JOC*Note*

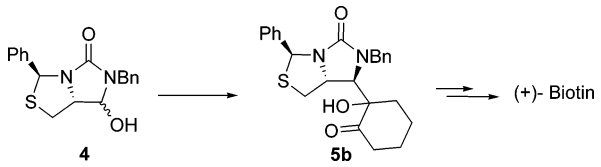
Diastereoselective Amidoalkylation of (3*S*,7a*R*)-6-Benzyl-7-hydroxy-3-phenyltetrahydro-5*H*-imidazo[1,5-*c*][1,3]thiazol-5-one : A Short and Highly Efficient Synthesis of (+)-Biotin

Subhash P. Chavan,* Amar G. Chittiboyina, T. Ravindranathan, Subhash K. Kamat, and Uttam R. Kalkote

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India 411 008

spchavan@dalton.ncl.res.in

Received July 13, 2004



A short and highly efficient synthesis of (+)-biotin in 10 steps with 20% overall yield has been achieved from L-cysteine involving amidoalkylation of hydroxy imidazothiazolone **4** via an acyliminium ion intermediate to furnish C-7-substituted imidazothiazolones **5b** as the key step.

Vitamin H,[1] more commonly known as (+)-biotin (Figure 1), is involved in an essential part of the metabolic cycle causing catalytic fixation of carbon dioxide in the biosynthesis of organic molecules. In the pharmaceutical context it is used as an additive and as an avidin complex in the area of drug delivery, immuno assay, isolation, and localization. To date, a number of new synthetic routes involving different strategies for control of three adjacent chiral centers are reported.[1] However, to the best of our knowledge, none of the known syntheses has a commercial advantage over the Sternbach synthesis developed by Hoffman-La Roche.[2] Our quest for and long-standing interest[1c,d] in this commercially important molecule led us to explore a practical synthesis of (+)-biotin.

Pioneering work by Speckamp et al.[3d,e] and others[3f] on the utility of acyliminium ion chemistry has provided a powerful protocol in effecting C−C bond formation. Of the various approaches described toward (+)-biotin synthesis, cystine/cysteine[1b,c,g,3] has attracted a great deal of attention by virtue of it possessing requisite stereochemistry and its ready availability. This has led to the development of elegant syntheses of (+)-biotin via an intramolecular cyclization by Speckamp[3d] and our group[1c] to generate the *cis*-biotin skeleton with excellent stereocontrol. Our interest in acyliminium ion chemistry[1c,d] led us to undertake the study of the diastereochemical outcome of intermolecular carbon−carbon bond formation. Herein we disclose our efforts in the stereoselective amido alkylations culminating in one of the highly efficient syntheses of (+)-biotin.

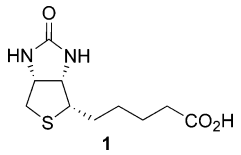


FIGURE 1. Structure of the (+)-biotin.

TABLE 1. Amidoalkylation of Hydroxy Imidazothiazlone 4[a]

	nucleophile[b] (equiv)	Lewis acid	*T* (°C)	time (min)	formation of products (%) **5**	**6**	yield (%)
1	5	$SnCl_4$ (3)	−78 to 25	300		100	98
2	5	$TiCl_4$ (2)[c]	−30 to 0	300	10	90	
3	1.5	$BF_3{\cdot}OEt_2$ (1.3)	0 to 25	10	100		>98

[a] All reactions were performed with 1.0 equiv of hydroxyimidazothiazolone **4**. [b] 1-Trimethylsilyloxycyclohexene was used as nucleophile. [c] 1 M solution in dichloromethane.

The hydantoin **3** developed by Poetsch et al.[3a,e] appeared to be an ideal scaffold to study the Lewis acid-mediated amido alkylation due to its rigid framework which would give rise to facial differentiation. Thus, the bicyclic hydantoin **3** was prepared from cysteine according to the procedure of Poetsch.[3a,e] The hydantoin was then reduced with sodium borohydride to afford hydroxy imidazothiazolone **4** in quantitative yield (Scheme 1).

Our initial attempts to effect carbon−carbon bond formation at the C-7 position of hydroxy imidazothiazolone **4** with 1-trimethylsilyloxy-1-cyclohexene in the presence of $SnCl_4$ at −78 °C resulted in exclusive formation of the eliminated product **6** (Scheme 2). Treatment of hydroxy imidazothiazolone **4** with 1-trimethylsilyloxy-1-cyclohexene in the presence of other Lewis acids, e.g., $TiCl_4$ or $SnCl_4$ in DCM at −78 °C, were also unsuccessful. After careful screening of various Lewis acids at different temperatures it was revealed that when the reaction was performed at −20 to 0 °C with $BF_3{\cdot}OEt_2$, the desired product was obtained in 50% yield. It follows then that the choice of temperature was a critical parameter for the successful formation of the desired product. Careful experimentation also revealed that 1.5 equiv of nucleophile was required to obtain optimum yields of the amidoalkylated product. As anticipated, performing the reaction between hydroxy imidazothiazolone **4** and 1-tri-

