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Synthesis, Chromatographic Separation, Vibrational Circular Dichroism Spectroscopy, and ab Initio DFT Studies of Chiral Thiepane Tetraol Derivatives

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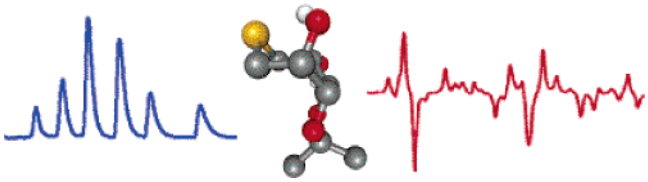

Optically pure enantiomers of the chiral tetrahydroxythiepane derivative 3,6-dihydroxy-4,5-*O*-isopropylidene-thiepane (**3**) are obtained using a novel protocol in which a library of all possible stereoisomers of **3** is synthesized, followed by two-step stereoselective chromatography, using, first, conventional achiral and, then, chiral stationary phases. Configurational and conformational analysis of **3** are carried out using Vibrational Circular Dichroism (VCD) spectroscopy in conjunction with ab initio DFT calculations. The absolute configuration of **3** is shown to be 3*R*,4*S*,5*R*,6*R*-(+)/3*S*,4*R*,5*S*,6*S*-(−).

Introduction

Polyhydroxylated thiepane derivatives are of great interest because of their potential therapeutic activity as glycosidase inhibitors.[1] This property has been tentatively ascribed to the flexibility of the seven-membered ring, which mimics the hypothetical transition state of enzymatic glycosidic cleavage. A potent HIV-1 protease inhibition[2] and a low cytotoxicity[3] have been reported for a number of thiepane derivatives. Moreover, in recent patents the use of some tri- and tetra-substituted thiepanes as immunogens, therapeutics, diagnostics, and for other industrial purposes, has been disclosed.[4] Recently, new enantiopure tetrahydroxy thiepane derivatives, obtained as intermediates during the synthesis of conduritols[5] and diaminoconduritols[6] from easily available alcohol sugars, have been tested to investigate the structural and stereochemical requirements for optimized inhibitory activity against a variety of glycosidases.[7] Interesting trends observed during the screening of these derivatives prompted us to attempt the synthesis of additional, previously unknown, tetrahydroxy thiepane derivatives to further elucidate the stereochemistry−activity relationship for these molecules as glycosidase inhibitors. Since the required precursor alcohol sugars are either very expensive or not available, the known synthetic method,[5] which maintains and transfers the stereochemistry of the starting material to the thiepane, could not be used. We have therefore developed a new strategy in which a library containing all of the individual

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(7) Arcelli, A.; Cerè, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron: Asymmetry* **2002**, *13*, 191−196.

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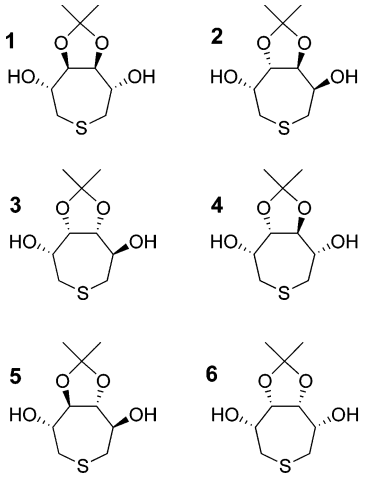


FIGURE 1. Structures of the stereoisomeric isopropylidene tetrahydroxy thiepane derivatives **1**−**6**. Only one enantiomer is shown for chiral derivatives **2**−**5**.

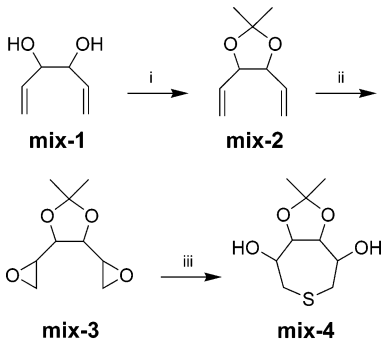
stereoisomers of the target tetrahydroxy thiepane derivatives are synthesized and a two-step chromatographic procedure is then used for the isolation of the library members. Simple elaboration of a commercially available substrate leads to the library (Figure 1). Then, a first chromatographic step over nonenantioselective stationary phases affords the six diastereomers (two meso, **1** and **6,** and four chiral, **2**, **3**, **4,** and **5**, stereoisomers), and a second step over enantioselective phases gives the individual enantiomers of the four chiral stereoisomers, **2**−**5**. The new method greatly reduces the synthetic effort required to obtain all the distinct components of the library and overcomes the difficulties encountered in obtaining precursor materials with the correct stereochemistry. The stereochemical identities of enantiopure materials obtained by chromatographic separation of the thiepane derivative enantiomers are established by a combination of experimental Vibrational Circular Dichroism (VCD) spectroscopy and ab initio Density Functional Theory (DFT) calculations,[8] in addition to FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopies.

