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A Novel Enantioselective Synthesis of (+)-Biotin

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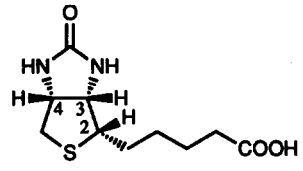
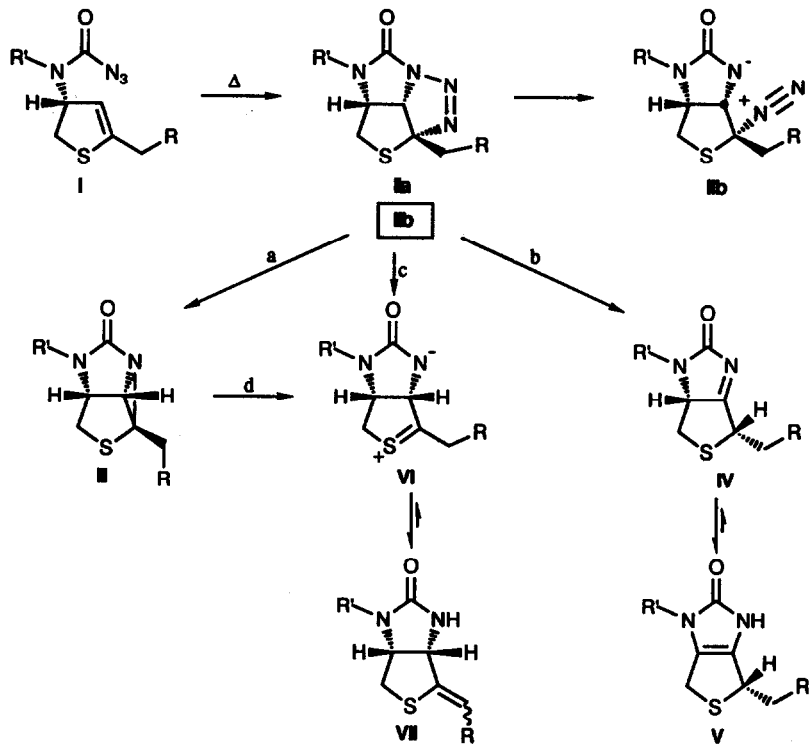
***Abstract** : A conceptually simple enantioselective 14-step synthesis of (+)-biotin from L-cysteine is reported based upon an intramolecular 1,3-dipolar cycloaddition sequence involving (i) elimination of bromide **8** to the endocyclic thioenol ether **9**, (ii) thermolysis of the ene carbamoyl azide **9** to the exocyclic thioenol ether **10**. Both the synthesis of **8** and the final transformation of **10** into (+)-biotin are based upon literature precedents.*

Ever since the discovery of its fundamental role as a cofactor in naturally occurring carboxylations (+)-biotin has been a favorite target for total synthesis.[1] The importance of biotin in human nutrition and animal health has further stimulated the development of potential commercial routes to synthetic vitamin.[2-5] To the best of our knowledge the 1949 Goldberg and Sternbach 14-step approach involving an intermediate resolution with possible recycling,[6] still remains nowadays unchallenged in terms of economical total synthesis. Indeed, all later *enantioselective* routes to (+)-biotin required sequences of at least 12 steps.[7,8] This is somewhat surprising in view of the apparent uncomplicated structure of biotin which basically consists of an all-*cis* substituted 2-alkyl-3,4-diaminothiophane. Herein we wish to report an enantioselective route to (+)-biotin which features conceptual simplicity and novelty, yet still lacks the brevety (14 steps are required from L-cysteine)[9] that should characterize any efficient alternative to the 1949 synthesis.



(+)-biotin

As shown in scheme 1, the synthesis centers around the thermal intramolecular 1,3-dipolar cycloaddition of a carbamoylazide onto a five-membered thioenol ether (**I**).[10,11,12] Both because of its strained tricyclic nature and because of the presence of the electron withdrawing amide substitution at N, the resulting triazoline adduct **IIa** is expected to ring fragment readily to the betaine intermediate **IIb**. Three reaction products can be expected from the further loss of nitrogen from the betaine **IIb** : (a) aziridine **III**; (b) imidazolidone **V** via 1,2-hydride shift to **IV** and tautomerization; (c) thioenol ether **VII** via sulfur assisted nitrogen expulsion to **VI** followed by proton transfer. Especially **V** and **VII** are potential precursors of biotin. In both cases catalytic hydrogenation is known to provide the required all-*cis* configuration of biotin.[13,14] Finally, we note that the required absolute configuration of (+)-biotin is stereospecifically induced in both cases by the sole stereogenic center in **I**.

