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Exo Diastereoselective Diels-Alder Reactions of (R)-2-Phenyl-4-Methylene-Oxazolidin-5-one

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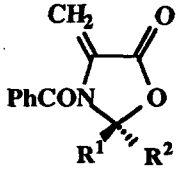
Abstract: The thermally induced Diels-Alder reactions of (R)-2-phenyl-4-methylene-oxazolidin-5-one 2 and substituted 1,3-cyclohexadienes and substituted 1,3-butadienes gives exo diastereomeric Diels-Alder adducts. In some cases the initially formed adducts undergo epimerization at the amino-acetal carbon, however the stereochemical integrity of the quaternary α-amino acid stereogenic centre is maintained and Diels-Alder adducts can be obtained in high enantiomeric purity (> 90% ee). The stereochemistry of these adducts has been elucidated by single crystal X-ray structure determinations and 2D ^{1}H NMR analysis.

Recently we reported that (S)-tert-butyl- and (R)-2-phenyl-4-methylene-oxazolidin-5-one, 1 and 2 respectively, underwent highly exo diastereoselective Diels-Alder reactions with cyclopentadiene.[1,2] The resulting Diels-Alder adducts could be converted to (2R)- and (2S)-2-aminonorbornane-2-carboxylic acid, respectively, in high enantiomeric purity.[2] Mattay[3] and Roush[4] have also reported highly exo selective Diels-Alder reactions on related 2-alkyl-5-methylene-1,3-dioxolan-4-ones and cyclic and acyclic dienes. The thermally induced reaction of 1 and 1,3-cyclohexadiene at 130°C was also highly exo-diastereoselective.[1] In contrast, the reaction of 2 and 1,3-cyclohexadiene at 130°C gave a mixture of two diastereomeric Diels-Alder adducts in a ratio of 67 : 33 that could not be readily separated. The stereochemistry of the major diastereomer was assigned the exo stereochemistry by analogy with the Diels-Alder chemistry of 1. The stereochemistry of the minor diastereoisomer, however, was uncertain and the reasons for the apparent poor diastereoselectivity in this latter reaction were not clear at the time of our earlier investigation. In this paper we report our findings from the reinvestigation of this reaction and the stereochemistry of the Diels-Alder reactions of 2 and substituted 1,3-cyclohexadienes by single-crystal X-ray structure determinations and 2 and substituted 1,3-butadienes by 2D ^{1}H NMR analysis.

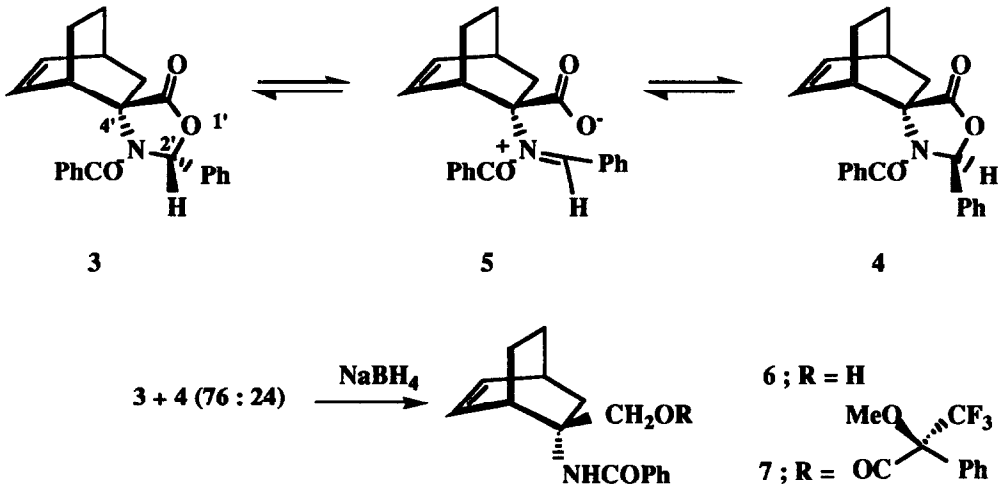


1 ; R ^{1} = Bu ^{t}, R ^{2} = H

2 ; R ^{1} = H, R ^{2} = Ph

Diels-Alder Reactions of 2 and Substituted 1,3-Cyclohexadienes

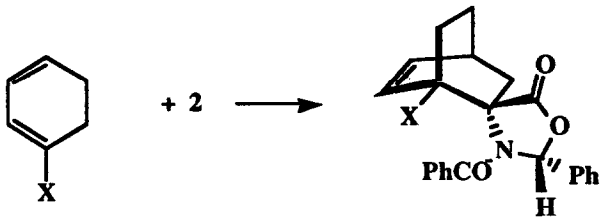
The thermally induced reaction of 2 and 1,3-cyclohexadiene gave two diastereomeric products. The ratio of these products was dependent upon the reaction temperature. When this reaction was performed at 130°C, the two diastereomeric adducts were obtained in a ratio of 67 : 33. This diastereomeric ratio was more favourable (74 : 26) at 60°C; although the reaction time for complete consumption of 2 was dramatically increased (15 days, Table). The major adduct from this reaction could be obtained diastereomerically pure by semi-preparative HPLC. When a solution of this single diastereoisomer was heated at 100°C or 130°C for 24 hr, a mixture (55 : 45) resulted of two diastereomeric products that were identical to the major and minor diastereomeric adducts, respectively, that were obtained from the Diels-Alder reaction of 2 and 1,3-cyclohexadiene. Reduction of the 74 : 26 mixture of diastereoisomers, that was obtained from the above Diels-Alder reaction at 60°C, with sodium borohydride ($NaBH_4$) gave the alcohol 6 in > 97% diastereoisomeric purity as judged from ^1H NMR analysis (400 MHz). The enantiomeric purity of this compound was determined to be 90% from ^1H NMR analysis of its Mosher ester 7 (95 : 5 mixture of diastereoisomers).[5]



