JOC Article

A Novel Synthesis of (+)-Biotin from L-Cysteine†

Masahiko Seki,* Yoshikazu Mori, Masanori Hatsuda, and Shin-ichi Yamada

CMC Research Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka, 532-8505, Japan

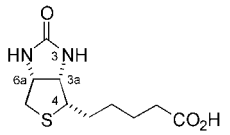
m-seki@tanabe.co.jp

Received April 4, 2002

(+)-Biotin (**1**) was synthesized in 25% overall yield over 11 steps from L-cysteine. The contiguous asymmetric centers at C-3a and C-6a were formed through a novel and highly stereoselective Lewis base-catalyzed cyanosilylation of α-amino aldehyde **3** to provide *anti*-*O*-TMS-cyanohydrin **4** with high stereoselectivity and in high yield (*anti*/*syn* = 92:8, 96%). Treatment of **4** with a di-Grignard reagent, 1,4-bis(bromomagnesio)butane, followed by carbon dioxide, efficiently installed the 4-carboxybutyl chain at C-4 to give keto acid **5**. The final cyclization to bicyclic compound **7b**, a precursor to **1**, was realized by a palladium-catalyzed intramolecular allylic amination of *cis*-allylic carbonate **6b** that was elaborated from **5**.

Introduction

(+)-Biotin (**1**) is a water-soluble vitamin isolated in 1941[1] that has aroused considerable attention as a synthetic target because of the useful biological properties for human nutrition and animal health.[2] Since the first total synthesis of **1** was accomplished about 50 years ago,[3,4] extensive research has been directed toward finding ever more efficient synthetic methodology and routes to **1**.[5] Although a great variety of synthetic approaches have been reported, such as diastereomeric or enzymatic resolutions,[6] chiral pool methods with L-cysteine,[7] L-aspartic acid,[8] or carbohydrates[9] used as a starting material, and asymmetric syntheses,[10] there are few routes that involve (1) few steps, (2) inexpensive reagents, and (3) mild reaction conditions. We have recently disclosed a preliminary result concerning a stereoselective synthesis of **1** from L-cysteine.[11] Reported herein are the full details of our exploratory efforts to accomplish the novel and practical approach to **1**.



(+)-Biotin (**1**)

Our synthesis of **1** is based on a retrosynthetic analysis depicted in Scheme 1. The crucial step to construct the *cis*-fused bicyclic ring skeleton of **1** is an intramolecular allylic amination of *cis*-allylic carbonate **6**. Since the palladium-catalyzed allylation takes place with retention of the configuration,[12] *cis*-isomer **6** is expected to be required for the ring closure. Compound **6** may be derived from keto acid **5** through esterification, *O*-methoxycarbonylation, removal of the Boc and the benzylidene groups, dehydrative cyclization, reductive alkylation, and ureido formation. The last five transformations are to be conducted in a successive manner, i.e., without isolation of the intermediates. The 4-carboxybutyl chain of **1** may be installed by the reaction of *O*-TMS-cyanohydrin **4** with a di-Grignard reagent prepared from 1,4-dibromobutane and subsequent treatment with carbon dioxide. An *anti*-selective cyanosilylation of α-amino aldehyde **3** is required to ensure the *cis* configuration of **6**. Compound **3** may be readily prepared from L-cysteine via *β*-amino alcohol **2**.

* To whom correspondence should be addressed. E-mail: m-seki@tanabe.co.jp

† This paper is dedicated to Professor Albert I. Meyers on the occasion of his 70th birthday.

(1) du Vigneaud, V.; Hofmann, K.; Melvile, D. B.; Rachele, J. *J. Biol. Chem.* **1941**, *140*, 763.

(2) (a) Mistry, P. S.; Dakshinamurti, K. *Vitam. Horm.* **1964**, *22*, 1. (b) Coggeshall, C. J.; Heggers, P. J.; Robson, C. M.; Baker, H. *Ann. N. Y. Acad. Sci.* **1985**, *447*, 389. (c) Maebashi, M.; Makino, Y.; Furukawa, Y.; Ohinata, K.; Kimura, S.; Sato, T. *J. Clin. Biochem. Nutr.* **1993**, *14*, 211.

(3) (a) Goldberg, M. W.; Sternbach, L. H. US Patent 2,489,232, Nov 22, 1949; *Chem. Abstr.* **1951**, *45*, 184b. (b) Goldberg, M. W.; Sternbach, L. H. US Patent 2,489,235, Nov 22, 1949; *Chem. Abstr.* **1951**, *45*, 186a. (c) Gerecke, M.; Zimmermann, J.-P.; Ashwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991.

(4) For recent improvements of the Goldberg−Sternbach synthesis, see: (a) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099. (b) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429. (c) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039.

(5) For a review, see: De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.

(6) (a) Senuma, M.; Fujii, T.; Seto, M.; Okamura, K.; Date, T.; Kinumaki, A. *Chem. Pharm. Bull.* **1990**, *38*, 882. (b) Iriuchijima, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907.

(7) (a) Poetsch, E.; Casutt, M. *Chimia*, **1987**, *41*, 148. (b) Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865. (c) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321. (d) Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2391. (e) Chaven, S. P.; Tejwani, B.; Ravindranathan, T. *J. Org. Chem.* **2001**, *66*, 6197.

(8) Seki, M.; Shimizu, T.; Inubushi, K. *Synthesis* **2002**, 361.

(9) Ravindranathan, T.; Hiremath, S. V.; Reddy, D. R.; Ramo Rao, A. V. *Carbohydr. Res.* **1984**, *134*, 332.

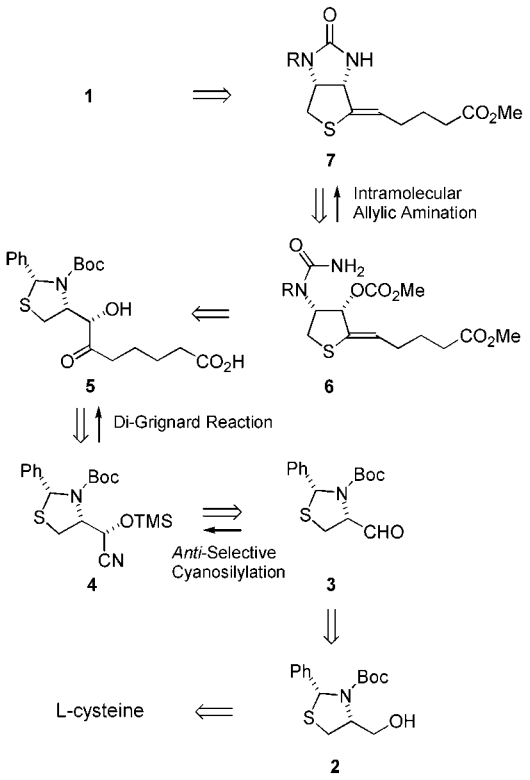
(10) (a) Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* **1993**, *34*, 1167. (b) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737.

(11) Seki, M.; Hatsuda, M.; Mori, Y.; Yamada, S. *Tetrahedron Lett.* **2002**, *43*, 3269.

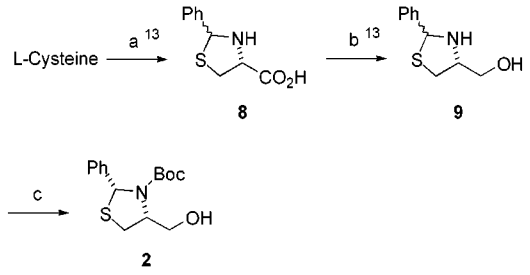
(12) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.

10.1021/jo025794+ CCC: $22.00
Published on Web 07/04/2002

SCHEME 1



SCHEME 2[a]

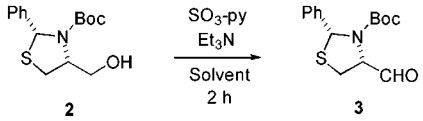


[a] Reagents and yields: (a) PhCHO, AcOK, EtOH, H_2O, 96%; (b) (i) $SOCl_2$, EtOH (ii) $Ca(BH_4)_2$, EtOH, quant; (c) $(Boc)_2O$, Na_2CO_3, THF, H_2O, 88%.

Results and Discussion

Preparation of α-Amino Aldehyde 3 from L-Cysteine. Compound **3** was prepared by oxidation of β-amino alcohol **2** which was derived from L-cysteine according to a reported procedure[7c,13] (Scheme 2). Although the oxidation of **2** by Swern oxidation has been reported to proceed in 81% yield, it requires a reaction temperature as low as −60 °C.[7c] To eliminate the unpractical low reaction temperature, an oxidation employing sulfur trioxide pyridine complex (SO_3-py)[14] was examined (Table 1). Treatment of **2** with SO_3-py (2.0 equiv) in the presence of Et_3N (2.0 equiv) in DMSO at 20 °C afforded **3** with 97% de in 82% yield (Table 1, entry 1). The yield was, however, poorer at higher temperature such as 30 and 40 °C to give **3** in 58 and 24% yield, respectively (Table 1, entries 2, 3). The reaction was thus conducted at 10 °C in a nonfreezing mixture of DMSO and toluene (5:1) to give the desired diastereomerically pure α-amino aldehyde **3** in 95% yield after crystallization with AcOEt−hexane (Table 1, entry 4).

