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# *Z*-2-Phenyl-4-[*(S)*- 2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone as the Dienophile in Asymmetric Diels-Alder Reactions. II

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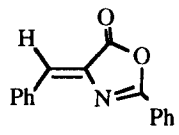
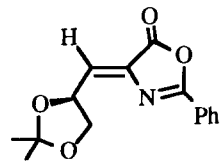
**Abstract:** Diels-Alder reaction of *Z*-2-phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone and Danishefsky's diene is studied. Thermally induced reaction took place at room temperature with a high diastereofacial selectivity and Diels-Alder adducts, obtained in very high diastereomeric purity, were easily transformed into valuable compounds. The stereochemistry of the adducts has been elucidated by single crystal X-ray structure determinations, $^1$H-NMR analysis and mechanistic considerations. Copyright © 1996 Elsevier Science Ltd

With the development of new therapeutic agents based on non-proteinogenic amino acids, the synthesis of new conformationally constrained amino acids has attracted the attention of several research groups.[1] In this context and as a part of our project on the synthesis of cyclic α-amino acids using oxazolones as dienophiles, we reported the Diels-Alder reaction between *(Z)*-2-phenyl-4-benzylidene-5(4H)-oxazolone (**I**) and several dienes[2] to obtain racemic compounds and the Diels-Alder reaction between *(Z)*-2-phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone (**II**) and several dienes[3] to obtain enantiomerically pure compounds.

Encouraged by the indubitable interest in these compounds, the excellent behaviour of *(Z)*-2-phenyl-4-benzylidene-5(4H)-oxazolone (**I**) towards Danishefsky's diene,[2e] and the good reactivity of *(Z)*-2-phenyl-4-[*(S)*- 2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone (**II**) in Diels-Alder reactions with a variety of dienes,[3] we decided to extend our study to the behaviour of the chiral oxazolone towards Danishefsky's diene, directed to the synthesis of new chiral 3-functionalised 4-oxo-1-aminocyclohexancarboxylic acids in enantiomerically pure form.



