Unexpected Ring Expansion of the (3a*S*,6a*R*)-γ-Thiolactone Moiety during the Introduction of the (+)-Biotin Side Chain

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The reaction of vinylmagnesium bromide with the (3a*S*,6a*R*)-γ-thiolactone **2** in THF afforded, after unexpected ring expansion of the γ-thiolactone moiety, the seven-membered-ring ketone **5** in excellent yield, instead of the expected tertiary alcohol **3**.

Introduction. – (+)-Biotin (**1**) is an important water-soluble B-complex vitamin bearing a *cis*-fused cyclic urea and tetrahydrothiophene ring, to which is attached a pentanoic acid side chain (*cf. Scheme 1*). Due to its useful biological properties for human nutrition and animal health [1], this vitamin has attracted considerable attention from both industries and academia for more than 60 years[1]). A great number of approaches to **1** have been reported so far [2]. However, the introduction of the pentanoic acid side chain at C(4) of the (3a*S*,6a*R*)-γ-thiolactone **2** still remains a challenging task.

As a continuation of our interest in the total synthesis of (+)-biotin (**1**) [3], we devised different *Grignard* reagents to realize the installation of the pentanoic acid side chain on **2**. For example, the reaction of (3-ethoxyprop-1-ynyl)magnesium bromide [3b] or (methoxymethyl)magnesium iodide [3h] with **2** introduced part of the side chain affording the corresponding tertiary alcohol with good yield. The *Grignard* reagent derived from 2-(4-bromobutyl)-2-methyl-1,3-dioxolane and magnesium [3c] also reacted well with **2** allowing a direct introduction of the side chain of biotin.

In an exploration for a new synthesis of (+)-biotin (**1**), our plan involved a *Grignard* reaction of vinylmagnesium bromide with **2** to introduce a C_2 side chain, followed by an Et_3SiH-mediated ionic hydrogenation [4][2]) to establish the third chiral center [5][3]), and subsequent chemical manipulation at the terminal olefin could install the full biotin side chain with correct configuration (*Scheme 1*).

Results and Discussion. – With these considerations in mind, we attempted the reaction of **2** with vinylmagnesium bromide in THF. The reaction proceeded smoothly

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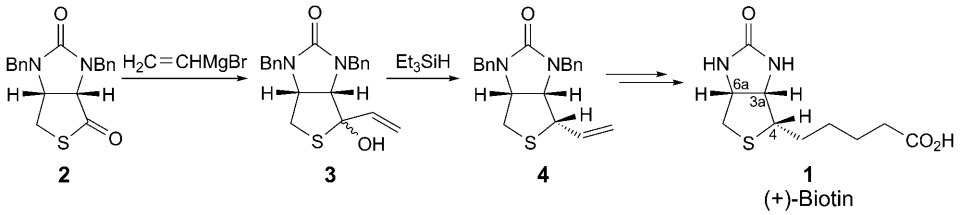
1) For reviews about the synthesis of (+)-biotin, see [2].

2) For a review about ionic hydrogenation, see [5].

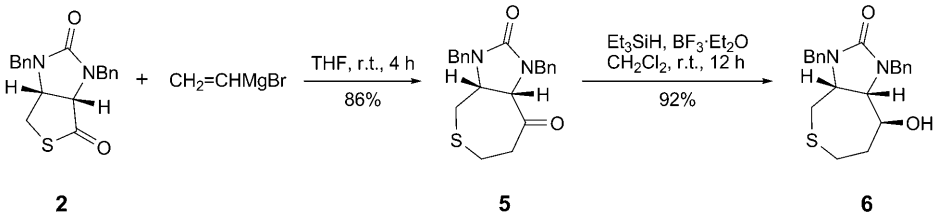
3) We have developed an efficient method to establish the third chiral center of (+)-biotin *via* a mild ionic hydrogenation, see [3k].

Scheme 1. *Planned Synthetic Approach toward* **1**



under stirring at room temperature for 4 h, and to our surprise only the ring expansion product **5** was isolated in 86% yield, and no expected **3** could be detected (*Scheme 2*).

Scheme 2. *The Unexpected Ring Expansion of Thiolactone* **2**



The fundamental architecture of compound **5** was unambiguously confirmed by the X-ray crystallographic analysis of alcohol **6** (*Fig.*), which was obtained by reduction of **5** *via* an Et_3SiH-mediated ionic hydrogenation (*Scheme 2*).