TABLE 1. Oxidation of β-Amino Alcohol 2[a]



entry	SO_3-py (equiv)	Et_3N (equiv)	solvent	T (°C)	yield (%)	de[b] (%)
1	2.0	2.0	DMSO	20	82	97
2	2.0	2.0	DMSO	30	58	97
3	2.0	2.0	DMSO	40	24	96
4	2.5	2.5	DMSO−toluene (5:1)	10	quant (95)[c]	96 (>99)[d]

[a] The reactions were conducted on 10 mmol scale except entry 4 (0.2 mol scale). [b] Determined by HPLC after reduction ($NaBH_4$) of the product **3** to **2**. [c] Isolated yield after crystallization from AcOEt−hexane. [d] De after crystallization from AcOEt−hexane.

The preparation of **3** was consequently carried out in 80% overall yield over four steps from L-cysteine without need of expensive reagents, quite low temperature, or silica gel column chromatography.

Formation of the Contiguous Stereogenic Centers. A highly *anti*-selective hydrocyanation of (*R*)-*N*-Boc-2,2-dimethylthiazolidine-4-carbaldehyde (Garner's aldehyde) with hydrogen cyanide in the presence of a Lewis acid has been reported.[15] We initially applied the procedure to the synthesis of *anti*-*O*-TMS-cyanohydrin **4**. However, the cyanosilylation of **3** in the presence of Lewis acid such as ZnI_2, $ZnBr_2$, or BF_3−diethyl etherate was problematic, leading to only traces of product **4**. Mukaiyama and co-workers have reported a high-yielding Lewis base-catalyzed cyanosilylation of aldehydes.[17] We applied the procedure to the cyanosilylation of **3** (Table 2). Treatment of **3** with trimethylsilyl cyanide (TMSCN) (1.1 equiv) in the presence of Et_3N (10 mol %) at −10 °C in CH_2Cl_2 afforded **4** in 96% yield albeit in a poor selectivity (*anti*/*syn* = 72:28) (Table 2, entry 1). We speculated that use of a more sterically demanding Lewis base should improve the diastereoselectivity, since a hypervalent silicate formed from TMSCN and Et_3N has been assumed to be an active species in the cyanosilylation,[17] and the stereochemical outcome may be accounted for by a Felkin−Ahn model[18] shown in Figure 1. In support of the hypothesis, more bulky secondary and tertiary amines including Cy_2NH, *i*-Pr_2NH, 2,2,6,6-tetramethylpiperidine, 1-ethylpiperidine, *i*-Pr_2NEt, *i*-Pr_3N, and *n*-Bu_3N in place of Et_3N were employed as the Lewis base to produce a higher degree of stereocontrol ranging from *anti*/*syn* = 77:13 to 90:10 (Table 2, entries

(13) Gonzalez, A.; Lavilla, R.; Piniella, J. F.; Alvarez-Larena, A. *Tetrahedron* **1995**, *51*, 3015.

(14) (a) Doering, W. V. E.; Parikh, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.

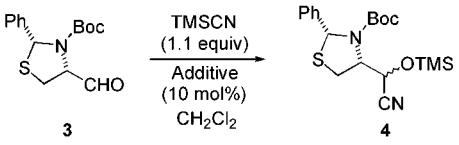
(15) Marcus, J.; Vandermeulen, G. W. M.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1617.

(16) *O*-TMS cyanohydrin **3** was desilylated quantitatively by the treatment with aqueous citric acid, and the yield and the diastereomeric ratio were determined by HPLC. The structure of the cyanohydrin was confirmed by single-crystal X-ray analysis.

(17) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537.

(18) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 114.

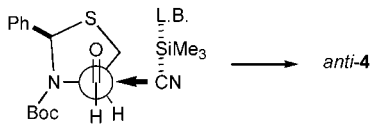
TABLE 2. Cyanosilylation of 3 in the Presence of Lewis Base[a]



3 4

Entry	Additive	*T* (°C)	*t* (h)	Yield (%)[b]	*anti*/*syn*[b]
1	Et_3N	-10	0.5	96	72:28
2	Cy_2NH	-10	0.5	98	84:16
3	*i*-Pr_2NH	-10	0.5	96	90:10
4		-10	0.5	99	88:12
5	TMEDA	-10	0.5	83	55:45
6		-10	0.5	96	74:26
7	*i*-Pr_2NEt	-10	0.5	97	89:11
8	*i*-Pr_3N	-10	0.5	96	90:10
9	*n*-Bu_3N	-10	0.5	92	77:23
10	*n*-Bu_3P	-10	0.5	96	92:8
11	*i*-Pr_3P	25	18	89	88:12
12	*t*-Bu_3P	25	19	84	88:12
13	$(n\text{-BuO})_3P$	25	27	95	80:20
14	$(i\text{-PrO})_3P$	25	18	95	86:14
15	Ph_3P	25	18	-	-

[a] The reactions were conducted on 1 mmol scale. [b] Determined by HPLC analysis of the crude mixture after desilylation with aqueous citric acid.[16]

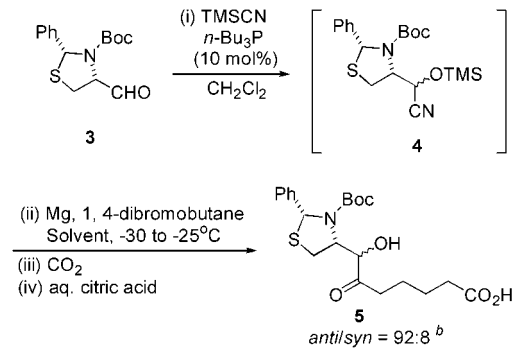


L.B.: Lewis Base

FIGURE 1. A proposed mechanism for the Lewis base-catalyzed cyanosilylation of **3**.

2−4 and 6−9). Further screening of the Lewis bases resulted in a finding that trialkylphosphines efficiently catalyzed the cyanosilylation. Among the trialkylphosphines tested, tri-*n*-butylphosphine effected the cyanosilylation with an excellent diastereoselectivity in high yield (*anti*/*syn* = 92:8, 96%) (Table 2, entry 10). Use of more sterically hindered trialkylphosphines (*i*-Pr_3P and *t*-Bu_3P) or more electron deficient trialkyl phosphites

TABLE 3. Formation of the 4-Carboxybutyl Chain with a Di-Grignard Reagent[a]



3 4 5

anti/*syn* = 92:8 [b]

entry	solvent	*t* (h)	yield[c] (%)
1	THF	1	20
2	Et_2O	1	61
3	Et_2O/toluene (1:3)	1	74
4	*n*-Bu_2O	0.5	76
5	*n*-Bu_2O/toluene (1:2)	0.5	79[d]

[a] The reactions were conducted on 10 mmol scale except entry 5 (0.15 mol scale). [b] The ratio obtained for all conditions. [c] Determined by HPLC. [d] Isolated yield.

[(*n*-BuO)$_3$P and (*i*-PrO)$_3$P] led to product **4** only at higher reaction temperature (25 °C) with poorer diastereoselectivities (Table 2, entries 11 to 14). An electron-deficient Ph_3P did not exert any catalytic activity (Table 2, entry 15).

Installation of the 4-Carboxybutyl Chain. The 4-carboxybutyl chain was formed by the reaction of in situ generated *O*-TMS-cyanohydrin **4** with di-Grignard reagent[7a,19] derived from 1, 4-dibromobutane and subsequent treatment with carbon dioxide (Table 3). Selection of the solvent significantly affected the efficiency of the coupling reaction. While the yield was poor in THF (20%), use of ether led to product **5** in 61% yield based on **3** (Table 3, entries 1 and 2). The structure of *anti*-**5** was unequivocally confirmed by single-crystal X-ray analysis. Choice of a mixed solvent of ether and toluene (1:3) further improved the yield to give **5** in 74% yield (Table 3, entry 3). Use of the much safer solvent system of *n*-butyl ether and toluene (1:2) was found to give **5** in 79% yield (Table 3, entry 5).

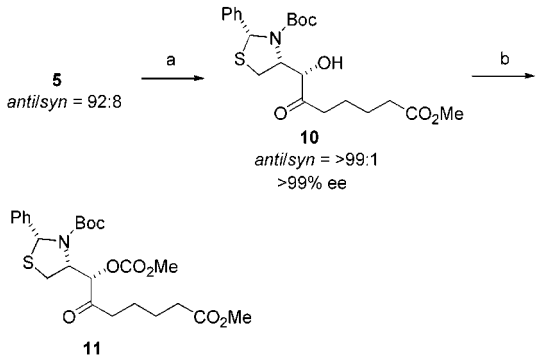
Keto acid **5** was then esterified and purified by crystallization to give enantiomerically and diastereomerically pure keto ester **10** in 73% yield (Scheme 3).

Removal of the Protective Groups and the Ring Closure. Removal of the protective groups and cyclization to the tetrahydrothiophene ring were initially investigated on hydroxy ketone **10** (Scheme 4). Treatment of **10** with HCl in AcOEt smoothly effected cleavage of the Boc and the benzylidene moieties. Ketone **13** along with cyclized product **14** (**13**/**14** = 3:1, 75%) were isolated after treatment with benzyl isocyanate. Compound **13** should be formed by an *endo*-selective dehydration of diol **12** in accordance with the Zaitsev's rule.[20] Conversion of

(19) Silverman, G. S.; Rakita, P. E. In *Handbook of Grignard Reagent*; Marcel Dekker: New York, Basel, Hong Kong, 1996; pp 497−526.