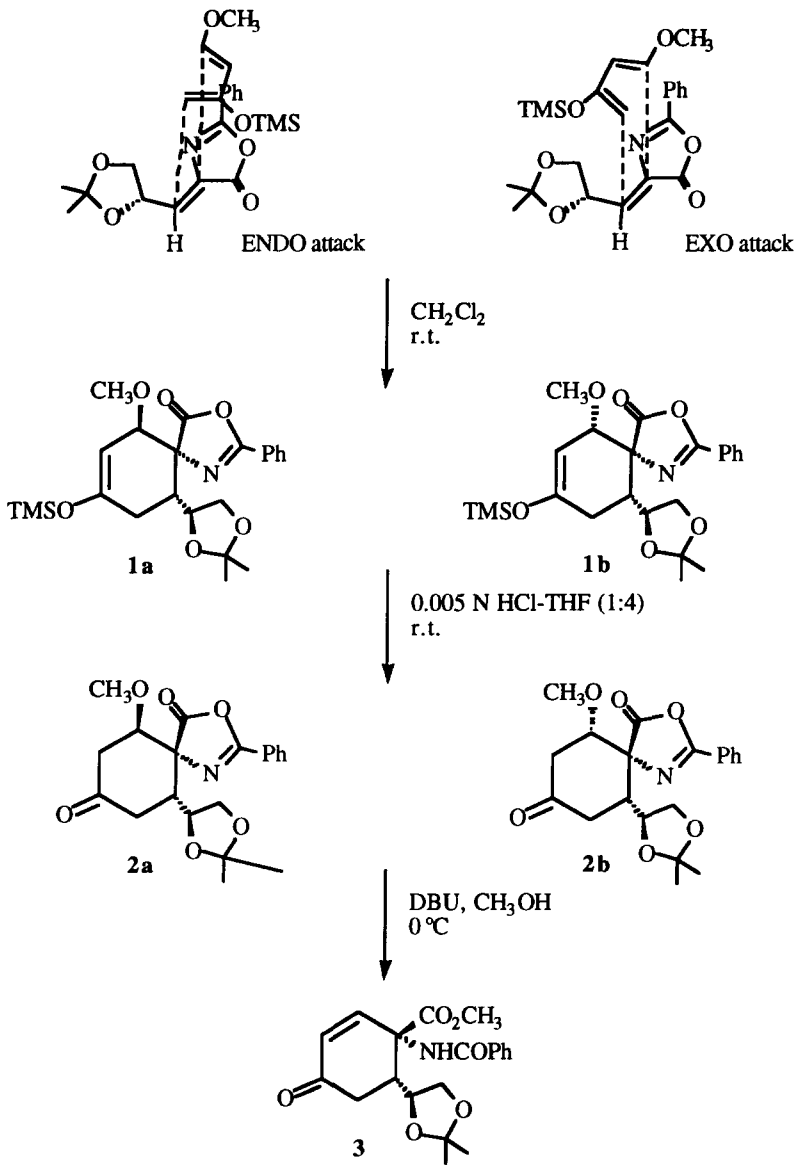

**I**




**II**

**Figure 1**

The thermally induced reaction between chiral oxazolone (**II**) and Danishefsky's diene was performed on a 2:1 mixture of diene and dienophile in dichloromethane at room temperature for 20 min until completion and afforded a 1/1 mixture of cycloadducts **1a** and **1b** which was treated with 0.005N HCl-THF (1:4) solution to give a mixture of **2a** and **2b** in a ratio 1:1 (scheme 1) which were isolated and fully characterised.




**Scheme 1**

Treatment of both isolated compounds **2a** and **2b** with DBU in methanol afforded the same compound **3** although with a different reaction rate. With **2a** the reaction was complete in 5 min whereas for compound **2b** 30 min were required, so we assumed that compound **2a** proceeded from the *endo* attack, and **2b** was the result of the *exo* attack as it has been previously described[2e] that the methoxy group is more easily eliminated when it is in a *pseudo-axial* position as in compound **2a** . The absolute stereochemistry of compounds **1a** , **1b** , **2a** , **2b** and **3** was assumed to be as represented in scheme 1, proceeding from the attack of the diene to the $C_{\alpha\text{-}Re}$ face according to the stereo-correlation model previously proposed[3b] for the

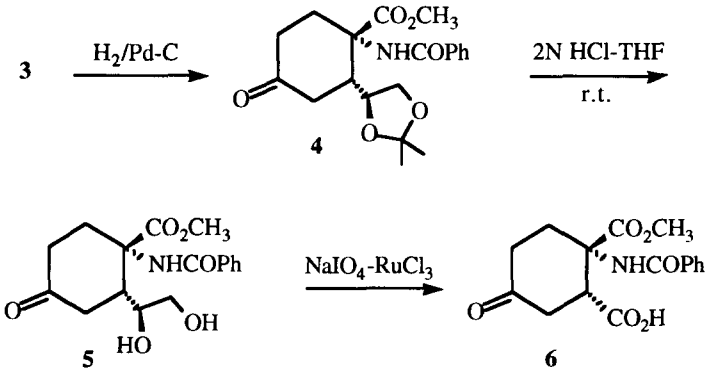
attack of cyclopentadiene on to chiral oxazolone (**II**), which also explains the stereochemical results in the case of cyclohexadiene and several open chain dienes.[3c] This assumption was confirmed later by X-ray analysis of a monocrystal of compound **2b** .

The reaction, initially performed with 1 mmol of compound, can be scaled up and 4 g of oxazolone (**II**) afforded an equimolecular mixture of compounds **1a** and **1b** , from which by successive treatment with a 0.005N HCl-THF (1:4) solution and elimination of the methoxy group with DBU in methanol at 0 °C, enone **3** can be isolated in excellent overall yield (76 %) after column chromatography purification.

Whereas, whilst we were preparing our manuscript, Ortuño *et al*[4] described the same cycloaddition reaction under slightly different conditions, to afford compound **3** with a 48 % overall yield working in a smaller scale (0.5 g of oxazolone).