As far as we can determine, this protocol has not been previously employed in the synthesis and stereochemical characterization of chiral molecules. The new protocol is exemplified here by the synthesis and stereochemical characterization of thiepane **3**, whose enantiomers have not previously been characterized from the stereochemical and chiroptical points of view.

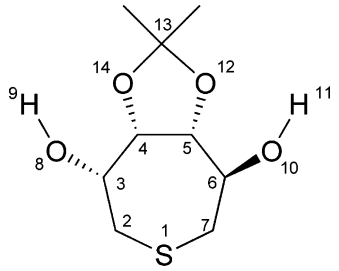
Results and Discussion

The library of thiepane stereoisomers was prepared (Scheme 1) from the commercially available mixture of

SCHEME 1. Synthesis of mix-4[a]



[a] Reagents and conditions: (i) acetone, *p*TSA (85%); (ii) *m*CPBA, TBHMP, $ClCH_2-CH_2Cl$ 3 h at 90 °C (89%); (iii) $Na_2S{\cdot}9H_2O$, EtOH 48 h at reflux (58%). *p*TSA = *p*-toluenesulfonic acid; *m*CPBA = *m*-chloroperoxybenzoic acid; TBHMP = 5-*tert*-butyl-4-hydroxymethylphenyl sulfide.



(3R,4S,5R,6R)-**3**

the (*R*,*R*), (*S*,*S*), and *meso*-divinyl diols **mix-1**,[9] which was easily converted into the related isopropylidene derivatives **mix-2**. Oxidation with *m*-CPBA at 90 °C for 3 h in the presence of a radical inhibitor afforded the corresponding diepoxy derivatives **mix-3**, with the two additional stereocenters. Intramolecular thiacyclization upon treatment with $Na_2S{\cdot}9H_2O$ yielded the mixture of 10 stereoisomeric thiepanes **mix-4** in 44% yield. Thiepane derivatives (+)-**3**, (−)-**3**, (+)-**4**, **1**, and **6**, to our knowledge, were previously unreported.

With the mixture of the whole set of stereoisomers in hand, we started a chromatographic study aimed at finding a method capable of affording the individual components in high yield and purity. We first examined the ability of several nonenantioselective HPLC stationary phases to resolve the six diastereoisomeric components of the mixture of thiepane derivatives. Despite careful optimization of the experimental parameters we found that none of the available stationary phases (bare silica, diol-silica, cyanopropyl-silica, aminopropyl-silica) was able to effect the complete resolution of the mixture. Next, we tried using two columns in tandem containing different stationary phases and found that the combination of a column packed with bare silica with a column packed with the racemic version of a chiral stationary phase[10] successfully achieved the required selectivity and efficiency. With this approach the six diastereoisomers

(8) (a) Stephens, P. J.; Devlin, F. J. *Chirality* **2000** *12*, 172−179. (b) Aamouche, A.; Devlin, F. J.; Stephens, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 2346−2354. (c) Stephens, P. J.; Aamouche, A.; Devlin, F. J.; Superchi, S.; Donnoli, M. I.; Rosini, C. *J. Org. Chem.* **2001**, *66*, 3671−3677. (d) Devlin, F. J.; Stephens, P. J.; Scafato, P.; Superchi, S.; Rosini, C. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1551−1558. (e) Devlin, F. J.; Stephens, P. J.; Scafato, P.; Superchi, S.; Rosini, C. *Chirality* **2002**, *14*, 400−406. (f) Devlin, F. J.; Stephens, P. J.; Oesterle, C.; Wiberg, K. B.; Cheeseman, J. R.; Frisch, M. J. *J. Org. Chem.* **2002**, *67*, 8090−8096.

(9) The prefix "mix" denotes here a mixture of all the possible stereoisomers.