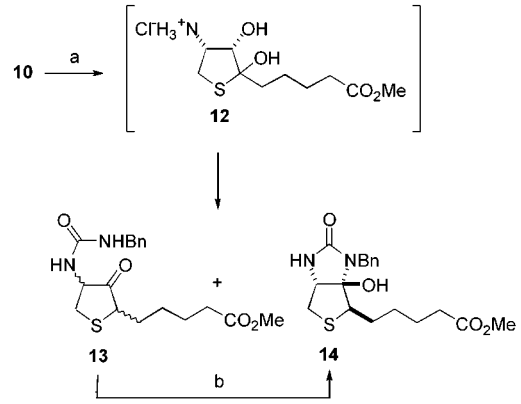
(20) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; A Wiley-Interscience Publication: John Wiley & Sons: New York, 2001; p 1314.

SCHEME 3[a]



[a] Reagents and yields: (a) (i) Me_2SO_4, K_2CO_3, DMF, (ii) crystallization from AcOEt−hexane, 73%; (b) $ClCO_2Me$, Et_3N, DMAP, THF, quant.

SCHEME 4[a]



[a] Reagents and yields: (a) (i) HCl−AcOEt, (ii) BnNCO, Et_3N, THF, 75%, **13**/**14** = 3:1; (b) DBU (0.1 equiv), THF, 73%.

13 to **14** was alternatively conducted in good yield by the treatment with DBU (0.1 equiv) in THF. Compound **14** was, however, found to have a configurationally incorrect C-4 side chain and to be completely *racemic* when derived from **13** using DBU.[21]

Because the *N*-benzyl group in the cyclized product **14** occupies the concave side of the bicyclic ring skeleton as shown by the X-ray structure (Figure 2), the 4-methoxycarbonylbutyl chain is formed *cis* to the hydroxyl group to avoid the steric repulsion between the *N*-benzyl group and the 4-methoxycarbonylbutyl chain. In an attempt to obtain the correct stereocenter at the C-4 position, a substrate **15** carrying an unsubstituted ureido group was then tried in the cyclization. While treatment of **11** with HCl in AcOEt followed by KOCN simultaneously effected the ureido formation and the cyclization, no stereocontrol was found at the C-4 position resulting in a 1:1 mixture of epimers **16** (Scheme 5). [22]

To obtain desirable *exo*-olefin circumventing the formation of the configurationally labile ketones **13** and **15**, compound **10** was converted to carbonate **11** (Scheme 3). This may permit the preferential formation of an *exo*-olefin over an *endo*-olefin by taking advantage of an inductive and/or a steric effect of the carbonate.[23]

As expected, treatment of **11** with HCl in AcOEt in the presence of MS 4 Å gave *exo*-olefin **6a** in good yield (83%) after treatment with potassium cyanate (Table 4, entry 1). However, in this case, a considerable amount of epimerization at the C-3 position of **6a** was observed (*cis*/*trans* = 62:38) (Table 4, entry 1). Use of toluene as the solvent and addition of MeOH not only improved the yield but also reduced the amount of epimerization to give **6a** in a ratio of *cis*/*trans* = 94:6 and in 74% yield (Table 4, entry 3). Use of acetyl chloride (20 equiv) in the presence of methanol (30 equiv) as a convenient source for hydrogen chloride considerably improved the reaction to give **6a** in higher yield with the original asymmetric center virtually retained as such (86%, *cis*/*trans* = 98:2) (Table 4, entry 4).

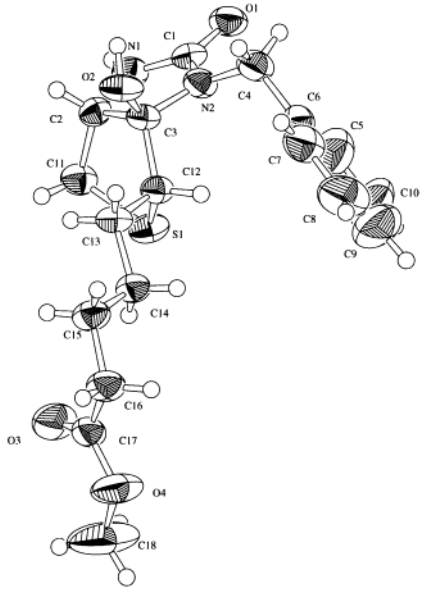
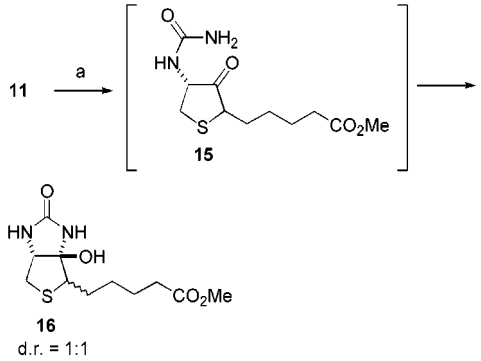


FIGURE 2. The ORTEP II diagram of compound **14**.

SCHEME 5[a]



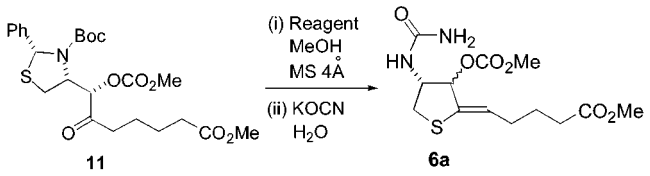
[a] Reagents and yields: (a) (i) HCl−AcOEt, (ii) KOCN, 74%.

With compound **6a** in hand, we attempted the palladium-catalyzed ring closure of **6a** (Table 5). Treatment of **6a** with $Pd(OAc)_2$ (30 mol %) in the presence of $P(OEt)_3$ and $NaHCO_3$ in aqueous THF[24]afforded the desired cyclized product **7a** albeit in a poor yield (30%) (Table 5, entry 1). Either lack of base or use of a strong base (NaH)

(21) While compound **14** obtained from **13** using DBU showed no optical rotation, that derived from **10** under less basic conditions had an optical rotation of $[\alpha]^{24}_D$ +2 (*c*, 1.01, $CHCl_3$).

(22) Product **16** was assigned to be a mixture of epimers at C-4 position, the ee of which was not determined while it showed some optical rotation {$[\alpha]^{24}_D$ +25.1 (*c*, 1.01, $CHCl_3$)].

TABLE 4. Synthesis of 6a from 11[a]

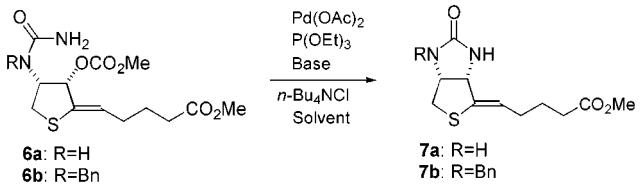


11 6a

entry	reagent (equiv)	MeOH (equiv)	mol sieves, 4 Å (wt %)	solvent	*T* (°C)	*t* (h)	yield[b] (%)	*cis*/*trans*[b]
1	HCl−AcOEt (20)	0	1	AcOEt	25	7	83	62:38
2	HCl−AcOEt (20)	0	1	toluene	0	5.5	74	85:15
3	HCl−AcOEt (20)	10	1	toluene	0	5	74	94:6
4	AcCl (20)	30	0	toluene	0	1	86[c]	98:2

[a] The reactions were conducted on 0.2 mmol scale. [b] Determined by HPLC. [c] Isolated yield.

TABLE 5. Palladium-Catalyzed Ring Closure

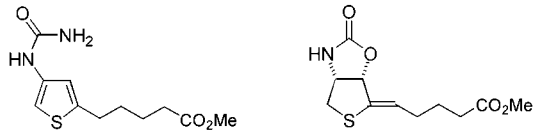


6a: R=H
6b: R=Bn

7a: R=H
7b: R=Bn

entry	compd	R	$Pd(OAc)_2$ (mol %)	base	*n*-Bu_4NCl (mol %)	solvent	*T* (°C)	*t* (h)	product	yield[a] (%)
1	**6a**	H	30	$NaHCO_3$	0	THF−H_2O	38	24	7a	30[b]
2	**6a**	H	30	none	0	THF−H_2O	38	24	17	78
3	**6a**	H	30	NaH	0	THF−H_2O	38	24	18	66
4	**6b**	Bn	10	$NaHCO_3$	0	THF−H_2O	38	24	7b	60
5	**6b**	Bn	10	$NaHCO_3$	10	DMF	80	5	7b	63
6	**6b**	Bn	10	$NaHCO_3$	10	DMF	100	2	7b	77[b]

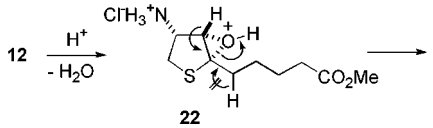
[a] Determined by HPLC. [b] Isolated yield.



