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SYNTHESIS OF (+)-BIOTIN: EFFICIENT RESOLUTION OF KEY INTERMEDIATES

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Enantiomerically pure 4-chlorothieno[3,4-d]imidazol-2-one (+)-2 and thieno[3,4-d]imidazol-2,4-dione (+)-5, key intermediates in independent routes to (+)-biotin (6), have been prepared by resolution via the corresponding diastereomeric ethers (**3d-g** and **3'd-g**). Efficient procedures to recycle the undesired diastereomers and recover the chiral auxiliary have been developed.

(+)-Biotin (6), a member of the vitamin B complex group, functions as a coenzyme in various biochemical carboxylation and decarboxylation reactions and is utilized as a nutritional suppplement for humans and animals.[1] In recent years, utilization of the strong biotin-avidin complex has emerged in biochemistry as an important method for isolation, localization, immunoassay, and drug delivery.[2] Although the first syntheses of biotin were reported more than forty-five years ago, new syntheses continue to be published[3] and patented.[4,5] Several ingeneous stratagies for control of the three adjacent chiral centers have been reported,[3] however none of the recent syntheses seems to have a commercial advantage over an early process developed at Hoffmann-La Roche and still utilized, with minor improvements, for large scale synthesis.[6]

Some time ago, we described a route to biotin which we envisioned might have practical utility. Readily available 2,5-dihydrothiophene 1,1-dioxide was efficiently transformed into thieno[3,4-d]imidazolone 1.[7] Chlorination alpha to the sulfur with N-chlorosuccinimide produced 2 which could be hydrolyzed and oxidized to give thieno[3,4-d]imidazol-2,4-dione 5. Biotin could be prepared by stereospecific introduction of the pentanoate side chain into either **2**[8] or 5,[5,6] followed by removal of the benzyl protecting groups.

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The only drawback of this otherwise efficient synthesis was that it afforded racemic biotin: Halogenation of 1, which is meso, afforded (±)-2. In order to avoid a wasteful resolution of biotin,[9] we decided to prepare the desired (+)-enantiomer of 2, the first racemic intermediate encountered. To this end, we briefly considered searching for a reaction capable of selectively oxidizing one of the two enantiotropic methylene groups alpha to the sulfur in 1. In principle this could be accomplished via Pummerer rearrangement of a chiral S-acyloxy derivative of 1. While transmission of chirality from sulfur to carbon has been reported,[10] a chiral Pummerer reaction, capable of efficiently distinguishing enantiotropic carbon atoms in the manner required, seemed unlikely because of the distance between the chiral carbon of the S-acyloxy group and the enantiotropic carbon atoms in the transition state.

