Novel Enantioselective Syntheses of (+)-Biotin

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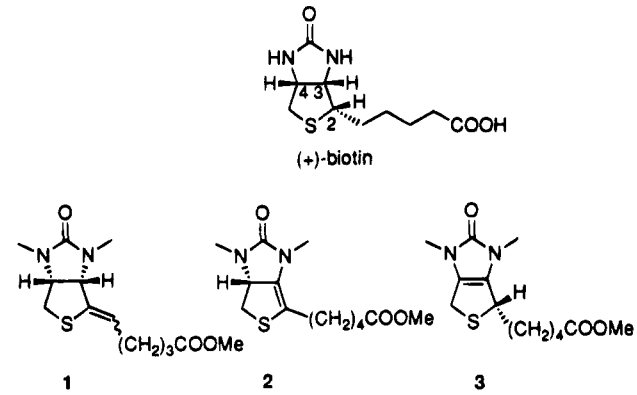
Two conceptually attractive enantioselective syntheses of (+)-biotin from L-cysteine are reported based upon an intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide. The first approach (12 steps) involves the following as key-steps: (i) the macrothiolactonization of acid **10b** to *Z*-olefin **14**, (ii) the thermolysis of the ene carbamoyl azide **15** in water with direct formation of a mixture of the benzylated derivatives of (+)-biotin **16a** and **17a**. The second approach (14 steps) involves the following: (i) elimination of bromide **29** to the endocyclic thioenol ether **30**, (ii) thermolysis of the ene carbamoyl azide **30** to the exocyclic thioenol ethers **31a** and **31b**. Both the synthesis of **29** and the final transformation of **31a** and **31b** into (+)-biotin are based upon literature precedents.

Introduction

Biotin is one of the water-soluble B vitamins. In bound form, it is distributed widely as a cell constituent of animal and human tissues. Biochemically, (+)-biotin functions as a cofactor in carboxylation reactions and is also involved in important processes such as gluconeogenesis and fatty-acid synthesis.[1] The importance of (+)-biotin in human nutrition and animal health has further stimulated the development of synthetic routes toward this vitamin.[2–5]

As a synthetic target, (+)-biotin presents a substantial challenge to the organic chemist. Indeed, despite numerous synthetic efforts, the 1949 Goldberg and Sternbach 14-step approach[2] involving an intermediate resolution with possible recycling, still remains nowadays the most attractive one from an economical point of view. Next to the great number of routes toward racemic biotin,[4,5c] *enantioselective* syntheses of (+)-biotin were reported and make use of the resolution of a key intermediate,[6] or of an asymmetric conversion,[3,7] or start from the chiral pool.[8] As natural building blocks, L-(+)-cysteine or L-(+)-cystine (sequences of 10–15 steps)[9] and some carbohydrates (>15 steps)[8] were applied.



1 2 3

The biotin skeleton consists of an all-*cis* substituted 2-alkyl-3,4-diaminothiophane, an apparently uncomplicated structural moiety. Indeed, it is known from earlier

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(1) Dakshinamurti, K.; Bhaganan, H. Eds.; *Ann. N.Y. Acad. Sci.* **1985**, *447*, 1–441.

(2) Goldberg, M. W.; Sternbach, L. H. U.S. Patents 2,489,232, 2,489,235, and 2,489,238 (1949).

(3) In 1975, Sumitomo chemists replaced the optical resolution–reduction sequence of the Sternbach synthesis (ref 2) by an efficient asymmetric conversion, see Hisao, A.; Yasuhiko, A.; Shigeru, O.; Hiroyiki, S. U.S. Patent 3,876,656 (1975).

(4) For earlier syntheses of biotin see Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 6460–6462 and references cited therein.

(5) For more recent syntheses of biotin see: (a) Deroose, F. D.; De Clercq, P. J. *Tetrahedron Lett.* **1994**, *35*, 2615–2618. (b) Deroose, F. D.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4365–4368. (c) Alcázar, V.; Tapia, I.; Moráu, J. R. *Tetrahedron* **1990**, *46*, 1057–1062. (d) Bihovsky, R.; Bodepudi, V. *Tetrahedron* **1990**, *46*, 7667–7676. (e) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57–60. (f) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148–150. (g) Lee, H. L.; Baggiolini, E. G.; Uskokovic, M. R. *Tetrahedron* **1987**, *43*, 4887–4903. (h) Bates, H. A.; Smilowitz, L.; Lin, J. *J. Org. Chem.* **1985**, *50*, 899–901. (i) Kinoshita, H.; Futagami, M.; Inomata, K.; Kotahe, H. *Chem. Lett.* **1983**, 1275–1276. (j) Volkman, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946–5948. (k) Schmidt, R. R.; Maier, M. *Synthesis* **1982**, 747–748. (l) Casutt, M.; Poetsch, E.; Speckamp, W. N. Ger. Offen. DE 3,926,690 (1991).

(6) For enantioselective syntheses based on resolution of a key intermediate, see refs 2, 5j, 10a, and (a) Vasilevskis, J.; Gualtieri, J. A.; Hutchings, S. D.; West, R. C.; Scott, J. W.; Parrish, D. R.; Bizzarro, F. T.; Field, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 7423–7424.

(7) For recent syntheses of enantiomerically pure biotin precursors, (i) obtained via enzyme-catalyzed kinetic resolution, see: (a) Tokuyama, S.; Yamano, T.; Aoki, I.; Takanohashi, K.; Nakahama, K. *Chem. Lett.* **1993**, 741–744. (b) Yamano, T.; Tokuyama, S.; Aoki, I.; Nishiguschi, Y.; Nakahama, K.; Takanohashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1456–1460. (c) Iriuchijima, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907–1910. (d) Wang, Y. F.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 4999–5002 or (ii) obtained via chemical enantioselective reduction, see (e) Matsuki, K.; Inoue, H., Takeda, M. *Tetrahedron Lett.* **1993**, *34*, 1167–1170.

(8) For a review of syntheses from the chiral pool see: Scott, J. W. Readily Available Chiral Carbon Fragments and Their Use in Synthesis. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, **1984**, Vol. 4, pp 195–201.

(9) For previous syntheses from L-cysteine or L-cystine, see refs 4, 5a,b,e,g,l.

(10) For the reduction of a derivative analogous to **1**, see 5e,g and (a) Sternbach, L. H. *Compr. Biochem.* **1963**, *11*, 66–81. For the reduction of a derivative analogous to **2**, see (b) Harris, S. A.; Wolf, D. E.; Mozingo, R.; Arth, G. E.; Anderson, R. C.; Easton, N. R.; Folkers, K. *J. Am. Chem. Soc.* **1945**, *67*, 2096–2106. For the reduction of a derivative analogous to **3**, see ref 6a.

(11) For previous biotin syntheses involving a 1,3-dipolar cycloaddition, see refs 4,5c,g and (a) Confalone, P. N.; Pizzolato, G.; Lollar Confalone, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954–1960. (b) Marx, M.; Marti, F.; Reisdorff, J.; Sandmeier, R.; Clark, S. *J. Am. Chem. Soc.* **1977**, *99*, 6754–6756.

(12) For reviews on intramolecular azide-alkene cycloadditions, see: (a) Padwa, A.: Intramolecular 1,3-Dipolar Cycloaddition Reactions. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons, Inc.: New York, **1984**; Vol. 2, pp 277–406. (b) Wade, P. A. Intramolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, Vol. 4, 1157–1159. For recent references on azide–alkene cycloadditions see (c) Pearson, W. H.; Bergmeier, S. C.; Degau, S.; Liu, K. C.; Poon, Y. F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719–5738 and references cited therein. For a review on intermolecular azide–alkene cycloadditions, see: Lwowski, W. Azides and Nitrous Oxide. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, E., Ed.; John Wiley and Sons, Inc.: New York, 1984; Vol. 1, pp 559–653.

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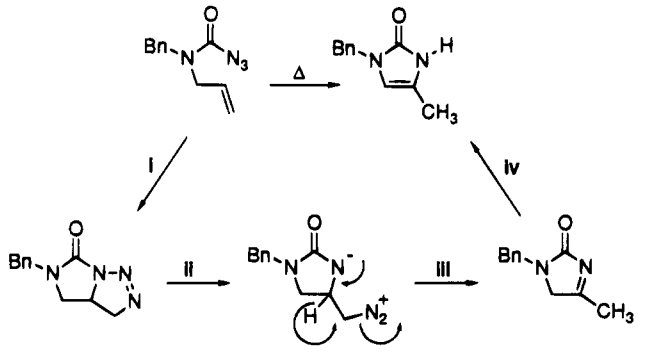
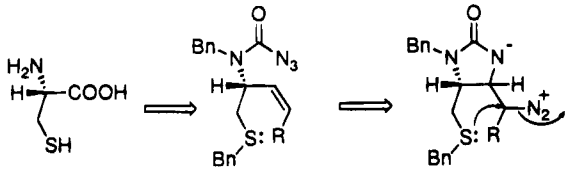


Figure 1.

syntheses that catalytic hydrogenation of the three isomeric didehydrobiotin derivatives **1**–**3** lead stereoselectively to the less stable *cis*-configuration of biotin.[10]

Herein we wish to describe two novel approaches to the synthesis of (+)-biotin, in which we plan to make use of a thermal intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide to an alkene.[11,12] To the best of our knowledge only one example of this reaction was reported previously and involved the thermolysis of *N*-benzyl,*N*-allylcarbamoyl azide (autoclave, CH_2Cl_2, 3 h, 150 °C), leading to the corresponding imidazolidone (71% yield) (Figure 1).[13] Its formation involves (i) cycloaddition to a triazoline; (ii) subsequent ring fragmentation to a betaine intermediate, which is facilitated by the presence of an electron-withdrawing amide substitution at N; (iii) the further loss of nitrogen and formation of an imine, with concomitant 1,2-hydride shift; (iv) and eventual prototropic shift. It is important to note that in this case no aziridine formation is observed. This is in contrast to other examples, such as (i) the intramolecular 1,3-dipolar cycloaddition of an alkyl azide onto an alkene,[14] which led to aziridine and to imine formation; (ii) the intramolecular cycloaddition of an azidoformate onto an α,β-unsaturated butenolide,[15] leading to aziridine formation.