The above experiments clearly demonstrate that the two diastereomeric Diels-Alder adducts had the same configuration at C4' and were epimeric at the amino-acetal carbon C2'. The major and minor diastereomeric Diels-Alder adducts are therefore structures 3 and 4 respectively. The poor diastereoselectivity in the Diels-Alder reaction of 2 and 1,3-cyclohexadiene is hence the consequence of a thermally induced epimerization, at C2', of the initially formed exo adduct 3 and is not due to the formation of the diastereomeric endo adduct. The thermally induced ring opening of the oxazolidinone ring of 3 to give an intermediate iminium ion 5, which could ring close to give either 3 or 4, would be facilitated by the C2' phenyl group which can stabilize the incipient carbocation ring-opened intermediate (5). Furthermore, the enantiomeric

purity of the alcohol 6 indicates that the extent of epimerization at C2 in the starting dienophile 2 is about 3-4% at 60°C over 15 days since the enantiomeric purity of 2 is > 97%.[2]

The Diels-Alder reactions of 2 and 1-methoxy- or 1-trimethylsilyloxy-1,3- cyclohexadiene at 60°C were highly regioselective and diastereoselective and gave 8 and 9 respectively, as the major diastereomeric adducts (Table). The diastereoselectivity of the latter reaction (diastereomeric ratio (d.r.) 97 : 3) was greater than that of the former reaction (d.r. 89 : 11).



8 ; X = OMe (d.r. = 89 : 11)
9 ; X = OTMS (d.r. = 97 : 3)

The structure and stereochemistry of the major diastereomeric adduct 8, from 1-methoxy-1,3-cyclohexadiene and 2, was established by a single crystal X-ray structural determination (Fig 1). The structural analysis showed that the diene had added to the face of the 4-methylene group that was anti to the C2' phenyl group and that the 'ortho' regioisomer had been obtained. The structure determination also showed that the oxazolidinone carbonyl group in 8 was exo to the ethano bridge of the bicyclo[2.2.2]octenyl ring system (Fig 1). The stereochemistry assigned to 9 was based on the similarity between its ^{1}H NMR spectra and that of 8 . In contrast to 3, heating a solution of 8 at 100°C for 24 hr resulted in the recovery of only diastereomerically pure starting material and no products that would result from epimerization at C2' could be detected. It seems likely the bridgehead MeO or TMSO in 8 and 9 respectively is responsible for an increase in the energy barrier for ring opening of the oxazolidinone ring in these compounds. This could be possibly due to an increase in steric interactions between the bridgehead substituent and the Ph and PhCO substituents about the developing iminium ion (cf 5). The minor cycloadducts from the above two reactions could not be isolated diastereomerically pure and therefore their structures could not be unequivocally determined.

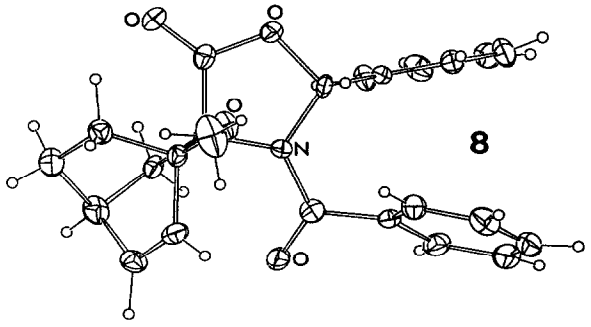


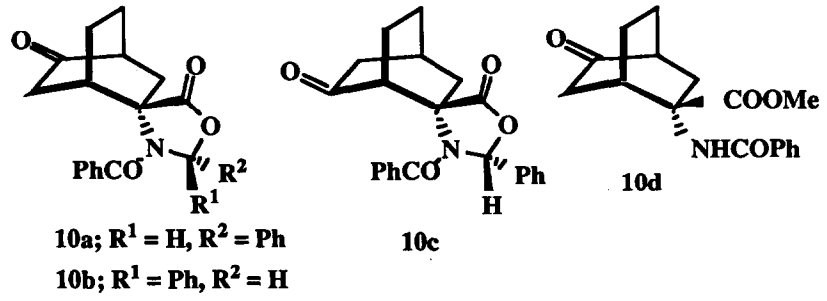
Figure 1. Molecular projection of 8, normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radius of 0.1 Å.

The Diels-Alder reaction of 2-trimethylsilyloxy-1,3-cyclohexadiene and 2 at 60°C, followed by hydrolysis of the crude reaction products with dilute acid, gave a mixture of four diastereomeric adducts (d.r. 50 : 26 : 12 : 12; Table). The major diastereoisomer 10a was shown to have the 'para' structure and exo stereochemistry, as depicted in structure 10a from a single crystal structure determination (Fig 2). One of the minor diastereoisomers was determined to be the 'meta' regioisomer 10c from COSY ^{1}H NMR analysis and the other C2' epi 10a (10b) by conversion of both 10a and 10b with MeOH/K_2CO_3 to the methyl ester 10d. This ester was different to that obtained from 10c.

Table. Diels-Alder products from the reaction of 2 and dienes at 60°C.