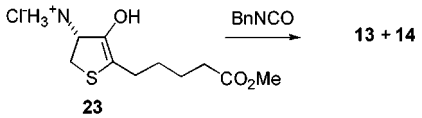
17 18

in place of $NaHCO_3$ was detrimental, yielding a thiophene **17** or a 2-oxazolidinone derivative **18**, respectively (Table 5, entries 2 and 3). De Clercq and co-workers have pointed out the importance of an *N*-benzyl group in their elegant thermal ring-closure of an ene carbamoyl azide

(23) After E_1-elimination of the tertiary hydroxyl group in **12**, generated carbocation may be trapped by the vicinal hydroxyl group to give oxiranium cation **22**, which may be responsible for the selective formation of *endo*-olefin **23**. In the case of the carbonate derivative, this neighboring group effect should be negligible due to the less basic nature of the oxygen atom attached to the electron-deficient methoxycarbonyl group (inductive effect), and a steric factor of the carbonate group may induce the exclusive formation of the *exo*-olefin.



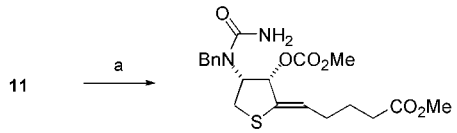
22



23

(24) Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *Synlett* **1995**, 609.

SCHEME 6[a]

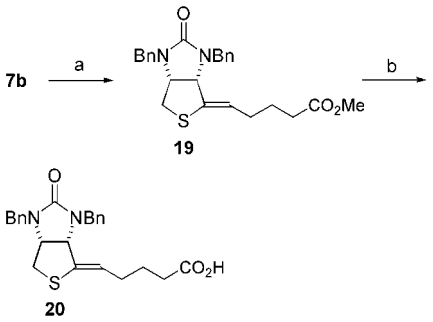


6b

[a] Reagents and yields: (a) (i) AcCl, MeOH, toluene, (ii) PhCHO, $NaBH_3CN$, THF, H_2O, (iii) KOCN, H_2O, 82%.

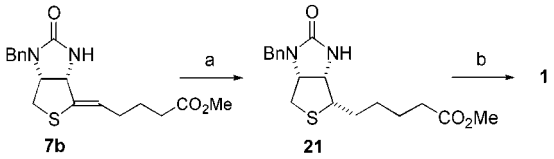
at the C-3 and C-3a positions of the (+)-biotin ring skeleton.[7c] Accordingly, an *N*-benzyl derivative **6b** was tested in place of **6a**. Compound **6b** was readily prepared from **11** in 82% yield by a slight modification of the reaction sequence involving a reductive alkylation with benzaldehyde (Scheme 6). The *Z*-configuration and enantiomeric purity (>99% ee) of **6b** were unequivocally confirmed by single-crystal X-ray analysis and HPLC, respectively. Compound **6b** was subjected to the same reaction conditions as those for the cyclization of **6a**, expectedly affording **7b** in better yield (60%, Table 5, entry 4). The reaction under solid−liquid-phase transfer conditions at 100 °C using a catalytic amount of tetrabutylammonium chloride in DMF[25] was found to be ex-

SCHEME 7[a]



[a] Reagents and yields: (a) BnBr, NaH, DMF, 92%; (b) NaOH, MeOH, H_2O, 72%.

SCHEME 8[a]



[a] Reagents and yields: (a) H_2, $Pd(OH)_2$/C, AcOEt, quant; (b) (i) NaOH, MeOH, H_2O (ii) $MeSO_3H$, xylene, 84%.

tremely effective in providing **7b** in much improved yield (Table 5, entry 6, 77%).[26] Olefin **7b** had been tentatively assigned[11] to have *E*-configuration by comparison of the ^1H and ^{13}C NMR spectra with those described in a literature.[7c] However, the assignment in the literature[7c] was found to be incorrect: *Z*-configuration of **7b** was unequivocally confirmed by single-crystal X-ray analysis of carboxylic acid **20** derived from **7b** through *N*-benzylation followed by hydrolysis (Scheme 7). The enantiomeric purity of **7b** was determined to be >99% ee by HPLC.

Conversion to (+)-Biotin (1). Compound **7b** was hydrogenated according to the reported procedure to give **21** in quantitative yield.[7c] Deblocking of **21** was sequentially conducted through hydrolysis of the ester group followed by cleavage of the benzyl group with methanesulfonic acid.[27] Isolation of (+)-biotin (**1**) was best performed by converting to the water soluble sodium salt, treating the aqueous solution with activated charcoal and subsequent crystallization with HCl (Scheme 8). Although we have previously used a reported procedure[7c] employing HBr for the conversion of **21** to **1**, the present protocol is practical since it avoids a tedious purification by an ion exchange chromatography. The target compound **1** obtained by the present method showed mp, optical rotation, IR, NMR, and MS spectra in complete accordance with those of the authentic sample.

Conclusion

In summary, a novel and efficient synthesis of (+)-biotin starting from readily accessible L-cysteine was accomplished. A highly diastereoselective cyanosilylation of an α-amino aldehyde derived from L-cysteine, a di-Grignard reaction of the resultant *O*-TMS-cyanohydrin, and a palladium-catalyzed intramolecular allylic amination efficiently established the contiguous stereogenic centers and the bicyclic ring skeleton of (+)-biotin. The high overall yield, lower number of steps, simple operational procedures, and use of the mild reaction conditions permit ready access to (+)-biotin, a compound of growing significance.

Experimental Section

General Method. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane used as an internal standard. Optical rotations were measured at the indicated temperature with a sodium lamp (D line, 589 nm). 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 was accomplished using 5% phosphomolybdic acid in ethanol−heat or visualized by UV light where feasible. All solvents and reagents were used as received.

(2*RS*,4*R*)-2-Phenylthiazolidine-4-carboxylic Acid (8).[13] To a solution of L-cysteine (121 g, 1 mol) in a mixed solvent of water (0.65 L) and EtOH (0.2 L) were successively added benzaldehyde (106 g, 1 mol) and ethanol (0.5 L). After the mixture was stirred at 25 °C for 3 h, the crystals formed were collected, washed with water, and dried to afford **8** (200 g, 95.6%) as colorless crystals. ^1H NMR (DMSO-d_6) δ 7.26−7.54 (m, 5H), 5.67 (s, 0.6H), 5.51 (s, 0.4H), 4.24 (dd, J = 7.0, 4.6 Hz, 0.6H), 3.90 (dd, J = 8.8, 7.0 Hz, 0.4H), 3.26−3.42 (m, 1H), 3.03−3.18 (m, 1H).

(2*RS*,4*R*)-4-(Hydroxymethyl)-2-phenylthiazolidine (9).[13] To ethanol (579 mL) was added $SOCl_2$ (87 mL, 1.19 mol) below 0 °C and subsequently was added **8** (121 g, 0.578 mol). After the mixture was stirred at 25 °C for 17 h, it was concentrated at reduced pressure. To the residue was added AcOEt, and the mixture was evaporated. To the residue were added CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was separated and washed with water, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to give (2*RS*,4*R*)-2-phenylthiazolidine-4-carboxylic acid ethyl ester (137 g, quant). To a solution of $CaCl_2$ (42 g, 0.38 mol) in EtOH (500 mL) was added a solution of $NaBH_4$ (19.6 g, 0.52 mol) in EtOH (660 mL) below −10 °C. To the suspension was added a solution of (2*RS*,4*R*)-2-phenylthiazolidine-4-carboxylic acid ethyl ester (137 g, 0.578 mol) in EtOH (270 mL) below −10 °C, and the mixture was warmed to 10 °C for 2 h. To the mixture was added HCl−MeOH (19.5 wt %, 390 mL). The mixture was evaporated and 25% aq NH_3 was added to adjust the pH value to 9. The mixture was extracted with CH_2Cl_2, and the extract was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure to give **9** (115 g, quant). IR (KBr) ν = 3239, 1464 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.19−7.54 (m, 5H), 5.61 (d, J = 8.8 Hz, 0.4H), 5.51 (d, J = 12 Hz, 0.6H), 4.85−4.91 (m, 0.6H), 4.75−4.81 (m, 0.4H), 3.68−3.73 (m, 1.2H), 3.44−3.61 (m, 0.8H), 3.15−3.40 (m, 1H), 3.06 (dd, J = 9.5, 6.1 Hz, 0.6H), 3.00−3.15 (m, 0.4H), 2.86 (dd, J = 9.5, 9.5 Hz, 0.6H), 2.65−2.95 (m, 1.4H); SIMS m/z 196 ($M^+ + 1$).

(2*R*,4*R*)-4-(Hydroxymethyl)-2-phenylthiazolidine-3-carboxylic Acid *tert*-Butyl Ester (2).[7c] To a solution of **9** (19.5 g, 0.10 mol) in a mixed solvent of THF (195 mL) and water (98 mL) were successively added $(Boc)_2O$ (23.8 g, 0.11 mol) and Na_2CO_3 (6.41 g, 0.06 mol) below 10 °C. The mixture was stirred at 10 °C for 30 min and extracted with CH_2Cl_2. The extract was washed with water and saturated aqueous NaCl, dried

(25) Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1287.

