A Practical Synthesis of (+)-Biotin from L-Cysteine

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Abstract: α-Amino aldehyde **4**, which is readily derived from L-cysteine through cyclization and elaboration of the carboxy group, was subjected to the Strecker reaction, which, via sodium bisulfite adduct **16**, afforded α-amino nitrile **5** with high diastereoselectivity (*syn*/*anti* = 11:1) and in high yield. Amide **6**, derived from **5**, was converted to thiolactone **8**, a key intermediate in the synthesis of (+)-biotin (**1**), by a novel *S*,*N*-carbonyl migration and cyclization reaction. The Fukuyama coupling reaction of **8** with the zinc reagent **21**, which has an ester group, in the presence of a heterogeneous Pd/C catalyst allowed the efficient installation of the 4-carboxybutyl chain to provide **9**. Compound **9** was hydrogenated and the protecting groups removed to furnish **1** in 10 steps and in 34% overall yield from L-cysteine.

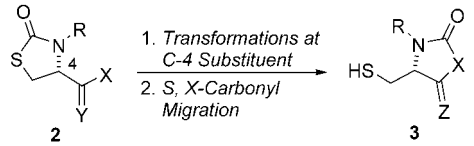
Keywords: amino acids · organozinc compounds · Strecker synthesis · total synthesis · vitamins

Introduction

(+)-Biotin (**1**) has recently induced intense research activity owing to its important biological role in human nutrition and animal health.[1] Because **1** cannot be produced efficiently by a fermentation approach,[2] the vast amount of **1** required throughout the world, that is, more than 80 ton per year, is said to be produced by a totally synthetic method. Of the synthetic approaches to **1**,[3] the Goldberg and Sternbach approach,[4] which was established about 50 years ago, is considered to be the most efficient one hitherto accomplished. While the Goldberg and Sternbach approach has been thoroughly optimized for many years, it has some fundamental drawbacks: 1) it is a multistep synthesis (more than 14 steps), 2) the use of toxic reagents and intermediates is necessary, and 3) it involves theoretically impractical diastereomeric or enzymatic resolution of racemic materials. To overcome these problems, we initially developed a synthetic method that involves L-cysteine as the starting material.[5] Although we attempted to scale up this method for industrial large-scale production, it failed because a low temperature, −20 °C, was needed. In addition, from the view point of atom economy,[6] the use of bulky *tert*-butyloxycarbonyl (*t*Boc) and benzylidene acetal to protect the cysteine derivatives is not satisfactory.

(+)-Biotin (**1**) L-Cysteine

In view of the need to eliminate the use of bulky protecting groups and to decrease the number of steps required for the protection-deprotection sequence, we sought to develop a novel protecting group for cysteine derivatives. We envisioned the possible use of 2-thiazolidinone derivatives **2** for protecting cysteine derivatives (Scheme 1). Compound **2**, which has a thiocarbamate group within the molecule, might be sufficiently stable to allow transformations at the C-4 substituent. After the transformations, if the relative hardness[7] of the carbonyl group is closer to the X atom (N, O, etc) than to the sulfur atom, *S*,*X*-carbonyl migration should



2 **3**

Scheme 1. A novel protecting group for L-cysteine derivatives.

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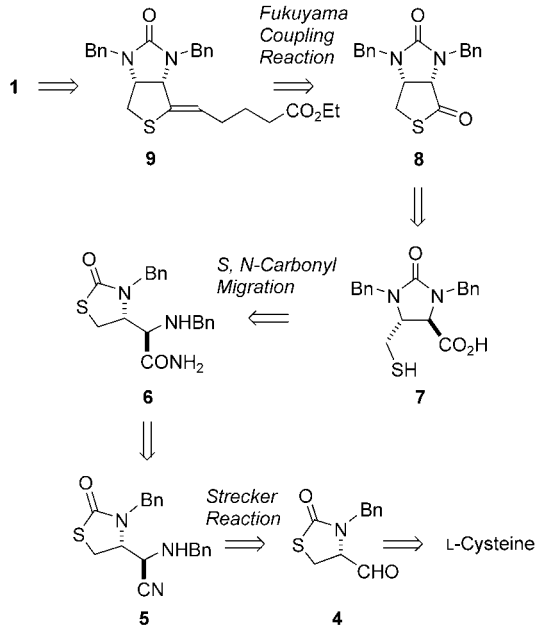
take place upon heating to readily liberate the thiol group (**2**→**3**). We therefore considered a route to biotin that involves this novel protecting surrogate.[8]

It was planned that the stereogenic centers of **1** would be established by the Strecker reaction of α-amino aldehyde **4** derived from L-cysteine (Scheme 2). Then, upon heating,



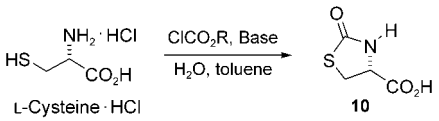
Scheme 2. Synthetic scheme for (+)-biotin from L-cysteine.

amide **6**, derived from **4**, should undergo *S*,*N*-carbonyl migration, and subsequent acid hydrolysis might provide the thiol carboxylic acid **7**. Thiolactone **8** obtained from **7** would then be subjected to Fukuyama coupling[9] with the zinc reagent, ethoxycarbonylbutylzinc iodide (**21**), which has an ester group, to give **9**, a precursor to **1**, in a highly efficient manner.

Results and Discussion

Synthesis of α-amino aldehyde 4: In our initial study, the synthesis of α-amino aldehyde **4** from L-cysteine was investigated. Treatment of L-cysteine hydrochloride with ethyl chloroformate in the presence of NaOH only led to a trace of (*R*)-2-oxothiazolidine-4-carboxylic acid **10** (Table 1, entry 1). The more reactive phenyl chloroformate was thus employed to effect the cyclization, which provided **10** in 96% yield, although the use of a weak base such as $NaHCO_3$ and Na_2CO_3 gave much lower yields (Table 1, entry 4 versus entries 2 and 3). A reduction in the amount of phenyl chloroformate from 2.2 to 1.2 equivalents and a decrease in the amount of NaOH from 5.0 to 3.5 equivalents combined with an increase in the reaction temperature from 20–30 to 40 °C had little effect on the reaction yield (Table 1, entry 5). However, when the time for the addition of the chloride was changed from 1 to 2 h, as might be required in a large-scale synthesis, the yield unexpectedly dropped to 69% (Table 1, entry 6). In this case the reaction was accompanied by the formation of diphenyl carbonate ($(PhO)_2CO$) by the reaction between phenyl chloroformate and the phenol generated by cyclization. A slight increase in the amount of phenyl chloroformate from 1.2 to 1.4 equiv was found to improve the yield dramatically (Table 1, entry 7).

Table 1. Synthesis of (*R*)-2-oxothiazolidine-4-carboxylic acid **10** from L-cysteine.

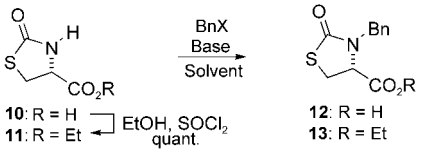


Entry	$ClCO_2R$ (equiv)	Base (equiv)	Addition time[a] [h]	*T* [°C]	Yield[b] [%]
1	$ClCO_2Et$ (2.2)	NaOH (5.0)	1	5–20	5
2	$ClCO_2Ph$ (2.2)	$NaHCO_3$ (5.0)	1	5–20	14
3	$ClCO_2Ph$ (2.2)	Na_2CO_3 (2.5)	1	5–20	32
4	$ClCO_2Ph$ (2.2)	NaOH (5.0)	1	20–30	96
5	$ClCO_2Ph$ (1.2)	NaOH (3.5)	1	40	94
6	$ClCO_2Ph$ (1.2)	NaOH (3.5)	2	40	69
7	$ClCO_2Ph$ (1.4)	NaOH (3.5)	2	40	98

[a] Time for the addition of $ClCO_2R$. After the addition, the mixture was further stirred at the indicated temperature for 1 h. [b] Assay yield.

