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Enantiospecific Synthesis of 3-Pyrrolines: A Route to Novel Polyhydroxylated Pyrrolidines.

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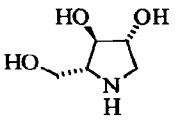
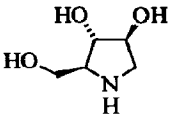
Abstract *Enantiopure acetamido ketones are converted by an intramolecular Wittig reaction into enantiopure 3-pyrrolines; the product from (S)-serine provides access to novel polyhydroxylated pyrrolidines.*

Polyhydroxylated pyrrolidines and piperidines have over recent years become synthetic targets of great interest. Many of these compounds show potentially useful activity due to their structural resemblance to sugars and their resultant ability to act as glycosidase inhibitors [1]. In particular the enantiomeric triols **(1)** and **(2)** show respectively yeast α-glucosidase inhibition [2] and anti HIV properties [3]. Most of the synthetic studies reported so far begin with carbohydrates, which have both suitable functionaliy and chirality [4], but glutamic acid has also served as a chiral starting material [5]. We describe here a method for the synthesis of analogues of **(2)** from (S)-serine, an approach which in general allows α-amino acids to be converted to 3-pyrrolines in optically pure form. Enantiomerically pure 3-pyrrolines have themselves been targets of some importance since they provide access to a number of alkaloid systems [6].



(1)

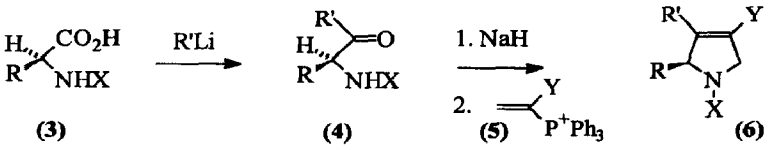


(2)

Our approach relies on the use of an intramolecular Wittig reaction [7] to form the 5-membered heterocyclic ring; there is a report of 3-pyrrolines being prepared via intramolecular Wittig reactions [8], but the starting materials were entirely different from those described here and the products were racemic.

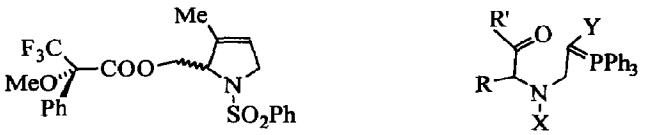
N-protected α-amino acids **(3)** were converted to the optically pure ketones **(4)** using the method developed by Rapoport [9]. In agreement with Rapoport's observations, we found that the only N-protection which could be used satisfactorily for serine was arenesulphonyl, whereas with other amino acids the more easily removable benzoyl or Cbz could be used. The ketones **(4)** were then treated with NaH (1.1 equiv.) in THF/CH_3CN (1:4), followed by the appropriate vinyl phosphonium salt **(5)** [7] (1.1 equiv., room temp., 2 hrs.) to give the 3-pyrrolines **(6)**. The yields are shown in the table below, and as we have previously noted [8], the yield is higher in such reactions with the salt **(5, Y=SPh)**.

compound	R	R'	X	Y	yield %
(6a)	CH_2OH	CH_3	SO_2Ph	SPh	78
(6b)	CH_2OH	Ph	SO_2Ph	SPh	74
(6c)	CH_2OH	CH_3	SO_2Ph	H	49
(6d)	$CH_2OTBDMS$	CH_3	SO_2Ph	SPh	60
(6e)	$CH_2OTBDMS$	Ph	SO_2Ph	SPh	55
(6f)	CH_3	CH_3	SO_2Ph	SPh	67
(6g)	CH_3	CH_3	COPh	SPh	90
(6h)	CH_2Ph	CH_3	COPh	SPh	60
(6i)	$(CH_3)_2CH$	CH_3	COPh	SPh	55
(6j)	CH_3	Ph	SO_2Ph	SPh	10



(3) **(4)** **(5)** **(6)**

The enantiospecificity of the cyclisation was investigated with the serine derivatives **(6a)**-**(6c)** by conversion to the corresponding Mosher's esters. Comparison of the 360 MHz ^1H NMR spectra of the esters originally derived from (S)-serine with those derived from (R,S)-serine clearly showed that the optical activity had been retained in the intramolecular Wittig reaction In particular, the signals for the olefinic methyl groups in (**7**) derived from (R,S)-serine were well resolved (δ1.55 and 1.60) as were the signals for the olefinic proton (δ 5.17 and 5.27). HPLC studies of the same esters indicated at least 97% ee. This oucome was not certain since there is an opportunity for racemisation to occur, under the basic reaction conditions, either on the original ketone or at the stage of the presumed intermediate (**8**) in the Wittig reaction.