(1) (a) For a recent review on biotin, see: DeClercq, P. J. *Chem. Rev*. **1997**, *97*, 1755. (b) Zhao, J.; Li, Y.-z.; Zhang, Q.-s. *Jingxi Huagong* **2004**, *21*, 30. (c) Seki, M.; Kimura, M.; Hatsuda, M.; Yoshida, S.; Shimizu, T. *Tetrahedron Lett.* **2003**, *44*, 8905. (d) Chavan, S. P.; Tejwani, B.; Ravindranathan, T. *J. Org. Chem*. **2001**, *66*, 6197. (e) Chavan, S. P.; Ramakrishna, G.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron Lett.* **2004**, *44*, 7307. (f) Shimizu, T.; Seki, M. *Tetrahedron Lett*. **2000**, *41*, 5099. (g) Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S.-c. *J. Org. Chem*. **2002**, *67*, 5527.

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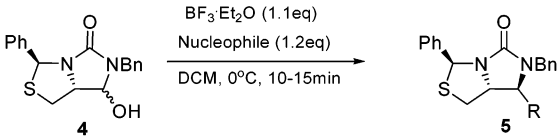
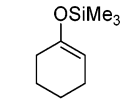
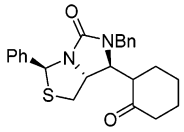
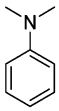
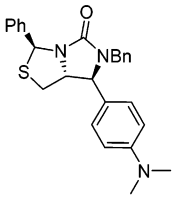
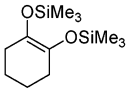
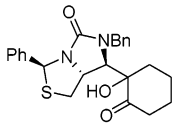
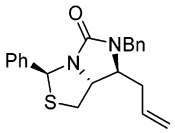
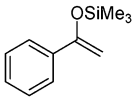
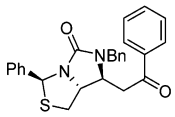
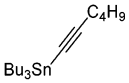
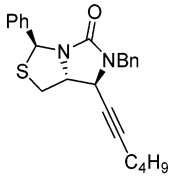
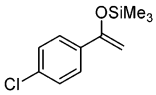
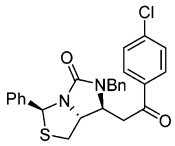
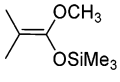
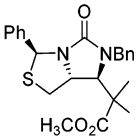
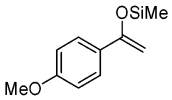
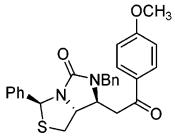
(3) (a) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148. (b) Fusijawa, T.; Nagai, M.; Kaike, Y.; Shimizu, M. *J. Org. Chem*. **1994**, *59*, 5865. (c) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem*. **1995**, *60*, 321. (d) Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2391. (e) Casutt, M.; Poetsch, E.; Speckamp, W. N. Ger. Offen. DE 3 926 690, 14 Feb 1991; *Chem. Abstr*. **1991**, *115*, 8429k. (f) Liao, Z.-K.; Kohn, H. *J. Org. Chem*. **1984**, *49*, 4745.

10.1021/jo0488107 CCC: $30.25 © 2005 American Chemical Society
Published on Web 01/27/2005

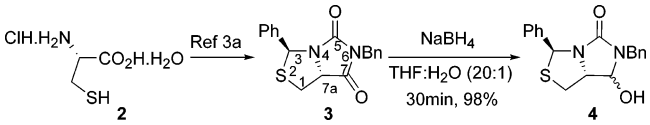
TABLE 2. Amidoalkylation of Hydroxy Imidazothiazolone 4[a] with Various Nucleophiles



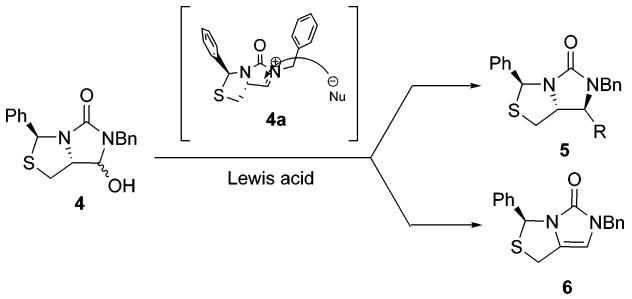
Entry	Nucleophile	Product	Yield (%)	Entry	Nucleophile	Product	Yield (%)
a			97	f			50[c]
b			98[b]	g			98
c			96	h			96
d			94	i			98
e			98				

[a] All reactions were performed with 1.0 equiv of hydroxy imidazothiazolone **4**. [b] 2 equiv of nucleophile was used. [c] 38% of eliminated product **6** was isolated.

