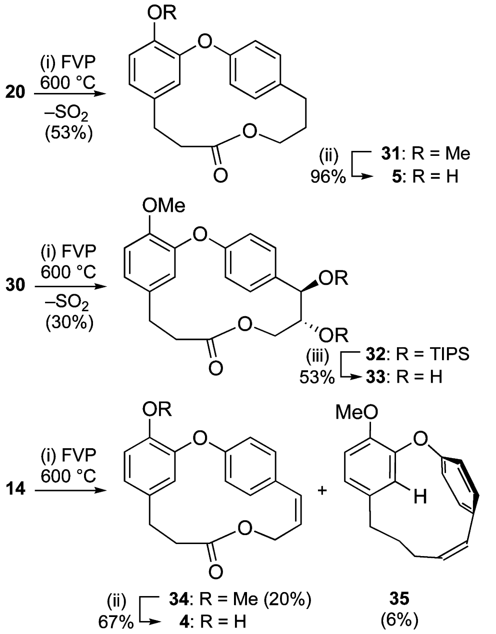
Scheme 3. Synthesis of Sulfone 30, a Precursor to Combretastatin D-1[a]



[a]Reagents and conditions: (i) PivCl, CH_2Cl_2, 40 °C, 20 h; (ii) ADmix-β, $MeSO_2NH_2$, tBuOH/H_2O (1:1), 3 °C, 28 h; (iii) TIPSOTf, 2,6-lutidine, DMF, 60 °C, 27 h; (iv) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (v) MnO_2, $CHCl_3$, rt, 22 h; (vi) *S*-acetylthioacetic acid, EDC, DMAP, CH_2Cl_2, rt, 18 h; (vii) $NaBH_4$, 20% MeOH/THF (1:1), rt, 10 min; (viii) H_2NNH_2, MeCN, rt, 2 h; (ix) SO_3·py, toluene, 111 °C, 8 h; (x) *m*CPBA, CH_2Cl_2, 0 °C → rt, 2 h, 83%.

and in the case of **14** to increased formation of **35** at the expense of the desired product **34**. The sterically least hindered sulfone **20** afforded the ring-contracted macrolide **31** in 53% yield when submitted to a FVP at 600 °C and 5×10^{-2} Torr. It was demethylated with $AlCl_3$/EtSH[16] to give combretastatin D-4 **5** in 96% yield (Scheme 4). The FVP of sulfone **30** bearing two bulky OTIPS groups also furnished the corresponding macrolide **32** albeit in only 30% yield. Deprotection of **32** with aqueous HF afforded the diol **33** in 53% yield. To complete the synthesis of combretastatin D-1, the diol **33** would have to be demethylated with $AlCl_3$/EtSH and converted to the target epoxide by dehydration according to Couladouros et al.[17] For sulfone **14**, void of bulky groups and featuring a *Z*-alkene that might confer some rigidity and preorientation for the SO_2 extrusion, we expected a smoothly proceeding FVP. What we actually found upon FVP of sulfone **14** was a separable mixture of the expected macrolide **34** (20%), which was demethylated with $AlCl_3$/EtSH to give combretastatin D-2 **4**, and of the first ever oxa[1.5]metaparacyclophane **35** (6%), originating from a concomitant extrusion of SO_2 and CO_2. A single crystal X-ray diffraction analysis of **35** showed that the two phenyl rings were oriented almost perpendicular to each other, with the isolated H atom of the trisubstituted phenyl ring located perpendicular to the center of the disubstituted phenyl ring at a remarkably short distance of 2.28 Å (Figure 2). The structure of **35** in solution probably does not deviate much from its crystal structure since in the ^{1}H NMR spectrum of **35**, this H atom resonates at a conspicuous high-field shift of 4.08 ppm.

Scheme 4. FVP of Sulfones 14, 20, and 30[a]



[a]Reagents and conditions: (i) FVP, 600 °C, 5×10^{-2} Torr; (ii) $AlCl_3$, EtSH, CH_2Cl_2, −17 °C, 1 h; (iii) $HF_{(aq)}$, THF, rt, 3 d.

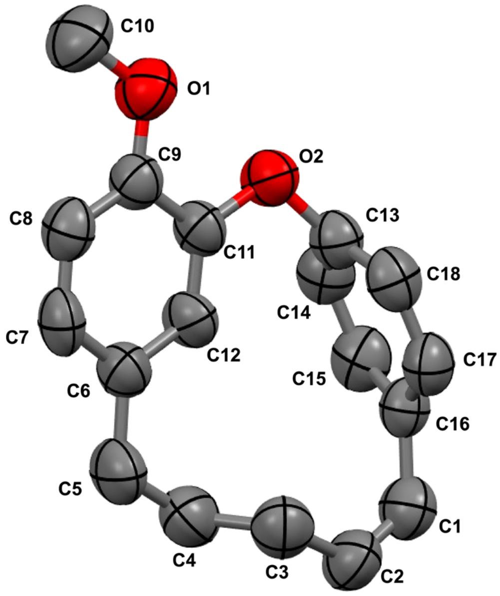


Figure 2. Molecular structure of oxa[1.5]metaparacyclophane **35**, as thermal ellipsoid representations at 50% probability level showing the atomic numbering schemes (H atoms omitted). CCDC 1505171. Selected bond lengths [Å] and angles [°]: O2−C11 1.408(6), O2−C13 1.426(6), C1−C2 1.330(9), C1−C16 1.492(8), C5−C6 1.515(7), O2−C11−C9 117.6(4), O2−C11−C12 123.6(4), C5−C6−C12 121.3(4), O2−C13−C14 117.9(5), O2−C13−C18 118.3(5), O2−C13−C18−C17 151.6(5), O2−C13−C14−C15 151.4(5), C1−C16−C17−C18−154.2(5), C16−C1−C2−C3−2.1(9), C1−C2−C3−C4 94.6(7).

■ CONCLUSIONS

The combretastatins D-1, D-2, and D-4 were synthezised by a conceptually new route harnessing a ring-contracting flash vacuum pyrolytic extrusion of sulfur dioxide from the respective 16-membered sulfone precursors. The latter were obtained by an intramolecular thiol benzylation followed by an oxidation of the resulting thioether. Via FVP, even the oxa[1.5]-metaparacyclophane **35** could be prepared as a side product en route to combretastatin D-2 by synchronous extrusion of SO_2 and CO_2. The mechanism of this process as well as the chemistry and potential chirality of such DAEP remain to be elucidated.

■ EXPERIMENTAL SECTION

General Remarks. All moisture- or air-sensitive reactions were performed in oven-dried glassware under an argon atmosphere using standard Schlenk techniques. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. Melting points were determined with a Büchi M-565 melting point apparatus and are uncorrected. Chemical shifts of NMR signals are given in parts per million (δ) downfield from tetramethylsilane for ^1H and ^{13}C NMR spectra. Mass spectra were obtained under EI (70 eV) conditions. High-resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. For chromatography, silica gel 60 (230–400 mesh) was used. FVP was carried out in a conventional flow system by subliming the starting material through a horizontal quartz tube (30 × 2.5 cm) externally heated by a tube furnace to 600 °C and maintained at a pressure of 5×10^{-2} Torr by a rotary vacuum pump. Products were collected in a liquid N_2 cooled U-shaped trap and purified as noted.