(26) Since the ring closure of **6** to 2-imidazolidinone derivative **7** occurred at the position originally substituted with a carbonate, the cyclization should proceed through a η^3-allyl species in contrast to the recently suggested pathway involving the aminopalladation. See: Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12. For another example of the cyclization through a η^3-allyl species, see: Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516.

(27) Takahashi, T.; Shimaji, K.; Maejima, K. Jpn Tokkyo Koho JP 63-8954, Feb 2, 1979.

over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1 to 2:1) to give **2** (26.1 g, 88%) as colorless crystals. mp 67−69 °C; $[\alpha]^{24}_D$ +102.6 (*c*, 1.0, $CHCl_3$) [lit.:[7c] mp 46−48 °C; $[\alpha]^{20}_D$ +65.2 (*c*, 1.0, $CHCl_3$)]; IR (Nujol) ν = 3458, 1698, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23−7.39 (m, 5H), 6.03 (s, 1H), 4.49−4.63 (m, 1H), 3.83−4.01 (m, 2H), 3.26 (dd, *J* = 12, 6.7 Hz, 1H), 2.87 (dd, *J* = 12, 4.0 Hz, 1H), 2.56 (brs, 1H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.7, 141.1 (2s), 128.2, 127.6, 125.9 (3d), 81.3 (s), 66.1 (d), 64.6 (t), 63.9 (d), 32.7 (t), 27.9 (q); SIMS *m*/*z* 296 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N,4.74. Found: C, 60.85; H, 7.03; N, 4.75; Diastereomeric purity: >99% de (HPLC: Inertsil ODS-2, CH_3CN/10 mM aq KH_2PO_4 (pH 3) = 40:60, 40 °C, 1 mL/min, 254 nm, *cis* (**2**): 15.1 min, *trans*: 13.8 min).

(2*R*,4*R*)-4-Formyl-2-phenylthiazolidine-3-carboxylic Acid *tert*-Butyl Ester (3).[7c] To a solution of **2** (59.1 g, 0.20 mol) in DMSO (296 mL) and toluene (59 mL) was added Et_3N (50.6 g, 0.50 mol) at 25 °C. To the solution was added SO_3−pyridine (79.6 g, 0.50 mol) at 10 °C, and the mixture was stirred for 2 h. The mixture was poured into ice and water (1.25 L) and extracted with AcOEt. The organic layer was washed with 10% aqueous citric acid and water, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The crude crystals formed were suspended in hexane and collected to give **3** (55.8 g, 95%) as colorless crystals. mp 84−85 °C (lit.:[7c] oil); IR (Nujol) ν = 1730, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.79 (brs, 1H), 7.28−7.43 (m, 5H), 6.01 (brs, 1H), 4.82 (br, 1H), 3.15−3.40 (m, 2H), 1.28 (brs, 9H).

A Typical Procedure for the Cyanosilylation of 3 (Table 2, entry 10). To a solution of **3** (0.293 g, 1 mmol) in CH_2Cl_2 (9 mL) were successively added *n*-Bu_3P (0.0249 mL, 0.1 mmol) and TMSCN (0.147 mL, 1.1 mmol) below −10 °C, and the mixture was stirred at −10 °C for 0.5 h. The solution was concentrated at reduced pressure to give the *O*-TMS cyanohydrin **4** (0.393 g, quant). To the residue was added 10% citric acid in MeOH (10 g), and the mixture was stirred at 25 °C for 4 h. The yield and diastereomeric ratio of the cyanohydrin (306 mg, 96%, *anti*/*syn* = 92:8) were determined by HPLC (Nucleosil 5C18, CH_3CN/H_2O = 50:50, 40 °C, 0.8 mL/min, 254 nm, *anti*: 8.1 min, *syn*: 9.4 min) after the volume of the mixture was adjusted to 100 mL by adding methanol. The MeOH solution was evaporated, and AcOEt and water were added to the residue. The organic layer was washed with water and dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$/AcOEt = 5:5:1) to give the *anti*-cyanohydrin (272 mg, 85%) and the *syn*-cyanohydrin (14 mg, 4%) both as colorless crystals.

(*S*)-2-[(2*R*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-phenylthiazolidin-4-yl]-2-hydroxyacetonitrile (*anti*-Cyanohydrin). mp 139−140 °C; $[\alpha]^{25}_D$ +118 (*c*, 1.0, $CHCl_3$); IR (KBr) ν = 3406, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24−7.46 (m, 5H), 6.04 (s, 1H), 4.84 (d, *J* = 5.3 Hz, 1H), 4.66−4.72 (m, 1H), 3.31 (dd, *J* = 12, 6.1 Hz, 1H), 3.16 (dd, *J* = 12, 3.9 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.5 (s), 129.0, 128.5, 126.4 (3d), 119.2, 83.3 (2s), 67.2, 65.7, 64.4 (3d), 32.9 (t), 28.4 (q); SIMS *m*/*z* 321 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N,8.74. Found: C, 59.91; H, 6.19; N, 8.72.

(*R*)-2-[(2*R*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-phenylthiazolidin-4-yl]-2-hydroxyacetonitrile (*syn*-Cyanohydrin). mp 117−118 °C; $[\alpha]^{25}_D$ +89.4 (*c*, 1.0, $CHCl_3$); IR (KBr) ν = 3305, 1657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.40 (m, 5H), 5.97 (s, 1H), 4.77−4.84 (m, 2H), 3.45 (dd, *J* = 13, 6.9 Hz, 1H), 3.00 (dd, *J* = 13, 0.9 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR δ 139.9 (s), 129.1, 128.8, 126.5 (3d), 119.0, 83.7 (2s), 67.4, 66.2, 65.2 (3d), 32.9 (t), 28.2 (q); SIMS *m*/*z* 321 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.75; H, 6.19; N, 8.52.

(*S*)-7-[(2*R*,4*R*)-3-*tert*-Butoxycarbonyl-2-phenylthiazolidin-4-yl]-7-hydroxy-6-oxoheptanoic Acid (5). To a solution of **3** (44 g, 0.15 mol) in CH_2Cl_2 (225 mL) were successively added *n*-Bu_3P (3 g, 0.015 mol) and TMSCN (16.4 g, 0.165 mol) at −10 °C, and the solution was stirred at the same temperature for 30 min. The solution was concentrated at reduced pressure. To the residue was added CH_2Cl_2 (150 mL), and the solution was concentrated at reduced pressure to give the *O*-TMS cyanohydrin **4** (58.9 g, quant). To a suspension of Mg (23.0 g, 0.95 mol) in *n*-Bu_2O (300 mL) was added a solution of 1,4-dibromobutane (97.2 g, 0.45 mol) in toluene (300 mL) at 40−70 °C for 30 min. After the mixture was stirred at 40−50 °C for 1 h, a solution of **4** (58.9 g, 0.15 mol) in toluene (300 mL) was added at −25 to −30 °C for 15 min, and the mixture was stirred at the same temperature for 30 min. Carbon dioxide was bubbled into the mixture at −30 °C for 1 h. The reaction mixture was poured into 10% aq citric acid [citric acid (101 g), water (909 g)] and extracted with AcOEt. The extract was filtered, washed with water, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. To the residue was added a mixture of citric acid, acetone, and water [citric acid (45 g), acetone (360 g), water (90 g)], and the mixture was stirred at 25 °C for 7.3 h. The mixture was concentrated at reduced pressure, and to the residue were added water and AcOEt. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:2 to 2:1) to give **5** (50.0 g, 79%; *anti*/*syn* = 13:1) (HPLC: Inertsil ODS-2, CH_3CN/10 mM aq KH_2PO_4 (pH 3) = 40:60, 40 °C, 1 mL/min, 230 nm, *anti*: 17.2 min, *syn*: 24.3 min). mp 101−103 °C; $[\alpha]^{23}_D$ +91.6 (*c*, 1.0, acetone); IR (Nujol) ν = 3470, 2976, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (d, *J* = 6.6 Hz, 2H), 7.30−7.40 (m, 3H), 6.07 (s, 1H), 4.73 (d, 1H), 4.42−4.51 (m, 1H), 3.23 (dd, *J* = 12, 5.1 Hz, 1H), 3.02 (dd, *J* = 12, 6.6 Hz, 1H), 2.57 (br, 2H), 2.34 (brt, *J* = 7.0 Hz, 2H), 1.51−1.80 (m, 4H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 210.7, 179.1, 154.3, 140.6 (4s), 128.1, 127.9, 127.0 (3d), 81.7 (s), 76.2, 66.6, 65.0 (3d), 33.6, 28.9 (2t), 28.0 (q), 24.5, 23.9, 22.7 (3t); SIMS *m*/*z* 424 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{29}NO_6S$: C, 59.55; H, 6.90; N, 3.31. Found: C, 59.60; H, 6.90; N, 3.13.

