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A new chiral oxathiane: synthesis, resolution and absolute configuration determination by vibrational circular dichroism

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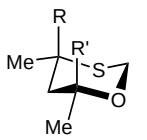
Abstract—A new oxathiane, derived from 5-hydroxy-1-tetralone has been synthesized in eight steps, fully characterized as *cis*-fused rings by 1D and 2D NMR and resolved by preparative chiral chromatography (CHIRALCEL OD-R). The second eluting (+, MeOH)-isomer was assigned (*S*,*S*)-configuration by VCD-ab initio simulation.

1. Introduction

Since the first use, in 1978,[1] of chiral 1,3-oxathianes **1** for the enantioselective synthesis of atrolactic acid methyl ester, Eliel et al. developed 1,3-oxathianes **2**[2] and **3**[3] derived from natural products. In 1992 we showed that oxathiane **3** could also be successfully used as a chiral sulfide[4,5] for asymmetric synthesis of monoaryl-epoxides, *trans*-diaryl-epoxides and *trans*-cyclopropanes and succeeded later to obtain in all cases high conversions (~90–95%) and high e.e.s (95–100%).[6–8]



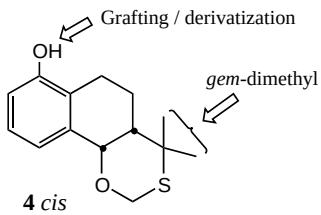
1 R = H, R' = Me
R = Me, R' = H

2

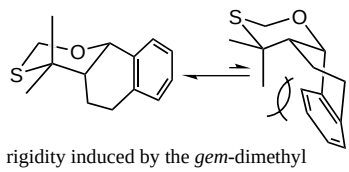
3

However, a drawback of these asymmetric syntheses is the necessary separation of the chiral auxiliary **3** from the desired epoxide or cyclopropane by chromatography,[9] we designed chiral oxathianes which could either be grafted onto a solid support (to allow easy separation by filtration) or derivatized with a polyfluoro group (to allow separation by extraction with a fluorous phase).[10,11] Such oxathianes should also be rigid enough to provide a single isomer of the corresponding sulfonium salts,[12] they should have a structure similar to that of **3** (with a *gem*-dimethyl group α to the sulfur atom) and both enantiomers should be available.

We present herein oxathiane **4**, which fulfils the above conditions. The synthesis, chromatographic resolution and assignment of absolute configuration, which has been done by vibrational circular dichroism (VCD)[13–16] (the difference in the infra red absorbance of a molecule for left versus right circularly polarized radiation) will be described.



4 *cis*



rigidity induced by the *gem*-dimethyl

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2. Results and discussion

2.1. Synthesis

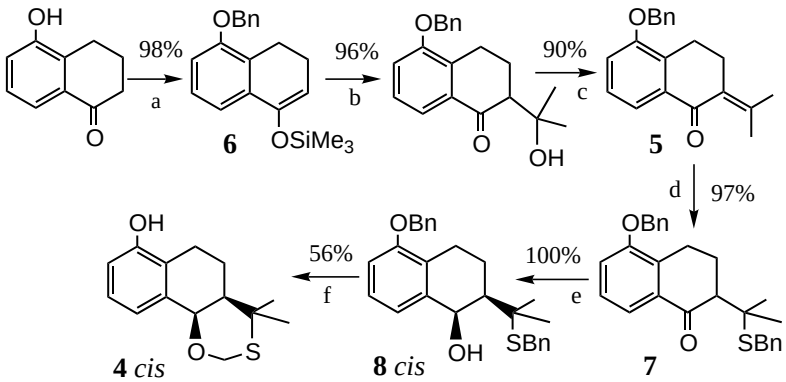
Oxathiane **4** has been obtained in eight steps from commercially available 5-hydroxy-1-tetralone (Scheme 1).

