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Novel chiral dithioethers derived from L-tartaric acid

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Abstract—The synthesis of a new family of systematically modified chiral dithioethers to be used as ligands is described. Phenylthioether derivative **5** and fluorine-containing dithioether ligands **6–8** and **13–15** were prepared by direct reaction of phenylthiol and *o*-, *m*- or *p*-fluorophenylthiol with two different ditriflate derivatives based on the L-tartaric skeleton. The chiral ditriflate **12** containing a dioxolane moiety was reacted with ethane- and propanedithiol, producing cyclic dithioethers **16** and **17**, respectively, in good yields (≈50%). The analogous ditriflate **4** with benzyl ether protecting groups, having a skeleton without restricted rotation, gave the thiolane **9** as the main product.

1. Introduction

Over the last ten years, the potential of chiral sulfur-containing ligands in transition-metal-catalysed asymmetric syntheses has been explored.[1] In particular, heterodonor ligands such as (*P*,*S*),[2] (*N*,*S*)[3] and (*O*,*S*)[4] have been used successfully in enantioselective reactions such as the hydrogenation of itaconic acid and α-enamide methyl esters,[2a,2b,3d] the allylic substitution reactions of 1,3-diphenylpropenyl acetate,[2c–e,3a–c] the hydrosilylation of ketones,[2f] alkene epoxidation[4] and cross-coupling reactions.[3e] Catalysts with chiral homodonor sulfur ligands, however, have not been investigated as much, mainly because electronic dissimilarity between the two donor sites is claimed to be important for obtaining favourable enantioselectivity for some processes.[2a,2d] Nevertheless, chiral homodonor dithioether ligands have provided good results in iridium-catalysed asymmetric hydrogenation under mild conditions[5] and they have recently been effective chiral inductors in palladium-catalysed allylic alkylations, where they have afforded e.e. of up to 81%.[6]

Since systematic chemical modification of dithioethers is easily achieved, the electronic and steric properties of catalysts can be modulated to improve their activity and selectivity. Therefore, to better understand how structural factors affect the performance of dithio donor ligands, we synthesised a family of chiral dithioethers derived from L-diethyl tartrate that share a 1,4-butanedithioether backbone. We present herein two design strategies. The first one is to introduce phenylthioether **5** and *o*-, *m*- or *p*-fluorophenylthioether **6–8**, **13–15** moiety to fine-tune the electronic properties of the sulfur donor atom.[3a] The second strategy is to construct cyclic dithioether structures **16** and **17** to modulate the ligand rigidity and avoid sulfur inversion upon metal coordination, which is considered to erode the enantioselectivity in asymmetric catalytic processes.[2e,7] Although some authors have already tried to diminish sulfur inversion using bulky thioethers,[2a,2e] our objective is to explore strategies focusing on the total eradication of it.

2. Results and discussion

The new compounds **5–8** were prepared from L-(+)-diethyl tartrate, **1** (Scheme 1). Diol **3**, prepared in accordance with a previously described procedure,[8,9] was converted into ditriflate **4** by adding pyridine and triflic anhydride to a dichloromethane solution of **3**. Compound **4** was treated with the appropriate sodium phenylthiolate salt to afford the dithioethers **5–8** in good yields. We tried several times to prepare cyclic

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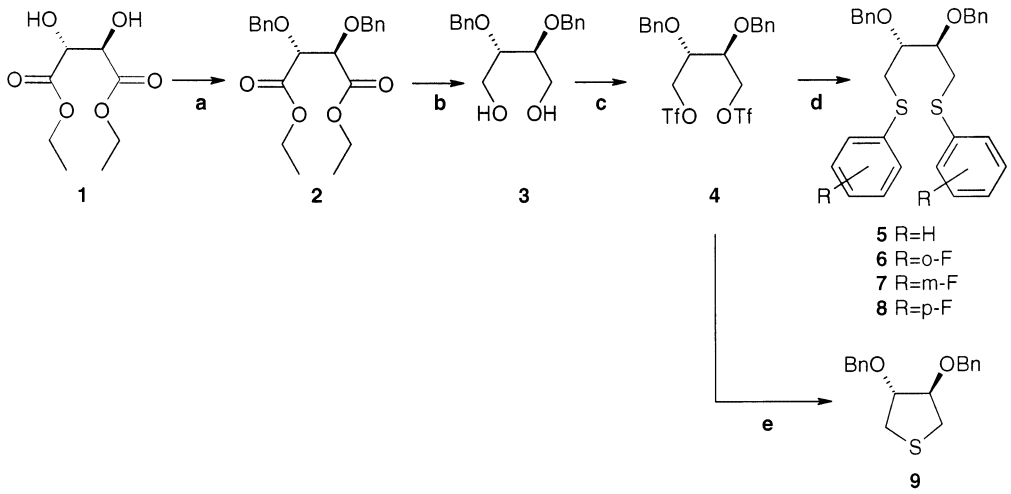
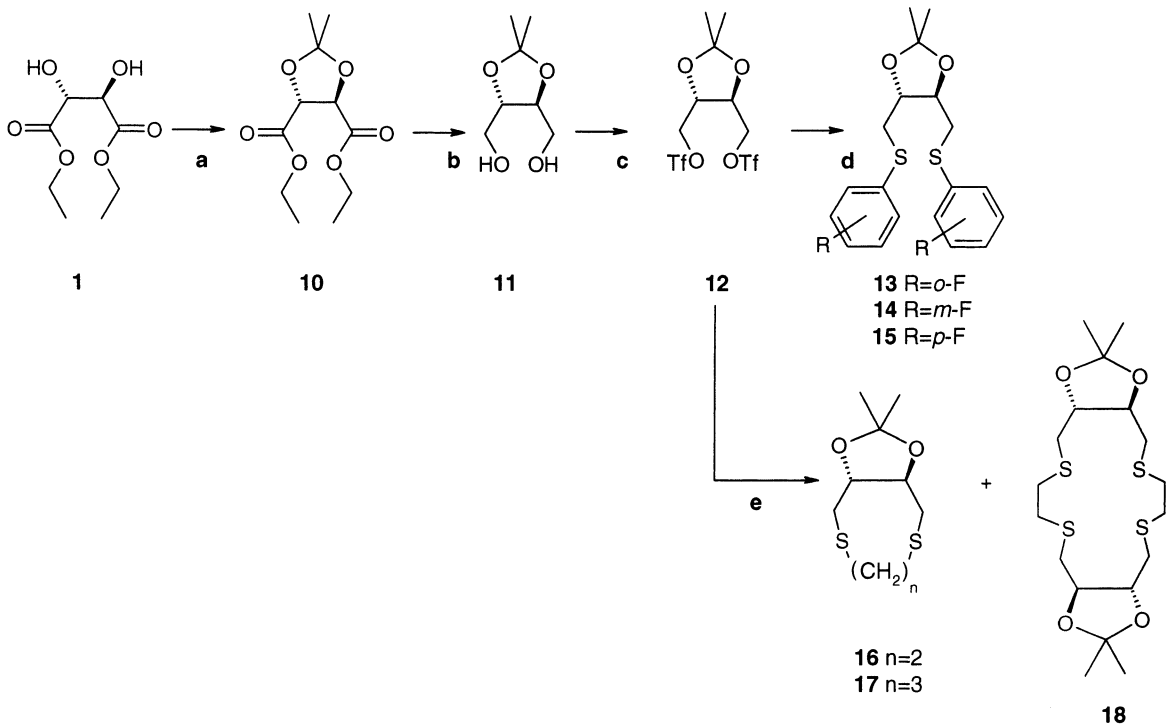


