A Total Synthesis of Biotin Based on the Stereoselective Alkylation of Sulfoxides[1]

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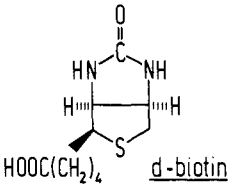
Abstract: A total synthesis of biotin, based on the stereoselective alkylation of sulfoxides, has been achieved. An intermediate sulfide, with the biotin bicyclic moiety, is first prepared. Oxidation of this sulfide with $NaIO_4$ yields 90% of the isomer with the sulfoxide cis to the junction hydrogens. The α carbanion, generated by CH_3Li in a HMPA–THF or HMPA–diglyme mixture, is then alkylated by *tert*-butyl ω-iodovalerate. The reaction is highly stereoselective and a single isomer, with the side chain trans to the S→O bond, is obtained with a 80% yield. The choice of the base and solvent is crucial for the alkylation yield. With BuLi a reaction at sulfur is taking place. Without HMPA, the reprotonation of the intermediate carbanion competes strongly with alkylation. After reduction of the sulfoxide and removal of the nitrogen protecting groups, *dl*-biotin is obtained. This synthesis is very versatile for the preparation of biotin analogues since different substituents can be introduced by alkylating the same key intermediate sulfoxide. This is illustrated by the preparation of the two isomeric 5-methylbiotins.

Biotin total synthesis has recently been the subject of a renewed interest and several new syntheses, involving very different strategies, have been reported.[2]



d-biotin

The synthesis that we have achieved takes advantage of the high stereoselectivity of the alkylation of sulfoxides.[3,4] We have already shown in previous studies that the methylation of six-membered cyclic sulfoxides occurs exclusively axially in axial sulfoxides and more than 90% equatorially in their equatorial isomers, thus always trans to the S→O bond.[4]

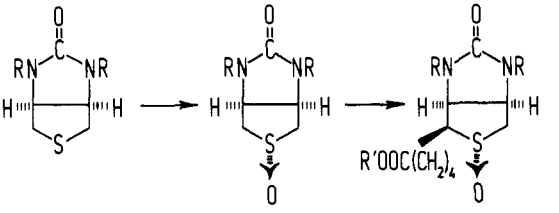
Assuming that this empirical rule was valid for five-membered rings, which proved to be true, we designed a simple route, summarized in Scheme I, for the preparation of *dl*-biotin.

One of the advantages of this route is its versatility for the preparation of biotin analogues differing in the side chain and/or possessing an α' substituent. It should provide an easy access to many biotin derivatives, including functionalized ones, very useful for the affinity labeling of biotin enzymes.

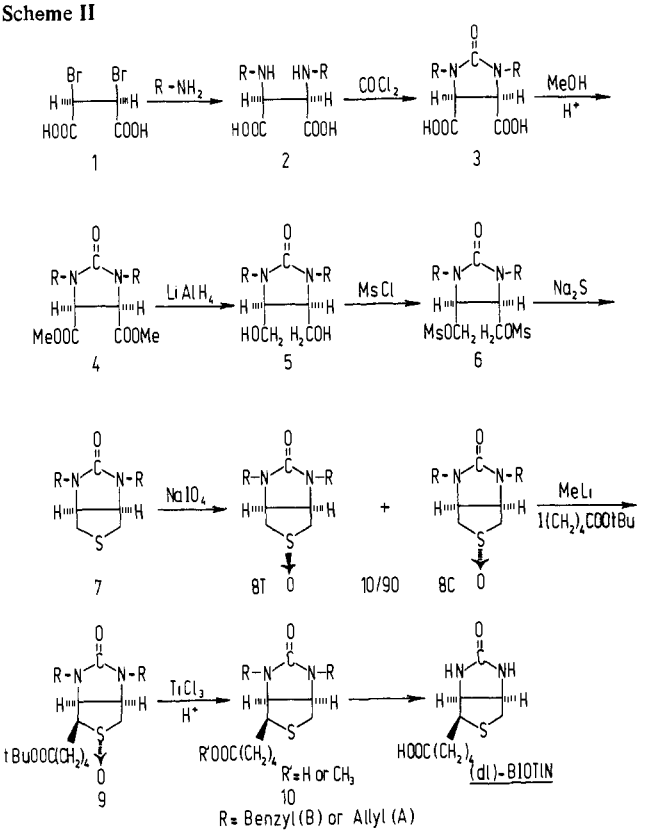
Synthesis of the Key Intermediate Sulfoxide 8C. The reaction sequence is depicted in Scheme II. The imidazolidone nitrogens had to be protected at least for the sulfoxide alkylation. We chose to introduce the protecting group at the beginning since the free NH derivatives are highly insoluble in most organic solvents. This group had to be stable to lithium aluminum hydride reduction and butyllithium treatment. The benzyl group, which fulfills these conditions, was first selected but the final debenzylation requires a very drastic acidic treatment. Therefore it must be avoided for compounds bearing acid-sensitive functions. The use of the allyl group, which can be cleaved under mild conditions, was then explored and the reactions are described in both series: R = B (benzyl) or A (allyl).

meso-Dibromosuccinic acid (**1**) was treated with allyl- or benzylamine to produce **2**, which was next cyclized to the diacid **3** by reaction with phosgene.[5] The corresponding diester **4** was then reduced by lithium aluminum hydride giving the alcohol **5** which was mesylated. The dimesylate **6** was cyclized with sodium sulfide into the key intermediate sulfide **7**. All these reactions are practically quantitative except one, the reduction of the diester **4A**.[6]

Scheme I



Scheme II



Oxidation of this sulfide **7** yielded a mixture of the two sulfoxides **8C** and **8T**. It is well known, since the classical work of Johnson,[7] that the oxidation stereochemistry of sulfides generally depends on the nature of the oxidizing agents. So in the hope of increasing the selectivity, we attempted different oxidation methods using sulfide **7B** (Table I).

