A Switch of Reactivity Profile in Ionic Intramolecular Annulation Reactions: A Short and Efficient Synthesis of D-(+)-Biotin

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Cyclization reactions to construct five- or six-membered rings constitute the backbone of any synthetic strategy. Although a variety of methods are available to effect these annulations, there is still a need to develop mild and efficient methods to effect these cyclizations. The significance of this is evident by increase in number of recent publications on newer methodologies to effect this transformations.[1]

The subtle difference between reactivity and selectivity becomes even more critical in effecting these transformations in the desired direction, and one needs to address this issue. This aspect becomes even more important while dealing with multifunctional groups where undesired side reactions become more prominent.

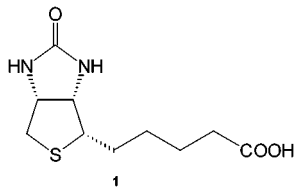
A revealing case study will be the conversion of thioenol ether **2** to 5,5-fused system (Scheme 1) in connection with an efficient D-(+)-biotin (**1**) synthesis described herein. D-(+)-Biotin (vitamin H), a biocatalyst of reversible metabolic reactions of carbondioxide transport in organisms, is one of the B-complex group of vitamins and has immense commercial importance in poultry feeds and animal nutrition. It finds application in pharmaceutical industries as an additive and as an avidin complex in the area of drug delivery immunoassay, isolation, and localization.

Although a variety of methods are known for its synthesis,[2] there exists a need to develop an efficient and practical synthesis of this compound. After completion of our work,[4,5] Speckamp et al.[2e] published an elegant synthesis of D-(+)-biotin based on a similar concept. However, there are remarkable differences between our approach and Speckamp's in terms of different products obtained and reaction conditions employed for the crucial cyclization.

Sulfides are well-known to complex with Lewis acids.[3] It was surmised that selective complexation of the sulfide to generate immonium ion followed by intramolecular trapping of ionic intermediate **5** should chemoselectively lead to formation of **3**. Although **2** has all the functionalities set for a 5,5-ring closure, all attempts to convert **2** to **3** met with failure under a variety of Lewis acid mediated conditions (entries 1−4, Table 1).

The use of silver triflate in stoichiometric amounts however led to the isolation of the desired 5,5-fused cyclized product **3**, albeit in poor yields (5% !) along with undesired **4** (20% yield) in the former and ureide **10** (40% yield) (Scheme 3).

Scheme 1



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Scheme 2

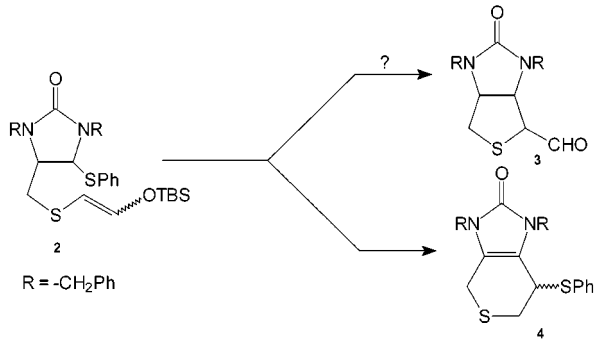

Table 1. Reaction of Compound 2 with Different Lewis Acids

entry	conditions	% of **3**	% of **9**	% of **4**	% of **10**
1	$AlCl_3$, −78 °C, rt			55	
2	$TiCl_4$, −78 °C, rt			62	
3	$BF_3{\cdot}Et_2O$, 0 °C, rt			43	
4	AgOTf, 0 °C, rt	5		20	40
5	TBSOTf, 0 °C, rt		20	30	
6	PhSH (1 equiv), rt,			61	
7	PhSTBS (1 equiv), TBSOTf (cat.), 0 °C, rt		70		
8	*p*-nitrobenzaldehyde/TBSOTf (cat.), rt, 5 min	95			

(1) For a recent review on cyclization, see: Thebtaranonth, C.; Thebtanonth, Y. *Tetrahedron* **1990**, *46*, 1385 and references therein.

