25 mg (70%) of 18: ^{1}H NMR ($CDCl_3$) δ 1.32–1.95 (4 H, m), 2.00–2.50 (1 H, br d), 2.97–3.18 (2 H, m), 3.20–3.94 (3 H, m), 5.14 (2 H, s), 7.35 (5 H, s); IR (neat) (cm^{-1}) 3350, 3050, 2950, 1700, 1530. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.13; H, 7.38; N, 5.85.

(*S*)-(−)-3-Piperidinol (1). Method A. To 15 mL of a 1 M solution of diborane in hexane was added 10 mL of dry tetrahydrofuran. The solution was cooled to 0 °C under argon, and a suspension of (*S*)-5-hydroxy-2-piperidinone (**7**) (0.50 g) in 15 mL of dry tetrahydrofuran was added slowly with stirring. The mixture was then heated to reflux under an argon atmosphere for 2 h. After cooling to room temperature, the reaction mixture was treated with 2.5 mL of cold 6 N hydrochloric acid and the volatile components were removed in vacuo. The residue was dissolved in 10 mL of water, and the aqueous solution was saturated with solid sodium hydroxide and extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residual oil was purified by chromatography using chloroform/methanol (7:3) as the elutant to yield 0.30 g (68%) of **1**. The ^{1}H NMR spectrum of **1** was identical with that of racemic 3-piperidinol (Aldrich Chemical); $[\alpha]^{22}_D$ −7.4° (*c* 0.4, CH_3OH) [lit.[1] −7.5° (*c* 2, CH_3OH)].

Method B. To a solution of 30 mg of (*S*)-*N*-[(benzyloxy)carbonyl]-3-piperidinol (**18**) dissolved in 10 mL of ethanol was added 3 mg of 10% palladium on carbon. The mixture was shaken overnight at 50 psi of hydrogen gas on a Parr hydrogenator. The reaction mixture was filtered through a Celite pad, and the pad was washed with ethanol. The filtrate and washings were evaporated in vacuo to yield 13 mg (100%) of **1**, which was identical in all respects with that reported[8] from the mass spectral data for this compound: mass spectrum, *m/e* 44 (base peak), 56, 57, 70, 100, 101, 102.

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Preparation of (3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazol-2(3*H*)-one: A Key Biotin Intermediate

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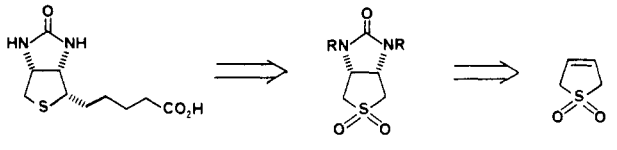
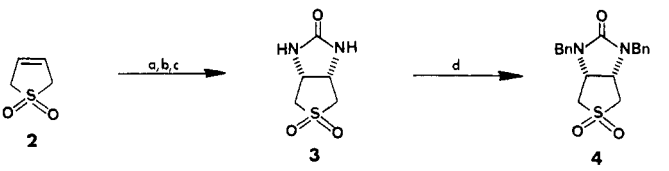
The vitamin biotin (**1**), which is prepared commercially by total synthesis,[1] has been the target of several ingenious