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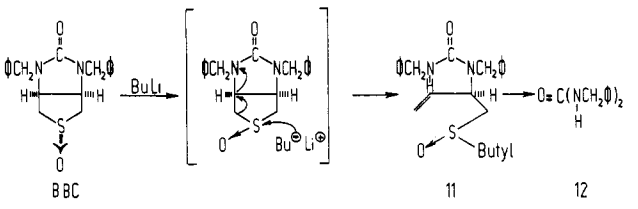
Table I. Oxidation Stereochemistry of Sulfide **7B**

	Oxidation method				
	$NaIO_4$ H_2O/MeOH	O_3 CH_2Cl_2	*m*-$ClC_6H_4CO_3H$ CH_2Cl_2	H_2O_2 CH_3COOH	$PhICl_2$[8] pyridine/H_2O
Yield, %	~100	~90	~100	~100	~100
8C/**8T**	90/10	90/10	85/15	80/20	55/45

Scheme **III**



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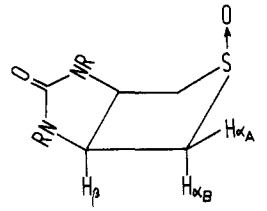


$^3J_{H_{\alpha_A}H_\beta} \sim 0$ Hz

$^2J_{H_{\alpha_A}H_{\alpha_B}}$ = 14.5 (R = A)
= 14.8 (R = B)

Figure 1. Conformation of **8T**.

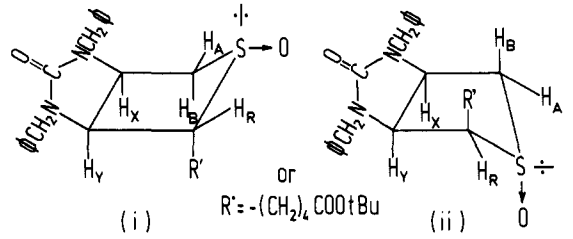


Figure 2. The two possible conformations of **9B**.

Sodium metaperiodate and ozone are the best reagents, but as ozone is more difficult to control, we chose the first method and obtained the two sulfoxides in a 90/10 ratio both with R = benzyl and with R = allyl.

The configuration of the minor isomer **8T** was readily established. Its NMR spectrum shows a zero coupling constant between H_β and one of the H_α protons. We had observed the same feature, in previous studies, for the sulfoxides of biotin and of some thiophane derivatives of related geometry.[9] We concluded, after a careful conformational analysis, that the envelope conformation, represented in Figure 1, was the only one where this was possible (dihedral angle $H_{\alpha_A}H_\beta \sim 90°$).

The conformation of **8T** is thus established and the configuration at sulfur can be deduced from the NMR data. As shown by our previous work,[9] the J_{gem} of an α-methylene group is a very reliable criterion. It is different for an axial and an equatorial sulfoxide, 14.5-15 and 13-13.5 Hz, respectively.

The observed value in **8T** proves that the sulfoxide is axial. This is confirmed by benzene-induced shifts. The H_{α_B} protons (those which are coupled with the H_β proton) are shielded by 1.04 ppm whereas H_{α_A} are shielded by only 0.4 ppm (Table II[31]).

Therefore, in **8T** and **8C**,[10] the S→O bond is respectively trans and cis to the junction hydrogens. According to the expected course of the alkylation (trans to the S→O bond), isomer **8C**, which had to be used to introduce the side chain with the correct orientation, was fortunately the predominant one.

Alkylation of Sulfoxide 8C. The alkylation was first classically carried out in tetrahydrofuran, the carbanion being generated with butyllithium, at −78 °C, and then treated with *tert*-butyl ω-iodovalerate at −30 °C.[11]

Whatever the alkylating agent we always obtained a single isomer as shown by NMR on the crude product. A careful NMR study carried out on **9B** proved the configuration of the side chain:[12] a W coupling constant is observed between H_R and H_A ($^4J_{H_RH_A} \sim 1.5$ Hz). Hence these protons are equatorial and the two possible structures are represented in Figure 2.

The value of $^2J_{H_AH_B}$ (14-15 Hz) indicates an axial sulfoxide and allows the choice of the ii configuration where the valerate chain is trans to the S→O bond. This result was confirmed by the Eu(dpm)$_3$-induced shifts: the H_A, H_R, H_X, and H_Y protons cis to S→O were strongly deshielded while the trans H_B proton was much less shifted (Table II[31]).

In the first experiments, with R = B, carried out with butyllithium in THF, the alkylation yield did not exceed 30%. Along with the starting material always present (~20-25%) a monoelimination product **11** and dibenzylurea (**12**) were isolated (Scheme III).

The structure of **11** was deduced from its mass spectrum (chemical ionization, $MH^+ = 399$) and NMR spectrum (one vinyl group; four protons highly deshielded, 2.72 and 3.11 ppm (α to S→O)). Its formation results from an attack at sulfur by butyllithium followed by a β-elimination reaction (or via a concerted process). This was rather unusual since substitution at sulfur by butyllithium was only mentioned for aryl alkyl sulfoxides[13] and the expected side reaction was the β-elimination from the α carbanion.

