Pergamon

Tetrahedron Letters, Vol. 35, No. 16, pp. 2615-2618, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0322-O

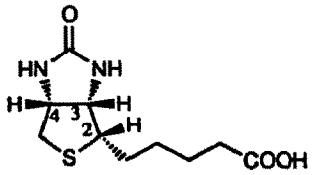
A Novel Enantioselective Synthesis of (+)-Biotin

Frederik D. Deroose and Pierre J. De Clercq*

State University of Gent, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

Abstract : *A conceptually attractive enantioselective 12-step synthesis of (+)-biotin from L-cysteine is reported based upon an intramolecular 1,3-dipolar cycloaddition sequence involving as key-steps (i) the macrothiolactonisation of acid 3 to Z-olefin 4, (ii) the thermolysis of the ene carbamoyl azide 5 in water with direct formation of a mixture of the benzylated derivatives of (+)-biotin 6a and 6b.*

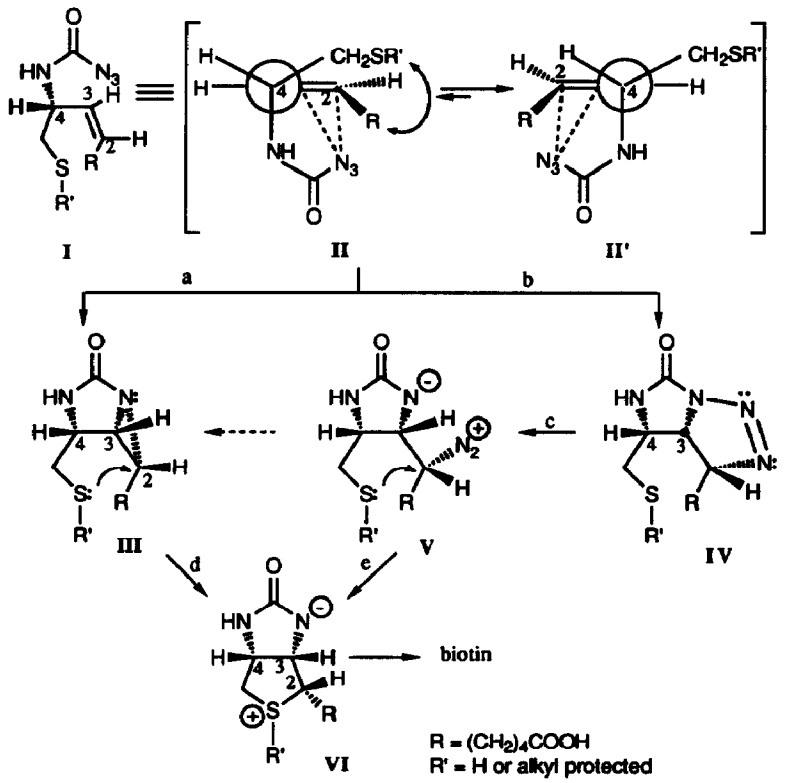
Because of its role as a cofactor in naturally occurring carboxylations and of its importance in human nutrition and animal health, (+)-biotin has been a favorite target for total synthesis ever since its discovery.[1] Quite remarkably, the early 1949 Goldberg and Sternbach 14-step total synthesis, involving an intermediate resolution with possible recycling, still remains nowadays the most economical approach.[2] All later *enantioselective* routes to (+)-biotin, including one that we have recently disclosed,[3] have required sequences of at least 12 steps.[4] In this paper we wish to describe a novel enantioselective route to (+)-biotin, starting from L-cysteine,[5] involving the one-step construction of monobenzylated biotin via the thermal intramolecular 1,3-dipolar cycloaddition of the 10-membered thiolactone carbamoyl azide **5** in water.



(+)-biotin

As shown in scheme 1, the synthesis centers around the thermal intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide as **I**, which can cyclize via the two different rotameric conformations **II** and **II'**.[6] Two reaction intermediates can be expected from the cycloaddition via acyl azide **II** : a) aziridine **III** after direct nitrene addition to the double bond;[7] (b) triazoline adduct **IV** after a (3+2)-cycloaddition.[8] Because of the presence of the electron withdrawing amide substitution at N, the triazoline adduct **IV** is expected to ring fragment readily to the betaine intermediate **V**. In either case biotin can be expected via : (i) nucleophilic sulfur attack at aziridine **III** to yield **VI** (path d); (ii) sulfur assisted nitrogen expulsion from **V** (path e).