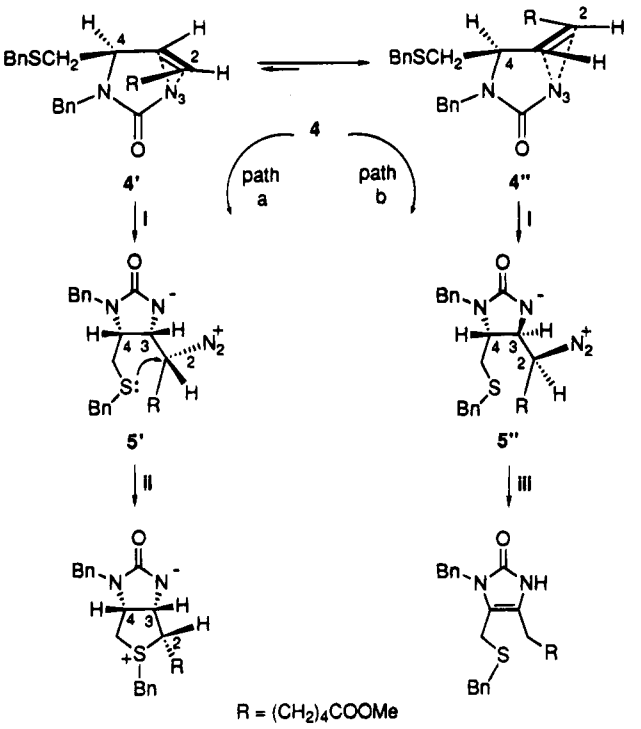


4 R = $(CH_2)_4COOMe$ **5**

On the basis of those observations, we were tempted to study the possible formation of the biotin skeleton in a single step in which the intramolecular cycloaddition of an analogous carbamoyl azide **4**, which contains a $-CH_2S-$ moiety, is performed. Ideally, the five-membered thiophane ring would be generated via intramolecular sulfur-assisted nitrogen expulsion from the betaine intermediate **5**. As will be discussed in detail in the following section the obtainment of the relative biotin configuration requires the *Z*-configuration of the olefinic precursor **4**. Finally, the structure of the latter strongly suggests the use of L-(+)-cysteine as starting material.[9]

Results and Discussion

The First Approach. As shown in Figure 2, the cycloaddition precursor **4** can cyclize via two different



R = $(CH_2)_4COOMe$

Figure 2.

rotameric conformations **4′** and **4″**. The cycloaddition via carbamoyl azide **4′** (path a), should lead to the all-*cis* substituted thiophane ring via (i) ring fragmentation of the first formed triazoline adduct to the corresponding betaine intermediate; (ii) nucleophilic sulfur attack at C-2. It is important to notice that the required configuration at C-2 is stereospecifically induced by the *Z*-geometry of the 2,3-double bond.

In close analogy to the work of Chupp (Figure 1),[13] the cycloaddition via rotamer **4″** (path b) is expected to lead to an imidazolidone via (i) betaine formation, followed by (iii) 1,2-hydride shift and prototropic shift. Obviously, the imidazolidone is of no further use in the context of an enantioselective biotin synthesis. We note that the desired relative *cis*-configuration at C-3 and C-4 only results from the reaction path a. In view of the $A^{1,3}$-strain resulting from repulsive interactions between the groups R = $(CH_2)_4COOMe$ and CH_2SBn in **4′**, one may expect pathway b to be preferred (cfr. Curtin–Hammett principle). Consequently, the required stereochemical outcome should result from a cycloaddition in which the particular conformation as in rotamer **4′** would be enforced, i.e. by connecting the thiol (instead of the benzylated sulfur moiety) and carboxy acid functions into a 10-membered thiolactone (vide infra). The above discussion has been fully corroborated by a first model study.

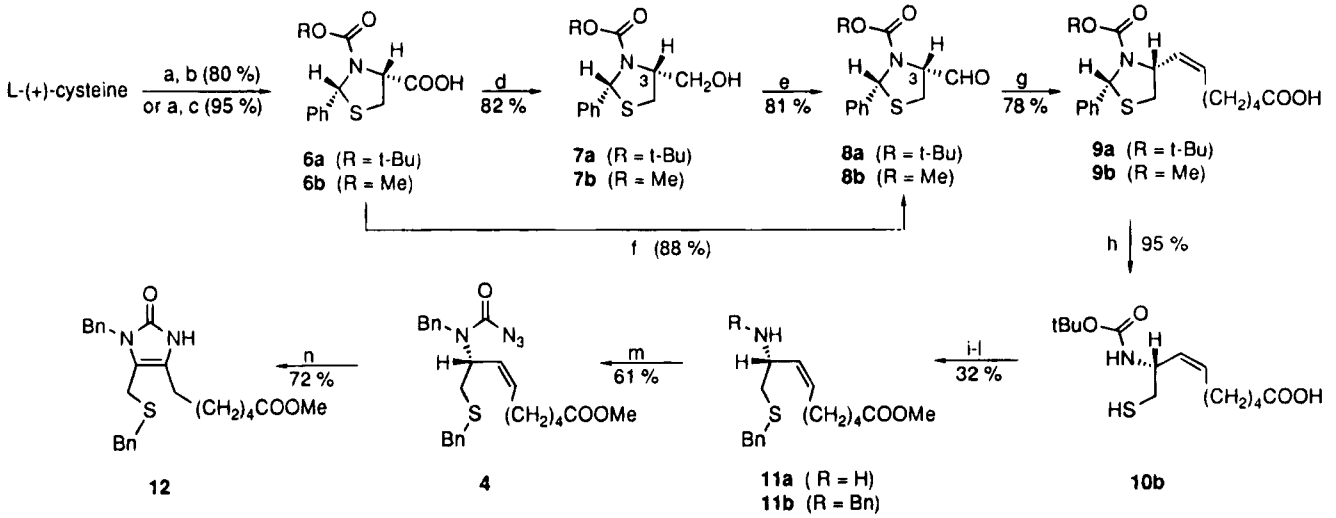
a. Exploratory Model Study. Acyclic Approach. The synthesis of the required cycloaddition precursor **4** is outlined in Scheme 1. In close analogy with a sequence developed by Hoffmann-La Roche chemists to the methyl analogue **8b**,[16] aldehyde **8a** is obtained via a four-step sequence from L-(+)-cysteine. First L-(+)-cysteine is condensed with benzaldehyde to yield a mixture of the

(13) Chupp, J. P. *J. Heterocycl. Chem.* **1971**, *8*, 557–563.

(14) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749–754.

(15) For an intramolecular cycloaddition of an acyl azide leading to aziridine formation, see Egli, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 1442–1460.

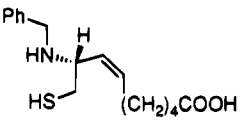
Scheme 1[a]



[a] **Reagents**: (a) PhCHO, KOAc, H_2O, EtOH, rt; (b) $(Boc)_2O$, NaOH, H_2O, dioxane; (c) $ClCOOCH_3$, $NaHCO_3$, H_2O, rt; (d) $Me_2S{\cdot}BH_3$, THF; (e) $COCl_2$, DMSO, −60 °C, Et_3N; (f) CH_2N_2; DIBALH, $PhCH_3$; (g) $[Ph_3P(CH_2)_5COOH]Br$, 2 equiv of LDA, THF, rt, 1 h; (h) Na, $NH_3(l)$; H_3O^+; (i) CH_2N_2, Et_2O; (j) NaH, $PhCH_2Br$, THF, 0 °C; (k) HCl, Et_2O, 0 °C; (l) PhCHO, $NaCNBH_3$, THF, H_2O (pH = 4), rt, 3 h; (m) $COCl_2$, DBU, CH_2Cl_2, −78 °C; NaN_3, acetone−H_2O, rt; (n) autoclave, CH_2Cl_2, 125 °C, 2 h.

cis- and *trans*-thiazolidines in a 1:1 ratio.[17] During subsequent amine protection both isomers led to the *cis*-*tert*-butylurethane **6a**.

The carboxyl function in **6a** was next transformed into the aldehyde **8a** via a two-step sequence, involving reduction with borane−methyl sulfide to the corresponding alcohol **7a**, followed by oxidation to the aldehyde **8a** via a classical Swern procedure. As an a alternative sequence, aldehyde **8a** could also be obtained in high yield by diisobutylaluminum hydride reduction of the corresponding methyl ester, formed after diazomethane treatment of **6a**. Since the aldehyde **8b** is known to readily isomerize at C-3 during purification by chromatography,[16] the crude aldehyde **8a** was used directly in the next reaction step. After treatment of (5-carboxypentyl)triphenylphosphonium bromide with 2 equiv of LDA in THF, aldehyde **8a** was added and the Wittig adduct **9a** obtained in 78% yield. No *E*-isomer could be detected. It is interesting to note that no Wittig adduct was found by preparing the same ylide with dimsylsodium in DMSO,[18a,b] or by the use of lithium bis(trimethylsilyl)amide in HMPA.[18c] This is presumably due to the eliminative ring opening of the thiazolidine. The release of the thiol and carboxy acid functions necessary for thiolactone formation was first attempted via classical methods which are used to deprotect thiazolidines. The mercury-catalyzed hydrolysis resulted in thiol **10b** in poor yield (<20% yield).[19] On the other hand reductive cleavage of the benzylic carbon−sulfur bond (Zn, HOAc, 85 °C)[20] gave thiol **10a**, albeit in low yield (25%). Eventually, thiol acid **10b** is obtained by reductive cleavage with sodium in liquid ammonia (95% yield).



10a

Via a rather uneventful sequence, carbamoyl azide **4** was obtained, as further shown in Scheme 1. After esterification of the acid function with diazomethane and benzylation of the thiol group, the urethane protective group was removed (HCl, Et_2O, 0 °C) to yield the primary amine **11a** (71% yield from **10b**). Among several procedures for the preparation of carbamoyl azides such as[21] (i) treatment of isocyanates with hydrazoic acid; (ii) oxidation of semicarbazides with HNO_2; (iii) treatment of carbamoyl chlorides with sodium azide, we preferred the latter method. At first, treatment of the primary amine **11a** with phosgene, followed by addition of sodium azide, only gave the desired carbamoyl azide in a very poor yield. We therefore prepared the secondary amine **11b**, since carbamoyl chlorides derived from secondary amines are known to be less water sensitive and cannot eliminate HCl to the corresponding isocyanates. Primary amine **11a** was easily benzylated via reductive amination with benzaldehyde and sodium cyanoborohydride (76% yield).[22] The introduction of the acyl azide moiety via treatment of **11b** with phosgene, followed by sodium azide in methanol−water, has to take place at low temperature (−78 °C), in order to prevent the formation

(16) (a) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1975**, *97*, 5936−5938. (b) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 7020−7026.

