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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

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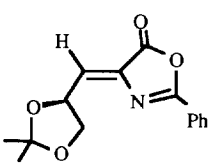
Abstract: Diels-Alder reactions of *Z*-2-phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone and several cyclic and open chain dienes are studied. Less-reactive dienes required longer reaction times and led to isomerization of the *Z*-oxazolone and isolation of products derived from the *E*-isomer; Lewis acid catalysts were used to shorten the reaction times. In all cases high diastereofacial selectivity is observed and Diels-Alder adducts can be obtained in high optical purity. The stereochemistry of adducts has been elucidated by single crystal X-ray structure determinations, ^{1}H-NMR analysis and mechanistic considerations.

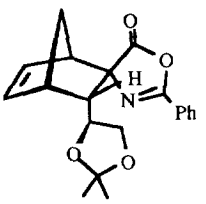
The interesting properties of amino acids with conformational rigidity has attracted the attention of numerous research groups as the incorporation of α,α-dialkylated amino acids into small bioactive peptides leads to conformationally restricted analogues which constitute a well established tool to study biologically active conformations and to develop stable, effective and selective ligands.[1] In particular, cyclic non-metabolizable α-amino acids have useful biological properties and have been used to study the transport of amino acids with hydrophobic side chains.[2] In addition, their incorporation into peptides is a powerful approach for generating analogues of bioactive peptides with enhanced biological activities.[3] Thus, the description of new products with these characteristics or new synthetic procedures to obtain these compounds is a subject of continuous interest. Although some asymmetric syntheses of these cycloaliphatic amino acids have been reported[4] the description of a general approach to their synthesis is still lacking. Encouraged by the undoubtable interest in these compounds we decided to use chiral *Z*-azlactone **1**, derived from glyceraldehyde, as the dienophile in asymmetric Diels-Alder reactions in order to stablish a general approach to the asymmetric synthesis of cycloaliphatic amino acids taking into account the intrinsic functionality of this molecule.



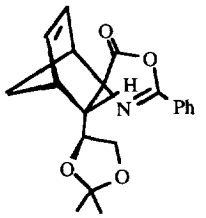
1

In this endeavour we recently reported[5] that *Z*-2-phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone **1** underwent an *exo* selective Diels-Alder reaction with cyclopentadiene. The reaction was highly diastereofacially selective and the major *exo* adduct *(1R,2S,3R,4S)*-3-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]} **(2a)** and the major endo adduct

(1S, 2S, 3R, 4R)- 3- [*(S)*- 2, 2- dimethyl- 1, 3- dioxolan- 4- yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]} (**3a**) could be obtained in optically pure form. Now we have studied the behaviour of this chiral oxazolone as a dienophile in the synthesis of several cyclic and acyclic dienes in order to develop new synthetic routes to optically pure, conformationally rigid amino acid precursors.



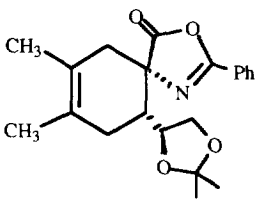
2a



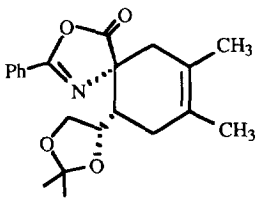
3a

Diels-Alder Reaction of 1 with 2,3-Dimethyl-1,3-butadiene

The thermally induced reaction between oxazolone **1** and 2,3-dimethyl-1,3-butadiene was carried out in dichloromethane until completion at room temperature for two weeks and afforded a 92/8 mixture of the two possible stereoisomeric adducts **4a** and **4b** in 82 % yield, together with an 18 % yield of a third adduct **4c** which was proved to proceed from *E*-oxazolone. When a 3:1 mixture of dioxane:water was used as solvent the reaction was complete in one week and the diastereoselectivity was the same as above.



4a



4b

Next we attempted to increase the rate of the reaction by the addition of a Lewis acid. In a study of catalyst influence previously communicated[5a] we showed that the use of some organometallic compounds, such as $EtAlCl_2$, $AlCl_3$ and $TiCl_4$ involved the formation of cycloadducts from *E*-azlactone together with the four adducts from *Z*-azlactone. Further, the amount of by-products obtained depended on the catalyst employed which was greater when $TiCl_4$ and $AlCl_3$ were used.

When other catalysts, such as ZnI_2, lithium perchlorate (5.0 M in diethyl ether) or boron trifluoride etherate were used no cycloadducts from *E*-azlactone were detected so we decided to use these to perform catalysed Diels-Alder reactions with 2,3-dimethyl-1,3-butadiene.

When the reaction was carried out in the presence of the Lewis acid lithium perchlorate (5.0 M in diethyl ether) the reaction rate increased and only 8 hours were needed to reach total conversion. With this catalyst a decrease in diastereofacial selectivity was observed and a 85/15 mixture of the two possible stereoisomeric adducts **4a** and **4b** was obtained. In this case only traces of cycloadducts from *E*-oxazolone were detected.

When ZnI_2 was used as a catalyst the reaction time for complete consumption of the starting oxazolone was 12 hours. In this case the diastereofacial selectivity was very poor and a 60/40 mixture of the two possible stereoisomeric adducts **4a** and **4b** was obtained.

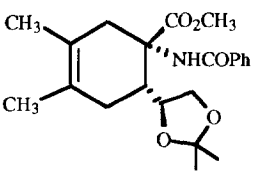
With the use of BF_3·OEt_2 as a boron catalyst only moderate yields of adducts, about 55 %, were detected after 6 days although all the starting dienophile disappeared. We observed a good diastereofecial selectivity (d.r. 92/8) although the presence of the cycloadduct derived from prior isomerization of the dienophile in about 2 % yield was observed.

