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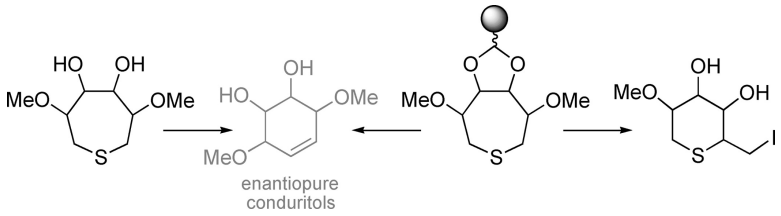

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A General Procedure for the Synthesis of Stereochemically Pure Conduritol Derivatives Practical also for Solid-Phase Chemistry

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A straightforward synthetic protocol apt to synthesize a library constituted by all conduritol stereoisomers in solution phase is described and successfully applied to some polymer-supported substrates. During the solid-phase sequence, an unprecedented rearrangement of a resin-bound sulfone performed under the Ramberg−Bäcklund conditions appears of particular interest. Upon treatment with Me_3Si-I, thiepanes supported on resin are found to undergo regio- and stereospecific ring contraction to a six-membered ring system with traceless cleavage from the solid support.

Introduction

Conduritols and their derivatives possess interesting biological activities as glycosidase inhibitors,[1] antibiotics, antileukemics, and growth-regulating compounds[2] and are also useful intermediates in the synthesis of inositol derivatives.[3] They exist as two meso compounds and four enantiomeric pairs, and a variety of synthetic approaches, although often complex, have been applied[4] to obtain enantiopure compounds. Recently, interesting synthetic routes leading to conduritols via efficient enzymatic resolution[5] and by integrated or convergent syntheses using a single chiral building block have been reported.[6] Indeed, the relevance of the target justifies the use of complex synthetic approaches including numerous steps.

We have previously reported a simple synthetic strategy, based on the intermediacy of thiepanes, in which the four stereocenters in the starting alcohol sugar are maintained in the target compound (Figure 1).[7] However, the unavailability of several alcohol sugars as starting materials prevented this straightforward strategy from being extended to the synthesis of all the stereoisomeric conduritols.

With the aim of finding a more general entry to all the possible conduritol stereoisomers, we devised a different approach to thiepanes which greatly alleviates the synthetic efforts. Starting from the commercially available mixture of *R,R, S,S* and meso 1,5-hexadiene-3,4-diols (A, Scheme 1), a library consisting of all the 10 thiepanes stereoisomers D (2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole-4,8-diols), some of them novel, was generated in only three steps (Scheme 1). The individual library members were obtained in high yield by HPLC separation, and their stereochemistry was unambiguously assigned.[8]

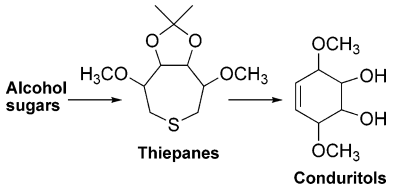
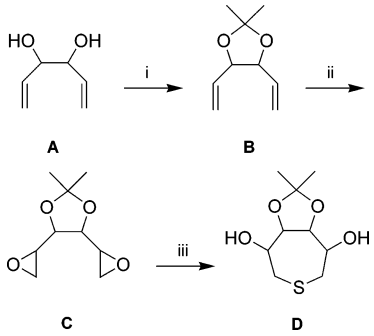


Figure 1.

Scheme 1



(i) Acetone, *p*-TSA (85%); (ii) MCPBA, 4,4′-thiobis-(6-*tert*-butyl-3-methylphenol), $ClCH_2-CH_2Cl$ (92%); (iii) $Na_2S{\cdot}9H_2O$, EtOH (58%).

Results and Discussion

With all 10 thiepanes available, we envisaged the possibility of their transformation into the corresponding conduritols to demonstrate the generality of our earlier reported synthetic procedure.[7] Then, to achieve this goal was sufficient to synthesize the conduritols derived from the novel thiepanes (+)-**1a**, **1b**, and **1c** (Figure 2) using our earlier reported procedure,[7] without giving any attention to the previously prepared conduritols obtained by the same procedure. Clearly, the synthesis of the related enantiomers was also disregarded.