(17) The stereochemical outcome of the condensation reaction of L-cysteine with aldehydes has been discussed in detail by: (a) Parthasarathy, R.; Paul, B.; Korytnyk, W. *J. Am. Chem. Soc.* **1976**, *98*, 6634−6643. (b) Szilàgyi, L.; Györgydéak, Z. *J. Am. Chem. Soc.* **1979**, *101*, 427−432.

(18) For the stereoselective introduction of the *Z*-configuration, see: (a) Crabbé, P.; Garcia, G. A.; Rius, C. *J. Chem. Soc. Perkin Trans. 1* **1973**, 810−816. (b) Greenwald, R.; Chaykovsky, M., Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128−1129. (c) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1981**, *59*, 870−877.

(19) Seebach, D.; Weber, T. *Helv. Chim. Acta* **1984**, *67*, 1650−1661.

(20) For a reduction on a analogous thiazolidine, see 51.

(21) Lieber, E.; Minnis, Jr. R. L.; Rao, C. N. R. *Chem. Rev.* **1965**, *65*, 377−384.

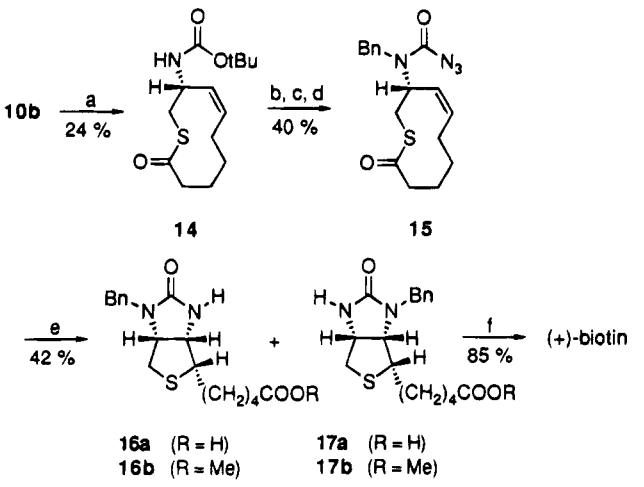
(22) One can either isolate the intermediate imine, or the reductive amination can be performed in a single operation.

(23) For a review on thioester and thiolactone formation, see Voss, J.: Synthesis of thioesters and thiolactones. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford **1991**; Vol. 6, pp 435−457.

(24) Barta, M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 5132−5138.

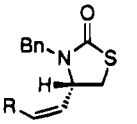
(25) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756−6758.

Scheme 2[a]



[a] **Reagents**: (a) $PhOP(O)Cl_2$–DMF, CH_2Cl_2, rt; (b) HCl(g), Et_2O, 0 °C; (c) PhCHO, $NaCNBH_3$, THF–H_2O (pH = 4), 0 °C; (d) $COCl_2$, DBU; NaN_3, acetone–H_2O, rt; (e) H_2O, autoclave, 145 °C, 2 h; (f) HBr (48%), reflux, 2 h.

of thiazolidinone **13**. Upon thermolysis of **4** in dichloromethane at 125 °C (autoclave, 3 h), only the formation of imidazolidone **12** was observed.

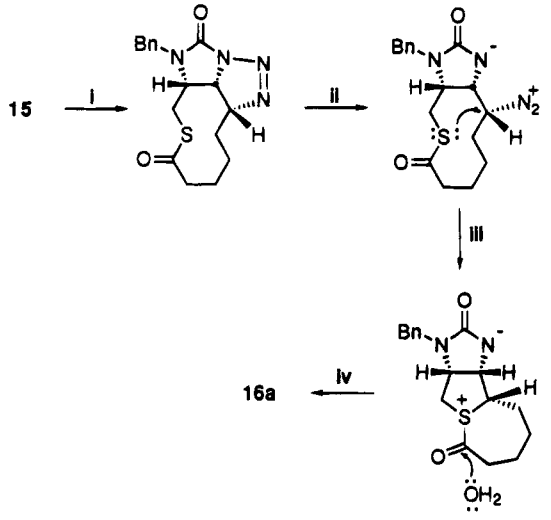


13 (R = $(CH_2)_4COOMe$)

b. The 10-Membered Thiolactone Approach. The first crucial step in this approach is obviously the macrothiolactonization to **14** (Scheme 2) Although various methods are known for thiolactone formation,[23] to the best of our knowledge there are no general methods available for the synthesis of strained medium ring-sized thiolactones. Since a 10-membered thiolactone combines a thermodynamically unstable ring size and a kinetically unstable thioester function, we were not surprised that the preparation of **14** was difficult to achieve. Cyclization with carbonyldiimidazole and with *N,N'*-dicyclohexylcarbodiimide gave only very polar unidentified products. Other methods tried unsuccessfully were originally designed for the preparation of strained lactones[24] and are based on a preceding or an *in situ* activation of the carboxy acid function via the formation of a mixed anhydride, such as trifluoroacetic acid-,[25] sulfonic acid-,[26] or phosphoric acid–anhydride.[27] A successful method consisted in the simultaneous activation of both thiol and carboxy acid functions and is better known as the "double activation" method developed by Corey and Nicolaou[28] for the preparation of macrocyclic lactones, based on the original work of Mukaiyama.[29] Under these conditions (2,2'-dipyridyl disulfide, triphenylphosphine, toluene) the desired **14** was obtained, albeit in low yield (11%). Eventually, the preferred thiolactonization method involved slow addition (6 h; syringe pump) of a solution of **10b** and of pyridine in dichloromethane to the *in situ* prepared phenyl dichlorophosphate–DMF complex, which led to **14** in a somewhat higher yield of 24%.[30] In close analogy to the transformation of **11a** to **4**, the urethane **14** was converted into the *N*-benzylcarbamoyl azide **15** via a sequence involving the removal of the urethane protective group, the reductive amination with benzaldehyde and sodium cyanoborohydride (at 0 °C), and the introduction of the acyl azide moiety (40% overall yield from **14**) (Scheme 2).

The thermolysis of **15** in dichloromethane–methanol (140 °C) led to decomposition. On the other hand, upon heating **15** in water at 150 °C (autoclave, 2 h), we were delighted to observe the direct formation of a mixture of the monobenzylated derivatives **16a** and **17a** in a 3:2 ratio (42% yield). The derivatives were characterized as the corresponding methyl esters **16b** and **17b**, since the latter could be separated by column chromatography.[31] Final deprotection of **16b** and **17b** was readily achieved by treatment with aqueous hydrobromic acid (reflux, 2 h; 85% yield).[32] Eventual purification of biotin is realized via ion-exchange chromatography on a strongly acidic resin (Amberlite IR-120 (plus)), followed by lyophilization.[33]

Presumably this unique ring closure involves (i) cycloaddition to the triazoline, (ii) facile triazoline ring fragmentation, (iii) nitrogen expulsion with assistance of the proximal sulfur with the concomitant formation of a tricyclic sulfonium intermediate, and (iv) final nucleophilic attack of water to form the carboxylic side chain of biotin.



Previously, the use of polar solvent systems has been shown to promote the cyclization process. In our case the use of water, which is obviously necessary as a nucleophile, is also expected to accelerate the cyclization via betaine stabilization.[34]

(26) (a) Baker, R.; Castro, J. L. *J. Chem. Soc. Chem. Commun.* **1989**, 378–381. (b) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439–1441.

(27) Yamada, S.; Yokoyama, Y.; Shiori, T. *J. Org. Chem.* **1974**, *39*, 3302–3303.

(28) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616.

(29) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763–4765.

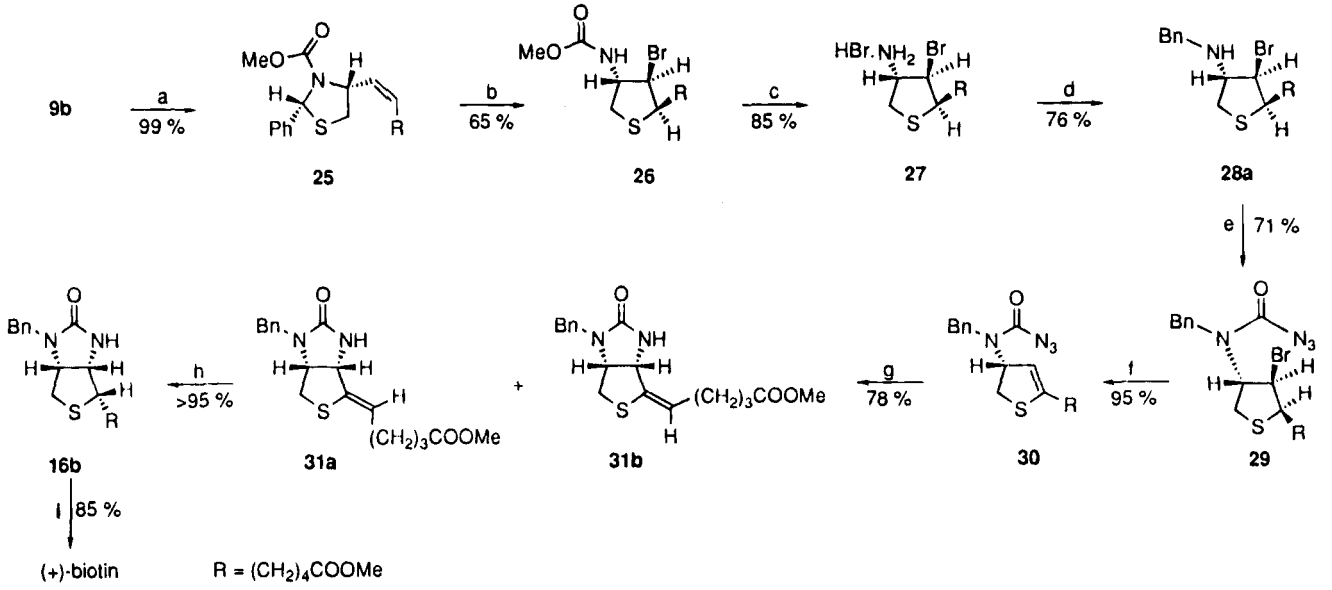
(30) This is an efficient method for intermolecular thioester formation, Arrieta, A.; Garcia, T.; Lago, J. M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471–487.

(31) The intermediate monobenzylated **16b** and **17b** were found identical with the corresponding derivatives obtained from the methyl ester of biotin via treatment with benzyl bromide (NaH, THF, rt, 14 h; 1:1 ratio, 65% yield). Distinction between both isomers follows from ^1H NMR decoupling of $^3J_{NH,H-3}$ in **16b** and $^3J_{NH,H-4}$ in **17b** upon irradiation of the NH of the urethane.

