Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2835–2843

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of kurzilactone and determination of its absolute configuration

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Received 12 October 2001; accepted 8 November 2001

Abstract—Both (5*S*,7*S*)- and (5*R*,7*S*)-isomers of kurzilactone were synthesized from a 'chiral epoxy-aldehyde synthon' through the coupling of an acyl anion equivalent and the dianion of acetoacetate, followed by formation of the Kawa-type lactone by cyclization and elimination. Comparing the spectral data of the synthesized and naturally occurring kurzilactone, the C(5)- and C(7)-stereogenic centers of the natural kurzilactone was assigned a corrected *anti*-relationship with (5*R*,7*S*)-absolute configuration. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We disclose herein a strategy for the synthesis of kurzilactone, a new Kawa-type lactone.[1] Our interest in this class of compounds stems from their close structural relationship to the pharmacologically important statin family which are highly potent inhibitors of 3-hydroxy-3-methylglutaryl agent coenzyme A reductase.[2] Kurzilactone was isolated from leaves of *Cryptocarya kurzii*, a plant which is indigenous to Malaysia. A preliminary report included a tentative stereochemical assignment established through an NMR experiment; both stereogenic centers bearing hydroxyl groups in the side chain were assigned a *syn*-relationship. Kurzilactone shows remarkable cytotoxicity against KB cells ($IC_{50}=1$ μg/mL).[1a] Because the absolute configuration of kurzilactone has not been assigned, our synthetic strategy was to develop an enantioselective synthetic method for kurzilactone with hydroxyl groups in both *syn*- or *trans*-relationship and to determine the absolute configuration of the natural product.

2. Results and discussion

A convergent route toward kurzilactone was devised through a simple disconnection of the two bonds, as illustrated in Fig. 1. We envisaged the introduction of the (7*S*)-stereochemistry by coupling an acyl anion equivalent **4** with an appropriate 'chiral epoxy aldehyde synthon' **3**, forming the C(5)-stereogenic center by condensation of the aldehyde function in the chiral synthon **3** with the acetoacetate dianion **5**. The α,β-unsaturated-δ-lactone was formed by reduction and elimination of the β-carbonyl group.

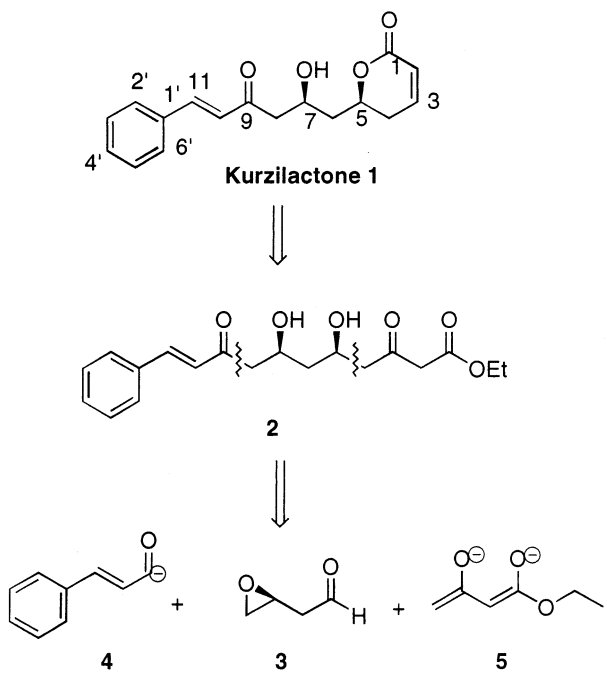

Figure 1. Retrosynthesis of kurzilactone.

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PII: S0957-4166(01)00506-7

The desired epoxy aldehyde synthon **3** was prepared from ethyl (*S*)-4-chloro-3-hydroxy butanoate **7**, which was obtained from the commercial 4-chloroacetoacetate **6**[3] in 94% yield (97% e.e.) by hydrogenation over catalytic ruthenium-optically active phosphine complex $Ru(OAc)_2$[(*R*)-(−)-BINAP] (0.1% mol) at a pressure of 40 kg/cm^2 at 100°C for 1.5 h. The chlorohydrin **7** was protected as the *tert*-butyldimethylsilyl ether **8** ($[\alpha]_D^{20} = -21.7$, *c* 1.03, $CHCl_3$), which was reduced with $LiAlH_4$ at 0°C,[4] and oxidized the resulting alcohol **9** under Swern conditions[5] to give aldehyde **10** in 92%. The aldehyde **10** was converted to diethyl acetal **11** in 74% yield by treatment with triethyl orthoformate with Amberlyst-15 as catalyst.[6] Subsequent cleavage of the silyl ether with tetrabutylammonium fluoride in THF[7] directly gave the desired 'chiral epoxy aldehyde synthon' equivalent **12**[8] (Scheme 1).

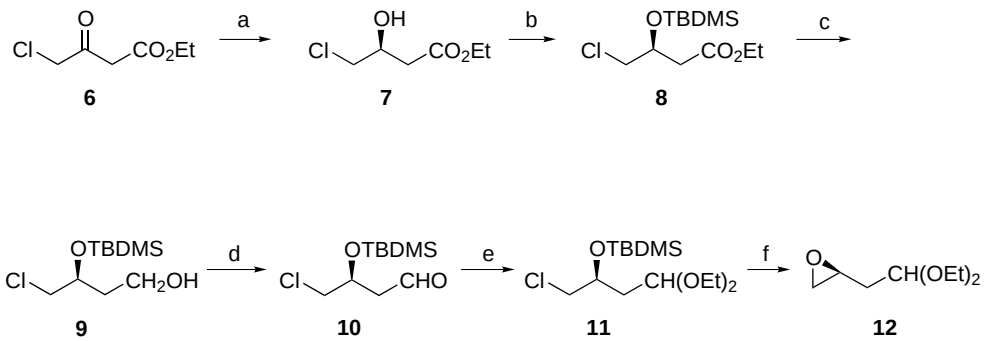
The aryl fragment was prepared from *trans*-cinnamaldehyde **13**, the aldehyde of which was transformed into the thioacetal **14** in 70% with 1,3-propanedithiol and ceric ammonium nitrate as the catalyst in chloroform.[9] The epoxide **12** was coupled with the acyl anion equivalent **14** (1.0 equiv.), prepared by metallation at −78°C with 1.0 equiv. of *n*-butyllithium in the presence of $BF_3{\cdot}Et_2O$ at −78°C to obtain **15** in 58% yield. After masking the resulting hydroxyl group with *tert*-butyldimethylsilyl chloride, the diethyl acetal **16** was treated with 50% aqueous CF_3CO_2H in chloroform[10] at 0°C over 2 h to give aldehyde **17** in 95% yield.