Scheme 1. (a) BnBr, NaH, THF; (b) $LiAlH_4$, THF; (c) $O(SO_2CF_3)_2$, CH_2Cl_2; (d) NaH, ArSH, THF; (e) NaH, $HS(CH_2)_nSH$, $n=2$, 3, THF, reflux.

thioethers by reacting 1,2-ethanedithiol and 1,3-propanedithiol with **4** or the corresponding ditosylate derivative under different temperatures, reaction times and solvents, but instead of the cyclic compound we obtained the thiolane **9**.

The analogous non-chiral cyclic dithioethers 1,4-dithiacyclooctane and 1,5-dithiacyclononane have been synthesised in very low yields (e.g. 0.2%,[10] 6%[11] and 0.6%,[12] 7%,[4] respectively) starting from sodium dithiolate and 1,4-dibromobutane; thiolane was not formed in either case. However, thiolane derivatives have previously been reported as the main product in the reaction of potassium thioacetate and 2,2,3,3-tetramethyl-1,4-butanedilolditosylate (90%)[13] or as a by-product when sodium methylthiolate is treated with (*S*,*S*)-(+)-3,4-dimethoxytetramethyleneditosylate (45%).[14]

Using a dioxolane skeleton, which is more rigid than **4**, we prepared the fluorinated phenyldithioethers **13**–**15** from ditriflate **12**[5a] and the corresponding sodium phenylthiolate (Scheme 2). Since free rotation of C(2) and C(3) of the butane backbone is restrained by the *O*-isopropylidene group, the thiolane formation was



Scheme 2. (a) 2,2-Dimethoxypropane, PTSA, MeOH; (b) $LiAlH_4$, Et_2O; (c) $O(SO_2CF_3)_2$, CH_2Cl_2; (d) NaH, ArSH, THF; (e) NaH, $HS(CH_2)_nSH$, THF, reflux.

disfavoured. This therefore allowed coupling between **12** and ethanedithiol or propanedithiol to produce **16** and **17** in good yields in very short reaction times. Similar results have been obtained when an aromatic backbone is used to prepare cyclic thioethers such as cyclophanes[15] and benzodithiecines[16] but this required slow additions and stirring over a long period.

If compound **16** is synthesised at 25°C with more concentrated solutions, the new chiral macrocyclic polythioether **18** is obtained as a by-product. Interesting applications are also expected for this.[17]

All of the new compounds were fully characterised by NMR spectral analysis. These exhibit C_2 symmetry for **5–8** and **13–15**. For cyclic dithioethers **16** and **17**, we must consider a fast equilibrium between conformations at 25°C to explain the NMR spectra, which show two independent magnetic systems. These correspond to the butane and ethane/propane fragments, respectively. The presence of the *O*-isopropylidene moiety restricts C(2) and C(3) free rotation and induces very different $^3J_{\mathbf{CH}_A\mathrm{H}_{A'}\text{–CH}}$ and $^3J_{\mathrm{CH}_A\mathbf{H}_{A'}\text{–CH}}$, which remain unaltered even at 50°C. The difference in chemical shifts between the two diastereotropic protons H_A and $H_{A'}$ when compared to their acyclic analogues, accounts for the additional restricted rotation imposed by the eight- and nine-membered cycles. Pseudoaxial proton H_A is more shielded than pseudoequatorial proton $H_{A'}$ which may be related to the lone-pair arrangement of the neighbouring sulfur.[18]

Iridium and palladium complexes of these ligands are currently being prepared and used in the iridium-catalysed asymmetric hydrogenation of acrylic and itaconic acid derivatives and palladium-catalysed allylic substitution reactions.