Methyl (*Z*)-4-Bromocinnamate 7. A solution of $(PhO)_2P(O)CH_2CO_2Me$[35] (11.4 g, 37.2 mmol) in dry THF (315 mL) was treated with KO*t*Bu (5.01 g, 44.7 mmol) at −78 °C for 15 min under an inert gas atmosphere. *p*-Bromobenzaldehyde **6** (6.25 g, 33.8 mmol) was added, and the mixture was stirred at −78 °C. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with EtOAc (30 mL). After separation of the layers, the aqueous phase was extracted three times with EtOAc (20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The volatiles were removed under reduced pressure, and the crude product was purified by column chromatography (cyclohexane/EtOAc 5:1) to yield **7** (7.91 g, 32.8 mmol, 97%) as colorless crystals of mp 41–44 °C [lit.[36] 40–42 °C]; R_f = 0.66 (cyclohexane/EtOAc 3:1). IR (ATR) ν_{max} 2950, 1721, 1632, 1587, 1488, 1439, 1197, 1168, 1072, 1011, 844, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.71 (s, 3 H), 5.98 (d, *J* = 12.7 Hz, 1 H), 6.88 (d, *J* = 12.7 Hz, 1 H), 7.47–7.50 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.5, 119.9, 123.4, 131.2, 131.4, 133.5, 142.3, 166.3; MS (EI) *m*/*z* (%) 242 (54), 240 (56) $[M]^+$, 211 (87), 209 (88), 183 (35), 181 (37), 102 (100), 75 (26), 51 (31).

(*Z*)-4-Bromocinnamyl Alcohol 8. A solution of ester **7** (9.20 g, 38.3 mmol) in CH_2Cl_2 (72 mL) was cooled to −78 °C and treated dropwise with DIBAL-H (1 M in hexane, 84.2 mL, 84.2 mmol). After 1 h, the reaction mixture was quenched with MeOH (20 mL), and the formed $Al(OH)_3$ precipitate was carefully dissolved by addition of 1 M aqueous HCl solution (100 mL). The reaction mixture was allowed to warm to room temperature, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was crystallized from hexane to afford 6.62 g of **8** (31.1 mmol, 81%) as colorless crystals of mp 69–71 °C [lit.[9] 69.3–70.6 °C]; R_f 0.38 (cyclohexane/EtOAc 3:1). IR (ATR) ν_{max} 3239, 3016, 1488, 1388, 1323, 1114, 1077, 1026, 1005, 974, 943, 835, 791, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.57 (t, *J* = 5.5 Hz, OH), 4.36–4.42 (m, 2 H), 5.90 (dt, *J* = 11.8, 6.5 Hz, 1 H), 6.50 (d, br, *J* = 11.8 Hz, 1 H), 7.05–7.11 (m, 2 H), 7.44–7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.5, 121.3, 130.0, 130.3, 131.4, 131.8, 135.3; MS (EI) *m*/*z* (%) 214 (88), 212 (90) $[M^+]$, 171 (80), 169 (78), 158 (28), 156 (30), 133 (100), 115 (51), 104 (38), 91 (63), 77 (43), 66 (25), 55 (31), 51(33).

(*Z*)-3-[4-(3-Hydroxyprop-1-en-1-yl)phenoxy]-4-methoxybenzaldehyde (*Z*)-9. A solution of alcohol **8** (3.74 g, 17.6 mmol) and isovanillin (4.00 g, 26.3 mmol) in 1,4-dioxane (13.4 mL) was treated with Cs_2CO_3 (11.4 g, 35.1 mmol), CuI (334 mg, 1.76 mmol), and dimethylglycine hydrochloride (544 mg, 5.27 mmol). The resulting suspension was stirred at 101 °C for 24 h, cooled, and treated with ethyl acetate (50 mL). The organic phase was washed with brine (50 mL), the aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The volatiles were removed under reduced pressure, and the remaining crude was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to yield (*Z*)-**9** (2.84 g, 9.99 mmol, 57%) as a light yellow oil of R_f 0.38 (cyclohexane/ethyl acetate 1:1). IR (ATR) ν_{max} 3349, 2844, 1683, 1598, 1578, 1503, 1432, 1273, 1220, 1163, 1119, 1012, 813, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67 (s, br, OH), 3.94 (s, 3 H), 4.43 (dd, *J* = 6.5, 1.3 Hz, 2 H), 5.84 (dt, *J* = 11.7, 6.5 Hz, 1 H), 6.52 (d, *J* = 11.7 Hz, 1 H), 6.91–6.97 (m, 2 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.15–7.20 (m, 2 H), 7.47 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1 H), 9.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.3, 59.6, 112.1, 117.6, 119.8, 128.3, 130.2, 130.25, 130.3, 130.5, 131.9, 146.0, 156.0, 156.3, 190.3; HRMS (ESI) *m*/*z* $[M - H_2O + H]^+$ calcd for $C_{17}H_{15}O_3^+$ 267.1016, found 267.1010.

(*E*)-9. Analogous to the synthesis of (*Z*)-**9**, the isomer (*E*)-**9** (5.94 g, 20.9 mmol, 80%) was obtained as a colorless oil from (*E*)-4-bromocinnamyl alcohol[17b] (5.61 g, 26.3 mmol), isovanillin (6.00 g, 39.4 mmol), Cs_2CO_3 (17.1 g, 52.6 mmol), CuI (0.50 g, 2.63 mmol), and dimethylglycine hydrochloride (0.82 g, 7.88 mmol). R_f 0.12 (cyclohexane/ethyl acetate 2:1). IR (ATR) ν_{max} 3502, 2843, 1671, 1598, 1580, 1506, 1435, 1402, 1264, 1228, 1172, 1123, 1088, 1012, 966, 854, 813, 790, 641, 632 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51 (t, *J* = 5.9 Hz, OH), 3.95 (s, 3 H), 4.32 (td, *J* = 5.9 Hz, 1.4 Hz, 2 H), 6.29 (dt, *J* = 15.9 Hz, 5.8 Hz, 1 H), 6.59 (d, *J* = 15.9 Hz, 1 H), 6.90–6.96 (m, 2 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.34–7.37 (m, 2 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 8.4 Hz, 2.0 Hz, 1 H), 9.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.3, 63.8, 112.0, 118.2, 119.5, 127.7, 127.9, 128.2, 130.1, 130.3, 132.2, 146.1, 156.2, 156.3, 190.4; HRMS (ESI) *m*/*z* $[M - H_2O + H]^+$ calcd for $C_{17}H_{15}O_3^+$ 267.1016, found 267.1013.

(*Z*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]allyl 2-Acetylthioacetate 10. A mixture of alcohol **9** (2.80 g, 9.84 mmol), CH_2Cl_2 (90 mL), *S*-acetylthioacetic acid[37] (1.45 g, 10.8 mmol), EDC (2.08 g, 10.8 mmol), and DMAP (602 mg, 4.94 mmol) was stirred for 3 h at room temperature and then washed with 0.1 M citric acid (50 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to yield **10** (2.65 g, 6.63 mmol, 67%) as a colorless oil. R_f 0.35 (cyclohexane/ethyl acetate 2:1). IR (ATR) ν_{max} 2957, 2844, 1738, 1686, 1598, 1578, 1504, 1432, 1394, 1273, 1221, 1155, 1119, 1110, 1016, 958, 840, 815, 623 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.38 (s, 3 H), 3.73 (s, 2 H), 3.94 (s, 3 H), 4.89 (dd, *J* = 6.8, 1.5 Hz, 1 H), 5.78 (dt, *J* = 11.7, 6.7 Hz, 1 H), 6.65 (d, *J* = 11.7 Hz, 1 H), 6.92–6.97 (m, 2 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.16–7.21 (m, 2 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 7.69 (dd, *J* = 8.4, 2.0 Hz, 1 H), 9.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.1, 31.5, 56.3, 62.7, 112.2, 117.6, 120.4, 124.4, 128.3, 130.25, 130.3, 131.1, 132.8, 145.7, 156.45, 156.5, 168.6, 190.2, 193.7; HRMS (ESI) *m*/*zs* $[M + Na]^+$ calcd for $C_{21}H_{20}NaO_6S^+$ 423.0873, found 423.0866.