Thus, the hydroxy groups of the thiepane derivatives **1a**−**c**, shown in Figure 2, were protected as methyl ethers (Scheme 2), obtaining the related 4,8-dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxoles (**2a**−**c**).

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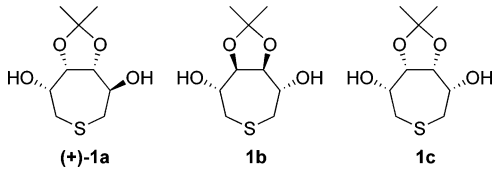
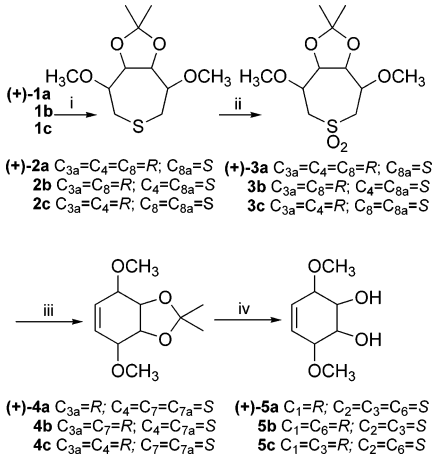


Figure 2.

Scheme 2



(i) NaH, CH_3I, THF; (ii) MCPBA, CH_2Cl_2; (iii) KOH, CCl_4, *t*-BuOH, H_2O; (iv) TFA, CH_3CN.

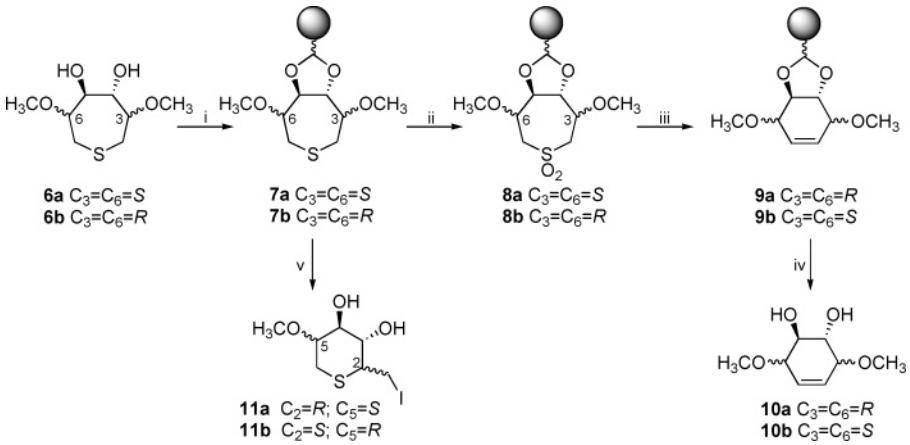
Oxidation of **2a**−**c** to the corresponding sulfones (**3a**−**c**) and extrusion of the SO_2 group by the Ramberg−Bäcklund reaction afforded conduritol derivatives (**4a**−**c**). Acidic treatment promoted removal of the isopropylidene protecting group, leading to compounds **5a**−**c**, unambiguously identified from the stereochemistry of the starting thiepane as the (+)-(1*R*,2*S*,3*S*,6*S*)-3,6-dimethoxycyclohex-4-ene-1,2-diol and the two meso forms (1*R*,2*S*,3*S*,6*R*)- and (1*R*,2*S*,3*R*,6*S*)-3,6-dimethoxycyclohex-4-ene-1,2-diols, respectively.