As shown by Durst et al.,[13] this reaction at sulfur does not take place with methyllithium. Indeed, using this base prepared according to Waack et al.,[14] it is possible to generate quantitatively the carbanion[15] and no elimination is observed for several hours at −30 °C. The carbanion was then alkylated with 5 equiv[16] of *tert*-butyl ω-iodovalerate and the solution was allowed to stir between −30 and −25 °C for 3 h.

The reaction was carried out in the presence of *o*-phenanthroline[17] (which gives a deep red color with α-lithio sulfoxides) and we considered that it was completed when the mixture turned to orange yellow.

After workup, a mixture of alkylated product **9B** and starting material **8BC** in a ratio of 58/42 was recovered. The starting material came neither from an incomplete formation of the carbanion[15] nor from an incomplete alkylation reaction, since by quenching with D_2O, no deuterium was incorporated either in **9B** or in **8BC**. It must arise from a reprotonation reaction, competitive with the alkylation, the proton source being the solvent[18] or the alkylating agent. When **8BC** was reacted with methyllithium in THF-d_8 for 3 h, at −30 °C, and then quenched with H_2O, it incorporated only 0.1 D. This proves that the protons come essentially from the valerate which is probably enolized by the carbanion.[19]

When the electrophile is methyl iodide, the alkylation yield is much higher (Table III). This was expected since it cannot be a proton donor and its smaller size favors alkylation.

To improve the yield of alkylation with the valerate side chain, two parameters were taken into consideration, namely, the leaving group and the solvent. The leaving group could not be widely varied. The bromide and the iodide gave about the same result. The mesylate and the tosylate cannot be used. As

Table III. Influence of the Nature of the Electrophile and of the Solvent on the Alkylation Yield[a]

Electrophile	Solvent			
	THF	Diglyme	THE + HMPA (2.5/1)	Diglyme + HMPA (6/1.5)
$I(CH_2)_4COO$-*t*-Bu	58/42	39/61	20/80	12/88
8BC/9B	3 h	3 h	1 h	1 h
ICH_3	17/72[b]	6/94[c]		
8BC/18B	1 h	1 h		

[a] The alkylations were carried out at −30 °C. The time for completion of the reaction was either 3 h or 1 h as indicated. Proportions of purified compounds are given, the total recovery, after chromatography, being about 90–95%. [b] As we used 1.25 equiv of methyllithium we obtained a *cis*-α,α'-dimethyl sulfoxide in 11% yield. [c] Only 1 equiv of methyllithium was used.

shown by Truce et al.[20] mesylates react with alkyllithium to yield an α carbanion and we have observed that methyl *p*-toluenesulfonate is quantitatively metalated by butyllithium, at −78 °C, at the ortho position. On the other hand, the solvent plays an important role and the addition of HMPA solved the problem. By adding it to THF or diglyme the yield of **9B** is improved respectively from 42% to 80% or from 61% to 88%. The reaction rate is also enhanced (Table III).

Transformation of the Alkylated Sulfoxide into Biotin

The sulfoxide **9** was easily reduced, either with triphenylphosphine in CCl_4[21] or with titanium(III) chloride in methanol-$CHCl_3$.[22,23]

Debenzylation. After hydrolysis of the *tert*-butyl ester in acidic medium debenzylation was effected by refluxing the acid for 3 h in 48% aqueous hydrobromic acid, yielding *dl*-biotin.[5] The other products are monobenzylbiotin, which can be recycled, and the diamino acid coming from the hydrolysis of the urea ring which can be recyclized with phosgene. The total yield is about 50%.

Deallylation. The allyl group has been widely used as an alcohol protecting group and mild conditions have been found to isomerize the allyl ethers into enol ethers which are then easily hydrolyzed. The isomerization of allylamines has been much less studied and we have investigated the scope of this reaction with different catalysts.[24] In the case of compound **10A,** we found that the best one was $(Ph_3P)_3RhCl$, in a benzene-water mixture.[25] The isomerization sometimes stops in a not very reproducible way,[27] but the minimal yield in dipropenylbiotin methyl ester is at least 40% and it is easily separated from the accompanying starting material **10A,** which is recycled. The dipropenyl derivative is then smoothly and quantitatively hydrolyzed into *dl*-biotin.

Preparation of Biotin Analogues

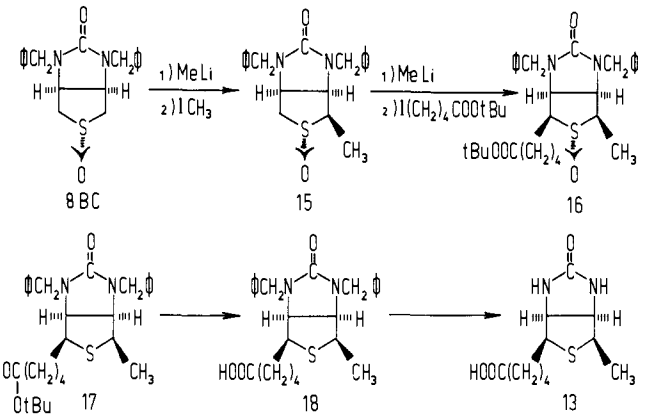
As was mentioned above, this synthesis is very well adapted to the preparation of biotin analogues since the key intermediate sulfoxide can be alkylated by a variety of side chains. We can also introduce other substituents at the α' position of the thiophane ring, taking advantage of the high regioselectivity of the alkylation of sulfoxides, observed in our model studies with thiane oxides.[4b] As the configuration at sulfur can be easily inverted by Meerwein's salt[28] a great number of compounds can thus be obtained. This is illustrated by the synthesis of the isomeric 5-methylbiotins **13** and **14.**

Synthesis of 13 is described in Scheme IV.