(*Z*)-3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]allyl 2-Acetylthioacetate 11. Aldehyde **10** (1.53 g, 3.82 mmol) was dissolved in a 1:1 mixture of THF and 20% aqueous MeOH (52 mL). After addition of $NaBH_4$ (72.0 mg, 1.91 mmol), the reaction mixture was stirred for 5 min at room temperature, quenched with water (30 mL), and diluted with ethyl acetate (30 mL). After separation of the layers, the aqueous one was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_2, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 2:1, R_f 0.32) to yield **11** (1.17 g, 2.90 mmol, 76%) as a colorless oil. IR (ATR) ν_{max} 3432, 1735, 1695, 1604, 1505, 1425, 1270, 1223, 1163, 1124, 1025, 962 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.69 (t, br, *J* = 4.4 Hz, OH), 2.38 (s, 3 H), 3.72 (s, 2 H), 3.83 (s, 3 H), 4.59 (d, *J* = 4.4 Hz, 2 H), 4.88 (dd, *J* = 6.7, 1.4 Hz, 2 H), 5.74 (dt, *J* = 11.7, 6.7 Hz, 1 H), 6.63 (d, *J* = 11.7 Hz, 1 H), 6.88–6.94 (m, 2 H), 6.99 (d, *J* =

8.4 Hz, 1 H), 7.01 (d, *J* = 2.1 Hz, 1 H), 7.11–7.18 (m, 3 H, 2-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.1, 31.5, 56.1, 62.8, 64.6, 112.8, 116.9, 120.2, 123.7, 123.9, 130.3, 130.1, 133.0, 134.1, 144.6, 150.9, 157.4, 168.6, 193.8; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}NaO_6S^+$ 425.1029, found 425.1023.

(*Z*)-3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]allyl 2-Mercaptoacetate 12. A solution of thioester **11** (2.02 g, 5.00 mmol) in MeCN (140 mL) was treated with hydrazine solution (5.40 mL; the upper layer of a 1:3 mixture of hydrazine monohydrate and MeCN), and the resulting mixture was stirred at room temperature for 2 h. After dilution with $CHCl_3$ (20 mL), the layers were separated, and the organic phase was washed successively with 1 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), then dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to afford thiol **12** (1.75 g, 4.86 mmol, 97%) as a colorless oil. R_f 0.19 (cyclohexane/ethyl acetate 2:1). IR (ATR) ν_{max} 3420, 2935, 1729, 1603, 1583, 1504, 1441, 1424, 1267, 1219, 1167, 1121, 1022, 944, 839, 811, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (s, br, 1 H, OH), 2.01 (t, *J* = 8.2 Hz, 1H, SH), 3.28 (d, *J* = 8.2 Hz, 2 H), 3.83 (s, 3 H), 4.59 (s, br, 2 H), 4.89 (dd, *J* = 6.7, 1.4 Hz, 2 H), 5.75 (dt, *J* = 11.7, 6.7 Hz, 1 H), 6.64 (d, *J* = 11.7 Hz, 1 H), 6.89–6.93 (m, 2 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 7.11–7.17 (m, 2 H), 7.15 (dd, *J* = 8.3, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.4, 56.1, 62.6, 64.6, 112.8, 116.9, 120.2, 123.8, 123.9, 130.1, 130.2, 133.0, 134.1, 144.5, 150.9, 157.4, 170.7; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{20}NaO_5S^+$ 383.0924, found 383.0923.

(14*Z*)-4-Methoxy-2,12-dioxa-9-thiatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,14,16,19-heptaen-11-one 13. A solution of thiol **12** (31 mg, 0.09 mmol) in MeCN (1 mL) was added slowly with a syringe pump (15 mL/h) to a vigorously stirred solution of H_2SO_4 (32.0 μL, 0.60 mmol) in MeCN (30 mL) at 0 °C. The final concentration of the mixture was ca. 3 mM. The reaction mixture was stirred for a further 30 min at 0 °C until TLC showed full consumption of the starting material and then quenched with saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was concentrated under reduced pressure and then distributed between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 7:1 → 3:1) to yield **13** (6.7 mg, 0.02 mmol, 22%) as a white solid of mp 164.5–166 °C. R_f 0.46 (cyclohexane/ethyl acetate 3:1). IR (ATR) ν_{max} 2927, 2854, 1732, 1603, 1505, 1442, 1271, 1224, 1169, 1124, 1027, 967, 841, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.82 (s, 2 H), 3.63 (s, 2 H), 3.96 (s, 3 H), 4.62 (dd, *J* = 5.9, 0.8 Hz, 2 H), 5.93 (d, *J* = 2.1 Hz, 1 H), 5.97 (dt, *J* = 11.2, 5.9 Hz, 1 H), 6.83 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 6.99 (d, br, *J* = 11.2 Hz, 1 H), 7.04–7.08 (m, 2 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 7.16–7.22 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.6, 33.7, 56.2, 60.6, 113.1, 118.9, 122.2, 122.5, 125.4, 129.3, 129.9, 134.5, 136.6, 148.3, 149.8, 156.7, 169.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}O_4S^+$ 343.0999, found 343.0988.

(14*Z*)-4-Methoxy-2,12-dioxa-9-thiatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,14,16,19-heptaen-11-one 9,9-dioxide 14. A solution of thioether **13** (10 mg, 0.03 mmol) in CH_2Cl_2 (1.2 mL) was cooled to 0 °C, treated with *m*CPBA (70–77% purity, 16.1 mg, 0.09 mmol), and stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous Na_2SO_3 solution (0.6 mL). The mixture was distributed between CH_2Cl_2 (2 mL) and H_2O (2 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to yield **14** (11.0 mg, 0.03 mmol, 98%) as a white solid of mp 190–192 °C. R_f 0.35 (cyclohexane/ethyl acetate 2:1). IR (ATR) ν_{max} 2936, 1724, 1506, 1315, 1303, 1267, 1210, 1192, 1113, 1030, 972, 874, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.41 (s, 2 H), 3.97 (s, 3 H), 4.38 (s, 2 H), 4.66 (d, *J* = 6.4 Hz, 2 H), 6.07 (dt, *J* = 11.0, 6.4 Hz, 1 H), 6.24 (d, *J* = 1.8 Hz, 1 H), 6.95–7.00 (m, 2 H, 7-H), 7.03–7.08 (m, 3 H), 7.12–7.16 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.3, 56.1, 59.1, 59.9, 113.0, 119.3, 120.6, 122.7, 125.6, 129.3, 134.2, 138.8, 150.1, 150.7, 157.1, 163.5; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}O_6S^+$ 375.0897, found 375.0888.

3-[4-(3-Hydroxypropyl)phenoxy]-4-methoxybenzaldehyde 15. A mixture of diaryl ether (*E*)-**9** (2.50 g, 8.79 mmol) and a catalytic amount of PtO_2 (40.0 mg, 0.18 mmol) in MeOH (75 mL) was stirred at room temperature under an atmosphere of hydrogen for 15 min. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (cyclohexane/ethyl acetate 1:1, R_f 0.33) to afford **15** (1.83 g, 6.38 mmol, 73%) as a colorless oil. IR (ATR) ν_{max} 3386, 2936, 1685, 1598, 1579, 1504, 1432, 1271, 1222, 1167, 1120, 1111, 1015, 813, 637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (s, br, 1 H), 1.84–1.94 (m, 2 H), 2.65–2.75 (m, 2 H), 3.65–3.73 (m, 2 H), 3.97 (s, 3 H), 6.87–6.96 (m, 2 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 7.13–7.21 (m, 2 H), 7.40 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 8.4 Hz, 2.0 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.2, 34.2, 56.3, 62.2, 111.8, 118.4, 118.5, 127.8, 129.7, 130.1, 137.2, 146.9, 154.5, 156.0, 190.5; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}O_4^+$ 287.1278, found 287.1277.