Entry	Diene	Time (days)	Yield(%)[a]	Diastereoselection[b] (products)
1	1,3-cyclohexadiene	15	60	74 : 26 (3, 4)
2	1-methoxy-1,3-cyclohexadiene	8	81	89 : 11 (8, c)
3	1-trimethylsilyl-oxy-1,3-cyclo-hexadiene	15	84	97 : 3 (9, c)
4	2-trimethylsilyl-oxy-1,3-cyclo-hexadiene	25	37[d]	50 : 26 : 12 : 12 (10a, 10c, 10b, c)
5		8 (80°C)	45[d]	19 : 24 : 47 : 10 (10a, 10c, 10b, c)
6	2,3-dimethyl-1,3-butadiene	1 (130°C)	ND	50 : 50
7		1(100°C)	52	86 : 14
8		2 (80°C)	59	91 : 9
9		9	81	97 : 3 (11, 12)
10	2-methyl-1,3-butadiene	10	96	66 : 32 : 3 (15, 16, c)
11	1-methyl-1,3-butadiene	15	50	94 : 6 (17a, 18a)
12	1-methoxy-1,3-butadiene	10	51	82 : 18 (17b, 18b)
13	1-methoxy-3-trimethylsilyloxy-1,3-butadiene	2	40[d]	50 : 50 (19, 20)

[a] After purification. [b] Determined on the crude reaction mixture by ^{1}H NMR (400 MHz).
[c] The structure of the minor isomer is uncertain. [d] Yield after acid hydrolysis.



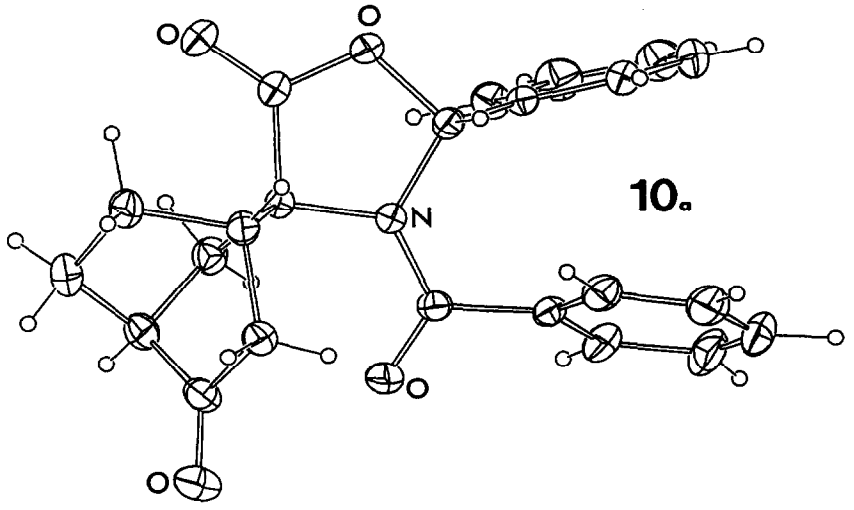
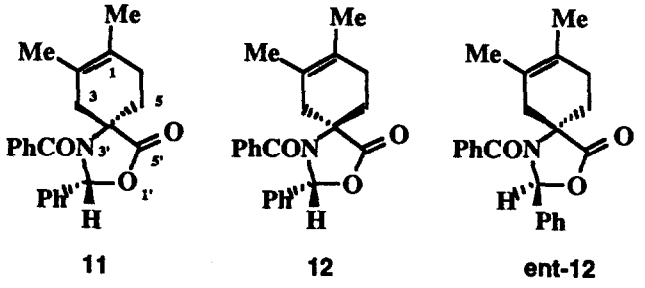


Figure 2. Molecular projection of 10a normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radius of 0.1 Å.

Diels-Alder Reactions of 2 and Substituted 1,3-Butadienes.

The thermally induced reaction of 2 and 2,3-dimethyl-1,3-butadiene gave two diastereomeric products. The diastereomeric ratio of these products was dependent upon the reaction temperature (Table). The reaction at 130°C for 24 hr, resulted ina 50 : 50 mixture of diastereoisomers, while at 60°C over a period of 9 days the diastereomeric ratio was 97 : 3. The major diastereomeric adduct 11 from the above reaction at 60°C could be obtained diastereomerically pure by recrystallization. The structure and stereochemistry of this compound was secured by a single-crystal structural determination (Fig. 3). This analysis showed that the 2,3-dimethyl-1,3-butadiene had, as expected, added to the least hindered diastereotopic face of the 4-methylene group of 2. This solid state structure revealed the N-benzoyl group of the oxazolidinone ring was pseudo-equatorial with respect to the cyclohexene ring moiety of 11. This structure is concordant with the solution structure of 11 from ^{1}H NMR analysis that showed both H3β and H5β are strongly deshielded (δ 3.36 and δ 3.15,

respectively, compared to H3α (δ 2.24) and H5α (δ 2.12)), which is consistent with the close disposition of these former two protons and the benzoyl carbonyl group in the solid state structure. This solid state structure has been extremely useful for assigning the stereochemistry of other Diels-Alder adducts of 2 and 1-substituted-1,3-butadienes.



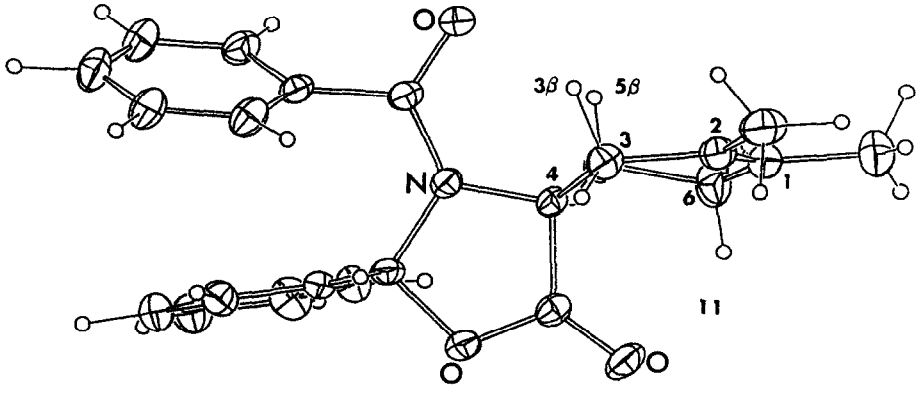
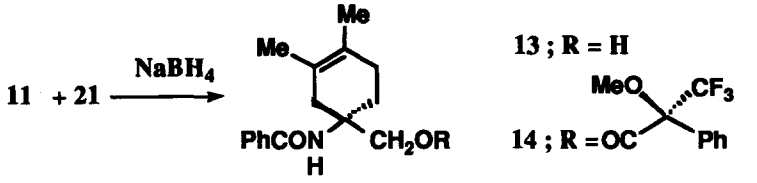


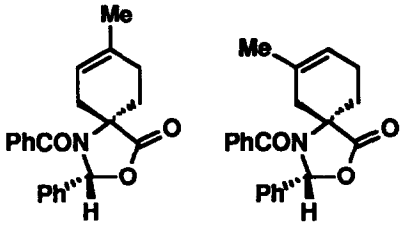
Figure 3. Molecular projection of 11 normal to the plane of the five-membered ring. 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radius of 0.1 Å.

