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Asymmetric Diels-Alder Reaction of a Chiral Azlactone

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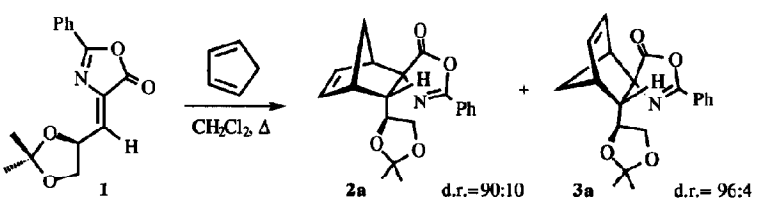
Abstract: *The chiral Z-azlactone derived from 1,2-O-isopropylidene-D-glyceraldehyde underwent facial diastereoselective Diels-Alder reaction with cyclopentadiene. Catalyst and temperature dependence of the product ratio is described. The absolute configuration of the major compound was established by an X-ray crystallographic analysis.*

Cyclic non-metabolisable amino acids have useful biological properties, in particular α-amino acids with a norbornane skeleton have been used to study the transport of amino acids with hydrophobic side chains (i.e. leucine, isoleucine and valine).[1] Moreover, it has been shown that the incorporation of one or more conformationally-constrained amino acids (generally cyclic amino acids) into bioactive peptides often gives rise to analogues with enhanced biological activities.[2]

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,[3] cycloaliphatic[4] and cyclopropylamino acids.[5] Moreover these compounds are easily transformed into N-acyl-α,β-didehydroamino acid derivatives which are powerful synthetic tools.[6]

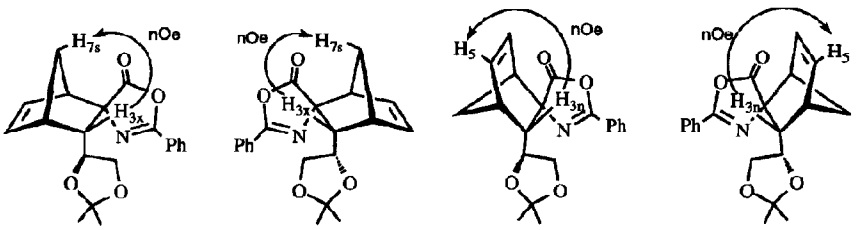
Recently Amstrong *et al.*[7] have reported the synthesis of chiral azlactone **1** derived from glyceraldehyde, and the subsequent halogenation of this compound with NBS or NIS to afford β-halodidehydroamino acid derivatives as well as the characterisation of these β-halocompounds. We decided to use this homochiral azlactone as a synthetic precursor of cyclic amino acids with a norbornane skeleton.



Scheme 1

Compound **1**, obtained by the Erlenmeyer-Plöchl azlactone synthesis from hippuric acid and 1,2:5,6-di-O-isopropylidene-*D*-mannitol under oxidative lead conditions,[5] was dissolved in methylene chloride containing an excess of cyclopentadiene (2.5 eq) and stirred at room temperature for 2 hours to afford a mixture of the four possible Diels-Alder adducts, which were easily isolated by medium pressure chromatography and fully characterized. (Scheme 1). Examination of the crude reaction mixture by h.p.l.c.[8] indicated a slight preference for *exo* adducts (64:36) as well as high facial diastereoselectivity for both *exo* (90:10) and *endo* (96:4) adducts.

The endo/exo stereochemistry of the four adducts was unequivocally determined on the basis of NOE difference ^{1}H NMR experiments. So, in those adducts in which the carbonyl group had the *exo* orientation (**2a** and **2b**) the signal due to the H_{7s} proton showed significant NOE enhancement when the H_{3x} proton was selectively irradiated, and in those adducts in which the carbonyl group had the *endo* orientation (**3a** and **3b**) the signal due to the olefinic proton H_5 exhibited a significant NOE enhancement when the H_{3n} proton was selectively irradiated (Figure 1).



2a **2b** **3a** **3b**

FIGURE 1

When the reaction was carried out at low temperature (-40 °C) there was a decrease in the reaction rate and four days were needed to reach a conversion of 82%. However, the *exo* selectivity (71:29) as well as facial diastereoselectivity for both *exo* (98:2) and *endo* (>98:2) adducts increased.

Then the above experiment was performed in the presence of the Lewis acid lithium perchlorate (5.0 M in diethyl ether) which is known to enhance the *endo* selectivity of Diels-Alder reactions.[9] Examination of the crude reaction mixture by h.p.l.c. indicated a decrease in *exo* selectivity (56:44), that is to say, an increase in the *endo* selectivity, as well as a decrease in both *exo* (80:20) and *endo* (78:22) facial diastereoselectivity.

