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1,3-Dipolar Cycloaddition of Diazomethane with a Chiral Azlactone

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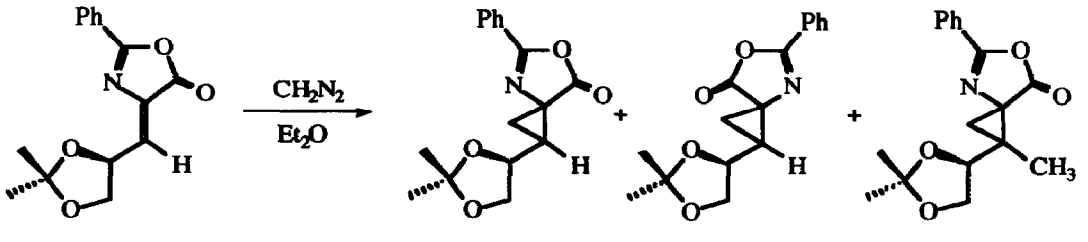
Abstract: *The chiral Z-azlactone derived from 1,2-O-isopropylidene-D-glyceraldehyde reacted with diazomethane to afford stereoselectively and diastereoselectively a cis spiro-azlactone. Solvent and temperature dependence of the ratio of the products is described.*

α,β-Didehydroamino acid derivatives are useful prochiral building blocks in synthetic organic chemistry. In particular, azlactones unsaturated in C_4 have proved to be versatile intermediates in the synthesis of amino acids,[1] cycloaliphatic[2] and cyclopropylamino acids.[3] Moreover, these compounds are easily transformed into N-acyl-α,β-didehydroamino acid derivatives, which are powerful synthetic tools.[4] Our interest in the asymmetric synthesis of cyclopropylamino acids has prompted us to use a chiral azlactone as a synthetic precursor of these compounds and we have tested 1,3-dipolar cycloaddition of diazomethane with the chiral azlactone **1Z** derived from glyceraldehyde.

Compound **1** was obtained by Erlenmeyer-Plöchl azlactone synthesis from hippuric acid and 1,2:5,6-di-O-isopropylidene-*D*- mannitol (lead tetraacetate, acetic anhydride, THF, reflux)[5] as a mixture of stereoisomers which were isolated and purified by medium pressure chromatography to afford a 60% yield of the **Z** isomer and a 15% of the **E** isomer. Measurement of the long range ^{13}C-^{1}H coupling constants between the olefinic proton and the C-5 carbonyl carbon in the fully coupled ^{13}C NMR (75 MHz) spectra allowed us to assign the configuration of each azlactone, as it is known[6] that $^{1,3}J^{t}_{CH} > {}^{1,3}J^{c}_{CH}$. The recorded values $^{1,3}J_{CH} \approx 5$ Hz for the major stereoisomer confirmed a *cis* stereochemistry for the hydrogen and carbonyl group, whereas $^{1,3}J_{CH} \approx$ 12.5 Hz measured for the minor stereoisomer predicted a *trans* stereochemistry for the hydrogen and carbonyl group.



1Z **2** **3** **4**

Scheme 1

When a solution of azlactone **1Z** dissolved in diethyl ether was treated with an ethereal solution of diazomethane[7] at 0 °C until completion, a mixture of five spiro-compounds was obtained. There were isolated by medium pressure chromatography and characterised as four diastereomeric spiro-azlactones, a pair of spiro-azlactones *cis* **2**, a pair of spiro-azlactones *trans* **3**, and spiro-azlactone **4** (Scheme 1). The formation of compound **4** can be rationalised since 1,3-dipolar cycloaddition of diazomethane with azlactones can afford C-methylation derivatives[8] which react with diazomethane again to yield spiro-azlactones. Examination of the crude reaction mixture by h.p.l.c.[9] indicated a high *cis/trans* selectivity (73/27) as well as excellent diastereoselectivity for both *cis* (84/16) and *trans* (92/8) compounds.

The stereochemical assignments of all the compounds were made after conversion to their methyl esters, upon treatment with 1% sodium methoxide in methanol. The *cis/trans* stereochemistries of the cyclopropyl esters were assigned on the basis of NOE difference ^1H NMR experiments. Cyclopropyl esters **5** were assigned as *cis* since the amide hydrogen exhibited a significant NOE enhancement on presaturation of the corresponding proton H_a (Figure 1). *Cis* stereochemistry of cyclopropyl ester **7** was assigned by NOE experiments as the amide hydrogen exhibited a significant NOE enhancement on presaturation of the corresponding proton H_a.

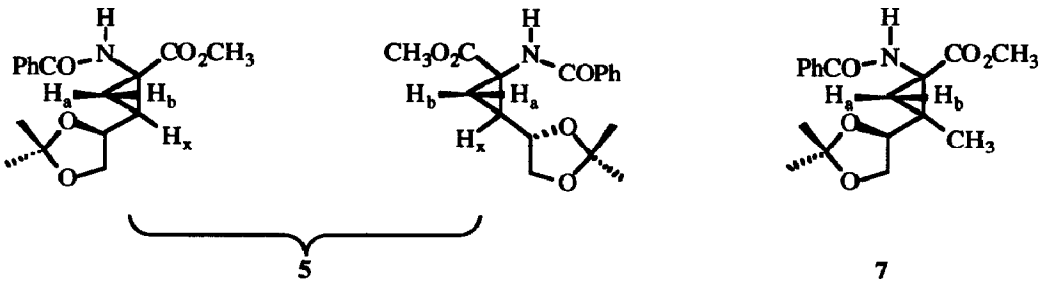


Figure 1

For cyclopropyl esters **6** the amide hydrogen exhibited a significant NOE enhancement on presaturation of both corresponding protons H_b and H_x which was consistent with their *trans* stereochemistry (Figure 2).