The acetoacetate dianion provides a four-carbon chain to homologate simpler molecules. The utility of this homologation is that all four carbons can subsequently be reacted regioselectively. Thus, the acetoacetate unit is one of the most versatile starting materials available in the synthesis of complex natural products. Despite the simplicity of the idea, only a few reactions of 1,3-dianions and 1,3-dianion equivalents with 1,2-dielectrophiles have been reported.[11] Ethyl acetoacetate **18** was treated with sodium hydride in THF at 0°C. The mixture was stirred for 10 min before cooling to −10°C; then a solution of *n*-butyllithium in hexane was added and the mixture was cooled to −50°C. Coupling the aldehyde **17** with the dianion of ethyl acetoacetate **5** gave a 76% yield of the 5,7-*cis*-dihydroxy ketone **19a** along with its *trans*-isomer **19b** in a ratio of 1.7:1. These isomers were separable by flash column chromatography (Scheme 2).

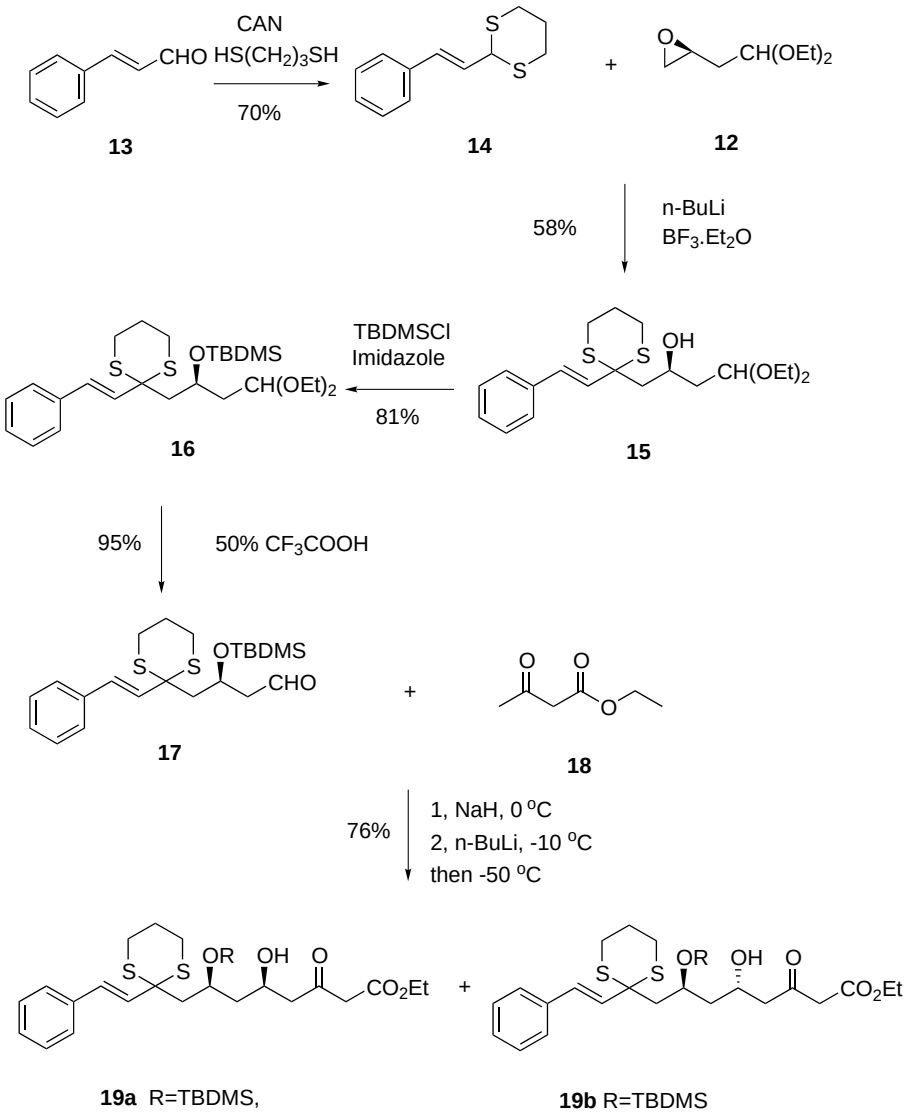
To identify the stereochemistry of the two stereogenic centers in **19a**, the silyl group was removed by treatment with pyridinium hydrofluoride. Treatment of the resulting diol with dimethoxypropane gave the fixed six-membered ring 1,3-dioxane **20**. The relative stereochemistry of C(5) and C(7) was assigned as *syn* with (5*R*,7*S*)-configuration based on the NOE correlation between the protons on C(5) and C(7) at chemical shift 4.10 and 4.25 ppm (Fig. 2), which was confirmed by X-ray structural analysis of the final product. Thus, the 5,7-dihydroxy system in **19b** had a *trans*-relationship with (5*S*,7*S*)-configuration.

Compound **19** has the fully elaborated backbone of kurzilactone. The *syn*-dihydroxyl group of natural kurzilactone was tentatively deduced on the basis of NOE correlation between C(5)H and C(7)H. To the best of our knowledge, it is difficult to assign the relationship between the 1,3-dihydroxyl system and the methylene group in the open chain.[12] To determine the correct absolute configuration of natural kurzilactone, both isomers of kurzilactone were synthesized by the following steps. The ketone function in **19** was reduced with $NaBH_4$ in THF at −40°C to yield the hydroxy ester **21**, which was cyclized by treatment with catalytic *p*-TsOH in CH_2Cl_2 at room temperature to form β-hydroxy-δ-lactone **22**.[13] Elimination of the β-hydroxyl group in **22** was effected via mesylate displacement by treatment with methanesulfonyl chloride and triethylamine in dichloromethane,[14] which afforded the α,β-unsaturated-δ-lactone **23**. After cleavage of the thioketal with $HgClO_4/CaCO_3$ in THF/H_2O (5:1)[15] and removal of the silyl protecting group,[16] (5*S*,7*S*)-kurzilactone **25a** and (5*R*,7*S*)-kurzilactone **25b** were obtained in 58 and 79% yields, respectively (Scheme 3, Fig. 3).

