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PUMMERER REACTION OF BIOTIN SULFOXIDES : AN ACCESS TO NEW FUNCTIONALIZED BIOTIN DERIVATIVES.[1]

Robert LETT* and Yoshiaki KUROKI

Laboratoire de Chimie Organique Biologique, ERA CNRS 823,

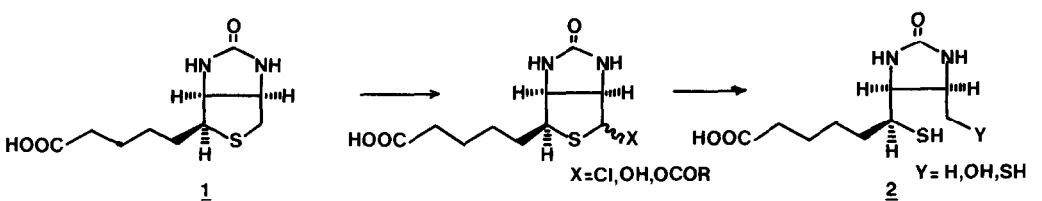
Université Pierre et Marie Curie, Tour 44-45, 4 place Jussieu

75230 - PARIS - Cedex 05 (France)

Abstract : Application of the Pummerer reaction to Biotin sulfoxides gives a good access to the corresponding thiolactol and thiolactone, which are key-compounds for the synthesis of new functionalized Biotin derivatives.

The last step of the biosynthesis of Biotin 1 is the conversion of dethiobiotin into Biotin. The mechanism of formation of the Carbon-sulphur bonds is still unknown, in spite of extensive studies.[2,3] Therefore, it is necessary to synthetize some hypothetic biosynthetic precursors of Biotin, such as 2, specifically labelled with either ^{2}H, ^{3}H or ^{35}S in order to get a definite proof of their "in vivo" conversion into Biotin.

A Pummerer reaction applied to Biotin sulfoxides appeared attractive because the synthesis should be short, versatile enough to prepare the compounds through a common intermediate and introduce the desired labels in the last steps of the sequence. Moreover, the use of (+) Biotin as starting material affords optically pure compounds.

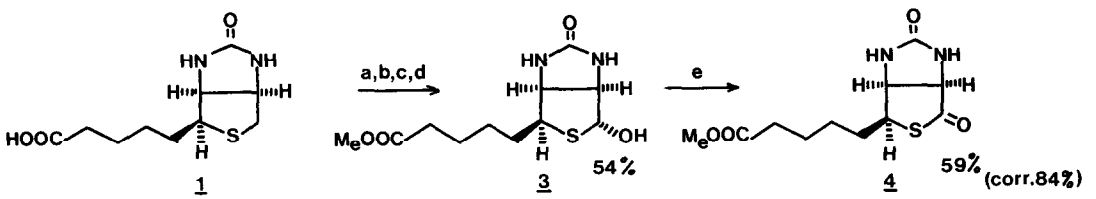


1 2

Surprisingly, there is no report in the litterature about Pummerer reactions applied to Biotin sulfoxides. Among the reagents we tried for the two diastereo-

isomeric sulfoxides[4], trifluoro acetic anhydride (TFAA) gave the best desired regioselective functionalization and the results were quite similar with this reagent for the (d) and (l) sulfoxides[1,5]. The thiolactol 3 is obtained in 54% overall yield starting from Biotin, with no intermediate purification (Scheme I). Then, we found that DMSO/TFAA/NEt_3 is an efficient method for the conversion of thiolactols into thiolactones[1,6], although no successfull example was previously reported[8]. Therefore, oxidation of 3 affords the thiolactone 4 in 59% yield (84% corrected from the recovered pure thiolactol which is recycled).