3. Experimental

Solvents were dried over standard drying agents and freshly distilled before use. ^{1}H, ^{19}F and ^{13}C NMR spectra were measured with a Varian Unity INOVA 300 MHz spectrometer operating at 299.7, 282, and 75 MHz, respectively. Chemical shifts were relative to TMS $\delta=0$ (^{1}H); CF_3COOH, $\delta=-77$ ppm (^{19}F) and $CDCl_3$ $\delta=77$ ppm (^{13}C). All species were studied in deuteriochloroform. ^{1}H and ^{19}F NMR spectra were simulated using gNMR V4.1.0 program.[19] Infrared spectra were recorded with a Nicolet AVATAR 320 FT-IR spectrometer. Electronic Impact and FAB$^+$ mass spectra were performed with a Jeol SX102A inverse geometry spectrometer. EI/GC spectra were obtained with a coupled HP5890 series II gas chromatograph using a capillary column HP5MS 30 m×0.25 mm ID 0.25 μm. FAB$^+$ mass spectra were acquired using 3-nitrobenzyl alcohol matrix. Optical rotations were measured with a Perkin–Elmer 241 polarimeter, and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were determined using FISONS EA1108 (CHNS-0) equipment. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated below 40°C in vacuum. TLC (Merck, silica gel 60) was used to monitor the progress of the reactions under study. The starting materials **1–3**[8,9] and **10–12**[15] were prepared according to literature methods.

3.1. Synthesis of triflates

3.1.1. Synthesis of (2*R*,3*R*)-2,3-bis(benzyloxy)butane-1,4-bis(trifluoromethanesulfonate) 4. Pyridine (0.17 mL, 2.11 mmol) was added to a solution of compound **3**[8] (0.30 g, 1 mmol) in dichloromethane (12 mL). The resulting solution was stirred for 15 min. It was then cooled to −20°C and triflic anhydride $(CF_3SO_2)_2O$ (0.4 mL, 2.4 mmol) was added dropwise. The reaction was monitored using TLC (hexane–ethyl acetate 3:2), and after 1 h the reaction was complete. The solvent was evaporated under vacuum and the residue purified by column chromatography (hexane–ethyl acetate 3:2) to give **4** as a white solid (0.52 g, 92%): $[\alpha]_D^{25}=+7.4$ (*c* 0.96 $CHCl_3$); IR (film) (cm^{-1}) (νSO_2) 1417 (s), (νSO_2) 1209 (s), (νCF) 1144 (m); ^{1}H NMR: δ 7.3 (m, 10H, C_6H_5), 4.691, 4.690 (AB, 4H, $C\mathbf{H}_A\mathbf{H}_B$-$C_6H_5$, $J_{AB}=-11.67$), 4.628, 4.525, 3.793, 3.793, 4.525, 4.628 (AA′MM′BB′, 6H, $C\mathbf{H}_A\mathbf{H}_{A'}$-$C\mathbf{H}_M$-$C\mathbf{H}_{M'}$-$C\mathbf{H}_B\mathbf{H}_{B'}$, $J_{A-A'}=J_{B'-B}=-10.7$, $J_{A-M}=J_{B'-M'}=3.23$, $J_{A'-M}=J_{B-M'}=6.18$, $J_{A-M'}=J_{B'-M}=0.13$, $J_{A'-M'}=J_{B-M}=-0.37$, $J_{M-M'}=4.88$); ^{13}C NMR: δ 136.2 (C_i), 128.8 (C_m), 128.6 (C_p), 128.3 (C_o), 118.5 (q, CF_3, $J_{C-F}=320.5$), 74.8 (CH), 74.4 ($\mathbf{C}H_2$-C_6H_5), 73.6 ($\mathbf{C}H_2$-$OS(O)_2CF_3$); ^{19}F NMR: δ −74.9 (CF_3). FAB$^+$: 565 *m*/*z* (M−1). Anal. calcd for $C_{20}H_{20}F_6O_8S_2$: C, 42.41; H, 3.56; S, 11.32. Found: C, 42.78; H, 3.58; S, 11.22.

3.2. Synthesis of thioethers

3.2.1. Synthesis of (2*R*,3*R*)-2,3-bis(benzyloxy)-1,4-dithiophenylbutane 5. A solution of phenylthiol (0.36 mL, 3.52 mmol) in THF (4 mL) was slowly added to a suspension of NaH (0.69 g at 60%, 17.36 mmol) in THF (4 mL) at 0°C. The resulting solution was stirred for 1 h at 25°C. A solution of compound **4** (0.74 g, 1.30 mmol) in THF (2 mL) was added dropwise at 0°C. After 3 1/2 h the solvent was evaporated and dichloromethane (5 mL) was added. The solution was cooled to 0°C and carefully treated with water (5 mL). Phases were separated and the aqueous phase was extracted with dichloromethane (3×3 mL). The organic phase was then dried and concentrated. The residue was purified by flash column chromatography (hexane–ethyl acetate, 20:1) and **5** was obtained as a pale yellow oil (0.54 g, 85%): $[\alpha]_D^{20}=+31.2$ (*c* 0.75 $CHCl_3$); IR (film) (cm^{-1}): (δ CH_{ar}) 739 (s), 695 (s); ^{1}H NMR: δ 7.3 (m, 20H, H_{ar}), 4.567, 4.398 (AB, 4H, $C\mathbf{H}_A\mathbf{H}_B$-$C_6H_5$, $J_{AB}=-11.39$), 3.171, 3.059, 3.78, 3.78, 3.059, 3.171 (AA′MM′BB′, 6H, $C\mathbf{H}_A\mathbf{H}_{A'}$-$C\mathbf{H}_M$-$C\mathbf{H}_{M'}$-$C\mathbf{H}_B\mathbf{H}_{B'}$, $J_{A-A'}=J_{B-B'}=-13.4$, $J_{A-M}=J_{B'-M'}=6.41$, $J_{A'-M}=J_{B-M'}=6.55$, $J_{A-M'}=J_{B'-M}=-0.26$, $J_{A'-M'}=J_{B-M}=-0.25$, $J_{M-M'}=2.48$); ^{13}C NMR: δ 137.8 ($\mathbf{C}_i$), 136 ($\mathbf{C}_i$-S), 129.7 ($\mathbf{C}_o$), 128.9 ($\mathbf{C}_o$-S), 128.4 ($\mathbf{C}_m$-S), 128.3 ($\mathbf{C}_m$), 127.8 ($\mathbf{C}_p$), 126.2 ($\mathbf{C}_p$-S), 77.1 (CH), 73 ($\mathbf{C}H_2$-C_6H_5), 33.8 (CH_2). EIMS: 486 *m*/*z* (M+·); High-resolution EIMS: 486.1710, $C_{30}H_{30}O_2S_2$ (Err[ppm/mmu]=+4.6/+2.2).