SCHEME 1



SCHEME 2. Nucleophilic Addition of 4a to Hydroxy Imidazothiazolone 4



methylsilyloxy-1-cyclohexene, at 0 °C to ambient temperature, furnished the desired product **5a** exclusively in almost quantitative yield. The results obtained are recorded in Table 1.

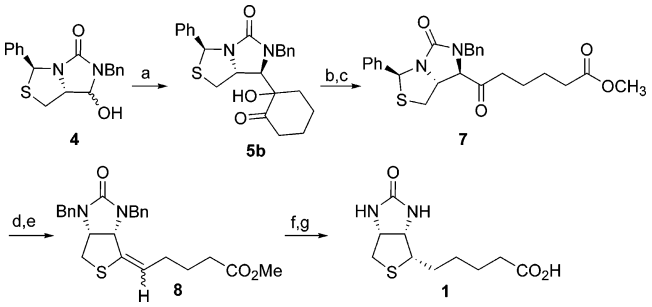
Having successfully established the appropriate conditions for carbon−carbon bond formation, the amidoalkylation was performed with a variety of nucleophiles such as enol ethers, aromatic compounds, allyltrimethylsilane, tin acetylides, and ketene silyl acetal. The results obtained are summarized in Table 2. From the table, it is evident that the reaction proceeds with a very high degree of diastereoselectivity to furnish the corresponding 7-substituted imidazothiazolone **5**. The *trans* stereochemistry was confirmed by ^{1}H NMR coupling constants (e.g., $J = 1.5$ Hz for product in entry h, Table 2).

The compounds **5a** and **5b** were obtained as a mixture of diastereomers in roughly equal amounts (^{1}H NMR). The establishment of exact stereochemistry at the third center (**5a** and **5b)** was of no consequence since it was to be destroyed at a later stage in the biotin synthesis.

We reasoned the high degree of diastereoselectivity was due to the facial differentiation of the bicyclic hydroxy imidazothiazolone **4** in which the nucleophilic attack takes place from the less hindered convex face of the bicyclic imidazothiazolone (Scheme 2).

Having established an efficient protocol for the synthesis of 7-substituted imidazothiazolones, the preparative usefulness of new carbon−carbon bond formation

SCHEME 3[a]



[a] Conditions: (a) 1,2-bis(trimethylsilyloxy)cyclohexene (1.5 equiv), $BF_3{\cdot}OEt_2$, DCM, 98%; (b) 70% TBHP, KOH-MeOH, 15 min; (c) CH_2N_2, 10 min, 70%; (d) Zn/AcOH, 80 °C, 5 h; (e) AcOH/ piperidine, 100 °C, 90 min, 70%; (f) H_2/Pd−C, MeOH, 200 psi, 100%; (g) 47% HBr, 5 h, 78%.

was demonstrated by efficiently converting **5b** to biotin (Scheme 3). The α-hydroxy ketone **5b** was subjected to Baeyer−Villiger oxidation with *tert*-butyl hydroperoxide in alkaline methanol to furnish the keto acid in 70% yield. This keto acid on esterification with diazomethane furnished the keto ester **7** in quantitative yield. The intermediate **7**, being epimeric at C-7 with respect to (+)-biotin, was epimerized by reductive cleavage of carbon−sulfur bond with Zn/AcOH. Further cyclization of thiol thus obtained with the carbonyl function was performed in the presence of piperidine and acetic acid followed by dehydration to afford the olefin **8**. [3a]

Stereospecific hydrogenation was carried out in the presence of 10% palladium on carbon to furnish *N*,*N*′-dibenzylbiotin methyl ester in quantitative yield. Removal of *N*-benzyl groups was achieved with aq HBr (47%) at reflux temperature to afford (+)-biotin. The biotin thus obtained was identical with an authentic sample with respect to mp, IR, ^{1}H NMR, mass spectra, and specific rotation: mp 230−231 °C; $[\alpha]_D = +89.7$ (c = 1.01, 0.1 N NaOH) (lit.[5] mp 229.5−230 °C; $[\alpha]_D = +91.5$ (c = 1, 0.1 N NaOH).

In conclusion, a highly stereospecific protocol for amidoalkylation of imidazothiazolone has been developed which has culminated in a highly efficient synthesis of (+)-biotin. We believe that this protocol would potentially provide easy access to *trans* vicinal diamines upon hydrolysis.

Acknowledgment. C.A.G. thanks CSIR, New Delhi, India, for the award of a fellowship. Funding from CSIR, New Delhi, India, under the YSA (S.P.C.) Scheme is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **5a**−**i**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0488107

(4) (a) For a review on acyliminium ion chemistry, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Schierle, K.; Vaule. R.; Steckhan, E. Eur. *J. Org. Chem*. **1998**, 509. (c) Schickli, C. P.; Seebach, D. *Liebigs. Ann. Chem*. **1991**, 655.

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