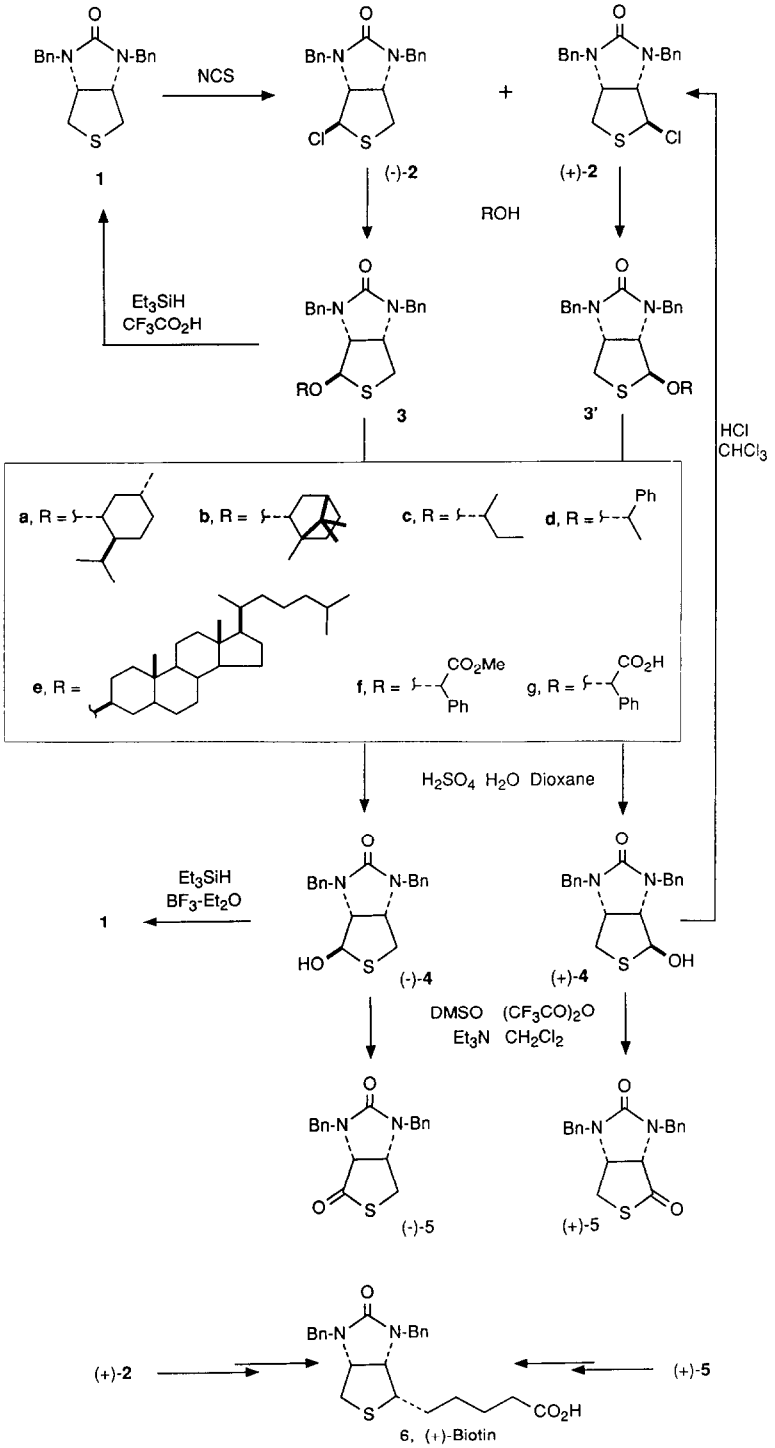
Therefore, we utilized resolution to obtain the optically active intermediates. This investigation provided a rare opportunity to exploit diastereomeric ether derivatives (i.e. 3 and 3') in a resolution.

Results and Discussion

Resolution of (±)-2 was accomplished by separation of diastereomeric 4-alkoxythieno[3,4-d]imidazolones, 3a-g and 3'a-g, prepared by reaction of (±)-2 with readily available chiral secondary alcohols in the absence of base, with a small amount of solvent. When a slight excess of alcohol was utilized, each reaction afforded essentially equal amounts of diastereomers 3a-g and 3'a-g, observable by ^{1}H and ^{13}C NMR. When (±)-2 was treated with a deficiency (40 mol %) of borneol, a modest kinetic resolution was achieved; the two diastereomers were formed in 1:2 ratio. It will be noted that 3a-g and 3'a-g were formed by attack from the less hindered convex face of (±)-2, with retention of configuration. Related S_N1 displacements were previously observed when 2 reacted with other nucleophiles.[8] When (±)-2 was treated with alkoxide anion (studied with sodium menthyloxide and lithium menthyloxide in THF or DME) no 3a or 3'a was detected; starting materials were recovered, accompanied by decomposition to 1,3-dibenzylurea.

Having determined conditions for formation of the desired diastereomeric 4-alkoxythieno[3,4-d]imidazolones 3a-g and 3'a-g we examined methods for their separation. We were unable to separate the diastereomers formed from (-)- menthol (3a, 3'a), (-)-borneol (3b, 3'b), or (R)-(-)-2-butanol (3c, 3'c), by chromatography on silica gel. In contrast, the 4-alkoxythieno[3,4-d]imid-azolone diastereomers formed from (S)-(-)-1-phenylethanol (3d, 3'd) and (S)-(+)-methyl mandelate (3f, 3'f) were chromatographically separable, presumably due to the effect of the additional phenyl ring on polarity.