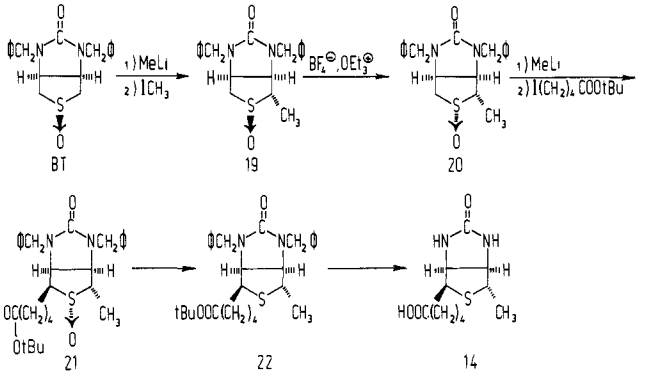
The sulfoxide **8BC** was reacted in THF with 1 equiv of methyllithium and then with methyl iodide to give only one methylated isomer **15** (84%) along with 10% of the initial sulfoxide. The NMR considerations used in the case of **9B** confirmed that the structure was the expected one, methyl trans to the sulfoxide (Table IV[31]).

Alkylation of **15** with *tert*-butyl ω-iodovalerate gave also one dialkylated sulfoxide **16** (57%) and **15** was recovered (31%). The pseudosymmetry of the NMR spectrum of **16**

Scheme IV



Scheme V



(Table IV[31]) implies that both substituents are cis. The alkylation stereochemistry is always identical.

This dialkylated sulfoxide **16** was then reduced with $TiCl_3$, hydrolyzed, and debenzylated as previously described to yield the α'-methylbiotin **13.**

Synthesis of 14 is described in Scheme V. To introduce a methyl cis to the junction hydrogens, it was necessary to methylate the minor isomer **8BT.** Once again, a single isomer **19** was produced (75%) and **8BT** was recovered (10%). The NMR data of **19** indicate that there are two protons cis to the S→O bond, less shielded in benzene, but more deshielded by $Eu(dpm)_3$ than the third one.

To introduce the valeric chain with the natural stereochemistry the configuration at sulfur had first to be inverted. The sulfoxide **19** was reacted with Meerwein's salt to yield **20,** which was alkylated by *tert*-butyl ω-iodovalerate. The dialkylated sulfoxide **21** was obtained (67%) together with 14% of the initial sulfoxide **20.** The NMR studies showed that the two protons α to the S→O bond are not geminal; their different chemical shifts in $CDCl_3$, in C_6D_6, or with $Eu(dpm)_3$ proved that these two substituents were trans to each other. By the same reactions we obtained the α'-methylbiotin **14.**

Conformational Analysis of 13 and 14

The conformation of biotin in the solid state, found by x-ray analysis, is represented in Figure 3.[29] NMR studies[9] have shown that in solution the thiophane ring has the same conformation characterized by a very small coupling constant between H_A and H_X. The *trans*-methylbiotin (**14**), which exhibits the same coupling pattern, has the same conformation (Table V[31]).

The analysis of the spectrum of **13** is more difficult since there are no protons trans to the junction hydrogens. But as the introduction of an axial methyl group in **14** does not perturb the conformation, the same is a fortiori true in **13** where the methyl is equatorial.

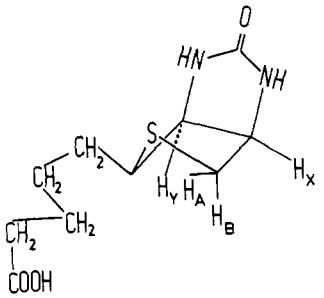


Figure 3. The conformation of biotin.

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. NMR spectra were recorded on a HA-100 spectrometer using tetramethylsilane as the internal reference. The results are given: δ ppm, multiplicity, protons number, J. Mass spectra were obtained with an AEI MS 30 mass spectrometer. Elemental analysis were performed by the C.N.R.S. Central Microanalysis Laboratory.

Dibenzylaminosuccinic Acid (2B).[5] To a refluxing solution of 30 g of dibromosuccinic acid (**1**) in 200 mL of ethanol was added, in 30 min, 90 mL of benzylamine. The reaction mixture was refluxed for 6 h and then cooled. After acidification with 30 mL of hydrochloric acid, 5 mL of acetic acid, and 50 mL of water, the residue was filtered and washed with water to afford 32.4 g of the diacid **2B**, mp 260–270 °C dec (lit.[5] 224–225 °C).

Diallylaminosuccinic Acid (2A). Following the procedure outlined for **2B**, the reaction of 30 g of dibromosuccinic acid (**1**) and 35 mL of diallylamine gave the diacid **2A**, 18 g, mp 270 °C dec.

1,3-Dibenzyl-4,5-*cis*-dicarboxylic Acid 2-Imidazolidone (3B).[5] To a solution of 32.4 g of the diacid **2B** in 100 mL of 3 N potassium hydroxide were added dropwise, in 35 min, at 0 °C, simultaneously through two funnels, 100 mL of a 5.3 M phosgene solution in toluene and 150 mL of 6 N KOH. After acidification by hydrochloric acid the residue was filtered and washed with water and then with hot ethanol. The residue was pure starting material **2B**, 7.4 g (20%). The aqueous solution was extracted with ethyl acetate to afford 1.2 g of the diacid **3B**. The evaporation of ethanol gave 23.6 g of the diacid **3B** (total yield 76%).