The structure of **25a** was confirmed by determination of the X-ray crystal structure, which demonstrated the C(5) and C(7) hydroxyl groups had *syn*-relationship. In comparing the spectral data of the synthesized and



Scheme 1. *Reagents*: (a) $H_2/Ru(OAc)_2$[(*R*)-BINAP]/EtOH, 40 kg/cm^2, 100°C, 1.5 h, 94%; (b) TBDMSCl/imidazole/DMAP/CH_2Cl_2, 24 h, 98%; (c) $LiAlH_4/Et_2O$, 0°C, 2 h, 91%; (d) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2, −60°C, 92%; (e) $HC(OEt)_3$/Amberlyst-15/CH_2Cl_2, rt, 48 h, 74%; (f) *n*-Bu_4NF/THF, 24 h, 60%.



Scheme 2.

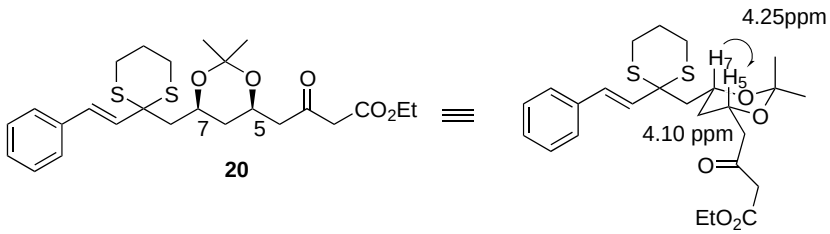
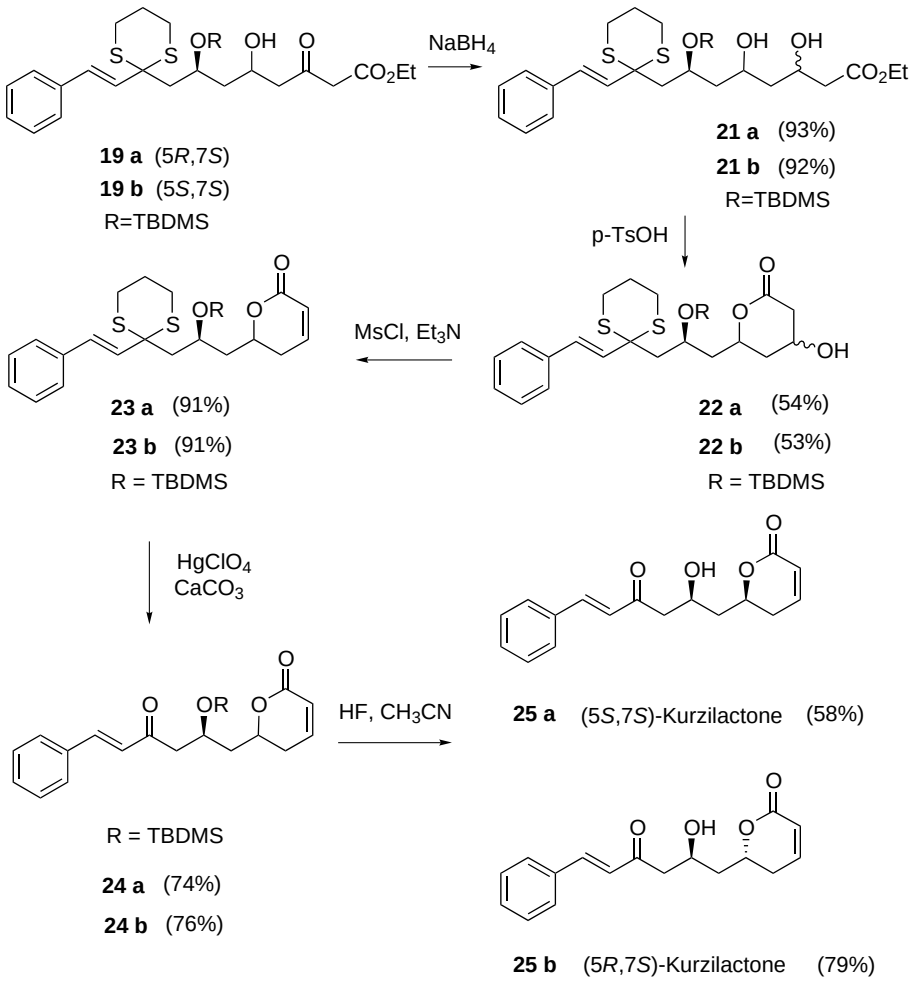


Figure 2. NOEs of C(5)H and C(7)H.

natural kurzilactone, the synthesized kurzilactone **25b** has the same spectral data [^{1}H NMR in $CDCl_3$, ^{1}H NMR in benzene-d_6, ^{13}C NMR, NOESY and a positive specific rotation: $[\alpha]_D^{20}=+84$ (c 0.23, $CHCl_3$) comparable with the reported specific rotation: $[\alpha]_D^{20}=+100$, c 2.4, $CHCl_3$)].[1a] Isomer **25a** has different C(5)H and C(7)H chemical shifts (δ_H: 4.40 and 4.20 ppm ^{1}H NMR in benzene-d_6), whereas the chemical shifts of C(5)H and C(7)H in the natural product are equivalent at δ_H: 4.48 ppm (Table 1). Compound **25a** also shows negative optical rotation ($[\alpha]_D^{20}=-60.8$, c 0.68, $CHCl_3$). By comparison of the spectral data for the synthesized and naturally isolated kurzilactones, the correct stereochemistry of the C(5) and C(7) stereogenic centers of naturally occurring Kurzilactone is *anti*-(5*R*,7*S*).



Scheme 3.

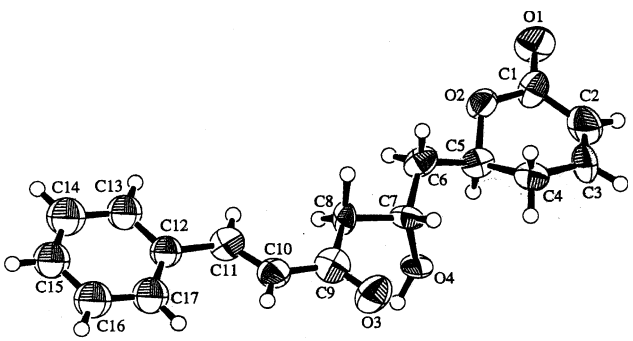


Figure 3. The X-ray crystal structure of compound **25a**.