Separation by crystallization was desired as more practical than chromatographic separation. None of the above diastereomeric pairs solidified. In order to obtain solid 4-alkoxythieno[3,4-d]imidazolones we utilized more polar or larger rigid alcohols. Accordingly, the diastereomeric 4-alkoxythieno[3,4-d]imidazolones derived from (+)-dihydrocholesterol (3e and 3'e) and from (S)-(+)-mandelic acid (3g, 3'g) were


Bn-N
N-Bn
NCS
1
(-)-2
(+)-2
ROH
Et3SiH
CF3CO2H
RO
OR
3
3'
HCl
CHCl3
a, R =
b, R =
c, R =
d, R =
Ph
e, R =
f, R =
CO2Me
Ph
g, R =
CO2H
H2SO4 H2O Dioxane
Et3SiH
BF3-Et2O
HO
OH
(-)-4
(+)-4
DMSO (CF3CO)2O
Et3N CH2Cl2
(-)-5
(+)-5
(+)-2
(+)-5
CO2H
6, (+)-Biotin

readily separated by crystallization. The (S)-(+)-mandelic acid derivatives (3g and 3'g) were more economical and more favorable for preparative purposes. (S)-(+)-Mandelic acid derivatives 3g and 3'g could also be obtained by hydrolysis of methyl esters 3f and 3'f, respectively, with sodium hydroxide. Esterification of 3'g with diazomethane afforded 3'f, identical to that prepared from (S)-(+)-methyl mandelate. Absolute configurations were tentatively assigned based upon the assumption that structures 3'd-g would have positive rotations, as does (+)-5. This was subsequently confirmed by correlation with (+)-5 (see below).

Ether derivatives have rarely been utilized in resolutions because of their resistance to cleavage. However in the case of 3 and 3', presence of the sulfur atom rendered the diastereomeric ethers were quite susceptible to acid-catalyzed hydrolysis. Thus hydrolysis of the separated diastereomeric 4-alkoxythieno-[3,4-d]imidazolones, 3d-g and 3'd-g, afforded 4-hydroxythieno[3,4-d]imidazol-2-ones (-)-4 and (+)-4, respectively, and enantiomerically pure (S)-(+)-mandelic acid. Oxidation of (+)-4 provided enantiomerically pure[11] thieno[3,4-d]imid-azol-2,4-dione (+)-5, which had previously been synthesized by an independent route[11] and has been utilized in several syntheses of (+)-biotin (6).[5,6] Treatment of (+)-4 with HCl gave 4-chloro-thieno[3,4-d]imidazol-2-one (+)-2, which could also be elaborated to give (+)-biotin (6).[8]

The undesired 4-hydroxythieno[3,4-d]imidazol-2-one enantiomer, (-)-4, was easily recycled to 1 by reduction with triethylsilane. Even more conveniently, recycling to 1 could be accomplished directly by reduction of 4-alkoxy-thieno[3,4-d]imidazolone 3g with triethylsilane. Enantiomerically pure (S)-(+)-mandelic acid could also be recovered.

In summary, enantiomerically pure (+)-2 and (+)-5, key intermediates in independent routes to (+)-biotin (6), have been prepared. With this methodology, (+)-biotin can now be efficiently synthesized from readily available 2,5-dihydrothiophene 1,1-dioxide.

Experimental Section

NMR spectra were recorded on a General Electric QE-300 spectrometer. High resolution mass spectra were recorded on a Kratos MS-30 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. Solvents were evaporated in vacuo with a rotary evaporator. Thin layer chromatography (TLC) was performed on EM 5539 silica gel 60 plates, and all column chromatography was performed with EM silica gel 60 (0.040 - 0.063 mm), eluted under pressure.

(±)-(3aα,4α,6aα)-4-Chlorotetrahydro-1,3-bis(phenylmethyl)-1H-thieno-[3,4-d]imidazol-2(3H)-one ((±)-2) was prepared by reaction of 1[7] with N-chlorosuccinimide as described.[8]