1,3-Diallyl-4,5-*cis*-dicarboxylic Acid 2-Imidazolidone (3A). To a solution of 10 g of diacid **2A** in 50 mL of 3 N KOH were added, dropwise, in 2 h, at 0 °C, simultaneously through two funnels, 100 mL of a 6 M phosgene solution in toluene and 100 mL of 6 N KOH. After acidification by HCl the residue was filtered and washed with water. The aqueous solution, previously saturated by sodium chloride, was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and evaporated to afford 9.1 g of the diacid **3A** (82%), recrystallized from methanol–chloroform, mp 150–152 °C.

1,3-Dibenzyl-4,5-*cis*-dicarbomethoxy-2-imidazolidone (4B). Method A. The diacid **3B** (4.6 g), previously dried with benzene, was dissolved in 46 mL of 1,2-dichloroethane, 15 mL of methanol, and 0.46 mL of sulfuric acid. The reaction mixture was refluxed for 17 h and then cooled. After addition of 100 mL of dichloromethane the mixture was extracted three times with 2 N sodium hydroxide and three times with water. The organic phase was dried (Na_2SO_4) and evaporated to afford 4 g of the diester **4B** (80%), recrystallized from methanol–water, mp 116 °C. The aqueous layers, after acidification by hydrochloric acid, were extracted by dichloromethane. Usual workup gave 640 mg of starting material **3B** (16%).

Method B. The diacid **3B** (2.2 g), dried with benzene, was dissolved in 40 mL of dry CH_3OH and 4 mL of $BF_3{\cdot}Et_2O$. The mixture was refluxed for 17 h; after cooling, water was added. The mixture was then extracted with dichloromethane. The organic layer was dried and evaporated to afford 2.3 g of the diester **4B** (97%). Anal. ($C_{21}H_{22}O_5N_2$) C, H, N. NMR ($CDCl_3$) δ 3.70, s, 6 H; 4.15; s, 2 H; 4.15 and 5.05, AB, 4 H, J = 15 Hz; 7.2, s, 10 H.

1,3-Diallyl-4,5-*cis*-dicarbomethoxy-2-imidazolidone (4A). Following the method B outlined for **4B**, the reaction of 3.1 g of **3A** gave 3.4 g of **4A** (98%), bp 205 °C (0.4 mm). Anal. ($C_{13}H_{18}N_2O_5$) C, H, N. NMR ($CDCl_3$) δ 3.75, s, 6 H; 4.05–4.4, m, 4 H; 4.9–6.1, m, 6 H.

1,3-Dibenzyl-4,5-*cis*-bis(hydroxymethyl)-2-imidazolidone (5B). A solution of the diester **4B** (10 g) in 150 mL of a 1/1 mixture of tetrahydrofuran–ether was added dropwise to a suspension, at 0 °C, of lithium aluminum hydride (5 g) in 100 mL of ether. The mixture was further stirred for 1 h at room temperature and poured, carefully, into 150 mL of 4 N HCl at 0 °C. The reaction mixture was then extracted with dichloromethane; the organic layer was dried and evaporated to afford 8.35 g of the diol **5B** (98%), recrystallized from dichloromethane–ether, mp 130 °C. Anal. ($C_{19}H_{22}N_2O_3$) C, H, N. NMR (Me_2SO) δ 3.4, m, 4 H; 3.6, m, 2 H; 4.15 and 4.80, AB, 4 H, J = 15 Hz; 7.4, s, 10 H.

1,3-Diallyl-4,5-*cis*-bis(hydroxymethyl)-2-imidazolidone (5A). To a solution of the diester **4A** (1.21 g) in 30 mL of ether was added, with vigorous stirring, 4.9 mL of a titrated ethereal $LiAlH_4$ solution (1.1 M). The mixture was stirred for 3 h and then hydrolyzed with ethyl acetate. The precipitate was filtered and washed with ethyl acetate. Removal of the solvent gave an oil (940 mg) which was purified by PLC (AcOEt) to yield 475 mg of the diol **5A** (46%) and 210 mg of a lactol which could be further reduced, following the same procedure, to afford the diol **5A** (36% after PLC). Diol **5A**, bp ~190 °C (0.35 mm). NMR ($CDCl_3$) δ 3.60 and 4.10, AB, 4 H, J = 15 Hz; 3.60–3.90, m, 8 H; 5.18, m, 4 H; 5.71, m, 2 H. Lactol, bp ~210 °C (0.7 mm). NMR ($CDCl_3$) δ 3.45–4.25, m, 9 H; 5.20, m, 4 H; 5.40, s, 1 H; 5.70, m, 2 H. Mass spectrum *m/e* 224 (M^+).

1,3-Dibenzyl-4,5-*cis*-bis(mesyloxymethyl)-2-imidazolidone (6B). To a solution of the diol **5B** (15 g) in 300 mL of dichloromethane and 30 mL of triethylamine, at 0 °C, was added, in 15 min, 10.5 mL of mesyl chloride. After stirring for an additional 20 min, at room temperature, dichloromethane was added. The organic layer was washed three times with 2 N HCl, with water, with 5% $NaCO_3H$, and then with water and then dried (Na_2SO_4) and evaporated to afford 21.2 g of the dimesylate **6B** (95%), recrystallized from dichloromethane–ether, mp 144 °C. Anal. ($C_{21}H_{26}N_2O_7S_2$) C, H, N. NMR ($CDCl_3$) δ 2.82, s, 6 H; 3.79, m, 4 H; 4.32, m, 2 H; 4.15 and 4.75, AB, 4 H, J = 15 Hz; 7.2, s, 10 H.