The silyl enolate **6** was obtained from the benzyl-protected ketone in quantitative yield after modification of the literature work-up.[17a,b] Compound **5** was obtained through $TiCl_4$-catalyzed condensation of acetone onto **6**, followed by dehydration (using 90% AcOH[18]). Then 1,4-addition of BnSH, using DBU as base, provided **7** in 97% isolated yield. BH_3/THF reduction of **7** afforded **8** as the single *cis*-diastereomer.[19] After debenzylation of **8** using NH_3/Na and Et_2O/MeOH (10/1) as solvent, oxathiane *cis*-**4** was formed by heating a mixture of the debenzylated compound and dried paraformaldehyde in refluxing benzene, in the presence of trace *p*-TsOH. (±)-*cis*-**4** was thus isolated in 46% overall yield.

2.2. Determination of the *cis*-structure of oxathiane 4: NMR

From H–C correlation, the multiplets at 1.95 and 2.30 ppm (Table 1) were assigned to one of the CH_2, those at 2.52 and 2.96 to the other CH_2, the double-triplet at 1.45 and the triplet at 4.69 to the two saturated CH.

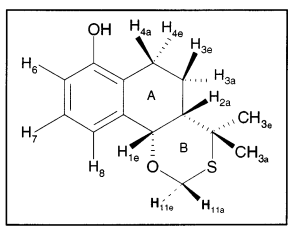
Examination of the COSY experiment then showed that the double-triplet at 1.45 was correlated with the two multiplets at 1.95 and 2.30, which were thus assigned to the H(3) protons. As a consequence, the double-triplet at 1.45, the multiplets at 2.52 and 2.96 and the triplet at 4.69 ppm were assigned to protons H(2), H(4), H(4) and H(1), respectively.



Scheme 1. (a) i. $PhCH_2Br/K_2CO_3$/acetone, reflux, ii. NEt_3/TMSCl/NaI/MeCN/pentane, reflux; (b) $Me_2CO/TiCl_4/CH_2Cl_2$, –20°C; (c) AcOH 90%/~105°C; (d) BnSH/DBU/THF, rt; (e) BH_3/THF, rt; (f) i. NH_3/Na/MeOH/EtOH, –78°C, ii. $(CH_2O)_n$/benzene/*p*-TsOH, reflux.

Table 1. ^{1}H NMR parameters of oxathiane *cis*-**4** ($CDCl_3$/TMS, 400 MHz)

δ ppm	H	Type of pattern	coupling constants (Hz)
1.34	CH_{3eq}*	s	
1.45	H_{2ax}**	td	$^3J_{2a3a}$=12.5 ; $^3J_{2a1e}$= $^3J_{2a3e}$= 2
1.68	CH_{3ax}*	s	
1.95	H_{3eq}**	ddq	$^2J_{3e3a}$=12.5 ; $^3J_{3e4a}$= 6 ; $^3J_{3e4e}$= $^3J_{3e2a}$= 2 = $^4J_{3e1e}$‡
2.30	H_{3ax}**	dq	$^2J_{3a3e}$= $^3J_{3a4a}$= $^3J_{3a2a}$= 12.5 ; $^3J_{3a4e}$= 6
2.52	H_{4ax}**	ddd	$^2J_{4a4e}$= 17 ; $^3J_{4a3a}$= 12.5 ; $^3J_{4a3e}$= 6
2.96	H_{4eq}**	ddd	$^2J_{4e4a}$= 17 ; $^3J_{4e3a}$= 6 ; $^3J_{4e3e}$= 2
4.69	H_{1eq}**	t	$^3J_{2a1e}$= $^4J_{3e1e}$= 2
4.78	OH	s	
4.79	H_{11eq}*	d	^2J= 11
5.21	H_{11ax}*	d	^2J= 11
6.72	H_6	d	$^3J_{67}$= 7.5
6.88	H_8	d	$^3J_{87}$= 7.5
7.09	H_7	t	$^3J_{76}$= $^3J_{78}$= 7.5



Equatorial or *axial* within ring B. **Equatorial* or *axial* within ring A. ‡After irradiation of H(1) at 4.69 ppm

Full analysis of the multiplets, (Table 1), suggested that the ring junction was *cis* with a vicinal coupling constant, $^3J_{12}$ of 2 Hz and that the C–O bond was *axial* (within ring A) while the C–C (*gem*-dimethyl) was *equatorial* (within ring A) with a W-long range coupling constant between H(1e) (*equatorial* in ring A) and H(3e) (*equatorial*) of 2 Hz and a $^3J_{180}$ of 12.5 Hz between H(2a) (*axial* in ring A) and H(3a) (*axial*).[20]