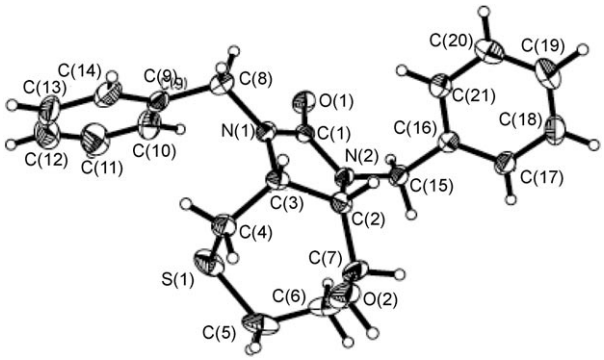
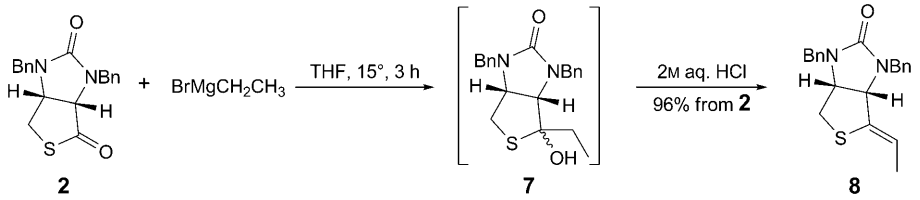


Figure. *ORTEP Drawing of the X-ray structure of* **6**

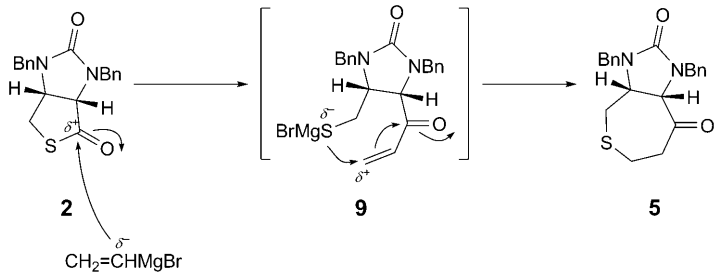
Next, we investigated an analogous reaction of ethylmagnesium bromide with **2**. The reaction proceeded *via* tertiary alcohol **7** as expected to furnish the desired compound **8** in 96% yield, and no ring-expansion product was detected (*Scheme 3*).

Scheme 3. *The* Grignard *Reaction of* **2** *with Ethylmagnesium Bromide*



Although the mechanistic details for the formation of compound **5** are not known, a plausible mechanism may be advanced to rationalize the ring expansion reaction (*Scheme 4*). Presumably, nucleophilic attack of the CO group of **2** by vinylmagnesium bromide produced the α,β-unsaturated keto compound **9**, and subsequent intramolecular *Michael* addition led to the seven-membered ring ketone **5** (*Scheme 4*).

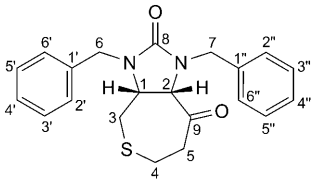
Scheme 4. *Plausible Mechanism for the Formation of* **5**



All products were new and were unequivocally characterized by IR, mass, and NMR spectra (^{1}H, ^{13}C, ^{1}H,^{1}H-COSY, ^{13}C,^{1}H-COSY, and HMBC). For compound **5**, the MS (*m*/*z* 367 ($[M+H]^+$) and 389 ($[M+Na]^+$)) and elemental analysis were in accord with the molecular formula $C_{21}H_{22}N_2O_2S$. The DEPT spectrum revealed the presence of five CH_2 groups. The ^{13}C-NMR data indicated the presence of two CO groups with signals at δ(C) 159 and 206. The atom numbering used for NMR assignment along with all diagnostic COLOC correlations between various H- and C-atoms *via* ^2J(C,H) and ^3J(C,H) couplings are presented in the *Table*.

Conclusions. – From the investigated reactions, the following conclusion can be drawn. Instead of the expected alcohol **3**, a seven-membered-ring ketone **5** can be conveniently obtained with high yield in the *Grignard* reaction of (3a*S*, 6a*R*)-γ-thiolactone **2** with vinylmagnesium bromide, most probably because of an intramolecular 1,4-conjugated addition. Further studies on the introduction of the pentanoic acid side chain *via* a *Grignard* reaction and the chemistry of the novel compound **5** are under investigation.

Table. *COLOC Correlation Between Various H- and C-Atoms of Ketone* **5**. Arbitrary atom numbering.