3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]propyl 2-Acetylthioacetate 16. Analogous to compound **10**, compound **16** (832 mg, 2.07 mmol, 79%) was prepared as a colorless oil from **15** (750 mg, 2.62 mmol), *S*-acetylthioacetic acid[37] (351 mg, 2.62 mmol), EDC (552 mg, 2.88 mmol), DMAP (160 mg, 1.31 mmol), and CH_2Cl_2 (50 mL). R_f 0.60 (cyclohexane/ethyl acetate 1:1); IR (ATR) ν_{max} 2933, 1733, 1688, 1599, 1579, 1505, 1432, 1271, 1222, 1163, 1120, 1110, 1013, 959, 815, 625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90–2.10 (m, 2 H), 2.38 (s, 3 H), 2.60–2.73 (m, 2 H), 3.69 (s, 2 H), 3.95 (s, 3 H), 4.15 (t, *J* = 6.6 Hz, 2 H), 6.88–6.95 (m, 2 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 7.12–7.16 (m, 2 H), 7.39 (d, *J* = 2.1 Hz, 1 H), 7.63 (dd, *J* = 8.4 Hz, 2.1 Hz, 1 H), 9.79 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 30.1, 31.2, 31.4, 56.2, 65.0, 111.8, 118.3, 118.8, 127.8, 129.7, 130.0, 136.3, 146.6, 154.7, 156.0, 168.7, 190.4, 193.8; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}NaO_6S^+$ 425.1029, found 425.1026.

3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]propyl 2-Acetylthioacetate 17. Analogous to **11**, compound **17** (654 mg, 1.62 mmol, 92%) was prepared as a colorless oil from **16** (710 mg, 1.76 mmol) and $NaBH_4$ (33.0 mg, 0.88 mmol) in a 1:1 mixture of THF and 20% aqueous MeOH (24 mL). R_f 0.48 (cyclohexane/ethyl acetate 1:1); IR (ATR) ν_{max} 3499, 2939, 1733, 1694, 1505, 1425, 1266, 1217, 1166, 1122, 1016, 959, 813, 625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90–1.98 (m, 2 H), 2.37 (s, 3 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 3.68 (s, 2 H), 3.82 (s, 3 H), 4.13 (t, *J* = 6.4 Hz, 2 H), 4.53 (s, br, 2 H), 6.83–6.89 (m, 2 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 7.05–7.12 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 30.1, 31.1, 31.4, 56.0, 64.5, 65.0, 112.4, 117.5, 119.3, 123.0, 129.4, 133.9, 135.2, 145.3, 150.1, 155.7, 168.7, 193.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{24}NaO_6S^+$ 427.1186, found 427.1182.

3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]propyl 2-Mercaptoacetate 18. Analogous to **12**, compound **18** (1.32 g, 3.65 mmol, 92%) was prepared as a colorless oil from **17** (1.60 g, 3.95 mmol) and hydrazine solution (4.30 mL) in MeCN (100 mL). R_f 0.27 (cyclohexane/ethyl acetate 2:1); IR (ATR) ν_{max} 3427, 2936, 1729, 1505, 1442, 1424, 1267, 1217, 1167, 1122, 1022, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.77 (t, *J* = 5.6 Hz, 1 H, OH), 1.92–2.01 (m, 2 H), 2.00 (t, *J* = 8.3 Hz, 1 H, SH), 2.64–2.69 (m, 2 H), 3.25 (d, *J* = 8.3 Hz, 2 H), 3.85 (s, 3 H), 4.15 (t, *J* = 6.6 Hz, 2 H), 4.56 (d, *J* = 5.6 Hz, 2 H), 6.85–6.91 (m, 2 H), 6.94 (d, *J* = 2.1 Hz, 1 H), 6.97 (d, *J* = 8.2 Hz, 1 H), 7.08–7.12 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.5, 30.1, 31.2, 56.0, 64.7, 64.9, 112.5, 117.6, 119.3, 123.1, 129.4, 133.8, 135.2, 145.4, 150.6, 155.8, 170.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{22}NaO_5S^+$ 385.1080, found 385.1079.

4-Methoxy-2,12-dioxa-9-thiatricyclo[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,19-hexaen-11-one 19. Analogous to **13**, compound **19** (126 mg, 0.37 mmol, 60%) was prepared from **18** (220 mg, 0.61 mmol) and H_2SO_4 (227 μL, 4.25 mmol) in MeCN (200 mL). After column chromatography (cyclohexane/ethyl acetate 7:1) and recrystallization from *n*-hexane/CH_2Cl_2 4:1, it was obtained as colorless crystals of mp 126.5−127 °C. R_f 0.56 (cyclohexane/ethyl acetate 2:1); IR (ATR) ν_{max} 2934, 2915, 2840, 1733, 1513, 1505, 1439, 1420, 1284, 1254, 1224, 1206, 1170, 1151, 1127, 1106, 1030, 988, 973, 953, 834, 808, 705, 676, 614, cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.10−2.16 (m, 2 H), 2.80 (s, 2 H), 2.84 (t, *J* = 6.4 Hz, 2 H), 3.55 (s, 2 H), 3.97 (s, 3 H), 4.12−4.16 (m, 2 H), 5.86 (d, *J* = 2.1 Hz, 1 H), 6.81 (dd, *J* = 8.2 Hz, 2.1 Hz, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 6.99−7.06 (m, 2 H), 7.24−7.29 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.4, 31.1, 33.9, 34.0, 56.2, 65.8, 113.1, 117.5, 121.6, 122.6, 129.5, 131.0, 137.6, 147.8, 149.8, 154.7, 169.4; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{19}H_{21}O_4S^+$ 345.1155, found 345.1161.

4-Methoxy-2,12-dioxa-9-thiatricyclo[14.2.2.1^{3,7}]henicosa-1-(18),3(21),4,6,16,19-hexaen-11-one 9,9-dioxide 20. Analogous to **14**, compound **20** was prepared from **19** (130 mg, 0.38 mmol) and *m*CPBA (70−77% purity, 287 mg, 1.66 mmol) in CH_2Cl_2 (30 mL). After column chromatography (cyclohexane/ethyl acetate 3:1) and recrystallization from *n*-hexane/CH_2Cl_2 4:1, **20** (140 mg, 0.37 mmol, 98%) was obtained as colorless crystals of mp 207−209 °C; R_f 0.28 (cyclohexane/ethyl acetate 2:1). IR (ATR) ν_{max} 2971, 2931, 1724, 1506, 1460, 1312, 1304, 1265, 1250, 1214, 1196, 1161, 1114, 1032, 972, 880, 871, 825, 818, 621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.16−2.23 (m, 2 H), 2.85 (t, *J* = 6.6 Hz, 2 H), 3.44 (s, 2 H), 3.98 (s, 3 H), 4.21−4.27 (m, 2 H), 4.32 (s, 2 H), 6.06 (t, *J* = 1.1 Hz, 1 H), 6.96−6.98 (m, 2 H), 6.98−7.02 (m, 2 H), 7.24−7.28 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.4, 33.2, 51.5, 56.1, 59.1, 65.6, 112.8, 117.6, 120.5, 122.5, 125.1, 131.3, 136.9, 149.6, 150.7, 154.9, 163.1; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{19}H_{20}O_6NaS^+$ 399.0873, found: 399.0878.

(*E*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]allyl Pivalate 21. A solution of alcohol (*E*)-**9** (1.00 g, 3.52 mmol) in CH_2Cl_2 (15 mL) was treated with pyridine (0.5 mL) and pivaloyl chloride (0.65 mL, 5.28 mmol) and stirred at 40 °C for 20 h. After cooling to room temperature, the organic phase was washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to yield **21** (0.97 g, 75%) as a yellowish oil; R_f 0.29 (cyclohexane/ethyl acetate 3:1). IR (ATR) ν_{max} 2969, 1722, 1688, 1599, 1579, 1505, 1433, 1274, 1224, 1147, 1119, 1019, 960, 812, 769, 636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 9 H), 3.94 (s, 3 H), 4.71 (dd, *J* = 6.4, 1.1 Hz, 2 H), 6.20 (dt, *J* = 15.9, 6.3 Hz, 1 H), 6.61 (d, br, *J* = 15.9 Hz, 1 H), 6.89−6.95 (m, 2 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.33−7.38 (m, 2 H), 7.46 (d, *J* = 1.9 Hz, 1 H), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1 H), 9.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2, 38.8, 56.3, 65.0, 112.1, 118.1, 119.7, 122.8, 128.1, 128.2, 130.2, 131.8, 132.9, 146.1, 156.3, 156.7, 178.3, 190.3; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{24}O_5Na^+$ 391.1516, found 391.1509.