3. Conclusions

In conclusion, a practical convergent pathway has been developed for the synthesis of both (5*S*,7*S*)- and (5*R*,7*S*)-isomers of kurzilactone by the coupling of an acyl anion equivalent with the dianion of acetoacetate and a 'chiral epoxy aldehyde synthon,' followed by formation of the Kawa type-lactone by cyclization and elimination. By comparison of the spectral data of the synthesized and naturally occurring kurzilactone, the two stereogenic carbons in natural kurzilactone were assigned a corrected (5*R*,7*S*)-configuration.

4. Experimental

4.1. Ethyl (*S*)-4-chloro-3-hydroxybutanonate 7

An autoclave was charged with a solution of ethyl 4-chloro-3-oxobutanonate **6** (20 g, 121.5 mmol) in methanol (300 mL) and was hydrogenated over $Ru(OAc)_2$[(*R*)-(−)-BINAP] (200 mg) at a pressure of 40 kg/cm^3 at 100°C for 1.5 h. The reaction mixture was concentrated under reduced pressure. The residue was distilled under reduced pressure to afford **7** (19 g, 94%) as a colorless oil, bp 95–97°C/3 mmHg. The enantiomeric excess of **7** was determined to be 97% e.e. by HPLC analysis of the corresponding (*R*)-MTPA ester. $[\alpha]_D^{20} = -20.5$ (*c* 5.5, $CHCl_3$) [lit.[3a] for (*S*)-**7** in 96% e.e., $[\alpha]_D^{24} = -19.1$ (*c* 7.71, $CHCl_3$)].

4.2. Ethyl (*S*)-4-chloro-3-(*tert*-butyldimethylsilyloxyl)-butanoate 8

A solution of compound **7** (1.66 g, 10 mmol) in CH_2Cl_2 (30 mL) was stirred with *tert*-butyldimethysilylchloride (2 g, 13.2 mmol), imidazole (3.4 g, 50 mmol) and a catalytic amount of DMAP (10 mg) overnight at rt under N_2. The reaction mixture was poured into water (20 mL) and was then neutralized by dropwise addition

Table 1. ^{1}H NMR in CCl_3D and C_6D_6 data for naturally isolated kurzilactone and synthesized (5*S*,7*S*)-kurzilactone **25a** and (5*R*,7*S*)-kurzilactone **25b**

C	Naturally isolated kurzilactone **1a**		(5*R*,7*S*)-Kurzilactone **25b**		(5*S*,7*S*)-Kurzilactone **25a**	
	δ_H (*J* Hz) $CDCl_3$	δ_H (*J* Hz) C_6D_6	δ_H (*J* Hz) $CDCl_3$	δ_H (*J* Hz) C_6D_6	δ_H (*J* Hz) $CDCl_3$	δ_H (*J* Hz) C_6D_6
2	6.00 dd, 1H (10, 2)	5.77 dd, 1H (10, 2)	6.00 dd, 1H (10, 2)	5.77 m, 1H	6.04 dd, 1H (10, 2)	5.80 dd, 1H (9.8, 2)
3	6.90 ddd, 1H (10, 5.5, 3)	5.97 m, 1H	6.90 m, 1H	5.97 m, 1H	6.90 m, 1H	5.97 m, 1H
4	2.39 m, 2H	1.59 m, 1H	2.39 m, 2H	1.59 m, 1H	2.47 m, 2H	1.50 m, 2H
5	4.77 m, 1H	4.48 m, 1H	4.77 m, 1H	4.48 m, 1H	4.78 m, 1H	4.40 m, 1H
6	1.88 m, 2H	1.59 m, 2H	1.88 m, 2H	1.59 m, 2H	2.10 m, 1H 1.90 m, 1H	2.50 m, 1H 2.30 m, 1H
7	4.50 m, 1H	4.48 m, 1H	4.50 m, 1H	4.48 m, 1H	4.40 m, 1H	4.20 m, 1H
8	2.81 dd, 1H (17, 8) 2.93 dd, 1H (17, 3.5)	2.53 m, 2H	2.81 dd, 1H (17.4, 8.8) 2.93 dd, 1H (17.4, 2.8)	2.53 m, 2H	2.95 m, 2H	1.50 m, 2H
10	6.73 d, 1H (16)	6.58 d, 1H (16)	6.73 d, 1H (16)	6.58 d, 1H (16)	6.74 d, 1H (16)	6.50 d, 1H (16)
11	7.58 d, 1H (16)	7.50 d, 1H (16)	7.58 d, 1H (16)	7.50 d, 1H (16)	7.60 d, 1H (16)	7.45 d, 1H (16)
2′						
3′	7.39–7.54, 5H	7.00–7.30, 5H	7.39–7.54, 5H	7.00–7.30, 5H	7.26–7.57, 5H	7.00–7.20, 5H
4′						
5′						
6′						

of cold aqueous HCl (0.5 M). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was washed with saturated aqueous Na_2CO_3 and brine, dried with anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether/CH_2Cl_2 = 3:1) to give **8** as a colorless oil (2.75 g, 98%): $[\alpha]_D^{20} = -21.7$ (*c* 1.03, $CHCl_3$); IR (neat) 2958, 2932, 2859, 1739, 1473, 1378, 1311 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.3 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.5 (m, 2H), 2.7 (dd, *J* = 15.2 Hz, 4.8 Hz, 1H), 2.5 (dd, *J* = 15.2 Hz, 7.2 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.0, 69.6, 60.7, 48.2, 40.5, 25.7, 18.0, 14.3, –4.6, –4.9 ppm; Ms m/e (relative intensity) 281 (M^++1, 85), 245 (59), 223 (100), 195 (46), 171 (17), 115 (26), 85 (41), 75 (36); HRMS calcd for $C_{12}H_{26}O_3SiCl$: 281.1339; found: 281.1336.

4.3. (*S*)-4-Chloro-3-(*tert*-butyldimethylsilyloxyl)butanol 9

A solution of **8** (560 mg, 2 mmol) in Et_2O (5 mL) was added slowly to a solution of $LiAlH_4$ (76 mg) in Et_2O (20 mL) at 0°C. The reaction mixture was allowed to warm to room temperature slowly. After stirring for 2 h at rt, a few drops of ethyl acetate was added to quench the reaction. The reaction mixture was filtered through Celite and washed with ether (3×20 mL). Concentration of the filtrate followed by flash column chromatography (eluted with petroleum ether/EtOAc = 3:1) gave **9** as a colorless oil (435 mg, 91%): $[\alpha]_D^{20} = -15.3$ (*c* 1.75, $CHCl_3$); IR (neat) 3359, 2957, 2859, 1473 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 1H), 3.75 (m, 2H), 3.5 (d, *J* = 5.77 Hz, 2H), 2.2 (br, 1H), 1.8 (m, 2H), 0.85 (s, 9H), 0.15 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 71.0, 59.4, 48.0, 36.6, 25.9, 18.1, –4.5, –4.8 ppm; Ms m/e (relative intensity) 238 (M^+, 0.2), 223 (100), 221 (2), 181 (4), 167 (12), 149 (44), 107 (50), 71 (20), 43 (100); HRMS calcd for $C_6H_{14}O_2SiCl$: 181.0451; found: 181.0453.