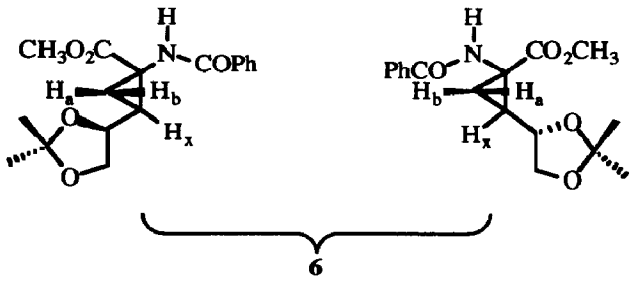


Figure 2

The absolute stereochemistry of the major compound was unambiguously determined by single crystal X-ray analysis of the corresponding methyl ester, (Figure 3), which showed that the cyclopropyl moiety had a *1S, 2R* configuration. These results indicated that the addition of diazomethane had occurred to the $C_{\alpha\text{-}Re}$ face of the double bond.

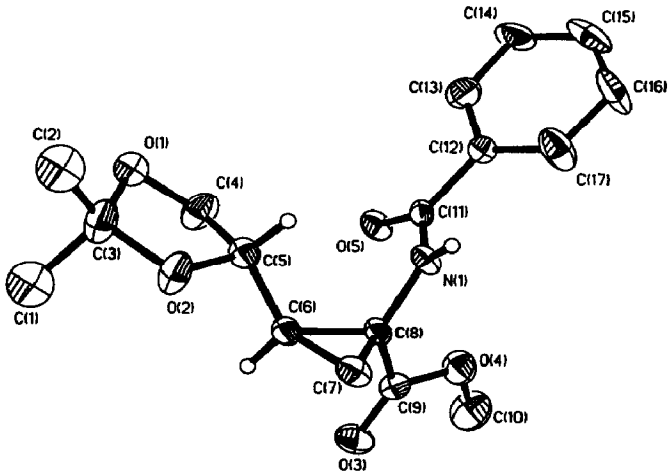


Figure 3

Finally the solvent dependence of the product ratio was examined[9]. In polar solvents (diethyl ether, ethyl acetate, chloroform...) extensive formation of azlactone **4** was observed. In non-polar solvents the amount of this compound was diminished to traces when diazomethane was generated in the same non-polar solvent so that the polarity solvent of the cycloaddition reaction would not increase. Then hexane, carbontetrachloride and benzene were chosen as non-polar solvents to carry out the cycloaddition reaction and in all cases a good *cis/trans* selectivity as well as a very good *cis* and *trans* stereoselectivity was observed. When the reaction was carried out at very low temperatures only an slight improvement in both *cis/trans* selectivity and stereoselectivity was observed. In all cases the stereoselectivity observed for *trans* spiro-azlactones was better than for *cis* spiro-azlactones. (Table 1)

Table 1. Solvent and temperature influence on diazomethane cycloaddition to **1Z** in non-polar solvents.

Solvent[a]	temp (°C)	4	cis/trans	cis d.r.	trans d.r.
hexane	0	traces	77/23	84/16	87/13
CCl_4	0	traces	84/16	88/12	91/9
benzene	0	traces	81/19	90/10	93/7
hexane	-20	traces	78/22	84/16	87/13
CCl_4	-20	traces	83/17	85/15	91/9
hexane	-50	traces	83/17	88/12	90/10
hexane	-75	traces	83/17	90/10	90/10

[a] Diazomethane was generated from N-methyl-N'-nitro-N-nitrosoguanidine in the same non-polar solvent used in the reaction.

In summary, we have developed methodology for the synthesis of methyl *(1S,2R)* 2[*(S)* -2,2-dimethyl-1,3-dioxolan-4-yl]-1-benzamidocyclopropancarboxylate in a diastereomerically pure form. This compound may be valuable as a synthetic intermediate to obtain cyclopropylamino acids. The versatility of this compound as a synthetic precursor is being tested and will be published in due course.

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7. **CAUTION!** Diazomethane is a very harmful and hazardous reagent and must be handled with caution and the preparation of a large amount of diazomethane is to be avoided. In a typical experiment a solution of diazomethane in hexane (from N-methyl-N'-nitro-N-nitrosoguanidine) was added to a solution (0 °C) of azlactone **1Z** (273 mg, 1 mmol) in hexane (20 ml) in a stoppered flask protected from the light. The solution was stirred for about 10 min and then treated with anhydrous $CaCl_2$ to destroy the excess diazomethane. The solution was filtered and concentrated *in vacuo*, and the resultant oil was dried over P_2O_5 to afford a mixture of the five spiro-azlactones. Medium pressure chromatography eluting with hexane/ethyl acetate 85:15 allowed the isolation of all the compounds in the mixture.
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9. The product ratio was determined by HPLC. Column radial pack silica (8 mp 10 mm). Eluent hexane-ethyl acetate 80/20. Flow rate 3 ml/min. Detection 248 nm.

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