(2*R*,3*R*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]-2,3-dihydroxypropyl Pivalate 22. A mixture of AD-mix-*β* (3.43 g, 1.4 g/mmol) and methanesulfonamide (233 mg, 95.0 mg/mmol) were suspended at room temperature in a H_2O/*t*BuOH mixture (1:1, 30.6 mL). After cooling to 0 °C, the olefin **21** (902 mg, 2.45 mmol) was added ,and the mixture was stirred vigorously for 2 d at 3 °C. The reaction was cooled again to 0 °C, Na_2SO_3 (3.7 g, 1.5 g/mmol) was added, and stirring was continued for 30 min. The phases were separated, and the aqueous one was acidified with saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 1:1, R_f 0.20) to yield **22** (575 mg, 1.44 mmol, 59%) as a yellowish oil; $[\alpha]_D^{23}$ −9.4 (*c* 1.00, acetone), ee >99%; IR (ATR) ν_{max} 3481, 2970, 1727, 1690, 1600, 1507, 1435, 1397, 1277, 1225, 1161, 1121, 1023, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19 (s, 9 H), 3.14 (s, br, 2 × OH), 3.85−3.95 (m, 2 H), 3.90 (s, 3 H), 4.14 (dd, *J* = 11.6, 3.5 Hz, 1 H), 4.60 (d, *J* = 6.4 Hz, 1 H), 6.90−6.94 (m, 2 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 7.27−7.31 (m, 2 H), 7.44 (d, *J* = 2.0 Hz, 1 H), 7.65 (dd, *J* = 8.4, 2.0 Hz, 1 H), 9.77 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.1, 38.8, 56.2, 65.0, 73.8, 74.1, 112.1, 117.7, 120.0, 128.1, 128.3, 130.0, 135.1, 145.7, 156.4, 156.8, 178.8, 190.5; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}O_7Na^+$ 425.1571, found 425.1568.

(2*R*,3*R*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]-2,3-bis-(triisopropylsilyloxy)propyl Pivalate 23. A solution of diol **22** (4.00 g, 9.94 mmol) and 2,6-lutidine (5.05 mL, 34.8 mmol) in DMF (100 mL) was slowly treated with TIPS-OTf (8.00 mL, 29.8 mmol) at 0 °C and then stirred at 60 °C for 27 h. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL), the aqueous layer was extracted twice with diethyl ether (50 mL), and the combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to obtain **23** (6.96 g, 9.73 mmol, 98%) as a colorless oil; R_f 0.43 (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{23}$ +3.7 (*c* 0.50, $CHCl_3$); IR (ATR) ν_{max} 2945, 2867, 1729, 1696, 1600, 1581, 1505, 1463, 1433, 1276, 1224, 1153, 1120, 1091, 1067, 1014, 996, 882, 844, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99−1.09 (m, 42 H), 1.16 (s, 9 H), 3.70 (dd, *J* = 11.6, 5.6 Hz, 1 H), 3.94 (s, 3 H), 4.20−4.25 (m, 1 H), 4.38 (dd, *J* = 11.6, 3.4 Hz, 1 H), 4.94 (d, *J* = 4.2 Hz, 1 H), 6.88−6.92 (m, 2 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 7.35−7.39 (m, 2 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 7.66 (dd, *J* = 8.4, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.4, 12.8, 17.95, 18.0, 18.1, 18.2, 27.2, 38.7, 56.2, 66.4, 74.9, 75.1, 112.1, 117.1, 120.0, 127.3, 128.7, 130.2, 136.1, 146.5, 156.0, 156.2, 178.5, 190.3; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{40}H_{66}O_7NaSi_2^+$ 737.4239, found 737.4231.

(2*R*,3*R*)-3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]-2,3-bis(triisopropylsilyl)oxypropan-1-ol 24. Analogous to **8**, alcohol **24** (5.42 g, 8.56 mmol, 94%) was prepared as a colorless oil from **23** (6.50 g, 9.09 mmol) and DIBAL-H (1 M in hexane, 29.1 mL, 29.1 mmol) in CH_2Cl_2 (120 mL). R_f 0.44 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{23}$ +19.0 (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 3410, 2944, 2865, 1608, 1505, 1463, 1426, 1270, 1222, 1121, 1058, 1031, 1013, 945, 881, 845, 773, 679, 655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96−1.10 (m, 42 H), 1.94 (s, br, 1 H, OH), 2.89 (dd, *J* = 8.3, 1.7 Hz, 1H, OH), 3.45 (ddd, *J* = 11.0, 8.3, 4.2, 1 H), 3.57 (ddd, *J* = 11.0, 8.0, 1.7, 1 H), 3.80 (s, 3 H), 4.23 (dt, *J* = 8.0, 4.2 Hz, 1 H), 4.54 (d, br, *J* = 2.4 Hz, 1 H), 5.04 (d, *J* = 4.2 Hz, 1 H), 6.88−6.92 (m, 2 H), 6.94 (d, *J* = 2.1 Hz, 1 H), 6.95 (d, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.31−7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 12.5, 17.8, 17.9, 18.0, 18.1, 55.9, 63.5, 64.6, 73.3, 77.8, 112.6, 116.6, 119.2, 122.9, 128.7, 133.85, 133.9, 145.5, 150.5, 156.9; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{35}H_{60}O_6NaSi_2^+$ 655.3821, found 655.3819.

(2*R*,3*R*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]-2,3-bis-(triisopropylsilyloxy)propan-1-ol 25. A mixture of diol **24** (5.39 g, 8.51 mmol), activated MnO_2 (22.2 g, 0.26 mol), and $CHCl_3$ (110 mL) was stirred at room temperature for 17 h and then filtered through Celite. The combined filtrate and washings with CH_2Cl_2 were concentrated under reduced pressure to give the crude product which was purified by column chromatography (cyclohexane/ethyl acetate 4:1) to afford **25** (5.33 g, 8.45 mmol, 99%) as a colorless oil; R_f 0.64 (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{23}$ −21.4 (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 2944, 2863, 1694, 1600, 1581, 1505, 1463, 1433, 1274, 1224, 1111, 1059, 1014, 997, 881, 847, 679, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95−1.14 (m, 42 H), 2.86 (s, br, 1 H, OH), 3.46 (dd, *J* = 10.9, 4.0 Hz, 1 H), 3.58 (dd, *J* = 10.9, 7.9 Hz, 1 H), 3.92 (s, 3 H), 4.24 (dt, *J* = 7.9, 4.3 Hz, 1 H), 5.06 (d, *J* = 4.3 Hz, 1 H), 6.90−6.96 (m, 2 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 7.34−7.39 (m, 2 H), 7.42 (d, *J* = 2.0 Hz, 1 H), 7.65 (dd, *J* = 8.4, 2.0 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 12.5, 17.85, 17.9, 18.0, 18.1, 56.1, 63.6, 73.3, 77.7, 112.0, 117.2, 119.5, 127.5, 129.0, 130.1, 134.8, 146.5, 156.0, 156.1, 190.2; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{35}H_{58}O_6NaSi_2^+$ 653.3664, found 653.3661.