Heating a solution of 11 at 130° for 24h gave a 50 : 50 mixture of the above two diastereoisomers. Reduction of the above mentioned 97 : 3 mixture of diastereoisomers with $NaBH_4$ gave the alcohol 13 of 94% enantiomeric purity from ^1H NMR analysis of its Mosher ester 14 (97 : 3 mixture of diastereoisomers)[5] Clearly the Diels-Alder adduct 11 is less prone to racemisation than 3. The minor diastereoisomeric adduct formed at 60°C could be either compound 12 or ent-12 or a mixture of these compounds. Compound 12 could arise from addition of the diene to the more hindered face of the 4-methylene group of 2, while ent -12 could arise from the epimerization of 11 at C2' during the course of the Diels-Alder reaction. Unfortunately this

minor adduct could not be separated from the major diastereomeric product and we were therefore unable to quantify the enantiomeric purity or determine the absolute stereochemistry of this compound.

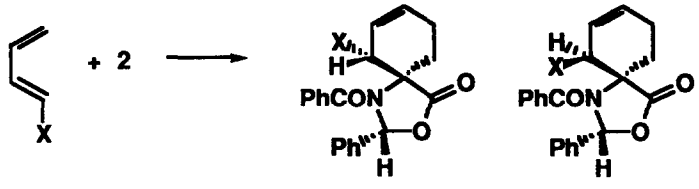


The Diels-Alder reaction of 2 and 2-methyl-1,3-butadiene at 60°C for 10 days gave a 66 : 31 : 3 mixture of three diastereomeric adducts in excellent yield (96%). The two major products were the 'ortho' and 'meta' products, 15 and 16, respectively. The third diastereoisomer could not be isolated in pure form and was possibly C4 epi-15.



15 16

The Diels-Alder reaction of 2 and 1-methyl-1,3-butadiene at 60°C for 15 days was highly diastereoselective (d.r. 94 : 6). The major and minor diastereomeric adducts were assigned the exo and endo diastereoisomers, 17a and 18a, respectively, from a combination of COSY and NOESY ^{1}H NMR and molecular Modelling (PCMODEL, using the MMX force field) studies.



17 18

a ; X = Me
b ; X = OMe

The energy minimized structures for 17a and 18a are shown in Fig. 4, along with the calculated proton-proton bond distances and observed NOE cross peaks in the NOESY NMR spectrum for each

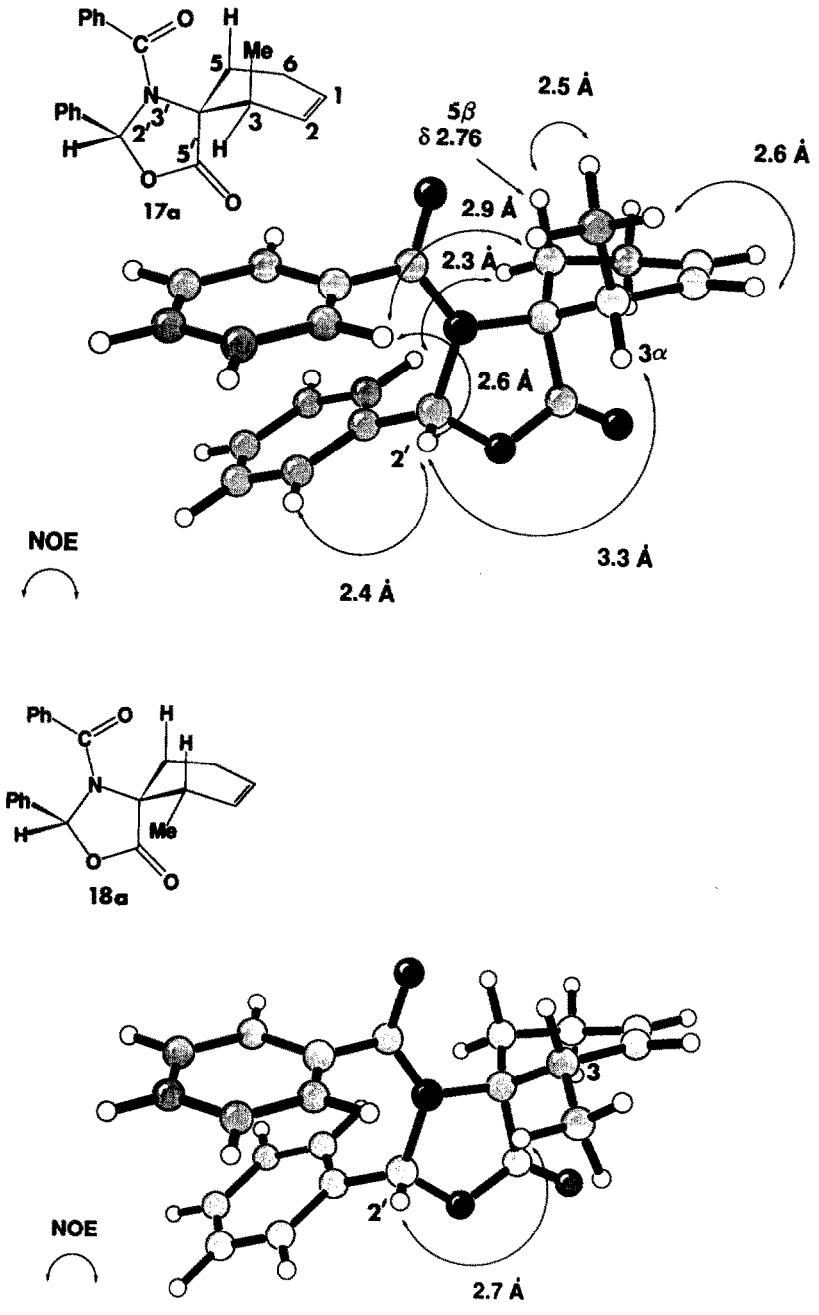
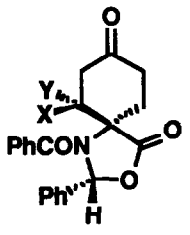