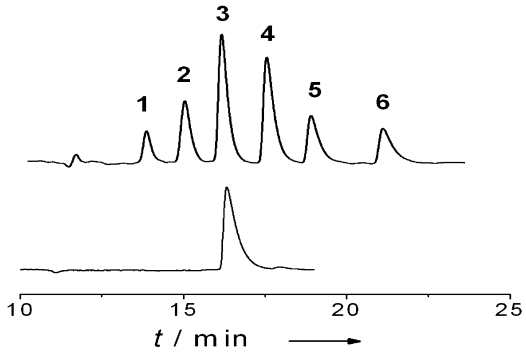


FIGURE 2. Analytical HPLC separation of thiepane derivatives **1**−**6** over nonenantioselective stationary phases. Two columns connected in series, one packed with LiChrosorb Si-60, 5 μm ,and one with (*rac*)-DACH-DNB Si-100, 5 μm; eluent hexane/2-propanol 90/10; flow rate 1.0 mL/min; room temperature (25 °C); refractive index detection ($k'_1 = 1.36$, $k'_2 = 1.58$, $k'_3 = 1.80$, $k'_4 = 2.06$, $k'_5 = 2.31$, $k'_6 = 2.73$; $\alpha_{1,2} = 1.16$, $\alpha_{2,3} = 1.14$, $\alpha_{3,4} = 1.14$, $\alpha_{4,5} = 1.12$, $\alpha_{5,6} = 1.18$). Bottom trace: peak purity check of the pooled fractions containing **3**, after semipreparative HPLC.

of the thiepane derivative mixture were completely resolved in less than 30 min (Figure 2) at the analytical level.

Scaling-up to semipreparative levels was straightforward, and 60 replicate separations (62 mg of sample each run) carried out on 1 cm internal diameter columns in tandem afforded the six stereoisomers with de greater than 98% and overall recovery of about 90%. In particular, 400 mg of (±)-**3** with de > 99% was obtained by pooling the proper fractions collected in this stage. When monitored by RI, the HPLC resolved mixture showed an uneven distribution of the six stereoisomers, with the stereoisomers **3** and **4** giving the most intense signals. However, the amounts of isolated products showed that the library was slightly enriched in the stereoisomers **4**, **5**, and **6** (26%, 19%, and 19%, respectively) at the expense of stereoisomers **1**, **2**, and **3** (8%, 16%, and 12%, respectively).[11]

A second screening procedure was then started for the chiral thiepane derivatives **2**−**5** to find a chromatographic method for the isolation of sizable amounts of enantiopure materials. The enantiomers of chiral thiepane derivatives **2**−**5** were well separated by HPLC on cellulose chiral stationary phases.[12] However, the analytical HPLC resolution of compound **3** was not scalable to preparative levels as the sample showed very limited solubility in the mobile phase. On the other hand, satisfactory enantioseparation values for **3** using good solvating eluents were obtained on a new polymeric chiral stationary phase containing a covalently bound oligomer of the (*R*,*R*)-diaminocyclohexane diacryloylamide.[13] Iterative enantioselective HPLC of 400 mg of racemic **3** on a 1 cm column afforded 170 mg of the pure (+)-**3** enantiomer (first eluted, $[\alpha]^{25}_D$ +9.76 ± 0.10 (*c* 1.0 in $CHCl_3$, ee >99%)) and 180 mg of the (−)-**3** enantiomer (second eluted, $[\alpha]^{25}_D$ −9.06 ± 0.10 (*c* 1.0 in $CHCl_3$, ee 95%)).[14]

VCD spectroscopy and DFT calculations were performed to establish the Absolute Configuration (AC) of **3** and to gain insight into its conformational preferences.[8] The structures, energies, and VCD spectra of the stable conformations of **3**, whose relative energies permit significant population at room temperature, were predicted by using DFT and the conformationally averaged VCD spectrum was obtained thence. Then, the predicted VCD spectra of the two enantiomers of **3** were compared to the experimental VCD spectrum of (+)-**3** and its absolute configuration deduced. The mid-IR IR and VCD spectra of **3** in $CHCl_3$ solution are shown in Figure 3.