This conclusion was then confirmed by a NOESY experiment which exhibits a correlation spot between one of the methyl groups of the *gem*-dimethyl system and H(1) (*axial* in ring B), one of H(11) (*axial* in ring B) and H(2), while there is no correlation between this methyl group and any H(3) proton (which would be the case if the ring junction were *trans*).[21]

2.3. Resolution

Resolution of oxathiane **4** was performed by liquid chromatography. After screening several polysaccharide-derived chiral stationary phases using pure acetonitrile as the eluent at a flow rate of 1 mL/min at 25°C, analytical separation was obtained on CHIRALCEL OD-R ($\phi = 4.6$ mm). Only few applications in pure acetonitrile with modest resolution have been reported in the literature using this stationary phase. The semi-preparative separation was transferred onto a CHIRALCEL OD ($\phi = 20$ mm). Since the quantities to be prepared were small, an analytical HPLC system was used for this purpose. A global recovery of 81% was obtained, the first eluting enantiomer (**4-1**) having 100% e.e. and 96% chemical purity and the second eluting enantiomer (**4-2**) having 100% e.e. and 99% chemical purity (from a CHIRALCEL OD-R analysis). The optical rotation of the first eluted enantiomer **4-1** is: $[\alpha]_D^{20} = -58$ ($c = 2.2$, MeOH).

This method could be applied for larger scale preparation by using a semi-preparative liquid chromatography device instead of an analytical one.

2.4. Determination of absolute configuration: VCD

Within the past few years, VCD has been shown to be a reliable new method for the determination of absolute configuration in chiral molecules.[22–25] The method consists of measuring the VCD and IR spectra of one enantiomer and, in parallel, carrying out an ab initio calculation of the VCD and IR spectra of one absolute configuration. Comparison of the calculated VCD spectrum of the compound with known absolute configuration, to the measured VCD spectrum of the sample molecule with the unknown absolute configuration yields the desired assignment as follows. If the calculated principal VCD bands have the same sign as the corresponding experimental VCD bands, the absolute configuration chosen for the calculations is the same as that for the measured sample, and if opposite, the absolute configuration chosen for the calculations is the opposite of that for the sample.

The absolute configuration of **4** was thus determined by comparing the measured VCD spectrum of a sample of (+, MeOH)-**4-2** (eluted second) having 100% e.e. and 99% chemical purity with that of an ab initio quantum calculation of the enantiomer (*S*,*S*)-**4**.

Several conformers of the molecule in the (*S*,*S*)-configuration were calculated, which differed in the conformation of the oxathiane ring, the sense of twist of the pair of adjacent methylene groups and the CCOH dihedral angle. Optimized geometries were calculated with Gaussian 98[26] at the B3LYP/6-31G* DFT level. Two having the same chair conformation for the oxathiane ring were more than 4 kcal/mol lower in energy than the others. The optimized geometries and relative energies of these two conformers, which differ in the OH orientation, are shown in Fig. 1.[27] We note that the conformation of the rings calculated for these two lowest energy conformers corresponds to that found by NMR.

Vibrational frequencies, IR and VCD intensities were calculated with Gaussian 98 at the B3LYP/6-31G* DFT level for both conformers C1 and C2 of the (*S*,*S*) isomer.

The observed spectrum is then compared to the sum of the calculated spectra of conformers C1 and C2 weighted by their Boltzmann populations ([C1]*0.723+[C2]*0.276) (Fig. 2).

The agreement between the observed and calculated VCD and IR spectra is consistent with the (*S*,*S*)-configuration for the (+, MeOH)-**4-2** studied.