4.4. (*S*)-4-Chloro-3-(*tert*-butyldimethylsilyloxyl)butanal 10

To a solution of oxalyl chloride (1.1 mL) in dry CH_2Cl_2 (30 mL) was added DMSO (1.8 mL) and the mixture heated at –60°C under N_2 for 25 min. A solution of compound **9** (2.14 g, 9 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for a further 2 h, Et_3N (7 mL) was added and the mixture stirred for 0.5 h. The mixture was allowed to warm to rt and then poured into ice-water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/CH_2Cl_2 = 3:1) yielded aldehyde **10** as a colorless oil (1.95 g, 92%): $[\alpha]_D^{20} = -17.6$ (*c* 1.650, $CHCl_3$); IR (neat) 2958, 2932, 2898, 2860, 1728, 1435, 1312 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.8 (t, *J* = 1.84 Hz, 1H), 4.35 (m, 1H), 3.55 (dd, *J* = 11 Hz, 4.8 Hz, 1H), 3.45 (dd, *J* = 11 Hz, 6.4 Hz, 1H), 2.75 (m, 2H), 0.9 (s, 9H), 0.15 (s, 3H), 0.1 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 200.4, 67.9, 48.8, 48.0, 25.6, 18, –4.6, –4.9 ppm; Ms m/e (relative intensity) 237 (M^++1, 4), 217 (M^+–29, 3), 179 (M^+–57, 26), 149 (47), 117 (100), 101 (96), 75 (83); HRMS calcd for $C_{10}H_{21}O_2SiCl$: 236.0999; found: 236.0955.

4.5. (*S*)-4-Chloro-1,1-diethoxy-(*tert*-butyldimethylsilyloxyl)butane 11

A mixture of orthoformic acid triethyl ester (8 mL) and compound **10** (2.36 g, 10 mmol) in CH_2Cl_2 (20 mL) was stirred with Amberlyst-15 (1 g) under N_2 for 48 h at rt. The catalyst was filtered and washed with CH_2Cl_2 (2×10 mL). After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/CH_2Cl_2 = 4:1) to give **11** as a colorless oil (2.28 g, 74%). $[\alpha]_D^{20} = -10.8$ (*c*, 0.481, $CHCl_3$); IR (neat) 2931, 1473, 1377, 1257, 1125, 1091, 1065 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 4.70 (m, 1H), 4.1

(m, 1H), 3.7 (m, 4H), 3.5 (m, 2H), 1.9 (m, 1H), 1.8 (m, 1H), 1.15 (m, 6H), 0.9 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (CD_3COCD_3) δ 101.3, 70.8, 62.4, 62.0, 50.9, 40.6, 26.8, 19.0, 16.3, −3.6, −3.9 ppm; Ms m/e (relative intensity) 310 (M^+, 0.4), 265 (42), 229 (19), 193 (100), 143 (40), 103 (72); HRMS calcd for $C_{12}H_{26}O_2SiCl$: 265.1390; found: 265.1385.

4.6. (*S*)-(1,1-Diethoxy)-3-epoxybutane 12

To a solution of **11** (1.18 g, 3.8 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of *n*-Bu_4NF in THF (1.0 M, 10 mL, 10 mmol) for 24 h at rt under N_2. The reaction mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure keeping the heating bath below 15°C. The residue was subjected to flash chromatography (eluted with petroleum ether (30–60)/CH_2Cl_2 = 5:1) to yield epoxide **12** as a colorless oil (367 mg, 60%): $[\alpha]_D^{20} = -7$ (*c* 0.502, $CHCl_3$); IR (neat) 2962, 1368, 1260, 1142, 1058, 981, 960, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.7 (dd, *J* = 6.7 Hz, 4.7 Hz, 1H), 3.65 (m, 4H), 3.1 (m, 1H), 2.75 (t, *J* = 4.5 Hz, 1H), 2.5 (dd, *J* = 5 Hz, 2.7 Hz, 1H), 1.8 (m, 2H), 1.25 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 101.5, 62.2, 61.7, 49.1, 46.8, 38.1, 15.6 ppm; Ms m/e (relative intensity) 160 (M^+, 10), 149 (100), 133 (5), 105 (11), 103 (15).

4.7. 2-(1-Styryl)-1,3-dithian 14

A mixture of *trans*-cinnamaldehyde (13.2 g, 12.6 mL, 100 mmol), 1,3-propanedithiol (12 mL, 120 mmol) and ceric amonium nitrate (5.48 g, 10 mmol) in dry $CHCl_3$ (250 mL) was stirred overnight at rt. The reaction mixture was diluted with $CHCl_3$ (1 L), then washed with 5% aqueous NaOH solution (3×100 mL) and dried. The solvent was removed under reduced pressure and the brown residue was purified through flash chromatography over silica gel (eluted with petroleum ether/EtOAc = 5:1) to afford **14** as needles (15.4 g, 70%): mp 57–58°C; IR (KBr) 3027, 2898, 1496, 1448, 1422, 1275, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 6.75 (d, *J* = 16 Hz, 1H), 6.25 (dd, *J* = 16 Hz, 7 Hz, 1H), 4.75 (d, *J* = 7 Hz, 1H), 2.9 (m, 4H), 2.15 (m, 1H), 1.85 (m, 1H) ppm; Ms m/e (relative intensity) 222 (M^+, 100), 189 (13), 147 (89), 129 (4), 115 (23), 103 (3). Anal. calcd for $C_{12}H_{14}S_2$: C, 64.81; H, 6.35. Found: C, 64.54; H, 6.34.