With (*R*)-2-oxothiazolidine-4-carboxylic acid **10** in hand, we next tried to synthesize the *N*-benzyl derivative **12** by benzylation of the ester derivative **11**. Although the benzylation proceeded in high yield with benzyl bromide and K_2CO_3 in DMA (Table 2, entry 1), the use of corrosive benzyl bromide proved to be commercially unviable for the large-scale production of **12** and an alternative method, which employed benzyl chloride, had to be investigated. The use of benzyl chloride for the benzylation of **11**, however, resulted in some racemization (Table 2, entry 2). It was eventually found that the use of benzyl chloride in aqueous DMSO smoothly underwent selective *N*-benzylation of **10**

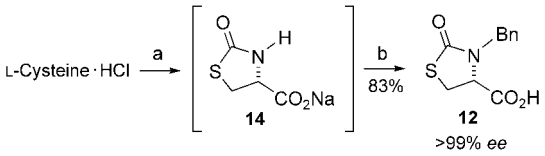
Table 2. Synthesis of *N*-benzyl-2-oxothiazolidine-4-carboxylic acid **12**.



Entry	R	BnX	Base	Solvent	*T* [°C]	*t* [h]	Yield[a] [%]	*ee* [%]
1	Et	BnBr	K_2CO_3	DMA	25	14	89	99
2	Et	BnCl	K_2CO_3	DMSO	25	2	60	81
3	H	BnCl	NaOH	CH_3CN/H_2O	25	21	trace	–[b]
4	H	BnCl	NaOH	DMF/H_2O	25	20	trace	–[b]
5	H	BnCl	NaOH	$DMSO/H_2O$	25	15	94	>99

[a] Assay yield. [b] Not determined.

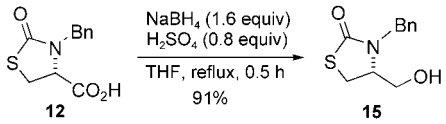
without converting to the ester derivative **11** (Table 2, entry 5). Note that the use of DMSO is essential and that the desired product was not obtained when either CH_3CN or DMF was used as the solvent (Table 2, entry 5 versus entries 3 and 4). The synthesis of **12** from L-cysteine was conveniently conducted in a one-pot procedure as shown in Scheme 3: compound **12** was synthesized in 83% yield by



Scheme 3. One-pot synthesis of **12** from L-cysteine. Reagents and conditions: a) $ClCO_2Ph$, NaOH, H_2O, toluene, 25°C, 2 h; b) to the aqueous phase were added BnCl, NaOH, DMSO, H_2O, 25°C, 15 h.

simple addition of benzyl chloride and NaOH to an aqueous solution of sodium (*R*)-2-oxothiazolidine-4-carboxylate **14**, which was prepared by the treatment of L-cysteine with phenyl chloroformate and NaOH in a mixture of water and toluene.

The synthesis of α-amino aldehyde **4** from **12** was then investigated. Because of the ready racemization of **4**, a synthetic scheme that involves the reduction of **12** followed by oxidation was examined. Although the reduction of the ester derivative **13** took place in high yield on treatment with $NaBH_4$ in EtOH, it was accompanied by considerable racemization (93% yield, 69% *ee*). Instead, the reduction of **12** with borane, generated in situ by treatment of $NaBH_4$ with H_2SO_4,[10] suppressed this racemization to give the desired alcohol **15** in 91% yield (Scheme 4).

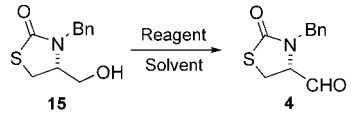


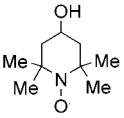
Scheme 4. Reduction of **12** to **15**.

The Swern or Corey–Kim oxidation of **15** was then conducted to give α-amino aldehyde **4** in high yields (Table 3, entries 1 and 2). However, as a temperature as low as −20 and −30°C cannot be applied in large-scale production, we investigated an alternative method and finally found that Moffatt oxidation,[11] which employs DCC in the presence of TFA, pyridine, and DMSO, provided **4** in 95% yield under industrially viable conditions, such as at 50°C (Table 3, entry 5). The oxidation of **15** by using the HO-TEMPO free radical,[12] which can be conducted under mild conditions, gave only a poor yield (Table 3, entry 3).

Construction of contiguous stereogenic centers: The amino aldehyde **4** was then treated with benzylamine followed by TMSCN to afford the *syn* isomer of α-amino nitrile **5** in high yield (Method A) (Table 4, entries 1–4). The *syn* selectivity largely depends on the nature of the solvent: the highest *syn* selectivity (*syn*/*anti* = 28:1) was achieved when toluene was used as the solvent (Table 4, entry 3).

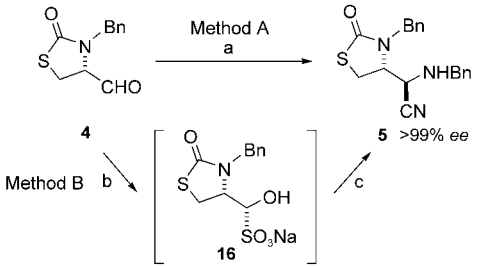
Table 3. Synthesis of 2-oxothiazolidine-4-carbaldehyde **4**.[a]



Entry	Reagent (equiv)	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]	*ee* [%]
1	$(COCl)_2$ (2.2) Et_3N(5)	DMSO/ CH_2Cl_2	−20 to −10	1	93	97
2	Cl_2 (2.2) DMS (4.8) Et_3N (5)	CH_2Cl_2	−30 to −20	1	93	>99
3	 (2 mol%)	CH_2Cl_2/H_2O	0	1	33	–[c]
4	DCC (1.5) H_3PO_4 (0.25) DMSO	toluene	50	3	74	99
5	DCC (1.2) TFA (0.2) pyridine (0.2) DMSO	AcOEt	50	3	95	>99

[a] DMS = dimethyl sulfide, DCC = 1,3-dicyclohexylcarbodiimide, DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid. [b] Assay yield. [c] Not determined.

Table 4. Synthesis[a] of α-amino nitrile **5**.



Entry	Method	Solvent	Yield [%][b]	*syn*/*anti*[c]
1	A	AcOEt	98	16:1
2	A	CH_2Cl_2	95	20:1
3	A	toluene	96	28:1
4	A	toluene/DMSO	94	7:1
5	B	AcOEt	quant.	11:1
6	B	CH_2Cl_2	quant.	11:1
7	B	toluene	quant.	11:1

[a] Reagents and conditions: a) 1) $BnNH_2$ (1.0 equiv), $MgSO_4$, 5–25°C, 3 h; 2) TMSCN (2 equiv), solvent, 0–25°C, 15 h; b) $NaHSO_3$ (1.1 equiv), AcOEt, H_2O, 20°C, 18 h; c) 1) $BnNH_2$ (1.7 equiv), CH_2Cl_2, 20°C, 2 h; 2) NaCN (1.2 equiv), 8–20°C, 20 h; 3) $NaHSO_3$ (0.3 equiv), NaCN (0.3 equiv), 20°C, 1.5 h. [b] Assay yield. [c] Determined by HPLC.