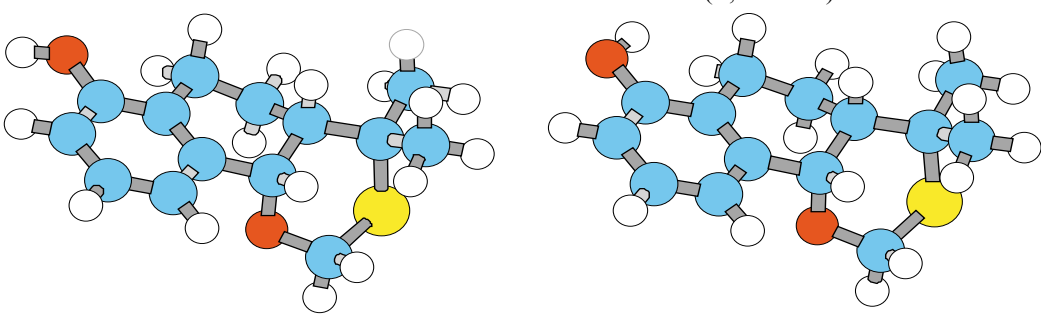


Figure 1. Optimized geometries of the two lowest energy conformers, C1 and C2, and potential energy as a function of HOCC dihedral angle.

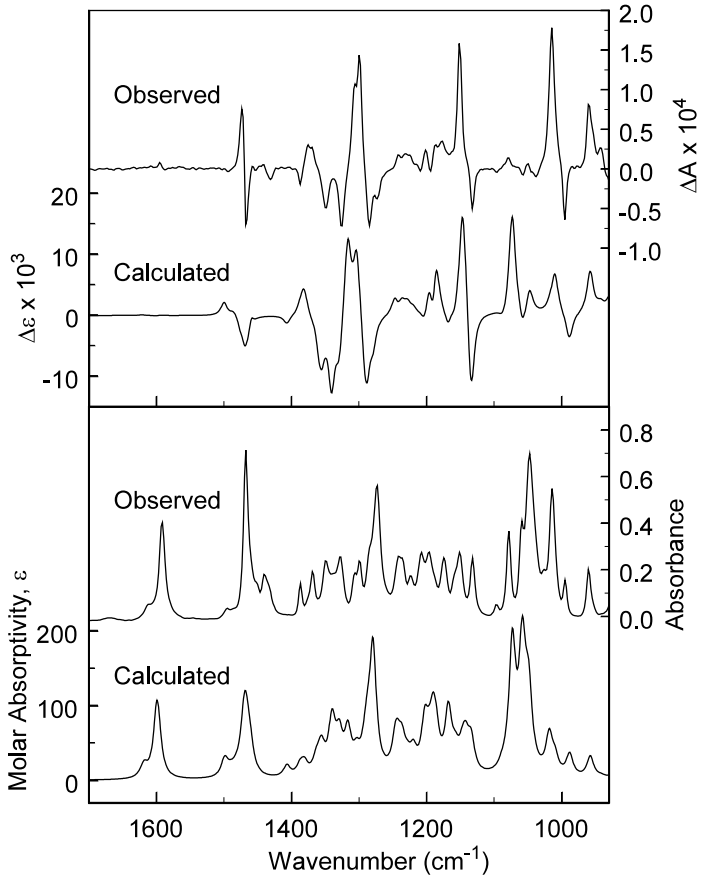
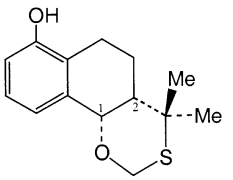


Figure 2. Comparison of observed IR and VCD spectra of (+, MeOH)-**4-2** with Boltzmann-population-weighted sum of spectra of conformers C1 and C2 of (*S*,*S*)-**4**.



4 (1*S*,2*S*)
Eluted second on CHIRALCEL-OD-R, MeCN
(+) in MeOH
Cis compound from NMR ($^3J_{12}$ = 2 Hz)

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker Avance (400 MHz) spectrometer with $CDCl_3$ or C_6D_6 as solvent. Chemical shifts (δ) are reported in ppm downfield from TMS. TLC were performed on Merck glass plates with silica gel 63 F_{254}. Silica gel Si 60 (40–60 μm) from Merck was used for the chromatographic purifications. 5-Hydroxy-1-tetralone, benzyl bromide and benzyl mercaptan were purchased from Fluka, Acros and Aldrich, respectively, and used without further purification. Usual IR spectra and rotations were recorded/determined on a Perkin–Elmer Spectrum one and a Perkin–Elmer 341, respectively.