Table 1. Diels-Alder Reaction of **1** with 2,3-Dimethylbutadiene.

temp	solvent-catalyst	t	yield	d.r.[a]
25 °C	CH_2Cl_2	7 d	93[b]	92/8
25 °C	CH_2Cl_2	14 d	100[b]	92/8
25 °C	dioxane:water (3:1)	7 d	100[b]	91/9
25 °C	ether-$LiClO_4$	8 h	100	85/15
25 °C	CH_2Cl_2-ZnI_2	12 h	96	60/40
25 °C	ether-BF_3·OEt_2	6 d	55[b]	92/8

[a] The product ratio was determined by HPLC. [b] Cycloadducts from *E*-azlactone were observed.

The major diastereomeric adduct **4a** formed in the above reaction in the absence of catalyst or in the presence of lithium perchlorate could be obtained in diastereomerically pure form by medium pressure chromatography. The structure and stereochemistry of its methanolysis product **4a'** was secured by a single-crystal structural determination (Figure 1). This analysis showed that the 2,3-dimethyl-1,3-butadiene had, as expected, added to the least hindered diastereotopic face, i. e. the $C_{\alpha\text{-}Re}$ face.



4a'

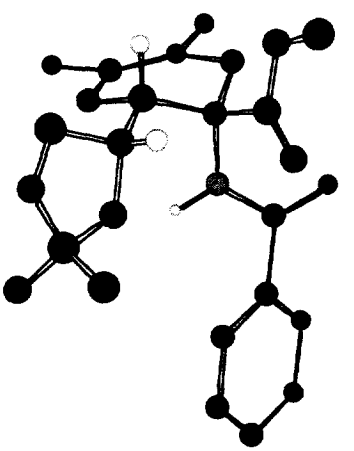
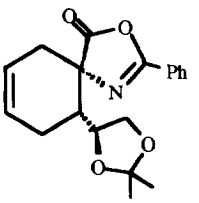


Figure 1

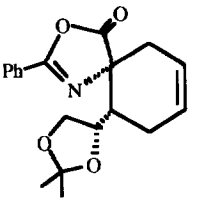
Diels-Alder Reaction of 1 with Butadiene

The thermally induced reaction of **1** with butadiene was not possible as this diene is less reactive than 2,3-dimethyl-1,3-butadiene so we tried catalysed Diels-Alder reactions. Taking into account the results obtained with 2,3-dimethyl-1,3-butadiene, lithium perchlorate was chosen as the catalyst. The reaction in the presence of this

catalyst for 5 days afforded an 81:19 mixture of the two possible stereoisomeric adducts **5a** and **5b** in 92 % yield together with about an 8 % yield of other cycloadducts, derived from cycloaddition on *E*-oxazolone.

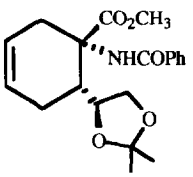


5a



5b

The major diastereoisomer **5a** was shown to have a *(1S, 2R)* stereochemistry from a single crystal structure determination on its methanolysis product **5a'** (figure 2). This stereochemistry results from the attack of the diene onto the $C_{\alpha\text{-}Re}$ face of the dienophile as has been previously observed in the case of other dienes such as cyclopentadiene and 2,3-dimethylbutadiene and is in accordance with the proposed model for the stereochemical course of the Diels-Alder reaction of oxazolone **1** with cyclopentadiene.[5b]



5a'

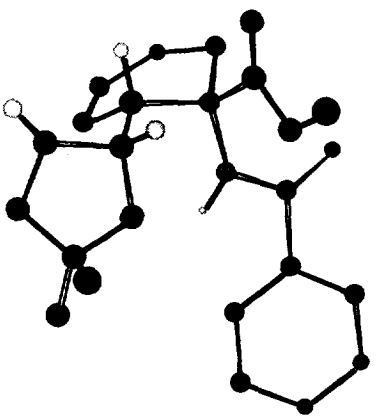


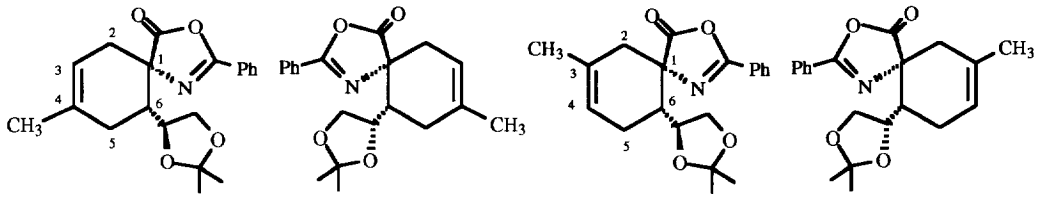
Figure 2

Diels-Alder Reaction of 1 with 2-Methyl-1,3-butadiene

The thermally induced Diels-Alder reaction of oxazolone **1** with 2-methyl-1,3-butadiene at room temperature for 14 days gave an inseparable mixture of several diastereomeric cycloadducts probably derived from *Z*- and *E*-oxazolone which were not analysed. Therefore we tested the lithium perchlorate catalysed reaction and obtained a mixture of the four cycloadducts derived from cycloaddition to *Z*-oxazolone in 90 % yield as well as a small amount, about 10 %, of by-products which were not fully characterized.