To avoid using the expensive TMSCN, we initially attempted to use HCN which was generated by the treatment of NaCN with acetic acid. However, the reaction was diffi-

cult to perform even in a laboratory-scale experiment owing to the difficulties of handling toxic and low-boiling HCN. In addition, there are serious drawbacks due to the chemical properties of **4**. The attempted purification of **4** by silica gel column chromatography resulted in considerable decomposition and racemization of the product. Taylor and Hauser reported that the Strecker reaction takes place with sodium bisulfite adducts of achiral aldehydes and inexpensive and easy-to-handle NaCN.[13a] We envisioned a possible use of this protocol for our diastereoselective synthesis of **5** by employing the chiral α-amino aldehyde **4** (Method B).[14] The solution of **4** in AcOEt obtained from the Moffatt oxidation of **15** was treated with aqueous sodium bisulfite (1.1 equiv) to give the water-soluble sodium bisulfite adduct **16** in 99% conversion and, as expected, a simple work up involving extraction and separation provided **16** which was pure enough to be used in the next step. The aqueous solution of **16** was then treated with benzylamine at 20°C for 2 h followed by NaCN (1.2 equiv) at 8°C and this mixture was stirred at ambient temperature for 20 h to provide α-amino nitrile **5** in high yield (*syn*/*anti* = 11:1, 95% yield based on **15**) (Table 4, entry 5). Although the diastereoselectivity of the reaction was unaffected by a change of solvent and poorer than was observed in the reactions that employed TMSCN, both *syn*-**5** and *anti*-**5** could be used for the subsequent transformation to (+)-biotin (vide infra). The ee value of **5** was confirmed to be >99% *ee* by HPLC analysis. Note that during the reaction the mixture was always basic and evolution of HCN gas in the reaction flask was much less than that observed in the reaction employing NaCN/AcOH.[15] The *syn* selectivity of the Strecker reaction may be accounted for by the Houk model shown in Figure 1.[16] Coordination of the hypervalent silicon or hydrogen atom to the imine nitrogen atom enables internal delivery of the cyanide to the imine from the opposite side of the bulky benzylamide group to provide *syn*-α-amino nitrile *syn*-**5** stereoselectively.

A CH_2Cl_2 solution of **5** was directly amidated by using

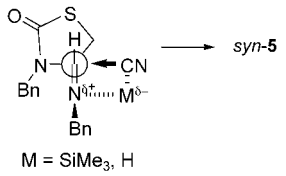
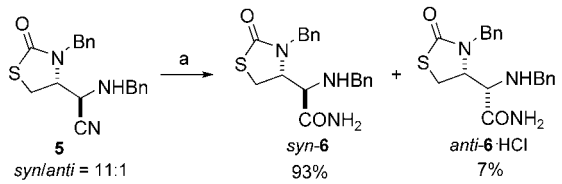


Figure 1. Proposed mechanism for the Strecker reaction of **4**.

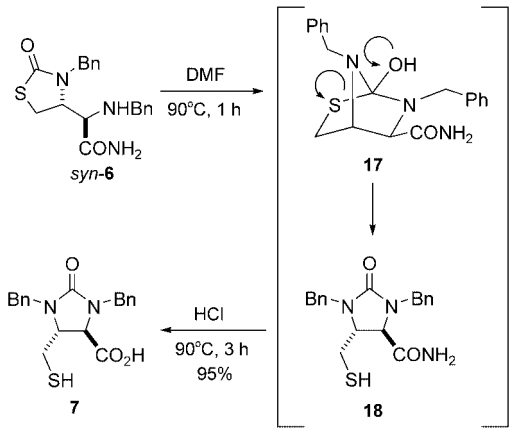
Katritzky's protocol,[17] which involves the use of H_2O_2, K_2CO_3, and DMSO (Scheme 5). The reaction proceeded smoothly, even in a mixture of DMSO and CH_2Cl_2, to afford the corresponding amide **6** in quantitative yield. Amide *syn*-**6** was obtained as a solid in 93% yield by just adding water to the reaction mixture followed by filtration and *anti*-**6** was isolated from the mother liquor as the hydrochloride salt in 7% yield (Scheme 5).

***S,N*-Carbonyl migration:** *S,N*-Carbonyl migration of amide **6** was the next subject of our investigation. As expected, when amide *syn*-**6** was heated to 90°C in DMF under a N_2 atmosphere,[18] *S,N*-carbonyl migration occurred over a period of



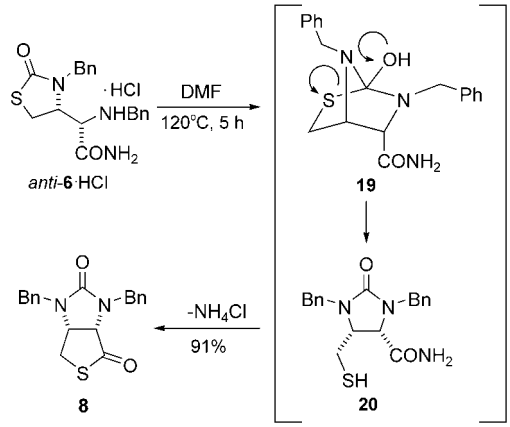
Scheme 5. Amidation of **5**. Reagents and conditions: a) 1) H_2O_2, K_2CO_3, DMSO/CH_2Cl_2, 20°C, 2.5 h; 2) H_2O, filtration; 3) aq. HCl was added to the filtrate to obtain *anti*-**6**·HCl.

1 h to give thiol amide **18** (Scheme 6). The resulting solution, which contained **18**, was directly treated with hydrochloric acid to afford thiol carboxylic acid **7** in 95% yield based on *syn*-**6**.



Scheme 6. *S,N*-Carbonyl migration of amide *syn*-**6**.

When the hydrochloride *anti*-**6**·HCl was heated at a higher temperature (120°C) for 5 h under a N_2 atmosphere, *S,N*-carbonyl migration took place to directly give thiolactone **8** in 91% yield (Scheme 7).

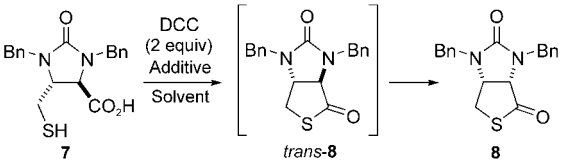


Scheme 7. *S,N*-Carbonyl migration of amide hydrochloride *anti*-**6**·HCl.

The conversion of thiol carboxylic acid **7**, derived from amide *syn*-**6** (Scheme 6), to thiolactone **8** was then investigated. Although Merck's group, by employing DCC in the

presence of *p*-toluenesulfonic acid (PTSA) in pyridine, have accomplished this transformation,[19] we only obtained a moderate yield (57%) by following their protocol (Table 5, entry 1). We then thoroughly investigated the reaction intermediates and found that the reaction took place through an initial cyclization to *trans*-**8** followed by epimerization to the desired thiolactone **8**.[20] We then tested the reaction by using DCC in the presence of various acid-base catalysts. While the use of Boden's catalyst,[21] DMAP·HCl, provided **8** in 63% yield, the use of the more acidic pyridinium *p*-toluenesulfonate (PPTS) resulted in a much better yield (Table 5, entries 2 and 3). Finally, when TFA and pyridine were employed as additives and a two-step procedure involving initial cyclization to *trans*-**8** at 10°C followed by epimerization at 60°C was conducted, compound **8** was obtained in 93% yield (Table 5, entry 4). Practically, compound **8** was isolated in 80% yield based on **7** by crystallization of the crude product from MeOH. Compound **8** is a well-established key intermediate in the synthesis of (+)-biotin.[3] Product **8** was identical to an authentic sample with respect to IR, NMR, and mass spectra and optical rotation.

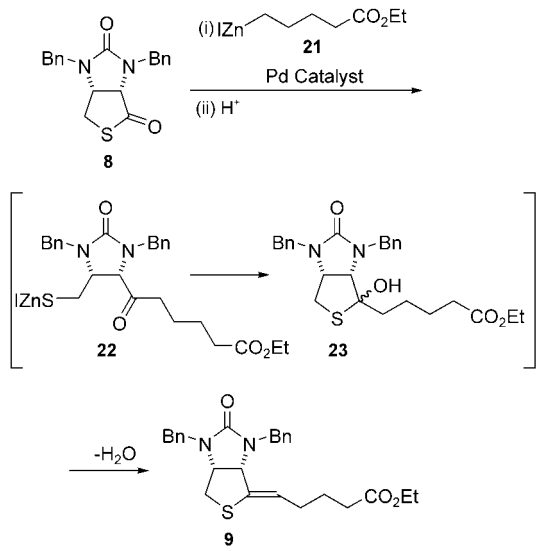
Table 5. Cyclization and epimerization of **7** to **8**.[a]



Entry	Additive (equiv)	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	PTSA·H_2O (0.05) pyridine (26)	none	25	7	57
2	DMAP·HCl (2) pyridine (2)	THF	65	3	63
3	PPTS (2) pyridine (3)	THF	65	3	87
4[c]	TFA (0.4) pyridine (1.4)	$CHCl_3$	10 60	1 6	93 (80)[d]

[a] PTSA = *p*-toluenesulfonic acid, DMAP = 4-(dimethylamino)pyridine, PPTS = pyridinium *p*-toluenesulfonate. [b] Assay yield. [c] DCC (1.0 equiv) was employed. [d] Yield of product isolated by crystallization from MeOH.