3.2.2. Synthesis of (2*R*,3*R*)-2,3-bis(benzyloxy)-1,4-bis(thio-*o*-fluorophenyl)butane 6. A solution of 2-fluorophenylthiol (0.74 mL, 7.01 mmol) in THF (6 mL) was treated sequentially—as described for **5**—with a suspension of NaH (1.47 g at 60%, 36.7 mmol) in THF (6 mL) and compound **4** (1.29 g, 2.28 mmol) in THF (10 mL). Compound **6** was obtained as a pale yellow oil (0.69 g, 58%): $[\alpha]_D^{20}=+26.9$ (*c* 0.77 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1156 (m); ^1H NMR: δ 7.2 (m, 18H, H_{ar}), 4.58, 4.406 (AB, 4H, CH_AH_B-C_6H_5, $J_{AB}=-11.54$), 3.067, 3.141, 3.756, 3.756, 3.141, 3.067 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-13.4$, $J_{A-M}=J_{B'-M'}=6.82$, $J_{A'-M}=J_{B-M'}=6.38$, $J_{A-M'}=J_{B'-M}=J_{A'-M'}=J_{B-M}=0$, $J_{M-M'}=3.11$); ^{13}C NMR: δ 161.6 (C_i-F, $J_{C-F}=245.2$), 137.7 (C_i), 132.4 (C_m-S, $^4J_{C-F}=2$), 128.6 (C_p-S, $J_{C-F}=8.1$), 128.4 (C_o), 128.3 (C_m), 127.9 (C_p), 124.5 (C_o-S, $J_{C-F}=4$), 122.7 (C_i-S, $J_{C-F}=17.2$), 115.7 (C_m-S, $^2J_{C-F}=22.2$), 77.3 (CH), 73 (CH_2-C_6H_5), 33.2 (CH_2); ^{19}F NMR: δ −110.4 (ABCDX, $H_AH_BH_CH_DF_X$, $^3J_{A-X}=9.48$, $^4J_{B-X}=7.32$, $^4J_{C-X}=0.05$, $^3J_{D-X}=5.34$,); EIMS: 522 (*m*/*z*); High-resolution EIMS: 522.1523, $C_{30}H_{28}F_2O_2S_2$ (Err[ppm/mmu]=+4.6/+2.4). Anal. calcd for $C_{30}H_{28}F_2O_2S_2$: C, 68.94; H, 5.4; S, 12.27. Found: C, 68.36; H, 5.45; S, 12.19%.

3.2.3. Synthesis of (2*R*,3*R*)-2,3-bis(benzyloxy)-1,4-bis(thio-*m*-fluorophenyl)butane 7. A solution of 3-fluorophenylthiol (0.36 mL, 3.43 mmol) in THF (2 mL) was treated sequentially—as described for **5**—with a suspension of NaH (0.69 g at 60%, 17.3 mmol) in THF (3 mL) and compound **4** (0.73 g, 1.30 mmol) in THF (3 mL). Compound **7** was obtained as a pale yellow oil (0.5 g, 74%): $[\alpha]_D^{20}=+24.9$ (*c* 0.85 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1159 (m); ^1H NMR: δ 7 (m, 18H, H_{ar}), 4.589, 4.461 (AB, 4H, CH_AH_B-C_6H_5, $J_{AB}=-11.39$), 3.057, 3.18, 3.766, 3.766, 3.18, 3.057 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-13.86$, $J_{A-M}=J_{B'-M'}=J_{A'-M}=J_{B-M'}=6.58$, $J_{A-M'}=J_{B'-M}=J_{A'-M'}=J_{B-M}=0$, $J_{M-M'}=2.7$); ^{13}C NMR: δ 162.8 (C_i-F, $J_{C-F}=249.2$), 138.4 (C_i-S, $J_{C-F}=8.1$), 137.5 (C_i), 130.2 (C_m-S, $J_{C-F}=9.1$), 128.4 (C_o), 128.4 (C_m), 128 (C_p) 124.5 (C_o-S, $^4J_{C-F}=3.1$), 115.8 (C_p-S, $J_{C-F}=22.2$), 113 (C_o-S, $^2J_{C-F}=21.1$), 76.8, (CH), 73.1 (CH_2-C_6H_5), 33.3 (CH_2); ^{19}F NMR: −113.5 (A_2BCX, $(H_A)_2H_BH_CF_X$, $^3J_{A-X}=8.69$, $^4J_{B-X}=6.06$, $^5J_{C-X}=0.09$); EIMS: 522 (*m*/*z*); High-resolution EIMS: 522.1523, $C_{30}H_{28}F_2O_2S_2$ (Err[ppm/mmu]=+4.6/+2.4). Anal. calcd for $C_{30}H_{28}F_2O_2S_2$: C, 68.94; H, 5.4; S, 12.27. Found: C, 68.45; H, 5.45; S, 12.25%.