H-atom	COLOC with C-atom
H–C(1)	C(6)
H–C(2)	C(3), C(5), C(7)
H–C(3)	C(2), C(4)
H–C(4)	C(1), C(2)
H–C(5)	C(3)
H–C(6)	C(1), C(7), C(8), C(2′), C(6′)
H–C(7)	C(2), C(6), C(8), C(2″), C(6″)

Experimental Part

General. THF was distilled over Na/benzophenone, and toluene over CaH_2. Other reagents were obtained from commercial sources and used as such. FC = Flash chromatography. M.p.: *WRS-1B* digital melting-point apparatus; uncorrected. Optical rotations: *Jasco-P1020* digital polarimeter. IR Spectra: *Jasco-FT/IR-4200* spectrometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-Avance-400* spectrometer; at 400 (^{1}H) and 100 MHz (^{13}C); $CDCl_3$ solns.; δ in ppm with $CHCl_3$ (δ(H) 7.26) and $CDCl_3$ (δ(C) 77.0) as internal standards, *J* values in Hz. ESI-MS: *Waters-Quattro-Micromass* instrument. Elemental analyses: *Carlo-Erba-1106* instrument; results for C, H, N, and S within $\pm$0.4% of the theoretical values.

*(3a*R*,8a*S*)-Tetrahydro-1,3-bis(phenylmethyl)-1*H*-thiepino[3,4-*d*]imidazole-2,8(3*H*,4*H*)-dione* (**5**). Bromoethene gas was introduced at r.t. into a mixture of Mg turnings (0.19 g, 7.6 mmol) in THF (10 ml) until the Mg turnings disappeared. Then, the resulting soln. was cooled to 0°, and a soln. of thiolactone **2** (1 g, 2.95 mmol) in THF (10 ml) was added dropwise. Then the mixture was allowed to warm to r.t. and stirred at r.t. for 4 h. The reaction was quenched by sat. aq. NH_4Cl soln. (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The combined org. phase was washed with brine, dried ($MgSO_4$), and concentrated, and the residue purified by FC: pure **5** (0.92 g, 86%). White solid. M.p. 143.4–145.3°. IR (KBr): 2906, 1659, 1604, 1451, 1359, 1246, 1148, 1086, 744, 701. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.42 (*dd*, *J* = 15.2, 9.2, 1 H); 2.53–2.61 (*m*, 3 H); 2.72 (*dd*, *J* = 15.2, 3.2, 1 H); 2.83–2.88 (*m*, 1 H); 3.76 (*td*, *J* = 9.6, 3.2, 1 H); 3.98 (*d*, *J* = 14.8, 1 H); 4.11 (*d*, *J* = 15.2, 1 H); 4.21 (*d*, *J* = 10.4, 1 H); 4.79 (*d*, *J* = 15.2, 1 H); 4.97 (*d*, *J* = 14.8, 1 H); 7.19–7.34 (*m*, 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.23; 32.77; 44.46; 45.80; 46.91; 53.04; 65.04; 127.70; 127.85; 127.91; 128.71; 128.78; 136.05; 136.59; 159.93; 206.12. ESI-MS: 367.2 ($[M+H]^+$), 389.2 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{22}N_2O_2S$ (366.483): C 68.82, H 6.05, N 7.64, S 8.75; found: C 68.73, H 6.14, N 7.76, S 8.66.

*(3a*R*,8*S*,8a*S*)-Hexahydro-8-hydroxy-1,3-bis(phenylmethyl)-1*H*-thiepino[3,4-*d*]imidazol-2(3*H*)-one* (**6**). $BF_3 \cdot Et_2O$ (2.78 ml, 22 mmol) was added dropwise at 0° to a soln. of **5** (0.2 g, 0.55 mmol) and Et_3SiH (1.765 ml, 10.9 mmol) in CH_2Cl_2 (5 ml). Then, the mixture was allowed to warm to r.t. and stirred at r.t. for 12 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ soln. to adjust the pH to 7, and the resulting mixture was extracted with AcOEt (3 × 20 ml). The combined org. phase was washed with brine, dried ($MgSO_4$), and concentrated, and the residue purified by FC: pure **6** (0.18 g, 92%). Colorless solid. M.p. 186.1–187.2°. IR (KBr): 3321, 2919, 1664, 1473, 1261, 1071, 968, 701. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.97–2.06 (*m*, 2 H); 2.15–2.21 (*m*, 1 H); 2.50–2.61 (*m*, 2 H); 2.67–2.73 (*m*, 1 H); 2.88 (*dd*, *J* = 15.2, 7.2, 1 H); 3.59 (*t*, *J* = 8.0, 1 H); 3.69 (*td*, *J* = 8.8, 2.8, 1 H); 3.98 (*d*, *J* = 15.2, 1 H); 4.09–4.11 (*m*, 1 H); 4.25 (*d*, *J* = 15.2, 1 H); 4.92 (*d*, *J* = 14.8, 2 H); 7.25–7.31 (*m*, 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.74;