1, Biotin **2**

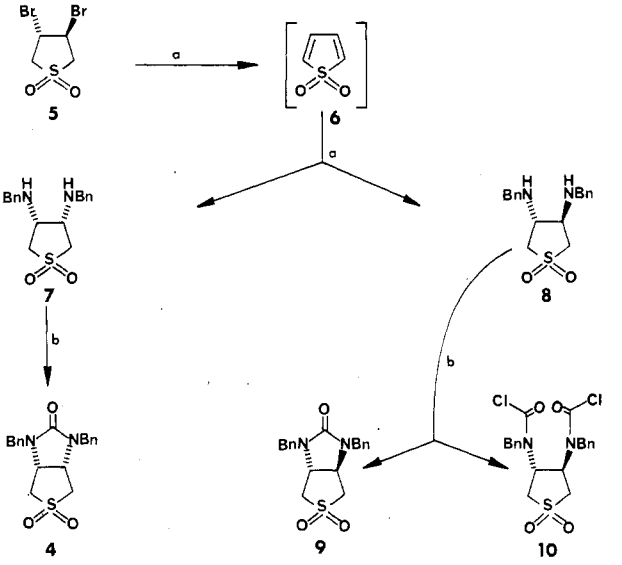
syntheses.[2] Our retrosynthetic analysis of biotin suggested that the abundantly available 2,5-dihydrothiophene 1,1-dioxide (**2**) might serve admirably as the ultimate starting material in a practical synthesis of biotin. Previous investigators with similar intentions have prepared (6aα,3aα)-hexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (**3**) from 2,5-dihydrothiophene 1,1-dioxide (**2**)[3,4] but have not reported further progress in conversion of **3** into biotin (**1**). When we prepared **3**,[4,5] we found that it was remarkably insoluble in organic solvents compatible with reduction of sulfone **3** to the corresponding sulfide.[6,7] In order to gain increased organic solubility, **3** was N-benzylated (Scheme I) with a large excess of benzyl bromide in aqueous sodium hydroxide to afford **4** in 95% yield.[8-10]

Scheme I[a]



[a] (a) EtO_2CNCl_2, $NaHSO_3$; (b) HBr; (c) KNCO; (d) $PhCH_2Br$, NaOH, H_2O.

Scheme II[a]



[a] (a) $PhNH_2$, CH_3OH; (b) $COCl_2$, Et_3N.

A shorter alternative synthesis of **4** was concurrently pursued. As shown in Scheme II, 2,5-dihydrothiophene 1,1-dioxide (**2**) may easily be brominated to afford dibromide **5**.[11] Dehydrobromination of **5** generated the unisolable thiophene 1,1-dioxide (**6**),[12,13] which reacted

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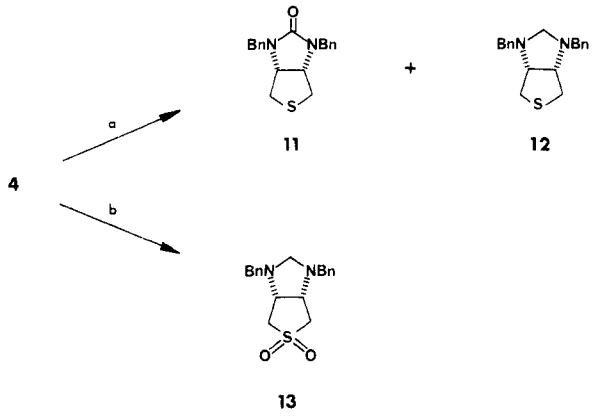
0022-3263/85/1950-0899$01.50/0

Scheme III



[a] (a) $LiAlH_4$, Et_2O; (b) Dibah.

further with benzylamine to yield a 1:2 mixture of cis diamine **7** and trans diamine **8**.[5,11,12,14] After careful separation by chromatography, cis diamine **7** affords **4** in essentially quantitative yield.[14,15] Unfortunately, this route to **4** involves an impractical chromatographic separation.

To improve the practicability of this approach, we decided to take advantage of the expected difference in the reactivity of cis and trans diamines **7** and **8**, respectively, with phosgene.[7,16] In practice, however, **8** reacted rapidly with excess phosgene to generate a mixture of trans-fused urea **9**, and a small amount of dicarbamoyl chloride **10**. Several trans-fused 3-thiabicyclo[3.3.0]octanes, known to be less strained than the corresponding carbocycles,[17,18] have previously been reported.[3,5,12,19,20] Fortunately, however, the solubility properties of ureas **4** and **9** were quite different. Accordingly, we treated the *crude mixture* of cis and trans diamines **7** and **8** with phosgene and obtained pure **4** in 36% yield by simple crystallization.

We were now in a position to examine the reduction[21-23] of sulfone **4** to sulfide **11** (Scheme III). Lithium aluminum hydride reduction of **4** had previously been reported without details.[14,15] Best yields of **11** were obtained with highly active LAH in ether between −15 and 0 °C. Slightly deactivated LAH failed to reduce **4** even though it did reduce ketones and esters. Attempted reduction in THF afforded a complex mixture of products and starting material. Use of excess LAH or higher temperatures gave concomitant reduction of the urea to afford **12**. Interestingly, an attempt to reduce **4** with Dibah, a reagent recommended for sulfone reduction,[24] reduced the urea moiety rather than the sulfone, producing **13**.