(*S*)-7-[(2*R*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-phenylthiazolidin-4-yl]-7-hydroxy-6-oxoheptanoic Acid Methyl Ester (10). To a solution of **5** (50.0 g, 0.12 mol; *anti*/*syn* = 13:1) in DMF (200 mL) were successively added K_2CO_3 (17.1 g, 0.12 mol) and Me_2SO_4 (15.6 g, 0.12 mol) at 10 °C for 10 min. The mixture was warmed to 25 °C for 2 h and stirred overnight at 25 °C. The mixture was diluted with AcOEt (300 mL), washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was dissolved in hot AcOEt (40 mL) and diluted with hexane (280 mL), and the mixture was cooled to 25 °C. The crystals formed were collected to give **10** (37.9 g, 73%) as colorless crystals. mp 110−113 °C; $[\alpha]^{20}_D$ +95 (*c*, 1.0, $CHCl_3$); IR (Nujol) ν = 3431, 1722, 1708, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (d, *J* = 6.6 Hz, 2H), 7.24−7.39 (m, 3H), 6.07 (s, 1H), 4.72 (br, 1H), 4.42−4.50 (m, 1H), 3.66 (s, 3H), 3.22 (dd, *J* = 12, 5.1 Hz, 1H), 3.02 (dd, *J* = 12, 6.6 Hz, 1H), 2.56 (br, 2H), 2.29 (brt, *J* = 7.0 Hz, 2H), 1.50−1.70 (m, 4H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.7, 154.3, 140.8, 128.4 (4s), 128.2, 127.9, 127.1 (3d), 81.7 (s), 76.3, 66.6, 65.1 (3d), 51.5 (q), 39.6, 33.7, 31.3 (3t), 28.1 (q), 24.3, 22.9 (2t); SIMS *m*/*z* 438 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.39; H, 7.14; N, 3.20. Found: C, 60.49; H, 7.21; N, 3.05; Optical purity: >99% ee (HPLC: CHIRALPAK AD, EtOH/*n*-hexane = 5:95, 40 °C, 0.5 mL/min, 254 nm, **10**: 35.9 min, the antipode of **10**: 25.2 min).

(*S*)-7-[(2*R*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-phenylthiazolidin-4-yl]-7-methoxycarbonyloxy-6-oxoheptanoic Acid Methyl Ester (11). To a solution of **10** (1.0 g, 2.29 mmol) and Et_3N (0.48 mL, 3.43 mmol) in THF (10 mL) were successively added DMAP (cat.) and methyl chloroformate (0.21 mL, 2.74 mmol) at 0 °C. After the mixture was stirred for 1 h, triethylamine (0.72 mL, 5.15 mmol) and methyl chloroformate (0.32 mL, 4.11 mmol) were added to the mixture at 0 °C. After the mixture was stirred for 1.5 h, it was diluted with AcOEt.

The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to give **11** (1.195 g, quant) as colorless crystals. mp 88−90 °C; $[\alpha]^{20}_D$ +51.8 (*c*, 1.0, MeOH); IR (KBr) 1750, 1730, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57−7.56 (m, 2H), 7.36−7.25 (m, 3H), 5.97 (br s, 1H), 5.42−5.29 (m, 1H), 4.72−4.68 (m, 1H), 3.76 (br s, 3H), 3.66 (s, 3H), 3.21−3.08 (m, 2H), 2.88−2.60 (m, 1H), 2.50−2.40 (m, 1H), 2.40−2.33 (m, 2H), 1.70−1.68 (m, 4H), 1.25 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 205.6, 174.2, 171.7, 155.2, 154.4, 140.6, 135.2 (7s), 128.6, 128.2, 127.3, 77.4, 67.2, 62.6 (6d), 55.8, 51.9 (2q), 34.3, 32.2 (2t), 28.4 (q), 24.6, 22.8 (2t); SIMS *m*/*z* 496 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{33}NO_8S$; C, 58.17; H, 6.71; N, 2.83. Found: C, 58.12; H, 6.64; N, 2.82.

(2*Z*,3*R*,4*R*)-2-{4-(Methoxycarbonyl)butylidene}-3-(methoxycarbonyloxy)-4-ureidotetrahydrothiophene (6a). To a stirred solution of MeOH (0.25 mL, 6.1 mmol) in toluene (1.0 mL) was added AcCl (0.29 mL, 4.0 mmol) at 0 °C. After the mixture was stirred for 15 min, **11** (0.1 g, 0.2 mmol) was added to the mixture at 0 °C. After the mixture was stirred for 1 h, the solvent was evaporated and coevaporated with AcOEt (4 × 2.0 mL). To the residue were added THF (2.0 mL), water (2.0 mL), and KOCN (32.8 mg, 0.4 mmol), and the mixture was stirred at 25 °C for 12 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 50:1) to give **6a** (57.8 mg, 86% yield) as colorless crystals. mp 101−104 °C; $[\alpha]^{20}_D$ −98.6 (*c*, 1.0, MeOH); IR (Nujol) 3358, 1750, 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.77 (t, *J* = 7.0 Hz, 1 H), 5.54 (br d, *J* = 8.2 Hz, 1H), 5.39 (d, *J* = 4.1 Hz, 1H), 4.78 (br s, 1H), 4.63−4.55 (m, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.22 (dd, *J* = 5.9, 11 Hz, 1H), 3.00 (dd, *J* = 7.8, 11 Hz, 1H), 2.34−2.28 (m, 2H), 2.09−2.05 (m, 2H), 1.82−1.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.8, 158.4, 155.2, 135.5 (4s), 124.4, 80.6 (2d), 55.5 (q), 53.7 (d), 52.1, 34.0, 33.7, 30.3, 24.0 (5t); SIMS *m*/*z* 333 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{20}N_2O_6S$; C, 46.98; H, 6.07; N, 8.43. Found: C, 46.96; H, 6.11; N, 8.32.

(2*Z*,3*R*,4*R*)-2-{4-(Methoxycarbonyl)butylidene}-3-(methoxycarbonyloxy)-4-(3-benzylureido)tetrahydrothiophene (6b). To a stirred solution of MeOH (5 mL, 120 mmol) in toluene (20 mL) was added AcCl (5.4 mL, 80 mmol) at 0 °C. After the mixture was stirred for 15 min, **11** (2.0 g, 4.0 mmol) was added to the mixture at 0 °C. The mixture was stirred for 1 h, and the solvent was evaporated and coevaporated with AcOEt (4 × 40 mL). To the residue dissolved in a mixed solvent of THF (20 mL) and a buffered aqueous solution (20 mL, pH = 4, citric acid-$NaHCO_3$) were successively added benzaldehyde (0.42 mL, 4.0 mmol) and $NaBH_3CN$ (1 M in THF, 2.0 mL, 2.0 mmol) at 5 °C over 1 h. After the mixture was stirred for 1.5 h, 1 M aq HCl (8.0 mL, 8.0 mmol) and KOCN (0.66 g, 8.0 mmol) were added at 5 °C. The mixture was stirred at 25 °C for 21 h and diluted with AcOEt. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1 to 1:2) to give **6b** (1.4 g, 82% yield) as colorless crystals. mp 105−108 °C; $[\alpha]^{20}_D$ −86.7 (*c*, 1.0, MeOH); IR (KBr) 3432, 1754, 1728, 1656, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44−7.21 (m, 5H), 5.90 (t, *J* = 7.2 Hz, 1H), 5.63 (d, *J* = 3.9 Hz, 1H), 5.16−5.10 (m, 1H), 4.71 (d, *J* = 18 Hz, 1H), 4.63 (brs, 1H), 4.61 (d, *J* = 18 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.33 (dd, *J* = 10, 11 Hz, 1H), 3.01 (dd, *J* = 6.9, 10 Hz, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.04−1.99 (m, 2H), 1.78−1.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.2, 159.6, 155.1, 137.5, 135.6 (5s), 129.5, 128.0, 126.0, 125.9, 81.2, 58.0 (6d), 55.1, 51.9 (2q), 48.9, 33.8, 30.5, 30.0, 24.1 (5t); SIMS *m*/*z* 423 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{26}N_2O_6S$; C, 56.86; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.04; N, 6.61; Optical purity: >99% ee (HPLC: CHIRALPAK AD, EtOH/*n*-hexane = 50:50, 40 °C, 0.45 mL/min, 254 nm, **6b**: 16.7 min, the antipode of **6b**: 26.2 min).

(3a*S*,4*Z*,6a*R*)-5-{Hexahydro-2-oxo-4*H*-thieno[3,4-*d*]imidazol-4-ylidene}pentanoic Acid Methyl Ester (7a). To a stirred solution of **6a** (10 mg, 0.03 mmol) and $NaHCO_3$ (5 mg, 0.06 mmol) in THF (0.6 mL) and water (0.1 mL) were added triethyl phosphite (6.9 mg, 0.0416 mmol) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol) at 25 °C, and the mixture was stirred at 37−40 °C for 24 h. After evaporation of the solvent, the residue was purified by silica gel preparative TLC ($CHCl_3$/MeOH = 10:1) to give **7a** (2.3 mg, 30% yield) as a colorless oil. IR (KBr) 3238, 1731, 1690 cm^{-1}; $[\alpha]^{22}_D$ +290 (*c*, 0.10, MeOH); ^1H NMR ($CDCl_3$) δ 5.55 (t, *J* = 7.1 Hz, 1H), 4.83 (br s, 1H), 4.76 (br s, 1H), 4.68 (d, *J* = 7.6 Hz, 1H), 4.51−4.49 (m, 1H), 3.68 (s, 3H), 3.24 (dd, *J* = 5.7, 12 Hz, 1H), 3.02 (dd, *J* = 3.1, 12 Hz, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.18−2.11 (m, 2H), 1.79−1.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.9, 161.9, 141.6 (3s), 122.9, 63.9, 58.3 (3d), 51.6 (q), 39.6, 33.4, 31.1, 24.1 (4t); SIMS *m*/*z* 257 ($M^+ + 1$). Anal. Calcd for $C_{11}H_{16}N_2O_3S$; C, 51.54; H, 6.29; N, 10.93. Found: C, 51.42; H, 6.05; N, 10.66.