3.2.4. Synthesis of (2*R*,3*R*)-2,3-bis(benzyloxy)-1,4-bis(thio-*p*-fluorophenyl)butane 8. A solution of 4-fluorophenylthiol (0.36 mL, 3.38 mmol) in THF (2 mL) was treated sequentially—as described for **5**—with a suspension of NaH (0.7 g at 60%, 17.38 mmol) in THF (3 mL) and compound **4** (0.74 g, 1.30 mmol) in THF (4 mL). Compound **8** was obtained as a pale yellow oil (0.6 g, 87.9%): $[\alpha]_D^{20}=+33.0$ (*c* 0.746 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1157(m); ^1H NMR: δ 7.1 (m, 18H, H_{ar}), 4.543, 4.376 (AB, $J_{AB}=-11.54$, 4H, CH_AH_B-C_6H_5), 2.981, 3.104, 3.719, 3.719, 3.104, 2.981 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-13.46$, $J_{A-M}=J_{B'-M'}=J_{A'-M}=J_{B-M'}=6.37$, $J_{A-M'}=J_{B'-M}=J_{A'-M'}=J_{B-M}=0$, $J_{M-M'}=2.69$); ^{13}C NMR: δ 161.8 (C_i-F, $J_{C-F}=247.2$), 137.6 (C_i), 132.5 (C_o-S, $J_{C-F}=8.1$), 130.8 (C_i-S, $J_{C-F}=3$), 128.4 (C_o), 128.3 (C_m), 127.9 (C_p), 116 (C_m-S, $J_{C-F}=22.2$), 76.7 (CH), 72.8 (CH_2-C_6H_5), 34.8 (CH_2); ^{19}F NMR: δ −116.7 (A_2B_2X, $(H_A)_2(H_B)_2F_X$, $^3J_{A-X}=8.63$, $^4J_{B-X}=5.2$); EIMS: 522 (*m*/*z*); High-resolution EIMS: 522.1523, $C_{30}H_{28}F_2O_2S_2$ (Err[ppm/mmu]=+4.6/+2.4). Anal. calcd for $C_{30}H_{28}F_2O_2S_2$: C, 68.94; H, 5.4; S, 12.27. Found: C, 68.38; H, 5.45; S, 12.16%.

3.2.5. Synthesis of (3*R*,4*R*)-3,4-*O*-bis(benzyloxy)thiolane 9. A solution of ethanedithiol (0.05 mL, 0.59 mmol) in THF (1.7 mL) was slowly added to a suspension of NaH (0.14 g at 60%, 4 mmol) in THF (4 mL). The resulting solution was stirred for 1 h at 25°C. Then a solution of compound **4** (0.3 g, 0.53 mmol) in THF (0.6 mL) was slowly added. After 2.5 h the mixture was heated and kept at reflux temperature for 3 h. The mixture was allowed to cool, the solvent evaporated and dichloromethane (5 mL) was added. The solution was cooled to 0°C and water (5 mL) was added slowly. Phases were separated and the aqueous phase was extracted with dichloromethane (3×3 mL). The organic phase was then dried and concentrated. The residue was purified by flash column chromatography (hexane–ethyl acetate, 20:1) and **9** was obtained as a white solid (0.11 g, 65%); ^1H NMR: δ 7.2 (m, 18H, H_{ar}) 4.596, 4.541 (AB, $J_{AB}=12.14$, 4H, CH_AH_B-C_6H_5), 2.898, 3.066, 4.175, 4.175, 3.066, 2.898 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=11.42$, $J_{B-B'}=11.46$, $J_{A-M}=3.46$, $J_{B'-M'}=3.02$, $J_{A'-M}=4.94$, $J_{B-M'}=4.54$, $J_{A-M'}=0.25$, $J_{B'-M}=0.51$, $J_{A'-M'}=-0.63$, $J_{B-M}=-0.25$, $J_{M-M'}=4.32$); ^{13}C NMR: δ 138 (C_i), 128.4 (C_o), 127.8 (C_m), 127.6 (C_p), 83.5 (CH), 71.4 (CH_2-C_6H_5), 33 (CH_2); EIMS: 300 (*m*/*z*) (M); High-resolution EIMS: 300.1176 (*m*/*z*), $C_{18}H_{20}O_2S$ (Err[ppm/mmu]=−2.7/−0.8).

3.2.6. Synthesis of (2*R*,3*R*)-2,3-*O*-isopropylidene-1,4-bis(thio-*o*-fluorophenyl)butane 13. A solution of 2-fluorophenylthiol (0.46 mL, 4.36 mmol) in THF (1.5 mL) was treated sequentially—as described for the preparation of **5**—with a suspension of NaH (1.11 g at 60%, 27.75 mmol) in THF (1.5 mL) and compound **12** (0.55 g, 1.29 mmol) in THF (5 mL). Compound **13** was obtained as a transparent oil (0.45 g, 92%): $[\alpha]_D^{25}=+35.8$ (*c* 0.75 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1161(m); ^1H NMR: δ 7.3 (m, 8H, H_{ar}) 3.195, 3.19, 4.054, 4.054, 3.19, 3.195 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-12.77$, $J_{A-M}=J_{B'-M'}=5.31$, $J_{A'-M}=J_{B-M'}=6.47$, $J_{A-M'}=J_{B'-M}=-0.46$, $J_{A'-M'}=J_{B-M}=-0.28$, $J_{M-M'}=6.94$), 1.4 (s, 6H, CH_3); ^{13}C NMR: δ 161.5 (C_i-F, $J_{C-F}=246.2$), 132.5 (C_m-S, $^4J_{C-F}=2$), 128.8 (C_p-S, $J_{C-F}=8.1$), 124.5 (C_o-S, $J_{C-F}=4$), 122.3 (C_i-S, $J_{C-F}=17.1$), 115.8 (C_m-S, $^2J_{C-F}=22.2$), 109.8 ($C(CH_3)_2$), 79.0 (CH), 36.5 (CH_3), 36.5 (CH_3), 27.2 (CH_2); ^{19}F NMR: δ −110.3 (ABCDX, $H_AH_BH_CH_DF_X$, $^3J_{A-X}=9.65$, $^4J_{B-X}=7.44$, $^5J_{C-X}=0.19$, $^4J_{D-X}=5.08$); EIMS: 382 *m*/*z* (M); High-resolution EI 382.0849 (*m*/*z*), $C_{19}H_{20}F_2O_2S_2$ (Err[ppm/mmu]=−6.1/−2.3).