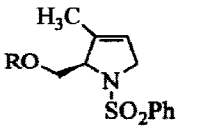


(7) **(8)**

The phenylthio group could be removed from the 3-pyrrolines **(6f)**-**(6j)** by m-CPBA oxidation to the corresponding sulphones, followed by dithionite reduction [10] (approx 80% over two steps) and this was usually preferable to the direct process towards the 3-pyrrolines unsubstituted at the 4-position (**6**, Y=H) , using the vinyl phosphonium salt (**5**, Y=H). However the dithionite reduction was not successful with the serine derivatives (**6a**) and (**6b**), where extensive decomposition occurred, and so we were forced here to use the direct method which yielded an acceptable 49% of the key intermediate (**6c**).

Oxidation of the 3-pyrroline (**6c**) with OsO_4 / Me_3NO gave only the α-diol (**9**) (98%). The same product was obtained by OsO_4 oxidation of the t-butyldimethylsilyl ether (**10**), followed by Bu_4NF

deprotection (84%). The stereochemistry of (**9**) was proved using NOE studies (fig. 1).



(**6c**), R=H
(**10**), R=TBDMS

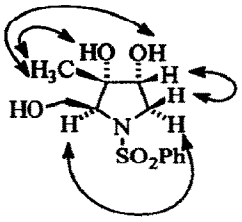
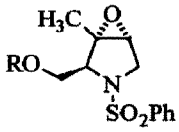
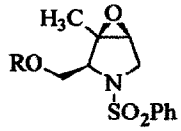


fig. 1 NOE interactions in (**9**)

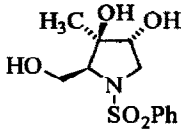
Epoxidation of the 3-pyrroline (**6c**) with m-CPBA gave a mixture of the α- and β-epoxides (**11**) and (**12**) (77% combined yield). Conversion to the corresponding TBDMS ethers allowed separation, showing the ratio of (**11**) to (**12**) was 3:2. More usefully, m-CPBA treatment of the 3-pyrroline (**10**) gave the α- and β-epoxides (**13**) and (**14**) (8:1) from which (**13**) was obtained in 72% yield. A number of unsuccessful attempts were made to open the epoxide ring in (**13**): 10% KOH in aqueous ethanol [11] and alumina / acetic acid [12] resulted only in recovered srarting material, whilst KOH in THF in the presence of 18-Crown-6 simply removed the silyl protecting group. Success was eventually achieved with 2M sulphuric acid in THF (room temp., 8hrs) and a crystalline product was isolated (48%) after chromatography. NMR studies showed this to be a 10:1 mixture of two isomeric triols, neither of which was identical to the OsO_4 product (**9**). It follows that they must therefore have been the 3,4-trans diols (**15**) and (**16**), and the major isomer was shown by NOE studies (fig. 2) to have the structure (**15**).



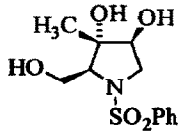
(**11**), R=H
(**13**), R=TBDMS



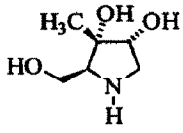
(**12**), R=H
(**14**), R=TBDMS



(**15**)



(**16**)



(**17**)

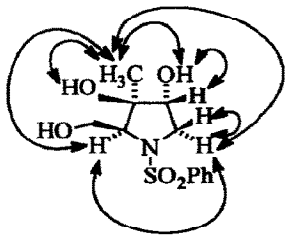


fig. 2 NOE interactions in (**15**)

N-deprotection was demonstrated on **(9)** using Na / NH_3 (81%) [13] which afforded the novel polyhydroxylated pyrrolidine **(17)** [14]. Clearly the method should be open to flexibility in terms of the 3-substituent on the ring simply by varying the organometallic reagent used to prepare the ketone **(4)**.

Acknowledgements.

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14. All new compounds gave satisfactory NMR and IR data together with either microanalysis or HRMS. Selected NMR data: **(9)**:δ_H (250 MHz, DDMSO+D_2O) 1.12(3H, s), 2.74(1H, t, J=8.5), 3.36(2H, m), 3.57(2H, m), 3.92(1H, m + OH)), 7.5(3H, m), 7.8(2H, d, J=7); δ_C (62.5 MHz, DDMSO) 19.8(CH_3), 50.7(C-5), 61.9(CH_2OH), 70.5(C-2), 73.0(C-4), 77.0(C-3), 127.6, 128.8, 132.5, 136.8; **(17)**:δ_H (250 MHz, D_2O) 1.56(3H. s), 2.99(1H, dd, J=5, 12.5), 3.39(2H, m), 3.6(1H, m), 3.79(1H, dd, J=4, 12), 3.94(1H, t, J=5); δ_C (62.5 MHz, D_2O) 21.1, 51.1, 61.7, 67.8, 77.7, 79.8.

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