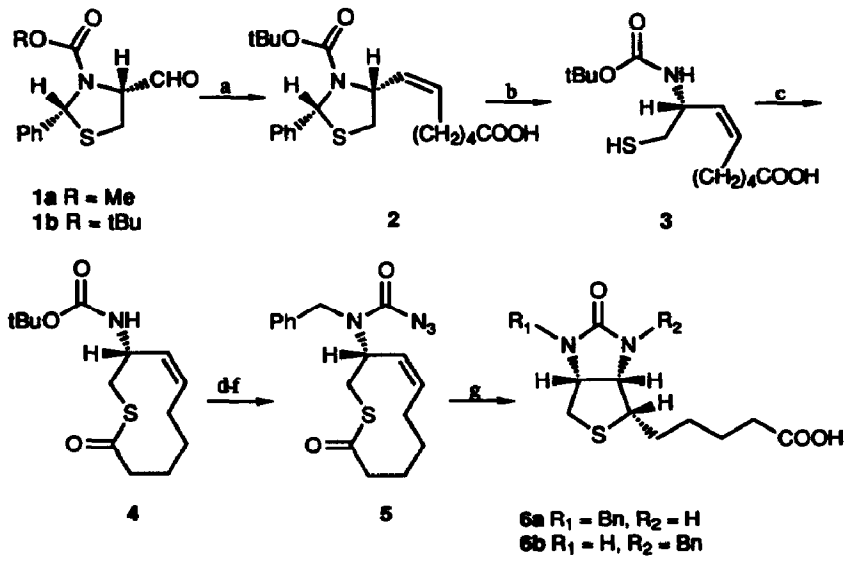
We note that the required configuration at C_2 is stereospecifically induced in both cases by the Z-geometry of the 2,3 double bond. We further note that the desired relative *cis*-configuration at C_3 and C_4 results from the reaction via rotamer **II**. However, the latter is destabilized by respulsive interactions between the groups $(CH_2)_4COOH$ and CH_2SH. Consequently, the required stereochemical outcome should result from a cycloaddition in which this particular conformation would be enforced, i.e. by connecting the thiol and carboxy



Scheme 1

acid functions into a 10-membered thiolactone as **5**. Finally, we note that the required absolute configuration of (+)-biotin is stereospecifically induced by the stereogenic center in I.

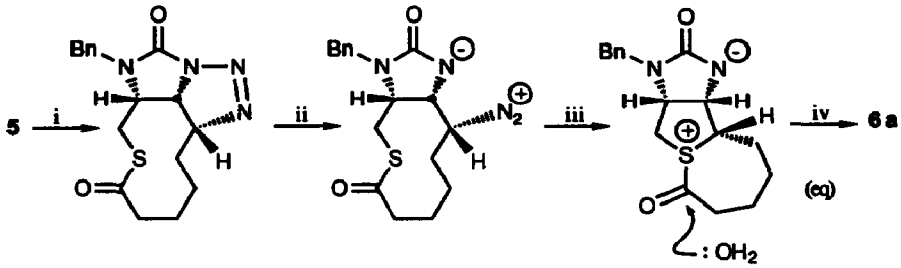
The synthesis of the required cycloaddition precursor **5** is outlined in scheme 2. It first involves the 4-step transformation of L-cysteine into aldehyde **1b** along a similar sequence as for the known methyl analogue **1a**.[9] After Wittig olefination, thiol acid **3** is released via reductive cleavage (Na, liq. NH_3) of **2** (74 % combined yield).[10] The first crucial step in the sequence involves the macrothiolactonisation of **3**. Although a few methods are known for thiolactone formation,[11] to the best of our knowledge there are no general methods available for the synthesis of strained medium ringsized thiolactones. This is not surprising in view of the combined thermodynamic instability of both the ring size and the thioester. In that respect we were satisfied to observe the formation of the desired **4**,[10] even in low yield. The preferred thiolactonization method involved slow addition (6 hrs; syringe pump) of a solution of **3** and of pyridine in dichloromethane to the *in situ* prepared phenyldichlorophosphate-DMF complex, an efficient method developed by Palomo for the intermolecular thioester formation.[12] In a next stage urethane **4** was transformed into the N-benzylcarbamoyl azide **5**[10] via : (i) removal of the urethane protective group (HCl (g), Et_2O, 0°C, 98 % yield); (ii) reductive amination (benzaldehyde; magnesium sulfate, dichloromethane to the imine followed by reduction with sodium cyanoborohydride at pH 4; 55 % yield); (iii) introduction of the acylazide (phosgene, followed by sodium azide in acetone-water, 72 % yield).