The major product, obtained with a 91/9 regioselectivity and a 82/18 diastereofacial selectivity was the 'para' product **6a.** The regiochemistries of **6a, 6b** and **7a** adducts were stablished on the basis of their NMR spectra. The ^{1}H-NMR spectrum of compound **6a** shows complex signals for all protons on the cyclohexane ring which rules out the possibility of a 'meta' regiochemistry that would be characterised by a clean AB system due to the two protons on C_2. In order to confirm the 'para' regiochemistry of compound **6a** a homonuclear COSY

spectrum was obtained. The signal for the methine proton on the C_6 substituent has a cross-peak connection to the signal at 2.56 ppm corresponding to the proton on C_6. This signal is also connected with the multiplet appearing in the 2.20-2.28 ppm region corresponding to the two protons on C_5. The absence of cross-peak connections between the signal corresponding to the protons on C_5 and the signal of the vinylic proton support the regiochemistry proposed for compound **6a**.



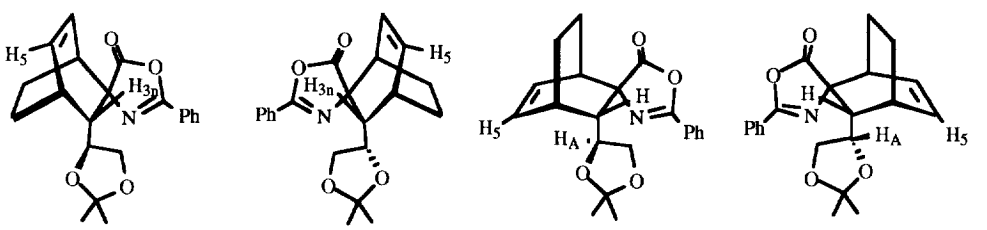
6a **6b** **7a** **7b**

The ^{1}H-NMR of compound **6b** follows a similar pattern to the spectrum of **6a** and leads to the same conclusions. In the case of compound **7a** the ^{1}H-NMR spectrum shows a clean AB system due to the two protons on C_2 (δ, 1.95, 2.60 ppm, J^{AB} = 17.5 Hz), which is consistent with a 'meta' regiochemistry.

The absolute stereochemistries of major 'para' and 'meta' adducts can be assumed by mechanistic considerations by taking into account that the attack of the diene would take place from the $C_{\alpha\text{-}Re}$ face of the dienophile which is sterically less hindered, as in the case of cyclopentadiene, 2,3-dimethylbutadiene, butadiene and, as we shall see later, cyclohexadiene.

Diels-Alder Reaction of 1 with 1,3-Cyclohexadiene

The thermally induced reaction between **1** with 1,3-cyclohexadiene afforded a mixture of four stereoisomers **11a**, **11b**, **12a** and **12b** which were easily isolated by medium-pressure chromatography and fully characterised. When the reaction was performed in methylene chloride at room temperature, examination of the crude reaction mixture by H.P.L.C. indicated a slight preference for *endo* adducts (**11a** + **11b**/**12a** + **12b** = 68:32) as well as a high facial diastereoselectivity for both *endo* (98:2) and *exo* (98:2) adducts although the reaction time for 84% conversion was 7 days. Under these conditions we also observed a considerable amount, about 24 %, of cycloadducts derived from isomerization of the starting *Z*-oxazolone and subsequent Diels-Alder reaction on the *E*-oxazolone. By increasing the reaction time almost total conversion was reached in 21 days although the amount of cycloadducts derived from *E*- oxazolone increased up to 39 %.



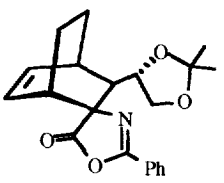
11a **11b** **12a** **12b**

A lithium perchlorate (5.0 M in diethyl ether) catalysed reaction was faster and only 4 days were needed to reach total conversion. With this catalyst a substantial decrease in both *endo* (69/31) and *exo* (75/25)

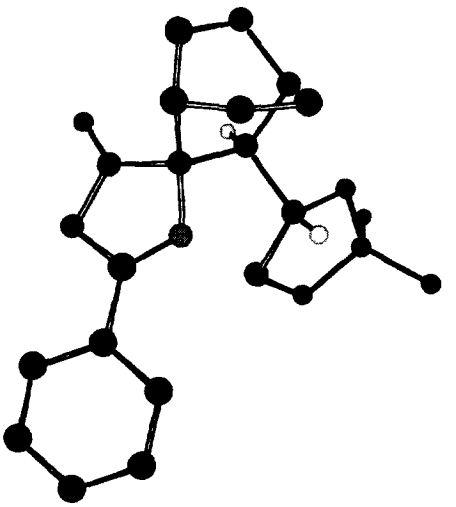
diastereofacial selectivity was observed and although it is known[6] to enhance the *endo/exo* ratio of Diels-Alder reactions the *endo* selectivity remainded in the same range.

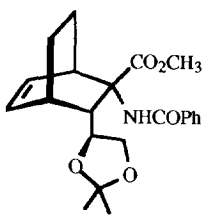
The four adducts from this reaction could be easily obtained in diastereomeric purity by flash chromatography and their endo/exo stereochemistry was unequivocally determined on the basis of the NOE difference ^{1}H NMR experiments. Thus, in those adducts in which the carbonyl group had the *endo* orientation (**11a** and **11b**) the signal due to the olefinic proton H_5 showed a significant NOE enhancement when the H_{3n} proton was selectively irradiated, and in those adducts in which the carbonyl group had the *endo* orientation (**12a** and **12b**) the signal due to the olefinic proton H_5 exhibited a significant NOE enhancement when the H_A proton was selectively irradiated.