Conformational analysis (see Supporting Information) of **3** at the B3LYP/TZ2P level led to five stable conformations within a range of 3 kcal/mol, **3a**−**e** (Table 1). Their structures for (3*R*,4*S*,5*R*,6*R*)-**3**[15] are given in Figure 4. In **3a**, the lowest energy conformer, the thiepane ring, is in a chair conformation and the dioxolane ring exhibits an envelope conformation. The two OH groups are oriented such that one hydrogen is hydrogen bonded to the adjacent oxygen atom of the dioxolane ring (H···O = 2.31 Å) and the other is hydrogen bonded to the sulfur atom (H···S = 2.40 Å). All other stable conformations of **3** were predicted to be more than 1 kcal/mol higher in energy than conformer **3a**. In **3b** and **3c** the thiepane ring is again in a chair conformation, whereas in **3d** the thiepane ring is in a boat conformation. In **3e**, the highest energy of the five conformations, the thiepane ring is substantially twisted. As in conformer **3a**, in conformers **3b**−**e** both OH groups are internally hydrogen bonded. H···O and H···S distances are given in Figure 4. The B3LYP/TZ2P and B3PW91/TZ2P VCD spectra of conformers **3a**−**e** have been calculated. Thence, the spectra of the equilibrium mixture of conformers have been obtained, weighting the spectrum of each conformer by its equilibrium population, which was calculated from relative free energies using Boltzmann statistics and T = 298K (Table 1 and Table 1S of the Supporting Information).

The conformationally averaged B3LYP/TZ2P VCD spectrum of (3*R*,4*S*,5*R*,6*R*)-**3** and of its mirror-image enantiomer are shown in Figure 5, together with the experimental VCD spectrum of (+)-**3**. As delineated in Figure 5, convincing assignment of the majority of the bands of the experimental spectrum can be made if the absolute configuration of (+)-**3** is taken to be (3*R*,4*S*,5*R*,6*R*)

(10) Silica stationary phase: LiChrosorb Si 60. Chiral stationary phase, racemic version: DACH-DNB stationary phase. Analytical separations: columns 4.0 × 250 and 3.9 × 300 mm, respectively. Eluent: hexane/2-propanol 90/10. Flow rate: 1.0 mL/min. Preparative separations: columns 10 × 250 mm. Eluent: hexane/2-propanol 90/10. Flow rate: 5.0 mL/min. Columns are available from Merck, Darmstadt, Germany and from Regis Chemical Company, Morton Groove, IL.

(11) Stereochemical identities of the separated species were established by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopies and by co-injection of samples of known stereochemistry available from previous studies.[5]

(12) Chiral stationary phases: Chiralcel OJ (thiepanes 2, 3, and 4) and Chiralcel OD (thiepane 5). Columns: 4.6 × 250 mm. Eluent: hexane/2-propanol 90/10. Flow rate 1.0 mL/min. Columns are available from Chiral Technologies, Illkirch, France.

(13) Chiral stationary phase: (*R*,*R*)-P-CAP containing a polymeric derivative of (*R*,*R*)-1,2-diaminocyclohexane. Columns: 4.6 × 250 mm (analytical) and 10 × 250 mm (preparative). Eluent: hexane/2-propanol/acetonitrile/dichloromethane 74/4/3/19. Flow rate: 2.0 mL/min (F. Gasparrini, D. Misiti, C. Villani, Italian Patent no. RM2002A000155, 20.03.2002; International Patent no. WO 03/079002 A2, 25.09.2003). Columns available from Astec Inc, Wippany, NJ.

(14) We used the individual enantiomers (+)-**3** and (−)-**3** for the synthesis of enantiopure conduritol derivatives (unpublished results).

(15) For the atom numbering used here see above. For the IUPAC nomenclature, see the Supporting Information.