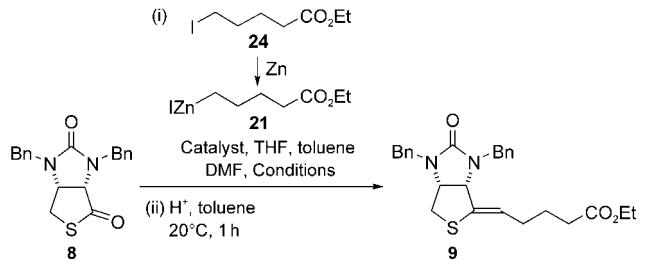
Introduction of a carbon chain at C-4: The introduction of a carbon chain at the C-4 position of thiolactone **8** was previously carried out by using Grignard reagents.[3] Although the yields are high, this reaction suffers from such drawbacks as multisteps, the use of hazardous reagents (Na metal, HBr, and NaCN) and a low reaction temperature.[22] Development of a better procedure is thus highly desirable. Fukuyama and co-workers have recently developed a highly efficient synthetic approach to functionalized ketones.[9] The treatment of thiol esters with zinc reagents in the presence of palladium catalyst [$PdCl_2(PPh_3)_2$] provides a variety of functionalized ketones in excellent yields. The reaction is characterized by unusually high chemoselectivity, mild reaction conditions and the use of nontoxic reagents. We envisioned the possible use of the Fukuyama coupling reaction for the introduction of the carbon chain at the C-4 position (Scheme 8). If zinc reagent **21** reacts with thiolactone **8**, a cyclic thiol ester, ketone **22**, would be formed. After treatment of **22** with acid, cyclization of **22** to **23** followed by dehydration should provide the desired compound **9** with the required C-4 chain.



Scheme 8. Introduction of the chain at C-4 by the Fukuyama coupling reaction.

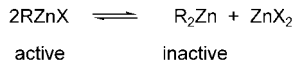
The reaction was initially tested by using the homogeneous catalyst [$PdCl_2(PPh_3)_2$].[9] Although six equivalents of iodide **24** was required for the reaction to go to completion, the desired product **9** was obtained in 80% yield (Table 6, entry 1).[23] Although the use of inexpensive [$Ni(acac)_2$][24] was tested with a view to reducing the cost of raw materials, it gave a moderate yield of **9** (78%, Table 6, entry 2). The use of easily recoverable heterogeneous Pd/C catalysts was then examined. While the use of standard conditions involving THF and toluene as the solvent resulted in a moderate yield (50%, Table 6, entry 3), the addition of DMF to the reaction mixture considerably improved the reaction to provide **9** in 94% yield (Table 6, entry 4).[25] Nonpyrophoric Pearlman's catalyst, $Pd(OH)_2/C$, was found to give **9** in excellent yield with a catalyst loading as low as 0.65 mol% (Table 6, entry 5).[26] While, in our previous studies, zinc dust was activated by the addition of 1,2-dibromoethane (0.026 equiv relative to Zn) followed by TMSCl (0.018 equiv relative to Zn),[26] here this approach allowed us to address the serious issues of poor reproducibility and the requirement to use an excess of iodide **24** (2.5 equiv relative to **8**) to complete the reaction. As the Fukuyama coupling reaction has been reported not to proceed with dialkylzinc (R_2Zn), the Schlenk equilibrium of the zinc reagents should lie to the left for maximum utilization of the reduced iodide (Scheme 9). We envisioned that addition of a Zn^{II} salt (ZnX_2) might shift the equilibrium toward the desired RZnX, thereby reducing the amount of iodide **24** required. When the suspension of zinc dust was treated with bromine (0.25 equiv relative to Zn dust) before the addition of iodide

Table 6. Introduction of the chain at C-4 by the Fukuyama coupling reaction.



Entry[a]	DMF [% (v/v)]	Catalyst (mol %[b])	**24** (equiv)	Conditions T [°C]	t [h]	Yield [%][c]
1	none	$[PdCl_2(PPh_3)_2]$ (10)	6.0	20	24	80
2	4	$[Ni(acac)_2]$ (10)	2.5	25–30	15	78
3	none	Pd/C[d] (5)	6.0	20	24	50
4	4	Pd/C[d] (5)	2.5	20	18	94[e]
5	4	$Pd(OH)_2$/C[f] (0.65)	2.5	25–30	2	92[e]
6[g]	4	Pd/C D1[h] (0.86)	1.4	28–40	5	94[e]

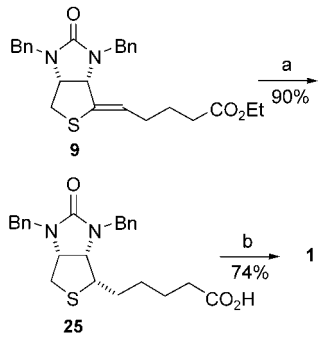
[a] Zinc dust was activated by the treatment with 1,2-dibromoethane (0.026 equiv relative to Zn dust) followed by TMSCl (0.018 equiv).[27] [b] mol % relative to **8**. [c] Yield of isolated product. [d] Purchased from Kawaken Fine Chemicals; Pd distribution: uniform; reduction degree: 25–99 %; Pd dispersion: 36 %; water content: 1.8 %. [e] Recovery of Pd: > 95 %. [f] Purchased from Kawaken Fine Chemicals. [g] Br_2 (0.26 equiv relative to Zn dust) was used to activate the Zn dust (1.9 equiv relative to **24**). [h] Purchased from Degussa Japan Co., Ltd.; Pd distribution: egg shell; impregnation depth: 50–150 nm; reduction degree: 0–25 %; Pd dispersion: 29 %; water content: 3 %.



Scheme 9. The Schlenk equilibrium of zinc reagents.

24, zinc reagent **21** was formed with high reproducibility, and, as expected, the amount of **24** needed was reduced from 2.5 to 1.4 equiv and provided **9** in high yield as well (Table 6, entry 6).[28]

Conversion to (+)-biotin (1): Hydrogenation of **9** to **25** inherently requires the use of high H_2 pressure because of the catalytic poison caused by the presence of the sulfide moiety in the substrate **9** (Scheme 10).



Scheme 10. Hydrogenation and deblocking of **9**. Reagents and conditions: a) 1) H_2, $Pd(OH)_2$/C (0.9 MPa), MeOH, H_2O; 2) NaOH; b) $MeSO_3H$, mesitylene.

The use of Pearlman's catalyst $[Pd(OH)_2/C]$ in aqueous MeOH was found to lower the required H_2 pressure to 0.9 MPa and provided **25** in 90 % yield after hydrolysis. Removal of the benzyl groups from **25** to give **1** was best conducted by using methanesulfonic acid.[29] The pure target compound **1**, which was identical to an authentic sample with respect to IR, NMR, and MS spectra and optical rotation, was obtained by simple crystallization from water.

Conclusion

As described above, a practical synthetic approach to (+)-biotin (**1**) from L-cysteine has been accomplished through 1) the formation of contiguous stereogenic centers by the highly diastereoselective Strecker reaction (**4**→**5**), 2) the novel ring transformation and deblocking by *S*,*N*-carbonyl migration (*syn*-**6**→**7** and *anti*-**6**·HCl→**8**), and 3) the introduction of the carbon chain at C-4 by the Fukuyama coupling reaction (**8**→**9**). The use of 2-thiazolidinone derivatives as a protecting surrogate for cysteine derivatives has considerably decreased the number of steps in the synthesis of (+)-biotin, which is now accessible in 10 steps and in 34 % overall yield from readily available L-cysteine. The high yield, ease of operation and mild reaction conditions of this approach permit ready access to (+)-biotin,[30] a compound of great biological significance.