(2) For the synthesis of D-(+)-biotin, see: (a) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099. (b) Chen, F.; Peng, Z.; Shao, L.; Cheng, Y. *Yaoxue Xuebao*, **1999**, *34*, 822 (Chinese) and reference cited therein. (c) Brieden, W.; Schroer, J. Eur. Pat. Appl. EP 827957 A1, 11 Mar 1998, 9 pp; *Chem. Abstr.* **1998**, *128*, 230190. (d) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755 and references cited therein. (e) Moolenaer, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2391. Casutt, M.; Poetsch, E.; Speckamp, W. N. Ger. Offen. DE 3.926,690, 14 Feb 1991; *Chem. Abstr.* **1991**, *115*, 8429k. (f) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321. (g) Deroose, F. D.; De Clercq, P. J. *Tetrahedron Lett.* **1994**, *35*, 265. (h) Fusijawa, T.; Nagai, M.; Kaike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865. (i) Goldberg, M. W.; Sternbach, L. H. US Patents 2,489,235 and 2,489,238. **1985**; *Chem. Abstr.* **1951**, *45*, 186a, 186g. (j) Aoki, S.; Suzuki, H.; Akiyama, H.; Akano, S. US Patent 3,-876,656, 1975; *Chem. Abstr.* **1974**, *80*, 95951z. (k) Declercq, P. J.; Deroose, F. D. *Tetrahedron Lett.* **1993**, *34*, 4365. (l) Alcazar, V.; Tapia, I.; Morau, J. R. *Tetrahedron* **1990**, *46*, 1057. (m) Bihovsky, R.; Bodepudi, V. *Tetrahedron* **1990**, *46*, 7667. (n) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57. (o) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148. (p) Lee, H. L.; Baggiolini, E. G.; Uskokivic, M. R. *Tetrahedron* **1987**, *43*, 4887. (g) Bates, H. A.; Rosenblum, S. R. *J. Org. Chem.* **1986**, *51*, 3447. (r) Bates, H. A.; Smilowtz, L.; Lin, J. *J. Org. Chem.* **1985**, *50*, 899. (s) Bates, H. A.; Smilowitz, L.; Rosenblum, S. B. *J. Chem. Soc., Chem. Commun.* **1985**, 353. (t) Kinoshita, H.; Futagami, M.; Inomata, K.; Kotahe, H. *Chem. Lett.* **1983**, 1275.

(3) (a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966. (b) Mann, A.; Ricci, A. *Tetrahedron Lett.* **1988**, *29*, 6175.

(4) Ravindranathan, T.; Chavan, S. P.; Tejwani, R. B.; Varghese, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1750.

(5) Ravindranathan, T.; Chavan, S. P.; Tejwani, R. B. Indian Patent Appl. No. 65/DEL/92, US patent 5,274,107; *Chem. Abstr.* **1994**, *120*, 217097t.

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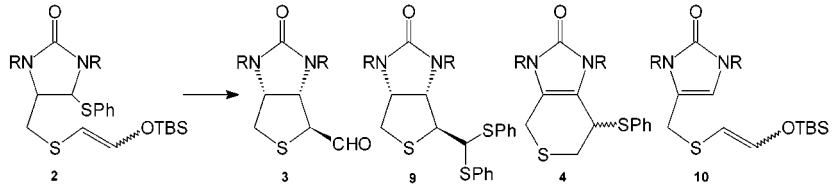
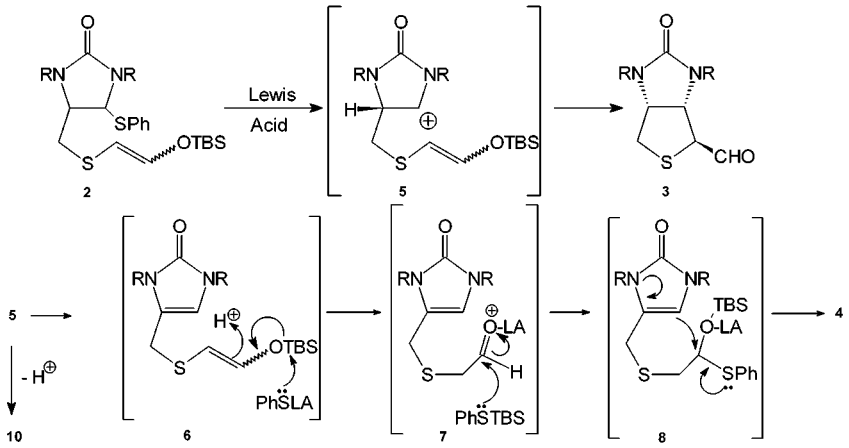
Scheme 3