(32) Gerecke, M.; Zimmerman, J. P.; Aschwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991–999.

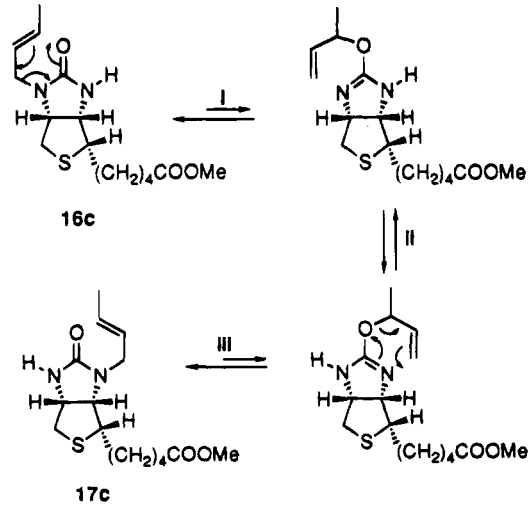
(33) The synthetic biotin (mp. 232 °C) so obtained had $[\alpha]^{20}_D = +91.4$ as compared to $[\alpha]^{20}_D = +90.9$ for an authentic sample.

Scheme 3[a]



[a] **Reagents**: (a) CH_2N_2, Et_2O, 0 °C; (b) Br_2, $CHCl_3$, 1 equiv of H_2O, rt, 20 min; (c) HBr, HOAc, 20 h, dark; (d) PhCHO, $NaCNBH_3$, THF, H_2O, rt; (e) phosgene, DBU, CH_2Cl_2, 0 °C; NaN_3, acetone, H_2O, rt; (f) DBU, THF, reflux, 12 h; (g) autoclave, CH_2Cl_2, 150 °C, 3 h; (h) $Pd(OH)_2$–C, H_2 (4 atm), EtOAc, rt, 1 h; (i) HBr (48%), reflux, 2 h.

The occurrence of the benzyl shift during the cyclization reaction was fully unexpected. Yet, the following experiments were performed in order to investigate the mechanism of this process. The shift is an equilibrium process since upon heating **17b** in water, again a mixture was observed of **16b** and **17b**. The intramolecularity of this rearrangement was further proven by treating a mixture of monobenzylated **16a** in the presence of the methyl ester of biotin: as the only rearranged product involved acid **17a**, the reaction must have taken place by an intramolecular process. Finally, the same rearrangement was observed when thermolyzing the *E/Z* crotyl derivative **16c**,[35] resulting in a 1:1 mixture of **16c** and **17c** after 1 h at 140 °C. This strongly suggests the following rearrangement, which is to the best of our knowledge unprecedented: (i) a 3,3′-sigmatropic rearrangement, followed by (ii) an intermediate prototropic shift and (iii) a final 3,3′-sigmatropic rearrangement to **17c**.[36] Under the same reaction conditions, but in CH_2Cl_2, no cycloaddition product was observed. In contrast to water, in CH_2Cl_2 the prototropic shift is not likely to occur.



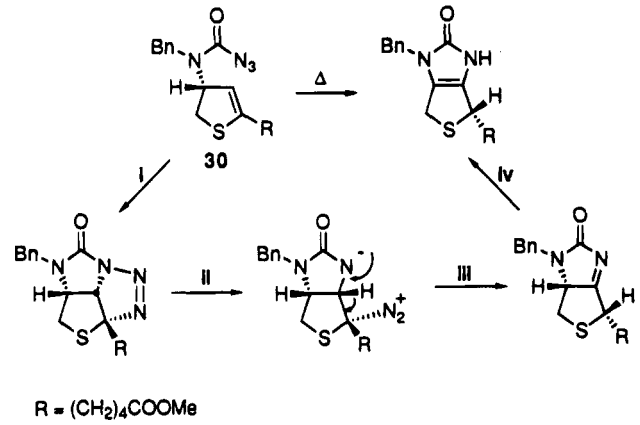


Figure 3.

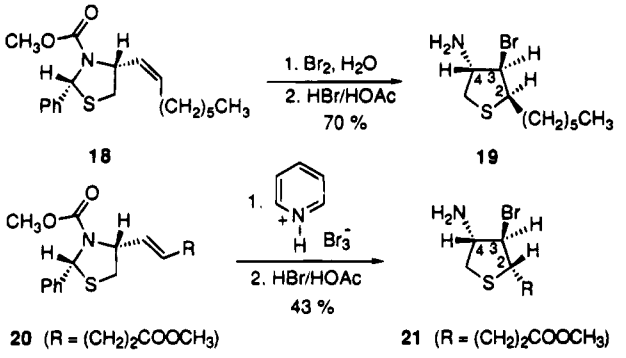
The Second Approach. Our second approach is also based on the intramolecular cycloaddition of a carbamoyl azide to an alkene. As shown in Figure 3, the process centers around (i) the thermal intramolecular 1,3-dipolar cycloaddition of the five-membered thioenol ether **30**, followed again by ring fragmentation of the resulting triazoline adduct to (ii) a betaine intermediate; (iii) loss of nitrogen with concomitant 1,2-hydride shift to the intermediate imine and final (iv) prototropic shift to an imidazolidone analogous to **3**. As mentioned in the introduction the latter compound **3** is a direct precursor of biotin.

The synthesis of the required cycloaddition precursor **30** is outlined in Scheme 3 and is in part based on the remarkable and stereospecific bromination reactions of thiazolidines **18** and **20**, reported by Confalone et al.:[16]

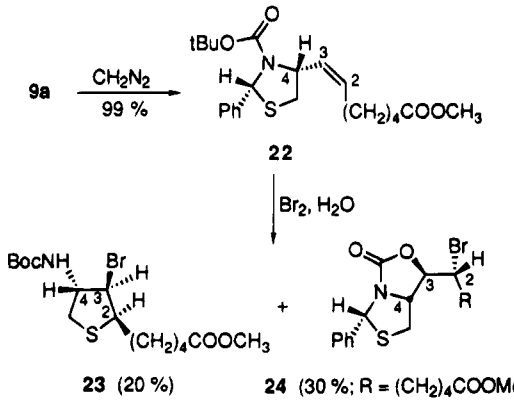
(34) For an example of intramolecular azide–alkene cycloaddition in aqueous diglyme, see: (a) Logothethis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749–754; for an example of an intermolecular azide–alkene cycloaddition in DMSO, see: (b) Oehlschlager, A. C.; Tillman, P.; Zalkow, L. H. *J. Chem. Soc. Chem. Commun.* **1965**, 596–599.

(35) The crotyl derivative was prepared by reaction of the methyl ester of biotin with *E/Z* 1-bromo-2-butene (NaH, THF, rt, 14 h; 55% yield), which led to a 1:1 mixture of **16c** and **17c**, both obtained as *E/Z* mixtures.

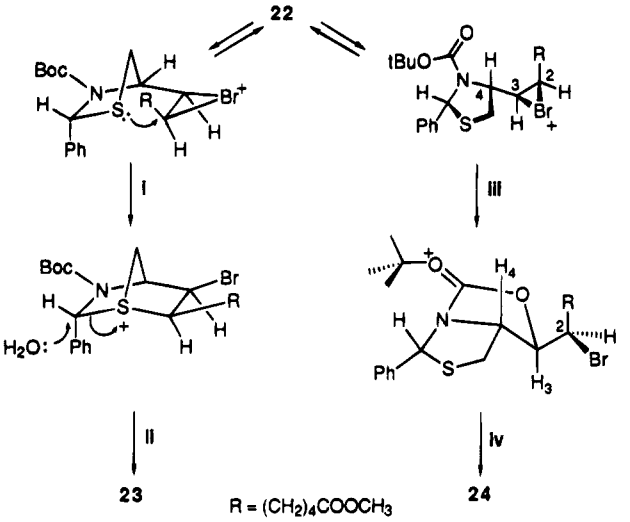
bromination of the *Z*-olefin **18**, followed by deprotection, led exclusively to thiophane **19**, whereas the *E*-olefin **20** gave **21**, isomeric at C-2.



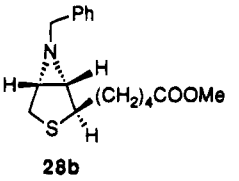
Whereas bromide **21** eventually led to (+)-biotin (12 steps; 2% yield),[16] the isomeric compound **19** was useless due to the incorrect stereochemistry at C-2. However, it occurred to us that bromide **19**, useless in terms of the Hoffmann-La Roche strategy, possesses the required stereochemistry for selective E2 elimination to the endocyclic $\Delta^{2,3}$-bond as present in the dihydrothiophene **30**. Upon adding bromine to **22**, we observed, next to the expected oxidative cyclization rearrangement to the bromourethane **23** (20% yield), also the formation of the cyclic urethane **24** (30% isolated yield). The assignment



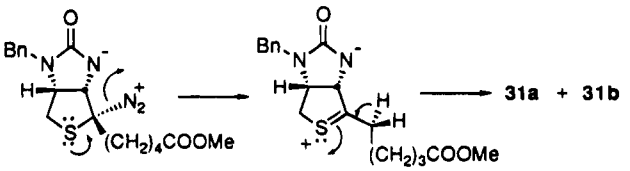
of the relative configuration of **23** follows the original assignment of Confalone, which rested on an X-ray analysis.[16] The stereochemistry of **24** was assigned by ^{1}H NMR.[37] The two derivatives would originate from the two diastereomeric bromonium cations, which suffer further opening with the assistance of either the proximate sulfur as in the case of **23**, or of the carboxy group in the case of **24**. In the latter case the cleavage of the *tert*-butyloxy bond results in the loss of isobutene. Obviously, in the sequence which eventually led to (+)-biotin use was made of a methylurethane as indicated in Scheme 3. Bromination of **25** now led to **26** (65% yield). As expected the formation of **24** was not observed. After



removal of the urethane protective group with hydrobromic acid, the amino bromide hydrobromide **27** was converted to the *N*-benzylcarbamoyl azide **29** via reductive amination and introduction of the acyl azide moiety. The reductive amination needs to be performed in buffered acid medium, as under neutral reaction conditions the formation of aziridine **28b** is observed.