Resolution of (±)-**4** has been optimized analytically using a CHIRALCEL®OD-R (250*4.6 mm, 10 μM) column with conditions: $t_1 = 3.79$ min, $t_2 = 9.36$ min, $k_1 = 0.26$, $k_2 = 2.12$, alpha = 8.08, $R_s = 14$. (Detection DAD 230 nm). Then semi-preparative resolution was carried out on a larger CHIRALCEL®OD-R (250*20 mm, 10 μM) column which was previously washed with 2-propanol for 2 h and then used in pure acetonitrile. Merck Hitachi L7100 Pump fixed at 9 mL/min, Autosampler L7250 with 2 mL injection loop, DAD L7450 fixed at 250 nm. Four injections of 2 mL each of a saturated (12.5 g/L) *racemic* solution in the mobile phase were performed. The chromatographic parameters of a 25 mg injection are as follows: $t_1 = 8.48$ min, $t_2 = 18.24$ min, $k_1 = 0.41$, $k_2 = 2.12$, alpha = 4.94, $R_s = 4.68$. Fractions were collected between 8.4–9.7 min and 17.2–24 min, the solvent evaporated under vacuum and the enantiomeric purity checked on CHIRALCEL®OD-R. The first eluted enantiomer, **4-1** (44 mg) has 100% e.e. and 95.4% chemical purity, while the second eluted enantiomer **4-2** (37 mg) has 100% e.e. and 99% chemical purity.

For the VCD determination of absolute configuration, infrared absorption and VCD spectra were recorded in a 100 μm path length BaF_2 cell, at 4 cm^{-1} resolution, using the Chiral*ir* Fourier transform VCD spectrometer from Bomem/BioTools, Quebec, Canada,[28,29] optimized for operation at 1400 cm^{-1}. VCD spectra were recorded for 2 h by co-adding approximately 4800 interferometric scans. The sample was dissolved in CCl_4 (100mg/mL). DFT calculations were performed using Gaussian 98 (Gaussian, Inc. Pittsburgh, PA).

3.1. Benzyl protection

5-Hydroxy-1-tetralone (5 g, 30.83 mmol, 1 equiv.) was dissolved in dry acetone (200 mL) and K_2CO_3 (8.52 g, 61.66 mmol, 2 equiv.) was added in one portion under argon, the mixture was stirred for 10 min at room temperature then $PhCH_2Br$ (3.85 mL, 32.37 mmol, 1.05 equiv.) was added dropwise. After stirring the mixture under reflux for 4 h, the reaction was complete (as seen from TLC), acetone was removed under reduced pressure and the residue was crystallized from hot hexane to afford a white solid (7.6 g, 98%), mp 50–51°C; ^{1}H NMR ($CDCl_3$): 2.13 (2H, m, H_3), 2.66 (2H, dd, $^3J=5$ Hz, $^3J=7$ Hz, H_2), 2.98 (2H, t, $^3J=6$ Hz, H_4), 5.12 (2H, s, O-CH_2), 7.09 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_6), 7.26 (1H, t, $^3J=8$ Hz, H_7), 7.3–7.5 (5H, m, H_{phenyl}), 7.69 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_8); ^{13}C NMR ($CDCl_3$): 22.9 (CH_2), 23.4 (CH_2), 39.3 (CH_2), 70.7 (CH_2-O), 116.2 (CH), 119.5 (CH), 127.1 (CH), 127.6 (CH_{ph}), 128.5 (CH_{ph}), 129.1 (CH_{ph}), 134.2 (C), 134.4 (C), 137.2 (C), 156.3 (C), 199.1 (C=O); IR: $\nu_{C=O}$ 1680 cm^{-1}.