Scheme 4



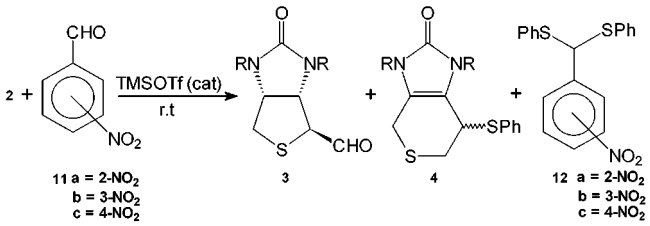
Treatment of **2** with TBSOTf however, led to the formation of thioacetal **9** in 20% yield! Formation of thioacetal **9** along with **3** and **4** indicates that there is a thin line of demarcation in the reaction pathways leading to the formation of these products. Encouraged by the formation of thioacetal **9**, it was obvious that its formation can be rationalized by the liberation of thiophenol from **2** and its further reaction with **2**. It was surmised that addition of external thiophenol should change the course of the reaction in favor of thioacetal **9**. However, performing the reaction in the presence of thiophenol led to the formation of **4** as the exclusive product in 61% yield. The failure of an additional 1 equiv of thiophenol to improve the yield of **9** led us to explore the silyl thiophenol. Thus, PhSTBS was generated in situ and silyl enol ether **2** was added to it followed by a catalytic amount of TBSOTf, and as expected, thioacetal **9** was the exclusive product obtained in 70% yield. Conventional methods of deprotection (e.g., CAN, HgO) of this thioacetal led to poor yields (30%) of aldehyde **3**. The thioacetal **9** was smoothly converted to aldehyde **3** by a novel catalytic transthioacetalization protocol developed by us[4] involving one-to-one exchange under anhydrous conditions employing 4-nitrobenzaldehyde as the acceptor and TMSOTf as the catalyst.

To achieve exclusive formation of aldehyde **3** from **2** directly without the intermediacy of thioacetal **9**, a study of product profile formed under a variety of conditions was taken up. Formation of **4** in annulation reactions along with formation of **10** and **3**, isolation of thioacetal **9** in 20% yield using TMSOTf (which was increased to 70%) employing external source of thiophenol, and our finding that thioacetals undergo facile conversion to parent carbonyl compounds with 4-nitrobenzaldehyde suggested that if thiophenol liberated in the reaction mixture could be selectively and effectively scavenged, formation of **4** and **9** could be suppressed or totally avoided.

Table 2. Role of Nitrobenzaldehydes in Cyclization

compd	% of **3**	% of **4**
2-nitrobenzaldehyde (**11a**)	50	40
3-nitrobenzaldehyde (**11b**)	75	20
4-nitrobenzaldehyde (**11c**)	95	

Scheme 5



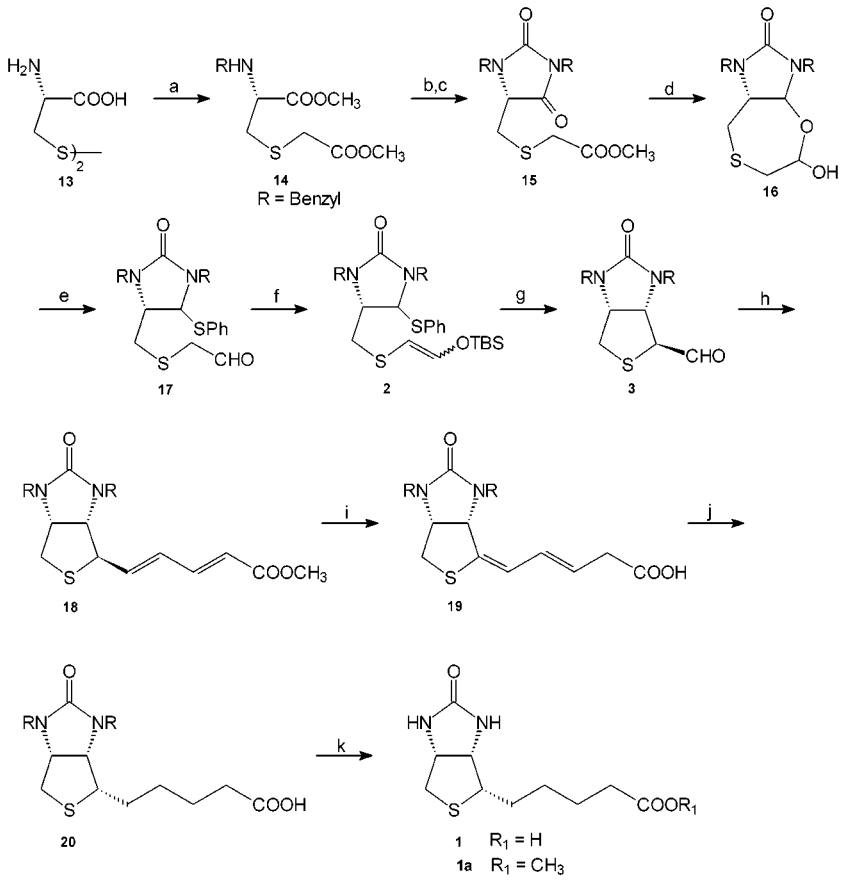
To effect the cyclization to the desired 5,5-fused system we chose nitrobenzaldehydes as the thiophenol scavengers (see Table 2). Gratifyingly, the assumption turned out to be the fact, when silyl enol ether **2** was treated with catalytic amount of TMSOTf/(or TBSOTf), in the presence of 4-nitrobenzaldehyde (**11c**), aldehyde **3** was obtained as the sole product in 95% (98%) yield along with formation of the thioacetal **12c** in 98% yields. Of the three nitroaldehydes screened (**11a**−**c**), **11c** was found to be the best thiophenol scavenger in terms of driving the reaction to the formation of the desired product **3** (Table 2) selectively and completely.

