Highly *exo*-Diastereoselective Diels–Alder Reactions of (2*S*)-*N*-Benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one

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(2*S*)-*N*-Benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one undergoes highly *exo*-diastereoselective Diels–Alder reactions with cyclopentadiene and cyclohexa-1,3-diene.

 α,β -Dehydroamino acids are extremely useful substrates for preparing both natural and non-proteinogenic amino acids.¹ These substrates have been employed as Diels–Alder dienophiles^{2.3} for the synthesis of racemic cycloalkane amino acids, which have a varety of biological activities.⁴ Racemic α -amino acids have also been prepared from the conjugate addition of nucleophilic reagents to α,β -dehydroamino acids.¹ Enantioselective catalytic hydrogenation of α,β -dehydroamino acids gives chiral α -amino acids in high enantiomeric purity,¹ little attention however, has been devoted to the asymmetric synthesis of chiral α -amino acids employing chiral α,β -dehydroamino acids.

In 1987, Seebach *et al.*⁵ reported the synthesis of the α , β -dehydroamino acid, (2S)-N-benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one **2** from the bromination and then dehydrobromination of the oxazolidinone **1**,⁶ derived from (S)-alanine. More recently, a modified synthesis of 2 has been reported by Beckwith *et al.*⁷ The latter author has employed 2 as a useful Michael acceptor for alkyl radicals for the enantioselective synthesis of α -amino acids. We report here, the Diels–Alder reaction of 2 with cyclopentadiene and



Scheme 1 i, N-Bromosuccinimide (2 equiv.), hv, (PhCO₂)O; ii, NaI, acetone, heat

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 Table 1 Diels-Alder reactions of 2

Diene	Lewis acid	t/days	T/°C	Diastereoselectivity	Yield (%)
 Cyclopentadiene Cyclopentadiene	 LiClO4	14	25	>97(4) : <3 (others)	70
Cyclopentualene	$(5.0 \text{ mol dm}^{-3})$	3	25	4:5;35:65	67
Cyclohexadiene		3	140	>97(6): <3 (others)	62



Fig. 1 Molecular projection 4, 20% thermal ellipsoids are shown for the non-hydrogen atoms. Hydrogen atoms have an arbitrary radii of 0.1 Å.



cyclohexa-1,3-diene, which proceed in a highly diastereoselective and efficient manner.

Compound (2S)-2 was prepared from 1 by a modified version to that reported by Beckwith.^{7.8} A side product from this reaction was the bromoalkene 3 (m.p. 123 °C) which was formed in 15–20% yield and as a single geometric isomer (Scheme 1). This material was extremely difficult to separate from 2 by column chromatography, however, most of 3 could be removed by crystallization from hexane. In this way 95% analytically pure 2^{\dagger} could be obtained ($[\alpha]_D^{24} - 92.6^{\circ}, c \ 0.49$, CHCl₃; lit.⁵ [α]_D²⁵ –148.6°, c 1.5, CHCl₃; lit.⁷ [α]_D²⁵ –186.3°, c 1.5, CHCl₃).⁷ The enantiomeric purity of 2 was determined to be 50% using an ionically bound 3,5-dinitrobenzoyl leucine Pirkle HPLC column using a mixture of hexane, ethanol and acetonitrile (99:0.66:0.33) as eluent.

When a solution of 2 dissolved in cyclopentadiene (10 equiv.) was stirred at room temperature for 14 days the Diels-Alder adduct 4 (m.p. 119.5 °C, $[\alpha]_D^{22} + 68^\circ$, *c* 2.25, CHCl₃) was isolated in 70% yield after purification by column chromatography. ¹H NMR analysis (400 MHz) of the crude reaction mixture indicated a product diasteroselection of >97 (4): <3 (other diastereoisomers) (Table 1). The stereochemistry of 4 was unequivocally determined by single crystal X-ray

analysis‡ (Fig. 1), which showed that the carbonyl group of 4 had the exo orientation and addition of the diene had occurred to the face of the alkene of 2 that was opposite to that of the bulky tert-butyl group of the 1,3-oxazolidin-5-one ring. A slight preference for exo-selectivity has been noted in the reaction of achiral α,β -dehydroamino acids with cyclic dienes.^{2,3} The high *exo*-diastereoselectivity shown by 2 is identical to that of the 1,3-dioxolan-4-one analogue of 2 in its reaction with cyclopentadiene.9 The Lewis acid catalysed reaction of 2 and cyclopentadiene with 5 mol dm^{-3} lithium perchlorate in diethyl ether (25 °C, 2 days) gave a mixture (65:35, 67% yield) of the endo- and exo-diastereoisomers 5 and 4 respectively (Table 1). The stereochemistry of 5 was based on the similarity of its ¹H NMR spectrum to that reported for the endo adduct from the 1,3-dioxolan-4-one analogue of 2 and cyclopentadiene.¹⁰ Lithium perchlorate (5.0 mol dm⁻³) in diethyl ether is known to enhance the rate and endo-selectivity in most Diels-Alder reactions.10

The thermally induced reaction of 2 and cyclohexa-1,3diene at 140 °C for 2 days gave a single adduct (>97% diastereoselectivity) in 62% yield after purification (Table 1). This was assigned the *exo*-diastereoisomer 6 (m.p. 126 °C) on the basis of NOE difference ¹H NMR experiments which showed a 7% enhancement of the signal due to the allylic proton at H(1) when the methine of the 1,3-oxazolidinone ring was selectively irradiated.

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 $^{^{\}dagger}$ ¹H NMR analysis (400 MHz) indicated **2** was contaminated with 5% of **3**.

[‡] Single crystal X-ray structure determination of 4: C₂₀H₂₃NO₃, M = 325.4, monoclinic, P_{21}/c , a = 6.194(4), b = 26.405(9), c = 10.847(4)Å, $\beta = 98.31(4)^\circ$, V = 1756Å³, $D_c = 1.23$ g cm⁻³, Z = 4.3116 Unique diffractometer data to 20 max = 50° [monochromatic Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 0.5$ cm⁻¹ (no correction)]; 1381 'observed' [$I > 3\sigma(I)$] used in full-matrix least-squares refinement [anisotropic thermal parameters for C, N, O; hydrogen atoms refined in (x, y, z, U_{iso})]. R = 0.051, R_w (statistical weights) = 0.049; $T \sim 295$ K.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.