4-[(1R,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyloxy]-[3aR- and 3aS-(3aα,4α,6aα)]-tetrahydro-1,3-

bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-2(3H)-one (3a and 3'a). (-)-Menthol (87 mg, 0.557 mmol) and (±)-2 (220 mg, 0.613 mmol, 110 mol%) were dissolved in dichloromethane (0.1 mL) and stirred at 25 °C for 48 h, at which time TLC indicated all of the menthol was consumed. The solvent was evaporated and the product was purified by column chromatography (hexane - EtOAc, 80:20) affording a 1:1 mixture of diastereomers 3a and 3'a (231 mg, 87% yield) as an oil: TLC R_f 0.33 (hexane - EtOAc, 75:25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 - 0.9 (9 H, m), 0.9 - 2.2 (8 H, m), 2.8 (1.5 H, m), 2.91 (0.5 H, dd, J = 4, 12 Hz), 3.08 (0.5 H, dt, J = 4.5, 10.5 Hz), 3.25 (0.5 H, dt, J = 4.2, 10.5 Hz), 3.96 (0.5 H, d, J = 8 Hz), 3.98 (0.5 H, d, J = 8 Hz), 4.21 (2.5 H, m), 4.51 (1 H, s), 4.78 (1.5 H, m), 4.94 (1 H, s), 7.32 (10 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.63, 16.24, 21.04, 22.28, 23.03, 23.14, 25.05, 31.22, 31.72, 34.28, 34.41, 34.77, 38.60, 42.36, 46.28, 47.03, 47.40, 47.67, 48.91, 60.60, 60.84, 68.18, 69.10, 75.31, 79.69, 88.30, 92.43, 127 - 129 (12 signals), 137.23, 137.33, 137.84, 159.50. HRMS calcd for $C_{29}H_{38}N_2O_2S$ 478.2654, found 478.2650 (10 %).

4-[(1S-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxy]-[3aR- and 3aS-(3aα,4α,6aα)]-tetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-2(3H)-one (3b and 3'b). (1S-endo)-(-)-Borneol (100 mol%) reacted with (±)-2 as above to afford a 1:1 mixture of 3b and 3'b (78 % yield) as an oil: TLC R_f 0.37 (hexane - EtOAc, 75:25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (1.5 H, s), 0.72 (1.5 H, s), 0.79 (6 H, s), 0.8 - 2.2 (7 H, m), 2.78 (2 H, m), 3.58 (0.5 H, dm), 3.78 (0.5 H, dm), 3.95 (0.5 H, d, J = 8 Hz), 3.98 (0.5 H, d, J = 8 Hz), 4.0 - 4.86 (6 H, m), 7.4 (10 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.30, 14.20, 18.88, 19.65, 26.84, 28.21, 34.52, 34.88, 37.26, 44.81, 45.04, 46.19, 47.55, 48.51, 49.32, 60.52 68.15, 68.34, 81.19, 84.77, 90.57, 93.10, 127 - 129 (12 signals), 137.16 137.34, 159.63; HRMS calcd for $C_{29}H_{36}N_2O_2S$ 476.2498, found 476.2497 (9 %).

4-[(R)-1-Methylpropoxy]-[3aR- and 3aS-(3aα,4α,6aα)]-tetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]-imidazol-2(3H)-one (3c and 3'c). (R)-(-)-2-Butanol (145 mol%) reacted with (±)-2 as above to afford a 1:1 mixture of 3b and 3'b (77 % yield) as an oil: TLC R_f 0.33 (hexane - EtOAc, 75:25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (1.5 H, t, J = 6 Hz), 0.78 (1.5 H, t, J = 6 Hz), 0.89 (1.5 H, d, J = 6 Hz), 1.01 (1.5 H, d, J = 6 Hz), 1.31 (2 H, m, J = 7.2 Hz), 2.82 (2 H, m), 3.49 (1 H, sextet, J = 6 Hz), 3.95 (1 H, d, J = 7.8 Hz), 4.1 - 4.8 (5 H, m), 4.88 (1 H, s), 7.30 (10 H, m); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 9.06 (q), 10.07 (q), 17.91 (q), 20.08 (q), 27.22 (t), 29.75 (t), 34.61 (t), 34.65 (t), 46.25 (t), 47.55 (t), 47.67 (t), 60.70 (d), 68.52 (d), 68.77 (d), 73.84 (d), 74.86 (d), 89.37 (d), 90.46 (d), 127.54 (d), 127.63 (d), 128.01 (d), 128.70 (d), 137.19 (s), 137.54 (s), 159.71 (s); HRMS calcd for $C_{23}H_{28}N_2O_2S$ 396.1872, found 396.1870 (7 %).