(2*R*,3*R*)-3-[4-(5-Formyl-2-methoxyphenoxy)phenyl]-2,3-bis-(triisopropylsilyloxy)propyl 2-Acetylthioacetate 26. Analogous to **10**, compound **26** was prepared from **25** (0.40 g, 3.25 mmol), *S*-acethylthioacetic acid[37] (0.96 g, 7.15 mmol), EDC (1.37 g, 7.15 mmol), and DMAP (160 mg, 1.31 mmol) in CH_2Cl_2 (130 mL). After column chromatography (cyclohexane/ethyl acetate 6:1), **26** (3.79 g, 5.08 mmol, 78%) was obtained as a colorless oil; R_f 0.41 (cyclohexane/

ethyl acetate 3:1); $[\alpha]_D^{23}$ +2.9 (*c* 0.5, CHCl$_3$); IR (ATR) ν_{max} 2944, 2865, 1743, 1694, 1600, 1581, 1505, 1463, 1433, 1275, 1224, 1120, 1067, 1013, 960, 881, 844, 680, 624 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.96−1.12 (m, 42 H), 2.36 (s, 3 H), 3.59−3.69 (m, 2 H), 3.71 (dd, J = 11.3, 7.1 Hz, 1 H), 3.92 (s, 3 H), 4.27 (ddd, J = 7.1, 4.2, 3.0 Hz, 1 H), 4.44 (dd, J = 11.3, 3.0 Hz, 1 H), 4.94 (d, J = 4.3 Hz, 1 H), 6.86−6.92 (m, 2 H), 7.09 (d, J = 8.4 Hz, 1 H), 7.33−7.37 (m, 2 H), 7.43 (d, J = 2.0 Hz, 1 H), 7.65 (dd, J = 8.4, 2.0 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 12.2, 12.7, 17.9, 17.95, 18.0, 18.1, 30.0, 31.3, 56.1, 67.4, 74.2, 75.2, 112.0, 117.0, 120.0, 127.4, 128.6, 130.1, 135.3, 146.3, 156.1, 156.2, 168.5, 190.2, 193.4; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{39}H_{62}O_8NaSSi_2^+$ 769.3596, found 769.3592.

(2*R*,3*R*)-3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]-2,3-bis(triisopropylsilyloxy)propyl 2-Acetylthioacetate 27. Analogous to **11**, compound **27** was prepared from **26** (3.59 g, 4.80 mmol) and NaBH$_4$ (91.0 mg, 2.40 mmol) in a 1:1 mixture of THF and 20% aqueous MeOH (66 mL). After column chromatography (cyclohexane/ethyl acetate 5:1), **27** (3.57 g, 4.77 mmol, 99%) was obtained as a colorless oil; R_f 0.27 (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{23}$ +0.5 (*c* 1.0, CHCl$_3$); IR (ATR) ν_{max} 3413, 2943, 2865, 1743, 1702, 1608, 1505, 1463, 1426, 1270, 1222, 1123, 1092, 1067, 1012, 881, 844, 680, 624 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.97−1.11 (m, 42 H), 1.62 (t, J = 5.8 Hz, 1 H, OH), 2.37 (s, 3 H), 3.59−3.69 (m, 2 H), 3.71 (dd, J = 11.3, 7.1 Hz, 1 H), 3.83 (s, 3 H), 4.26 (ddd, J = 7.1, 4.2, 2.9 Hz, 1 H), 4.42 (dd, J = 11.3, 2.9 Hz, 1 H), 4.57 (d, J = 5.8 Hz, 2 H), 4.93 (d, J = 4.3 Hz, 1 H), 6.85−6.90 (m, 2 H), 6.95 (d, J = 2.1 Hz, 1 H), 6.97 (d, J = 8.3 Hz, 1 H), 7.11 (dd, J = 8.3, 2.1 Hz, 1 H), 7.30−7.34 (m, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 12.3, 12.7, 17.95, 18.0, 18.1, 18.2, 30.1, 31.4, 56.0, 64.8, 67.5, 74.3, 75.3, 112.7, 116.7, 119.4, 123.0, 128.4, 133.9, 134.6, 145.6, 150.7, 156.8, 168.6, 193.5; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{39}H_{64}O_8NaSSi_2^+$ 771.3753, found 771.3749.

(2*R*,3*R*)-3-[4-(5-Hydroxymethyl-2-methoxyphenoxy)phenyl]-2,3-bis(triisopropylsilyloxy)propyl 2-Mercaptoacetate 28. Analogous to **12**, compound **28** was prepared from **27** (4.22 g, 5.63 mmol) and hydrazine solution (6.10 mL) in MeCN (158 mL). After column chromatography (cyclohexane/ethyl acetate 3:1), **28** (3.73 g, 5.27 mmol, 94%) was obtained as a colorless oil; R_f 0.27 (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{23}$ +2.6 (*c* 1.0, CHCl$_3$); IR (ATR) ν_{max} 2944, 2866, 1740, 1505, 1463, 1425, 1270, 1221, 1122, 1091, 1066, 1012, 881, 844, 754, 680 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.97−1.10 (m, 42 H), 1.57 (s, br, 1 H, OH), 1.94 (t, J = 8.2 Hz, 1 H, SH), 3.17 (dd, J = 8.2, 4.6 Hz, 2 H), 3.71 (dd, J = 11.3, 7.1 Hz, 1 H), 3.83 (s, 3 H), 4.27 (ddd, J = 7.1, 4.3, 2.8 Hz, 1 H), 4.43 (dd, J = 11.3, 2.8 Hz, 1 H), 4.58 (s, 2 H), 4.93 (d, J = 4.3 Hz, 1 H), 6.86−6.90 (m, 2 H), 6.95 (d, J = 2.1 Hz, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 7.11 (dd, J = 8.3, 2.1 Hz, 1 H), 7.30−7.34 (m, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 12.2, 12.7, 17.95, 18.0, 18.1, 18.2, 26.4, 56.0, 64.8, 67.3, 74.3, 75.3, 112.6, 116.6, 119.4, 123.0, 128.4, 133.9, 134.5, 145.5, 150.7, 156.8, 170.8; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{37}H_{62}O_7NaSSi_2^+$ 729.3647, found 729.3635.

(14*R*,15*R*)-4-Methoxy-14,15-bis[(triisopropylsilyl)oxy]-2,12-dioxa-9-thiatricyclo-[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,-19-hexaen-11-one 29. A solution of thiol **28** (1.88 g, 2.66 mmol) in toluene (887 mL) was treated with SO$_3$·pyridine (423 mg, 2.66 mmol) and stirred for 2 h at 110 °C under reflux. The mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate 30:1, R_f 0.27) followed by crystallization from hexane/CH$_2$Cl$_2$ to yield **29** (780 mg, 1.13 mmol, 43%) as a colorless waxy solid; $[\alpha]_D^{23}$ +19.3 (*c* 1.0, CHCl$_3$); IR (ATR) ν_{max} 2947, 2865, 1736, 1504, 1265, 1215, 1124, 1087, 1066, 1013, 881, 681 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.01−1.12 (m, 42 H), 2.78 (d, J = 2.3 Hz, 2 H), 3.49 (d, J = 4.0 Hz, 2 H), 3.97 (s, 3 H), 4.15−4.26 (m, 3 H), 5.00 (d, J = 4.2 Hz, 1 H), 6.03 (d, J = 2.1 Hz, 1 H), 6.80 (dd, J = 8.3, 2.1 Hz, 1 H), 6.93 (d, J = 8.3 Hz, 1 H), 7.01 (dd, J = 8.2, 2.4 Hz, 1 H), 7.04 (dd, J = 8.4, 2.4 Hz, 1 H), 7.45 (dd, J = 8.2, 2.2 Hz, 1 H), 7.64 (dd, J = 8.4, 2.2 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 12.4, 12.5, 18.05, 18.1, 18.2, 31.8, 34.1, 56.2, 63.3, 74.3, 75.7, 113.1, 117.4, 120.9, 121.5, 122.4, 127.8, 129.4, 129.5, 137.9, 147.9, 149.6, 155.7, 169.5; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{37}H_{60}O_6NaSSi_2^+$ 711.3541, found 711.3526.