3.2. Silyl enol–ether 6

The above benzyl-protected hydroxytetralone (5 g, 19.82 mmol, 1 equiv.) was dissolved, under argon in dry acetonitrile (5 mL). Then pentane (25 mL), triethylamine (3.87 mL, 27.74 mmol, 1.4 equiv.) and chlorotrimethylsilane (3.27 mL, 25.76 mmol, 1.3 equiv.) were added, followed by dropwise addition of anhydrous sodium iodide (3.86 g, 25.76 mmol, 1.3 equiv.) in acetonitrile (25 mL). After stirring at room temperature for 30 min, then stirring under reflux for 90 min, the reaction mixture was allowed to cool and the upper organic layer (pentane) was transferred into a dry flask. The remaining mixture was extracted with dry pentane (5×10 mL). The pentane layer was evaporated to give **6** as a colorless oil, pure by NMR analysis (6.25 g, 96%). The usual method[30] leads to lower yields and avoiding water is essential. ^{1}H NMR: ($CDCl_3$): 0.27 (9H, s, CH_3Si), 2.31 (2H, ddd, $^3J=8.5$ Hz, $^3J=8$ Hz, $^3J=4.5$ Hz, H_3), 2.85 (2H, dd, $^3J=8.5$ Hz, $^3J=8$ Hz, H_4), 5.09 (2H, s, CH_2-O), 5.21 (1H, t, $^3J=4.5$ Hz, =CH), 6.87 (1H, dd, $^3J=7$ Hz, $^4J=2.5$ Hz), 7.1–7.2 (2H, m, H_{arom}), 7.3–7.5 (5H, m, H_{phenyl}); ^{13}C NMR: ($CDCl_3$): 0.3 (CH_3), 20.5 (CH_2), 21.6 (CH_2), 70.4 (CH_2-O), 105.7 (CH), 111.7 (CH), 115.3 (CH), 125.6 (C), 126.4 (CH), 127.3 (CH), 127.9 (CH), 128.6 (CH), 134.9 (C), 137.6 (C), 148.0 (C), 155.0 (C).

3.3. Synthesis of 5

3.3.1. Condensation with acetone. The silyl enol ether 6 (6.25 g, 19.26 mmol) was condensed with acetone following the usual procedure[31] and the product (5.66 g, 96%) was used for the next reaction without purification. ^{1}H NMR ($CDCl_3$): 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.85 (1H, dq, $^2J=^3J=^3J=13$ Hz, $^3J=4.5$ Hz, H_{3a}), 2.29 (1H, m, H_{3b}), 2.63 (1H, dd, $^3J=13$ Hz, $^3J=4$ Hz, H_2), 2.75 (1H, ddd, $^2J=17.5$ Hz, $^3J=13$ Hz, $^3J=4.5$ Hz, H_{4b}), 3.34 (1H, ddd, $^2J=17.5$ Hz, $^3J=4.5$ Hz, $^3J=3$ Hz, H_{4a}), 5.08 (1H, s, OH), 5.14 (2H, AB, CH_2-O), 7.12 (1H, dd, $^3J=8$ Hz, $^4J=0.5$ Hz, H_6), 7.29 (1H, t, $^3J=8$ Hz, H_7), 7.35–7.5 (5H, m, H_{phenyl}), 7.68 (1H, d, $^3J=8$ Hz, H_8). ^{13}C NMR ($CDCl_3$): 23.5 (CH_2), 25.2 (CH_3), 25.9 (CH_2), 28.9 (CH_3), 57.1 (CH), 70.7 (CH_2-O), 73.1 (C-OH), 116.5 (CH), 119.7 (CH), 127.4 (CH), 127.6 (CH_{ph}), 128.5 (CH_{ph}), 129.1 (CH_{ph}), 134.1 (C), 134.5 (C), 137.1 (C), 156.1 (C), 203.1 (C=O). IR: $\nu_{OH}=3479$ cm^{-1}, $\nu_{C=O}=1664$ cm^{-1}.

3.3.2. Dehydration. The above cetol (5.66 g) was dehydrated following the usual procedure[32] and the residue, crystallized from ether, was purified by flash chromatography to afford a white crystalline solid (4.32 g, 90%). ^{1}H NMR ($CDCl_3$): 1.98 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.81 (2H, t, $^3J=6.5$ Hz, H_{3a}+H_{3b}), 3.01 (2H, t, $^3J=6.5$ Hz, H_{4a}+H_{4b}), 5.13 (2H, s, CH_2-O), 7.07 (1H, d, $^3J=8$ Hz, H_6), 7.29 (1H, t, $^3J=8$ Hz, H_7), 7.36–7.48 (5H, m, H_{phenyl}), 7.78 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_8). ^{13}C NMR ($CDCl_3$): 23.3 (CH_3), 23.8 (CH_3), 24.0 (CH_2), 28.3 (CH_2), 70.7 (CH_2-O), 115.5 (CH), 120.3 (CH), 127.2 (CH), 127.6 (CH_{ph}), 128.4 (CH_{ph}), 129.0 (CH_{ph}), 130.8 (C), 133.4 (C), 136.5 (C), 137.4 (C), 145.3 (C), 156.0 (C), 190.5 (C=O). IR: $\nu_{C=O}=1665$ cm^{-1}.