Figure 4. Energy minimized structures for 17a and 18a showing interatomic distances calculated using PCMODEL and the MMX force field parameters. Double headed arrows indicate observed NOE cross peaks in the 2D ^{1}H NMR NOESY spectrum of these compounds.

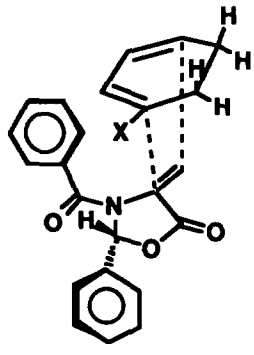
diastereoisomer. These energy minimized conformations showed close correlation to the solid state structure of 11 (Fig. 3). The ^{1}H NMR spectrum of 17a showed H5β was highly deshielded (δ 2.76, compared to H5α, δ 2.30), as expected from the close proximity of this proton to the benzoyl carbonyl group. The stereochemistry of 17a was evident from the strong NOE cross-peaks between H5β and the C3 Me group and between H2' and H3α. In contrast the minor diastereoisomer 18a, showed a significant NOE cross peak between H2' and the C3 Me consistent with the 'endo' stereochemistry.

The Diels-Alder reaction of 2 and 1-methoxy-1,3-butadiene at 60°C for 10 days gave a 82 : 18 mixture of the exo and endo cycloaddition products 17b and 18b respectively. The stereochemistry of these adducts was assigned on the basis of COSY and NOESY NMR experiments. The major diastereoisomer showed a NOE cross peak between H2' and H3α, while in the minor diastereoisomer a NOE cross peak was observed between H2' and the OMe group.

The reaction of 2 and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene at 60°C, followed by acid hydrolysis, gave a 50 : 50 mixture of the exo and endo cycloaddition products, 19 and 20.



19 ; X = OMe, Y = H
20 ; X = H, Y = OMe



21 (exo TS)

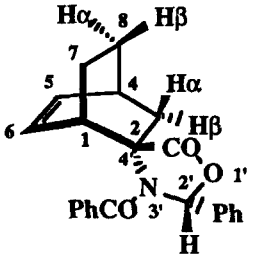
Attempts to increase the rate of the reactions described above by the addition of a Lewis acid were unsuccessful. These experiments resulted in either no enhancement of the rate or in the destruction of the dienophile 2. In one case studied, lithium perchlorate was found to enhance the rate of the Diels-Alder reaction of 1 and cyclopentadiene,[1,2] however, a mixture of endo and exo diastereomeric adducts resulted.

In summary, we have shown that the Diels-Alder reactions of 2 and 1-substituted 1,3-cyclohexadienes and 1-substituted-1,3-butadienes give cycloadducts that arise from exo diastereoselective transition states. These stereochemical results are similar to those obtained from 2-*tert*-butyl-5-methylene-1,3-dioxolan-4-one which gives exo adducts with both cyclic 1,3-dienes and substituted 1,3-butadienes.[3,4] Normally, in the absence of destabilizing steric interactions, the endo transition state would be expected to be favoured because of a stabilizing secondary orbital overlap between the p-orbitals on the diene and on the dienophile.[6] Exo-selective Diels-Alder reactions of cyclic dienes and α-substituted acrylic esters[7] and related dienophiles[3,4,8] are well documented.[9] With these dienophiles and 2, the endo transition state would be expected to be destabilized due to an unfavourable steric interaction between the α-substituent (the stericaly demanding

PhCON group in our reactions) and the methylene proton(s) on the cyclic diene and thus the exo transition state 21 would be expected to be favoured. Using this stereochemical argument however, one would expect that the reaction of 2 with 1-substituted-1,3-butadienes to give endo cycloaddition products rather than the observed exo cycloadducts, since there is now no significant destabilizing steric interaction between the α-substituent and the diene in the endo transition state. It appears the electronic factors rather than steric factors are responsible for the high exo selectivity in the Diels-Alder reactions of 2 and related dienophiles. It has been recently suggested that dipole-dipole interactions between the diene and dienophile are responsible for the exo selectivity in the Diels-Alder reactions of cyclic exocyclic-methylene dienophiles, like 2.[4b] Our reactions however, showed no rate enhancement, or change in exo/endo selectivity, when the reaction solvent was changed from CH_2Cl_2 to benzene or acetonitrile.