Having achieved the crucial cyclizaton (note: all of the cyclization reactions were performed on the racemic substrates), the next task was to convert **3** to D-(+)-biotin (**1**). As depicted in Scheme 4, chiral hydantoin **13** was obtained from L-cystine **12** in four steps.[5]

Reduction of the hydantoin **15** was effected employing 2.2 equiv of DIBAL-H[6] in toluene at −78 °C to furnish lactol **16** (72% yield). Treatment of lactol in thiophenol

(6) Winterfeldt, E. *Synthesis* **1975**, 617.

Scheme 6[a]



[a] Conditions: (a) ref 12; (b) (i) BnNCO, DCM, rt, 1 h; (c) pTSA, rt, 6 h, 90% (two steps); (d) DIBAL-H, Tol, −78 °C, 2 h, 72%; (e) PhSH, pTSA, 0 °C, 5 min, 70%; (f) DBU, TBSCl, DCM, reflux, 2 h, 92%; (g) *p*-nitrobenzaldehyde, DCM, TBSOTf, 5 min, 95%; (h) $Ph_3P{=}CHCH{=}CHCOOCH_3$, DCM, rt, 12 h, 89%; (i) 1 M NaOH, MeOH, 0 °C, 12 h, 97%; (j) 10%Pd−C/H_2 (3 atm), 8 h, 92%; (k) 48% HBr, reflux, 2 h, 80%.

with pTSA as the catalyst furnished the desired thiophenyl aldehyde **17** (70% yield). Aldehyde **17** was converted to its silyl enol ether **2** (92% yield).[7] Enol ether **2** was transformed to the cyclized product **3** in 95% yield employing the protocol developed by us as described previously (treatment with catalytic amount of TMSOTf in the presence of 4-nitrobenzladehyde). Alternatively, **17** could be smoothly converted to **3** in one pot without isolation of **2**. The bicycloaldehyde **3** obtained was epimeric at C-2 with respect of biotin. Rectification of the stereochemistry at C-2 and its conversion to D-(+)-biotin was efficiently effected by the following sequence.

Thus, Wittig homologation of **3** furnished the unsaturated ester **18** having biotin framework in 89% yield. Usually $\alpha,\beta,\gamma,\delta$ unsaturated esters require strong bases (viz. LDA) for their conversion into $\beta,\gamma,\delta,\epsilon$ esters.[8,9] However, we have observed that treatment with mild bases such as NaOH (in MeOH) brings about deconjugation and concomitant hydrolysis in one step in almost quantitative yields! We believe that this is the first report of a sulfur-assisted deconjugation of $\alpha,\beta,\gamma,\delta$ unsaturated esters to $\beta,\gamma,\delta,\epsilon$ acids under mild conditions. A variety of other bases were also shown to effect this transformation.

The acid **19** on hydrogenation provided the saturated acid **20** in 96% yield (characterized as its methyl ester) having cis stereochemistry as required for biotin. Debenzylation of **20** afforded D-(+)-biotin (**1**) (mp 230 °C (lit. mp 232−233 °C)), which was also characterized as its methyl ester (**1a**), in 80% yield. ^{1}HNMR, mass, and optical rotation of synthetic as well as authentic samples of D-(+)-biotin as well as biotin methyl ester (**1a**) were in perfect agreement with the ones reported in the literature.