Experimental Section

General: Melting points were measured on a Büchi melting point apparatus (B-450) and are uncorrected. ^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker Avance 400 spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured on a Perkin–Elmer 243 automatic polarimeter at the indicated temperature by using a sodium lamp (D line, 589 nm); $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer and on a Finnigan MAT LC-Q instrument. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development of the plates was accomplished by using 5 % phosphomolybdic acid in ethanol-heat or they were visualized by UV light where feasible. All solvents and reagents were used as received.

(*R*)-3-Benzyl-2-oxothiazolidine-4-carboxylic acid (12): Whilst cooling with ice water, L-cysteine hydrochloride monohydrate (176 g, 1 mol) was added to a solution of NaOH (184 g, 4.6 mol) in water (0.88 L). A solution of phenyl chloroformate (313 g, 2 mol) in toluene (0.35 L) was added dropwise to this mixture at < 30 °C. After the mixture had been stirred at 25 °C for 2 h, the aqueous layer was separated and washed with toluene (0.35 L) to afford the sodium salt of (*R*)-2-oxothiazolidine-4-carboxylic acid **14** (Net: 246 g) as an aqueous solution that was used in the next step without further purification. The purified sample of **10** was obtained as follows: The aqueous solution of **14** was acidified (pH 1) by adding concentrated HCl and then the solvent was evaporated in vacuo. The residue was extracted with AcOEt. The extracts were evaporated and the solids that formed were collected and recrystallized from water to afford **10** as colorless crystals. M.p. 168–170 °C; $[\alpha]_D^{25} = -62.8$ ($c = 1.0$ in H_2O); ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 13.22$ (br s, 1H), 8.45 (s, 1H), 4.40 (ddd, $J = 1.3$, 3.4, 8.6 Hz, 1H), 3.72 (dd, $J = 8.6$, 11.4 Hz, 1H), 3.46 ppm (dd, $J = 3.4$, 11.4 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 173.5$ (s), 172.8 (s), 55.7 (d), 32.1 ppm (t); IR (KBr): $\tilde{\nu}_{max} = 3280$, 1738, 1627, 1231 cm^{-1}; MS (70 eV, SI): *m*/*z*: 148 $[M+H]^+$; elemental analysis

calcd (%) for $C_4H_5NO_3S$: C 32.65, H 3.42, N 9.52; found: C 32.04, H 3.26, N 9.39. The aqueous solution of **14** (Net: 162 g, 0.95 mol) obtained above was evaporated. Whilst cooling with ice water, a solution of NaOH (57 g, 1.4 mol) in water (143 mL) and DMSO (418 mL) were added to the residue. Benzyl chloride (219 mL, 1.9 mol) was then added at 25 °C and the mixture was stirred for 15 h. The mixture was acidified (pH 1) with concentrated HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent evaporated to afford **12** (213 g, 83 %) as colorless crystals. M.p. 95–97 °C; $[\alpha]_D^{25} = -102.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.39–7.32 (m, 3H), 7.27–7.25 (m, 2H), 5.23 (d, $J = 15.1$ Hz, 1H), 5.21 (dd, $J = 2.4$, 8.6 Hz, 1H), 4.06 (d, $J = 15.1$ Hz, 1H), 3.57 (dd, $J = 8.6$, 15.1 Hz, 1H), 3.43 ppm (dd, $J = 2.4$, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 171.8$ (s), 171.4 (s), 136.8 (s), 128.9 (d), 128.1 (d), 127.8 (d), 60.0 (d), 47.5 (t), 29.2 ppm (t); IR (KBr): $\tilde{\nu}_{max} = 3029$, 1729, 1619 cm^{-1}; MS (70 eV, SI): *m/z*: 238 $[M+H]^+$; elemental analysis calcd (%) for $C_{11}H_{11}NO_3S$: C 55.68, H 4.67, N 5.90; found: C 55.97, H 4.82, N 5.77.

(*R*)-3-Benzyl-4-hydroxymethyl-2-oxothiazolidine (15): H_2SO_4 (2 g, 19.4 mmol) was added dropwise to a suspension of **12** (8 g, 33.7 mmol) and $NaBH_4$ (1.53 g, 40.4 mmol) in THF (32 mL) at 40–50 °C and the mixture was stirred at the same temperature for 3 h. Whilst cooling with ice water, the mixture was carefully acidified to pH 1 with 2N aq. HCl and then extracted with AcOEt. The extracts were washed twice with water, dried over $MgSO_4$, and the solvent evaporated. The residue was crystallized by adding isopropyl ether to give **15** (6.82 g, 91 %) as colorless crystals. M.p. 87–90 °C; $[\alpha]_D^{25} = -26.7$ ($c = 1.0$ in MeOH); optical purity: >99.9 % ee [HPLC: Chiralcel AD (Daicel), EtOH/hexane = 10:90, 0.8 mL min^{-1}, 40 °C, 225 nm]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.26 (m, 5H), 4.85 (d, $J = 15.2$ Hz, 1H), 4.27 (d, $J = 15.2$ Hz, 1H), 4.13–3.76 (m, 2H), 3.66–3.64 (m, 1H), 3.34–3.27 (m, 2H), 1.90 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.1$, 136.2 (2s), 128.9, 128.1, 128.0 (3d), 61.0 (t), 59.5 (d), 47.1, 28.0 ppm (2t); IR (KBr): $\tilde{\nu}_{max} = 3446$, 1645 cm^{-1}; MS (70 eV, SI): *m/z*: 224 $[M+H]^+$; elemental analysis calcd (%) for $C_{11}H_{13}NO_2S$: C 59.17, H 5.87, N 6.27; found: C 58.75, H 5.68, N 6.09.

(*R*)-3-Benzyl-2-oxothiazolidine-4-carbaldehyde (4): Pyridine (1.45 mL, 17.9 mol), TFA (1.38 mL, 17.9 mol) and DCC (22.2 g, 0.107 mol) in toluene (40 mL) were successively added to a solution of **15** (20 g, 0.084 mol) in DMSO (45 mL) at 25 °C and the mixture was stirred at 45 °C for 4.5 h. Toluene (200 mL) was added to the mixture, which was then cooled in an ice bath and filtered. The filtrate was washed with brine and water while the aqueous layer was extracted with AcOEt. The extracts were combined, washed with brine and water, dried over $MgSO_4$ and the solvent evaporated to afford **4** (16.6 g, 90 %) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.55$ (d, $J = 1.8$ Hz, 1H), 7.41–7.24 (m, 5H), 5.00 (d, $J = 14.9$ Hz, 1H), 4.30 (d, $J = 14.9$ Hz, 1H), 4.07 (ddd, $J = 1.8$, 3.3, 8.8 Hz, 1H), 3.52 (dd, $J = 8.8$, 11.5 Hz, 1H), 3.34 ppm (dd, $J = 3.3$, 11.5 Hz, 1H); IR (KBr): $\tilde{\nu}_{max} = 1649$ cm^{-1}; HRMS: *m/z* for $[M-H]^-$: calcd for $C_{11}H_{11}NO_2S$: 221.0501; found: 221.0502.

2-[(4*R*)-3-Benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetonitrile (5): The crude **4** (30 g, 0.13 mol) obtained above was dissolved in toluene (150 mL) and $MgSO_4$ (15 g) was added at 25 °C followed by benzylamine (14.7 mL, 0.13 mol) at <5 °C. After the mixture had been stirred at 25 °C for 2 h, TMSCN (35.8 mL, 0.27 mol) was added at −5 °C and the mixture was stirred at 20 °C for 15 h. The mixture was concentrated under reduced pressure and the solids that formed were collected and washed with water and hexane to give **5** (42.1 g, 96 %, *syn*/*anti* = 28:1) as a colorless solid [HPLC; L-Column ODS (Daicel), 0.01 M KH_2PO_4 (pH 3) buffer/CH_3CN = 50:50, 0.5 mL min^{-1}, 40 °C, 225 nm]. Compounds *syn*-**5** and *anti*-**5** were purified by silica gel column chromatography (hexane/$CHCl_3$/AcOEt = 5:5:1).