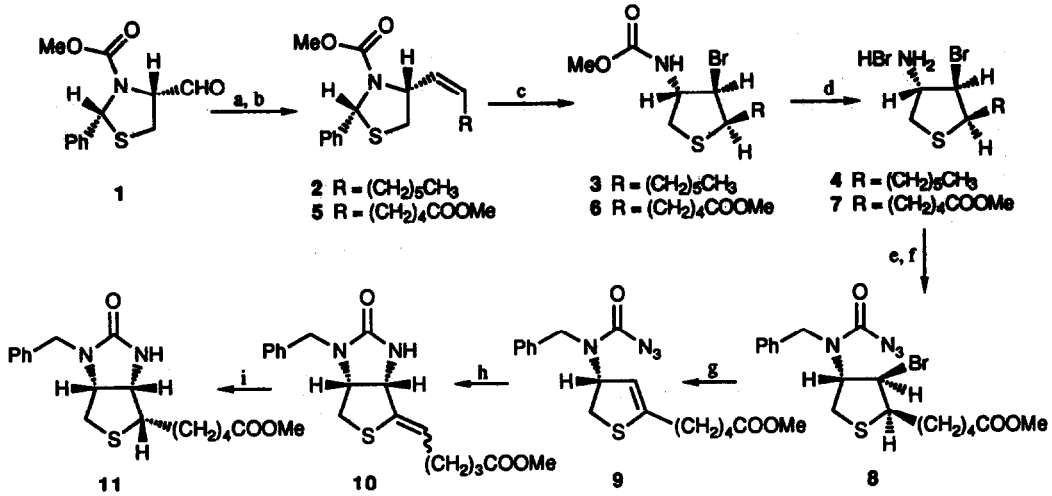


Scheme 1

The synthesis of the required cycloaddition precursor **9** is outlined in scheme 2 and is based on the known conversions of (i) L-cysteine into aldehyde **1** and (ii) the transformation of the latter into the hydrobromide salt **4**.[15] The synthesis of **4** was part of an original study for the synthesis of (+)-biotin by Confalone et al. which was based on the remarkable and stereospecific conversion of (Z)-olefin **2** into bromide **3**.[15b] The analogous bromide, but epimeric at C-2, was obtained from the corresponding (E)-alkene and eventually transformed into (+)-biotin. It occurred to us that bromides such as **7** or **8**, useless in terms of the above strategy, possess the required stereochemistry for facile E2 elimination to the required endocyclic $\Delta^{2,3}$-bond as present in **9**.

In close analogy with the synthesis of **4**,[15b] the aldehyde **1**, available in 4 steps from L-cysteine,[15b] was subjected to Wittig olefination, followed by diazomethane to ester **5** (75 % combined yield). The oxidative cyclization rearrangement of (Z)-alkene **5** (bromine, 1 eq water, chloroform) gave the bromourethane **6** in 65 % yield. After removal of the urethane protective group (hydrobromic acid, acetic acid, 20 hrs, 85 % yield),[15b] the aminobromide hydrobromide **7** was converted to the N-benzylcarbamoyl azide **8**[16] via : (i) reductive amination (benzaldehyde; magnesium sulfate, dichloromethane to the imine, followed by reduction with sodium cyanoborohydride at pH 5; 76 % yield); (ii) introduction of the acylazide (phosgene, followed by sodium azide in acetone-water; 71 % yield).[17]

As expected, the *anti*-E2 elimination of hydrogen bromide from **8** (DBU in refluxing tetrahydrofuran) led to the dihydrothiophene **9**[16] (95 % yield). Thermolysis of the latter in dichloromethane at 150°C (autoclave, 3 hrs)[18] gave thioenol ether **10**[16] as a 3:2 mixture of E:Z alkenes (78 % isolated yield).[19] Catalytic hydrogena-



(a) $[Ph_3P(CH_2)_5COOH]Br$, 2 eq LDA, THF, r.t., 1 h (75 %); (b) CH_2N_2, Et_2O, 0°C (99 %); (c) Br_2, $CHCl_3$, 1 eq H_2O, r.t., 20 min (65 %); (d) HBr, HOAc, 20 h, dark (85 %); (e) PhCHO, $NaB(CN)H_3$, THF, H_2O pH = 4, r.t., 3 h (76 %); (f) phosgene, PVP, CH_2Cl_2, 0°C; NaN_3, acetone, H_2O, r.t. (71 %); (g) DBU, THF, reflux, 12 h (95 %); (h) autoclave, CH_2Cl_2, 150°C, 3 h (78 %); (i) $Pd(OH)_2$-C, H_2 4 atm, EtOAc, r.t., 1 h (95 %); (j) HBr 48 %, reflux, 2 h to (+)-biotin (85 %).