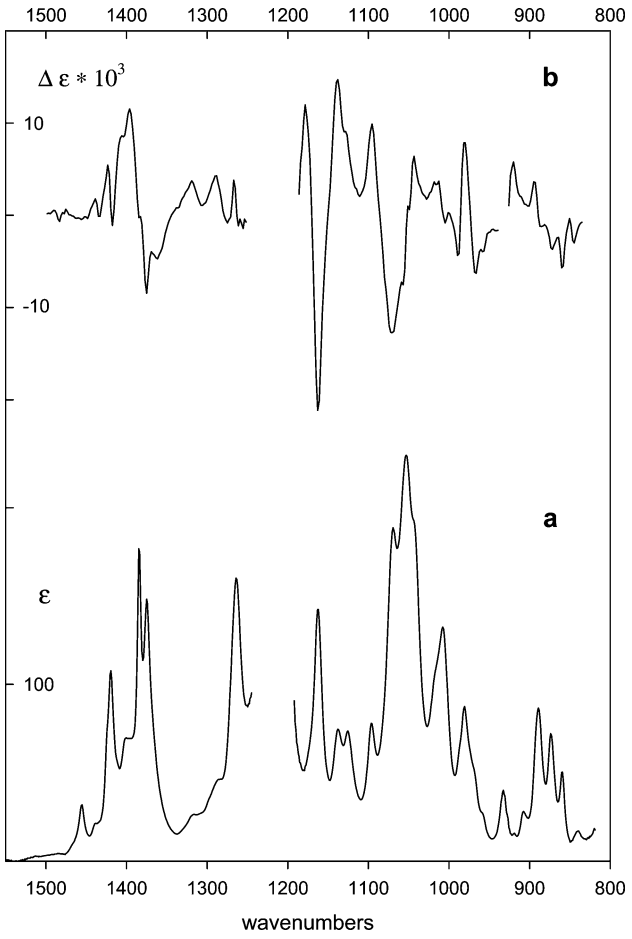


FIGURE 3. Experimental IR and VCD spectra of **3** in $CHCl_3$ solution. The IR spectrum (**a**) is of (±)-**3**. The VCD spectrum (**b**) is the "half-difference" spectrum: $^1/_2[\Delta\epsilon(+) - \Delta\epsilon(-)]$. Solution concentrations were the following: (±)-**3**, 0.066 M; (+)-**3**, 0.059 M; and (−)-**3**, 0.068 M. Enantiomeric excesses of (+)- and (−)-**3** were >99% and 95%, respectively. Path length was 597 μm. The gaps are due to $CHCl_3$ absorption.

TABLE 1. B3LYP/TZ2P Energies, Free Energies, and Populations of the Conformations of 3[a]

	B3LYP/TZ2P		
conformer	ΔE	ΔG	P
a	0.00	0.00	72.1
b	1.18	0.81	17.9
c	1.49	1.47	5.8
d	1.82	1.66	4.2
e	2.51	2.58	0.0

[a] ΔE and ΔG are in kcal/mol; populations P are in %.

and cannot be made for the mirror-image structure. It follows that the absolute configuration of (+)-**3** is (3*R*,4*S*,5*R*,6*R*). The same conclusion follows from the B3PW91/TZ2P VCD spectrum (see the Supporting Information).

Conclusion

In summary, the procedure described offers an easy access to enantiomerically pure tetrahydroxy thiepane derivatives with unambiguously assigned stereochemistry. In view of its inherent flexibility, we believe that the novel combination of synthetic and stereoselective analytical strategies with advanced spectroscopic methodologies is of general use for the production and structural characterization of the individual members of small stereoisomer libraries, and additional applications will be reported soon.