Typical heterogeneous hydrogenation of the double bond of enone **3** , using 10% palladium-carbon as the catalyst afforded, ketone **4** in nearly quantitative yield. This compound can be a valuable synthetic intermediate in the synthesis of new conformationally constrained 4-oxo-1-aminocyclohexancarboxylic acid, as the 2,2-dimethyl-1,3-dioxolan-4-ylmethylene group can be easily transformed into a variety of functional groups as we have demonstrated[5] in the case of 1-amino cyclopropanecarboxylic derivatives with the same substituent in C-2.

To test the versatility of the intermediate 2,2-dimethyl-1,3-dioxolan-4-ylmethylene group was transformed into a carboxylic acid group, as this compound can be considered a new-conformationally constrained aspartic acid. To this end, ketone **4** was treated with 2N hydrochloric acid in THF to afford compound **5** with a 84 % yield. Consequently, transformation of the 1,2-diol moiety into a carboxylic acid group could be easily performed by treatment of compound **5** with an excess of sodium periodate in the presence of ruthenium trichloride to afford the desired compound with a 82 % yield. (Scheme 2).




**Scheme 2**

In summary, we have shown that the Diels-Alder reactions of chiral azlactone **1** and Danishefsky's diene takes place with a high diastereofacial selectivity which allows diastereomerically pure compounds in high yields to be obtained. These cycloadducts may be valuable synthetic intermediates in the synthesis of cycloaliphatic amino acids as it has been shown in the synthesis of *(1R,2S)*-2-benzamido-2-carbomethoxy-5-oxo-cyclohexan-1-carboxylic acid with about a 70 % overall yield from enone **3** .

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## EXPERIMENTAL

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in deuteriochloroform and referenced with respect to the residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants *(J)* are measured in Hertz. Elemental analyses were performed on a Perkin-Elmer 200 C,H,N,S elemental analyser.
Chemicals: The reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Danishefsky's diene was purchased from the Aldrich Chemical Co. *Z*-2-Phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone **(II)** was obtained according to the literature procedure.[3b] TLC was performed on Merck pre-coated silica gel plates, which were visualised using UV light. Medium pressure chromatography was performed using 230-400 mesh (SDS) silica gel.

**Diels-Alder cycloadditions of chiral oxazolone (II) with Danishefsky's diene.**
Danishefsky's diene (5 g, 29.3 mmol) was added by means of a syringe to a stirred solution of *Z* -2-phenyl-4-[*(S)*- 2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone **(II)** (4 g, 14.65 mmol) in methylene chloride (60 ml) and the mixture was stirred at room temperature for 20 min. After completion the solvent was evaporated under vacuum to give a mixture of cycloadducts, the composition of which was analysed by $^1H$-NMR. The residue was then dissolved in THF (60 ml) and a 0.005 N solution of hydrochloric acid (15 ml) was added. The reaction mixture was stirred for 1h at room temperature and neutralised with saturated $NaHCO_3$. The organic solvent was then evaporated, the residue diluted with dichloromethane (60 ml) and the organic layer dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a mixture of compounds **(2a)** and **(2b)** in an equimolecular ratio which can be used in the next step without purification; yield 4.9 g (90 %). Flash chromatography on silica-gel using hexane-ethyl acetate 7/3 as an eluent afforded analytically pure samples of compounds **2a** and **2b** .

*(1S,2R,6R)*-6-[*(S)*-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methoxy-4-oxo-cyclohexan-1-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} **2a**

Oil; $[\alpha]_D^{25}$ = - 53.0 (c = 1 in $CHCl_3$), lit.[4] $[\alpha]_D$ = - 46.6 (c = 3.97 in $CHCl_3$); IR 1815, 1725, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.34 (s, 3H), 2.31 (ddd, 1H, J = 6.3, J = 3.6, J = 2.4), 2.52 (ddd, 1H, J = 16, J = 3.6, J = 1.5), 2.78 (ddd, 1H, J = 15.7, J = 9.3, J = 0.6), 2.93 (ddd, 1H, J = 15.7, J = 5.7, J = 1.5), 2.95 (ddd, 1H, J = 16, J = 6.3, J = 0.6), 3.30 (s, 3H), 3.59 (dd, 1H, J = 8.4, J = 7.2), 4.03 (dd, 1H, J = 8.4, J = 7.2), 4.09 (dd, 1H, J = 9.3, J = 5.7), 4.71 (ddd, 1H, J = 7.2, J = 7.2, J = 2.4), 7.46-7.52 (m, 2H), 7.56-7.62 (m, 1H), 8.01-8.06 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 24.9, 25.1, 35.7, 41.9, 42.1, 58.3, 67.6, 73.8, 73.9, 78.4, 110.6, 125.6, 128.1, 128.8, 133.0, 161.7, 176.9, 205.4.