The physical and spectral properties of **11**, which has been converted into biotin by alkylation of the corresponding sulfoxide,[25] matched those of an authentic sample prepared via independent synthesis.[25,26]

Experimental Section

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazol-2(3*H*)-one 5,5-Dioxide (4). A mixture of (3aα,6aα)-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 5,5-dioxide (**3**)[4] (500 mg, 2.85 mmol), water (8.5 mL), aqueous 8.4 M NaOH (3.4 mL, 28.5 mmol, 1000 mol %), and benzyl bromide (12.4 mL, 19.5 g, 114 mmol, 4000 mol %) was vigorously stirred and refluxed for 24 h. The product was extracted with three portions of CH_2Cl_2. The resulting oil was treated with ether, and the white precipitate (963 mg, 95 %) was collected by filtration: mp 174–176 °C (lit.[14] mp 184 °C); IR (KBr) 1695 cm^{-1}; mass spectrum, *m/e* (relative intensity) 356 (12), 265 (51), 201 (7), 132 (31), 91 (100); ^1H NMR ($CDCl_3$) δ 2.98 (4 H, m), 4.10 (2 H, m), 4.21 (2 H, d), 4.66 (2 H, d), 7.27 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 46.25 (t), 52.35 (t), 53.02 (d), 127.73 (d), 128.43 (d), 128.85 (d), 137.60 (s), 160 (s). Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66. Found: C, 63.99; H, 5.77.

***cis*- and *trans*-*N*,*N*-Dibenzyltetrahydrothiophene-3,4-diamine 1,1-dioxide (7 and 8).**[5,14] were prepared from 3,4-dibromotetrahydrothiophene 1,1-dioxide (**5**)[11] and separated by chromatography on silica gel with ether–benzene–pyridine (50:50:1). The faster eluting compound was cis diamine **7**: mp 105–106 °C (lit.[14] mp 111–111.5 °C); ^1H NMR ($CDCl_3$) δ 2.0 (2 H, s), 2.9–3.4 (6 H, m), 3.54 (4 H, AB quartet), 7.13 (10 H, s). The slower eluting compound was trans diamine **8**: mp 106–107 °C (lit.[5] mp 109–110.5 °C; lit.[14] mp 114–115 °C); ^1H NMR ($CDCl_3$) δ 1.8 (2 H, s), 2.5–3.4 (6 H, m), 3.58 (4 H, s), 7.13 (10 H, s).[5]

(3aα,6aα)- and (3aα,6aβ)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 5,5-Dioxide (4 and 9). A 2:1 mixture of trans and cis diamines **8** and **7** (3.54 g, 10.7 mmol) dissolved in CH_2Cl_2 (45 mL) and Et_3N (4.4 mL, 31.5 mmol, 294 mol %) at 0 °C was treated with phosgene in CH_2Cl_2 (5.5 mL of 3.85 mg/mL, 2.12 g, 2.14 mmol, 200 mol %). After 15 min at 0 °C, the phosgene and CH_2Cl_2 were evaporated. The residue was treated with water at 50 °C for 5 min and extracted with three portions of CH_2Cl_2 to give a mixture of **4**, **9**, and **10** (3.66 g).

The mixture was recrystallized from hot chloroform (25 mL) to afford cis urea **4** (1.38 g, 36 % yield) as a white crystalline solid: mp 176–179 °C (lit.[14] mp 184 °C). A quantitative yield of cis urea **4** was obtained when pure cis diamine **7** was treated with phosgene.

The above filtrate was recrystallized from hot benzene–hexanes (2:1) to afford trans urea **9** (2.0 g, 53% yield) as a white solid: mp 144–147 °C; IR 1730 cm^{-1}; mass spectrum, *m/e* (relative intensity) 356 (6), 265 (19), 201 (6), 132 (14), 91 (100); ^1H NMR ($CDCl_3$) δ 3.0 (6 H, m), 4.16 (2 H, d), 4.61 (2 H, d), 7.26 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 49.35 (t), 57.03 (t), 58.57 (d), 128.24 (d), 128.52 (d), 128.88 (d), 135.62 (s), 162.62 (s). Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66. Found: C, 64.09; H, 5.71.

