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SYNTHESIS OF d-BIOTIN FROM L-CYSTINE VIA INTRAMOLECULAR [3+2] CYCLOADDITION

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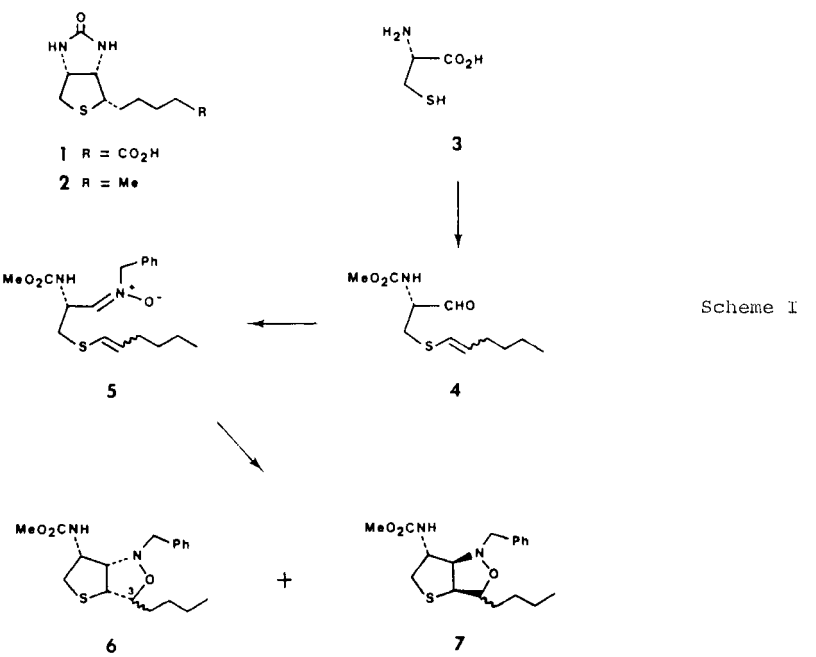
The recent revival of interest in the synthesis of biotin[1,2] is due to an increased awareness of the importance of this vitamin in human nutrition and therapy[3] as well as in animal health[4]. Biochemically, biotin functions as an indispensable coenzyme in numerous naturally occurring carboxylation reactions which are part of important physiological processes such as gluconeogenesis and fatty acid synthesis[5]. In our present approach to the synthesis of d-biotin (1) we planned to effect in a single step the formation of the thiophane ring and the simultaneous creation of two out of three chiral centers with proper absolute stereochemistry by a nitrone to thioenol ether thermal intramolecular cycloaddition[6,7] of 5 to give 6 (Scheme 1). The latter would then be converted to desoxy biotin (2) and finally to biotin via known microbiological oxidation[8].

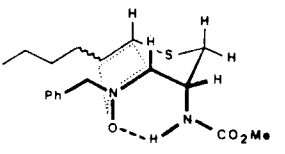
The intermediate 5, easily prepared from L-cysteine (3)[9] underwent spontaneous cyclization at room temperature to give in high yield a mixture of the



Scheme I

desired all-cis cycloadduct 6 and the diastereomer 7, in the disappointing ratio of 1.9:1[10,11].

A careful inspection of Dreiding models of the possible transition states for the cyclization of 5 seems to favor the two conformations 8 and 9 of the zusammen nitrone configuration as the source of the observed products 6 and 7, respectively. Furthermore, the transition state 8, leading to the desired all-cis product 6 should be of even lower energy than 9 due to stabilizing effects of the indicated hydrogen bonding. This may account for the observed product ratio, favoring 6.



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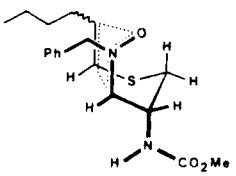

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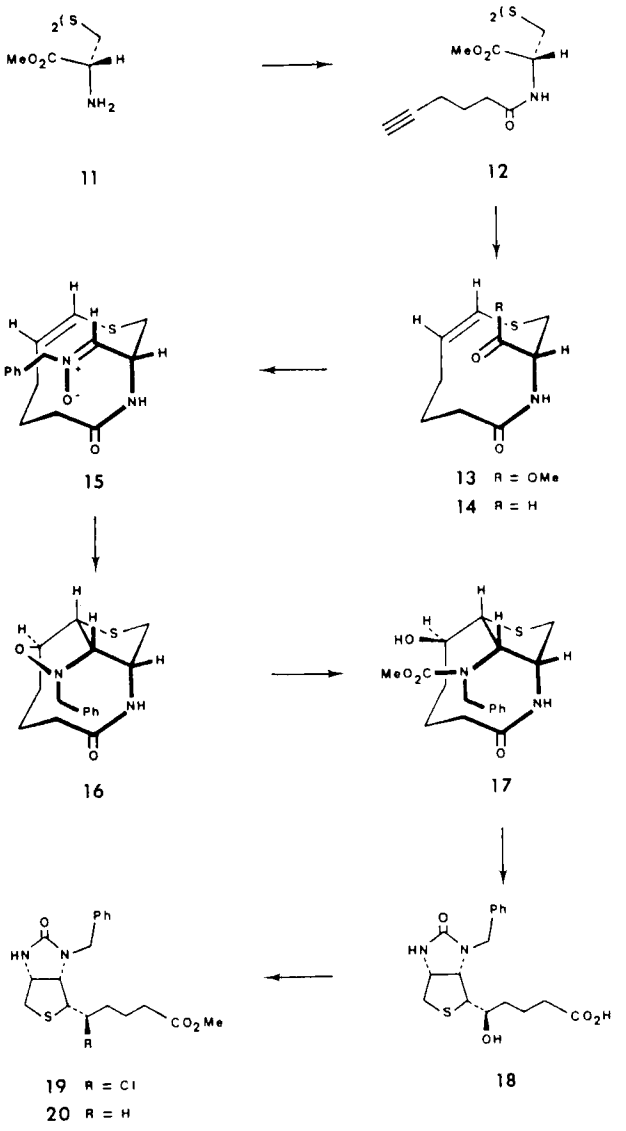
An obvious conclusion from the above transition state analysis was that the desired specificity in the cycloaddition step could be achieved using a modified precursor which would cyclize exclusively through a transition state conformation corresponding to 8. This led us to the design of the ten-membered ring intermediate 15 (Scheme 2) containing the Z thioenolether double bond, which was prepared in the following manner. L-Cystine dimethyl ester (11) was acylated at the nitrogen with 5-hexynoyl chloride[12] to give 12 (pyridine/CH_2Cl_2, 0°C, 90% yield) which was then treated with zinc dust in acetic acid. Under these conditions, the disulfide bond of 12 is cleaved, and, if the reaction is carried out in the presence of air, cyclization takes place simultaneously to produce a 9:1 mixture of the Z olefinic product 13[13] (65% yield) and the corresponding E isomer. After chromatographic separation, the desired isomer 13 was reduced with diisobutylaluminium hydride to 14 (toluene, -78°C, 95% yield)[14] which in turn was treated with benzylhydroxylamine hydrochloride[15,16] (CH_2Cl_2, 72% yield) to give nitrone 15[17] as an amorphous powder.

