A STRAIGHTFORWARD SYNTHESIS OF (±)-4-AMINO-4-DEOXYERYTHROSE *VIA* ITS BISULFITE ANOMER

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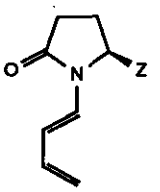
Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday

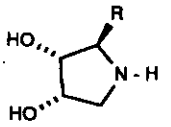
Abstract - Hetero-Diels-Alder reaction of *N*-butadienyl-2-pyrrolidone (**1a**) with acylnitroso dienophile (**3**) led with very high regioselectivity to the racemic cycloadduct (**6**). A sequence of stereospecific reactions, as well as some protection/deprotection steps, gave the bisulfite derivative (**2b**) of (±)-4-amino-4-deoxyerythrose (**2a**) as a single and crystalline anomer. Asymmetric induction as applied to the Diels-Alder cycloaddition step with various *N*-butadienylpyroglutamate esters (**1b-e**) permitted to work out optimal experimental conditions, the best d.e. value being 76%.

INTRODUCTION - *N*-Dienylpyrrolidones (**1**) can easily be prepared and proved to be useful synthons for Diels-Alder reactions with C=C dienophiles, leading thereby either to racemic[1] or to chiral cycloadducts.[2] In a previous communication hetero-Diels-Alder cycloadditions of chiral *N*-butadienyl-L-pyroglutamate (**1b**) with acylnitroso dienophiles were shown to proceed with complete regioselectivity.[3] Furthemore the asymmetric outcome of these reactions is strongly dependent on the nature of the acylnitroso dienophile, the major diastereoisomer being always (6S).[3] The acylnitroso dienophiles are highly reactive species which must be prepared *in situ*, in the presence of their diene partners, by oxidation of the corresponding hydroxamic acids with nPr_4NIO_4.[4]

We describe herein the steric influence of the pyroglutamate's ester bulkiness upon the asymmetric induction of the above cited hetero-Diels-Alder cycloadditions. We describe furthemore the transformation of primary racemic cycloadducts (**6**) into (±)-4-amino-4-deoxyerythrose (**2a**) *via* its bisulfite derivative (**2b**).

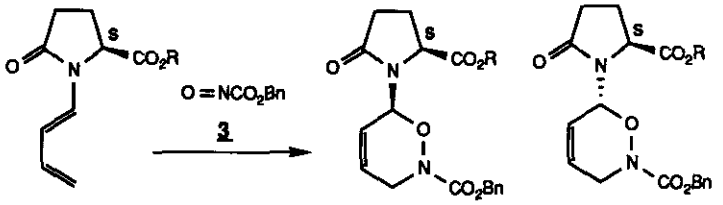


1a Z = H
1b Z = CO_2Me



2a R = OH
2b R = SO_3H

Asymmetric induction - The chiral *N*-butadienylpyroglutamate derivatives (**1b-e**) were reacted *via* standard reaction conditions with the benzyloxycarbonyl-nitroso dienophile (**3**). In **Table 1** the d.e. values are reproduced as determined by ^1H nmr with the crude reaction mixtures. The bulkiness of the ester group clearly plays the dominant role in these asymmetric cycloadditions, the highest d.e. values being obtained with the cholesteryl and the *t*-butyl groups. In this latter instance the d.e. could be increased when replacing CH_2Cl_2 with MeOH and by cooling the reaction mixture to -20°C, as shown already in a previous communication.[3]



1b-e **4b-e** **5b-e**

Table 1: Relative amounts of cycloadducts (**4**) and (**5**) obtained by Diels-Alder reaction of dienes (**1b-e**) with nitrosodienophile (**3**).

	R	Solvent/Temperature	4(%)	5(%)	d.e.(%)
b[3]	Me	CH_2Cl_2 / 0°C	73	27	46
c	*i*Pr	CH_2Cl_2 / 0°C	80	20	60
d	Cholesteryl	CH_2Cl_2 / 0°C	85	15	70
e	*t*Bu	CH_2Cl_2 / 0°C	84	16	68
e	*t*Bu	MeOH / -20°C	88	12	76

