Asymmetric Synthesis of a New Proline Analogue

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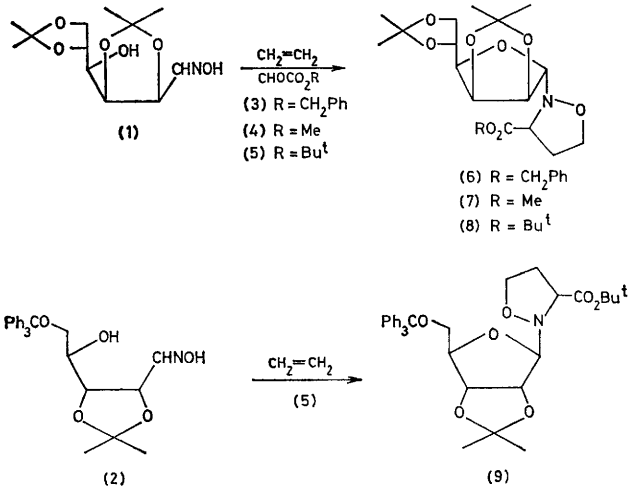
Summary The 1,3-dipolar cycloaddition to ethylene of *N*-glycosylnitrones, formed *in situ* from the partially protected D-mannose- or D-ribose-oximes and various glyoxalates, gave compounds which could be transformed into both enantiomers of 3-t-butoxycarbonyl-isoxazolidine and derivatives thereof.

ANALOGUES of proline possessing a heterocyclic ring other than pyrrolidine[1–3] are useful biochemical probes.[4] We report the asymmetric synthesis of the two enantiomers of isoxazolidine-3-carboxylic acid ('5-oxaproline') and of some of their derivatives. The synthesis is based on the 1,3-dipolar cycloaddition of *N*-glycosylnitrones[5,6] to ethylene. When the partially protected D-mannose-, or D-ribose-oximes (**1**)[5] and (**2**)[6] were allowed to react with 1·3 to 3 mol. equiv. of the glyoxylic esters† (**3**), (**4**), or (**5**), in the presence of ethylene ($CHCl_3$, 75 °C, 65 bar, 17 h), mixtures of the diastereomeric *N*-glycosyl-3(*R*,*S*)-alkoxycarbonyl-isoxazolidines (**6**)—(**9**) were formed in high chemical yields and with useful diastereoselectivities (Scheme 1 and Table).



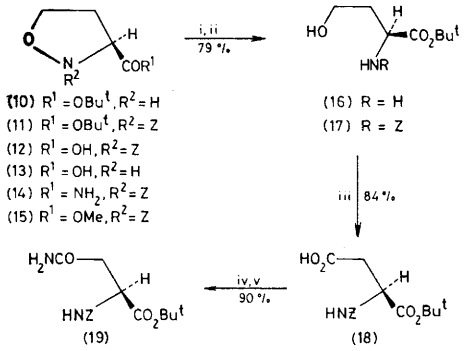
SCHEME 1

TABLE. Yields and diastereoselectivities of the cycloadditions.

Oxime	Glyoxylic ester	Product	Yield/%	Diastereoselectivity[a]/%	Major isomer formed
(**1**)	(**3**)	(**6**)	86	36	(3*S*)
(**1**)	(**4**)	(**7**)	92	54	(3*S*)
(**1**)	(**5**)	(**8**)	93	54	(3*S*)
(**2**)	(**5**)	(**9**)	78	72	(3*R*)

[a] The diastereoselectivities were determined by g.l.c. (capillary column Si 60) for compounds (**6**)—(**8**), by h.p.l.c. (Lichrosorb 60) for (**8**), and by weighing after chromatographic separation for (**9**).

The major diastereomer (**8**), shown below to possess the (3*S*) configuration, crystallized spontaneously from the reaction mixture and was obtained pure after 3—4 recrystallizations from hexane (43%, m.p. 96—97 °C, $[\alpha]_D^{25} = -38{\cdot}8°$ (*c* 0·98, $CHCl_3$).‡ Acid hydrolysis of (3*S*)-(**8**) (1 M HCl, 6% aq. MeOH, 40 °C, 4 h, then Na_2CO_3) gave the ester (**10**) (90%) m.p. 52—53 °C, $[\alpha]_D^{25} = -25{\cdot}7°$ (*c* 0·98, $CHCl_3$), ^{13}C n.m.r. ($CDCl_3$): δ 27·92(q), 34·87(t), 61·11(d), 69·36(t), 82·09(s), and 171·07(s) p.p.m., further characterized as its hydrochloride, m.p. 96—97 °C, $[\alpha]_D^{25} = -35{\cdot}2°$ (*c* 0·94, EtOH).



