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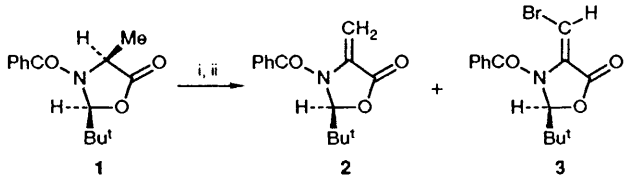
(2*S*)-*N*-Benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one undergoes highly *exo*-diastereoselective Diels–Alder reactions with cyclopentadiene and cyclohexa-1,3-diene.

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, (2*S*)-*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



1 **2** **3**

Scheme 1 i, *N*-Bromosuccinimide (2 equiv.), *hν*, $(PhCO_2)O$; ii, NaI, acetone, heat

Table 1 Diels–Alder reactions of **2**

Diene	Lewis acid	*t*/days	*T*/°C	Diastereoselectivity	Yield (%)
Cyclopentadiene	—	14	25	>97(4) : <3 (others)	70
Cyclopentadiene	$LiClO_4$ (5.0 mol dm^{-3})	3	25	4 : 5; 35 : 65	67
Cyclohexadiene	—	3	140	>97(6) : <3 (others)	62

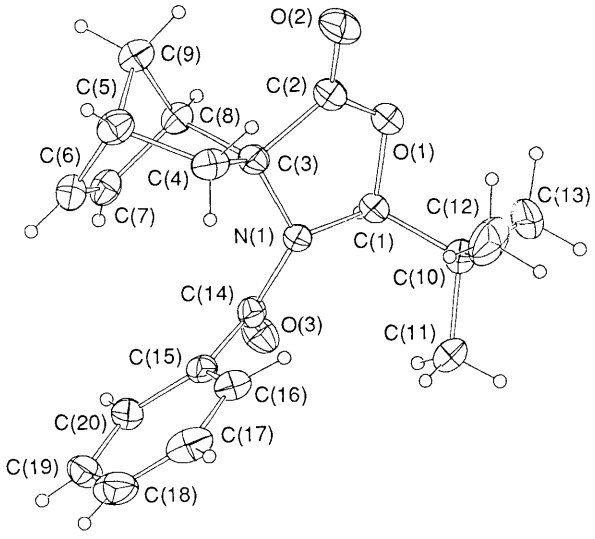
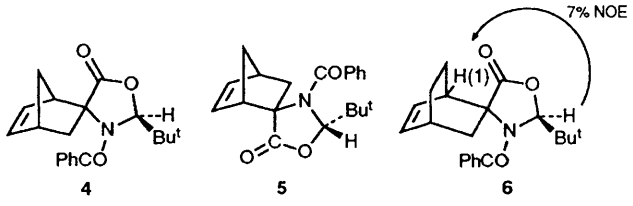


Fig. 1 Molecular projection **4**, 20% thermal ellipsoids are shown for the non-hydrogen atoms. Hydrogen atoms have an arbitrary radii of 0.1 Å.



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

Compound (2*S*)-**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**† could be obtained ($[\alpha]_D^{24}$ −92.6°, *c* 0.49, $CHCl_3$; lit.[5] $[\alpha]_D^{25}$ −148.6°, *c* 1.5, $CHCl_3$; lit.[7] $[\alpha]_D^{25}$ −186.3°, *c* 1.5, $CHCl_3$).[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°, *c* 2.25, $CHCl_3$) 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-1,3-diene 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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† ^1H NMR analysis (400 MHz) indicated **2** was contaminated with 5% of **3**.

‡ *Single crystal X-ray structure determination of* **4**: $C_{20}H_{23}NO_3$, *M* = 325.4, monoclinic, $P2_1/c$, *a* = 6.194(4), *b* = 26.405(9), *c* = 10.847(4) Å, β = 98.31(4)°, *V* = 1756 Å^3, D_c = 1.23 g cm^{-3}, *Z* = 4. 3116 Unique diffractometer data to 2θ max = 50° [monochromatic Mo-Kα radiation, λ = 0.71073 Å, μ = 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* ~ 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.