***trans*-*N*,*N*-Dibenzyltetrahydrothiophene-3,4-dicarbamoyl Chloride 1,1-Dioxide (10).** Chromatography of the mother liquor from the second recrystallization on silica gel with CH_2Cl_2–EtOAc (98:2) afforded a small amount of dicarbamoyl chloride **10**. Pure **8** afforded a mixture of **9** and **10**: mass spectrum, *m/e* (relative intensity) 265 (0.2), 197 (3), 195 (10), 116 (17), 91 (100); mp 87–90 °C; ^1H NMR ($CDCl_3$) δ 2.9 (2 H, m), 3.35 (2 H, m), 4.36 (2 H, d), 4.86 (2 H, d), 4.95 (2 H, m), 7.31 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 51.47 (t), 56.28 (t), 57.11 (d), 127.31 (d), 128.91 (d), 129.35 (d), 134.07 (s), 149.66 (s);[27] IR (KBr) 1735 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_4SCl_2$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.37; H, 4.30; N, 5.94.

(3α,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazol-2(3*H*)-one (11).[14,15] To a vigorously stirred suspension of sulfone **4** (736 mg, 2.07 mmol) in anhydrous ether (15 mL) was added a freshly prepared solution of LAH in anhydrous ether (22.9 mg/mL, 7.5 mL, 172 mg, 4.52 mmol, 219 mol %) at 0 °C over 5 min. The mixture was stirred 15 min at 0 °C and 15 min at 20

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°C, cooled to 0 °C, and quenched with water (0.17 mL), 15% NaOH (0.17 mL), and water (0.51 mL). The aluminum salts were removed by filtration and rinsed with ether (2 × 20 mL). The combined filtrate afforded the crude product which was redissolved in benzene (10 mL) and washed 3 times with 1 M HCl. The benzene layer residue was dissolved in a minimum quantity of CH_2Cl_2 and ether was added to afford a precipitate of 11 (402 mg, 60% yield), spectroscopically and chromatographically identical with an independently prepared sample:[25] mp 108–110 °C (lit. mp 110–111 °C,[14] 125 °C[25]); ^1H NMR ($CDCl_3$) δ 2.70 (4 H, m), 3.98 (2 H, m), 4.17 (2 H, d), 4.75 (2 H, d), 7.27 (10 H, s);[25] ^{13}C NMR ($CDCl_3$) δ 159.5, 137.4, 128.8, 128.3, 127.7, 61.4, 46.5, 37.5.

The aluminum salts were further extracted 3 times with CH_2Cl_2 to afford the starting material (140 mg, 19% recovery) which could be recrystallized from hot chloroform and recycled.

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazole (12). The combined HCl phase was basified with NaOH and extracted 3 times with CH_2Cl_2. The organic phase was dried and evaporated to afford overreduced product 12 (90 mg, 14% yield): mp 48–50 °C; mass spectrum, *m/e* (relative intensity) 310.1512 (12, M^+; calcd *m/e* 310.1506), 309 (47), 219 (4), 91 (100); ^1H NMR ($CDCl_3$) δ 2.55 (4 H, m), 3.02 (1 H, d, J = 5 Hz), 3.42 (2 H, m), 3.64 (4 H, s), 3.94 (1 H, d, J = 5 Hz), 7.25 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 37.69 (t), 58.00 (t), 72.03 (d), 77.91 (t), 127.23 (d), 128.22 (d), 129.04 (d), 138.11 (s).