(2*R*)-2-[(4*R*)-3-Benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetonitrile (*syn*-5): M.p. 124–125 °C; $[\alpha]_D^{25} = +46.1$ ($c = 1.0$ in $CHCl_3$); optical purity: >99 % *ee* [HPLC: Chiralcel AD-H (Daicel), EtOH/hexane = 10:90, 0.8 mL min^{-1}, 40 °C, 225 nm]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.25 (m, 8H), 7.12 (dd, $J = 3.4$, 7.4 Hz, 2H), 5.04 (d, $J = 15.3$ Hz, 1H), 4.30 (d, $J = 15.3$ Hz, 1H), 4.06 (d, $J = 13.1$ Hz, 1H), 3.86–3.76 (m, 3H), 3.40 (dd, $J = 8.2$, 11.5 Hz, 1H), 3.23 ppm (dd, $J = 4.5$, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.6$, 137.6, 135.8, 117.8 (4s), 129.6, 129.5, 129.3, 128.8, 128.6, 128.4, 59.3, 52.13 (8d), 52.07, 48.5, 28.8 ppm (3t); IR (KBr): $\tilde{\nu}_{max} = 2220$, 1648 cm^{-1}; MS (70 eV, SI): *m/z*: 338 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{19}N_3OS$: C 67.67, H 5.81, N 12.45; found: C 67.35, H 5.81, N 12.41.

(2*S*)-2-[(4*R*)-3-Benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetonitrile (*anti*-5): M.p. 134 °C; $[\alpha]_D^{25} = -183.8$ ($c = 0.24$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$–7.23 (m, 8H), 7.15–7.07 (m, 2H), 5.03 (d, $J =$ 15.4 Hz, 1H), 4.05 (d, $J = 13.0$ Hz, 1H), 3.96 (d, $J = 15.4$ Hz, 1H), 3.78–3.68 (m, 2H), 3.52 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 137.8, 135.8, 118.8 (4s), 129.5, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 128.43, 128.37, 128.3, 128.1, 59.0, 50.3 (14d), 51.7, 47.9, 28.5 ppm (3t); IR (film): $\tilde{\nu}_{max} = 2220$, 1674 cm^{-1}; MS (70 eV, SI): *m/z*: 338 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{19}N_3OS$: C 67.63, H 5.68, N 12.45, S 9.50; found: C 67.59, H 5.63, N 12.47, S 9.24.

Preparation of 2-[(4*R*)-3-benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetonitrile (5) via sodium bisulfite adduct 16: Pyridine (2.92 mL, 0.036 mol), TFA (2.78 mL, 0.036 mol) and DCC (44.4 g, 0.22 mol) were successively added to a solution of **15** (40 g, 0.18 mol) in a mixture of AcOEt (90 mL) and DMSO (90 mL) at <43 °C. After the mixture had been stirred at 50 °C for 3 h, AcOEt (200 mL) was added and the mixture was cooled in an ice bath. The precipitated DCU 1,3-dicyclohexylurea (DCU) was filtered and the filtrate was washed with 12 % aq. NaCl (200 mL). The aqueous layer was extracted with AcOEt (100 mL) and the combined organic phases were washed with 12 % aq. NaCl (200 mL). The AcOEt solution contained α-amino aldehyde **4** (35.9 g, 90 %) [HPLC; Capcell Pak C18 SG 120A (Shiseido), 15 cm × 4.6 mm, 15 mM Na_2HPO_4/CH_3CN = 5:1, 1 mL min^{-1}, 40 °C, 220 nm]. Water (80 mL) and sodium bisulfite (18.6 g, 0.178 mol) were added to compound **4** (35.9 g, 0.162 mol) in AcOEt and the mixture was stirred at 20 °C for 30 min. After the solution was concentrated under reduced pressure, AcOEt (80 mL) was added to the residue. The mixture was stirred at 20 °C for 17 h and the aqueous layer containing bisulfite adduct **16** (35.4 g, 0.16 mol) was suspended in CH_2Cl_2 (106 mL). Benzylamine (23.2 g, 0.27 mol) was added to this suspension and the mixture was stirred at 20 °C for 2 h. The mixture was then cooled to 8 °C and NaCN (9.4 g, 0.19 mol) was added. After the mixture had been stirred at 20 °C for 20 h, $NaHSO_3$ (5.0 g, 0.048 mol) and NaCN (2.35 g, 0.048 mol) were added and the mixture was stirred for 1.5 h. Aq. NaOH (10 %, 40 mL) was added to the mixture. The organic phase was separated and washed with water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL) and the combined extracts were dried over anhydrous $MgSO_4$ and filtered to afford α-amino nitrile **5** (51.1 g, 95 %) in CH_2Cl_2 as a mixture of *syn* and *anti* isomers [*syn*/*anti* = 11:1, HPLC; L-Column ODS (Shimadzu), 0.01 M KH_2PO_4 buffer (pH 3)/CH_3CN = 55:45, 1 mL min^{-1}, 40 °C, 225 nm].

(2*R*)-2-[(4*R*)-3-Benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetamide (*syn*-6): DMSO (140 mL), K_2CO_3 (fine powder, 2.7 g, 0.019 mol), and 30 % H_2O_2 (46.3 g) were added to a CH_2Cl_2 solution of **5** (vide supra) (Net 46.9 g, 0.14 mol). After the mixture had been stirred at 20 °C for 6 h, water was added and the crystals that formed were collected and washed with CH_2Cl_2 and water to afford *syn*-**6** (46 g, 93 %) as colorless crystals. M.p. 194–195 °C; $[\alpha]_D^{25} = -38.8$ ($c = 0.45$ in DMF); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.64$ (s, 1H), 7.41 (s, 1H), 7.36–7.14 (m, 10H), 4.91 (d, $J = 16.0$ Hz, 1H), 4.33 (d, $J = 16.0$ Hz, 1H), 3.87–3.82 (m, 1H), 3.78 (d, $J = 16.0$ Hz, 1H), 3.53 (d, $J = 16.0$ Hz, 1H), 3.41–3.25 ppm (m, 2H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 173.4$, 171.5, 140.5, 137.0 (4s), 129.0, 128.6, 128.2, 127.9, 127.7, 127.1, 62.1, 59.5 (8d), 51.5, 47.2, 27.7 ppm (3t); IR (KBr): $\tilde{\nu}_{max} = 3397$, 1660 cm^{-1}; MS (70 eV, SI): *m/z*: 356 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{21}N_3O_2S$: C 64.20, H 5.95, N 11.82; found: C 63.99, H 5.84, N 11.79.

(2*S*)-2-[(4*R*)-3-Benzyl-2-oxothiazolidin-4-yl]-2-benzylaminoacetamide hydrochloride (*anti*-6·HCl): $Na_2S_2O_3 \cdot 5H_2O$ (48.5 g) in H_2O (100 mL) was added to the mother liquor of *syn*-**6** (vide supra). The organic phase was washed successively with brine (twice), 4 % aq. citric acid and water, and the solvent evaporated. Acetone (36 g) and concentrated HCl (5 g) were added to the residue and the solids that formed were collected and washed with acetone to afford *anti*-**6**·HCl (3.8 g, 7 %) as colorless crystals. M.p. 200–207 °C; $[\alpha]_D^{25} = -29.3$ ($c = 1.0$ in MeOH); IR (KBr): $\tilde{\nu}_{max} = 1702$, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.01$ (brs, 1H), 9.58 (brs, 1H), 8.67 (s, 1H), 8.06 (s, 1H), 7.61–7.26 (m, 10H), 4.78 (d, $J = 15.9$ Hz, 1H), 4.38–4.35 (m, 1H), 4.27 (s, 1H), 4.10 (d, $J = 15.6$ Hz, 1H), 3.99 (s, 2H), 3.77 (dd, $J = 12.0$, 3.2 Hz, 1H), 3.52 ppm (dd, $J = 12.1$, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 171.1$, 136.3 (4s), 130.5, 129.0,

128.5, 128.4, 127.4, 127.4, 58.8, 57.8 (8d), 49.7, 46.5, 27.3 ppm (3t); MS (70 eV, SI): *m/z*: 356 $[M+H]^+$.