The absolute stereochemistries of the *endo* and *exo* adducts **11a** and **12a** were assigned by single crystal X-ray structure determinations of **11a** and **12a'**, the methanolysis product of **12a.** (Figure 3).



11a





12a

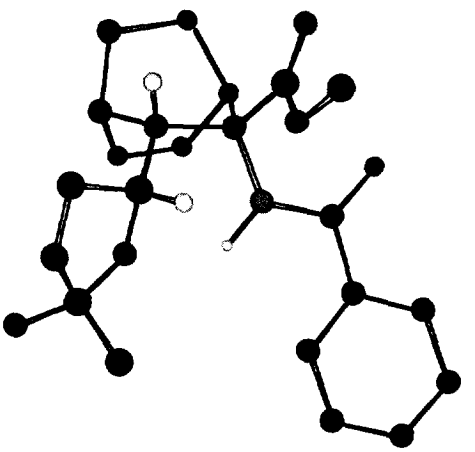


Figure 3

In summary we have shown that the Diels-Alder reactions of chiral azlactone **1** and several dienes takes place with a high diastereofacial selectivity which allows to obtain diastereomerically pure compounds in high yields in most cases. These cycloadducts may be valuable synthetic intermediates in the synthesis of cycloaliphatic amino acids. The establishment of new synthetic routes to conformationally constrained amino acids from these compounds is currently underway and will be published in due course.

Acknowledgement: This work was supported by the Dirección General de Investigación Científica y Técnica, project numbers PB91-0696 and PB94-0578. E.B. would like to express her gratitude to the Diputación General de Aragón for a grant.

EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 spectrometer in deuteriochloroform using the solvent signal as internal standard. Chemical shifts are expressed in ppm. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25°C. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. H.P.L.C. analyses were carried out with a Waters 600-E chromatograph equipped with a photodiode array detector. Elemental analyses were made on a Perkin-Elmer 2400 C,H,N,S elemental analyser.

Chemicals: The reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Dicyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, 2-methyl-1,3-butadiene and Lewis acids used as catalysts were purchased from the Aldrich Chemical Co, butadiene was purchased from Fluka. *Z*-2-Phenyl-4-[*(S)*- 2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone **1** was obtained according to the literature procedure.[5b] TLC was performed on Merck pre-coated silicagel plates, which were visualised using UV light. Medium pressure chromatography was performed using 230-400 mesh (SDS) silicagel.

X-Ray Structure Determinations. In order to determine the absolute stereochemistries of major cycloadducts, single crystal structure determinations on the crystalline compounds obtained, **11a** or its crystalline methanolysis products, **4a'**, **5a'**, and **12a'** were performed. The room temperature single crystal X-ray structure determinations are derivatives of unique diffractometer data sets ($\omega/2\theta$ scan mode; monochromatic Mo Kα radiation, $\lambda = 0.71073$ Å) yielding N independent reflections, N_O of these with $F \geq 4.0\,\sigma(F)$ being considered 'observed'. The structures were solved by direct methods using the SHELXTL PLUS program system in all cases except for **12a'**, which was solved with SIR92. The refinements of **5a'** and **11a** were performed using the SHELXTL PLUS program system, being computed against F ignoring data with F_o less than $4.05(F_o)$. Conventional residuals R, wR on /F/ are quoted at convergence. The structures **4a'** and **12a'** were refined against all F_o^2 values in full matrix least squares using the SHELXL-93 program systems. Residuals R, wR are quoted at convergence. Weighted R-factors (wR) are based on F_o^2, conventional R-factors (R) are based on /F/ with F set to zero for negative F^2. Absorption correction was not applied in any case. Anisotropic thermal paramentrers were refined for C, N, O; $(x, y, z, U_{iso})_H$ were also refined. Derivative connectivities, conformations and stereochemistries are shown pictorially in the figures, geometries being essentially as expected. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. Details of the crystals and refinement are as follows.

4a' - $C_{22}H_{29}NO_5$, M = 387.46. Orthorhombic, space group $P2_12_12_1$, a = 10.424(2), b = 13.774(3), c = 15.038(3) Å, V = 2159.2(8) Å^3, D_c (Z = 4) = 1.192 g/cm^3. $F(000)$ = 832. μ_{Mo} = 0.84 cm^{-1}; crystal size; 0.20 x 0.38 x 0.38 mm. $2\theta_{max}$ = 50°; N = 2645, N_O = 1687; R = 0.0667, wR = 0.1599.

5a' - $C_{20}H_{25}NO_5$, M = 359.4. Orthorhombic, space group $P2_12_12_1$, a = 8.561(2), b = 14.170(3), c = 15.887(3) Å, V = 1927.2(7) Å^3, D_c (Z = 4) = 1.239 g/cm^3. $F(000)$ = 768. μ_{Mo} = 0.89 cm^{-1}; crystal size; 0.32 x 0.40 x 0.50 mm. $2\theta_{max}$ = 50°; N = 2386, N_0 = 1849; R = 0.0441, wR = 0.0564.

11a - $C_{21}H_{23}NO_4$, M = 353.4. Orthorhombic, space group $P2_12_12_1$, a = 9.851(2), b = 12.600(3), c = 14.738(3) Å, V = 1829.3(7) Å^3, D_c (Z = 4) = 1.283 g/cm^3. $F(000)$ = 752. μ_{Mo} = 0.89 cm^{-1}; crystal size; 0.26 x 0.38 x 0.50 mm. $2\theta_{max}$ = 50°; N = 2251, N_0 = 1795; R = 0.0442, wR = 0.0532.