(14*R*,15*R*)-4-Methoxy-14,15-bis(triisopropylsilyloxy)-2,12-dioxa-9-thiatricyclo-[14.2.2.1^{3,7}]henicosa-1(18),3(21),4,6,16,-19-hexaen-11-one 9,9-dioxide 30. Analogous to **14**, compound **30** was prepared from **29** (440 mg, 0.64 mmol) and *m*CPBA (353 mg, 2.04 mmol) in CH$_2$Cl$_2$ (25 mL). After column chromatography (cyclohexane/ethyl acetate 5:1) and recrystallization from hexane/CH$_2$Cl$_2$ 4:1, **30** (384 mg, 0.53 mmol, 83%) was obtained as colorless crystals of mp 176−178 °C; R_f 0.18 (cyclohexane/ethyl acetate 8:1); $[\alpha]_D^{23}$ −23.3 (*c* 1.0, CHCl$_3$); IR (ATR) ν_{max} 2942, 2865, 1738, 1519, 1462, 1318, 1268, 1214, 1126, 1110, 1089, 1066, 1014, 882, 858, 680, 654 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.99−1.14 (m, 42 H), 3.34 (dd, J = 17.5, 1.5 Hz, 1 H), 3.47 (d, J = 17.5 Hz, 1 H), 3.98 (s, 3 H), 4.05 (dd, J = 11.9, 6.4 Hz, 1 H), 4.17 (dd, J = 14.3, 1.5 Hz, 1 H), 4.27 (dd, J = 6.4, 4.5 Hz, 1 H), 4.29 (d, J = 11.9 Hz, 1 H), 4.37 (d, J = 14.3 Hz, 1 H), 4.96 (d, J = 4.5 Hz, 1 H), 6.16 (s, br, 1 H), 6.95−6.99 (m, 2 H), 6.97 (dd, J = 8.3, 2.6 Hz, 1 H), 7.09 (dd, J = 8.4, 2.6 Hz, 1 H), 7.49 (dd, J = 8.3, 2.1 Hz, 1 H), 7.65 (dd, J = 8.4, 2.1 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 12.6, 12.65, 18.0, 18.05, 18.1, 18.2, 51.4, 56.1, 59.2, 64.1, 74.8, 76.7, 112.9, 117.3, 120.4, 121.1, 122.8, 125.1, 128.3, 129.7, 137.8, 149.6, 150.3, 155.7, 162.6; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{37}H_{60}O_8NaSSi_2^+$ 743.3440, found 743.3420.

11-*O*-Methylcorniculatolide A 31. Sulfone **20** (200 mg, 0.53 mmol) was subjected to FVP at 600 °C and 5 × 10^{-2} Torr. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 6:1) to yield **31** (88 mg, 0.26 mmol, 53%) as a white solid of mp 141−143 °C [lit.[11] 142−145 °C]; R_f 0.44 (cyclohexane/ethyl acetate 3:1); IR (ATR) ν_{max} 2925, 1727, 1586, 1516, 1505, 1465, 1435, 1414, 1358, 1263, 1212, 1149, 1127, 1029, 1008, 978, 906, 891, 867, 830, 799, 727, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.06−2.13 (m, 2 H), 2.23−2.28 (m, 2 H), 2.81 (t, J = 6.6 Hz, 2 H), 2.83−2.87 (m, 2 H), 3.95 (s, 3 H), 4.05−4.10 (m, 2 H), 5.34 (d, J = 2.1 Hz, 1 H), 6.63−6.67 (m, 1 H), 6.81 (d, J = 8.2 Hz, 1 H), 7.01−7.06 (m, 2 H), 7.27−7.32 (m, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 26.9, 28.6, 32.7, 34.0, 56.2, 64.0, 111.8, 113.3, 120.8, 123.6, 131.0, 133.2, 137.4, 146.1, 151.2, 154.5, 173.8; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{19}H_{21}O_4^+$ 313.1434, found 313.1433.

Combretastatin D-4 5. A mixture of anhydrous AlCl$_3$ (75.0 mg, 0.56 mmol) and ethanethiol (0.52 mL, 7.04 mmol) in CH$_2$Cl$_2$ (3.5 mL) was cooled to −17 °C and treated with 11-*O*-methylcorniculatolide A **31** (22.0 mg, 0.07 mmol). The mixture was stirred at −17 °C for ca. 1 h until TLC indicated consumption of the starting material. Water (5 mL) was added, the layers were separated, and the aqueous one was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic phases were washed with brine (15 mL), dried over Na$_2$SO$_2$, and concentrated under reduced pressure. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 3:1, R_f 0.32) followed by crystallization from hexane/acetone 4:1 to yield **5** (20.0 mg, 0.07 mmol, 96%) as colorless crystals of mp 153−156 °C [lit.[10] 155.4−156.3 °C]; IR (ATR) ν_{max} 3416, 2938, 1701, 1595, 1518, 1504, 1448, 1359, 1243, 1219, 1190, 1160, 1115, 942, 912, 870, 884, 805, 602 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.07−2.12 (m, 2 H), 2.24−2.27 (m, 2 H), 2.79−2.85 (m, 4 H), 4.04−4.08 (m, 2 H), 5.29 (d, J = 2.1 Hz, 1 H), 5.50 (s, br, 1 H, OH), 6.60 (dd, J = 8.1, 2.1, Hz, 1 H), 6.83 (d, J = 8.1 Hz, 1 H), 6.99−7.04 (m, 2 H), 7.29−7.32 (m, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 27.0, 28.7, 32.7, 34.0, 63.9, 112.6, 114.9, 121.5, 123.5, 131.1, 132.6, 137.9, 142.5, 149.0, 154.2, 173.9; HRMS (ESI) *m/z* [M−H+Na]$^+$ calcd for $C_{18}H_{17}NaO_4^+$ 320.1019, found 320.1017.

(13*R*,14*R*)-4-Methoxy-13,14-bis(triisopropylsilyl)oxy-2,11-dioxatricyclo-[13.2.2.1^{3,7}]icosa-1(17),3(20),4,6,15,18-hexaen-10-one 32. Analogous to **31**, compound **32** was prepared by FVP of sulfone **30** (700 mg, 0.97 mmol). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 40:1) to yield **32** (158 mg, 0.24 mmol, 25%) as a colorless waxy solid; R_f 0.44 (cyclohexane/ethyl acetate 3:1). $[\alpha]_D^{23}$ −5.0 (*c* 0.2, CHCl$_3$); IR (ATR) ν_{max} 2944, 2867, 1737, 1519, 1504, 1463, 1264, 1216, 1127, 1089, 1067, 1014, 993, 882, 799, 755, 733, 680 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.02−1.14 (m, 42 H), 2.18−2.34 (m, 2 H), 2.72 (dd, J = 17.0, 8.2 Hz, 1 H), 2.97 (dd, *J* = 17.0, 10.3 Hz, 1 H), 3.85 (dd, *J* = 12.1, 6.6 Hz, 1 H), 3.94 (s, 3 H), 4.22−4.27 (m, 2 H), 4.96 (d, *J* = 4.3 Hz, 1 H), 5.41 (d, *J* = 2.0 Hz, 1 H), 6.65 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 7.01−7.04 (m, 2 H), 7.42−7.45 (m, 1 H), 7.66−7.70 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5, 12.55, 18.1, 18.15, 26.9, 32.7, 56.3, 63.1, 74.5, 76.5, 111.9, 113.6, 120.7, 122.0, 123.5, 127.8, 128.9, 133.0, 137.6, 146.1, 151.2, 155.8, 173.9; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{37}H_{60}NaO_6Si_2^+$ 679.3821, found 679.3811.