Scheme 2

tion of the latter mixture (palladium hydroxide[20] on carbon, 4 atm, ethyl acetate) led stereoselectively to the all-*cis* substituted **11**[16] (95 % yield),[5c] which was deprotected by treatment with aqueous hydrobromic acid (reflux, 2 hrs)[21] to yield (+)-biotin (85 % yield) which was found identical in every respect with authentic material.[22]

Among previous examples of similar cycloaddition-rearrangement sequences we note : (i) the intramolecular cycloaddition of N-benzyl-N-allyl carbamoylazide which led to the imidazolidone (path b);[23] (ii) the intramolecular cycloaddition of an acylazide onto a α,β-unsaturated butenolide which led to aziridine formation presumably via nitrene addition.[24] Although in our case direct nitrene addition to **III**, followed by opening of the aziridine ring (path d) cannot be excluded, path c is probably preferred : the intramolecular mode forces the electronpoor azide (LUMO) and the electronrich thioenol ether (HOMO) to combine to form a unique triazoline in which the sulfur is ideally placed to direct the fragmentation of the triazoline.

The synthesis as it presently stands is certainly too long to be of economical value. Yet the simplicity of the 3-step transformation of **9** into (+)-biotin warrants further investigations into efficient routes for **9**.

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16. Satisfactory analytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) data were obtained. Relevant ^{1}H NMR data : **8** ($CDCl_3$) : 7.35 (5H, m), 5.03 (1H, dd : 6.1, 8.2 Hz), 4.77 (1H, d : 16.6 Hz), 4.65 (1H, m), 4.48 (1H, d : 16.5 Hz), 4.41 (1H, dd : 7.8, 15.9), 3.67 (6H, s), 3.25 (1H, ddd : 4.4, 5.9, 10.4 Hz), 2.95 (1H, dd : 7.6, 11.0 Hz), 2.74 (1H, dd : 8.0, 11.0 Hz), 2.32 (2H, t : 6.3 Hz), 1.60-1.20 (6H, m); **9** ($CDCl_3$) : 5.75 and 5.46 (1H, d), 5.01 (1H, d), 4.62 and 4.53 (1H, d), 4.45 and 4.39 (1H, d), 3.66 (3H, s), 3.61 and 3.52 (1H, dd), 3.32 and 2.99 (1H, dd); **10**(Z) ($CDCl_3$) : 7.35 (5H, m), 5.65 (1H, t : 7 Hz), 4.11 (1H, dd : 7.5, 15.0 Hz), 3.98 (1H, d : 12.5 Hz), 3.88 (1H, d : 12.5 Hz), 3.69 (1H, d : 8.0 Hz), 3.65 (3H, s), 3.23 (1H, dd : 7.2, 11.8 Hz), 3.06 (1H, dd : 7.6, 11.7 Hz), 2.32 (2H, dt : 1.5, 7.3 Hz), 2.10 (2H, m), 1.75 (2H, m); **10**(E) ($CDCl_3$) : 7.30 (5H, m), 5.53 (1H, t : 7.1 Hz), 4.93 (1H, br s); 4.72 (1H, d : 15.4 Hz), 4.51 (1H, d : 7.6 Hz), 4.20 (1H, ddd : 5.2, 7.7, 4.7 Hz), 4.15 (1H, d : 15.4 Hz), 3.66 (3H, s), 3.02 (1H, dd : 3.3, 12.2 Hz), 2.99 (1H, dd : 4.9, 12.1 Hz), 2.32 (2H, t : 7.4 Hz), 2.11 (2H, m), 1.75 (2H, m); **11** ($CDCl_3$) : 7.30 (5H, m), 4.73 (2H, d : 15.5 Hz), 4.62 (1H, br s), 4.24 (1H, ddd : 1.1, 5.0, 9.1 Hz), 4.17 (1H, ddd : 2.3, 4.7, 7.5 Hz), 4.11 (2H, d : 15.5 Hz), 3.67 (3H, s), 3.15 (1H, ddd : 4.9, 6.3, 8.5 Hz), 2.82 (1H, d : 12.8 Hz), 2.68 (1H, dd : 5.0, 13.0 Hz), 2.33 (2H, t : 7.7 Hz), 1.80-1.30 (6H, m).
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