(3a*S*,4*Z*,6a*R*)-5-{Hexahydro-1-benzyl-2-oxo-4*H*-thieno-[3,4-*d*]imidazol-4-ylidene}pentanoic Acid Methyl Ester (7b).[7c] To a stirred mixture of **6b** (1.7 g, 3.9 mmol), $NaHCO_3$ (990 mg, 15 mmol), and tetrabutylammonium chloride (110 mg, 0.39 mmol) in DMF (78 mL) and H_2O (13 mL) were added $P(OEt)_3$ (440 mg, 2.6 mmol) and $Pd(OAc)_2$ (90 mg, 0.39 mmol) at 25 °C, and the mixture was stirred at 100 °C for 2 h. After evaporation of the solvent, the residue was dissolved in AcOEt and washed with water, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to give **7b** (1.1 g, 77% yield) as a colorless oil. IR (Nujol) 3218, 2948, 1726, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.27 (m, 5H), 5.55 (t, *J* = 7.0 Hz, 1H), 5.10 (br s, 1H), 4.72 (d, *J* = 15 Hz, 1H), 4.52 (d, *J* = 7.6 Hz, 1H), 4.23−4.19 (m, 1H), 4.15 (d, *J* = 15 Hz, 1H), 3.67 (s, 3H), 3.06−2.97 (m, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.15−2.09 (m, 2H), 1.78−1.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.3, 160.7, 142.3, 137.1 (4s), 129.1, 128.8, 128.1, 123.0, 62.0 (5d), 61.4 (s), 52.0 (q), 46.1, 36.4, 33.8, 31.5, 24.5 (5t); SIMS *m*/*z* 347 ($M^+ + 1$); Optical purity: >99% ee (HPLC: CHIRALPAK AD, EtOH/*n*-hexane = 50:50, 30 °C, 0.45 mL/min, 254 nm, **7b**: 32.3 min, the antipode of **7b**: 126.1 min).

2-{4-(Methoxycarbonyl)butyl}-4-(3-benzylureido)-3-oxotetrahydrothiophene (13). To a stirred suspension of **10** (880 mg, 2.01 mmol) in AcOEt (10 mL) was added 4 N HCl in AcOEt (8.8 mL, 35.2 mmol) at 0 °C. After the mixture was stirred at 25 °C for 2 h, the solvent was evaporated and coevaporated with AcOEt (3 × 10 mL). The resulting residue was dissolved in water (10 mL) and washed with AcOEt (10 mL). The organic phase was extracted with water (10 mL), and combined aqueous solution was washed with AcOEt (10 mL), evaporated and coevaporated with toluene (3 × 10 mL). To the residue dissolved in THF (8.8 mL) were successively added benzylisocyanate (0.25 mL, 2.01 mmol) and Et_3N (0.28 mL, 2.01 mmol) at 0 °C. After the mixture was stirred at 25 °C for 2.5 h, the mixture was diluted with AcOEt (20 mL). The organic phase was washed with water and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/acetone = 20:1 to $CHCl_3$/MeOH = 20:1) to give **13** (417 mg, 57%) as a yellow powder and **14** (128 mg, 18%) as colorless crystals. **13**: IR (KBr) 3289, 1737, 1626, 1569 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.35−7.22 (m, 10H), 6.81−6.69 (m, 2H), 6.50−6.39 (m, 2H), 4.46−4.30 (m, 2H), 3.62−3.51 (m, 2H), 3.58 (s, 6H), 3.21−3.04 (m, 2H), 2.93−2.76 (m, 2H), 2.34−2.27 (m, 4H), 1.93−1.80 (m, 2H), 1.56−1.21 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 200.5, 186.2, 170.3, 170.2, 153.5 (5s), 141.2, 140.0, 139.6, 71.2, 70.9 (5d), 64.2 (q), 61.8, 59.9 (2d), 55.9, 46.1, 46.0, 45.3, 43.8, 41.9, 41.3, 39.4, 39.1, 37.1, 37.0 (11t); SIMS *m*/*z* 365 ($M^+ + 1$); HRMS *m*/*z* ($M + H)^+$: Calcd for $C_{18}H_{25}N_2O_4S$, 365.1535. Found, 365.1501. **14**: mp 173−174 °C; $[\alpha]^{20}_D$ +2 (*c*, 1.0, MeOH); IR (neat) 3283, 1737, 1671 cm^{-1}; ^1H NMR (DMSO-d_6)

δ 7.34−7.20 (m, 5H), 7.10 (s, 1H), 6.39 (s, 1H), 4.78 (d, J = 16 Hz, 1H), 4.17 (d, J = 16 Hz, 1H), 3.81−3.80 (m, 1H), 3.56 (s, 3H), 3.14 (dd, J = 6.3, 12 Hz, 1H), 2.70 (dd, J = 3.0, 8.2 Hz, 1H), 2.42 (dd, J = 4.7, 12 Hz, 1H), 2.15 (t, J = 7.3 Hz, 2H), 1.71−1.61 (m, 1H), 1.39−1.18 (m, 4H), 0.89−0.77 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 173.5, 159.7, 140.3 (3s), 128.4, 127.3, 126.9 (3d), 99.5 (s), 65.7, 56.3 (2d), 51.5 (q), 41.8, 39.2, 28.8, 28.0, 24.3 (5t); SIMS m/z 365 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{24}N_2O_4S$; C, 59.32; H, 6.64; N, 7.69; S, 8.80. Found: C, 59.30; H, 6.61; N, 7.52; S, 8.68.

(3a*R,4*R**,6a*R**)-Hexahydro-3-benzyl-3a-hydroxy-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (14).** To a stirred solution of **13** (50 mg, 0.137 mmol) in THF (0.5 mL) was added DBU (2 μL, 0.014 mmol) at 25 °C. The mixture was stirred at 25 °C for 15 h and diluted with AcOEt. The organic phase was washed with water and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude crystals formed were suspended in MeOH and collected to give **14** (36.7 mg, 73%) as colorless crystals. The product **14** showed the same IR, NMR, and MS spectra as those of the compound **14** prepared from **10** except the optical rotation {$[\alpha]^{20}_D$ 0 (*c*, 1.0, MeOH) }.

Hexahydro-3a-hydroxy-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (16). To a stirred suspension of **10** (880 mg, 2.01 mmol) in AcOEt (10 mL) was added 4 N HCl in AcOEt (8.8 mL, 35.2 mmol) at 0 °C. After the mixture was stirred at 25 °C for 2 h, the solvent was evaporated and coevaporated with AcOEt (3 × 10 mL). The resulting residue was dissolved in water (10 mL) and washed with AcOEt (10 mL). The organic phase was extracted with water (10 mL), and the combined aqueous solution was washed with AcOEt (10 mL), evaporated, and coevaporated with toluene (3 × 10 mL). To the residue dissolved in water (8.8 mL) was added KOCN (196 mg, 2.2 mmol) at 0 °C. After the mixture was stirred at 25 °C for 15 h, it was diluted with $CHCl_3$ (20 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give **16** (407 mg, 74%) as a yellow powder. IR (KBr) 3276, 1710, 1685 cm^{-1}; $[\alpha]^{24}_D$ +25.1 (*c*, 1.01, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.25 (br s, 1H), 7.03 (br s, 1H), 6.70 (br s, 1H), 6.57 (br s, 1H), 6.15 (s, 1H), 6.08 (s, 1H), 3.86−3.84 (m, 1H), 3.77−3.69 (m, 1H), 3.58 (s, 6H), 3.15−3.06 (m, 2H), 3.01−2.89 (m, 2H), 2.45−2.36 (m, 2H), 2.30 (m, 4H), 1.91−1.17 (m, 12H); SIMS m/z 275 ($M^+ + 1$); HRMS m/z ($M - H)^-$: Calcd for $C_{11}H_{17}N_2O_4S$, 273.0909. Found, 273.0889.

4-Ureidothiophene-2-pentanoic Acid Methyl Ester (17). To a stirred solution of **6a** (100 mg, 0.3 mmol) in THF (6.0 mL) were added $P(OEt)_3$ (19.9 mg, 0.12 mmol) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) at 25 °C, and the mixture was stirred at 65−70 °C for 22 h. After evaporation of the solvent, the residue was purified by silica gel preparative TLC ($CHCl_3$/MeOH = 10:1) to give **17** (50.8 mg, 66%) as a colorless oil. IR (neat) 3445, 3355, 1710, 1683, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.04 (br s, 1H), 6.90 (d, J = 1.5 Hz, 1H), 6.65 (d, J = 1.5 Hz, 1H), 4.90 (br s, 2H), 3.67 (s, 3H), 2.80−2.72 (m, 2H), 2.38−2.31 (m, 2H), 1.73−1.64 (m, 4H); SIMS m/z 257 ($M^+ + 1$); HRMS m/z ($M - H)^-$: Calcd for $C_{11}H_{15}N_2O_3S$, 255.0803. Found, 255.0816.