1,3-Diallyl-4,5-*cis*-bis(mesyloxymethyl)-2-imidazolidone (6A). The diol **5A** was mesylated following the procedure described for **6B**. The reaction of 1.13 g of the diol **5A** gave 1.7 g of **6A** (95%), recrystallized from ethyl acetate–ether, mp 85–86 °C. Anal. ($C_{13}H_{22}N_2O_7S_2$) C, H, N. NMR ($CDCl_3$) δ 3.05 s, 6 H; 3.60 and 4.20, AB, 4 H, J = 6 Hz; 4.00, m, 2 H; 4.40, m, 4 H; 5.10, m, 4 H; 5.70, m, 2 H.

3,4-(1,3-Dibenzyl-2-oxoimidazolido)thiophane (7B). To a solution of sodium sulfide (8 g), freshly crystallized from ethanol and dried under vacuum, was added, dropwise, the dimesylate **6B** (10 g) in 100 mL of ethanol. The mixture was then refluxed for 3 h and cooled. After addition of dichloromethane, the organic layer was washed with water and then dried (Na_2SO_4) and evaporated to afford 6.4 g of the sulfide **7B** (95%), recrystallized from dichloromethane–ether, mp 125 °C. Anal. ($C_{19}H_{20}N_2OS$) C, H, N. NMR ($CDCl_3$) δ 2.66–2.70, m, 4 H; 3.95, m, 2 H; 4.15 and 4.70, AB, 4 H, J = 15 Hz; 7.2, s, 10 H. NMR (C_6D_6) δ 2.08, m, 2 H; 2.32, m, 2 H, J = 12.5 Hz; 3.36, m, 2 H; 3.89 and 4.59, AB, 4 H, J = 15 Hz.

3,4-(1,3-Diallyl-2-oxoimidazolido)thiophane (7A). Following the method outlined for **7B**, the reaction of 6.9 g of the dimesylate **6A** gave 3.4 g of the sulfide **7A** (86%), recrystallized from ether-hexane, mp 57–58 °C. Anal. ($C_{11}H_{16}N_2OS$) C, H, N. NMR ($CDCl_3$) δ 2.87, m, 4 H; 3.65 and 4.07, AB, 4 H, J = 15 Hz; 4.21 m, 2 H; 5.22, m, 4 H; 5.70, m, 2 H.

3,4-(1,3-Dibenzyl-2-oxoimidazolido)thiophane Oxides (8BC and 8BT). The sulfide **7B** was oxidized by $NaIO_4$, O_3, H_2O_2, and $PhICl_2$ according to the methods described previously.[7,8] The two sulfoxides

were separated by PLC (C_6H_6-CH_3COCH_3-MeOH, 8/1/1) or column chromatography (AcOEt-MeOH, 8.5/1.5), and recrystallized from dichloromethane-ether: **8BC**, mp 151 °C; **8BT**, mp 216 °C. Anal. ($C_{19}H_{20}N_2O_2S$) C, H, N.

3,4-(1,3-Diallyl-2-oxoimidazolido)thiophane Oxides (8AC and 8AT). To a solution of 1 g of sodium periodate in 35 mL of water was added dropwise, at 0 °C, a solution of 960 mg of the sulfide **7A** in 40 mL of methanol. The mixture was further stirred for 17 h at 5 °C. The methanol was evaporated at room temperature and the residue was extracted with dichloromethane after saturation with sodium chloride. The organic layer was dried and evaporated to afford 990 mg of the two sulfoxides which were separated by chromatography (AcOEt-MeOH, 9/1) to give 736 mg of **8AC** and 75 mg of **8AT**, recrystallized from ethyl acetate-hexane: **8AC**, mp 88 °C; **8AT**, mp 127 °C. Anal. ($C_{11}H_{16}N_2O_2S$) C, H, N.

***tert*-Butyl ω-Iodovalerate.** Bromovaleric acid[30] (29 g) and sodium iodide (51 g) in 300 mL of acetone were refluxed for 17 h. The acetone was evaporated and the residue was dissolved in ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give 34 g of ω-iodovaleric acid (93%), recrystallized from ether-hexane, mp 58-59 °C. To a solution of this iodide (10 g) in 50 mL of ether were added, at 0 °C, 25 mL of isobutylene and 0.8 mL of sulfuric acid. After 48 h, the mixture was extracted three times by 2 N sodium hydroxide and three times with water. The organic phase was dried and evaporated to afford 10 g of *tert*-butyl ω-iodovalerate (80%). The aqueous layers, after acidification by HCl, were extracted by ether. Usual workup gave 1.5 g of the starting iodovaleric acid (15%).

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazolido)thiophane Oxide (9B). All reactions involving organolithium reagents are carried out under argon atmosphere and all the reagents are introduced with a syringe through a rubber stopper.

To a solution, containing a trace of *o*-phenanthroline, of sulfoxide **8BC** (340 mg, 1 mmol), dried with benzene, in 5 mL of THF (*or* in 8 mL of diglyme *or* in the mixture of 2.5 mL of THF, 1 mL of HMPA *or* 6 mL of diglyme, 1.5 mL of HMPA) was added, at −78 °C, 1.25 equiv of methyllithium in THF (1.6 M). A deep red coloration and a methane evolution were immediately observed. After 15 min, 5 equiv of *tert*-butyl ω-iodovalerate was added dropwise and the temperature was raised to −30 °C. The solution was stirred at −30 °C until decoloration from red to orange yellow. After addition of water the mixture was extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and then evaporated to dryness (diglyme was evaporated at 60 °C, 5 mm). The crude oil was purified by PLC (benzene-acetone-methanol, 8/1/1), and the excess of valerate, the alkylated sulfoxide **9B**, and the initial sulfoxide **8BC** were separated. Recrystallization from dichloromethane-ether gave mp 105 °C. Anal. ($C_{28}H_{36}N_2O_4S$) C, H, N.