4-[(S)-1-Phenylethoxy]-[3aR- and 3aS-(3aα,4α,6aα)]-tetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]-imidazol-2(3H)-one (3d and 3'd). (S)-(-)-1-Phenylethanol (102 mg, 0.83 mmol), (±)-2 (300 mg, 0.83 mmol, 100 mol%) and dichloromethane (1.0 mL) were stirred at 25 °C for 4 days. Evaporation of the solvent afforded an oil (270 mg, 73% yield). TLC indicated two diastereomers which were separated by column chromatography (EtOAc-hexane, 5:95 to 40:60).

3d. Oil: R_f 0.41 (EtOAc-hexane, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3 H, d, J = 6.6 Hz), 2.79 (1 H, d, J = 12.6 Hz), 2.95 (1 H, dd, J = 4.5, 12.6 Hz), 3.74 (1 H, d, J = 15 Hz), 3.97 (1 H, d, J = 7.8 Hz), 4.2 - 4.8 (6 H, m), 7.0 - 7.5 (15 H, m); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 23.91 (q), 34.82 (t), 46.20 (t), 46.59 (t), 60.47 (d), 67.66 (d), 75.01 (d), 89.11 (d), 126 - 129 (9 signals, d), 136.89 (s), 137.12 (s), 141.89 (s), 159.34 (s); $[\alpha]_D^{20}$ -175° (c 2.5, $CHCl_3$); HRMS calcd for $C_{27}H_{28}N_2O_2S$ 444.1872, found 444.1868 (1 %).

3'd. Oil: R_f 0.37 (EtOAc-hexane, 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3 H, d, J = 6.6 Hz), 2.73 (1 H, d, J = 12.6 Hz), 2.82 (1 H, dd, J = 4.2, 12.6 Hz), 4.0 - 4.8 (7 H, m), 4.97 (1 H, s), 7.2 - 7.5 (15 H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.36, 34.81, 46.19, 47.57, 60.63, 68.66, 74.54, 89.74, 126 - 129 (9 signals), 137.03, 137.42, 142.88, 159.59; $[\alpha]_D^{20}$ +118° (c 0.8, $CHCl_3$); HRMS calcd for $C_{27}H_{28}N_2O_2S$ 444.1872, found 444.1875 (1 %).

4-[(3β,5α)-Cholestan-3-yloxy]-[3aR- and 3aS-(3aα,4α,6aα)]-tetrahydro-1,3-bis(phenylmethyl)-1H-thieno-[3,4-d]imidazol-2(3H)-one (3e and 3'e). (+)-(3β,5α)-Cholestan-3-ol ((+)-dihydrocholesterol) (210 mg, 0.55 mmol), racemic (±)-2 (200 mg, 0.56 mmol, 102 mol%) and carbon tetrachloride (1.5 mL) were refluxed for 12 h. The mixture was diluted with dichloromethane (10 mL) and washed once with water (3 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexane, 5:95 to 30:70) to afford a 1:1 mixture of diastereomers 3e and 3'e (265 mg, 67% yield) as a white solid: R_f 0.3 (25:75 EtOAc-hexane). Recrystallization from dichloromethane - hexane afforded pure 3'e (121 mg).

3e. The filtrate was evaporated to afford solid 3e, contaminated with 15 % 3'e. $[\alpha]_D^{20}$ -43.8° (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.5 - 2.0 (46 H, m), 2.76 (1 H, d, J = 12 Hz), 2.87 (1 H, dd, J = 4, 12 Hz), 3.35 (1 H, m), 3.94 (1 H, d, J = 8 Hz), 4.19 (2 H, m), 4.45 (1 H, d, J = 15 Hz), 4.52 (1 H, d, J = 15 Hz), 4.77 (1 H, d, J = 15 Hz), 4.91 (1 H, s), 7.29 (10 H, br. s).

3'e. mp 183 - 4°C; $[\alpha]_D^{20}$ +121° (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.5 - 2.0 (46 H, m), 2.76 (1 H, d, J = 12 Hz), 2.87 (1 H, dd, J = 4, 12 Hz), 3.35 (1 H, m), 3.94 (1 H, d, J = 8 Hz), 4.20 (2 H, m), 4.38 (1 H, d, J = 15 Hz), 4.58 (1 H, d, J = 15 Hz), 4.77 (1 H, d, J = 15 Hz), 4.94 (1 H, s), 7.29 (10 H, br. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.03, 12.20, 18.63, 21.20, 22.54, 22.79, 23.79, 24.16, 26.53, 27.98, 28.20, 28.61, 31.96, 34.53, 35.42, 35.59, 35.75, 36.12, 36.65, 39.46, 39.97, 42.53, 44.79, 46.19, 47.53, 54.24, 56.22, 56.39, 60.65, 68.66, 76.08, 89.24, 127.47, 127.55, 127.94, 128.22, 128.63, 137.08, 137.42, 159.59; mass spectrum, m/e (relative intensity) 711 (0.2), 710 (0.2, M^+), 277 (32), 240 (15), 187 (60), 91 (100).