*(1S,2S,6R)*-6-[*(S)*-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methoxy-4-oxo-cyclohexan-1-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} **2b**

M.p.= 155-156 °C, lit.[4] m.p.= 148-150 °C; $[\alpha]_D^{25}$ = + 84.0 (c = 1 in $CHCl_3$), lit.[4] $[\alpha]_D$ = + 78.5 (c = 0.56 in $CHCl_3$); IR 1850, 1740, 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.25 (s, 3H), 2.52-2.70 (m, 3H), 2.86 (d, 2H, J = 8.6), 3.27 (s, 3H), 3.73-3.81 (m, 3H), 3.93-4.00 (m, 1H), 7.45-7.51 (m, 2H), 7.55-7.61 (m, 1H), 8.01-8.07 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.6, 39.4, 40.9, 42.9, 57.8, 66.5, 74.3, 74.8, 81.4, 109.3, 125.7, 128.2, 128.8, 132.9, 161.9, 178.8, 205.3.

**Methyl *(1R,6R)*-1-benzamido-6-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-2-cyclohexen-1-carboxylate 3**

To a solution of crude mixture **2a** , **2b** (4.85 g, 13 mmol) in methanol (250 ml) at 0 °C was added DBU (1.97 g, 13 mmol) and the mixture was stirred for 30 min at 0 °C. After evaporation of the solvent, the residue was purified by Flash chromatography on silica gel using hexane-ethyl acetate (1:1) as eluent to afford 4.15 g (85 %) of compound **(3)** as a white solid.

M.p.= 163 °C, lit.[4] m.p.= 168-170 °C; $[\alpha]_D^{25}$ = + 85.4 (c = 1 in $CHCl_3$), lit.[4] $[\alpha]_D$ = + 74.4 (c = 0.86 in $CHCl_3$); IR 3370, 1750, 1710, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 1.53 (s, 3H), 2.49-2.60 (m, 2H), 2.76-2.87 (m, 1H), 3.74 (dd, 1H, J = 8.7, J = 5.8), 3.82 (s, 3H), 4.11 (dd, 1H, J = 8.7, J = 7.3), 4.54 (dd, 1H, J = 8.7, J = 8.7), 6.07 (d, 1H, J = 10.2), 7.40-7.45 (m, 2H), 7.49-7.54 (m, 1H), 7.72 (d, 1H, J = 10.2), 7.76-7.79 (m, 2H), 8.42 (brs, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.8, 32.6, 42.8, 53.4, 61.0, 66.9, 73.9, 110.7, 127.1, 127.9, 128.6, 132.0, 133.3, 147.5, 167.7, 171.7, 197.2.

**Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-cyclohexan-1-carboxylate 4**

A solution of compound **3** (3.94 g, 10.5 mmol) in ethyl acetate (150 ml) was hydrogenated at atmospheric pressure for 8 h using 10 % Pd-C (100 mg) as a catalyst. Removal of the catalyst by filtration and the solvent *in vacuo* gave compound **4** as a white solid in nearly quantitative yield.