(4*R*,5*R*)-1,3-Dibenzyl-5-mercaptomethyl-2-oxothiazolidine-4-carboxylic acid (7): A solution of *syn*-**6** (100 g, 0.28 mol) in DMF (200 mL) was degassed by bubbling with N_2 gas and then stirred at 90 °C for 3 h under a N_2 atmosphere. Concentrated HCl (200 mL, 1.9 mol) was added dropwise to the mixture at 90 °C over 1.75 h. After the mixture had been stirred at the same temperature for a further 1.25 h, water (100 mL) was added dropwise at 85 °C over 30 min. The mixture was cooled to 0 °C and the solids that formed were collected to afford **7** (95.1 g, 95 %) as colorless crystals. M.p. 159–160 °C; $[\alpha]_D^{20}=+48.8$ ($c=0.62$ in DMF); optical purity: >99 % *ee* [HPLC: Chiralcel AD (Daicel), EtOH/hexane/THF = 10:90:0.1, 0.8 mL min^{-1}, 40 °C, 225 nm]; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=7.58$ (s, 1H), 7.37–7.22 (m, 10H), 4.83 (d, $J=16.0$ Hz, 1H), 4.54 (d, $J=16.0$ Hz, 1H), 4.13 (d, $J=16.0$ Hz, 1H), 4.06 (d, $J=16.0$ Hz, 1H), 3.82 (d, $J=4.0$ Hz, 1H), 3.61–3.58 (m, 1H), 2.75–2.65 (m, 2H), 2.13–2.11 ppm (m, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta=170.6$, 160.7, 136.9, 136.4 (4s), 128.8–127.5, 58.3, 58.0 (8d), 46.5, 46.3, 23.4 ppm (3t); IR (KBr): $\tilde{\nu}_{max}=1735$, 1625 cm^{-1}; MS (70 eV, SI): *m/z*: 357 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{20}N_2O_2S$: C 64.02, H 5.66, N 7.86; found: C 63.83, H 5.38, N 7.96.

Bis{[(4*R*,5*R*)-4-carbamoyl-1,3-dibenzyl-2-oxothiazolidin-5-yl]methyl} disulfide (26): A mixture of *syn*-**6** (14 g, 0.039 mol) and $NaHCO_3$ (3.96 g, 0.047 mol) in DMF was stirred at 80–85 °C for 17 h. The mixture was evaporated and water (20 mL) was added and the mixture was stirred at 5 °C for 1 h. The crystals that formed were collected and washed with a mixture of MeOH (80 mL) and water (40 mL), and dried at 50 °C for 17 h to afford **26** (12.1 g, 87 %) as colorless crystals. M.p. 208–211 °C; $[\alpha]_D^{20}=+55.4$ ($c=0.29$ in DMF); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=$ 7.60 (s, 1H), 7.12–7.42 (m, 11H), 4.80 (d, $J=16$ Hz, 1H), 4.69 (d, $J=$ 16 Hz, 1H), 4.09 (d, $J=16$ Hz, 1H), 3.84 (d, $J=16$ Hz, 1H), 3.67 (d, $J=$ 4 Hz, 1H), 3.51–3.55 (m, 1H), 2.86–2.98 ppm (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta=169.2$, 157.2, 135.2, 135.1 (4s), 126.63, 126.6, 125.9, 125.8, 125.4, 125.3, 57.4, 53.7 (8d), 43.9, 42.8, 39.0 ppm (3t); IR (KBr): $\tilde{\nu}_{max}=3356$, 1682 cm^{-1}; MS (70 eV, SI): *m/z*: 709 $[M+H]^+$.

(4*S*,5*R*)-1,3-Dibenzyl-3,3a,6,6a-tetrahydro-1*H*-thieno[3,4-*d*]imidazole-2,4-dione (8): Pyridine (32 mL, 0.39 mol) and TFA (8.7 mL, 0.11 mol) were added to a solution of **7** (100 g, 0.28 mol) in $CHCl_3$ (400 mL) at 0 °C. A solution of DCC (86.8 g, 0.42 mol) in $CHCl_3$ (136 mL) was then added to this mixture at 25 °C, which was then stirred at 0 °C for 1 h and refluxed for 6 h. The mixture was cooled to 25 °C and the solids that formed were collected. The filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **8** (88.1 g, 93 %) as colorless crystals. Pure **8** was obtained in 80 % yield by recrystallization of the crude residue from MeOH. M.p. 122–123 °C (Lit.:[4c] 125.5–127 °C); $[\alpha]_D^{25}=+90.5$ ($c=1.0$ in $CHCl_3$) {Lit.:[4c] $[\alpha]_D^{20}=+91.3\pm0.9$ ($c=1.0$ in $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.39$–7.25 (m, 10H), 5.04 (d, $J=15.0$ Hz, 1H), 4.69 (d, $J=15.0$ Hz, 1H), 4.37 (d, $J=15.0$ Hz, 1H), 4.36 (d, $J=15.0$ Hz, 1H), 4.16–4.09 (m, 1H), 3.81(d, $J=7.8$ Hz, 1H), 3.38 (dd, $J=13.0$, 5.6 Hz, 1H), 3.29 ppm (dd, $J=13.0$, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta=205.6$, 158.1, 137.1, 136.7 (4s), 128.5–127.3, 62.4, 56.0 (12d), 45.2, 44.6, 32.5 ppm (3t); IR (KBr): $\tilde{\nu}_{max}=1697$, 1686 cm^{-1}; MS (70 eV, SI): *m/z*: 339 $[M+H]^+$.

(4*S*,5*R*)-1,3-Dibenzyl-3,3a,6,6a-tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2,4-dione (8): A solution of *anti*-**6**·HCl (3.8 g, 9.7 mmol) in DMF (18 g) was degassed by bubbling with N_2 gas and stirred at 120 °C for 5 h. AcOEt (50 mL) and water (50 mL) was added to the mixture and the aqueous phase was extracted with AcOEt. The combined extracts were collected and washed twice with water, and the solvent evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **8** (2.99 g, 91 %) as colorless crystals. The spectral properties of the product were identical to those of **8** obtained from *syn*-**6**.

(4*R*,5*R*)-1,3-Dibenzyl-3,3a,6,6a-tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2,4-dione (*trans*-8): Pyridine (32 mL, 0.39 mol) and TFA (8.7 mL, 0.11 mol) were added to a solution of **7** (100 g, 0.28 mol) in $CHCl_3$ (400 mL) at 0 °C. A solution of DCC (63.5 g, 0.31 mol) in $CHCl_3$ (200 mL) was then added to the mixture at <15 °C, which was then stirred at 25 °C for 1 h. The mixture was diluted with AcOEt and filtered. The filtrate was washed successively with 2N aq. HCl, water, sat. aq. $NaHCO_3$, and brine, dried over $MgSO_4$ and the solvent evaporated. The residue was crystallized from AcOEt to afford *trans*-**8** (40.0 g, 42 %) as colorless crystals. M.p. 115–116 °C; $[\alpha]_D^{26}=+10.6$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.29 (m, 8H), 4.95 (d, $J=7.3$ Hz, 1H), 4.61 (d, $J=$ 7.3 Hz, 1H), 4.31 (d, $J=5.5$ Hz, 1H), 4.27 (d, $J=5.5$ Hz, 1H), 3.49 (m, 1H), 3.38 (d, $J=7.0$ Hz, 1H), 2.95 (dd, $J=4.8$, 5.2 Hz, 1H), 2.81 ppm (dd, $J=4.6$, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta=170.9$, 140.9, 136.8 (3s), 128.5, 128.4, 128.0, 127.9, 127.4, 127.3, 126.5, 57.9 (8d), 52.8, 48.4, 46.0, 28.7 ppm (4t); IR (KBr): $\tilde{\nu}_{max}=2944$, 1741, 1710 cm^{-1}; MS (70 eV, SI): *m/z*: 339 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.48; found: C 67.27, H 5.31, N 8.30, S 9.49.