(13*R*,14*R*)-13,14-Dihydroxy-4-methoxy-2,11-dioxatricyclo-[13.2.2.1^{3,7}]icosa-1(17),3(20),4,6,15,18-hexaen-10-one 33. A solution of silyl ether **32** (73.0 mg, 0.11 mmol) in THF (5 mL) was treated with 48% aqueous HF (23.0 μL, 1.33 mmol). The mixture was stirred at room temperature for 24 h, then further HF (23.0 μL, 1.33 mmol) was added, and the mixture was stirred for another 3 d at room temperature. The reaction was terminated by addition of saturated aqueous $NaHCO_3$ solution (3 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was taken up in THF (1 mL) and treated once more with HF (50 μL, 2.87 mmol) for 7 d at room temperature. The identical workup gave a crude product which was purified by column chromatography (cyclohexane/ethyl acetate 1:2, R_f 0.36) to afford **33** (20.0 mg, 0.06 mmol, 53%) as a white solid of mp 222−225 °C. $[\alpha]_D^{23}$ −35 (*c* 1.0, $CHCl_3$); IR (ATR) ν_{max} 3522, 3401, 2956, 2919, 1720, 1589, 1517, 1504, 1460, 1435, 1413, 1343, 1270, 1215, 1163, 1147, 1126, 1109, 1098, 1037, 1016, 995, 976, 954, 910, 878, 848, 803 cm^{-1}; ^{1}H NMR (MeOD, 500 MHz) δ 2.11 (ddd, *J* = 17.0, 11.8, 1.2 Hz, 1 H), 2.45 (ddd, *J* = 17.0, 7.2, 1.2 Hz, 1 H), 2.59 (dd, *J* = 16.6, 7.2 Hz, 1 H), 2.98 (ddd, *J* = 16.6, 11.8, 0.8 Hz, 1 H), 3.59 (d, *J* = 11.8 Hz, 1 H), 3.82 (t, *J* = 7.6 Hz, 1 H), 3.89 (s, 3 H), 4.26 (dd, *J* = 11.8, 7.6 Hz, 1 H), 4.50 (d, *J* = 8.0 Hz, 1 H), 5.30 (d, *J* = 2.1 Hz, 1 H), 6.67 (dd, *J* = 8.2, 2.1 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.94 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.12 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.29 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.65 (dd, *J* = 8.5, 2.2 Hz, 1 H); ^{13}C NMR (MeOD, 125 MHz) δ 27.9, 33.5, 57.0, 68.8, 76.6, 79.5, 114.0, 114.7, 122.4, 124.1, 125.2, 130.1, 131.4, 134.7, 139.1, 147.8, 152.7, 157.9, 175.0; HRMS (ESI) *m*/*z* $[M - H_2O + H]^+$ calcd for $C_{19}H_{19}O_5^+$ 327.1227, found 327.1224.

Methylcombretastatin D-2 34 and (11*Z*)-4-methoxy-2-oxatricyclo[11.2.2.1^{3,7}]octadeca-1(15), 3(18),4,6,11,13,16-heptaene 35. Analogous to the synthesis of **31**, sulfone **14** (150 mg, 0.40 mmol) was submitted to a FVP. The crude product was purified and separated by column chromatography (cyclohexane/ethyl acetate 40:1) to yield **34** (25 mg, 0.08 mmol, 20%) as white solid of mp 131−133 °C [lit.[12] 130−132 °C] and **35** (6 mg, 0.03 mmol, 6%), which was obtained as colorless crystals of mp 122−124 °C after crystallization from pentane/hexane 3:1.

Compound 34. R_f 0.30 (cyclohexane/ethyl acetate 5:1); IR (ATR) ν_{max} 2961, 2908, 1729, 1583, 1519, 1502, 1464, 1433, 1376, 1345, 1264, 1217, 1149, 1127, 1029, 978, 904, 869, 837, 803, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27−2.31 (m, 2 H), 2.87−2.91 (m, 2 H), 3.95 (s, 3 H), 4.66 (d, *J* = 6.8 Hz, 2 H), 5.11 (d, *J* = 2.1 Hz, 1 H), 6.05 (dt, *J* = 11.0, 6.8 Hz, 1 H), 6.66−6.70 (m, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 7.08−7.13 (m, 3 H), 7.29−7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 31.2, 59.0, 59.2, 112.1, 113.2, 121.2, 123.9, 125.4, 128.9, 132.3, 135.0, 137.8, 146.0, 151.3, 155.9, 173.2; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}O_4^+$ 311.1278, found 311.1275.

Compound 35. R_f 0.66 (cyclohexane/ethyl acetate 5:1); IR (ATR) ν_{max} 2928, 1578, 1517, 1491, 1461, 1408, 1258, 1212, 1191, 1149, 1123, 1091, 1029, 962, 918, 869, 831, 791, 730, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22−1.29 (m, 2 H), 1.71−1.82 (m, 2 H), 2.37−2.45 (m, 2 H), 3.93 (s, 3 H), 4.08 (d, *J* = 2.1 Hz, 1 H), 5.87 (dt, *J* = 10.9, 8.2 Hz, 1 H), 6.53−6.57 (m, 1 H), 6.74 (d, *J* = 8.2 Hz, 1 H), 6.93 (d, *J* = 10.9 Hz, 1 H), 7.21−7.26 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 26.3, 30.3, 56.3, 112.0, 115.6, 121.5, 126.0, 130.6, 131.4, 133.1, 134.8, 136.4, 145.2, 153.8, 160.4; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}O_2^+$ 267.1380, found 267.1372.

Crystal Data. $C_{18}H_{18}O_2$, M = 1052.36, monoclinic, space group $P2_1/c$, a = 8.4129(17), b = 18.533(4), c = 9.925(2) Å, $\alpha = \gamma$ = 90°, β = 112.62(3)°, V = 1428.4(5) Å^3, Z = 4, λ = 0.71073 Å, μ = 0.079 mm^{-1}, T = 293(2) K; 10498 reflections measured, 2652 unique; final refinement to convergence on F^2 gave R = 0.0540 and Rw = 0.0990, GOF = 0.608. CCDC 1505171.

Combretastatin D-2 4. Analogous to **5**, compound **4** was prepared from **34** (11.0 mg, 35.4 μmol), anhydrous $AlCl_3$ (37.0 mg, 0.28 mmol), and ethanethiol (0.26 mL, 3.54 mmol) in CH_2Cl_2 (1.48 mL). After column chromatography (cyclohexane/ethyl acetate 5:1, R_f 0.27) followed by crystallization from hexane/acetone 4:1, **4** (7.0 mg, 23.6 μmol, 67%) was obtained as colorless crystals of mp 152−154 °C [lit.[7b] 148−151 °C]. IR (ATR) ν_{max} 3426, 2923, 2854, 1730, 1594, 1519, 1503, 1439, 1376, 1283, 1215, 1159, 1111, 978, 869, 807, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27−2.31 (m, 2 H), 2.85−2.89 (m, 2 H), 4.64 (d, *J* = 6.8 Hz, 2 H), 5.06 (d, *J* = 2.0 Hz, 1 H), 5,46 (s, br, 1 H, OH), 6.06 (dt, *J* = 11.1, 6.8 Hz, 1 H), 6.63 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 7.08−7.13 (m, 3 H), 7.31−7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8, 31.3, 59.0, 112.4, 115.3, 121.8, 123.9, 125.6, 129.0, 131.9, 135.5, 137.7, 142.5, 148.6, 155.5, 173.3; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}O_4^+$ 297.1121, found 297.1113.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02586.

Crystal data for **35** (CIF)

^{1}H and ^{13}C NMR spectra of **4**, **5**, **7**−**35**; HPLC chromatograms of the ee determination of **22** (PDF)

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Notes

The authors declare no competing financial interest.

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