We also studied the Diels-Alder reaction of cyclopentadiene and compound **1** catalyzed by the soluble organometallic compounds $EtAlCl_2$, $AlCl_3$ and $TiCl_4$.In all cases the formation of cycloadducts from oxazolone E together with the four adducts from oxazolone Z was observed, which indicated a Z-E isomerization in the in the presence of the Lewis acid[10] previous to the cycloaddition reaction. The amount of by-products depended on the catalyst used and was greater when $TiCl_4$ and $AlCl_3$ were used. All these catalysts improved the *exo* selectivity as well as *exo* and *endo* facial diastereoselectivity.

When BF_3 was used as a catalyst *exo* selectivity was slightly increased and both *exo* and *endo* facial diastereoselectivity were excellent while the use of the Lewis acid ZnI_2 as a catalyst did not improve either *exo* selectivity or *exo* and *endo* facial diastereoselectivity.

Table 1. Temperature and catalyst influence on Diels-Alder reaction of **1** with cyclopentadiene

temp (°C)	catalyst(eq)	t	Conversion	exo/endo	exo d.r.	endo d.r.
25	none	2 h	100	64/36	90/10	96/4
-40	none	96 h	82	71/29	98/2	>98/2
25	$LiClO_4$[a]	2 h	100	56/44	80/20	78/22
25	$EtAlCl_2$(0.2)[b]	1 h	100	72/28	95/5	97/3
25	$AlCl_3$(0.2)[b]	1 h	100	73/27	93/7	97/3
25	$TiCl_4$(0.2)[b]	0.5 h	100	75/25	93/7	>98/2
25	BF_3(1)	0.5 h	100	77/23	94/6	94/6
25	ZnI_2(0.2)	0.5 h	100	60/40	77/23	66/34

[a] The reaction was performed in a solution 5.0 M of lithium perchlorate in diethyl ether. [b] Cycloadducts from oxazolone E were observed.

The relative stereochemistry within the major *exo*-compound **2a** was determined by single crystal X-ray analysis,[11] (Figure 2), which showed that the carbonyl group had in effect the *exo* orientation and addition of the diene had occurred to the $C_{\alpha\text{-Re}}$ face of the double bond. Given the known absolute configuration of the starting azlactone *(S)*- **1** the X-ray also establishes the absolute configuration.

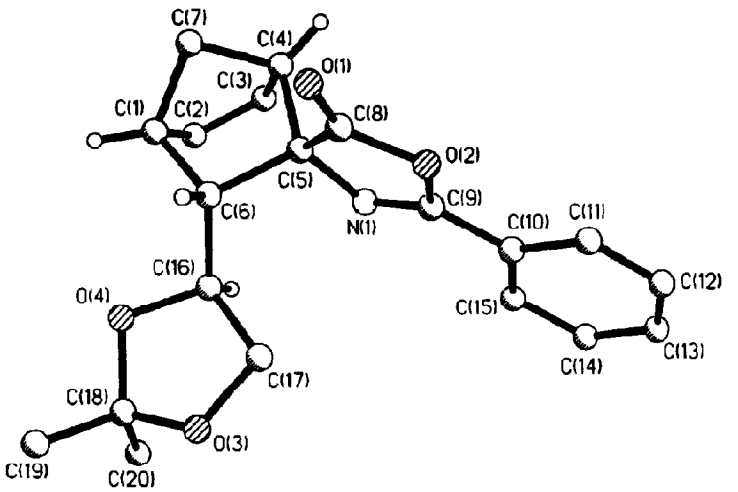


FIGURE 2

In conclusion, we have developed a method for the asymmetric synthesis of exo compound **2a** and endo compound **3a** in diastereomerically pure form which might be extremely valuable as synthetic intermediates to obtain bicycloaliphatic amino acids. The versatility of these compunds as synthetic precursors is being tested and will be published in due course.

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8. The product ratio was determined by HPLC. Column radial pack silica (8 mp 10 mm). Eluent hexane-ethyl acetate 96/4. Flow rate 3.5 ml/min. Detection 254 nm.
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11. Crystal data: $C_{20}H_{21}NO_4$, orthorhombic, space group $P2_12_12_1$, a = 10.2407(2), b = 12.7510(3), c = 13.3553(3) Å, V = 1744 Å^3, Z = 4. Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, $\omega/2\theta$ scan technique. A total of 2774 reflections were measured, and merged to 2440 unique reflections (R_{merg} = 0.0228). From them, 1607 with $F \geq 4.0\ s(F)$ were considered observed and used in the successive refinements. A periodic check of three standard reflections during data collection showed no statistically-significant crystal decay (≤ 0.3%). The structure was solved by direct methods (SHELXTL Plus). Least-squares (full matrix) refinement yielded R and R_W-vaules of 0.0396 and 0.0410 respectively. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

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