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazole 5,5-Dioxide (13). Reduction of 4 in CH_2Cl_2 with Dibah (460 mol %) in toluene for 14 h, followed by quenching with HCl, afforded crude product which was purified by chromatography on silica gel eluted with CH_2Cl_2–EtOAc (95:5) to afford the product as a white solid (35 mg, 62% yield): mp 107–111 °C; IR (KBr) 3000 cm^{-1}; mass spectrum, *m/e* (relative intensity) 342.1398 (4, M^+; calcd *m/e* 342.1404), 341 (16), 251 (13), 146 (23), 91 (100); ^1H NMR ($CDCl_3$) δ 2.81 (4 H, m), 3.19 (1 H, d, J = 5 Hz), 3.45 (2 H, m), 3.64 (4 H, AB quartet), 3.99 (1 H, d, J = 5 Hz), 7.26 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 55.36 (t), 57.46 (t), 62.27 (d), 76.54 (t), 127.76 (d), 128.55 (d), 128.89 (d), 137.29 (s).

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Ozonolysis of Styrene and *p*-Nitrostyrene. Secondary Deuterium Isotope Effects

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It is widely accepted that the initial attack of ozone at a sterically unhindered alkene proceeds via a concerted 1,3-dipolar cycloaddition.[1] The recent observation of an inverse kinetic secondary isotope effect (KSIE, $k_H/k_D \approx 0.88$) for the reaction between O_3 and $CH_3CD{=}CH_2$ or $CH_3C{=}CHD$ lent support to this picture and indicated that both carbon atoms at the double bond are significantly perturbed in the transition state.[2]

Table I. Kinetic Secondary Isotope Effect for the Addition of Ozone to Styrene and *p*-Nitrostyrene in CCl_4 at 25 °C

mixture	runs	k_H/k_D[a]
styrene-d_0/styrene-α-d_1	7	0.93 ± 0.02
styrene-d_0/styrene-β-d_2	7	0.93 ± 0.02
p-nitrostyrene-d_0/*p*-nitrostyrene-α-d_1	4	0.91 ± 0.04
p-nitrostyrene-d_0/*p*-nitrostyrene-β-d_2	4	0.94 ± 0.01

[a] Per deuterium basis.

There have been several previous deuterium KSIE studies of addition reactions to styrene resulting in normal, inverse, or negligible isotope effects at C_α and C_β depending on the reaction system (polymerization,[3] (2 + 2) cycloaddition,[4] epoxidation,[5] acid-catalyzed hydration,[6] electrophilic addition of halogens,[7] addition of methyl radical,[8] or oxidation by chromyl chloride[9]). A particularly curious result was the inverse isotope effect observed at C_β and the normal effect at C_α for the concerted (2 + 2) cycloaddition between styrene and diphenylketene.[4] Oxidation reactions of styrene derivatives with *m*-chloroperbenzoic acid,[5a] chromyl chloride,[9] and cytochrome P-450 rat liver microsomes[5b] also show different KSIE at C_α and C_β. In the first two systems there is a 9–12% inverse KSIE at C_β and a negligible effect at C_α. In the third system, there is a 7% inverse effect at C_α and negligible effect at C_β. Since styrene derivatives have proven to be a sensitive probe of the transition state in cycloaddition and oxidation reactions, we decided to investigate the addition of ozone to deuterated styrene. We were interested to learn if different KSIE would be seen at C_α and C_β as in other styrene cyclizations or if the same inverse KSIE would be found as in the ozonolysis of propene.[2]

The reaction of ozone with styrene and other phenyl-substituted alkenes has already been the subject of considerable investigation.[10] For example, kinetic measurements on ring-substituted styrenes have shown that the ozone attack is electrophilic in nature.[10a,b] Styrene and *p*-nitrostyrene were chosen for this KSIE investigation. The substituted styrene was selected in order to make a direct comparison with the *m*-chloroperbenzoic acid epoxidation study[5a] where it also was a substrate.

Results and Discussion

Ozonolysis was carried out in CCl_4 using a 1:1 mixture of $PhCH{=}CH_2/PhCD{=}CH_2$ or $PhCH{=}CH_2/PhCH{=}CD_2$ to evaluate the corresponding secondary deuterium isotope effects. Analogous mixtures of *p*-nitrostyrenes were also ozonized. These competition reaction were run to 30% completion. The reaction mixture was then analyzed by 360-MHz ^1H NMR spectroscopy, which provides a well-resolved spectrum for quantitative analysis of each species remaining in the solution. The resultant values for k_H/k_D

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