Thus, convenient synthesis of D-(+)-biotin has been achieved from L-cystine involving facile intramolecular cyclization to furnish 5,5-fused system and incorporation extremely mild conditions of deconjugation as the key steps.

Experimental Section

General Methods. All reactions with moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were dried by distillation from sodium benzophenone (THF) or from CaH_2 (DCM). Starting materials that were commercially available were used without purification. Melting points are uncorrected and were determined using crystallized samples. NMR spectra were obtained at Bruker WH90/22.63, Bruker AC200/50 and Bruker MSL300/75.49 MHz in $CDCl_3$ unless otherwise noted. *N*-aryl-*S*-carboxymethyl-L-cysteine was prepared from L-cystine **14** according to literature procedure.[12]

(7) Weimer, D. F.; Becicka, b. T.; Koerwith, F. L.; Dritna, G. J.; Baenzigei, N. C. *J. Org. Chem.* **1990**, *50*, 5613.

(8) Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274

(9) Martin, S. F.; Desai, S. R.; Philip, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294.

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

(*R*)-(+)-1,3-Dibenzyl-5-(3-methoxycarbonyl-2-thiapropyl)hydantoin (15). A solution of benzyl isocyanate (10 mmol), *N*-aryl-*S*-carboxymethyl-L-cysteine **14** (10 mmol) in dichloromethante (10 mL) was stirred under argon atmosphere. After 1 h, pTSA (190 mg, 1 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h. Dichloromethane was removed, and the residue was loaded on column and eluted with (EtOAc/*n*-hexane 1:3) to furnish N,N-disubstituted hydantoin **15** in 90% yield.

IR ($CHCl_3$): 3040, 2910, 1765, 1740, 1705, 1600, 1590, 1495, 1260, 1000 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): δ 7.25 (10H, m), 5.05 (1H, d, J = 15 Hz), 4.7 (2H, s), 4.1 (1H, d, J = 15 Hz), 4.0 (1H, t, J = 4 Hz), 3.7 (3H, s), 3.1 (2H, d, J = 4 Hz), 3.1 (1H, d, J = 14 Hz), 2.9 (1H, d, J = 14 Hz).

^{13}C NMR ($CDCl_3$, 22.63 MHz): δ 170.92 (s), 169.95 (s), 156.43 (s), 135.89 (s), 135.57 (s), 129.10 (d), 128.49 (d), 128.34 (d), 127.91 (d), 58.49 (d), 51.86 (q), 44.78 (t), 42.37 (t), 33.53 (t), 31.00 (t).

MS: 398 (M^+, 9), 366 (4), 333 (4), 292 (100), 279 (15), 215 (6), 201 (31), 173 (16), 149 (12), 132 (18), 119 (23), 91 (23).

Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5,56; N, 7.03; S, 8.05. Found: C, 63.15; H, 5.50; N, 6.95; S, 8.00.

1,3-Dibenzyl-5-hydroxy-1,4-oxxathiopano[5,4-*f*]dihydroimidazolid-2-one (16). DIBAL-H (10.23 mL, 2.2M solution in toluene) was added very slowly (during 1h) to a precooled (−78 °C) solution of hydantoin **15** (3.98 g, 10 mmol) in dry toluene (30 mL) at −78 °C under argon atmosphere. The reaction mixture was stirred for an additional 2 h and quenched by addition of methanol (10 mL) at −78 °C. Water (2 mL) was then added, and the resulting precipitate was filtered through Celite. Rotary evaporation of the solvent afforded the residue that when column chromatographed (1:1 EtOAc/*n*-hexane) furnished lactol **16** in 2.66 g (72%) as a white solid.

Mp: 141−143 °C.

IR (Nujol): 3243, 2926, 1652, 1585, 1495, 1076, 950, 825 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): δ 7.3 (10H, m), 4.95 (1H, d, J = 6.0 Hz), 4.83 (1H, d, J = 14.5 Hz), 4.69 (1H, d, J = 15.4 Hz), 4.6 (1H, m), 4.25 (1H, d, J = 14.5 Hz), 4.14 (1H, d, J = 15.4 Hz), 3.7 (bs, D_2O exchangeable), 3.5 (1H, m), 2.55 (5H, m).