Experimental

The dienes, 2-trimethylsilyloxy-1,3-cyclohexadiene and 1-trimethylsilyloxy-1,3-cyclohexadiene were prepared according to the literature [10]. Infrared spectra were run as nujol mulls. All NMR spectra were run in $CDCl_3$ at 400MHz (^{1}H NMR) or 100 MHz (^{13} C NMR). Proton and carbon assignments were assisted by running COSY and NOESY ^{1}H NMR spectra and DEPT ^{13}C NMR spectra. For compounds 3, 4, 6,-9 and 10 (a-d) the carbons have been numbered as shown in the structure below. In the ^{1}H NMR analysis of these compounds the protons have been assigned α or β as indicated in the structure below. In the ^{1}H NMR spectrum protons like H3β are observed as a ddd due to W-coupling (to H8α). For compounds 11-20 the carbons have been numbered as shown for 17a in Figure 4. All crystalline compounds were recrystallized from ethyl acetate/hexane. Molecular modelling was performed using PCMODEL (Serena Software, Box 3076, Bloomington, Indiana) using the MMX force field parameters.



X-ray Structure Determinations.

The room temperature (~295K) single crystal X-ray structure determinations are derivative of unique diffractometer data sets (2θ/θ scan mode; monochromatic Mo Kα radiation, λ = 0.7109$_3$ Å) yielding N independent reflections, N_0 of these with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinement without absorption correction after solution by direct methods. Anisotropic thermal parameters were refined for C, N, O; (x, y, z, U_{iso})$_H$ were also refined. Conventional residuals R, R_w on /F/ are quoted at convergence, statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004\ \sigma^4(I_{diff})$ being used; chiralities were adopted from the chemistry. Neutral atom complex scattering factors were employed, computation using the XTAL 3.0 program system implemented by S. R. Hall. Derivative connectivities,

conformation and stereochemistries are shown pictorially in the Figures, geometries being essentially as expected. Full tabulations of atom coordinates and thermal parameters, molecular geometries and structure factor amplitudes have been deposited with the Cambridge Crystallographic Data Centre. Details of the specimens and refinement are as follows:

8 - $C_{24}H_{23}NO_4$, M = 389.5. Orthorhombic, space group $P2_12_12_1$ (D_2^4, No. 19), a = 22.094(5), b = 12.588(5), c = 7.211(2) Å, V = 2005(1) Å^3. D_c(Z = 4) = 1.29 g. cm.$^{-3}$; F(000) = 824. μ_{Mo} = 0.9 cm.$^{-1}$; specimen: 0.17 x 0.24 x 0.28 mm. $2\theta_{max}$ = 50°; N = 2045, N_o =1024; R = 0.051, R_w = 0.049.

10 - $C_{23}H_{21}NO_4$, M = 375.4. Monoclinic, space group $P2_1$ (C_2^2, No. 4), a = 8.125(1), b = 10.703(2), c = 11.337(2) Å, β = 103.40(1)°, V = 959.0(3) Å^3. D_c(Z = 2) = 1.30 g. cm.$^{-3}$; F(000) = 396. μ_{Mo} = 0.9 cm.$^{-1}$; specimen: 0.58 x 0.48 x 0.40 mm. $2\theta_{max}$ = 55°; N = 2316, N_o =1922; R = 0.037, R_w = 0.036.

11a - $C_{23}H_{23}NO_3$, M = 361.4. Orthorhombic, space group $P2_12_12_1$, a = 22.225(9), b = 9.635(4), c = 9.181(6) Å, V = 1966(3) Å^3. D_c(Z = 4) = 1.22 g. cm.$^{-3}$; F(000) = 864. μ_{Mo} = 0.8 cm.$^{-1}$; specimen: 0.90 x 0.60 x 0.38 mm. $2\theta_{max}$ = 50°; N = 1853, N_o =1510 R = 0.037, R_w = 0.044.

Diels-Alder Reactions of 2 and Dienes, A General Procedure:

A solution of 2 (225mg, 0.8 m mol) and the diene (10 molar equiv.) in dichloromethane (3 mL) under nitrogen was heated at 60°C in a sealed tube for several days, as reported in the Table. The solution was then cooled and evaporated to dryness. The crude products were purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent. The diastereoselection of these reactions were determined from ^{1}H NMR (400 MHz) analysis of the crude reaction product. The adducts 10, 19 and 20 were obtained by hydrolysis of the crude reaction product in a two phase system using hydrochloric acid solution (5%) and ether for 30 min,[11] followed by purification of the crude reaction mixture by column chromatography on silica gel.

(1S,2S,2'R,4S)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2]oct-5-ene-2,4'oxazolidin]-5'-one (3).

The two isomers (3) and (4) were separated by semi-preparative HPLC (silica gel, 1% EtOAc/hexane as eluent). Mp 123-5°C, $[\alpha]_D^{23}$ - 92 (c 0.25 $CHCl_3$). ^{1}H NMR δ 7.38-7.14 (m, 10H), 6.57 (s, 1H, H2'), 6.25 (dd, J=7.6, 8 Hz, 1H, H6), 6.16 (dd, J=7.4, 8 Hz, 1H, H5), 3.12 (m, 1H, H1), 2.90 (m, 1H, H3β), 2.69 (m, 1H, H4), 2.23 (m, 1H, H3α), 1.98 (m, 1H, H7α), 1.72 (m, 1H, H8β), 1.22 (m, 2H, H7β/8α). ^{13}C NMR δ 173.5 (CO), 173.1 (CO), 138.7, 138.2, 137.3, 136.2, 130.7, 129.7, 129.2, 128.5, 127.9, 127.4, 89.7, 68.2, 37.4, 35.4, 30.2, 23.6, 21.1. IR 1790, 1642, 1334, 1209, 1174, 1016, 714, 694 cm^{-1}. Mass spectrum (FAB positive) m/z 360 (11%, M+H$^+$), 226 (31), 210 (47), 165 (53), 148 (78), 127 (100). Anal Cald for $C_{23}H_{21}NO_3$: 76.86; H, 5.89; N, 3.90. Found: C, 77.06; H, 6.25; N, 3.78.

(1S,2S,2'S,4S)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2]oct-5-ene-2,4'-oxazolidin]-5'-ene (4).