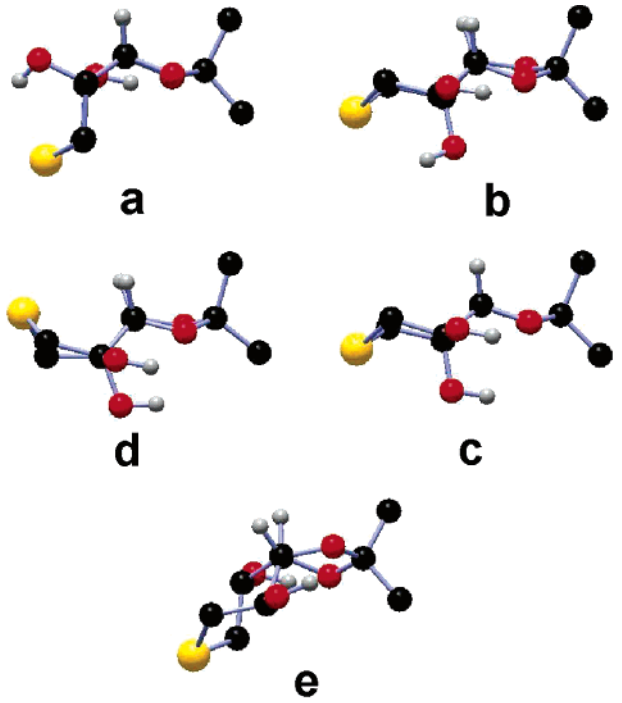


FIGURE 4. B3LYP/TZ2P structures of conformers **a**−**e** of (3*R*,4*S*,5*R*,6*R*)-**3**. The molecules are viewed along the C4−C5 bond (the atom numbering used is detailed in the text). Hydrogen atoms are not shown, except for those on the OH groups and on the C4 and C5 carbon atoms. Internal hydrogen-bonding distances are the following: (**a**) H9···O14 = 2.31 Å, H11···S = 2.40 Å; (**b**) H9···S = 2.42 Å, H11···O12 = 2.32 Å; (**c**) H9···O14 = 2.31 Å, H11···O12 = 2.28 Å; (**d**) H9···O14 = 2.25 Å, H11···O12 = 2.24 Å; (**e**) H9···O14 = 2.32 Å, H11···O12 = 2.24 Å.

Experimental Section

2,2-Dimethyl-4,5-di(2-oxiranyl)-1,3-dioxolane (mix-3). 0.452-g (2.9 mmol) of the *d*,*l*- and *meso*-2,2-dimethyl-4,5-divinyl-1,3-dioxolane (**mix-2**)[16] and 0.208 g (0.58 mmol) of 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide were dissolved in 40 mL of $ClCH_2CH_2Cl$. The reaction mixture was stirred for 10 min and then, after addition of 2 g (5.8 mmol) of 50% *m*-CPBA, was warmed at 90 °C under stirring for 3 h, using a previously reported procedure.[17] To the solution, cooled to 0 °C, was added a saturated solution of $NaHSO_3$ to destroy the unreacted *m*-CPBA, using a starch iodide paper to monitor the complete disappearance of the peracid. The mixture was filtered and the organic layer was extracted with a saturated solution of $NaHCO_3$ (3×15 mL) and washed with brine. Evaporation of the solution, dried with $MgSO_4$, gave 0.479 g (88.9%) of a crude product as a yellow oil, which was used without any purification to prevent possible diastereomeric separations. The spectroscopic data of the complex mixture are the following: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98−3.52 (m,

(16) Wiberg, K. B.; Snoonian, J. R. *J. Org. Chem.* **1998**, *63*, 1402−1407.

(17) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64−65.

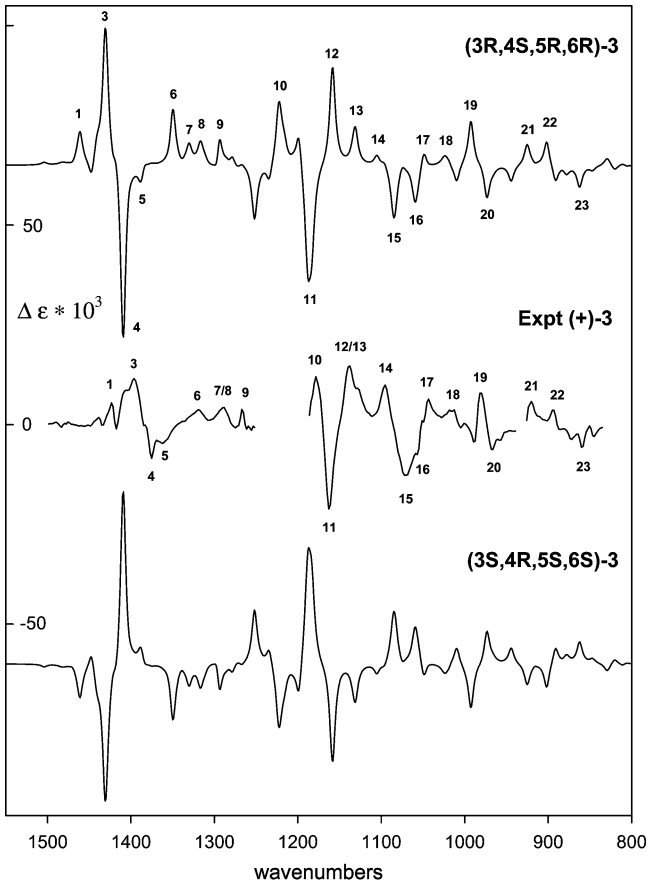


FIGURE 5. Calculated and experimental VCD spectra of **3**. The calculated spectra (3*R*,4*S*,5*R*,6*R*)-**3** and (3*S*,4*R*,5*S*,6S)-**3** are the conformationally averaged B3LYP/TZ2P spectra for the (3*R*,4*S*,5*R*,6*R*) and (3*S*,4*R*,5*S*,6*S*) enantiomers of **3**. The experimental spectrum is from Figure 3. Numbers indicate corresponding features in the calculated spectrum (3*R*,4*S*, 5*R*,6*R*)-**3** and the experimental spectrum of (+)-**3**.