3.4. Conjugate-addition of $PhCH_2SH$: 7

The usual procedure[33] was modified to provide ca. quantitative conversion; DBU (1 equiv.) was used instead of NaOH and the reaction was carried out at room temperature instead of refluxing THF. After chromatography on silica gel (toluene) **7** was obtained as a colorless oil (6.98 g, 97%; from 5.11 g of **5**). ^{1}H NMR ($CDCl_3$): 1.45 (3H, s, CH_3) 1.80 (3H, s, CH_3), 2.01 (1H, dq, $^2J=^3J=^3J=12.5$ Hz, $^3J=4.5$ Hz, H_{3a}), 2.60 (1H, dd, $^3J=12.5$ Hz, $J=4.5$ Hz, H_2), 2.60 (1H, ddd, $^2J=18$ Hz, $^3J=12.5$ Hz, $^3J=4.5$ Hz, H_{4b}), 2.78 (1H, dq, $^2J=12.5$, $^3J=^3J=^3J=4.5$ Hz, H_{3b}), 3.19 (1H, td, $^2J=18$ Hz, $^3J=^3J=4.5$ Hz, H_{4a}), 3.78 (2H, s, CH_2-S), 5.12 (2H, AB, CH_2-O), 7.06 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_6), 7.20–7.50 (6H, m, H_{arom}), 7.59 (1H, dd, $^3J=8$ Hz, $^4J=1$Hz, H_8). ^{13}C NMR ($CDCl_3$): 24.3 (CH_2), 24.6 (CH_3), 26.1 (CH_2), 29.6 (CH_3), 33.7 (CH_2-S), 49.5 (C-S) 55.4 (CH-CO), 70.6 (CH_2-O), 115.7 (CH), 119.5 (CH), 127.2 (CH), 127.3 (CH), 127.6 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 133.3 (C), 136.1 (C), 137.3 (C), 138.8 (C), 156.2 (C), 199.3 (C=O). IR: $\nu_{C=O}=1687$ cm^{-1}.

3.5. Reduction with BH_3·THF, 8

A solution of **7** (6.98 g) in dry THF (70 mL) was treated with BH_3 (1 M solution in THF, 33.5 mL) dropwise at room temperature under an argon atmosphere. The mixture was stirred overnight, quenched carefully with saturated aqueous NH_4Cl (300 mL) and extracted with ether (5×15 mL). The combined organic layer was washed with water (1×10 mL), dried (Na_2SO_4) and concentrated. The residue (7.02 g, 100%) was used for the next reaction without purification. ^{1}H NMR ($CDCl_3$): 1.55 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.78 (1H, dt, $^3J=12.5$ Hz, $^3J=^3J=2$ Hz, H_2), 2.00 (1H, dq, $^2J=^3J=^3J=12.5$ Hz, $^3J=5.5$ Hz, H_{3a}), 2.13 (1H, m, H_{3b}), 2.39 (1H, d, $J=4$ Hz, OH), 2.53 (1H, ddd, $^2J=18$ Hz, $^3J=12.5$ Hz, $^3J=6$ Hz, H_{4b}), 3.16 (1H, ddd,

$^2J=18$ Hz, $^3J=5.5$ Hz, $^3J=1.5$ Hz, H_{4a}), 3.82 (2H, AB, CH_2-S), 5.09 (1H, m, H_1), 5.11 (2H, CH_2-O), 6.86 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_6), 6.97 (1H, d, $^3J=8$ Hz, H_8), 7.20 (1H, t, $^3J=8$ Hz, H_7), 7.21–7.48 (10 H, m, H_{phenyl}). ^{13}C NMR ($CDCl_3$): 18.5 (CH_2), 25.1 (CH_2), 27.9 (CH_3), 28.0 (CH_3), 33.6 (CH_2-S), 48.7 (CH), 49.6 (C-S), 70.0 (CH-OH), 70.2 (CH_2-O), 110.9 (CH), 122.7 (CH), 126.5 (C), 127.1 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 128.9 (CH), 129.4 (CH), 137.8 (C), 138.5 (C), 140.7 (C), 156.8 (C). IR: $\nu_{O\text{-}H}=3435$ cm^{-1}.