(3a*S*,4*Z*,6a*R*)-5-{Hexahydro-2-oxo-4*H*-thieno[3,4-*d*]-oxazol-4-ylidene}pentanoic Acid Methyl Ester (18). To a solution of **6a** (10 mg, 0.03 mmol) in THF (0.6 mL) were successively added NaH (1 mg, 0.03 mmol), $P(OEt)_3$ (6.9 mg, 0.0416 mmol), and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol) at 25 °C, and the mixture was stirred at 37−40 °C for 40 min. After evaporation of the solvent, the residue was purified by silica gel preparative TLC ($CHCl_3$/MeOH = 10:1) to give **18** (6.0 mg, 78%) as a colorless oil. IR (neat) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.11 (br s, 1H), 5.89 (t, J = 7.1 Hz, 1H), 5.38 (d, J = 7.3 Hz, 1H), 4.61−4.54 (m, 1H), 3.68 (s, 3H), 3.22 (dd, J = 5.5, 12 Hz, 1H), 3.02 (dd, J = 2.2, 12 Hz, 1H), 2.34 (t, J = 7.4 Hz, 2H), 2.26−2.10 (m, 2H), 1.85−1.68 (m, 2H); SIMS m/z 258 ($M^+ +$ 1); HRMS m/z ($M - H)^-$: Calcd for $C_{11}H_{14}N_2O_3S$, 256.0644. Found, 256.0638.

(3a*S*,4*Z*,6a*R*)-5-{Hexahydro-1,3-dibenzyl-2-oxo-4*H*-thieno[3,4-*d*]imidazol-4-ylidene}pentanoic Acid Methyl Ester (19). To a solution of **7b** (50 mg, 0.14 mmol) in DMF (1 mL) were successively added NaH (12 mg, 0.29 mmol) and benzyl bromide (49 mg, 0.29 mmol) at −40 °C, and the mixture was warmed to 25 °C over 3 h. After the mixture was stirred at 25 °C for 18 h, it was diluted with AcOEt. The organic phase was washed twice with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by preparative TLC (hexane/AcOEt = 2:1) to give **19** (58 mg, 92%) as a colorless oil. IR (neat) 1733, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37−7.24 (m, 10H), 5.42 (t, J = 7.1 Hz, 1H), 4.96 (d, J = 16 Hz, 1H), 4.81 (d, J = 15 Hz, 1H), 4.28 (d, J = 7.7 Hz, 1H), 4.22 (d, J = 15 Hz, 1H), 4.20−4.05 (m, 1H), 4.06 (d, J = 16 Hz, 1H), 3.66 (s, 3H), 2.98 (dd, J = 3.7, 12 Hz, 1H), 2.94 (dd, J = 5.7, 12 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 2.13−2.05 (m, 2H), 1.72−1.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.7, 159.0, 138.0, 137.2, 137.1 (5s), 128.7 (2d), 127.9, 127.6, 127.5, 127.3, 125.6, 64.5, 59.0 (7d), 51.5, 46.5, 44.9, 37.1, 33.4, 31.1, 24.2 (6t); SIMS m/z 437 ($M^+ + 1$); HRMS m/z ($M + H)^+$: Calcd for $C_{25}H_{29}N_2O_3S$, 437.1899. Found, 437.1914.

(3a*S*,4*Z*,6a*R*)-5-{Hexahydro-1,3-dibenzyl-2-oxo-4*H*-thieno[3,4-*d*]imidazol-4-ylidene}pentanoic Acid (20). To a solution of **19** (118 mg, 0.26 mmol) in MeOH (1.2 mL) and H_2O (0.3 mL) was added NaOH (13 mg, 0.32 mmol) at 10 °C, and the mixture was stirred at 25 °C for 17 h. After evaporation of MeOH, the aqueous solution was washed with ether and acidified by adding concd HCl. The mixture was extracted with AcOEt, and the organic phase was washed with water, dried over anhydrous $MgSO_4$, and evaporated. The residue was crystallized by adding hexane to afford **20** (82 mg, 72%) as colorless crystals. mp 86−87 °C; $[\alpha]^{20}_D$ +234 (*c*, 1.0, MeOH); IR (KBr) 1728, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.15 (brs, 1H), 7.23−7.36 (m, 10H), 5.42 (t, J = 7.1 Hz, 1H), 4.94 (d, J = 16 Hz, 1H), 4.80 (d, J = 15 Hz, 1H), 4.88 (d, J = 7.7 Hz, 1H), 4.22 (d, J = 15 Hz, 1H), 4.03−4.09 (m, 3H), 2.90−2.99 (m, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.04−2.15 (m, 2H), 1.55−1.70 (m, 2H); ^{13}C NMR (DMSO-d_6) δ178.2, 159.0, 137.8, 136.9, 136.8 (5s), 128.6, 128.4, 128.0, 127.7, 127.6, 127.2, 125.6, 64.6, 58.9 (9d), 46.4, 44.8, 37.0, 33.3, 30.9, 23.9 (6t); SIMS m/z 423 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{26}N_2O_3S$; C, 68.22; H, 6.20; N, 6.63. Found: C, 68.14; H, 6.09; N, 6.49.

(3a*S*,4*S*,6a*R*)-Hexahydro-1-benzyl-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (21).[7c] A mixture of 10% $Pd(OH)_2$ on carbon (50% wet) (1.6 g, 0.57 mmol) in AcOEt (490 mL) was stirred at 25 °C for 1 h under H_2 (4 atm). Then, a solution of **7b** (1.9 g, 5.7 mmol) in AcOEt (200 mL) was added to the mixture. The mixture was stirred under H_2 (4 atm) at 25 °C for 2 h and filtered through activated carbon under N_2 atmosphere. The filtrate was evaporated to give **21** (2.0 g, quant) as an amorphous solid. IR (KBr) 3216, 2928, 1727, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35−726 (m, 5H), 4.72 (d, J = 15 Hz, 1H), 4.27−4.23 (m, 1H), 4.21−4.19 (m, 1H), 4.11 (d, J = 15 Hz, 1H), 3.66 (s, 3H), 3.15 (m, 1H), 2.82 (d, J = 13 Hz, 1H), 2.68 (dd, J = 4.8, 13 Hz, 1H), 2.33 (t, J = 7.3 Hz, 2H), 1.75−1.64 (m, 3H), 1.48−1.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.3, 161.8, 137.1 (3s), 129.1, 128.4, 128.1, 64.1, 59.7, 55.6 (6d), 51.9 (q), 36.6, 34.0, 28.7, 28.5, 25.1 (5t); SIMS m/z 349 ($M^+ + 1$).

(+)-Biotin (1). To a stirred solution of **21** (5.2 g, 0.015 mol) in MeOH (10 mL) and water (31 mL) was added NaOH (2.4 g, 0.06 mol) at 25 °C. After the mixture was stirred at 40 °C for 3 h, the solvent was evaporated. The resulting mixture was acidified with concd HCl, extracted with AcOEt (50 mL), washed with water (50 mL), and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was coevaporated with toluene (3 × 20 mL). To the mixture were added $MeSO_3H$ (15.5 g, 0.16 mol) and xylene (16 mL) at 25 °C. After the mixture was 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 was stirred at 10 °C for 1 h, the crystals formed were collected and washed with water and acetone to give the crude product. To a stirred suspension of the crude crystals in water (45 mL) was added NaOH (0.54 g, 0.014 mol) at 25 °C, and pH of the mixture was adjusted to 7.5−8.0 at 90 °C by adding concd HCl. Activated carbon (2.5 g) was added to the mixture at same temperature and the mixture was filtered. The filtrate was acidified to pH 1.6−1.8 with concd HCl at 95 °C. After the mixture was stirred at 10 °C for 1 h, the crystals formed were collected and washed with water to give (+)-biotin (3.06 g, 84%) as colorless crystals. mp 231−232 °C (lit.:[28] 229.5−230 °C), $[\alpha]^{24}_{D}$ +91.0 (*c*, 1.0, 0.1 N NaOH) {lit.:[28] $[\alpha]^{25}_{D}$ +91.3 (*c*, 1.0, 0.1 N NaOH)}; IR (neat) 3299, 2920, 1686 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.02 (br s, 1H), 6.49 (br s, 1H), 6.40 (br s, 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 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 174.8, 163.1 (2s), 61.4, 59.5, 55.7 (3d), 40.0, 33.8, 28.44, 28.36, 24.9 (5t); SIMS *m*/*z* 245 ($M^+ + 1$). Anal. 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.

(28) Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946.

Acknowledgment. The authors are indebted to Mr. Koichi Inubushi and Mr. Hajime Hiramatsu, Tanabe Seiyaku Co., Ltd., for the X-ray crystallographic analysis.

Supporting Information Available: ORTEP drawings of *anti*- and *syn*-cyanohydrin and compounds **5**, **6b**, and **20**, and copies of HPLC traces were used to determine diastereoselectivity and optical purity. This material is available free of charge via the Internet at http//:pubs.acs.org.

JO025794+