The relevance of conduritols as biologically active compounds useful also as intermediates in the synthesis of ciclitols,[3] in combination with the availability of thiepanes, prompted us to adapt our flexible and efficient solution-phase preparation of conduritols to the solid phase. Our starting point was to consider polystyrene−CHO resin-bound (3*S*,4*S*,5*S*,6*S*)- and (3*R*,4*S*,5*S*,6*R*)-3,6-dimethoxythiepane-4,5-diols **6a** and **6b**, respectively[9] (Scheme 3). The 1,2-diols provided a suitable handle for the reversible attachment to the solid support.[10] The acetalization was carried out by adding to a polystyrene−CHO resin (P−CHO), preswollen for 12 h in benzene, thiepanes and *p*-TSA as catalyst. The mixture was refluxed for 20 h with azeotropic removal of water by Dean−Stark trap. The progress of the reaction was monitored by FT-IR spectrum in KBr of the resin-bound thiepanes **7a**,**b**. The diol-loaded resin showed- in fact- the disappearance of the strong carbonyl streching at 1698 cm^{-1}, corresponding to the C═O frequency of the starting P−CHO resin, suggesting that a complete reaction had occurred. The yield of the condensation (∼95%) was estimated from the increase in the weight of the resin. The subsequent oxidation of the sulfur atom, performed with *m*-chloroperbenzoic acid, leading to the sulfone derivatives **8a**,**b** was easily evidenced in the IR spectrum by the strong absorption at 1307 and 1100 cm^{-1}. Submitting **8a**,**b** to the Ramberg−Bäcklund reaction under the modified conditions reported by Meyers[11] resulted in the resin-supported cyclohexene derivatives **9a**,**b** being obtained. Again, the IR analysis of the resin evidenced the disappearance of the SO_2 absorptions. Worth noting is that although several important applications of the Ramberg−Bäcklund reaction for the synthesis of natural products in solution phase[12,7a,b] have been reported, to the best of our knowledge, the application of this reaction using sulfones supported on solid phase is totally unprecedented. Finally, trifluoroacetic acid (TFA) treatment led to removal of the immobilized organic molecule, and no memory of the immobilization (traceless cleavage) remained on the target. Highly pure conduritol derivatives **10a**,**b** were obtained in slightly higher yields with respect to those using solution-phase reactions.[7b]

These results demonstrate that using the P−CHO as solid support, which acts as a very efficient protecting group of the two vicinal alcoholic groups of the substrate, general and easy access to stereochemically pure conduritol derivatives can be envisaged using the same reagents and solvents employed in the corresponding solution reactions. Moreover, supporting thiepanes on resin greatly simplifies the isolation and makes purification of the final products unnecessary.

In addition to the transformation into conduritols, the resin-bound thiepane derivatives could be subjected to other

Scheme 3



(i) Polystyrene−CHO, *p*-TSA, benzene, 20 h at reflux (95%); (ii) MCPBA, CH_2Cl_2; (iii) KOH, CCl_4, *t*-BuOH, H_2O; (iv) TFA, CH_2Cl_2; (v) Me_3SiI, CH_3CN, 3 h at reflux.

chemical manipulations, such as the transannular ring contractions in which a sacrificial OH group is lost. So far, in line with the reaction behavior in solution phase previously reported by us,[13] by treating thiepanes supported on resin (**6a**,**b**) with 3 equiv of trimethylsilyl iodide, a ring contraction from a seven- to a six-membered cyclic sulfide (Scheme 3) with contemporary cleavage of the substrate from the resin leading to **11a** and **11b**, respectively, was achieved.

Conclusions

In this paper, we have demonstrated the suitability of the thiepane-based methodology for the synthesis in liquid phase of all the components of the 10-membered library of enantiopure conduritols and the successful application of this sequence starting from solid-phase supported substrates. In the framework of this procedure, the synthetic utility of the Ramberg−Bäcklund rearrangement on resin-supported substrates has emerged for the first time as a general potential route for the preparation, in addition to conduritols, also of olefins, which are difficult to synthesize with other methods. Finally, two ring-contraction reactions mediated by electrophiles have been performed. A featured aspect of all the reactions performed using solid-phase supported substrates is the traceless cleavage which leads to the expected compounds without the need for any further chemical manipulation.