12a' - $C_{22}H_{27}NO_5$, M = 385.45. Orthorhombic, space group $P2_12_12_1$, a = 8.088(2), b = 12.105(2), c = 21.085(4) Å, V = 2064.3(7) Å^3, D_c (Z = 4) = 1.240 g/cm^3. $F(000)$ = 824. μ_{Mo} = 0.88 cm^{-1}; crystal size; 0.50 x 0.44 x 0.32 mm. $2\theta_{max}$ = 45°; N = 2690, N_0 = 2352; R = 0.0418, wR = 0.0987.

General Procedure for thermal Diels-Alder Cycloadditions.

A typical experiment was run as follows: The diene (6 mmol) was added by means of a syringe to a stirred solution of the dienophile (1 mmol) in methylene chloride (4 ml) and the mixture was stirred at room temperature for the time indicated in the text. For analysis the solvent was evaporated under vacuum to give a mixture, the composition of which was analysed by HPLC. Quantitative determinations of stereoisomer ratios and yields were made by using correction factors which were calculated from calibration curves. These were made from the starting dienophile and pure isolated cycloadducts.

General Procedure for Catalysed Diels-Alder Cycloadditions.

A typical experiment was run as follows: The Lewis acid (1 mmol) was added to a stirred solution of dienophile (1 mmol) in methylene chloride (4 ml) and the mixture was stirred at room temperature for 30 min. Then the diene (6 mmol) was added by means of a syringe and the resulting solution was stirred at room temperature for the time indicated in the text. For analysis the mixture was diluted with methylene chloride and $Na_2CO_3.10\ H_2O$ was added to the stirred solution. Then the solution was filtered and the solvent evaporated under vacuum to give a mixture, the composition of which was analysed by HPLC. Quantitative determinations of stereoisomer ratios and yields were made by using correction factors which were calculated from calibration curves. These were made from the starting dienophile and pure isolated cycloadducts.

General Procedure for Lithium Perchlorate Catalysed Diels-Alder Cycloadditions.

A typical experiment was run as follows: The diene (6 mmol) was added to a stirred solution of the dienophile (1 mmol) in a 5M solution of lithium perchlorate in dry ether. The resulting solution was stirred at room temperature for the time indicated in the text. For analysis the mixture was diluted with methylene chloride and silicagel was added to the stirred solution. Stirring was continued for 30 min, the solution was filtered, the solid washed with methylene chloride and the solvent evaporated under vacuum to give a mixture, the composition of which was analysed by HPLC. Quantitative determinations of stereoisomer ratios and yields were made by using correction factors which were calculated from calibration curves. These were made from the starting dienophile and pure isolated cycloadducts.

Cycloadducts from 2,3-dimethyl-1,3-butadiene

(1S,6R)-6-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-dimethylcyclohex-3-en-1-spiro[4'[2'-phenyl-5'(4'H)-oxazolone]] ***(4a)***

Mp 64 °C; $[\alpha]_D$ = + 151.6 (c = 0.5 in $CHCl_3$); IR 1808, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.26 (s, 3H), 1.63 (s, 3H), 1.72 (s, 3H), 1.95 (d, 1H, J = 17.5 Hz), 2.13-2.33 (m, 2H), 2.53 (ddd, 1H,

J = 11 Hz, J = 6.5 Hz, J = 6.5 Hz), 2.65 (d, 1H, J = 17.5 Hz), 3.78 (dd, 1H, J = 8.5 Hz, J = 7.9 Hz), 3.82 (dd, 1H, J = 7.9 Hz, J = 6.0 Hz), 3.99 (ddd, 1H, J = 8.5 Hz, J = 6.5 Hz, J = 6.0 Hz), 7.40-7.48 (m, 2H), 7.50-7.58 (m, 1H), 7.96-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 18.8, 24.8, 25.6, 31.0, 41.5, 42.4, 66.9, 69.8, 75.8, 108.6, 120.8, 124.6, 126.1, 127.9, 128.7, 132.5, 160.3, 181.0. Anal. cal. for $C_{21}H_{25}NO_4$ C: 70.99, H: 7.04, N: 3.94; found C: 70.84, H: 6.75, N: 3.95.

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

Mp 87 °C; $[\alpha]_D$ = - 136.9 (c = 1 in $CHCl_3$); IR 1810, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 3H), 1.33 (s, 3H), 1.63 (s, 3H), 1.69 (s, 3H), 1.76-1.85 (m, 1H), 1.95 (d, 1H, J = 17.5 Hz), 2.06-2.19 (m, 1H), 2.30 (ddd, 1H, J = 11.4 Hz, J = 9.7 Hz, J = 5.7 Hz), 2.68 (d, 1H, J = 17.5 Hz), 3.62 (dd, 1H, J = 7.8 Hz, J = 6.9 Hz), 3.70 (ddd, 1H, J = 9.7 Hz, J = 6.9 Hz, J = 5.7 Hz), 3.97 (dd, 1H, J = 7.8 Hz, J = 5.7 Hz), 7.40-7.48 (m, 2H), 7.50-7.56 (m, 1H), 7.98-8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.4, 18.8, 25.6, 25.9, 31.2, 41.8, 44.2, 68.0, 69.6, 76.5, 109.5, 121.5, 123.4, 126.5, 128.0, 128.6, 132.4, 161.1, 181.4. Anal. cal. for $C_{21}H_{25}NO_4$ C: 70.99, H: 7.04, N: 3.94; found C: 70.90, H: 7.14, N: 4.03.