4.8. (*S*)-4,4-Diethoxy-1-(2-styryl-[1,3]dithian-2-yl)butan-2-ol 15

To a solution of **14** (444 mg, 2 mmol) and **12** (160 mg, 1 mmol) in dry THF (25 mL) was added a solution of *n*-BuLi in hexane (1.0 M, 2 mL, 2 mmol) at −78°C under N_2 for 25 min. Then a solution of $BF_3{\cdot}Et_2O$ (0.07 mL) in dry THF (2 mL) was added dropwise. After 1 h, the reaction was quenched by the slow addition of MeOH (0.2 mL) followed by saturated aqueous NH_4Cl (2 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL). The extracts were washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 5:1) yielded **15** as a colorless oil (220 mg, 58%): $[\alpha]_D^{20} = -4.2$ (*c* 0.502, CH_3COCH_3); IR (neat) 3487, 2974, 2929, 1447, 1423, 1375, 1124 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 7.5 (m, 2H), 7.3 (m, 2H), 7.25 (m, 1H), 6.9 (d, *J* = 15.9 Hz, 1H), 6.4 (d, *J* = 15.9 Hz, 1H), 4.7 (m, 1H), 4.1 (m, 1H), 3.65 (m, 2H), 3.45 (m, 2H), 2.9 (m, 2H), 2.75 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.8 (m, 1H), 1.7 (m, 1H), 1.1 (m, 6H) ppm; Ms m/e (relative intensity) 382 (M^+, 3), 336 (M^+–46, 79), 290 (51), 237 (57), 221 (100), 185 (36), 161 (37), 129 (90), 103 (48); anal. calcd for $C_{20}H_{30}O_3S_2$: C, 62.79; H, 7.90. Found: C, 63.16; H, 8.13%.

4.9. 2-((4,4-Diethoxy-(2*S*)-(*tert*-butyldimethylsiloxyl))butyl)-2-(2-phenyl-1-ethenyl)-1,3-dithiane 16

A solution of **15** (200 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) was treated with *tert*-butyldimethylsilylchloride (150 mg, 1 mmol) and imidazole (200 mg, 2.94 mmol) under N_2 overnight at rt. The mixture was diluted with CH_2Cl_2 (20 mL), and the resulting solution was washed with cold aqueous HCl (0.5 M, 2×10 mL), saturated Na_2CO_3, and brine. The organic phase was dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by flash chromatography on silica gel (eluted with petroleum ether/EtOAc = 20:1) to give **16** as a colorless oil (210 mg, 81%): $[\alpha]_D^{20} = +17.3$ (*c*, 1.32, CH_3COCH_3); IR (neat) 2956, 2930, 2857, 1472, 1447, 1377, 1255, 1118, 1066 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 7.5 (m, 2H), 7.3 (m, 3H), 6.8 (d, *J* = 15.9 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 4.8 (m, 1H), 4.15 (m, 1H), 3.55 (m, 2H), 3.3 (m, 2H), 2.9 (m, 2H), 2.7 (m, 2H), 2.15 (m, 2H), 2.05 (m, 2H), 1.8 (m, 1H), 1.6 (m, 1H), 1.05 (m, 6H), 0.9 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H) ppm; Ms m/e (relative intensity) 450 (M^+–46, 10), 439 (M^+–57, 2), 379 (4), 221 (92), 189 (45), 129 (56), 103 (100), 75 (71); anal. calcd for $C_{26}H_{44}O_3S_2Si$: C, 62.85; H, 8.93. Found: C, 63.03; H, 8.90%.

4.10. (3*S*)-(*tert*-Butyldimethylsilyloxyl)-4-(2-styryl-[1,3]dithian-2-yl)-butyraldehyde 17

To a solution of **16** (218 mg, 0.44 mmol) in chloroform (4 mL) was added 50% aqueous CF_3COOH (2 mL) in dropwise at 0°C. After 2 h the mixture was poured into saturated aqueous Na_2CO_3 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with brine and dried (Na_2SO_4). After removal of solvent in vacuo, the residue was purified by flash chromatography on silica gel (eluted with petroleum ether/EtOAc = 10:1) to give **17** as a white solid (176 mg, 95%): mp 56–58°C; $[\alpha]_D^{20} = +10.5$ (*c* 0.605, CH_3COCH_3); IR (KBr) 2957, 2911, 2851, 2726, 1720, 1472, 1253, 1127, 1086, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.8 (s, 1H), 7.45 (m, 2H), 7.35 (m, 3H), 6.82 (d, *J* = 15.8 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 4.5 (m, 1H), 2.95 (m, 2H), 2.8 (m, 1H), 2.7 (m, 2H), 2.6 (m, 1H), 2.25 (d, *J* = 5.8 Hz, 2H), 2.0 (m, 2H), 0.85 (s,

9H), 0.15 (s, 3H), 0.12 (s, 3H) ppm; Ms m/e (relative intensity) 422 (M^+, 1), 365 (M^+–57, 0.7), 291 (2), 247 (4), 221 (15), 129 (100), 73 (34); anal. calcd for $C_{22}H_{34}O_2S_2Si$: C, 62.51; H, 8.11. Found: C, 62.64; H, 8.09%.

4.11. Preparation of compounds 19a and 19b

To a suspension of NaH (60%, 48 mg) in dry THF (20 mL) under N_2 was added dropwise ethyl acetoacetate (130 mg) in dry THF (5 mL) at 0°C over 1 h. The mixture was stirred for 10 min before cooling to –10°C; then a solution of *n*-BuLi in hexane (2.0 M, 0.5 mL, 1 mmol) was added dropwise and cooled to –50°C. The mixture was stirred for a further 25 min and then a solution of aldehyde **17** (400 mg, 0.95 mmol) in dry THF (5 mL) was added and the mixture stirred for 1 h, followed by addition of MeOH (0.3 mL) and saturated NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 4:1) yielded **19a** (250 mg) and **19b** (148 mg) in 76% of yield. Data for **19a**: $[\alpha]_D^{20} = +16$ (*c* 0.104, CH_3COCH_3); IR (neat) 3528, 2955, 2930, 2857, 1743, 1714, 1472, 1412, 1368, 1316 cm^{-1}; ^1H NMR (C_6D_6) δ 7.5 (m, 2H), 7.3 (m, 3H), 7.1 (d, $J = 15.8$ Hz, 1H), 6.5 (d, $J = 15.8$ Hz, 1H), 4.65 (m, 1H), 4.5 (m, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.2 (s, 2H), 2.8 (m, 2H), 2.6 (d, $J = 6.1$ Hz, 2H), 2.5 (m, 2H), 2.42 (m, 2H), 1.9 (m, 2H), 1.75 (m, 1H), 1.5 (m, 1H), 1.15 (s, 9H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.4 (s, 3H), 0.35 (s, 3H) ppm. Ms m/e (relative intensity) 552 (M^+, 1), 506 (M^+–46, 4), 495 (3), 445 (7), 357 (7), 313 (8), 221 (42), 167 (58), 129 (100), 115 (22), 73 (43); anal. calcd for $C_{28}H_{44}O_5S_2Si$: C, 60.83; H, 8.02. Found: C, 61.01; H, 8.20%.