2H), 3.18−2.88 (m, 2H), 2.83−2.56 (m, 4H), 1.45−1.23 (ss, 6H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 110.5, 110.3, 110.1, 109.9, 80.1, 78.3, 78.1, 77.6, 51.5, 51.3, 51.1, 50.2, 49.6, 49.4, 46.4, 45.9, 45.5, 44.1, 43.7, 43.6, 43.5, 43.3, 29.2, 28.7, 27.4, 27.1, 26.9, 26.8, 26.6, 26.5, 25.1, 24.9.

2,2-Dimethylhexahydrothiepino[4,5-*d*][1,3]dioxole-4,8-diol (mix-4). Following a literature procedure,[18] to 400 mL of EtOH, refluxing under nitrogen, was added 4.5 g of $Na_2S\cdot 9H_2O$ (18.7 mmol) dissolved in 75 mL of EtOH. To this refluxing solution was simultaneously added dropwise 2.4 g (12.9 mmol) of the dioxiranyl derivative **mix-3** dissolved in 150 mL of EtOH and 4.5 g of $Na_2S\cdot 9H_2O$ (18.7 mmol) dissolved in 75 mL of EtOH. After 48 h refluxing, the crude product, obtained from evaporation of the solvent, was extracted repeatedly with CH_2Cl_2. The dried organic layer was purified by flash chromatography (SiO_2; Et_2O) yielding 1.64 g (57.8%) of a mixture with the diastereoisomeric ratio of the crude product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30−3.75 (m, 4H), 3.32 (br s, 2H), 3.00−2.38 (m, 4H), 1.45−1.22 (ss superimposed 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.4, 109.1, 108.8, 108.6, 108.0, 81.4, 80.7, 79.8, 79.1, 78.7, 78.6, 75.9, 73.9, 73.2, 71.6, 70.9, 66.2, 66.0, 38.1, 38.0, 37.6, 37.2, 33.5, 33.0, 32.8, 32.5, 27.2, 27.0, 26.9, 26.7, 26.4, 26.0, 23.8.

(3*R*,4*R*,5*S*,6*S*)-3,6-Dihydroxy-4,5-*O*-isopropylidene-thiepane (1, meso form). The title compound, isolated by preparative HPLC, was obtained as a pale yellow deliquescent solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, 2H, J = 1.9, 5.9 Hz), 4.05 (br t, 2H, J = 6.0−8.0 Hz), 3.05 (br s, 2H, 2OH), 2.89 (d, 2H, J = 14.2 Hz), 2.57 (dd, 2H, J = 8.54, 14.4 Hz), 1.50 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ108.6 (C), 80.8 (2CHO), 73.3 (2CHO), 33.4 ($2CH_2S$), 27.2 (CH_3), 24.4 (CH_3); IR (KBr) (cm^{-1}) 3368, 2974, 2909, 1377, 1208, 1091, 1045, 896; ESI-MS 221 (MH^+). Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32. Found: C, 49.06; H, 7.30.

(3*R*,4*S*,5*R*,6*S*)-3,6-Dihydroxy-4,5-*O*-isopropylidene-thiepane (6, meso form). The title compound, isolated by preparative HPLC, was obtained as a white crystalline product (mp 176 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (br s, 2H), 4.14 (t, 2H, J = 8.1 Hz), 3.35 (d, 2H, 2OH, J = 8.2 Hz), 2.97 (dd, 2H, J = 8.5, 14.7 Hz), 2.61 (d, 2H, J = 14.7 Hz), 1.58 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8 (C), 79.5 (CHO), 70.6 (CHO), 33.0 (CH_2S), 26.1 (CH_3), 23.8. (CH_3); IR (KBr) (cm^{-1}) 3333, 2936, 1421, 1250, 1184, 1013, 909; *m/z* 59 (100), 71 (50), 89 (25), 101 (41), 161 (39), 202 (38), 205 (33), 220 (10). Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32. Found: C, 49.00; H, 7.29.