Cycloadducts from 1,3-butadiene

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

Oil; $[\alpha]_D$ = + 156.3 (c = 1 in $CHCl_3$); IR 1814, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.27 (s, 3H), 2.08-2.19 (m, 1H), 2.28-2.40 (m, 2H), 2.52 (ddd, 1H, J = 10.2 Hz, J = 6.6 Hz, J = 6.6 Hz), 2.60-2.70 (m, 1H), 3.77 (dd, 1H, J = 8.2 Hz, J = 8.2 Hz), 3.87 (dd, 1H, J = 8.2 Hz, J = 6.2 Hz), 4.02 (ddd, 1H, J = 8.2 Hz, J = 6.6 Hz, J = 6.2 Hz), 5.64-5.74 (m, 1H), 5.84-5.94 (m, 1H), 7.40-7.48 (m, 2H), 7.50-7.58 (m, 1H), 7.96-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.6, 24.9, 25.7, 36.1, 40.9, 67.2, 69.0, 75.7, 108.6, 121.8, 125.9, 126.0, 127.9, 128.7, 132.6, 160.4, 180.8. Anal. cal. for $C_{19}H_{21}NO_4$ C: 69.72, H: 6.42, N: 4.28; found C: 69.84, H: 6.31, N: 4.42.

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

Mp 93 °C; $[\alpha]_D$ = - 168.8 (c = 0.5 in $CHCl_3$); IR 1815, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.33 (s, 3H), 2.01-2.20 (m, 3H), 2.33 (ddd, 1H, J = 9.5 Hz, J = 9.5 Hz, J = 6.6 Hz), 2.64-2.76 (m, 1H), 3.63 (dd, 1H, J = 7.8 Hz, J = 6.7 Hz), 3.71 (ddd, 1H, J = 9.5 Hz, J = 6.7 Hz, J = 5.7 Hz), 3.97 (dd, 1H, J = 7.8 Hz, J = 5.7 Hz), 5.70-5.78 (m, 1H), 5.82-5.88 (m, 1H), 7.40-7.48 (m, 2H), 7.50-7.60 (m, 1H), 7.80-8.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.8, 25.6, 25.9, 35.7, 43.3, 67.9, 68.6, 76.5, 109.6, 122.4, 124.7, 126.2, 128.1, 128.6, 132.5, 161.4, 181.0. Anal. cal. for $C_{19}H_{21}NO_4$ C: 69.72, H: 6.42, N: 4.28; found C: 69.98, H: 6.59, N: 4.17.

Cycloadducts from 2-methyl-1,3-butadiene

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

Oil; $[\alpha]_D$ = + 173.2 (c = 0.5 in $CHCl_3$); IR 1813, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.27 (s, 3H), 1.78 (s, 3H), 2.06-2.15 (m, 1H), 2.20-2.28 (m, 2H), 2.56 (ddd, 1H, J = 9.9 Hz, J = 6.6 Hz, J = 6.6 Hz), 2.60-2.70 (m, 1H), 3.77 (dd, 1H, J = 8.1 Hz, J = 8.1 Hz), 3.87 (dd, 1H, J = 8.1 Hz, J = 6.3 Hz), 4.03 (ddd, 1H, J = 8.1 Hz, J = 6.6 Hz, J = 6.3 Hz), 5.37-5.39 (m, 1H), 7.42-7.49 (m, 2H), 7.50-7.58 (m, 1H), 7.95-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 24.8, 25.7, 29.4, 36.6, 41.4, 67.0, 68.9, 75.7, 108.5, 115.8, 126.0, 127.9, 128.6, 132.5, 133.0, 160.4, 181.0. Anal. cal. for $C_{20}H_{23}NO_4$ C: 70.38, H: 6.74, N: 4.11; found C: 70.56, H: 6.83, N: 4.05.

(1S,6R)-6-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-methylcyclohex-3-en-1-spiro{4'[2'-phenyl-5'(4'H)-oxazolone} ***(7a)*** [7]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.26 (s, 3H), 1.69 (s, 3H), 1,95 (d, 1H, J = 17.5 Hz), 2.24-2.36 (m, 2H), 2.43-2.52 (m, 1H), 2.60 (d, 1H, J = 17.5 Hz), 3.78 (dd, 1H, J = 8.1 Hz, J = 8.1 Hz), 3.85 (dd, 1H, J = 8.1 Hz, J = 6.3 Hz), 4.02 (ddd, 1H, J = 8.1 Hz, J = 6.6 Hz, J = 6.3 Hz), 5.55-5.62 (m, 1H), 7.42-7.49 (m, 2H), 7.50-7.58 (m, 1H), 7.95-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 24.8, 25.7, 29.7, 40.7, 41.0, 67.1, 69.6, 75.7, 108.6, 119.9, 126.1, 128.0, 128.7, 132.6, 133.2, 160.4, 181.1.

(1R,6S)-6-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-methylcyclohex-3-en-1-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} ***(6b)*** [7]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.33 (s, 3H), 1.75 (s, 3H), 1.79-1.875 (m, 1H), 2.04-2.12 (m, 2H), 2.35 (ddd, 1H, J = 11.4 Hz, J = 9.3 Hz, J = 5.7 Hz), 2.65-2.72 (m, 1H), 3.63 (dd, 1H, J = 7.5 Hz, J = 6.9 Hz), 3.71 (ddd, 1H, J = 9.6 Hz, J = 6.9 Hz, J = 5.7 Hz), 3.97 (dd, 1H, J = 7.5 Hz, J = 5.7 Hz), 5.40-5.43 (m, 1H), 7.42-7.49 (m, 2H), 7.50-7.58 (m, 1H), 7.95-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 25.5, 25.8, 29.5, 36.1, 43.9, 67.8, 68.5, 77.3, 109.5, 116.5, 126.3, 127.9, 128.5, 131.8, 132.3, 161.1, 181.4.