Experimental Section

All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive pressure of dry nitrogen. Organic extracts were dried over $CaSO_4$. Melting points are uncorrected. Preparative flash chromatographic experiments were performed using ICN silica gel 230−400 mesh. For TLC, precoated glass plates were used (Stratochrom SIF_{254}, 0.25 mm thick), and the spots were developed at 110 °C with an aqueous solution of $(NH_4)_6Mo_7O_{24}$ (2.5%) and $(NH_4)_4Ce(SO_4)_4$ (1%) in 10% H_2SO_4 or $KMnO_4$ 0.1 M/H_2SO_4 1 M, 1/1. Yields are for isolated compounds. Unless specified otherwise, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent. Chemical shifts are in parts per million downfield of TMS, and signal multiplicities were established by DEPT experiments. Signal assignments, if necessary, were elucidated by decoupling ^1H NMR. Optical rotations were measured at 589 nm. Infrared spectra were recorded on an FT-IR spectrophotometer. Mass spectra (MS) were recorded using electron impact at 70 eV (EI) or electrospray ionization (ESI). Light petroleum had bp 35−60 °C.

The polystyrene−CHO resin (P−CHO) (0.7−1.5 mmol/g, 100−200 mesh, cross-linking 1% DVB) was from Advanced Chem Tech. FT-IR spectra of polymer-bound substrates were obtained in the form of KBr pellets, and the units are in cm^{-1}.

(+)-(3a*R*,4*R*,8*R*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole (2a). Using the Kuszmann procedure,[9] to 0.18 g (3.7 mmol) of NaH 50% w/w (twice washed under nitrogen with light petroleum) in 8 mL of THF, 0.68 g (3.1 mmol) of the stereochemically related thiepane derivative **(+)-1a** (Figure 2)[8] dissolved in 10 mL of THF was added under vigorous stirring. After hydrogen evolution, 0.43 mL (6.9 mmol) of CH_3I was added, and the reaction mixture was stirred for 1 h. Again, 0.18 g (3.7 mmol) of NaH 50% w/w and 0.43 mL (6.9 mmol) of CH_3I were added. After stirring 2 h, the residue was extracted twice with CH_2Cl_2. The crude **2a** was purified by flash chromatography (SiO_2; light petroleum/Et_2O, 2/1), obtaining 0.74 g (96.5%) of a colorless, viscous oil.^1H NMR (acetone-d_6) δ: 4.32 (m, 2H, 2CHO), 3.81 (m, 2H, 2CHO), 3.37 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.10−2.45 (m, 4H, $2CH_2$), 1.43 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). ^{13}C NMR (acetone-d_6) δ: 109.2 (C), 83.3 (CHO), 82.7 (CHO), 80.4 (CHO), 79.3 (CHO), 57.4 (OCH_3), 57.3 (OCH_3), 30.0 (CH_2), 29.8 (CH_2), 27.2 (CH_3), 25.0 (CH_3). IR (neat) cm^{-1}: 2989, 2922, 2827, 1454, 1421, 1381, 1259, 1207, 1100, 1060, 890. $[\alpha]_D^{20} = +12.6$ (c = 1.1, $CHCl_3$). *m*/*z* (EI): 58 (100), 73 (45), 85 (72), 100 (67), 132 (37), 175 (40), 190 (25), 216 (18), 233 (22), 248 (28). Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.15; H, 8.10.

(+)-(3a*R*,4*R*,8*R*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole-6,6-dioxide (3a). To 0.090 g (0.363 mmol) of **2a**, dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C, 0.171 g (0.76 mmol) of 70% *m*-chloroperbenzoic acid was added. After 4 h at room temperature, $NaHSO_3$ solution was added to destroy the unreacted peracid. The reaction mixture, washed with saturated solution of $NaHCO_3$, was extracted with CH_2Cl_2. After solvent evaporation, the organic layers, washed with brine and dried, gave a crude product which was purified by flash chromatography (SiO_2; Et_2O/CH_3OH, 95/5). 0.092 g (91%) of a white crystalline product (mp 147 °C) was obtained. ^1H NMR ($CDCl_3$) δ: 4.47 (d, 2H, J = 3.8 Hz), 4.11 (d, 1H, J = 9.6 Hz), 3.95 (m, 1H), 3.66 (dd, 1H, J = 9.6, 14.9 Hz), 3.46−3.25 (m, 2H), 3.44 (s, 3H, superimposed), 3.37 (s, 3H, superimposed), 3.05 (dd, 1H, J = 3.7, 15.0 Hz), 1.50 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 109.6 (C), 77.7 (CHO), 75.4 (CHO), 75.0 (CHO), 74.5 (CHO), 58.6 (OCH_3), 57.9 (OCH_3), 53.0 (CH_2), 50.7 (CH_2), 26.6 (CH_2), 24.3(CH_2). *m*/*z*: 100 (100), 109 (17), 265 (19). IR (neat) cm^{-1}: 2922, 1454, 1380, 1247, 1211, 1141, 1067, 875. $[\alpha]_D^{20} = +6.3$ (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{11}H_{20}O_6S$: C, 47.13; H, 7.19. Found: C, 47.18; H, 7.22.