^{13}C NMR ($CDCl_3$, 77.49 MHz): δ 158.99 (s), 136.51 (s), 136.32 (s), 128.39 (d), 128.32 (d), 128.23 (d), 127.46 (d), 127.30 (d), 127.24 (d), 101.15 (d), 84.44 (d), 60.35 (d), 45.43 (t), 43.91 (t), 39.69 (t), 30.63 (t).

MS: 370 (M^+, 3), 352 (4), 324 (12), 277 (70), 264 (12), 233 (18), 203 (26), 187 (16), 175 (17), 132 (8), 119 (6), 106 (5), 91 (100).

Anal Calcd for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56; S, 8.65. Found: C, 65.00; H, 6.16; N, 7.51; S, 8.29.

1,3-Dibenzyl-2-oxo-5-(3-formyl-2-thiopropyl)-4-phenylthioimidazolidine (17). To a solution of lactol **16** (3.7 g, 10 mmol) in thophenol (5 mL) at 0 °C was added pTSA (190 mg, 1 mmol). The reaction mixture was stirred at 0 °C for 5 min. Water (10 mL) was then added, and the mixture was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhyd Na_2SO_4 and filtered. Removal of solvent under reduced pressure afforded a residue that when purified by column chromatography (10−50% EtOAc/*n*-hexane) furnished 3.23 g (70%) of **17**.

IR (neat): 3010, 2900, 1710, 1700, 1600, 1580, 1495, 1450, 1360 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): δ 9.2 (1H, t, J = 4 Hz), 7.25 (12H, m), 7.0 (3H, m), 5.1 (1H, d J = 15 Hz), 4.52 (1H, d, J = 4 Hz), 4.45 (1H, d, J = 15 Hz), 4.3 (1H, d, J = 15 Hz), 4.0 (1H, d, J = 15 Hz), 3.55 (1H, m), 2.85 (2H, d, J = 4 Hz), 2.38 (2H, m).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 192.60 (s), 157.65 (s), 136.07 (s), 135.91 (s), 129.82 (d), 128.53 (d), 128.42 (d), 128.10 (d), 127.90 (d), 127.50 (d), 126.6 (d), 66.32 (d), 57.98 (d), 45.97 (t), 44.54 (t), 40.50 (t), 32.52 (t).

MS: 353 (M^+ −109, 5), 294 (6), 149 (5), 141 (7), 132 (14), 109 (79), 91 (100), 84 (11), 77 (17), 69 (13), 65 (18).

Anal. Calculated for $C_{26}H_{26}N_2O_2S_2$: C, 67.50; H, 5.66. Found: C, 67.32; H, 5.40.

1,3-Dibenzyl-2-oxo-5-[(3*E*,3*Z*)-4-*tert*-butyldimethylsilyloxy-2-thiabut-3-enyl]-4-phenylthioimidazolidine (2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.33 mL, 2.2. mmol) was added via syringe to a solution of aldehyde **17** (924 mg, 2 mmol) in dichloromethane (20 mL). After 5 min, a solution of TBSCl (330 mg, 2.2 mol) in DCM (5 mL) was added dropwise and the mixture was heated to reflux. After 2 h, the mixture was diluted with DCM and washed with 1% HCl (5 mL) and saturated $NaHCO_3$ solution (5 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and rotary evaporated. Purification of the oily residue by column chromatography (1:9 EtOAc/*n*-hexane) furnished 1.06 g of silyl enol ether **2** as a viscous liquid in 92% yield.

IR (neat): 2910, 2840, 1695, 1595, 1450, 1420, 1210, 1100, 940 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): δ 7.35 (12H, m), 7.0 (3H, m), 6.56 (1H, d, J = 11.6 Hz), 5.15 (1H, d J = 11.6 Hz), 5.0 (1H, d, J = 15 Hz), 4.55 (1H, d, J = 3.5 Hz), 4.3 (d, 1H, J = 15 Hz), 4.2 (1H, d, J = 15 Hz), 3.9 (1H, d, J = 15 Hz), 3.4 (1H, m), 2.4 (1H, dd, J = 13, 4 Hz), 2.2 (1H, dd, J = 13, 7 Hz), 0.8 (9H, s), 0.1(6H, s).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.94 (s), 149.94 (d), 136.51 (s), 134.75 (d), 129.05 (d), 128.80 (d), 128.47 (d), 128.26 (d), 127.93 (d), 127.41 (d), 127.26 (d), 100.58 (d), 66.95 (d), 58.82 (d), 45.63 (t), 44.66 (t), 37.11 (t), 25.43 (q), 25.38 (q), 18.4 (s), −5.34 (q), −5.42 (q).