Mp 40°C, $[\alpha]_D^{23}$ -102 (c 0.3 $CHCl_3$). ^{1}H NMR δ 7.4-7.26 (m, 10 H), 6.78 (s, 1H, H2'), 6.58 (dd, J = 7.2, 7.6 Hz, 1H, H6), 6.24 (dd, J=7.2, 7.4 Hz, 1H, H5), 2.80 (m, 2H, H1/3β), 2.43 (m, 1H, H4), 1.98 (m, 1H, H3α), 1.86 (m, 1H, H7α), 1.70 (m, 1H, H8α), 1.25 (m, 1H, H7β), 0.90 (m, 1H, H8β). ^{13}C NMR δ 173.8 (CO), 168.5 (CO), 137.6, 137.4, 136.8, 136.23, 129.9, 129.4, 123.6, 128.6, 126.4, 125.7, 88.0, 66.9, 37.5, 34.1, 29.7,

24.3, 20.3. IR 1796, 1675, 1333, 1146, 1029 cm^{-1}. Mass spectrum (ESI positive) m/z 398 (13%; $M+K^+$), 382 (15, $M+Na^+$) 360 (100, $M+H^+$).

(1R,2S,2'R,4S)-2-Methoxy-3'-benzoyl-2'-phenylspiro[bicyclo[2.2.2.]oct-5-ene-2,4'-oxazolidin]-5'-one (8).

Mp 159-60°C, $[\alpha]_D^{30}$ (on 90:10 mixture) +99.8 (c 0.54 in $CHCl_3$). ^1H NMR (of mixture, in part) δ 7.26-6.80 (m, 10H), 6.54 (s, 1H, H2'), [minor isomer: 6.51(s, 1H, H2')] 6.39 (m, 2H, H5/6), 3.57 (m, 4H, OCH_3 and H4), [minor isomer 3.56 (s, 1H, OCH_3)], 2.88 (m, 1H, H3β), 2.34 (m, 1H, H3α), 2.07 (m, 1H, H7α), 1.99 (m, 1H, H7β), 1.62 (m, 1H, H8β), 1.47 (m, 1H, H8α). ^{13}C NMR δ 173.3 (CO), 171.8 (CO), 138.8, 137.7, 137.1, 135.8, 130.1, 129.3, 128.4, 128.2, 127.3, 126.3, 92.2, 84.9, 71.0, 51.8, 37.5, 30.7, 25.1, 23.5. IR 1780, 1664, 1178, 1101, 1026, 769, 693. Mass spectrum (CI) m/z 390 (15%, $M+H^+$), 280 (12), 256 (19), 240 (30), 174 (28), 135 (93), 121 (100). Anal Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.00; H, 6.00; N, 3.64.

(1R,2S,2'R,4S)-2-Trimethylsilyloxy-3'-benzoyl-2'-phenylspiro[bicyclo[2.2.2.]oct-5-ene-2,4'-oxazolidin]-5'-one (9).

Mp 135-6°C, $[\alpha]_D^{26}$ (on 93:7 mixture) +96.1 (c 0.52 $CHCl_3$). ^1H NMR (of mixture) δ 7.2- 6.8 (m, 10H), 6.51 (s, 1H, H2') [minor isomer, 6.47 (s, 1H, H2')], 6.30 (m, J = 3.2, 8.8 Hz, 1H, H5), 6.22 (d, J = 8.8 Hz, 1H, H6), 3.56 (m, 1H, H4), 2.85 (brs, 1H, H3β), 2.35 (m, 1H, H7β), 2.31 (dd, J = 2,13.2 Hz, 1H, H3α), 1.97 (m, 1H, H7α), 1.46 (m, 2H, H8α/8β), 0.22 (s, 9H). ^{13}C NMR δ 173.3 (CO), 171.8 (CO), 138.8, 137.1, 136.3, 134.4, 130.1, 129.3, 128.4, 128.2, 127.3, 126.3, 92.4, 82.4, 72.3, 36.9, 30.6, 29.4, 25.8, 2.34. IR 1786, 1667, 1251, 1217, 1134, 1099, 754, 704. Mass spectrum (CI) m/z 447 (42%, M^+), 279 (73), 235 (29), 121 (26), 100 (100). Anal Calcd for $C_{29}H_{29}NO_4Si$: C, 69.77; H, 6.53; N, 3.13. Found: 69.56; H, 6.59; N, 2.99.

(1S,2S,2'R,4S)-3'-Benzoyl-2'-phenylspiro[bicyclo[2.2.2.]oct-5-one-2-4'-oxazolidin]-5'-one (10a).

Separation of the crude reaction mixture by column chromatography gave pure 10a and an inseparable mixture of three minor diastereoisomers. Fractional crystallization of this mixture from ethyl acetate/hexane gave a mixture (about 1 : 1) of 10b and 10c, which could not be separated by further crystallizations.
10a: Mp 212-14°C, $[\alpha]_D^{22}$ +174.3 (c 0.35 $CHCl_3$). ^1H NMR δ 7.26-6.76 (m, 10H), 6.54 (s, 1H, H2'), 3.63 (ddd, J = 2.4, 6, 14 Hz, 1H, H6β), 2.85 (ddd, J = 3, 6, 17 Hz, 1H, H3β), 2.72 (m, 1H, H1), 2.65 (m, 1H, H4), 2.57 (dd, J = 2.4, 14 Hz, 1H, H6α), 2.50 (m, 1H, H8α), 2.29 (dd, J = 2.4, 17 Hz, 1H, H3α), 2.14 (m, 1H, H7α), 1.88 (m, 1H, H7β), 1.64 (m, 1H, H8β). ^{13}C NMR δ 211.4 (CO), 172.9 (CO), 171.3 (CO), 137.0, 136.7, 130.3, 129.8, 128.7, 128.4, 126.6, 125.9, 90.3, 63.3, 43.0, 41.4, 39.9, 33.8, 22.4, 21.2. IR 1780, 1718, 1660, 1205, 1170, 933, 871, 725 cm^{-1}. Mass spectrum (FAB positive) m/z 376 (15%, $M+H^+$), 242 (40), 165 (47), 154 (100). Anal Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.35; H, 5.77; N, 3.35.
10b: ^1H NMR (in part) δ 6.86 (s, 1H, H2') , 10c: ^1H NMR (in part) δ 6.51 (s, 1H, H2').