(+)-(3a*R*,4*S*,7*S*,7a*S*)-4,7-Dimethoxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole (4a). To 0.09 g (0.32 mmol) of **3a** 0.85 mL of *t*-BuOH, 1.26 mL of CCl_4 and 0.13 mL of H_2O were added using the Meyers conditions.[11] The mixture was stirred to a complete solution, then under nitrogen, 0.65 g of KOH finely powdered was added. After stirring for 6 h at room temperature, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layers were washed with H_2O, dried, and evaporated to yield the title compound **4a**, which was purified by flash chromatography (SiO_2; light petroleum/Et_2O, 3:1) to give 0.041 g (60%) of a white lower-melting compound (mp 20 °C). ^1H NMR ($CDCl_3$) δ: 6.05 (m, 2H), 4.65 (dd, 1H, J = 3.6, 7.3 Hz), 4.39 (dd, 1H, J = 7.3, 2.4 Hz), 4.06 (m, 1H), 3.84 (dd, 1H, J = 4.5, 2.4 Hz), 3.49 (s, 3H), 3.32 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 133.6 (CH═), 127.7 (CH═), 109.4 (C), 77.4 (CHO), 76.6 (CHO), 75.1 (CHO),

74.9 (CHO), 57.6 (OCH_3), 56.8 (OCH_3), 26.2 (CH_2), 24.7 (CH_2). $[\alpha]_D^{20} = +94.1$ ($c = 0.8$, $CHCl_3$). *m/z* (EI): 73 (35), 114 (100), 127 (75), 199 (10), 214 (<1). IR(neat) cm^{-1}: 2924, 2854, 1462, 1377, 1211, 1107, 1087. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.61; H, 8.50.

(+)-(1*R*,2*S*,3*S*,6*S*)-3,6-Dimethoxycyclohex-4-ene-1,2-diol (5a). The suspension constituted by 0.043 g (0.20 mmol) of **4a** and 2.0 mL of 0.1 N H_2SO_4 was heated to 90 °C for 4 h. The mixture was neutralized with Na_2CO_3 aqueous solution, and after evaporation of the aqueous phase, a solid residue was obtained. After extraction with CH_2Cl_2 and evaporation of the dried solution, a crude compound was obtained which was purified by flash chromatography (SiO_2; Et_2O/CH_3OH, 19/1) obtaining 0.032 g (92%) of **5a** as a colorless oil. ^1H NMR (acetone-d_6) δ: 5.88 (dt, 1H, J = 2.2, 10.4 Hz), 5.73 (m, 1H), 4.05 (m, 2H), 3.68 (m, 2H), 3.57 (s, 3H), 3.53 (s, 3H), 3.08 (brs, 2H, 2OH). ^{13}C NMR (acetone-d_6) δ: 128.7 (CH═), 128.0 (CH═), 80.6 (CHO), 78.9 (CHO), 74.5 (CHO), 71.4 (CHO), 57.9 (OCH_3), 56.7 (OCH_3). $[\alpha]_D^{20} = +146.0$ ($c = 1.4$, CH_3OH). *m/z* (EI): 71 (50), 99 (43), 113 (54), 114 (100). IR (neat) cm^{-1}: 3402, 2922, 1458, 1314, 1259, 1089, 846. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.12; H, 8.08.