MS: 467 (M^+ − 109, 5), 277 (40), 203 (7), 110 (29), 91 (100), 73 (28), 65 (13).

Anal. Calcd for $C_{32}H_{40}N_2O_2S_2Si$: C, 66.62; H, 6.99. Found: C, 66.3; H, 6.89.

1,3-Dibenzyl-4-formyl-1*H*-tetrahydrothieno[3,4-*d*]imidazol-2(3*H*)-one (3). To a solution of enol ether **2** (576 mg, 1 mmol) and 4-nitrobenzaldehyde (90 mg, 0.6 mmol) in DCM (5 mL) under argon atmosphere was added a catalytic amount of TBSOTf (0.02 mL) at room temperature. After 5 min, saturated $NaHCO_3$ solution (1 mL) was added. The dichloromethane layer was separated, washed with water (2 × 2 mL), dried over anhyd Na_2SO_4, and filtered. Removal of dichloromethane in vacuo and chromatography of the residue (2:3 EtOAc/*n*-hexane) furnished the aldehyde **3** (334 mg, 95%) as viscous liquid and thioacetal of 4-nitrobenzaldehyde (171 mg, 97%).

IR (neat): 3120, 2940, 1705, 1695, 1605, 1595, 1500, 1450, 1250 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 9.13 (1H, s), 7.25 (10H, m), 4.68 (1H, d J = 15.4 Hz), 4.47 (1H, d, J = 15.4 Hz), 4.36 (1H, d, J = 15.4 Hz), 4.34 (1H, d, J = 7.94 Hz), 4.16 (1H, d, J = 15.4 Hz), 4.11 (1H, dd, J = 7.78, 4.74 Hz), 3.59 (1H, s), 2.68 (1H, d, J = 13.15 Hz), 2.29 (1H, dd, J = 13.15, 4.78 Hz).

^{13}C NMR ($CDCl_3$, 77.49 MHz): δ 189.90 (d), 159.75 (s), 137.02 (s), 136.77 (s), 128.71 (d), 128.65 (d), 127.78 (d), 127.68 (d), 127.59 (d), 61.96 (d), 60.63 (d), 59.30 (d), 47.16 (t), 46.42 (t), 34.71 (t).

MS: 352 (M^+, 5), 323 (5), 277 (93), 264 (6), 91 (100), 65 (6).

Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.1. Found: C, 67.95; H, 5.70; N, 7.84; S, 9.5.

1,3-Dibenzyl-4-[1-(1*E*,3*E*)-4-methoxycarbonyl-1,3-butadienyl]-1*H*-tetrahydro-thieno[3,4-*d*]imidazol-2(3*H*)-one (18). A mixture of aldehyde **3** (352 mg, 1 mmol) and 3-methoxycarbonyl-2-propenylidine triphenyl phosphonate (432 mg, 1.2 mmol) in dichloromethane (5 mL) was stirred for 12 h and then concentrated under reduced pressure at room temperature. The residue was purified by column to give ester **18** (386 mg, 89%) as a viscous liquid.

IR (neat): 3020, 2920, 1700, 1650, 1600, 1510, 1450, 1370, 1260, 1150, 1020 cm^{-1}.

^1H NMR (C_6D_6, 200 MHz): δ 7.25 (11H, m), 5.76 (1H, d, J = 15.2 Hz), 5.53 (1H, dd, J = 15.2, 10.78 Hz), 5.27 (1H, dd, J = 15.2, 8.29 Hz), 4.7 (2H, d, J = 15.2 Hz), 4.67 (2H, t, J = 15.2 Hz), 3.42 (3H, s), 3.27 (1H, dd, J = 8.89, 3.86 Hz), 2.35 (1H, dd, J = 12.25, 4.3 Hz), 2.22 (1H, dd, J = 12.25, 5.8 Hz).

^{13}C NMR ($CDCl_3$, 75.49 MHz): δ 166.6 (s), 158.88 (s), 142.70 (d), 138.6 (d), 136.77 (s), 136.7 (d), 129.59 (d), 128.49 (d), 127.93 (d), 127.45 (d), 121.68 (d), 65.91 (d), 61.51 (d), 55.12 (q), 51.30 (d), 46.48 (t), 46.25 (t), 36.98 (t), 36.67 (t).

MS: 434 (M^+, 43), 402 (7), 277 (100), 264 (13), 187 (15), 155 (9), 91 (76).