Cycloadducts from 1,3-cyclohexadiene

(1S,2S,3R,4R)-3-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.2]-oct-5-en-2-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} ***(11a)***

Mp 129 °C; $[\alpha]_D$ = + 14.2 (c = 1 in $CHCl_3$); IR 1812, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12-1.30 (m, 2H), 1.29 (s, 3H), 1.32 (s, 3H), 1.92-1.97 (m, 1H), 1.94 (ddd, 1H, J = 10.5 Hz, J = 1.8 Hz, J = 1.8 Hz)), 1.98-2.10 (m, 1H), 2.18-2.28 (m, 1H), 2.42-2.48 (m, 1H), 3.02-3.08 (m, 1H), 3.07 (dd, 1H, J = 7.7 Hz, J = 6.6 Hz), 3.78 (dd, 1H, J = 7.7 Hz, J = 6.2 Hz), 4.38 (ddd, 1H, J = 10.5 Hz, J = 6.6 Hz, J = 6.2 Hz), 6.30 (ddd, 1H, J = 7.8 Hz, J = 6.9 Hz, J = 1.2 Hz), 6.63 (ddd, 1H, J = 7.8 Hz, J = 6.9 Hz, J = 1.2 Hz), 7.42-7.50 (m, 2H), 7.52-7.60 (m, 1H), 7.94-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 21.5, 25.4, 26.7, 31.3, 40.7, 51.4, 68.6, 70.6, 73.4, 108.6, 125.8, 127.8, 128.8, 130.3, 132.8, 137.5, 160.1, 180.8. Anal. cal. for $C_{21}H_{23}NO_4$ C: 71.39, H: 6.52, N: 3.97; found C: 71.50, H: 6.34, N: 3.95.

(1R,2S,3R,4S)-3-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.2]-oct-5-en-2-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} ***(12a)***

Mp 126 °C; $[\alpha]_D$ = + 121.0 (c = 0.5 in $CHCl_3$); IR 1805, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06-1.18 (m, 1H), 1.25 (s, 3H), 1.33 (s, 3H), 1.32-1.44 (m, 1H), 1.69-1.79 (m, 1H), 2.18-2.28 (m, 1H), 2.20 (dd, 1H, J = 10.3 Hz, J = 1.5 Hz), 2.45-2.50 (m, 1H), 3.07 (dd, 1H, J = 7.9 Hz, J = 6.6 Hz), 3.08-3.13 (m, 1H), 3.70 (dd, 1H, J = 7.9 Hz, J = 6.4 Hz), 3.91 (ddd, 1H, J = 10.3 Hz, J = 6.6 Hz, J = 6.4 Hz), 6.39 (ddd, 1H, J = 7.5 Hz, J = 6.9 Hz, J = 0.9 Hz), 6.51 (m, 1H, J = 7.5 Hz, J = 7.5 Hz), 7.40-7.48 (m, 2H), 7.50-7.58 (m, 1H), 7.90-7.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9, 23.7, 25.1, 26.7, 32.2, 40.3, 53.5, 68.2, 73.2, 76.0, 108.3, 125.7, 127.8, 128.8, 132.7, 132.9, 160.1, 180.2. Anal. cal. for $C_{21}H_{23}NO_4$ C: 71.39, H: 6.52, N: 3.97; found C: 71.29, H: 6.22, N: 3.98.

(1R,2R,3S,4S)-3-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.2]-oct-5-en-2-spiro{4'[2'-phenyl-5'(4'H)-oxazolone]} ***(11b)***

Mp 90 °C; $[\alpha]_D$ = - 16.2 (c = 1 in $CHCl_3$); IR 1813, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3H), 1.08-1.20 (m, 1H), 1.16 (s, 3H), 1.22-1.34 (m, 1H), 1.78-1.88 (m, 1H), 1.94 (ddd, 1H, J = 10.6 Hz, J = 1.8 Hz, J = 1.8 Hz), 2.29-2.38 (m, 1H), 2.40-2.44 (m, 1H), 2.52-2.58 (m, 1H), 3.53 (dd, 1H, J = 7.8 Hz, J = 7.8 Hz), 3.99 (dd, 1H, J = 7.8 Hz, J = 5.7 Hz), 4.34 (ddd, 1H, J = 10.6 Hz, J = 7.8 Hz, J = 5.7 Hz), 6.35

(m, 1H, J = 7.2 Hz, J = 7.2 Hz), 6.55 (m, 1H, J = 7.5 Hz, J = 7.5 Hz), 7.40-7.48 (m, 2H), 7.48-7.56 (m, 1H), 7.94-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 22.8, 25.6, 26.6, 32.0, 39.2, 53.2, 68.3, 70.4, 73.7, 108.6, 126.8, 127.7, 128.5, 131.3, 132.1, 136.6, 159.6, 181.9. Anal. cal. for $C_{21}H_{23}NO_4$ C: 71.39, H: 6.52, N: 3.97; found C: 71.42, H: 6.48, N: 3.79.