(a) $[Ph_3P(CH_2)_5COOH]Br$, 2 eq LDA, THF, r.t., 1 h (78 %); (b) Na, $NH_3(l)$; H_3O^+ (95 %); (c) $PhOP(O)Cl_2$-DMF, CH_2Cl_2, r.t. (24 %); (d) HCl (g), Et_2O, 0°C (98 %); (e) PhCHO, $NaCNBH_3$, THF-H_2O (pH=4), r.t., 3 h (55 %); (f) $COCl_2$, DBU, CH_2Cl_2, 0°C, followed by NaN_3, acetone-H_2O, r.t. (72 %); (g) H_2O, 150°C, autoclave, 2 h (42 %); (h) HBr (48°C), reflux, 2 h to (+)-biotin (85 %).

Scheme 2

Upon thermolysis of **5** in water, we were delighted to observe the direct formation of a mixture of the monobenzylated derivatives **6a**[10] and **6b**[10]. This remarkable transformation is further outlined in the equation and presumably involves : (i) cycloaddition, (ii) facile triazoline ring fragmentation, (iii) nitrogen expulsion with assistance of the proximal sulfur with the formation of a tricyclic intermediate, and (iv) nucleophilic attack of water to form the carboxylic side chain of biotin. The use of water which is obviously necessary as a nucleophile is expected to accelerate the cyclisation via betaine stabilisation.[13] In this respect and based on our previous experience,[3] we favour the triazoline fragmentation process rather than the aziridine pathway.



Following the mechanism of this transformation the formation of **6b** remains unclear.[14] Deprotection of **6a** and **6b** was readily achieved by treatment with aquous hydrobromic acid (reflux, 2 hrs)[15] to yield (+)-biotin (85 %), that was found identical in every respect with authentic material.[16]

Acknowledgements. F. Deroose is indebted to the National Fund for Scientific Research for a position as Research Assistant. The Fund and the "Ministerie voor Wetenschapsbeleid" are thanked for financial support.