19b: $[\alpha]_D^{20} = -15.0$ (*c*, 0.254, CH_3COCH_3); IR (neat) 3499, 2955, 2931, 2857, 1744, 1715, 1472, 1412, 1314 cm^{-1}. ^1H NMR (C_6D_6) δ 7.5 (m, 2H), 7.3 (m, 3H), 7.1 (d, $J = 15.8$ Hz, 1H), 6.5 (d, $J = 15.8$ Hz, 1H), 4.78 (m, 1H), 4.6 (m, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.2 (s, 2H), 2.8 (m, 2H), 2.65 (d, $J = 6.1$ Hz, 2H), 2.42 (m, 2H), 2.38 (d, $J = 3.6$ Hz, 2H), 2.1 (m, 1H), 1.75 (m, 2H), 1.55 (m, 1H), 1.1 (s, 9H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.4 (s, 3H), 0.35 (s, 3H) ppm. Ms m/e (relative intensity) 552 (M^+, 1), 506 (M^+–46, 3), 449 (8), 357 (7), 313 (11), 221 (43), 167 (38), 129 (100), 115 (26), 73 (53); anal. calcd for $C_{28}H_{44}O_5S_2Si$: C, 60.83; H, 8.02. Found C, 61.04; H, 8.06%.

4.12. Preparation of compound 20

A solution of **19a** (40 mg, 0.072 mmol) in dry THF (2 mL) was treated with pyridinium hydrofluoride (0.1 mL, 65–70% in THF) under N_2 for 10 h at 0°C. Then a saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phase was washed with brine and distilled water, dried (Na_2SO_4) and filtered. After removal of the solvent in vacuo, the residue was treated with 2,2-dimethoxylpropane (2 mL), DMF (0.1 mL) and *p*-TsOH (10 mg) at 0°C overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous Na_2CO_3 (20 mL), brine and distilled water, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 10:1) yielded **20** as a colorless oil (10 mg, 29%). $[\alpha]_D^{20} = +3.7$ (*c* 0.301, CH_3COCH_3); IR (neat) 2935, 2846, 1739, 1709, 1472, 1379, 1285 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.0 (m, 5H), 6.95 (d, $J = 15.8$ Hz, 1H), 6.35 (d, $J = 15.8$ Hz, 1H), 4.25 (m, 1H), 4.10 (m, 1H), 3.9 (m, 2H), 3.1 (s, 2H), 2.7 (m, 2H), 2.4–2.2 (m, 6H), 2.05 (m, 2H), 1.65 (m, 2H), 1.25–1.5 (m, 6H), 0.95 (m, 3H) ppm; FAB Ms m/e (relative intensity) 479 (M^++1, 100). Ms m/e: anal. calcd for $C_{25}H_{34}O_5S_2$: C, 62.73; H, 7.16. Found C, 62.80; H, 7.45%.

4.13. Preparation of compounds 21a and 21b

A solution of **19a** (400 mg, 0.72 mmol) in dry THF (20 mL) under N_2 was treated with $NaBH_4$ (10 mg) in one portion for 1 h at –40°C, then 0.2 M aqueous HCl (10 mL) was added to end the reaction. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phase was washed with saturated aqueous Na_2CO_3, brine, dried (Na_2SO_4) and filtered. After removal of solvent in vacuo, the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 2:1) to yield **21a** as a colorless oil (373 mg, 93%). IR (neat) 3467, 2955, 2929, 2857, 1734, 1472, 1447, 1375, 1256, 1190 cm^{-1}; Ms m/e (relative intensity) 552 (M^+–2, 1), 447 (34), 315 (24), 221 (38), 169 (100), 129 (57), 81 (58).

21b was prepared same procedure as **21a** in 92% yield: IR 3490, 2954, 2931, 2857, 1735, 1472, 1373, 1333, 1257 cm^{-1}; Ms m/e (relative intensity) 554 (M^+, 5), 5.08 (M^+–46, 13), 169 (88), 129 (100), 81 (46).

4.14. Preparation of compounds 22a and 22b

To a solution of **21a** (370 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonic acid (1 mg) and the mixture stirred at rt for 2 h. The mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 1:1) yielded **22a** as a colorless oil (184 mg, 54%). IR (neat) 3443, 2955, 2929, 2856, 1756, 1735, 1472, 1389, 1361 cm^{-1}; Ms m/e (relative intensity) 508 (M^+, 8), 451 (M^+–57, 11), 433 (M^+–57–18, 16), 377 (15), 273 (96), 221 (60), 129 (100), 73 (63).

22b was prepared same procedure as **22a** in 53% yield. IR (neat) 3441, 2955, 2929, 2856, 1729, 1389, 1255 cm^{-1}; Ms m/e (relative intensity) 508 (M^+, 9), 451 (M^+–57, 11), 433 (M^+–57–18, 17), 401 (7), 377 (12), 273 (39), 221 (51), 129 (100), 73 (65).

4.15. Preparation of compounds 23a and 23b

To a solution of **22a** (180 mg, 0.35 mmol) and dry Et_3N (0.05 mL) in CH_2Cl_2 (20 mL) was added CH_3SO_2Cl (0.08 mL, 1 mmol) at −40°C for 30 min. The mixture was warmed to room temperature and was poured into water (20 mL) and then extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash chromatography on silica gel (eluted with petroleum ether/EtOAc = 2:1) yielded **23a** as a colorless oil (158 mg, 91%): $[\alpha]_D^{20} = -28.1$ (*c* 0.906, CH_3COCH_3); IR (neat) 2954, 2929, 2856, 1727, 1472, 1388, 1251, 1075, 1033, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, $J = 7$ Hz, 2H), 7.3 (3H, m), 6.82 (d, $J = 15.9$ Hz, 1H), 6.8 (m, 1H), 6.2 (d, $J = 15.9$ Hz, 1H), 5.95 (d, $J = 9.7$ Hz, 1H), 4.6 (m, 1H), 4.15 (m, 1H), 2.95 (m, 2H), 2.7 (m, 2H), 2.4–2.2 (m, 8H), 0.9 (s, 9H), 0.15 (s, 3H), 0.1 (s, 3H) ppm; Ms m/e (relative intensity) 490 (M^+, 12), 433 (M^+−57, 42), 293 (29), 255 (92), 221 (31), 169 (29), 129 (100), 75 (65); HRMS calcd for $C_{26}H_{38}O_3S_2Si$: 490.2031; found: 490.2025.