Elimination Product 11. To a solution of **8BC** (340 mg) in 5 mL of dry THF, at −78 °C, was added 1 equiv of butyllithium in hexane (1.6 M). The solution was stirred for 1 h, at −78 °C, and then hydrolyzed by water. The mixture was extracted by dichloromethane, and the organic layer was washed, dried, and then evaporated to afford 340 mg of an oil which was purified by PLC (C_6H_6-CH_3COCH_3-MeOH, 8/1/1) to give the sulfoxide **8BC** (220 mg) and the elimination product **11** as an oil (110 mg): mass spectrum (chemical ionization) MH^+, *m/e* 399 (100), 293 (59), 266 (32), 160 (26), 107 (12). NMR ($CDCl_3$) 0.93, t, 3 H; 1.47-1.68, m, 4 H; 2.72, m, 2 H; 3.11 m, 2 H; 4.31, m, 4 H; 4.95, m, 1 H; 5.31, m, 2 H; 6.07, m, 1 H; 7.2, s, 10 H.

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-diallyl-2-oxoimidazolido)thiophane Oxide (9A). Following the method described for **9B**, the reaction of 360 mg of **8AC** in 10 mL of diglyme with 1.1 equiv of methyllithium in THF (1.6 M) and then with 5 equiv of *tert*-butyl ω-iodovalerate gave 267 mg of the alkylated sulfoxide **9A** (45%) and 145 mg of the starting material **8AC** (40%), mass spectrum *m/e* 396 (M^+).

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazolido)thiophane (10B). Method A. A solution of the sulfoxide **9B** (700 mg) and triphenylphosphine (620 mg) in 28 mL of carbon tetrachloride was refluxed for 3 h and cooled. The mixture was extracted with dichloromethane, dried, and evaporated to afford an oil which was purified by PLC (AcOEt) to give triphenylphosphine oxide and 580 mg of sulfide **10B** (89%), recrystallized from ether-pentane, mp 94 °C.

Method B. A solution of the sulfoxide **9B** (498 mg) in 2 mL of methanol, 1 mL of chloroform, and 4 mL of a 15% aqueous solution of $TiCl_3$ was refluxed for 4 h. The mixture was extracted with dichloromethane, dried, and evaporated to give 430 mg of the sulfide **10B** (90%). Anal. ($C_{28}H_{36}N_2O_3S$) C, H, N. NMR ($CDCl_3$) δ 1.46, s, 9 H; 1.55, m, 6 H; 2.21, m, 2 H; 2.70, m, 2 H; 3.08, m, 1 H; 3.88, m, 2 H; 4.0-5.4, 2AB, 4 H, J = 15 Hz; 7.2, s, 10 H.

2-(4-Methoxycarbonylbutyl)-3,4-(1,3-diallyl-2-oxoimidazolido)thiophane (10A). Following method B outlined for **10B**, the solution of 1.545 g of sulfoxide **9A** in 8 mL of methanol, 4 mL of chloroform, and 16 mL of $TiCl_3$ was refluxed for 8 h. Usual workup gave a mixture of *tert*-butyl and methyl ester. This mixture was refluxed for 4 h in 10 mL of methanol and some drops of sulfuric acid to afford the pure methyl ester **10A** (1.03 g, 78%).

***dl*-Biotin. Debenzylation of 10B.** The *tert*-butyl ester (430 mg) was hydrolyzed by refluxing (6 h) in 5 mL of CH_3COOH and some drops of 4 N hydrochloric acid. Usual workup gave the acid (370 mg, 96%). Then the sulfide was debenzylated as previously described,[5] yield 50% of *d*-biotin isolated as its methyl ester, mp 128-130 °C.

Deallylation of 10A. A solution of the sulfide **10A** (50.7 mg), $RhCl(PPh_3)_3$ (10 mg), and Dabco (8.4 mg) in 6.75 mL of benzene and 0.75 mL of water (degassed solvents) was refluxed for 18 h under argon atmosphere. The solvents were evaporated and the residue was purified by PLC (ethyl acetate-hexane, 3/7) to afford the sulfide **10A** (19 mg) and the dipropenyl sulfide (22 mg): mass spectrum *m/e* 338 (M^+). NMR ($CDCl_3$) δ 1.2-1.9 m, 12 H (-(CH_2)$_3$$CH_2CO_2Me$; =CH$CH_3$); 2.2, t, 2 H (-$CH_2CO_2Me$); 2.5-3.5, m, 3 H ($CH_2SCHR$); 3.65, s, 3 H (-$OCH_3$); 4.35-5.15 m, 4 H (2 H junction, =$CH$$CH_3$); 6.65-6.8, m, 2 H (NCH=).

The dipropenyl sulfide (100 mg) dissolved in 15 mL of methanol and 2 mL of 4 N hydrochloric acid was stirred for 15 min at room temperature. The solvents were evaporated at 40 °C and, after extraction by dichloromethane, usual workup gave the *dl*-biotin isolated as its methyl ester (54 mg, 75%), mp 128-130 °C.

3,4-(1,3-Dibenzyl-2-oxoimidazolido)-5-methylthiophane Oxide (15). Following the procedure previously described for **9B**, to a solution containing a trace of *o*-phenanthroline and 2.04 g of sulfoxide **8BC**, dried with benzene, in 60 mL of diglyme was added, at −78 °C, 1 equiv of methyllithium in THF (1.6 M). After 15 min, 5 equiv of methyl iodide was added and the temperature was raised to −30 °C. The solution was stirred at −30 °C for 1 h. Usual workup gave 0.23 g of sulfoxide **8BC** (10%) and 1.78 g of sulfoxide **15** (84%). Recrystallization from dichloromethanemethane-ether gave mp 120 °C. Anal. ($C_{20}H_{22}N_2O_2S$) C, H, N.