Using the same synthetic sequence adopted to obtain **5a**, the two *meso*-conduritol derivatives **5b** and **5c** were also synthesized starting from the related thiepanes **1b** and **1c**, respectively (Figure 2).[8] The spectral data and characterization of the new compounds are reported below.

(3a*R*,4*S*,8*R*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole (2b). 97.0% yield. ^1H NMR ($CDCl_3$) δ: 4.08 (m, 2H), 3.40 (m, 2H), 3.40 (s superimposed, 6H), 2.68 (d, 2H, J = 14.4 Hz), 2.38 (dd, 2H, J = 9.6, 14.8 Hz), 1.45 (s, 3H), 1.33 (s, 3H).^{13}C NMR ($CDCl_3$) δ: 108.3, 84.1, 80.4, 57.9, 31.1, 27.7, 24.6. *m/z* (EI): 58 (100), 85 (93), 100 (97), 132 (34), 175 (48), 190 (85), 233-(17), 248 (22). IR (neat) cm^{-1}: 2980, 2919, 2830, 1379, 1207, 1089, 1050, 894. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.17; H, 8.15.

(3a*R*,4*S*,8*R*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole-6,6-dioxide (3b). 90.0% yield. ^1H NMR ($CDCl_3$) δ: 4.21 (m, 2H), 3.69 (m, 2H), 3.44 (s, 6H), 3.23 (d, 4H, J = 6.5 Hz), 1.47 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 109.0 (C), 79.0 (CHO), 74.8 (CHO), 58.5 (OCH_3), 54.0 (CH_2), 27.9 (CH_3), 25.1 (CH_3). *m/z* (EI): 71 (32), 85 (27), 100 (100), 265 (13), 280 (<1). IR (neat) cm^{-1}: 2987, 2923, 1450, 1381, 1213, 1053, 876. Anal. Calcd for $C_{11}H_{20}O_6S$: C, 47.13; H, 7.19. Found: C, 47.09; H, 7.22.

(3a*R*,4*S*,7*R*,7a*S*)-4,7-Dimethoxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole (4b). 60.5% yield. ^1H NMR ($CDCl_3$) δ: 4.89 (s, 2H), 4.10 (m, 2H), 3.75 (m, 2H), 3.52 (s, 6H), 1.50 (s, 3H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 128.9, 109.6, 80.3, 78.1, 57.8, 27.4, 24.6. *m/z* (EI): 73 (33), 114 (100), 127 (75), 199 (11), 214 (<1). IR (neat) cm^{-1}: 2926, 2854, 1466, 1372, 1211, 1108, 1085. Anal. Calcd for $C_8H_{14}O_4$: C, 61.66; H, 8.47. Found: C, 61.62; H, 8.50.

(1*R*,2*S*,3*S*,6*R*)-3,6-Dimethoxycyclohex-4-ene-1,2-diol (5b). 93.0% yield. The spectroscopic data are identical to these reported in a previous paper.[14]

(3a*R*,4*R*,8*S*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole (2c). 96.0% yield. ^1H NMR ($CDCl_3$) δ: 4.46 (brs, 2H), 3.30 (m, 2H), 3.29 (s superimposed, 6H), 2.95 (dd, 2H, J = 14.6, 9.6 Hz), 2.33 (d, 2H, J = 14.6 Hz), 1.43 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 108.5 (C), 85.1 (CHO), 76.1 (CHO), 57.1 (OCH_3), 27.4 (CH_2), 25.5 (CH_3), 23.4 (CH_3). *m/z* (EI): 43 (100), 58 (80), 73 (50), 85 (47), 100 (38), 132 (19), 175 (30), 248 (12). IR (neat) cm^{-1}: 2989, 2925, 1379, 1251, 1214, 1138, 1060, 874. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.13; H, 8.18.