References

1. Dakshinamurti, K.; Bhagavan, H.N. 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); for a further asymmetric improvement see Hisao, A.; Yasuhiko, A.; Shigeru, O.; Hiroyiki, S. *U.S. Pat.* 3,786,656 (1975).
3. Deroose, F.D.; De Clercq, P.J. *Tetrahedron Lett.* **1993**, *34*, 4365-4368.
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; for more recent syntheses see : 3 en references cited therein.
5. For previous syntheses from L-cysteine or L-cystine, see : 3, 4, 6b and (a) Corey, E.J.; Mehrotra, H.M. *Tetrahedron Lett.* **1988**, *29*, 57-60; (b) Casutt, M.; Poetsch, E.; Speckamp, W.N. *Ger. Offen. DE* 3,926,690.
6. For previous biotin syntheses involving a 1,3-dipolar cycloaddition, see : (a) Alcázar, V.; Tapia, I.; Morâu, J.R. *Tetrahedron* **1990**, *46*, 1057-1062; (b) Lee, H.L.; Baggiolini, E.G.; Uskokovic, M.R. *Tetrahedron* **1987**, *43*, 4887-4903; (c) Confalone, P.N.; Pizzolato, G.; Lollar Confalone, D.; Uskokovic, M.R. *J. Am. Chem. Soc.* **1980**, *102*, 1554-1560; (d) Marx, M.; Marti, F.; Reisdorff, J.; Sandmeier, R.; Clark, S. *J. Am. Chem. Soc.* **1977**, *99*, 6754-6756
7. For an intramolecular cycloaddition of an acylazide leading to aziridine formation, see Egli, M.; Dreiding, A.S. *Helv. Chim. Acta* **1986**, *69*, 1442-1460.
8. For an intramolecular cycloaddition of a N-benzyl carbamoyl azide via triazoline formation, see 3 and Chupp, J.P. *J. Heterocycl. Chem.* **1971**, *8*, 557-563.
9. Confalone, P.N.; Pizzolato, G.; Baggiolini, E.G.; Lollar, D.; Uskokovic, M.R. *J. Am. Chem. Soc.* **1977**, *99*, 7020-7026.
10. Satisfactory analytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) data were obtained. Relevant ^{1}H NMR data : **3** ($CDCl_3$) : 5.63 (1H, dt : 10.7, 7.5 Hz), 5.30 (1H, dd : 10.6, 9.1 Hz), 4.80 (1H, bs), 4.50 (1H, b), 2.55-2.80 (2H, m), 2.35 (2H, t : 7.4 Hz), 2.20 (2H, t : 7.3 Hz), 1.50-1.75 (4H, m), 1.50 (9H, s); **4** ($CDCl_3$) : 5.55 (1H, dt : 10.0, 2.9 Hz), 5.11 (1H, t : 10.0 Hz), 4.68 (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); **5** (DMSO-D_6) : 7.40 (5H, m), 5.39-5.55 (2H, m), 5.00 and 4.85 (1H, m), 4.65 and 4.56 (1H, d : 16.7 Hz), 4.58 and 4.47 (1H, d : 16.6 Hz), 3.26 (1H, m), 3.01 and 2.28 (1H, dd : 12.6, 12.1 Hz), 2.70 (1H, m), 2.51 (2H, m), 2.29 (1H, m), 2.10-1.50 (4H, m); **6a** ($CDCl_3$) : 7.30 (5H, m), 4.73 (1H, d : 15.5 Hz), 4.62 (1H, bs), 4.24 (1H, ddd : 8.0, 5.0, 1.1 Hz), 4.17 (1H, ddd : 7.5, 4.8, 2.3 Hz), 4.11 (1H, d : 15.5 Hz), 3.15 (1H, ddd : 8.5, 6.3, 4.9 Hz), 2.82 (1H, d : 12.8 Hz), 2.68 (1H, dd : 13.0, 5.0 Hz), 2.33 (2H, t : 7.7 Hz), 1.80-1.30 (6H, m); **6b** ($CDCl_3$) : 7.30 (5H, m), 5.00 (1H, d : 15.2 Hz), 4.67 (1H, bd : 1.0 Hz), 4.32 (H, dddd : 9.3, 6.4, 3.1, 1.0 Hz), 4.03 (1H, dd : 9.3, 5.6 Hz), 3.92 (1H, d : 15.2 Hz), 3.11 (1H, ddd : 8.8, 5.6, 3.3 Hz), 2.95 (1H, dd : 12.4, 6.4 Hz), 2.78 (1H, dd : 12.5, 3.9 Hz), 2.34 (2H, t : 7.8 Hz), 1.80-1.30 (6H, m).
11. 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, *vol. 6*, **1991**; pp. 435-457.
12. Arrieta, A.; Garcia, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471-487.
13. For an example of an intramolecular azide-alkene cycloaddition in aquous diglyme, see : Logothetis, A.L. *J. Am. Chem. Soc.* **1965**, *87*, 749-754; for an example of an intermolecular azide-alkene cycloaddition in dimethylsulfoxide, see : Oehlschlager, A.C.; Tillman, P.; Zalkow, L.H. *J. Chem. Soc. Chem. Commun.* **1965**, 596-599.
14. Whereas **6a** is identical with an intermediate from our previous synthesis, (ref. 3), the structure of **6b** was unambiguously proven via the monobenzylation of biotin, which led to a 1:1 ratio of **6a** and **6b** (NaH, $PhCH_2Br$, THF, r.t., 14 hrs; 65 % yield).
15. Gerecke, M.; Zimmermann, J.P.; Aschwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991-999.
16. The synthetic biotin so obtained had $[\alpha]_D^{20}$ = +91.4 and mp 232°C as compared to $[\alpha]_D^{20}$ = +90.9 for an authentic sample (Aldrich Chemie).

(*Received in UK* 27 *January* 1994; *accepted* 11 *February* 1994)