*(1S,2R,3S,4R)-3-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.2]-oct-5-en-2-spiro[4'[2'-phenyl-5'(4'H)-oxazolone]] **(12b)***

Oil; $[\alpha]_D$ = - 106.4 (c = 0.5 in $CHCl_3$); IR 1808, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (s, 3H), 1.08-1.22 (m, 1H), 1.21 (s, 3H), 1.28-1.38 (m, 1H), 1.70-1.82 (m, 1H), 2.28-2.38 (m, 1H), 2.31 (m, 1H), 2.47-2.53 (m, 1H), 2.57-2.64 (m, 1H), 3.60 (dd, 1H, J = 7.8 Hz, J = 7.5 Hz), 3.86 (ddd, 1H, J = 9.4 Hz, J = 7.5 Hz, J = 5.8 Hz), 3.96 (dd, 1H, J = 7.8 Hz, J = 5.8 Hz), 6.34-6.42 (m, 2H), 7.38-7.46 (m, 2H), 7.48-7.54 (m, 1H), 7.90-7.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7, 25.4, 26.1, 26.6, 31.9, 39.4, 53.1, 68.1, 73.9, 75.9, 108.4, 126.5, 127.8, 128.5, 131.7, 132.2, 133.2, 159.6, 181.1. Anal. cal. for $C_{21}H_{23}NO_4$ C: 71.39, H: 6.52, N: 3.97; found C: 71.30, H: 6.60, N: 3.94.

General Procedure for Methanolysis of Cycloadducts

A suspension of the cycloadduct (10 mmol) in a solution of sodium methoxide (20 mg) in absolute methanol (80 ml) was stirred at room temperature for 30 min. After completion the solution was concentrated *in vacuo* and the residue was disolved in methylene chloride washed with water dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the methanolysis product in nearly quantitative yield.

*Methyl (1S,2R)-1-benzamido-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,5-dimethyl-4-cyclohexen-1-carboxylate **(4a')***

Mp 130 °C; $[\alpha]_D$ = - 22.6 (c = 1 in $CHCl_3$); IR 1742, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.52 (s, 3H), 1.59 (s, 3H), 1.63 (s, 3H), 1.95-2.06 (m, 1H), 2.10-2.20 (m, 1H), 2.24-2.40 (m, 1H), 2.76 (d, 1H, J = 17.4 Hz), 3.45 (d, 1H, J = 17.4 Hz), 3.74 (s, 3H), 3.77 (dd, 1H, J = 8.4 Hz, J = 6.6 Hz), 4.02 (dd, 1H, J = 8.4 Hz, J = 7.2 Hz), 4.24 (ddd, 1H, J = 7.2 Hz, J = 6.6 Hz, J = 1.2 Hz), 7.36-7.50 (m, 3H), 7.48 (brs, 1H), 7.74-7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.5, 18.7, 24.7, 25.9, 26.5, 37.3, 41.4, 52.6, 63.3, 67.1, 75.2, 109.8, 121.8, 122.9, 126.9, 128.3, 131.2, 135.3, 167.6, 173.8. Anal. cal. for $C_{22}H_{29}NO_5$ C: 68.21, H: 7.49, N: 3.62; found C: 68.53, H: 7.35, N: 3.78.

*Methyl (1S,2R)-1-benzamido-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-cyclohexen-1-carboxylate **(5a')***

Mp 128 °C; $[\alpha]_D$ = - 12.4 (c = 1 in $CHCl_3$); IR 1725, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.51 (s, 3H), 1.95-2.60 (m, 1H), 2.14-2.24 (m, 2H), 2.33-2.46 (m, 1H), 2.76 (d, 1H, J = 18.8 Hz), 3.65 (dd, 1H, J = 18.8 Hz, J = 4.65 Hz), 3.75 (s, 3H), 3.70-3.79 (m, 1H), 4.03 (dd, 1H, J = 8.2 Hz, J = 7.2 Hz), 4.24 (dd, 1H, J = 7.2 Hz, J = 6 Hz), 5.58-5.71 (m, 2H), 7.37-7.53 (m, 3H), 7.51 (brs, 1H), 7.75-7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 24.7, 25.9, 31.3, 40.9, 52.7, 62.7, 67.0, 75.3, 110.0, 123.6, 123.9, 126.9, 128.4, 131.4, 135.2, 167.8, 173.8. Anal. cal. for $C_{20}H_{25}NO_5$ C: 66.85, H: 6.96, N: 3.90; found C: 66.70, H: 7.06, N: 4.08.

*Methyl (1R,2S,3R,4S)-2-benzamido-3-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.2]-oct-5-en-2-carboxylate **(12a')***

Mp 120 °C; $[\alpha]_D$ = - 12.4 (c = 1 in $CHCl_3$); IR 1748, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 3H), 1.23-1.26 (m, 2H), 1.41 (s, 3H), 1.45-1.60 (m, 1H), 1.90-2.04 (m, 1H), 2.49-2.51 (m, 1H), 2.70-2.72 (m, 1H), 3.32-3.34 (m, 1H), 3.70 (dd, 1H, J = 8.0 Hz, J = 7.7 Hz), 3.76 (s, 3H), 4.02 (dd, 1H, J = 8.0 Hz, J = 7.2 Hz), 4.46 (ddd, 1H, J = 7.7 Hz, J = 7.2 Hz, J = 1.7 Hz), 6.05- 6.10 (m, 1H), 6.44- 6.50 (m, 1H), 7.13

(brs, 1H), 7.35-7.46 (m, 3H), 7.65-7.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 24.9, 26.1, 26.5, 30.3, 37.7, 49.2, 52.5, 65.2, 67.8, 74.2, 109.3, 127.0, 128.4, 128.6, 131.4, 134.0, 137.8, 166.4, 173.0. Anal. cal. for $C_{22}H_{27}NO_5$ C: 68.57, H: 7.01, N: 3.64; found C: 68.43, H: 6.97, N: 3.82.

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7. Spectral data obtained from very enriched mixtures of cycloadducts

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