3.2.7. Synthesis of (2*R*,3*R*)-2,3-*O*-isopropylidene-1,4-bis(thio-*m*-fluorophenyl)butane 14. A solution of 3-fluorophenylthiol (0.34 mL, 3.24 mmol) in THF (2.5 mL) was treated sequentially—as described for the preparation of **5**—with a suspension of NaH (0.72 g at 60%, 18 mmol) in THF (2.5 mL) and compound **12** (0.41 g, 0.96 mmol) in THF (1 mL). Compound **14** was obtained as a transparent oil (0.35 g, 94%): $[\alpha]_D^{25}=+38.7$ (*c* 0.77 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1161 (m); ^1H NMR: δ 7.2 (m, 8H, H_{ar}), 3.236, 3.202, 4.087, 4.087, 3.202, 3.236 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-13.78$, $J_{A-M}=J_{B'-M'}=5.56$, $J_{A'-M}=J_{B-M'}=6.42$, $J_{A-M'}=J_{B'-M}=-0.07$, $J_{A'-M'}=J_{B-M}=-0.66$, $J_{M-M'}=7.01$), 1.4 (s, 6H, CH_3); ^{13}C NMR: δ 162.8 (C_i-F, $J_{C-F}=248.2$), 138.1 (C_i-S, $J_{C-F}=8.1$), 130.2 (C_m-S, $J_{C-F}=8.1$), 124.3 (C_o-S, $^4J_{C-F}=3$), 115.6 (C_p-S, $J_{C-F}=23.2$), 113.2 (C_o-S, $^2J_{C-F}=21.2$), 110 ($\mathbf{C}(CH_3)_2$), 78.8 (CH), 36.4 (CH_3), 27.3 (CH_2); ^{19}F NMR: δ −113.4 (A_2BCX, $(H_A)_2H_BH_C\mathbf{F}_X$, $^3J_{A-X}=9.02$, $^4J_{B-X}=5.87$, $^5J_{C-X}=0.52$); EIMS: 382 (*m*/*z*) (M); High-resolution EIMS: 382.0849 (*m*/*z*), $C_{19}H_{20}F_2O_2S_2$ (Err[ppm/mmu]=−6.1/−2.3).

3.2.8. Synthesis of (2*R*,3*R*)-2,3-*O*-isopropylidene-1,4-bis(thio-*p*-fluorophenyl)butane 15. A solution of 3-fluorophenylthiol (0.46 mL, 4.32 mmol) in THF (5 mL) was treated sequentially—as described for the preparation of **5**—with a suspension of NaH (1.07 g at 60%, 26.75 mmol) in THF (5 mL) and compound **12** (0.55 g, 1.29 mmol) in THF (10 mL). Compound **15** was obtained (0.42 g, 84.9%) as a transparent oil: $[\alpha]_D^{25}=+30.6$ (*c* 0.83 $CHCl_3$); IR (film) (cm^{-1}): (νC_{ar}–F) 1157 (s); ^1H NMR: δ 7.2 (m, 8H, H_{ar}), 3.161, 3.139, 4.024, 4.024, 3.139, 3.161 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-12.77$, $J_{A-M}=J_{B'-M'}=5.57$, $J_{A'-M}=J_{B-M'}=6.49$, $J_{A-M'}=J_{B'-M}=-0.5$, $J_{A'-M'}=J_{B-M}=0.05$, $J_{M-M'}=6.81$), 1.42 (s, 6H, CH_3), 1.4 (s, 6H, CH_3); ^{13}C NMR: 161.9 (C_i-F, $J_{C-F}=247.3$), 132.5 (C_o-S, $J_{C-F}=8.1$), 130.5 (C_i-S, $J_{C-F}=3$), 116.2 (C_m-S, $J_{C-F}=22.2$), 109.8 ($\mathbf{C}(CH_3)_2$), 78.8 (**C**H), 38.2 ($\mathbf{C}H_3$), 27.3 ($\mathbf{C}H_2$); ^{19}F NMR: δ −116.4 (A_2B_2X, $(H_A)_2(H_B)_2\mathbf{F}_X$, $^3J_{A-X}=8.46$, $^4J_{B-X}=5.22$). EIMS: 382 *m*/*z* (M); High-resolution EIMS: 382.0849(*m*/*z*), $C_{19}H_{20}F_2O_2S_2$ (Err[ppm/mmu]=−6.1/−2.3).