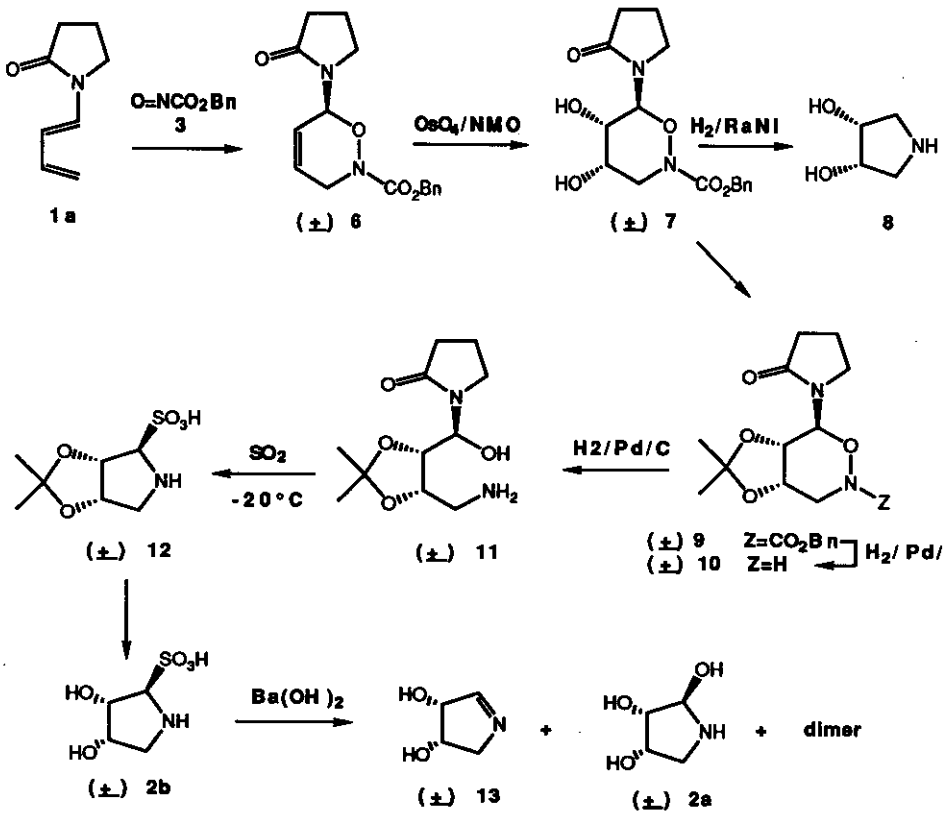
(±)-3-Amino-3-deoxyerythrose - A model reaction was performed with achiral *N*-butadienyl-γ-lactame (**1a**) and the *in situ* generated acylnitroso dienophile (**3**) which led to the racemic cycloadduct (**6**) with total regioselectivity (yield 82%). Catalytic osmylation of (±)-**6** in the presence of *N*-methylmorpholine-*N*-oxide (NMO)[5] led to the *cis* -diol (**7**) (96%; mp 154°C) which proved to be *anti* with respect to the pyrrolidone moiety. The reductive cleavage of the N-O bond did not proceed satisfactorily with H_2-Pd/C. In the presence of Raney nickel the reduction went too far since only the *meso* pyrrolidinediol (**8**) could be isolated, a result which we had already described previously.[6] The acetonide (**9**) though, which was easily formed with dimethoxypropane in the presence of Amberlyst-15 (93%; mp 143°C), proved amenable to hydrogenolysis in the presence of Pd/C and oxazine (**10**) could be isolated in good yield (80%; mp 145°C). Further treatment of **10** with the same experimental conditions gave the hemiaminal (**11**) which was characterised *via* its diacetyl derivative (mp 142°C) and its picrate (mp 134-139°C). Compound (**11**) is but a multifunctional derivative of (±)-4-amino-4-deoxyerythrose (**2a**) which proved difficult to deprotect both in acidic and in basic media, particularly when it comes to the removal of the pyrrolidone moiety. This latter step could be performed at -20°C in liquid SO_2 and ether, whereby the bisulfite pyrrolidine derivative of (±)-**12** could be isolated as a crystalline material (50%; sublimes at 178°C). Prolonged treatment of (±)-**12** with the same experimental conditions gave the bisulfite derivative of (±)-4-amino-4-deoxyerythrose (**2b**) (quant.; mp 170°C,decomp.) as a single anomer. Saponification of (±)-**2b** with $Ba(OH)_2$ gave the expected free base which appeared to be a mixture of the 1-hydroxy compound (±)-**2a**, of the imine (±)-**13** and of a dimer of **2a** ; these compounds could not be separated. Paulsen has described a similar complex mixture formed when the amino derivative of L-lyxose was treated with a base.[7]

Now that the racemic bisulfite compound (**2b**) has been obtained as a stable derivative of (±)-4-amino-4-deoxyerythrose,[8] we shall turn our attention to the synthesis of an optically pure bisulfite derivative of **2b** starting from the major chiral diastereoisomer (**4**) (see above).

ACKNOWLEDGEMENTS

The support of the *Centre National de la Recherche Scientifique* (URA-135) is gratefully

acknowledged. We also wish to thank the *Ministère de l' Enseignement Supérieur et de la Recherche* for a PhD-grant to one of us (J.-B. B.).



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Received, 12th October, 1993