Compounds (±)-**2**,[19] (−)-**4**,[20] and (±)-**5**[19] have spectroscopic data in agreement with those reported in the literature. Compound (+)-**4** {$[\alpha]^{25}_D$ +36.2 (*c* 1.0 in $CHCl_3$)} has spectroscopic data in perfect agreement with those of the corresponding enantiomer (−)-**4**.

(+)-(3*R*,4*S*,5*R*,6*R*)-3,6-Dihydroxy-4,5-*O*-isopropylidene-thiepane ((+)-3). The title compound, enantiomerically pure after enantioselective HPLC separation, was obtained as a white solid (mp 119−120 °C). ^{1}H NMR (300 MHz, acetone-d_6) δ 4.38 (m, 1H, CHO), 4.20 (m, 3H, 1CHO and 2OH), 3.87 (m, 2H, 2CHO), 3.03−2.42 (m, 4H, $2CH_2$), 1.43 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 108.2 (C), 81.3 (CHO), 80.3 (CHO), 72.7 (CHO), 72.3 (CHO), 33.7 (CH_2), 33.3 (CH_2), 26.8 (CH_3), 24.2 (CH_3); IR (KBr) (cm^{-1}) 3288, 2986, 2917, 1383, 1259, 1211, 1166, 1085, 1057, 1007, 893; $[\alpha]^{25}_D$ +9.76 (*c* 1.0 in $CHCl_3$, ee >99%); *m/z* 59 (100), 71 (52), 89 (26), 101 (41), 161 (40), 202 (38), 205 (32), 220 (13). Anal. Calcd for $C_9H_{16}O_4S$: C, 49.09; H, 7.34. Found: C, 49.11; H, 7.34.

Chromatographic Procedures. For the analytical HPLC experiments the following equipment was used: pump Waters 600E, Refractive Index detector Waters R401, UV detector Waters 448, Rheodyne 20 μL loop injector. Preparative separations: pump Waters Delta Prep 3000, RI detector Waters 410, Rheodyne 0.5 mL loop injector. Preparative separations: samples were dissolved in the mobile phase at a concentration of about 0.1 g/mL and injected through a 0.5 mL loop.

Vibrational Circular Dichroism Spectroscopy and DFT Calculations. IR and VCD spectra of **3** were measured in $CHCl_3$ solution. IR spectra were measured using a Nicolet MX-1 FTIR instrument at 1 cm^{-1} resolution. VCD spectra were measured using a Bomem/BioTools ChiralIR spectrometer at 4 cm^{-1} resolution. VCD data acquisition times were 1 h. Solutions of (+)- and (−)-**3** were ~0.06 M. Enantiomeric excesses of (+)- and (−)-**3** were >99% and >95%, respectively. Solutions of (±)-**3** of comparable concentration were used to obtain VCD baselines. VCD spectra are reported as "half-difference" spectra: $^1/_2[\Delta\epsilon(+) - \Delta\epsilon(-)]$.

Conformational analysis of **3** was carried out using the Spartan 02[21] and Gaussian 98[22] programs, using the following protocol. A Monte Carlo conformational search was initially carried out using the MMFF94 molecular mechanics force field via the Spartan 02 program. All structures found within a 10 kcal/mol window were reoptimized, first using the AM1 semiempirical method and then using the Hartree-Fock (HF)/6-31G* ab initio method. Finally, all structures within a 3.0 kcal/mol window at the HF/6-31G* level were reoptimized using Density Functional Theory (DFT), the functionals

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B3LYP and B3PW91, and the basis sets 6-31G* and TZ2P.[23] The procedure was then repeated, beginning with a Monte Carlo search using the AM1 method.

The harmonic frequencies, dipole strengths, and rotational strengths of the stable conformations of **3** were calculated using DFT,[24] the functionals B3LYP and B3PW91, and the basis set TZ2P at the corresponding equilibrium geometries via the Gaussian 98 program. IR and VCD spectra were obtained thence using Lorentzian line shapes,[25] with $\gamma = 4.0$ cm^{-1}.

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Supporting Information Available: Structures of thiepanes **1**−**6**, general experimental synthetic procedures, chromatographic plots on preparative and analytical columns, comparison of relative energies of conformations **a**−**e** of **3**, B3LYP/TZ2P dihedral angles of conformations **a**−**e** of **3**, experimental and calculated VCD spectra of **3** at the B3LYP/TZ2P and B3PW91/TZ2P levels, and text files containing B3LYP/TZ2P optimized geometries in Cartesian coordinates of conformers **a**−**e** of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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