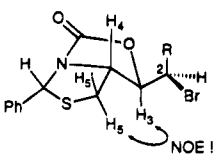
The *anti*-E2 elimination of hydrogen bromide from **29** (DBU, THF, reflux, 12 h) led smoothly to the dihydrothiophene **30** (95% yield). Thermolysis of the latter in dichloromethane at 150 °C (autoclave; 3 h) gave rise to a 3:2 mixture of (*E*)-**31b** and (*Z*)-**31a** alkenes (78% yield). A similar result is obtained in water as the solvent (130 °C). A distinction between both isomers was made by a NOE-*difference* experiment.[38] The observed mixture of thioenol ether **31** would result from sulfur-assisted nitrogen expulsion, followed by proton transfer, as shown below. Catalytic hydrogenation of the mixture of **31a** and



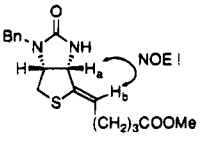
31b with Pearlmans reagent ($Pd(OH)_2$–C, H_2 4 atm,

(36) The observed rearrangement bears some resemblance with the Chapman isourea rearrangement, see: Suttle, N. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1369.

(37) The relative configuration at C-2 merely follows from the proposed mechanism. The coupling pattern between H-5, H-5′, and H-4 allow the assignment of H-5 and H-5′ ($J_{H\text{-}4/H\text{-}5}$ = 10.1 Hz; $J_{H\text{-}4/H\text{-}5'}$ = 6.0 Hz). The NOE-*difference* experiment showed a strong through-space interaction between H-3 (δ = 4.63) and H-5 (δ = 2.95), indicating a relative *trans*-relationship between H-4 and H-3 ($J_{H\text{-}3/H\text{-}4}$ = 2.8 Hz).



(38) The NOE-*difference* experiment of **31a** showed a strong through-space interaction between H_a (δ = 3.69) and H_b (δ = 5.65). This reaction was not found for **31b**.



EtOAc, 1 h; 95% yield)[39] led stereoselectively to the all-*cis* substituted **16b**, which was deprotected by treatment with aqueous hydrobromic acid to yield (+)-biotin in high yield.[40] A pure sample of (+)-biotin was obtained as described in the previous approach and was found identical to all respects with the natural product.

The two routes which have been developed are attractive in their concept, especially in that they are quite different yet based on a same unusual intramolecular cycloaddition of a carbamoyl azide. However, it is clear that both routes are yet too long to be of economical value. Furthermore, the first approach (12 steps; 2% overall yield) suffers from an intrinsically difficult thiolactone formation. The second approach, which is somewhat longer (14 steps; 13% overall yield) remains more attractive due to the rather efficient conversion of the dihydrothiophene **30** into biotin. This certainly warrants further investigations into efficient routes for this cycloaddition precursor.

Experimental Section

General Procedure. All reactions involving air and/or moisture sensitive materials were conducted under atmospheres of N_2 or Ar, which were dried and purified by passage through a column containing copper on charcoal, anhydrous $CaSO_4$, and 4 Å molecular sieves. All solvents were purified before use. Et_2O and THF were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Et_3N and DIA were distilled from CaH_2. CH_2Cl_2 was distilled from P_2O_5. HMPA and DMSO were distilled from CaH_2 under vacuum and immediately stored over freshly activated 4 Å molecular sieves. Analytical and preparative thin-layer chromatography was performed using glass plates precoated (0.25-mm layer) with silica gel 60 F_{254}. Flash chromatography was performed using Merck silica gel 60 (70–235 or 230–400 mesh). The ^1H NMR spectra were obtained at 500, 360, and 200 MHz and the ^{13}C NMR spectra at 50.3 MHz. Chemical shifts are reported in parts per million (ppm) downfield from TMS using residual $CHCl_3$ (7.27 ppm) as internal standard. Melting points are uncorrected. Infrared (IR) were recorded on a FT-IR spectrometer using KBr plates with film or in solution. Mass spectra (MS) were recorded at 70 eV.

2(*R*)-Phenylthiazolidine-3,4(*R*)-dicarboxylic Acid 3-*tert*-Butyl Ester (6a). To a stirred solution of 4(*R*)-carboxy-2-phenylthiazolidine (36.0 g, 0.172 mol) in dioxane (350 mL), distiiled H_2O (175 mL), and 1 N NaOH solution (175 mL) was added di-*tert*-butyl dicarbonate (42 g, 0.189 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The solvent was partly removed (250 mL) and cooled to 0 °C. AcOEt (300 mL) was added. The aqueous layer was acidified at 0 °C with 10% $NaHSO_4$ (pH = 2–3) and extracted with AcOEt (2x 200 mL). The combined organic fractions were washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain **6a** (43.7 g, 82%) as a white solid: mp 144–146 °C; $[\alpha]_D^{20}$ +52.7° (c 1.0, $CHCl_3$); IR (KBr) 3000, 1725 (C=O), 1632, 1550, 1368 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30 (5H, m), 5.90 (1H, br s), 4.90 (1H, m), 3.40 (2H, m), 1.40 (9H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.2, 154.7, 140.5, 127.9, 127.7, 127.4, 126.1, 81.6, 66.2, 63.7, 32.3, 27.6; MS *m/z* 287(2), 266(2), 242(2), 219(3), 175(3), 41(100). Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.20; H, 6.20; N, 4.55.

4(*R*)-(Hydroxymethyl)-2(*R*)-phenylthiazolidine-3-carboxylic Acid *tert*-Butyl Ester (7a). To a stirred solution of **6a** (31.0 g, 0.100 mol) in dry THF (50 mL) was added dropwise a 2.0 M solution (100 mL) of borane–methyl sulfide complex in THF at room temperature. The reaction mixture was allowed to stir at 50 °C for 12 h. The mixture was then cooled to room temperature and poored slowly into ice cold water (250 mL). The water phase was acidified by adding a 10% $NaHSO_4$ solution (100 mL), stirred for 0.5 h, and finally extracted with Et_2O (3 × 250 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel with pentane–AcOEt (70:30 v/v) to yield the alcohol **7a** (24.4 g, 82%) as a white solid: mp 46–48 °C; $[\alpha]_D^{20}$ +65.2° (c 1.0, $CHCl_3$); IR (KBr) 3452 (OH), 1737, 1698 (C=O), 1495, 1369 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40 (5H, m), 6.10 (1H, s), 4.55 (1H, m), 3.95 (1H, dd, J = 10.3, 7.3 Hz), 3.86 (1H, dd, J = 10.3, 5.0 Hz), 3.25 (1H, dd, J = 11.9, 6.7 Hz), 2.85 (1H, dd, J = 11.9, 2.5 Hz), 1.70 (1H, br s), 1.25 (9H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 154.7, 140.8, 128.0, 127.4, 126.9, 124.1, 81.2, 65.9, 64.9, 63.7, 32.4, 27.7; MS *m/z* 295 (M^+, 1), 264 (1), 240 (2), 239 (12), 194 (14), 91 (18), 77 (10), 57 (100). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.96; H, 7.12; N, 4.83.

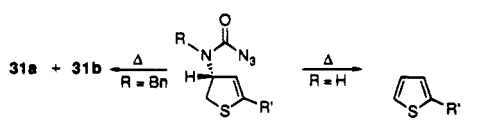
4(*R*)-Formyl-2(*R*)-phenylthiazolidine-3-carboxylic Acid *tert*-Butyl Ester (8a). To a cooled solution (−60 °C) of oxalyl chloride (1.7 mL, 18.9 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise a solution of DMSO (2.9 mL, 41.3 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was allowed to stir at −60 °C for 10 min and treated dropwise with a solution of the alcohol **7a** (5.0 g, 17.1 mmol) in dry CH_2Cl_2 (15 mL). After 1 h stirring at −60 °C, Et_3N (11.9 mL, 85.5 mmol) was added dropwise at −60 °C. After 15 min stirring at −60 °C, the reaction mixture was warmed up to room temperature. The mixture was poored into an ice cold 10% $NaHSO_4$ (250 mL) solution and extracted several times with CH_2Cl_2 (3 × 250 mL). The combined extracts were washed with brine (250 mL), dried over $MgSO_4$, and evaporated to afford the aldehyde **8a** (4.0 g, 81%) as a colorless oil, pure by TLC and used directly in the next step: IR (neat) 3000, 1705 (C=O), 1480, 1376 cm^{-1}; ^1H NMR (360 MHz, C_6H_6) δ 9.50 (1H, m), 7.00 (5H, m), 5.70 (1H, br s), 4.53 (1H, m), 2.67 (1H, m), 2.35 (1H, m), 1.20 (9H, s).

***cis*-4(*R*)-(6-Carboxyhex-1-enyl)-2(*R*)-phenylthiazolidine-3-carboxylic Acid *tert*-Butyl Ester (9a).** A stirred solution of 6-bromohexanoic acid (80.0 g, 0.41 mol) in CH_3CN (400 mL) and triphenylphosphine (113.0 g, 0.43 mol) was heated at reflux under dry N_2 for 16 h. Upon cooling to room temperature, the phosphonium salt soon begins to crystallize. The product was filtered, washed with Et_2O (2x 200 mL), and dried to afford (5-carboxypentyl)triphenylphosphonium bromide (187 g, 100%): mp >240 °C; IR (KBr) 2927, 1705 (COOH), 1636 (C=C), 1585 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 7.85 (15H, m), 3.34 (2H, m), 2.27 (2H, t, J = 7.4 Hz), 1.60 (6H, m); ^{13}C NMR (50.3 MHz, CD_3OD) δ 179.0, 138.1, 136.8, 136.6, 133.5, 133.2, 122.6, 120.9, 36.2, 33.0, 32.7, 27.0, 25.2, 24.9, 23.9.

A stirred solution of diisopropylamine (7.2 mL, 0.05 mol) in dry THF (125 mL) was treated under N_2 at −30 °C with n-butyllithium (20.5 mL, 2.5 M in hexane). The solution was allowed to stir at −30 °C for 30 min and was added to a suspension of (5-carboxypentyl)triphenylphosphonium bromide (11.8 g, 0.025 mol) in dry THF (125 mL). The blood red solution was stirred for 30 min at room temperature and treated dropwise with a solution of the aldehyde **8a** (5.0 g, 17.0 mmol) in dry THF (15 mL). The mixture was allowed to stir for 1 h. An ice cold 10% solution of $NaHSO_4$ (250 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 250 mL). The extracts were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography with pentane–AcOEt (60:40 v/v), to yield the *cis*-olefin **9a** (5.0 g, 78%) as a white solid: mp 83–85 °C; $[\alpha]_D^{20}$ +122.6° (c 1.0, $CHCl_3$); IR (neat) 3226, 1736, 1700 (C=O), 1669 (C=O; t-Boc), 1457, 852, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (5H,

(39) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663–1664.

