

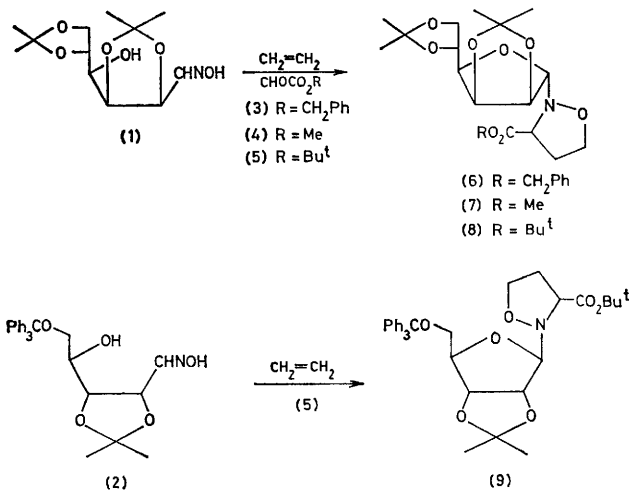
## Asymmetric Synthesis of a New Proline Analogue

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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<sup>1-3</sup> are useful biochemical probes.<sup>4</sup> 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<sup>5,6</sup> to ethylene. When the partially protected *D*-mannose-, or *D*-ribose-oximes (**1**)<sup>5</sup> and (**2**)<sup>6</sup> 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<sub>3</sub>, 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.

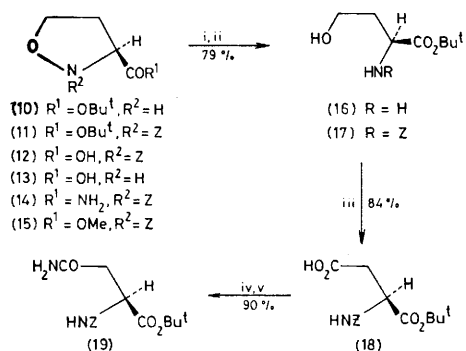
Oxime	Glyoxylic ester	Product	Yield/%	Diastereo-selectivity <sup>a</sup> /%	Major isomer formed
(1)	(3)	(6)	86	36	(3 <i>S</i> )
(1)	(4)	(7)	92	54	(3 <i>S</i> )
(1)	(5)	(8)	93	54	(3 <i>S</i> )
(2)	(5)	(9)	78	72	(3 <i>R</i> )

<sup>a</sup> 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**).

† 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 <sup>1</sup>H and 25 MHz <sup>13</sup>C n.m.r.) data or by chemical correlation with thus-characterized compounds.

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 re-crystallizations from hexane (43%, m.p. 96—97 °C, [α]<sub>D</sub><sup>25</sup> = -38.8° (*c* 0.98, CHCl<sub>3</sub>).‡ Acid hydrolysis of (3*S*)-(**8**) (1 M HCl, 6% aq. MeOH, 40 °C, 4 h, then Na<sub>2</sub>CO<sub>3</sub>) gave the ester (**10**) (90%) m.p. 52—53 °C, [α]<sub>D</sub><sup>25</sup> = -25.7° (*c* 0.98, CHCl<sub>3</sub>), <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>): 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, [α]<sub>D</sub><sup>25</sup> = -35.2° (*c* 0.94, EtOH).



SCHEME 2. Reagents and conditions, i, H<sub>2</sub>, 5% Rh-C, EtOH; ii, Z-Cl, NaHCO<sub>3</sub>, aq. EtOH; iii, KMnO<sub>4</sub>, acetone, AcOH; iv, isobutoxycarbonyl chloride, *N*-methylmorpholine, tetrahydrofuran, -20 °C; v, NH<sub>3</sub>, H<sub>2</sub>O, -15 to 10 °C.

Compound (**10**) was transformed by standard methodology into the derivatives (**11**)—(**15**) (Scheme 2). The *N*-benzyloxycarbonyl derivative (**12**), [α]<sub>D</sub><sup>25</sup> = -9.3° (*c* 1, 95% aq. AcOH) was obtained from the ester (**11**), m.p. 48.5—49 °C, [α]<sub>D</sub><sup>25</sup> = -86.3° (*c* 1.1, CHCl<sub>3</sub>) and also by immediate benzyloxycarbonylation of the acid (**13**), formed by treating the ester (**10**) with CF<sub>3</sub>CO<sub>2</sub>H. The <sup>1</sup>H n.m.r. spectrum (CDCl<sub>3</sub>) 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<sup>8</sup> *L*-asparagine derivative (**19**) (Scheme 2). This involved a novel synthesis of the *L*-homoserine derivatives (**16**), [α]<sub>D</sub><sup>25</sup> = +4.9° (*c* 2.04, EtOH), <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>): 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, [α]<sub>D</sub><sup>25</sup> = -12.70 (*c* 2, EtOH), <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>): δ 27.92(q), 37.98(t), 51.6(d), 58.32(t), 67.11(t), 82.33(s), 127.97(d),

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, (*3R*)-(9), was isolated by silica gel chromatography. Detritylation<sup>5</sup> (FeCl<sub>3</sub> in 1% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) 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 hydro-

genolytic 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,<sup>9</sup> not affected by the conditions of Pd-catalysed hydrogenolysis. Thus, preliminary experiments have shown that under hydrogenolytic conditions (H<sub>2</sub>, 10% Pd-C, EtOAc) Ac-Opro-OBzl cleanly leads to Ac-Opro-OH.

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