(3a*R*,4*R*,8*S*,8a*S*)-4,8-Dimethoxy-2,2-dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole-6,6-dioxide (3c). Crystallization of the crude product from CH_2Cl_2/*n*-hexane, 1:1 ratio, gave a white solid (mp 146−147 °C). 92.0% yield. ^1H NMR ($CDCl_3$) δ: 4.60 (brs, 2H), 3.68 (m, 4H), 3.39 (s, 6H), 2.98 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 109.3 (C), 76.1 (CHO), 74.4 (CHO), 57.5 (OCH_3), 51.6 (CH_2), 25.7 (CH_3), 23.5 (CH_3). *m/z* (EI): 85 (32), 100 (100), 109 (18), 265 (13). IR (KBr) cm^{-1}: 2988, 2927, 1381, 1298, 1269, 1216, 1168, 1139, 1125, 1083, 1058, 989, 940, 912, 885, 821. Anal. Calcd for $C_{11}H_{20}O_6S$: C, 47.13; H, 7.19. Found: C, 47.17; H, 7.23.

(3a*R*,4*R*,7*S*,7a*S*)-4,7-Dimethoxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole (4c). 63.5% yield. ^1H NMR ($CDCl_3$) δ: 5.80 (brs, 2H), 4.63 (brs, 2H), 3.55 (brs, 2H), 3.47 (s, 6H), 1.38 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 128.3 (CH═), 110.1 (C), 76.7 (CHO), 74.2 (CHO), 57.7 (OCH_3), 25.7 (CH_3), 24.4 (CH_3). *m/z*(EI): 73 (28), 99 (31), 114 (100), 127 (68), 139 (15), 199 (10). IR (neat) cm^{-1}: 2918, 2850, 1463, 1380, 1209, 1105, 1083. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.70; H, 8.51.

(1*R*,2*S*,3*R*,6*S*)-3,6-Dimethoxycyclohex-4-ene-1,2-diol (5c). 95.0% yield.^1H NMR (CD_3OD) δ: 5.87 (brs, 2H), 3.89 (brs, 2H), 7.76 (2brs, 2H), 3.41 (s, 6H). ^{13}C NMR (CD_3OD) δ: 128.6 (CH═), 78.6 (CHO), 70.5 (CHO), 58.1 (OCH_3). *m/z* (EI): 71 (53), 99 (42), 113 (53), 114 (100). IR (neat) cm^{-1}: 3405, 2921, 1456, 1315, 1257, 1087, 850. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C,55.20; H, 8.06.

General Procedure for the Preparation of Resin-Bound Substrates (7a,b). To a solution of sulfur derivatives **6a** and **6b**[9] (4 mmol) in benzene (20 mL) and *p*-TSA as catalyst (15 mg) was added preswollen P−CHO (1 g, 0.7−1.5 mmol) in benzene, and the mixture was refluxed for 20 h under slow magnetic stirring, with azeotropic removal of H_2O by Dean−Stark trap. The resin was filtered and washed sequentially with benzene (2 × 10 mL); dioxane (2 × 10 mL); DMF (2 × 10 mL); H_2O (2 × 10 mL); and finally, with EtOH (2 × 10 mL). The resin was dried under vacuum to yield 1.190 g (0.91 mmol) of polymer-bound sulfide. To recover the excess of the unsupported thiepanes, the filtrate was evaporated after elimination of the acid catalyst by means of an ion-exchange resin. The IR of the diol leaded resin showed the nearly complete disappearance of the strong carbonyl stretch at 1700 cm^{-1}, corresponding to the C═O frequency.

Oxidation of 7a,b to the Corresponding Resin-Bound Sulfones 8a,b. Compounds **7a**,**b** were submitted to identical reaction conditions. Compound **7a** or **7b** was treated with

CH_2Cl_2 and gently stirred for 3 h at room temperature. To the slurry was added the *m*-CPBA (2 mmol), and the stirring was carried out for 4 h at room temperature. The resin was filtered and washed sequentially with CH_2Cl_2 (2 × 10 mL); dioxane (2 × 10 mL); DMF (2 × 10 mL); H_2O (2 × 10 mL); and finally, with EtOH (2 × 10 mL). The resin was dried under vacuum, giving 1.21 and 1.22 g, respectively (0.89 mmol of the sulfones polymer-bound, R = 98%). IR showed two absorptions at 1307 and 1100 cm^{-1}.