(40) In contrast to **30**, thermolysis of debenzylated derivative **32** was found to lead exclusively to the corresponding thiophene **33**. Presumably the presence of the benzyl group enforces a productive rotameric conformation for successful cycloaddition. For a similar case, see: Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, *19*, 1689–1692.



30 (R = Bn, R' = $(CH_2)_4COOMe$) **33** R' = $(CH_2)_4COOMe$)
32 (R = H, R' = $(CH_2)_4COOMe$)

m), 6.15 (1H, s), 5.68 (1H, dd, J = 10.8, 8.8 Hz), 5.53 (1H, dt, J = 10.8, 7.2 Hz), 5.13 (1H, m), 3.24 (1H, dd, J = 11.6, 6.5 Hz), 2.75 (H, dd, J = 11.6, 5.4 Hz), 2.40 (2H, t, J = 7.5 Hz), 2.30 (2H, t, J = 8.0 Hz), 1.72–1.40 (4H, m), 1.30 (9H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 177.7, 153.3, 141.5, 131.8, 131.2, 129.8, 128.3, 80.3, 65.7, 58.8, 36.4, 33.6, 28.6, 27.9, 26.9, 24.0; MS m/z 367(1), 361(1), 333(1), 290(5), 277(1), 244(5), 207(1), 181(8), 158(1), 132(10), 104(12), 77(22), 57(100). Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.40; H, 7.47; N, 3.55.

***cis*-8(*R*)-[(*tert*-Butoxycarbonyl)amino]-9-mercaptonon-6-enoic Acid (10b).** To a stirred solution of the *cis*-olefin **9a** (10.3 g, 0.026 mol) in liquid ammonia (300 mL; freshly distilled over sodium) was added sodium until a dark blue color is obtained. The reaction mixture was allowed to stir for 2 h (if necessary more sodium was added to maintain the blue color). Solid NH_4Cl was added until the blue color disappeared and the solvent was slowly evaporated under a continuous flow of N_2. A 10% solution of $NaHSO_4$ (200 mL) was added and the aqueous phase was extracted several times with Et_2O (3 × 250 mL). The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with pentane–AcOEt (65:35 v/v) to afford **10b** (7.5 g, 95%) as a white solid: mp 66–68 °C; IR (KBr) 3360, 1725 (C=O), 1710 (C=O), 1240, 860, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.63 (1H, dt, J = 10.7, 7.5 Hz), 5.30 (1H, dd, J = 10.6, 9.1 Hz), 4.80 (1H, br s), 4.50 (1H, br), 2.55–2.80 (2H, m), 2.35 (2H, t, J = 7.4 Hz), 2.20 (2H, t, J = 7.3 Hz), 1.50–1.75 (4H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.2, 155.7, 134.0, 128.6, 80.2, 66.2, 49.8, 34.2, 30.5, 29.2, 28.7, 27.9, 24.6; MS m/z 257, 256, 212, 200-(5), 156(18), 138(4), 110(4), 94(22), 59(100). Anal. Calcd for $C_{14}H_{25}NO_4S$: C, 56.42; H, 8.31; N, 4.62. Found: C, 56.16; H, 8.37; N, 4.47.

1,1-Dimethylethyl [*R*-(*Z*)]-(3,6,7,8,9,10-hexahydro-10-oxo-2*H*-thiecin-3-yl)carbamate (14). Phenyl dichlorophosphate (1.48 mL, 9.90 mmol) was added to DMF (0.99 mL, 12.50 mmol) at 0 °C and the mixture was stirred for 3–5 min at the same temperature. To the white solid was added dry CH_2Cl_2 (40 mL), and the obtained solution was added to dry CH_2Cl_2 (1.0 L). A solution of **10b** (3.0 g, 9.90 mmol) and pyridine (4.0 mL, 49.40 mmol) in dry CH_2Cl_2 (50 mL) was added, by means of a syringe pump, during 10 h at room temperature. The reaction mixture was allowed to stir for 12 h at room temperature. A 10% solution of $NaHSO_4$ (1.0 L) was added and the aqueous phase was extracted several times with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography with pentane–AcOEt (85:15 v/v) to afford thiolactone **14** (675 mg, 24%): $[\alpha]^{20}_D$ +35.8° (c 0.8, $CHCl_3$); IR (NaCl, $CHCl_3$) 2977, 1709 (C=O), 1605, 1496 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (1H, dt, J = 10.0, 2.9 Hz), 5.11 (1H, t, J = 10.0 Hz), 4.68 (1H, br), 4.56 (1H, br), 3.35 (1H, m), 2.59 (2H, m), 2.41 (2H, m), 2.05 (2H, m), 1.82 (2H, m), 1.68 (1H, m), 1.40 (9H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 202.7, 155.1, 134.8, 128.2, 80.1, 47.4, 47.3, 46.5, 33.6, 28.7, 28.5, 27.0, 26.8; MS m/z 288 (M^+ – t-Bu, 5), 212(3), 181(1), 168(10), 152(8), 139(10), 111(11), 67-(10), 57(100). Anal. Calcd for $C_{14}H_{23}NO_3S$: C, 58.92; H, 8.13; N, 4.91. Found: C, 58.94; H, 8.09; N, 4.89.

[*R*-(*Z*)]-(3,6,7,8,9,10-Hexahydro-10-oxo-2*H*-thiecin-3-yl)-(phenylmethyl)carbamoyl azide (15). An ice cold solution of thiolactone **14** (337 mg, 1.18 mmol) in dry Et_2O (25 mL) was treated with dry HCl gas (generated by adding concentrated H_2SO_4 (97%) to a concentrated HCl (37%) solution) for 15 min. The reaction mixture was allowed to stir for 30 min at 0 °C. A slow stream of argon was passed through the reaction mixture, and the amine hydrochloride soon began to crystallize as a white solid. The material was washed several times with Et_2O (3 × 350 μL), to obtain pure amine hydrochloride (260 mg, 98%): mp 159–161 °C; IR (NaCl, CH_2Cl_2) 3090, 1686 (C=O), 1604, 805 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 5.65 (1H, dt, J = 10.4, 3.3 Hz), 5.32 (1H, t, J = 10.3 Hz), 4.31 (1H, m), 3.62 (1H, m), 3.44 (3H, s), 2.73 (1H, br s), 2.58 (1H, m), 2.33 (1H, m), 2.10 (3H, m), 1.70 (3H, m); MS m/z 185 (M^+ – HCl, 5), 170(1), 152(3), 139(8), 124(4), 111(12), 94(13), 82(100).

To a solution of amine hydrochloride (260 mg, 1.80 mmol) in CH_2Cl_2 (50 mL) was added a saturated $NaHCO_3$ solution (50 mL). The aqueous phase was extracted several times with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were dried and concentrated at 0 °C to a volume of 10 mL of CH_2Cl_2. To this solution was added benzaldehyde (121 μL, 1.19 mmol) and $MgSO_4$ (300 mg), and the reaction mixture was allowed to stir at room temperature for 3 h. The solvent was removed to obtain a colorless oil (450 mg). The material was purified by column chromatography with pentane–AcOEt (95:5 v/v), to obtain pure imine (392 mg, 80%): IR (neat) 3690, 2830, 1688 (C=O), 1604, 1550, 960, 805 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, s), 7.40–7.80 (5H, m), 5.63 (1H, dt, J = 11.7, 3.6 Hz), 5.50 (1H, dt, J = 11.7, 2.0 Hz), 4.62 (1H, ddd, J = 10.2, 5.7, 5.0 Hz), 3.45 (1H, dd, J = 13.0, 4.8 Hz), 2.72 (1H, dd, J = 8.2, 3.1 Hz), 2.69 (1H, dd, J = 8.3, 3.1 Hz), 2.43 (1H, ddd, J = 13.0, 10.3, 2.7 Hz), 2.20–2.30 (2H, m), 1.70–1.90 (4H, m); MS m/z 273(M^+, 20), 245(10), 213(2), 198(18), 184(3), 170(17).

To an ice cold solution of imine (322 mg, 1.18 mmol) in THF (12 mL) and a buffered solution (12 mL, pH = 4, citric acid) was added $NaCNBH_3$ (92 mg, 1.42 mmol) in small portions. The reaction mixture was allowed to stir at 0 °C for 40 min. A saturated aqueous $NaHCO_3$ solution (50 mL) was added and the water phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with brine (40 mL) and dried ($MgSO_4$). The solvent was removed to obtain a colorless oil. The material was purified by column chromatography with pentane–AcOEt (70:30 v/v) to afford the secondary amine (223 mg, 69%): $[\alpha]^{20}_D$ +45.8° (c 0.75, $CHCl_3$); IR (neat) 2930, 1680 (C=O), 1600 (C=C), 1552, 1435, 792 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (5H, m), 5.66 (1H, dt, J = 11.5, 3.4 Hz), 5.14 (1H, dt, J = 11.5, 2.1 Hz), 3.92 (1H, dt, J = 9.8, 4.5 Hz), 3.81 (1H, d, J = 12.9 Hz), 3.70 (1H, d, J = 12.9 Hz), 3.54 (1H, br), 2.62 (1H, ddd, J = 11.4, 8.3, 3.0 Hz), 2.37 (1H, ddd, J = 13.0, 10.0, 2.5 Hz), 2.32 (1H, br), 2.15 (2H, m), 1.94 (1H, br), 1.69–1.82 (4H, m); MS m/z 275(M^+, 10), 247(5), 215(2), 198(15), 184(4), 156(40), 132(10), 117(35), 104(45), 41 (100).

An ice cold mixture of the secondary amine (98.4 mg, 0.358 mmol) and DBU (271 μL) in dry CH_2Cl_2 (4 mL) was treated dropwise with a 1.6 M solution of phosgene in CH_2Cl_2 (1.04 mL, 1.61 mmol). The reaction mixture was allowed to stir at 0 °C for 3.5 h under dry Ar. The solvent was removed and the residue was purified by column chromatography with CH_2Cl_2, to obtain the carbamoyl chloride (120 mg, 100%). A solution of sodium azide (28 mg, 0.428 mmol) in acetone–H_2O (3 mL, 80:20 v/v) was added. The obtained suspension was allowed to stir for 12 h at room temperature. After adding brine (5 mL), the water phase was extracted several times with Et_2O (3 × 5 mL). The combined organic fractions were dried and concentrated to obtain a colorless oil. The material was purified by column chromatography with pentane–AcOEt (95:5 v/v) to obtain pure carbamoyl azide **15** (88 mg, 72%): $[\alpha]^{20}_D$ +32.8° (c 0.95, $CHCl_3$); IR (neat) 3355, 2150 (N_3), 1730 (C=O), 1691 (C=O), 1234 (N_3) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (5H, m), 5.39–5.55 (2H, m), 5.00 and 4.85 (1H, m), 4.65 and 4.56 (1H, d, J = 16.7 Hz), 4.58 and 4.47 (1H, d, J = 16.6 Hz), 3.26 (1H, m), 3.01 and 2.28 (1H, dd, J = 12.6, 12.1 Hz), 2.70 (1H, m), 2.51 (2H, m), 2.29 (1H, m), 2.10–1.50 (4H, m); MS m/z 344(M^+, 18), 316(13), 297(5), 288(2), 255-(10), 91(100). Anal. Calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.86; N, 16.28. Found: C, 59.25; H, 5.79; N, 15.82.