M.p.= 115-116 °C; $[\alpha]_D^{25}$ = - 22.2 (c = 1 in $CHCl_3$); IR 3460, 1765, 1735, 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3H), 1.50 (s, 3H), 2.26-2.53 (m, 5H), 2.69 (dd, 1H, J = 16.2, J = 13.5), 3.49 (ddd, 1H, J = 13.5, J = 5.1, J = 2.7), 3.67 (dd, 1H, J = 9, J = 6), 3.78 (s, 3H), 4.04 (dd, 1H, J = 9, J = 7.5), 4.35 (dd, 1H, J = 7.5, J = 6), 7.42-7.48 (m, 2H), 7.50-7.56 (m, 1H), 7.81-7.85 (m, 2H), 7.93 (brs, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 24.6, 25.8, 30.7, 35.5, 36.4, 45.0, 53.0, 63.3, 66.8, 74.5, 110.5, 126.9, 128.6, 131.8, 134.3, 168.3, 172.7, 208.7. Anal. cal. for $C_{20}H_{25}NO_6$ C: 63.99, H: 6.71, N: 3.73; found C: 64.07, H: 6.57, N: 3.64.

**Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-1,2-dihydroxyethyl]-4-oxo-cyclohexan-1-carboxylate 5**

5N Hydrochloric acid (2.5 ml) was added to a solution of compound **4** (1.12 g, 3 mmol) in THF (50 ml) at room temperature and the mixture was stirred for 24 h. After completion, the solution was treated with water and extracted with dichloromethane (3 x 100 ml). The organic layer was dried with anhydrous magnesium sulphate and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column (eluent hexane-ethyl acetate 1:9) afforded the corresponding diol **(5)** (844 mg, 84 %) as a white solid.

M.p.= 68 °C; $[\alpha]_D^{25}$ = + 27.7 (c = 1 in $CHCl_3$); IR 3320, 1740, 1715, 1655 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.98 (brs, 1H), 2.24-2.58 (m, 5H), 2.87 (dd, 1H, J = 17.2, J = 14.8), 3.27 (brs, 1H), 3.44-3.56 (m, 3H), 3.77 (s, 3H), 3.98-4.05 (m, 1H), 7.38-7.45 (m, 2H), 7.45-7.54 (m, 1H), 7.80-7.86 (m, 2H), 8.43 (brs, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 30.5, 36.1, 36.4, 44.0, 53.1, 63.7, 64.4, 71.4, 127.0, 128.7, 132.0, 134.0, 168.7, 173.0, 209.7. Anal. cal. for $C_{17}H_{21}NO_6$ C: 60.89, H: 6.31, N: 4.18; found C: 60.94, H: 6.42, N: 4.28.

***(1R,2S)*-2-Benzamido-2-carbomethoxy-5-oxo-cyclohexan-1-carboxylic acid 6**

Small portions of $NaIO_4$ (2.67 g, 12 mmol) were added to a stirred solution of the corresponding diol **5** (800 mg, 2.5 mmol) in 1:1:3 acetonitrile-carbon tetrachloride-water (75 ml). The biphasic solution was then treated with $RuCl_3 \cdot H_2O$ (34.5 mg, 0.17 mmol) and after being vigorously stirred for 48 h at room temperature, a saturated solution of $NaHCO_3$ was added until pH 8-9 and the mixture was stirred for additional 5 min. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 150 ml). Dichloromethane was then added to the aqueous layer and the mixture was acidified by addition of 6N hydrochloric acid until pH 1-2 and vigorously stirred for 5 min. The organic phase was separated and the aqueous phase thoroughly extracted with dichloromethane (5 x 100 ml). The organic extracts were dried over $MgSO_4$, concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica gel, treated with 6 N hydrochloric acid, column (eluent ethyl acetate ) afforded the corresponding carboxylic acid **6** (654 mg, 82 %) as a white solid.

M.p.= 184-185 °C; $[\alpha]_D^{25}$ = - 11.2 (c = 0.91 in $CHCl_3$); IR 3330, 1725, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.38-2.55 (m, 3H), 2.65-2.80 (m, 2H), 3.17-3.20 (m, 1H), 3.52 (dd, 1H, J = 9, J = 6.6), 3.72 (s, 3H), 7.35-7.45 (m, 2H), 7.45-7.53 (m, 2H), 7.72-7.78 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 30.3, 36.3, 39.2, 47.2, 53.2, 59.7, 127.1, 128.8, 132.3, 133.3, 168.4, 171.6, 174.7, 206.7. Anal. cal. for $C_{16}H_{17}NO_6$ C: 60.18, H: 5.37, N: 4.39; found C: 60.34, H: 5.51, N: 4.42.

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