Cyclohexene Resin-Bound Derivatives Obtained from 8a,b by Ramberg−Bäcklund Reaction (9a,b). The resin-supported sulfones **8a**,**b** (500 mg) were treated for 14 h with CCl_4 under nitrogen, then *t*-BuOH (4 mL) and finely powdered KOH (4.0 g) were added. Vigorous stirring was maintained for 30 h at room temperature. The resin was filtered and washed sequentially with benzene (2 × 10 mL); dioxane (2 × 10 mL); DMF (2 × 10 mL); H_2O (2 × 10 mL); and finally, with EtOH (2 × 10 mL). The resin was dried under vacuum, giving the cyclohexene polymer-bound. IR clearly indicated the disappearance of SO_2 signals at 1307 and 1100 cm^{-1}.

Cleavage of Conduritols from Resin (10a,b). The cyclohexene resin-bound derivatives **9a**,**b** were treated with trifluoroacetic acid (0.5 mL) in CH_2Cl_2 (10 mL). After 30 min at reflux, the resin was filtered, and the conduritol derivatives recovered by evaporation of the solvent were identical to these obtained in liquid phase, and the overall yields were comparable.

(2*R*,3*S*,4*S*,5*S*)-2-(Iodomethyl)-5-methoxytetrahydro-2*H*-thiopyran-3,4-diol (11a) and **(2*S*,3*S*,4*S*,5*R*)-2-(Iodomethyl)-5-methoxytetrahydro-2*H*-thiopyran-3,4-diol (11b).** The resin-supported substrates **7a**,**b** were submitted to identical reaction conditions: ∼1 mmol of **7a** or **7b** was suspended for 6 h in CH_3CN then treated for 24 h at room temperature with 4 mmol of Me_3SiI (prepared in situ from 4 mmol of Me_3SiCl and 4 mmol of dried NaI). The resin was filtered off, and the thiane derivatives recovered by evaporation of the solvent were purified by flash chromatography on SiO_2, eluting wth Et_2O. The title compounds were obtained in 80% yield as pale yellow oils which quickly darken. Spectroscopic data for **11a**: ^{1}H NMR (CD_3OD): δ 4.03 (dd, 1H, CHO, J = 4.95 Hz, J = 1.38 Hz), 3.82 (m, 1H, CHO), 3.55 (ddd, 1H, CHO, J = 10.99 Hz, J = 3.85 Hz, J = 2.47 Hz), 3.26 (s, 3H, CH_3), 3.18 (m, 3H, CHS, CH_2I), 2.82 (dd, 1H, C*H*HS, J = 12.63 Hz, J = 10.99 Hz), 2.26 (dd, 1H, CH*H*S, J = 12.65 Hz, J = 3.85 Hz). ^{13}C NMR (CD_3OD): δ 78.3 (CHO), 72.8 (CHO), 71.2 (CHO), 56.9 (OCH_3), 44.2 (CHS), 26.2 (CH_2S), 3.9 (CH_2I). *m*/*z* (ESI^+): $[304 + 23]^+$. IR (neat) cm^{-1}: 3406, 2921, 2851, 1739, 1631, 1463, 1381, 1261, 1091, 1023. The $[\alpha]_D^{20}$ value was not determined, due to the brown color of the methanolic solution.

Spectroscopic data for **11b**: ^{1}H NMR (CD_3OD): δ 3.60 (m, 2H, 2CHO), 3.37 (s, 3H, CH_3), 3.35 (m superimposed, 1H, CHO), 3.20 (m, 3H, CHS, CH_2I), 2.75 (m, 2H, CH_2S). ^{13}C NMR (CD_3OD): δ 83.6 (CHO), 77.9 (CHO), 77.1 (CHO), 57.8 (CH_3), 47.7 (CHS), 29.4 (CH_2S), 7.5 (CH_2I). *m*/*z* (ESI^+): $[304 + 23]^+$. IR (neat) cm^{-1}: 3440, 2929, 1732, 1627, 1458, 1427, 1314, 1265, 1083, 1020. The $[\alpha]_D^{20}$ value was not determined due to the brown color of the methanolic solution.

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