[3a*S*-(3aα,4β,6α)]-Hexahydro-2-oxo-1-(phenylmethyl)-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (16b); [3a*S*-(3aα,4β,6aα)]-Hexahydro-2-oxo-3-(phenylmethyl)-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (17b). A solution of the carbamoyl azide **15** (12 mg, 0.349 mmol) in H_2O (3 mL) was heated at 145 °C for 3 h in a small autoclave. Toluene (10 mL) and CH_3OH (2 mL) were added to the reaction mixture at room temperature, and this solvent mixture was concentrated by azeotropic distillation. Methanol (3 mL) and a catalytic amount of concentrated H_2SO_4 (97%, 2 drops) were added, and the reaction mixture was refluxed for 1 h. The residue upon workup was chromatographed on silica gel with pentane–AcOEt (30:70 v/v) as

eluant to give **16b** (2 mg, 17%) and **17b** (3 mg, 25%): IR of **16b** (NaCl, CH_2Cl_2) 3689, 3020, 1730 (C=O, COOMe), 1698 (C=O, RNCONR'), 1601, 1451 cm^{-1}; ^1H NMR of **16b** (500 MHz, $CDCl_3$) δ 7.30 (5H, m), 4.73 (1H, d, J = 15.5 Hz), 4.62 (1H, br s), 4.24 (1H, ddd, J = 8.0, 5.0, 1.1 Hz), 4.17 (1H, ddd, J = 7.5, 4.8, 2.3 Hz), 4.11 (1H, d, J = 15.5 Hz), 3.67 (3H, s), 3.15 (1H, ddd, J = 8.5, 6.3, 4.9 Hz), 2.82 (1H, d, J = 12.8 Hz), 2.68 (1H, dd, J = 13.0, 5.0 Hz), 2.33 (2H, t, J = 7.7 Hz), 1.80–1.30 (6H, m); ^1H NMR of **17b** (500 MHz, $CDCl_3$) δ 7.30 (5H, m), 5.00 (1H, d, J = 15.2 Hz), 4.67 (1H, br d, J = 1.0 Hz), 4.32 (1H, dddd, J = 9.3, 6.4, 3.1, 1.0 Hz), 4.03 (1H, dd, J = 9.3, 5.6 Hz), 3.92 (1H, d, J = 15.2 Hz), 3.68 (3H, s), 3.11(1H, ddd, J = 8.8, 5.6, 3.3 Hz), 2.95 (1H, dd, J = 12.4, 6.4 Hz), 2.78 (1H, dd, J = 12.5, 3.9 Hz), 2.34 (2H, t, J = 7.8 Hz), 1.80–1.30 (6H, m); MS m/z of **16b** 348(M^+, 8), 317(4), 275(2), 257(2), 187(20), 91(100). Anal. Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.95; N, 8.04. Found: C, 61.89; H, 7.00; N, 7.97.

***cis*-4-(*R*)-[6-(Methoxycarbonyl)hex-1-enyl]-2(*R*)-phenylthiazolidine-3-carboxylic Acid Methyl Ester (25).** A stirred solution of diisopropylamine (26.9 mL, 187.0 mmol) in dry THF (450 mL) was treated under N_2 at −30 °C with n-butyllithium (76.6 mL, 2.5 M in hexane). The solution was allowed to stir at −30 °C for 30 min and was added to a suspension of (5-carboxypentyl)triphenylphosphonium bromide (44.1 g, 93.0 mmol) in dry THF (125 mL). The blood red solution was stirred for 30 min at room temperature and treated dropwise with a solution of the aldehyde **8b** (16.0 g, 63.75 mmol) in dry THF (50 mL). The mixture was allowed to stir for 1 h. An ice cold 10% solution of $NaHSO_4$ (600 mL) was added, and the aqueous phase was extracted with Et_2O (4 × 500 mL). The extracts were dried over $MgSO_4$ and concentrated to 150 mL. To the reaction mixture was added a freshly prepared solution of CH_2N_2 in Et_2O, until quantitative esterification was observed by TLC. The solvent was removed and the residue was purified by silica gel column chromatography with isooctane–AcOEt (90:10 v/v), to yield pure methyl ester **25** (17.3 g, 75%): $[\alpha]^{20}_D$ + 162.8° (c 0.99, $CHCl_3$); IR (neat) 2951, 1789 (C=O), 1738 (C=O, COOMe), 1443, 769, 698 cm^{-1}; ^1H NMR 360 MHz, $CDCl_3$), δ 7.16 (5H, m), 6.28 (1H, s), 5.56 (1H, dd, J = 10.6, 9.4 Hz), 5.34 (1H, dt, J = 10.6, 7.4 Hz), 5.10 (1H, br s), 3.32 (6H, s), 2.71 (1H, dd, J = 11.7, 6.5 Hz), 2.40 (1H, dd, J = 11.7, 6.0 Hz), 1.10–2.20 (8H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3, 155.5, 141.6, 132.8, 129.5, 128.6, 128.4, 127.9, 126.4, 66.6, 59.9, 53.2, 51.8, 36.7, 34.2, 29.3, 27.5, 24.9; MS m/z 363(M^+, 7), 332(12), 316-(15), 304(10), 288(2), 258(4), 195(100), 164(100). Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.93; N, 3.86. Found: C, 62.71; H, 6.92; N, 3.91.

5-[3(*R*)-Bromo-4(*S*)-[(methoxycarbonyl)amino]-tetrahydrothiophen-2(*R*)-yl]pentanoic Acid Methyl Ester (26). To a stirred solution of Z-alkene **25** (37.0 g, 0.102 mol) in $CHCl_3$ (1100 mL) and H_2O (2 mL), was added dropwise a solution of bromine (16.3 g, 0.120 mol) in $CHCl_3$ (100 mL) at room temperature. After 20 min was added a mixture of NaS_2O_3 (500 mL; 0.05 M) and $NaHCO_3$ (500 mL; 10% solution) to the reaction mixture, and the water phase was extracted several times with $CHCl_3$. The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography with isooctane–AcOEt (75:25 v/v), to afford bromide **26** (23.5 g, 65%) as a white solid: mp 58–60 °C; $[\alpha]^{20}_D$ +55.9° (c 1.01, $CHCl_3$); IR (KBr) 3335, 1739 (C=O), 1695 (C=O), 1543, 1436, 776 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.18 (1H, m), 4.58 (1H, m), 4.50 (1H, m), 3.69 (6H, s), 3.62 (1H, dd, J = 11.6, 5.4 Hz), 3.48 (1H, m), 2.66 (1H, dd, J = 11.6, 1.6 Hz), 2.32 (2H, t, J = 7.3 Hz), 1.25–1.90 (6H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 155.8, 61.8, 60.0, 52.1, 51.4, 48.8, 33.6, 28.0, 24.6; MS m/z 322(22), 304(4), 292(8), 279(20), 199(40), 167(100). Anal. Calcd for $C_{12}H_{20}BrNO_4S$: C, 42.69; H, 5.69; N, 3.95. Found: C, 42.52; H, 5.74; N, 3.74.

5-[4(*S*)-Amino-3(*R*)-bromotetrahydrothiophen-2(*R*)-yl]-pentanoic Acid Methyl Ester Hydrobromide (27). A solution of methyl carbamate **26** (5.4 g, 0.015 mol) in dry acetic acid (55 mL), that has been saturated with HBr (37%), was stirred in the dark for 20 h at room temperature. The mixture was concentrated by azeotropic distillation with toluene (40 mL), to yield the amino bromide hydrobromide **27** (4.8 g, 85%). The crude product was used directly in the next step without any purification. Treatment of a small sample of the amino bromide hydrobromide **27** with $NaHCO_3$ yielded some amino bromide: IR (NaCl, CH_2Cl_2) 3690, 2859, 1732 (C=O), 1496; ^1H NMR (360 MHz, $CDCl_3$) δ 4.26 (1H, t, J = 4.6 Hz), 3.82 (1H, m), 3.66 (3H, s), 3.40 (1H, dd, J = 10.9, 5.8 Hz), 2.64 (1H, dd, J = 10.9, 3.7 Hz), 2.31 (2H, t, J = 7.3 Hz), 1.20–2.10 (7H, m).

[2*S*-(2α,3β,4α)]-3-Bromotetrahydro-4-[(phenylmethyl)-amino]-2-thiophenepentanoic Acid Methyl Ester (28a). To a solution of amino bromide hydrobromide **27** (11.25 g, 0.030 mol) in CH_2Cl_2 (100 mL) was added a saturated $NaHCO_3$ solution (100 mL). The water phase was extracted several times with CH_2Cl_2 (3 × 75 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to a volume of 180 mL. $MgSO_4$ (10 g) and benzaldehyde (3.20 mL, 0.030 mol) were added, and the reaction mixture was stirred for 12 h. The mixture was filtered and evaporated. The residue was purified by silica gel column chromatography with pentane–Et_2O (90:10 v/v), to yield the imine (9.56 g, 83%) as a colorless oil: $[\alpha]^{20}_D$ +204.9° (c 1.95, $CHCl_3$); IR (neat) 2942, 1734, 1699, 1684, 1641, 1579, 1540, 758, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.75–7.30 (5H, m), 4.47 (1H, dd, J = 4.5, 4.5 Hz), 4.27 (1H, ddd, J = 6.0, 4.5, 3.5 Hz), 3.79 (1H, dt, J = 4.5, 2.1 Hz), 3.65 (3H, s), 3.40 (1H, dd, J = 10.9, 6.0 Hz), 2.90 (1H, dd, J = 10.9, 3.5 Hz), 2.35 (2H, t, J = 7.1 Hz), 2.10–1.35 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.9, 162.4, 135.5, 131.3, 128.6, 128.5, 62.6, 51.4, 50.4, 34.7, 33.9, 33.6, 28.1, 24.8; MS m/z 386–384(M^+, 2), 354(6), 352(5), 304(3), 199(45), 167-(40), 106(100).