Anal. Calcd for $C_{46}H_{66}N_2O_2S$: C, 77.69; H, 9.36; N, 3.94. Found: C, 77.52; H, 9.40; N, 3.89.

Methyl (S)-α-[3aR- and 3aS-(3aα,4α,6aα)]-2-Hexahydro-2-oxo-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]-imidazol-4-yloxy]benzeneacetate (3f and 3'f). (S)-(+)-Methyl mandelate (740 mg, 4.42 mmol), (±)-2 (1.59 g, 4.42 mmol), and carbon tetrachloride (10 mL) was refluxed for 50 h. The reaction mixture was diluted with dichloromethane (60 mL) and washed with water (2 X 5 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated to afford a 1:1 mixture of diastereomers **3f** and **3'f** (1.70 g, 79% yield). TLC R_f 0.34 and 0.28 (50:50 EtOAc-hexane). The mixture was separated by column chromatography (EtOAc-hexane, 5:95 to 40:60).

3f. R_f 0.34 (50:50 EtOAc-hexane); $[\alpha]_D^{24}$ -105°, (c 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (2 H, m), 3.68 (3 H, s), 4.1 - 4.4 (4 H, m), 4.74 (1 H, d, J = 15.6 Hz), 4.77 (1 H, J = 15.3 Hz), 5.19 (1 H, s), 5.20 (1 H, s), 7.22 - 7.45 (15 H, m); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 35.02 (t), 46.21 (t), 46.97 (t), 52.18 (q), 60.41 (d), 68.22 (d), 77.14 (d), 91.36 (d), 127 - 129 (d, 9 signals), 135.72 (s), 136.93 (s), 137.31 (s), 159.34 (s), 170.44 (s); HRMS calcd for $C_{28}H_{28}N_2O_4S$ 488.1770, found 488.1768 (8 %).

3'f. R_f 0.28 (50:50 EtOAc-hexane); $[\alpha]_D^{24}$ +185° (c 2, $CHCl_3$); IR (neat) 3040, 2930, 1740, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78 (1 H, d, J = 12.6 Hz), 2.98 (1 H, dd, J = 4.5, 12.6 Hz), 3.56 (3 H, s), 3.94 (1 H, d, J = 15.3 Hz), 4.12 (3 H, m), 4.59 (1 H, d, J = 15.3 Hz), 4.72 (1 H, d, J = 15.3), 4.77 (1 H, s), 5.08 (1 H, s), 7.05 - 7.37 (15 H, m); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 34.95 (t), 46.07 (t), 46.73 (t), 52.01 (q), 60.45 (d), 67.71 (d), 77.44 (d), 89.69 (d), 127 - 129 (9 signals, d), 134.58 (s), 136.65 (s), 136.84 (s), 159.14 (s), 169.99 (s); mass spectrum, m/e (relative intensity) 488 (5, M^+), 339 (7), 320 (12), 277 (23), 229 (3), 187 (8), 121 (3), 107 (45), 91 (100); HRMS calcd for $C_{28}H_{28}N_2O_4S$ 488.1770, found 488.1765 (5 %).

3'f was also prepared in 98 % yield by reaction of **3'g** (40 mg) with excess diazomethane in ether for 30 min at 20 °C. $[\alpha]_D^{24}$ +187° (c 0.9, $CHCl_3$).

(S)-α-[3aR- and 3aS-(3aα,4α,6aα)]-2-Hexahydro-2-oxo-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-4-yloxy]benzeneacetic acid (3g and 3'g). A. A 1:1 mixture of diastereomeric esters **3f** and **3'f** (400 mg, 0.82 mmol) was treated with 1 M methanolic NaOH (1.0 mL). After 14 h at 20 °C, the methanol was evaporated. The residue was dissolved in water (2 mL) and extracted with dichloromethane. The aqueous layer was acidified with HCl and extracted with EtOAc (5 x 5 mL). The EtOAc extracts were dried over $MgSO_4$ and the solvent was evaporated to afford a 1:1 mixture of diastereomers **3g** and **3'g** (332 mg, 86% yield).