3.6. Oxathiane 4

3.6.1. Deprotection with Na/NH$_3$. The benzylic deprotection was carried out following usual procedure[33] and yielded 3.19 g (90%, from 6.2 g of **8**) of a crude product, which was used without further purification in the next step. ^{1}H NMR ($CDCl_3$): 1.60 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.7 (1H, m, H_2), 2.04 (2H, m, H_{3a}+ H_{3b}), 2.07 (s, 1H, SH), 2.33 (1H, d, $J=4$ Hz, CHOH), 2.56 (1H, ddd, $^2J=17.5$ Hz, $^3J=10.5$ Hz, $^3J=7$ Hz, H_{4b}), 3.02 (1H, ddd, $^2J=17.5$ Hz, $^3J=4$ Hz, $^3J=3$ Hz, H_{4a}), 4.96 (1H, s, OH-Ar), 5.07 (1H, dd, H_1), 6.73 (1H, dd, $^3J=8$ Hz, $^4J=1$ Hz, H_6), 6.94 (1H, d, $^3J=8$ Hz, H_8), 7.13 (1H, t, $J=8$ Hz, H_7). ^{13}C NMR ($CDCl_3$): 18.8 (CH_2), 24.3 (CH_2), 31.5 (CH_3), 33.1 (CH_3), 47.2 (C-S), 50.4 (CH), 69.9 (CH-O), 114.7 (CH), 122.7 (CH), 123.4 (C), 127.5 (CH), 140.9 (C), 153.7 (C-O). IR: $\nu_{OH}=3369$ and $\nu_{S\text{-}H}=2561$ cm^{-1}.

3.6.2. Bridging. This last step was done following the usual procedure[33] and led to oxathiane **4** in 62% yield (after chromatographic purification). ^{1}H NMR ($CDCl_3$): 1.34 (3H, s, CH_{3eq}), 1.45 (1H, td, $^3J=12.5$ Hz, $^3J=^3J=2$ Hz, H_2), 1.68 (3H, s, CH_{3ax}), 1.95 (1H, m, H_{3b}), 2.30 (1H, dq, $^2J=^3J=^3J=12.5$ Hz, $^3J=6$ Hz, H_{3a}), 2.52 (1H, ddd, $^2J=17$ Hz, $^3J=12$ Hz, $^3J=6$ Hz, H_{4b}), 2.96 (1H, ddd, $^2J=17$ Hz, $^3J=6$ Hz, $^3J=2$ Hz, H_{4a}), 4.69 (1H, t, $^3J=^4J=2$ Hz, H_1), 4.78 (1H, OH), 4.79 (1H, B of AB, JAB=11 Hz, H_{eq}), 5.21 (1H, A of AB, JAB=11 Hz, H_{ax}), 6.72 (1H, dd, $^3J=7.5$ Hz, $^4J=1$ Hz, H_6), 6.88 (1H, d, $^3J=7.5$ Hz, H_8), 7.09 (1H, t, $^3J=7.5$ Hz, H_7). ^{13}C NMR ($CDCl_3$): 18.0 (CH_2), 23.2 (CH_2), 28.3 (CH_3), 29.3 (CH_3), 42.1 (C), 43.8 (CH), 68.1 (CH_2), 74.1 (CH-O), 114.6 (CH), 123.4 (CH), 124.0 (C), 126.8 (CH), 137.2 (C), 153.2 (C-O). IR: $\nu_{OH}=3391$ cm^{-1}. After resolution on CHIRALCEL OD (eluent=MeCN) the first eluting enantiomer has an e.r. of 100/0 and a chemical purity of 96%: $[\alpha]_D^{20}=-58$ ($c=2.2$, MeOH).

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