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazolido)-5-methylthiophane Oxide (16). Following the procedure previously described for **9B**, reaction of 726 mg of sulfoxide **15** in 20 mL of diglyme gave, after 5 h at −30 °C, 584 mg of sulfoxide **16** (57%) and 228 mg of sulfoxide **15** (31%).

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazolido)-5-methylthiophane (17). Following method B outlined for **10B**, the solution of 360 mg of sulfoxide **16** in 2.8 mL of methanol, 1.5 mL of chloroform, and 3 mL of $TiCl_3$ was refluxed for 4.5 h. Usual workup gave 115 mg of the sulfoxide **16** and 215 mg of the sulfide **17**.

α′-Methylbiotin (13). Following the method described for *dl*-biotin, the *tert*-butyl ester **17** was hydrolyzed by refluxing (4.5 h) in acetic acid and some drops of 4 N hydrochloric acid. The acid **18** (350 mg) was refluxed for 3.5 h in 5 mL of 48% hydrobromic acid at 125 °C and HBr was eliminated by several distillations of water (15 mm). The mixture was washed with dichloromethane and the residue recrystallized in water to give 65 mg of α′-methylbiotin **13** (25%): mp 260 °C; mass spectrum *m/e* 258 (M^+). NMR (D_2O-Na_2CO_3) δ 1.59, d, 3 H, J = 7 Hz; 3.74, m, 2 H; 4.76, m, 2 H.

3,4-(1,3-Dibenzyl-2-oxoimidazolido)-5-methylthiophane Oxide (19). Following the procedure previously described for **15** and **9B**, the reaction of 1.02 g of sulfoxide **8BT** in 120 mL of diglyme gave (1.5 h at −30 °C) 0.105 g of the sulfoxide 8BT (10%) and 0.793 g of the sulfoxide **19** (75%). Recrystallization from dichloromethane-ether gave mp 172 °C. Anal. ($C_{20}H_{22}N_2O_2S$) C, H, N.

3,4-(1,3-Dibenzyl-2-oxoimidazolido)-5-methylthiophane Oxide (20). To a solution of 0.69 g of triethyloxonium tetrafluoroborate in 5 mL of dry dichloromethane, 1.068 g of sulfoxide **19** in 10 mL of dry CH_2cl_2 was added. the solution was stirred for 2 h at room temperature and then a solution of 1 N KOH was added. The mixture was extracted with dichloromethane. Usual workup gave 1.084 g which was purified by PLC (benzene-acetone-methanol, 8/1/1) to afford the sulfoxide **20** (0.65 g). Recrystallization from dichloromethane-ether gave mp 150 °C. Anal. ($C_{20}H_{22}N_2O_2S$) C, H, N.

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazol-

ido)-5-methylthiophane Oxide (21). Following the procedure previously described for **9B,** the reaction of 1.06 g of **20** in 60 mL of diglyme gave, after 3 h at −30 °C, 0.15 g of sulfoxide **20** (14%) and 1.04 g of sulfoxide **21** (67%). Recrystallization from ether–hexane gave mp 92 °C. Anal. ($C_{29}H_{28}N_2O_4S$) C, H, N.

2-(4-*tert*-Butoxycarbonylbutyl)-3,4-(1,3-dibenzyl-2-oxoimidazolido)-5-methylthiophane (22). Following method B outlined for **10B,** the solution of 550 mg of sulfoxide **21** in 3.5 mL of methanol, 1.2 mL of chloroform, and 8 mL of $TiCl_3$ was refluxed for 18 h to give a mixture of *tert*-butyl ester sulfide **22** and of the corresponding methyl ester (~50%) and 237 mg of sulfoxide **21.**

α′-Methylbiotin (14). Following the procedure described for *dl*-biotin, after hydrolysis of the ester and debenzylation **14** was obtained. Recrystallization from methanol gave mp ~240 °C. Anal. ($C_{11}H_{18}N_2O_3S$) C, H, N. NMR (D_2O–Na_2CO_3) δ 1.67, d, 3 H, J = 7 Hz; 3.58, q, 1 H, J = 7 Hz; 3.98, m, 1 H; 4.59, d, 1 H, J_{XY} = 8–9 Hz; 4.87, m, 1 H.

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Supplementary Material Available: A listing of NMR data concerning compounds **8C, 8T,** and **9** (Table II), **15, 16, 19, 20,** and **21** (Table IV), and **13** and **14** (Table V) (3 pages). Ordering information is given on any current masthead page.

References and Notes

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(10) The conformation of **8C** is more difficult to determine since the two $H_\alpha H_\beta$ coupling constants are of the same order of magnitude. As it is not necessary to have another proof of configuration, this point is not discussed.
(11) It is necessary to use a *tert*-butyl ester to prevent the addition of the lithiated sulfoxide on the ester group. Thus, if the alkylation is carried out with methyl ω-iodovalerate or methyl *tert*-butylglutarate the methyl esters are selectively attacked giving respectively the $I(CH_2)_4CO$– and *t*-$BuOCO(CH_2)_3CO$– side chains.
(12) With **9A,** analysis of the NMR spectrum did not allow such a conclusion (no detectable W coupling between H_R and H_A; overlap with allyl groups signals). But, as expected the side chain has the same orientation, as shown by the final transformation into *dl*-biotin.
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