23b was obtained in 91% yield as a colorless oil using the same procedure as that described for **23a**: $[\alpha]_D^{20} = +21.3$ (*c* 0.402, CH_3COCH_3); IR (KBr) 2954, 2929, 2856, 1720, 1389, 1251 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (d, $J = 7.1$ Hz, 2H), 7.4 (m, 2H), 7.3 (m, 1H), 6.9 (d, $J = 15.9$ Hz, 1H), 6.8 (m, 1H), 6.25 (d, $J = 15.9$ Hz, 1H), 5.95 (d, $J = 9.8$ Hz, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 3.0 (m, 2H), 2.7 (m, 2H), 2.3 (m, 4H), 2.1 (m, 2H), 1.75 (m, 2H), 0.9 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H) ppm; Ms m/e (relative intensity) 490 (M^+, 9), 433 (M^+−57, 27), 415 (M^+−57–18, 9), 358 (37), 255 (54), 199 (52), 129 (100), 73 (44); HRMS calcd for $C_{26}H_{38}O_3S_2Si$: 490.2031; found: 490.2029.

4.16. Preparation of compounds 24a and 24b

A solution of **23a** (140 mg, 0.29 mmol), $CaCO_3$ (150 mg) in THF/H_2O (5:1, 10 mL) was treated with 4 M aqueous $HgClO_4$ (0.5 mL) for 5 min at 0°C. The mixture was diluted with Et_2O (50 mL) and then filtered with Celite. Concentration of the filtrate followed by flash chromatography on silica gel (eluted with petroleum ether/EtOAc = 5:1) yielded **24a** as a pale yellow solid (84 mg, 74%): mp 47–49°C; $[\alpha]_D^{20} = -17.3$ (*c* 0.365, CH_3COCH_3); IR (KBr) 2955, 2931, 2857, 1715, 1652, 1626, 1392 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 7.7 (m, 3H), 7.4 (m, 3H), 7.05 (m, 1H), 6.9 (d, $J = 16.2$ Hz, 1H), 5.95 (m, 1H), 4.7 (m, 1H), 4.55 (m, 1H), 2.95 (m, 2H), 2.45 (m, 2H), 1.9 (m, 2H), 0.85 (s, 9H), 0.10 (s, 3H), 0.05 (S, 3H) ppm; Ms m/e (relative intensity) 401 (M^++1, 2), 343 (M^+−57, 74), 325 (M^+−57–18, 17), 255 (7), 231 (25), 131 (100), 103 (28), 75 (43); HRMS calcd for $C_{19}H_{23}O_4Si$: 343.1365; found: 343.1363.

24b was obtained in 76% as a pale yellow solid using the same procedure as **24a**: mp 60–62°C; $[\alpha]_D^{20} = +40.6$ (*c* 0.715, CH_3COCH_3); IR (KBr) 2955, 2931, 2857, 1715, 1652, 1626, 1392 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (m, 3H), 7.4 (m, 3H), 6.9 (m, 1H), 6.8 (d, $J = 16.2$ Hz, 1H), 6.0 (d, $J = 9.8$ Hz, 1H), 4.6 (m, 2H), 2.9 (dd, $J = 15$ Hz, 5.0 Hz, 1H), 2.8 (dd, $J = 15$ Hz, 6.5 Hz, 1H), 2.3 (m, 2H), 2.05 (m, 1H), 1.75 (m, 1H), 0.85 (s, 9H), 0.15 (s, 6H) ppm; Ms m/e (relative intensity) 401 (M^++1, 7), 343 (M^+−57, 100), 325 (M^+−57–18, 19), 255 (17), 231 (25), 131 (70); anal. calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05; found: C, 68.47; H, 8.09%.

4.17. (5*S*,7*S*)-Kurzilactone 25a

To a solution of **24a** (60 mg, 0.15 mmol) in CH_3CN (15 mL) was added dropwise 70% aqueous HF (2 mL) and the mixture stirred for 50 min at rt. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and filtered. Concentration of the filtrate followed by flash column chromatography on silica gel (eluted with petroleum ether/EtOAc = 1:1) yielded **25a** as a white solid (25 mg, 58%): mp 122–123°C; $[\alpha]_D^{20} = -60.8$ (*c* 0.683, $CHCl_3$); IR (KBr) 3402, 2933, 1714, 1656, 1629, 1398, 1379, 1260, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) and ^1H NMR (C_6D_6) are listed in Table 1; ^{13}C NMR ($CDCl_3$) δ 200.4, 164.2, 145.3, 144.0, 130.9, 129.0, 128.5, 134.1, 126.0, 121.3, 75.5, 64.6, 46.6, 40.6, 30.0 ppm; Ms m/e (relative intensity) 287 (M^++1, 2), 269 (M^++1–18, 3), 201 (7), 173 (13), 145 (20), 131 (100), 103 (33), 77 (13). X-Ray crystallation $a = 9.239(5)$, $b = 31.292(4)$, $c = 5.160(7)$ Å, $V = 1491(2)$ Å^3; for $Z = 4$ and $F_w = 286.33$, the calcd forted density is 1.27 g/cm^3. The systematic absences of: $h00$: $h \cdot 2n$ $0k0$: $k \cdot 2n$ $00l$: $l \cdot 2n$. Uniquely determine the space group to be: $P2_12_12_1$ (#19).

4.18. (5*R*,7*S*)-Kurzilactone 25b

Following the same procedure described as above, **25b** was obtained in 79% yield as a white solid. Mp 77–79°C; $[\alpha]_D^{20} = +84$ (*c* 0.231, $CHCl_3$); IR (KBr) 3476, 1710, 1637, 1426, 1386, 1266, 1254, 1184, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) and ^1H NMR (C_6D_6) are listed in Table 1; ^{13}C NMR ($CDCl_3$) δ 200.4, 164.2, 145.1, 144.0, 134.1, 130.9, 129.0, 128.5, 126.1, 121.5, 75.0, 64.2, 46.9, 41.7, 30.0 ppm; Ms m/e (relative intensity) 287 (M^++1, 6), 269 (M^++1–18, 6), 201 (7), 173 (12), 145 (17), 131 (100), 103 (29); HRMS calcd for $C_{17}H_{18}O_4$: 286.1204; found: 286.1202.

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