Synthesis of 8 from *trans*-8: Pyridine (0.5 mL, 6 mmol) was added to a solution of *trans*-**8** (100 mg, 0.296 mmol) in $CHCl_3$ (1 mL) and the mixture was stirred at 25 °C for 23 h. The mixture was washed successively with 2N aq. HCl, water, sat. aq. $NaHCO_3$, and brine, dried over $MgSO_4$ and the solvent evaporated. The residue was crystallized from isopropyl ether to afford **8** (75.1 mg, 75 %) as colorless crystals. The spectral properties of the product were identical to those of **8** obtained from **7**.

Ethyl (3a*S*,4*Z*,6a*R*)-5-(1,3-dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-ylidene)pentanoate (9): Bromine (5.8 g, 36 mmol) was added to a suspension of zinc dust (9.3 g, 0.14 mol) in THF (18 mL) and toluene (12 mL) at 10–40 °C over 15 min and the mixture was heated to 50 °C. Ethyl 5-iodopentanoate (18.6 g, 72.8 mmol) was then added dropwise to the mixture at 50–60 °C over 1 h. After stirring the mixture for 1 h, the mixture was cooled to 30 °C. Compound **8** (17.6 g, 52 mmol), toluene (36 mL), DMF (4.4 mL), and 10 % Pd/C D1 (0.5 g, 0.45 mmol) were added to the resulting mixture and the mixture was stirred at 28–40 °C for 5 h. The mixture was treated with 18 % HCl (34 mL) at 10–30 °C. After the mixture had been stirred at 20 °C for 1 h, the mixture was filtered. The organic phase of the filtrate was washed successively with water, saturated aq. sodium sulfite, and water, dried over $MgSO_4$ and the solvent evaporated to give **9** (22 g, 94 %) as a viscous oil. $[\alpha]_D^{25}=+190.9$ ($c=0.95$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.08$–6.95 (m, 10H), 5.13 (t, $J=8.0$ Hz, 1H), 4.59 (m, 2H), 3.99–3.72 (m, 6H), 2.71–2.62 (m, 2H), 1.99–1.95 (m, 2H), 1.88–1.72 (m, 2H), 1.45–1.35 (m, 2H), 0.96 ppm (t, $J=8.0$ Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta=173.3$, 159.0, 137.9, 137.1 (4s), 129.0–127.3, 125.7, 64.6, 59.0 (13d), 60.3, 46.5, 44.9, 37.1, 33.6, 31.1, 24.2 (7t), 14.3 ppm (1q); IR (KBr): $\tilde{\nu}_{max}=2932$, 1691 cm^{-1}; HRMS: *m/z* for $[M-H]^-$: calcd for $C_{26}H_{30}N_2O_3S$: 450.1977; found: 450.1966.

(3a*S*,4*S*,6a*R*)-5-(1,3-Dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-yl)pentanoic acid (25): A mixture of **9** (100 g, 0.22 mol) and 20 % $Pd(OH)_2$/C (50 % wet) (7.3 g, 6.9 mmol) in MeOH (730 mL) and H_2O (200 mL) was stirred under H_2 (0.9 MPa) at 110 °C for 12 h. The mixture was cooled to 25 °C and filtered. Water (2 mL) and 31 % aqueous NaOH [86 g: NaOH (27 g) and H_2O (59 mL)] were added to the filtrate and the mixture was stirred at 40 °C for 2 h and the solvent evaporated. The residue was diluted with AcOEt and acidified to pH 1 with 10 % aq. HCl. The organic phase was separated and washed twice with H_2O and the solvent evaporated. Hexane was added to the residue and the solid that formed was collected to afford **25** (85 g, 90 %) as colorless crystals. M.p. 94 °C; $[\alpha]_D^{20}=-28.0$ ($c=0.5$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=10.58$ (br s, 1H), 7.34–7.23 (m, 10H), 5.07 (d, $J=$ 15.0 Hz, 1H), 4.75 (d, $J=15.0$ Hz, 1H), 4.15 (d, $J=15.0$ Hz, 1H), 3.99–3.83 (m, 3H), 3.10–3.05 (m, 1H), 2.76–2.64 (m, 2H), 2.36–2.32 (m, 2H), 1.68–1.45 (m, 5H), 1.37–1.23 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=178.6$, 161.1, 136.9, 136.7 (4s), 128.7–127.7, 62.7, 61.2, 54.2 (13d), 48.0, 46.6, 34.7, 33.9, 28.6, 28.5, 24.4 ppm (7t); IR (ATR): $\tilde{\nu}_{max}=1725$, 1660 cm^{-1}; MS (70 eV, SI): *m/z*: 425 $[M+H]^+$; elemental analysis calcd (%) for $C_{24}H_{28}N_2O_3S$: C 67.90, H 6.65, N 6.60, S 7.55; found: C 67.69, H 6.69, N 6.56, S 7.47.

(+)-Biotin (1): $MeSO_3H$ (15.5 g, 0.16 mol) was added to a solution of **25** (6.36 g, 0.015 mol) in mesitylene (16 mL) at 25 °C. After the mixture had been stirred at 135 °C for 3 h, it was cooled to 85 °C. The lower phase was separated and poured into water (100 mL). After the mixture had been stirred at 10 °C for 1 h, the crystals that formed were collected and washed with water and acetone to give the crude product. NaOH (0.54 g, 0.014 mol) was added to a stirred suspension of the crude solid in water (45 mL) at 25 °C, and the pH value of the mixture was adjusted to 7.5–8.0 at 90 °C by adding concentrated HCl. Activated carbon (2.5 g) was added to the mixture at the same temperature and the mixture was filtered. The

filtrate was acidified to pH 1.6–1.8 with concentrated HCl at 95 °C. After the mixture had been stirred at 10 °C for 1 h, the crystals that formed were collected and washed with water to give **1** (2.71 g, 74 %) as colorless crystals. M.p. 231–232 °C (Lit.[31] 229.5–230 °C): $[\alpha]_D^{24} = +91.0$ ($c = 1.0$ in 0.1 N NaOH) {Lit.:[31] $[\alpha]_D^{25} = +91.3$ ($c = 1.0$ in 0.1 N NaOH)}; IR (neat): $\tilde{\nu}_{max} = 3299, 2920, 1686\ cm^{-1}$; ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 12.02$ (brs, 1H), 6.49 (brs, 1H), 6.40 (brs, 1H), 4.31 (dd, $J = 5.2$, 7.6 Hz, 1H), 4.16–4.13 (m, 1H), 3.12–3.10 (m, 1H), 2.81 (dd, $J = 5.1$, 12 Hz, 1H), 2.58 (d, $J = 12$ Hz, 1H), 2.21 (t, $J = 7.3$ Hz, 2H), 1.54–1.36 (m, 4H), 1.36–1.32 ppm (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 174.8$, 163.1 (2s), 61.4, 59.5, 55.7 (3d), 40.0, 33.8, 28.44, 28.36, 24.9 ppm (5t); MS (70 eV, SI): *m/z*: 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{10}H_{16}N_2O_3S$: C 49.16, H 6.60, N 11.47, S 13.13; found: C 49.28, H 6.63, N 11.54, S 13.09.

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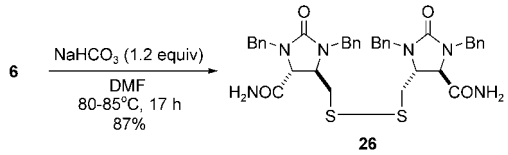

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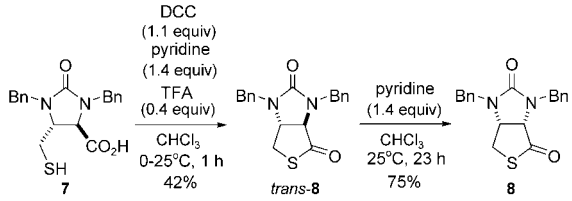

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