To an ice cold solution of imine (1.67 g, 4.36 mmol) in THF (50 mL) and a buffered solution (50 mL, pH = 4, citric acid) was added $NaCNBH_3$ (330 mg, 5.23 mmol) in small portions. The reaction mixture was allowed to stir at 0 °C for 20 min. A saturated aqueous $NaHCO_3$ solution (200 mL) was added and the water phase was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic fractions were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was removed to obtain a colorless oil. The material was purified by column chromatography with pentane–Et_2O (70:30 v/v), to afford the secondary amine **28a** (1.6 g, 95%): $[\alpha]^{20}_D$ +59.1° (c 0.22, $CHCl_3$); IR (NaCl, CH_2Cl_2) 2949, 1731 (C=O), 1602, 1495, 1438 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50–7.20 (5H, m), 4.47 (1H, dd, J = 4.5, 4.5 Hz), 3.86 (2H, dd, J = 17.0, 13.2 Hz), 3.70 (1H, m), 3.67 (3H, s), 3.57 (1H, m), 3.39 (1H, dd, J = 10.9, 5.6 Hz), 2.73 (1H, dd, J = 10.9, 2.7 Hz), 2.32 (2H, t, J = 7.3 Hz), 2.10 (1H, br s), 2.10–1.35 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.2, 128.9, 128.5, 127.9, 127.8, 68.03, 61.6, 52.1, 51.8, 49.6, 34.3, 34.2, 34.1, 34.0, 28.4, 25.0; MS m/z 356–354($M^+ - OCH_3$, 8), 306(20), 272(64), 260(36), 165(10), 91(100). Anal. Calcd for $C_{17}H_{24}BrNO_2S$: C, 52.90; H, 6.27; N, 3.63. Found: C, 52.88; H, 6.22; N, 3.51.

***N*-(Phenylmethyl)-3(*R*)-bromo-2(*R*)-(carbomethoxybutyl)tetrahydrothiophene-4(*S*)-carbamoyl Azide (29).** An ice cold mixture of the secondary amine **28a** (1.68 g, 4.36 mmol) and DBU (1.95 mL, 13.08 mmol) in dry CH_2Cl_2 (40 mL) was treated dropwise with a 2 M solution of phosgene in CH_2Cl_2 (30 mL). The reaction mixture was allowed to stir at 0 °C for 14 h under dry Ar. The solvent was removed under reduced pressure. To a solution of the residue in acetone (16 mL) was added a solution of NaN_3 (1.15 g, 17.7 mmol) in H_2O (16 mL). The reaction mixture was stirred for 12 h at room temperature. After adding brine (50 mL), the water phase was extracted several times with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were dried and concentrated to obtain a colorless oil. The material was purified by column chromatography with pentane–AcOEt (90:10 v/v), to yield pure carbamoyl azide **29** (1.4 g, 72%): $[\alpha]^{20}_D$ +81.9° (c 0.88, $CHCl_3$); IR (neat) 3689, 2157 (N_3), 1731 (C=O), 1677 (C=O), 1602, 1558, 1235 (N_3) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.03 (1H, dd, J = 8.2, 6.1 Hz), 4.77 (1H, d, J = 16.6 Hz), 4.65 (1H, m), 4.48 (1H, d, J = 16.5 Hz), 4.41 (1H, dd, J = 15.9, 7.8 Hz), 3.67 (6H, s), 3.25 (1H, ddd, J = 10.4, 5.9, 4.4 Hz), 2.95 (1H, dd, J = 11.0, 7.6 Hz), 2.74 (1H, dd, J = 11.0, 8.0 Hz), 2.32 (2H, t, J = 6.3 Hz), 1.60–1.20 (6H, m); ^{13}C NMR (90

MHz, $CDCl_3$) δ 173.8, 156.9, 136.7, 128.6, 128.3, 127.9, 66.9, 56.0, 51.8, 51.4, 47.5, 33.2, 32.8, 30.2, 29.6, 28.1; MS *m/z* 454–456(M^+, 1), 425(1), 423(1), 375(4), 91(100). Anal. Calcd for $C_{18}H_{23}BrN_4O_3S$: C, 47.48; H, 5.09; N, 12.30. Found: C, 49.28; H, 5.36; N, 11.28.

$\Delta^{2,3}$,*N*-(Phenylmethyl)-2-(carbomethoxybutyl)dihydrothiophene-4(*S*)-carbamoyl Azide (30). To a solution of carbamoyl azide **29** (277 mg, 0.608 mmol) in dry THF (7 mL) was added DBU (140 μL, 0.912 mmol). The reaction mixture was refluxed for 12 h under dry Ar. The formed salt ($DBUH^+Br^-$) was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane–AcOEt (85:15 v/v), to yield the carbamoyl azide **30** (216 mg, 95%): $[\alpha]^{20}_D$ −124.2° (*c* 1.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.75 and 5.46 (1H, d, J = 9.4 Hz), 5.01 (1H, d, J = 2.2 Hz), 4.62 and 4.53 (1H, d, J = 16.8 Hz), 4.45 and 4.39 (1H, d, J = 16.8 Hz), 3.66 (3H, s), 3.61 and 3.52 (1H, dd, J = 12.6, 9.6 Hz), 3.32 and 2.99 (1H, dd, J = 12.6, 5.5 Hz), 2.25 (4H, m), 1.60 (2H, m), 1.40 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.8, 149.4, 148.6, 138.6, 128.4, 128.4, 128.3, 127.1, 126.1, 115.0, 65.5, 63.9, 51.5, 47.8, 47.4, 36.9, 36.6, 33.6, 30.7, 27.8, 24.3; MS *m/z* 374(M^+, 10), 346(10), 313(10), 303(32), 167(30), 91-(100), 77(23). Anal. Calcd for $C_{18}H_{22}N_4O_3S$: C, 57.73; H, 5.92; N, 14.96. Found: C, 57.86; H, 5.91; N, 14.90.

[3a*S*-(3aα,4*Z*,6aα)]-5-[Hexahydro-2-oxo-1-(phenylmethyl)-4*H*-thieno[3,4-*d*]imidazol-4-ylidene]pentanoic Acid Methyl Ester (31a); [3a*S*-(3aα,4*E*,6aα)]-5-[Hexahydro-2-oxo-1-(phenylmethyl)-4*H*-thieno[3,4-*d*]imidazol-4-ylidene]pentanoic Acid Methyl Ester (31b). A solution of carbamoyl azide **30** (113 mg, 0.302 mmol) in CH_2Cl_2 (5.6 mL) was heated for 3 h at 150 °C in a small autoclave under dry Ar. The residue upon evaporation of the solvent was chromatographed on silica gel with pentane–AcOEt (70:30 v/v), to yield two cyclization products:

(Z)-**31a**: 34 mg, 32%; IR (neat) 3434, 2850, 1731 (C=O), 1693 (C=O), 1649, 1436, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.65 (1H, t, J = 7.0 Hz), 4.11 (1H, dd, J = 15.0, 7.5 Hz), 3.98 (1H, d, J = 12.5 Hz), 3.88 (1H, d, J = 12.5 Hz), 3.69 (1H, d, J = 8.0 Hz), 3.23 (1H, dd, J = 11.8, 7.2 Hz), 3.06 (1H, dd, J = 11.7, 7.6), 2.32 (2H, dt, J = 7.3, 1.5 Hz), 2.10 (2H, m), 1.75 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3, 171.9, 135.7, 134.8, 129.6, 129.1, 128.6, 122.7, 70.2, 64.7, 51.8, 50.6, 36.3, 33.7, 31.2, 24.5; MS *m/z* 346(M^+, 15), 315(8), 199-(29), 91(100), 77(11). Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.41; N, 8.09. Found: C, 62.02; H, 6.47; N, 7.95.

(E)-**31b**: 48 mg, 46%; IR (neat) 3241, 1731 (C=O), 1697 (C=O), 1495, 1265, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (5H, m), 5.53 (1H, t, J = 7.1 Hz), 4.93 (1H, br s), 4.72 (1H, d, J = 15.4 Hz), 4.51 (1H, d, J = 7.6 Hz), 4.20 (1H, ddd, J = 7.7, 5.2, 4.7 Hz), 4.15 (1H, d, J = 15.0 Hz), 3.66 (3H, s), 3.02 (1H, dd, J = 12.2, 3.3 Hz), 2.99 (1H, dd, J = 12.1, 4.9 Hz), 2.32 (2H, t, J = 7.4 Hz), 2.11 (2H, m), 1.75 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.1, 160.5, 142.2, 136.9, 129.0, 128.3, 127.9, 122.8, 61.9, 61.3, 51.9, 45.9, 36.3, 33.7, 31.4, 24.4; MS *m/z* 346(M^+, 30), 315(5), 196(30), 91(100). Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.41; N, 8.09. Found: C, 62.04; H, 6.48; N, 7.99.

[3a*S*-(3aα,4β,6aα)]-Hexahydro-2-oxo-1-(phenylmethyl)-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic Acid Methyl Ester (16b). A catalytic amount of $Pd(OH)_2$ on carbon, suspended in AcOEt (5 mL) was preactivated for 1 h under an atmosphere of H_2 (4 atm). A solution of the cyclization product *(Z)*-**31a** (20 mg, 0.057 mmol) in AcOEt (2 mL) was added. The reaction mixture was shaken for 1 h at room temperature under an atmosphere of H_2 (4 atm) and then passed through Celite. The solvent was removed under reduced pressure, to obtain the product **16b** (20 mg, 100%). The cyclization product *(E)*-**31b** was hydrogenated under the same experimental conditions, to yield the product **16b**. For spectral data of product **16b** vide supra.

(+)-Biotin. A stirred solution of **16b** (8 mg, 0.023 mmol) in concentrated HBr (48%, 1.5 mL) was refluxed for 2 h. To the reaction mixture was added a 0.1 N NaOH solution (pH = 14), and the water phase was extracted with pentane-Et_2O (50:50 v/v; 5 × 10 mL). The water phase was chromatographed on an ion-exchange strongly acidic gel-type resin (Amberlite IR-120 (plus)), with water as eluant (100 mL). The combined water fractions were lyophilized, to yield pure (+)-biotin (5 mg, 85%). The obtained (+)-biotin was recrystallized in water.

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