3.2.9. Synthesis of (6*R*,7*R*)-6,7-*O*-isopropylidene-1,4-dithiacyclooctane 16. A solution of 1,2-ethanedithiol (0.2 mL, 2.38 mmol) in THF (28 mL) was slowly added to a suspension of NaH (1.19 g at 60%, 29.66 mmol) in THF (60 mL). The resulting solution was stirred for 30 minutes at 25°C The solution was heated under reflux (64°C) and a solution of compound **12** (1 g, 2.35 mmol) in THF (60 mL) was slowly added over 35 min. The solution was left to cool with continuous stirring. The solvent was evaporated and the crude purified as described for **5**. Compound **16** was obtained as a white solid (0.25 g, 49%): $[\alpha]_D^{25}=+95.8$ (*c* 0.79 $CHCl_3$); ^1H NMR: δ (25°C) 2.846, 3.274, 4.282, 4.282, 3.274, 2.846 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=-14.78$, $J_{B-B'}=-14.77$, $J_{A-M}=7.43$, $J_{B'-M'}=7.62$, $J_{A'-M}=4.07$, $J_{B-M'}=4.19$, $J_{A-M'}=-0.37$, $J_{B'-M}=-0.61$, $J_{A'-M'}=-0.22$, $J_{B-M}=-0.23$, $J_{M-M'}=8.23$), 2.944, 2.88, 2.88, 2.944 (AA′BB′, 4H, S-$CH_AH_{A'}$-$CH_BH_{B'}$-S, $J_{A-A'}=J_{B-B'}=-15.64$, $J_{A-B}=J_{A'-B'}=2.49$, $J_{A-B'}=6.45$, $J_{A'-B}=9.39$), 1.4 (s, 6H, CH_3); δ (50°C) 2.853, 3.27, 4.282, 4.282, 3.27, 2.853 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=-14.78$, $J_{B-B'}=-14.77$, $J_{A-M}=7.43$, $J_{B'-M'}=7.62$, $J_{A'-M}=4.07$, $J_{B-M'}=4.19$, $J_{A-M'}=-0.37$, $J_{B'-M}=-0.61$, $J_{A'-M'}=-0.22$, $J_{B-M}=-0.23$, $J_{M-M'}=8.23$), 2.935, 2.9, 2.9, 2.935 (AA′BB′, 4H, S-$CH_AH_{A'}$-$CH_BH_{B'}$-S, $J_{A-A'}=J_{B-B'}=-15.64$, $J_{A-B}=J_{A'-B'}=2.49$, $J_{A-B'}=6.45$, $J_{A'-B}=9.39$), 1.5 (s, 6H, CH_3); ^{13}C NMR: δ 107.7 ($\mathbf{C}(CH_3)_2$), 79.9 (CH), 35.2 (S-$\mathbf{C}H_2$-$\mathbf{C}H_2$-S), 34.2 ($\mathbf{C}H_2$-CH), 27 (CH_3); EIMS: 220 (*m*/*z*) (M); High-resolution EIMS: (*m*/*z*): 220.0578 (*m*/*z*), $C_9H_{16}O_2S_2$ (Err [ppm/mmu]=−6.2/−1.4).

3.2.10. Synthesis of (*R*,*R*)-7,8-*O*-isopropylidene-1,5-dithiacyclononane 17. A solution of 1,3-propanedithiol (0.36 mL, 3.59 mmol) in THF (34.5 mL) was slowly added to a suspension of NaH (1.78 g at 60%, 44.56 mmol) in THF (120 mL). The resulting solution was stirred for 1 h at 25°C and treated as described for **16**. Compound **17** was obtained as a white solid (0.4 g, 48%): $[\alpha]_D^{25}=+54.8$ (*c* 0.825 $CHCl_3$); ^1H NMR: δ (25°C) 2.874, 3.201, 4.233, 4.233, 3.201, 2.874 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-15.17$, $J_{A-M}=J_{B'-M'}=8.03$, $J_{A'-M}=3.03$, $J_{B-M'}=3.12$, $J_{A-M'}=-0.47$, $J_{B'-M}=-0.39$, $J_{A'-M'}=-0.23$, $J_{B-M}=-0.38$, $J_{M-M'}=7.6$), 2.994, 2.89, 1.943, 1.946, 2.887, 2.994 (AA′MM′BB′, 6H, S-$CH_AH_{A'}$-$CH_MH_{M'}$-$CH_BH_{B'}$-S, $J_{A-A'}=J_{B-B'}=-14.48$, $J_{A-B}=J_{A'-B'}=J_{A-B'}=J_{A'-B}=0$, $J_{A-M}=4.8$, $J_{A-M'}=4.52$, $J_{A'-M}=6.38$, $J_{A'-M'}=7.15$, $J_{B'-M}=4.33$, $J_{B'-M'}=4.79$, $J_{B'-M}=7.33$, $J_{B-M'}=8.58$, $J_{M-M'}=-12.3$), 1.4 (s, 6H, CH_3); δ (50°C) 2.871, 3.2, 4.237, 4.237, 3.2, 2.871 (AA′MM′BB′, 6H, $CH_AH_{A'}$-CH_M-$CH_{M'}$-$CH_BH_{B'}$, $J_{A-A'}=J_{B-B'}=-15.17$, $J_{A-M}=J_{B'-M'}=8.03$, $J_{A'-M}=3.03$, $J_{B-M'}=3.12$, $J_{A-M'}=-0.47$, $J_{B'-M}=-0.39$, $J_{A'-M'}=-0.23$, $J_{B-M}=-0.38$, $J_{M-M'}=7.6$), 3.004, 2.91, 1.935, 1.938, 2.905, 3.004 (AA′MM′BB′, 6H, S-$CH_AH_{A'}$-$CH_MH_{M'}$-$CH_BH_{B'}$-S, $J_{A-A'}=J_{B-B'}=-14.48$, $J_{A-B}=J_{A'-B'}=J_{A-B'}=J_{A'-B}=0$, $J_{A-M}=4.8$, $J_{A-M'}=4.52$, $J_{A'-M}=6.38$, $J_{A'-M'}=7.15$, $J_{B'-M}=4.33$, $J_{B'-M'}=4.79$, $J_{B-M}=7.33$, $J_{B-M'}=8.58$, $J_{M-M'}=-12.3$) 1.4 (s, 6H, CH_3); ^{13}C NMR: δ 107.8 ($\mathbf{C}(CH_3)_2$), 82 (CH), 36.9 ($\mathbf{C}H_2$-CH_2-$\mathbf{C}H_2$), 31.7 ($\mathbf{C}H_2$-CH), 30.9 (CH_2-$\mathbf{C}H_2$-CH_2), 27 (CH_3); EIMS: 234 (*m*/*z*); High-resolution EIMS: 234.0737 (*m*/*z*), $C_{10}H_{18}O_2S_2$ (Err [ppm/mmu]=−5.0/−1.2).