Scheme I

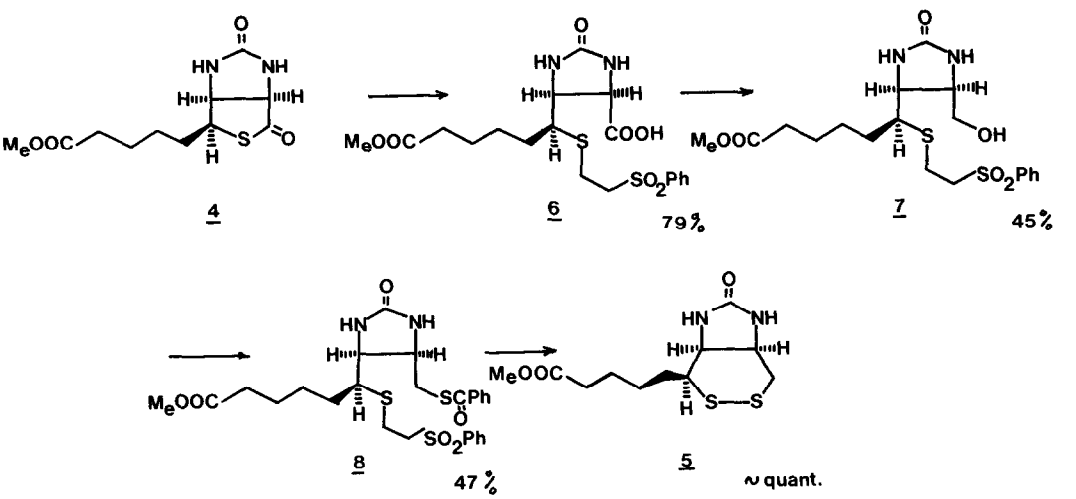


1 3 4

a: CH_3OH reflux, IR-120; b: 1 eq H_2O_2 30%, AcOH, r.tp; c: TFAA 3.7 eq, anhydrous alcohol-free $CHCl_3$, -60° to r.tp; d: CH_3OH/CH_3ONa; e: 3.1 eq DMSO, 2.3 eq TFAA, anhydrous alcohol-free $CHCl_3$, -60°, 0.5hr and 4.4 eq NEt_3, -60° to r.tp.

The cyclic disulfide 5 could be postulated as a reasonable intermediate between dethiobiotin and biotin[9]. This compound was prepared according to Scheme II, starting from the key thiolactone 4.

Scheme II



4 6 7 8 5

Selective saponification of the thiolactone, under Argon, with LiOH-H_2O (1.0eq) in THF and in situ protection of the resulting thiol via the Michaël adduct with phenyl vinyl sulfone[10] (1.1 eq) gave the carboxylic acid 6 in 79% yield.

Unexpectedly, reduction of the carboxylic acid in 6 was very slow and competitive with that of the methyl ester either with BH_3-THF or BMS. A stable acylborane was formed, probably stabilized through an internal complex with the sulfide or the urea; the acylborane formation was prooved by further reduction with $NaBH_4$/THF. On the other hand, reduction of the methyl ester was unusually fast with $NaBH_4$/THF, probably due also to a complexation of the reagent as observed recently in other examples.[12] Finally, the desired selective reduction was achieved via the mixed anhydride with diethyl phosphochloridate (DMF / lutidine 1/3; 0° to room temperature) and sodium borohydride in anhydrous THF (cold room) to give the alcohol 7 [13] in 45% yield; reduction of less reactive mixed anhydrides (from ClCOOEt, ⩘OCOCl, mesitylenesulfonyl chloride) were found to be less satisfactory.

The thiobenzoate 8 was prepared (47%) via the mesylate (sulfene procedure[14]) which was treated in situ, under Argon, with a preformed solution in THF of lithium thiobenzoate buffered with excess thiobenzoïc acid, in order to avoid basic conditions which convert the mesylate into Biotin. Final deprotection with CH_3ONa/CH_3OH 0.1M, under Argon at room tp, was almost quantitative.

The intermediate dithiol was oxidized in situ, just by stirring in the air, into the cyclic disulfide 5. $[\alpha]_D^{20°}$=+164° (c=0.5; EtOH).

$C_{11}H_{18}N_2O_3S_2$: M^+ = 290.07721 (mes.); M^+ = 290.07604 (calc.)

Mass Spectrum :(E.I.) : 290(7.2) ; 259 (7.6) ; 257 (2.3) ; 225 (6.9); 211 (4.1); 131 (10.1) ; 130 (11.5) ; 97 (54.5) ; 84 (100.0).

^{1}H NMR : ($CDCl_3$-250 MHz ; δ/TMS) $CH_{2\alpha}$: 2.74 (^2J=13.5 Hz, $^3J_{\alpha\beta}$=5.5Hz) and 2.93 (^2J=13.5Hz and $^3J_{\alpha\beta}$=11Hz) ; $H_{\alpha'}$: 3.27 ($^3J_{\alpha'\beta'}$=3Hz) ; H_β: 3.66±0.02 ($^3J_{\alpha\beta}$=11 and 5.5Hz, $^3J_{\beta\beta'}$=5.5Hz) ; $H_{\beta'}$: 3.91 ($^3J_{\alpha'\beta'}$=3Hz, $^3J_{\beta\beta'}$=5.5Hz) ; $\underline{CH_2}$-C(=O) : 2.32 (t, ^3J=7Hz) ; OCH_3: 3.66; NH: 4.76 and 4.84 ; CH_2 aliphat. : 1.3-1.7

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References and Notes

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The present sequence can have some advantages over the methodology of VEDEJS et al[7], especially when other functional groups are present.
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10) We found that phenyl vinyl sulfone is a very convenient protecting group of thiols. With a slight excess of reagent, the Michaël adduct is formed in very efficient yield even with hindered thiols, in aqueous or alcoholic solvents. Deprotection requires mild basic conditions (KOH or NaOH 0.1M ; CH_3ONa/CH_3OH 0.1M; room tp)[1]. Simultaneously, L. HORNER and H. LINDEL have shown that phenylvinyl sulfone is a good protecting group of thiols for amino acids, peptides and proteins.[11]
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