31.03; 37.62; 45.14; 48.19; 57.30; 61.06; 70.71; 127.53; 127.59; 128.04; 128.12; 128.69; 137.5; 138.2; 161.7. ESI-MS: 369.2 ($[M+H]^+$). Anal. calc. for $C_{21}H_{24}N_2O_2S$ (368.4988): C 68.44, H 6.56, N 7.60, S 8.70; found: C 68.63, H 6.44, N 7.74, S 8.62.

*(3a*S*,4Z,6a*R*)-4-Ethylidenetetrahydro-1,3-bis(phenylmethyl)-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one* (**8**). To a mixture of Mg turnings (0.18 g, 7.6 mmol) in THF (3 ml) was added a soln. of bromoethane (0.57 ml, 7.6 mmol) in THF (4 ml), and the mixture was stirred at r.t. until the Mg turnings had disappeared. The soln. was cooled to 0°, a soln. of **2** (1 g, 2.95 mmol) in THF (11 ml) added dropwise, and the resulting mixture stirred at 15° for 3 h. Then, sat. aq. NH_4Cl soln. (10 ml) was added and the mixture extracted with AcOEt (3 × 20 ml). The combined org. phase was washed with brine, dried ($MgSO_4$), and concentrated to afford crude **7** (ESI-MS: 369.5 ($[M+H]^+$) and 391.5 ($[M+Na]^+$)). To the crude **7**, 2M HCl (6 ml) and toluene (6 ml) were added, and the soln. was heated to reflux for 1 h. Cooled to r.t., the aq. phase was extracted with toluene (3 × 10 ml), and the combined org. phase was washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and concentrated: **8** (1.0 g, 96%). White solid. M.p. 132–134°. IR (KBr): 2930, 1695, 1470, 1250, 1158, 1025, 756. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.70 (*d*, *J* = 6.8, 3 H); 2.92–3.00 (*m*, 2 H); 4.03 (*d*, *J* = 15.2, 1 H); 4.06–4.09 (*m*, 1 H); 4.21 (*d*, *J* = 15.2, 1 H); 4.27 (*d*, *J* = 7.6, 1 H); 4.82 (*d*, *J* = 15.2, 1 H); 4.96 (*d*, *J* = 7.6, 1 H); 5.52 (*dt*, *J* = 6.8, 6.8, 1 H); 7.24–7.37 (*m*, 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 46.78; 46.85; 53.15; 56.51; 57.04; 128.00; 128.60; 128.67; 128.84; 135.36; 135.48; 159.52; 167.37; 171.56. ESI-MS: 351.6 ($[M+H]^+$), 373.6 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{22}N_2OS$ (350.4836): C 71.96, H 6.33, N 7.99, S 9.15; found: C 71.81, H 6.45, N 7.85, S 9.26.

X-Ray Crystallographic Data of **6**. Crystals of **6** suitable for X-ray analysis were obtained by recrystallization from AcOEt/cyclohexane 2:1 at r.t. CCDC-689299 contains the supplementary crystallographic data (excluding structure factors) for the structure of **6** in this article. These data can be obtained free of charge *via* http://www.ccdc. cam.ac.uk/data_request/cif. Structure-determination and refinement data: $C_{21}H_{24}N_2O_2S$, M_r 368.48; crystal size 0.30 × 0.15 × 0.12 mm; orthorhombic; $a = 8.261(4)$, $b = 14.045(6)$, $c = 32.656(15)$ Å; $\alpha = 90$, $\beta = 90$, $\gamma = 90°$; space group $P2_12_12_1$, $Z = 8$, $V = 3789(3)$ Å^3, $D_{calc.} = 1.292$ g/cm^3; $R = 0.0599$, $Rw = 0.1052$; $-9 \le h \le 10$, $-17 \le k \le 15$, $-40 \le l \le 41$; MoK_α radiation (λ 0.71073 Å); T 293(2) K.

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