3.2.11. Synthesis of (6*R*,7*R*,14*R*,15*R*)-6,7,14,15-bis(*O*-isopropylidene)-1,4,9,12-tetrathiacyclohexadecane 18. A solution of ethanedithiol (0.06 mL, 0. 71 mmol) in THF (1.5 mL) was treated sequentially—as described for the preparation of **5**—with a suspension of NaH (0.19 g at 60%, 4.8 mmol) in THF (1.5 mL) and compound **12** (0.31 g, 0.71 mmol) in THF (1.5 mL). Compound **16** was obtained as the major product (0.04 g, 28%) and compound **18** was also isolated as a white solid (0.03 g, 9%); $[\alpha]_D^{25}=-10.8$ (*c* 0.06, $CHCl_3$); ^1H NMR: δ 4 (m, 4H, C**H**), 2.9 (m, 8H, $\mathbf{C}H_2$-CH), 2.841–2.899 (m, 8H, S-$\mathbf{C}H_2$-$\mathbf{C}H_2$-S), 1.42, 1.425 (s, 12H, CH_3); ^{13}C NMR: δ 110.3, 110.1 ($\mathbf{C}(CH_3)_2$), 80.1, 79.8 (CH), 36.5, 35.7 ($\mathbf{C}H_2$-**C**H), 33.6, 33.5 ($\mathbf{C}H_2$-$\mathbf{C}H_2$), 28 (CH_3); EIMS: 440 (*m*/*z*) (M); High-resolution EIMS: (*m*/*z*): 440.1170 (*m*/*z*); $C_{18}H_{32}O_4S_4$ (Err [ppm/mmu]=−3.0/−1.3).

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References

1. Bayón, J. C.; Claver, C.; Masdeu-Bultó, A. M. *Coord. Chem. Rev.* **1999**, *193–195*, 73–145.
2. (a) Hauptman, E.; Fagan, P. J.; Marshall, W. *Organometallics* **1999**, *18*, 2061–2073; (b) Pámies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Organometallics* **2000**, *19*, 1488–1496; (c) Barbaro, P.; Currao, A.; Jörg, H.; Nesper, R.; Pregosin, P. S.; Salzmann, R. *Organometallics* **1996**, *15*, 1879–1888; (d) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Forrest, E. M.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994–2995; (e) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Forrest, E. M.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920; (f) Hiraoka, M.; Mishikawa, A.; Marimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 704.
3. (a) Alloen, J. V.; Bower, J. F.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1895–1898; (b) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065–2072; (c) Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256–8262; (d) Tommasino, M. L.; Casalta, M.; Breuzard, J. A. J.; Lemaire, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4835–4841; (e) Vriesema, B. K.; Lemaire, M.; Buter, J.; Kellog, R. M. *J. Org. Chem.* **1986**, *51*, 5169–5177.
4. Gonsalves, I. S.; Santos, A. M.; Romão, C. C.; Lopes, D. A.; Rodríguez-Borges, J. E.; Pillinger, M. P. F.; Rocha, J.; Kühn, F. E. *J. Organomet. Chem.* **2001**, *626*, 1–10.
5. (a) Diéguez, M.; Orejón, A.; Masdeu-Bultó, A. M.; Echarri, R.; Castillón, S.; Claver, C.; Ruiz, A. *J. Chem. Soc., Dalton Trans.* **1997**, 4611–4618; (b) Diéguez, M.; Ruiz, A.; Claver, C.; Pereira, M. M.; d'A. Rocha, G. A. M. *J. Chem. Soc., Dalton Trans.* **1998**, 3517–3522.
6. Jansat, S.; Gómez, M.; Muller, G.; Diéguez, M.; Aghmiz, A.; Claver, C.; Masdeu-Bultó, A. M.; Flores-Santos, L.; Martin, E.; Maestro, M. A.; Mahía, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1469–1474.
7. Albinati, A.; Eckert, J.; Pregosin, P.; Rüegger, H.; Salzmann, R.; Stössel, C. *Organometallics* **1997**, *16*, 579–590.
8. Nemoto, H.; Takamatsu, S.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 1321–1322.
9. Cunningham, A. F.; Kundig, E. P. *J. Org. Chem.* **1988**, *53*, 1823–1825.
10. Tucker, N.; Beverley, R.; Emmet, E. *J. Am. Chem. Soc.* **1933**, *55*, 775–781.
11. Musker, W. K.; Wolford, T. L.; Roush, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 6416–6421.
12. Meadow, J. R.; Reid, E. E. *J. Am. Chem. Soc.* **1934**, *56*, 2177–2180.
13. Juaristi, E.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1988**, *53*, 3334–3338.
14. Seebach, D.; Kalinowski, H.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; Du Peerez, N. P.; Ehrig, V.; Langer, W.; Nüsler, C.; Oei, H.; Schmidt, M. *Helvet. Chim. Acta* **1977**, *60*, 301–325.
15. (a) Tam, T.-F.; Wong, P.-C.; Siu, T.-W.; Chan, T.-L. *J. Org. Chem.* **1976**, *41*, 1289–1291; (b) Au, M.-K.; Mak, T. C. W.; Chan, T.-L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1475–1477; (c) Lai, Y.-H. *J. Org. Chem.* **1988**, *53*, 2306–2362; (d) Hanton, L. R.; Sikanyika, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1883–1884.
16. Shimizu, H.; Watanabe, H.; Mizuno, M.; Kataoka, T.; Hori, M. *Heterocycles* **2001**, *54*, 139–150.
17. (a) Ochrymowycz, L. A.; Mak, C.-P.; Michna, J. D. *J. Org. Chem.* **1974**, *39*, 2079–2084; (b) Lemaire, M.; Vriesema, B. K.; Kellog, R. M. *Tetrahedron Lett.* **1985**, *26*, 3499–3502; (c) Vriesema, B. K.; Lemaire, M.; Buter, J.; Kellog, R. M. *J. Org. Chem.* **1986**, *51*, 5169–5177.
18. Juaristi, E.; Cuevas, G.; Flores-Vela, A. *Tetrahedron Lett.* **1992**, *33*, 6927–6930.
19. gNMR version 4.1.0, Cherwell Scientific Publishing Ltd.: Oxford, 1995–1999.