On refluxing in toluene, 15 underwent cycloaddition in the anticipated fashion with the exclusive formation of the tricyclic intermediate 16[18] (63% yield), the structure of which was confirmed by a complete three dimensional X-ray single-crystal analysis. A major problem that we had to deal with was a partial racemization during this cyclization step. Eventually we found that traces of acids in the reaction medium were catalyzing the loss of optical activity, which could be completely prevented by addition of small amounts of barium or calcium oxide[19].

Cleavage of the isoxazolidine ring (Zn dust, AcOH/H_2O, 70°C) and acylation of the free amine ($ClCO_2Me$, THF/2n Na_2CO_3, 0°C) gave the bicyclic intermediate 17 (65% yield from 16) which, on treatment with barium hydroxide in refluxing aqueous dioxane underwent hydrolysis of the lactam moiety and concommitant cyclization to the imidazolidinone 18 (87% yield). Left to be solved at this point was the elimination of the superfluous hydroxy group in the side chain



Scheme II

without affecting the vicinal chiral center. This was effected as follows. Thionyl chloride treatment in ether and subsequent quenching with methanol gave the chloroester 19 (68% yield). X-Ray single-crystal analysis of this product revealed that the hydroxy group was replaced with retention of configuration. Dechlorination to 20 was effected with excess of sodium borohydride in dimethylformamide (80°C, 76% yield). Finally, treatment of 20 with aqueous hydrobromic acid[19] gave d-biotin (1) (85% yield) which was isolated and characterized as the corresponding methyl ester[20] : mp 165-166°C; $[\alpha]_D^{25}$ + 80.5 (c 0.3, MeOH). Its spectroscopic data were identical with those of d-biotin methyl ester prepared from the natural product.

ACKNOWLEDGEMENTS

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10. Isoxazolidines 6 and 7 are both a mixture of epimers at C-3, since the starting 5 was a mixture of geometrical isomers. If the cycloaddition is carried out using pure Z or E 5, the products 6 and 7 are formed as single epimers but in the same 1.9:1 ratio.

11. Intramolecular cycloaddition of the nitrile oxides corresponding to 5 gave a 1:1 mixture of the isoxazolines corresponding to 6 and 7.

12. Prepared from the corresponding carboxylic acid and oxalyl chloride. See :
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13. 13: mp 160-161°C: $[\alpha]_D^{25}$ -144.8 (c 0.2, MeOH); NMR ($CDCl_3$) δ 2.02 (1H, dd, J_1 = 11.6 Hz, J_2 = 14.0 Hz), 3.18 (1H, dd, J_1 = 5.0 Hz, J_2 = 14.0 Hz), 3.73 (3H, s), 4.99 (1H, m), 5.67 (1H, br s), 5.94 (1H, dt, J_1 = 3.5 Hz, J_2 = 9.0 Hz), 6.17 (1H, d, J = 9.0 Hz).
The structure of 13 and the Z geometry of the double bond was also independently confirmed by X-ray crystal structure analysis.

14. To avoid racemization of the product, the reaction mixture was quenched at -78°C with a 4:1 mixture of THF/2n HCl after its completion.

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16. The formation of 15 using the corresponding free base always took place with extensive racemization of the substrate.

17. 15: $[\alpha]_D^{25}$ = -241.9 (c 0.2, $CHCl_3$); NMR ($CDCl_3$) δ 4.85 (2H, s), 5.02 (1H, m), 5.96 (1H, dt, J_1 = 4.4Hz, J_2 = 9.2Hz), 6.22 (1H, d, J = 9.2Hz), 6.81 (1H, d, J = 7.2Hz), 6.87 (1H, br d, J = 10.0Hz), 7.41 (5H, br s).

18. 16: mp 129-130 C; $[\alpha]_D^{25}$ = +78.3 (c 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 4.00 (1H, d, J = 8.2Hz), 4.28 (1H, d, J = 8.2Hz), 4.50 (1H, br, s), 6.10 (1H, br s), 7.33 (5H, br m).

19. The determination of the optical purity of 16 was carried out by converting it to 17, forming the corresponding ester with (+)-α-methoxy-α-trifluoromethylphenylacetic acid and analyzing the NMR spectrum and HPLC trace of the product. See: Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.

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