B. (S)-(+)-Mandelic acid (508 mg, 3.34 mmol), (±)-2 (1.20 g, 3.34 mmol), and carbon tetrachloride (6 mL) were refluxed for 14 h beneath a condenser fitted with a drying tube. The initially heterogeneous mixture became homogeneous after 5 min, and then heterogeneous again. The product was collected by filtration, affording a 1:1 mixture of **3g** and **3'g** (1.18 g, 75% yield). Recrystallization from 2-propanol,

dichloromethane, and hexane (1:2:13) afforded **3'g** as a solid (520 mg, 33 % yield), while the mother liquor was enriched in 3g.

3g was contaminated with 8% **3'g**. Viscous glass: $[\alpha]_D^{20}$ -97.6° (c 2.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (1 H, dd, J = 4.5, 12.5 Hz), 2.91 (1 H, d, J = 12.9 Hz), 4.2 (4 H, m), 4.53 (1 H, d, J = 15.9 Hz), 4.66 (1 H, d, J = 15.3 Hz), 5.09 (1 H, s), 5.36 (1 H, s) 7.3 (15 H, m); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 34.98, 46 19, 46.77, 60.58, 68.08, 77.13, 91.29, 126 - 129 (9 signals), 136.02, 136.73, 136.95, 159.54, 172.24.

3'g. White solid: mp 223 - 225 °C; $[\alpha]_D^{23}$ +221° (c 1.0, 1,4-dioxane); IR (mineral oil) 3110, 2915,2830, 1745, 1665, 1455 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.86 (2 H, m), 3.92 (1 H, d, J = 15.5 Hz), 3.95 (1 H, d, J = 7.5 Hz), 4.18 (1 H, J = 15.9 Hz), 4.22 (1 H, dd, J = 7.8, 4.2, NCH), 4.37 (1 H, d, J = 15.6 Hz), 4.46 (1 H, d, J = 15.6 Hz), 4.88 (1 H, s), 4.89 (1 H, s), 7.0 - 7.4 (15 H, m); ^{13}C NMR (75 MHz, APT, DMSO-d_6) δ 35.88 (t), 46.08 (t), 46.99 (t), 61.44 (d), 68.48 (d), 78.54 (d), 91.38 (d), 128.20 (d), 128.47 (d), 129.37 (d), 136.70 (s), 138.90 (s), 138.57 (s), 159.73 (s), 171.89 (s); HRMS calcd for $C_{27}H_{26}N_2O_4S$ 474.1613, found 474.1621 (2 %).

Anal. Calcd for $C_{27}H_{26}N_2O_4S$: C, 68.33; H, 5.52 ;N, 5.90. Found: C, 68.02; H, 5.45; N, 5.71.

(+)-(3aα,4α,6aα)-4-Tetrahydro-4-hydroxy-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-2(3H)-one ((+)-4). Ether **3'g** (200 mg, 0.42 mmol) was refluxed with 1.5 M H_2SO_4 (4 mL) in 1,4-dioxane (8 mL) for 3 h. The solvent was evaporated, water was added, and the product was extracted into chloroform (5 x 10 mL). The organic extract was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. The solvent was evaporated, and (+)-4 was recrystallized from dichloromethane (3 mL) and hexane (15 mL): White fluffy solid (124 mg, 86%): mp 164 - 165 °C; R_f 0.35 (50:50 EtOAc - hexane); $[\alpha]_D^{22}$ +76.0° (c 0.76, $CHCl_3$); mass spectrum m/e (relative intensity) 340 (15, M^+), 277 (18), 187 (72), 91 (100); IR, ^1H and ^{13}C NMR spectra identical with those of the racemate.[8] Acidification of the $NaHCO_3$ wash and extraction with ether afforded (+)-mandelic acid. Hydrolysis of **3'd**, **3'e**, and **3'f** according to the same procedure also gave (+)-4. Hydrolysis of the diastereomeric ethers (3) gave (-)-**4**.

Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.08; H, 5.75; N, 8.03.

(+)-(3aα,4α,6aα)-4-Chlorotetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-2(3H)-one ((+)-2). HCl gas was bubbled into a suspension of thiolactol (+)-**4** in $CHCl_3$ for 10 min at 0 °C. The resulting homogeneous solution was stirred for 1 h, then quickly rinsed twice with 10 % $NaHCO_3$, then water, and dried over $MgSO_4$. Evaporation of the solvent afforded (+)-**2**: mp 104 - 6 °C; $[\alpha]^{21}_D$ +125° (c 0.3, $CHCl_3$); IR, ^1H and ^{13}C NMR spectra identical with those of the racemate.[8]

(3aS-cis)-Tetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazole-2,4-dione ((+)-5). Trifluoroacetic

anhydride (0.25 mL, 0.37 g, 1.76 mmol, 550 mol%) was added slowly to dry DMSO (0.15 mL, 0.165 g, 2.11 mmol, 660 mol%) and dry dichloromethane (1 mL) at -78 °C (bath temp). After 15 minutes at -78 °C, a solution of thiolactol (+)-4 (110 mg, 0.32 mmol) in dry dichloromethane (2 mL) and dry DMSO (0.05 mL) was added very slowly. After 1 h at -78 °C and 1 h at -60 °C, the reaction was cooled to -78 °C and triethylamine (0.3 mL, 0.22 g, 2.15 mmol 672 mol%) was added dropwise. After 5 min, the mixture was allowed to warm to room temperature over 1.5 h. Water (5 mL) was added and the product was extracted into dichloromethane (5 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Flash column chromatography on silica gel (hexane - EtOAc 95:5 to 80:20) and recrystallization from 2-propanol gave thiolactone (+)-5 (93 mg, 85% yield) as a white solid: R_f 0.38 (50:50 EtOAc - hexane); mp 124 - 125 °C (lit. mp 125 - 127 °C;[11] $[\alpha]_D^{24}$ +90.9° (c 1.0, $CHCl_3$), lit. $[\alpha]_D^{20}$ + 91.3 ± 0.9° (c 1, $CHCl_3$);[11] IR, and ^1H NMR spectra identical with those of the racemate;[8] ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 32.88 (t), 45.10 (t), 46.32 (t), 55.75 (d), 62.01 (d), 127.57 (d), 127.77 (d), 128.58 (d), 128.75 (d), 136.08 (s), 136.28 (s), 158.16 (s), 203.50 (s).

cis-Tetrahydro-1,3-bis(phenylmethyl)-1H-thieno[3,4-d]imidazol-2(3H)-one (1). A. Thiolactol (-)-4 (50 mg, 0.13 mmol) and triethylsilane (0.06 mL, 0.043 g, 0.37 mmol, 285 mol%) in dry dichloromethane (1 mL) were cooled to -60 °C. Boron trifluoride-etherate (0.04 mL, 46 mg, 0.32 mmol, 250 mol%) was added. After 1 h, the mixture was gradually warmed to 20 °C and stirred for 14 h. Water (3 mL) was added and the product was extracted into dichloromethane (5 x 5 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent afforded 1 as a white solid (44 mg) in 94% yield; mp 109 - 110 °C (lit. mp 108 - 110 °C);[7] IR, ^1H and ^{13}C NMR spectra identical with those of an authentic sample.[7]

B. A mixture of 3g (60 mg, 0.13 mmol), trifluoroacetic acid (0.2 mL, 0.30 g, 2.6 mmol, 2000 mol%) and triethylsilane (0.09 mL, 65 mg, 0.56 mmol, 430 mol%) was refluxed for 14 h. The reaction mixture was diluted with water (5 mL) and basified with $NaHCO_3$. The aqueous layer was extracted with dichloromethane (5 x 5 mL). The combined extracts were washed with saturated NaCl solution (3 x 2 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 1 as a white solid: (37 mg, 90% yield); mp 109 - 110 °C; spectra as above. The aqueous layer was acidified to pH 2 with cold conc. HCl and extracted with ether (5 x 5 mL). The ether layer was rinsed twice with saturated NaCl solution and dried over $MgSO_4$. Evaporation gave (+)-mandelic acid, identical in all respects with an authentic sample.

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