SCHEME 2. *Reagents and conditions*, i, H_2, 5% Rh–C, EtOH; ii, Z–Cl, $NaHCO_3$, aq. EtOH; iii, $KMnO_4$, acetone, AcOH; iv, isobutoxycarbonyl chloride, *N*-methylmorpholine, tetrahydrofuran, −20 °C; v, NH_3, H_2O, −15 to 10 °C.

Compound (**10**) was transformed by standard methodology into the derivatives (**11**)—(**15**) (Scheme 2). The *N*-benzyloxycarbonyl derivative (**12**), $[\alpha]_D^{25} = -9{\cdot}3°$ (*c* 1, 95% aq. AcOH) was obtained from the ester (**11**), m.p. 48·5—49 °C, $[\alpha]_D^{25} = -86{\cdot}3°$ (*c* 1·1, $CHCl_3$) and also by immediate benzyloxycarbonylation of the acid (**13**), formed by treating the ester (**10**) with CF_3CO_2H. The ^1H n.m.r. spectrum ($CDCl_3$) of the urethane (**11**) is well resolved already at 90 MHz: δ 2·59 (2H, ddd, *J* 8, 7·8, and 6 Hz), 3·78(1H, q, *J* 8 Hz), 4·14(1H, m), 4·74(t, *J* 7·8 Hz), 5·25(2H, s), 5·82(1H, br), 5·55(1H, br), and 7·38(5H, s). This should facilitate the conformational analysis of 5-oxaproline derivatives and hence of proline-containing peptides.

The absolute configuration of (**10**) was shown to be (*S*) by correlation with the known[8] L-asparagine derivative (**19**) (Scheme 2). This involved a novel synthesis of the L-homoserine derivatives (**16**), $[\alpha]_D^{25} = +4{\cdot}9°$ (*c* 2·04, EtOH), ^{13}C n.m.r. ($CDCl_3$): δ 27·98(q), 35·56(t), 54·73(d), 61·41(t), 81·25(s), and 174·41(s) p.p.m., and (**17**), m.p. 78—79 °C, $[\alpha]_D^{25} = -12{\cdot}70$ (*c* 2, EtOH), ^{13}C n.m.r. ($CDCl_3$): δ 27·92(q), 37·98(t), 51·6(d), 58·32(t), 67·11(t), 82·33(s), 127·97(d),

† Ester (**3**) was prepared by periodate cleavage of tartaric acid dibenzyl ester (T. S. Patterson, *J. Chem. Soc.*, 1913, **103**, 176) (80% yield); (**4**) and (**5**) were prepared by ozonolysis (J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 1966, 4273) of the corresponding maleic acid esters (83—85% yield).

‡ All new compounds were characterized either by elemental analysis and spectroscopic (i.r. and 90 MHz ^1H and 25 MHz ^{13}C n.m.r.) data or by chemical correlation with thus-characterized compounds.

128·06(d), 128·36(d), 135·95(s), 156·69(s), and 171·38(s) p.p.m.

Access to the compounds with (*R*)-configuration was gained *via* the addition products (**9**). The major isomer, (3*R*)-(**9**), was isolated by silica gel chromatography. Detritylation[5] ($FeCl_3$ in 1% MeOH–CH_2Cl_2) followed by hydrolysis (HCl, aq. MeOH) gave the enantiomer of (**10**) in 43% yield from (**2**).

5-Oxaproline (Opro) is easily incorporated in synthetic peptides. Using *O*- or *N*-protected derivatives (**10**), (**12**), and (**14**), a few protected model dipeptides containing either *C*-terminal or *N*-terminal Opro have been synthesized. In all Z-protected 5-oxaproline derivatives, the hydrogenolytic cleavage of the *N*-benzyloxycarbonyl group was accompanied by cleavage of the N–O bond. However, in 5-oxaproline derivatives possessing an *N*-acyl group which is stable to hydrogenolytic conditions, such as *N*-acetyl or *N*-peptidyl 5-oxaprolines, the N–O bond is, as expected,[9] not affected by the conditions of Pd-catalysed hydrogenolysis. Thus, preliminary experiments have shown that under hydrogenolytic conditions (H_2, 10% Pd–C, EtOAc) Ac–Opro–OBzl cleanly leads to Ac–Opro–OH.

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