Anal. Calcd for $C_{25}H_{26}N_2O_3S$: C, 69.09; H, 6.03; N, 6.45; S, 7.38. Found: C, 69.40; H, 5.85; N, 6.1; S, 7.40.

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(12) Bevezovski, V. M.; Mikhno, S. D.; Kulachkina, N. S.; Zhuk, V. B.; Preobrazhenskii, N. A. *Zh. Obshch. Khim.* **1963**, *33*, 2888.

Pentanoic Acid, 5-[Hexahydro-2-oxo-1,3-dibenzyl-4*H*-thieno(3,4-*d*)imidazol-3,5-dienyl] Methyl Ester (19). To a solution of ester **18** (434 mg, 1 mmol) in methanol (5 mL) was added 1 M NaOH (5 mL), and the reaction mixture was stirred for 3 h and left at 0 °C for 12 h. Methanol was removed by rotary evaporation under reduced pressure, and the reside was diluted with dichloromethane (20 mL) and water (5 mL). The pH of the solution was adjusted to pH 2 with 1 N hydrochloric acid and stirred for 5 min. The organic layer was washed with water and brine, dried, and evaporated in vacuo to give acid **19** (310 mg, 97%) as viscous liquid, and it was characterized as its methyl ester **19a**.

IR (neat): 3040, 2940, 1740, 1700, 1610, 1600, 1510, 1460, 1380, 1260, 1190 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.30 (10H, m), 6.2−5.5 (3H, m), 5.1−4.6 (3H, m), 4.3−3.7 (3H, m), 3.65 (3H, s), 3.1 (1H, d, J = 7.1 Hz), 3.0−2.6 (3H, m).

^{13}C NMR ($CDCl_3$, 50 MHz); δ 171.30 (s), 158.72 (s), 138.47 (s), 137.14 (s), 136.93 (s), 135.60 (s), 130.90 (d), 128.68 (d), 128.60 (d), 128.26 (d), 128.08 (d), 127.99 (d), 127.68 (d), 127.56 (d), 127.38 (d), 127.16 (d), 126.35 (d), 124.08 (d), 125.95 (d), 64.80 (d), 58.95 (d), 51.70 (q), 46.66 (t), 44.93 (t), 37.87 (t), 37.43 (t).

MS: 434 (M^+, 6), 343 (3), 277 (7), 238 (3), 136 (5), 106 (29), 91 (100), 65 (10).

Anal. Calcd for $C_{25}H_{26}N_2O_3S$: C, 69.09; H, 6.03; N, 6.45; S, 7.40. Found: C, 69.26; H, 5.96; N, 6.51; S, 7.44.

1*H*-Thieno(3,4-*d*)imidazol-4-pentanoic Acid Hexahydro-2-oxo-1,3-dibenzyl Methyl Ester (20). A mixture of unsaturated ester **19a** (434 mg, 1 mmol) and 10% palladium on charcoal (150 mg) in methanol (10 mL) was hydrogenated (3 atm) for 8 h. Filtration of the catalyst and the removal of the solvent under reduced pressure furnished a residue which was purified by column chromatography (1:5 ethyl acetate/*n*-hexane) to furnish ester **20** (403 mg, 92%) of biotin as a white solid.

Mp: 78 °C.

IR (Nujol + $CHCl_3$): 2970, 2840, 1740, 1690, 1600, 1500, 1460, 1250 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.25 (10H, m), 5.15 (1H, d, J = 15.2 Hz), 4.75 (1H, d, J = 15.2 Hz), 4.17 (1H, d, J = 15.2 Hz), 4.0−3.84 (1H, m), 3.97 (1H, d, J = 15.2 Hz), 3.70 (3H, s), 3.2-(1H, m), 2.80 (1H, dd, J = 12.6, 4.0 Hz), 2,68 (1H, dd, J = 12.6, 5.8 Hz), 2.34 (2H, t, J = 7 Hz), 1.75−1.25 (6H, m).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.09 (s), 161.24 (s), 137.25 (s), 137.01 (s), 128,90 (d), 128.47 (d), 127.83 (d), 62.90 (d), 61.44 (d), 54.44 (d), 51.68 (q), 48.20 (t), 46.85 (t), 34.07 (t), 28.70 (t), 28.00 (t), 24.85 (t).

MS: 438 (M^+, 6), 347 (15), 277 (29), 265 (14), 240 (9), 187 (17), 91 (100), 85 (6), 65 (9).

Anal. Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.38; S, 7.31. Found: C, 68.52; H, 7.0; N, 6.52; S, 7.62.

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