Synthesis of methyl (1S,2S,4S)-2-benzenecarboxamido-5-oxo-bicyclo[2.2.2.]octane-2-carboxylate (10d) and methyl (1S,2S,4R)-2-benzenecarboxamido-6-oxo-bicyclo[2.2.2.]octane-2-carboxylate (10e)

To a solution of 10a or a mixture (1 : 1) of 10b and 10c (50 mg, 0.13 mmol) in dry methanol (10ml) under nitrogen was added powered anhydrous potassium carbonate (20 mg, 0.14 mmol). The mixture was stirred at room temperature for 16 hrs. The mixture was then diluted with ethyl acetate (20 ml) and washed with saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (2 x 10 ml). The combined extracts were washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo. Starting from pure 10a the ester 10d was obtained in nearly quantitative yield. Starting with a mixture of 10b and 10c then a 1 : 1 mixture of 10d and 10e was obtained, these could be separated by preparative TLC using 40% ethyl acetate/hexane as eluent. In one experiment a mixture of 10b and a small amount of the fourth unidentified Diels-Alder diastereomeric product was converted to mainly 10d. The unidentified Diels-Alder diastereomeric product gave an ester that was different to both 10d and 10e, but could not be obtained in sufficient quantity or diastereomeric purity for structural elucidation studies.

10d: ^{1}H NMR δ 7.75-7.42 (m, 5H), 6.47 (brs, 1H, NH), 3.77 (s, 3H, OCH_3), 3.32 (dd, J = 2.8, 15 Hz, 1H, H6α), 2.70 (ddd, J = 2.8, 5.6, 18.8 Hz, 1H, H3β), 2.50 (m, 1H, H1), 2.46 (m, 1H, H4), 2.30 (dd, J = 2.8,18.8 Hz, 1H, H3α), 2.04 (m, 1H, H8α), 2.00 (ddd, J = 2.8, 12.8, 15 Hz, 1H, H6β), 1.80 (m, 1H, H7α), 1.78 (m, 1H, H7β), 1.64 (m, 1H, H8β). Mass spectrum (ESI positive) m/z 302 (100%, M+H$^+$).

10e: ^{1}H NMR δ 7.8-7.45 (m, 5H), 6.68 (brs, 1H, NH), 3.74 (s, 3H, OCH_3), 3.20 (ddd, J = 2.6, 5.6, 15 Hz, 1H, H5β), 2.50 (t, J = 2.8 Hz, 1H, H1), 2.46 (m, 1H, H4), 2.38 (ddd, J = 2.8, 3.2, 19 Hz, 1H, H3β), 2.32 (m, 1H, H7α), 2.26 (dt, J = 2.8, 19 Hz, 1H, H3α), 2.20 (m, 1H, H8α), 2.00 (m, 1H, H8β), 1.97 (dd, J = 2.6, 15 Hz, 1H, H5α), 1.70 (m, 1H, H7β). Mass spectrum (ESI positive) m/z 302 (100%, M+H$^+$).

(2'R, 4S) -3'-Benzoyl-2'-phenyl-1,2-dimethylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (11).

Mp 166-8°C, $[\alpha]_D^{25}$ (on 97:3 mixture) + 188.6 (c 0.5, $CHCl_3$). ^{1}H NMR (of mixture, in part) δ 7.38-6.97 (m, 10H), 6.60 (s, 1H, H2') [minor isomer, 6.55 (s, 1H, H2')]; 3.36 (d, J = 17.2 Hz, 1H, H3β), 3.15 (m, 1H, H5β), 2.60 (m, 1H, H6α), 2.24 (d, J = 17.2 Hz, 1H, H3α), 2.16 (m, 1H, H6β), 2.12 (m, 1H, H5α), 1.72 (s, 3H), 1.68 (s, 3H). ^{13}C NMR δ 172.5 (CO); 169.3 (CO), 136.6, 136.3, 130.0, 129.7, 128.5, 128.4, 126.6, 126.2, 125.6 (C), 120.8 (C), 89.2 (CH), 61.1 (C), 35.8 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 18.9 (CH_3), 18.7 (CH_3). IR 1770, 1638, 1158, 1032, 731, 639 cm^{-1}. Mass spectrum (CI) m/z 362 (100%, M+H$^+$). Anal. Calcd for C_{23} H_{23} NO_3: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.87; H, 6.81; N, 3.72.

(2'R, 4S)-3'-Benzoyl-2'-phenyl-1-methylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (15).

Mp 182-3°C, $[\alpha]_D^{27}$ (on 81:19 mixture of regioisomers) +177.6 (c 0.5, $CHCl_3$). ^{1}H NMR (on mixture) δ 7.33-6.98 (m, 10H), 6.61 (s, 1H, H2') [minor isomer, 6.62 (s, 1H, H2')], 5.37 (m, 1H, H2) [minor isomer, 5.58 (m, 1H)], 3.38 (dd, J = 2.4, 17 Hz, 1H, H3α), 3.21 (ddd, J = 5.6, 12.8, 18 Hz, 1H, H6β), 2.58 (m, 1H, H6α), 2.38 (br. d, J = 18 Hz, 1H, H3β) [minor isomer, 2.23 (br. d)], 2.14 (m, 2H, H5α/5β), 1.77 (s, 3H) [minor isomer, 1.75 (s, 3H)]. ^{13}C NMR δ 172.4 (CO), 169.3 (CO), 136.7, 136.4, 133.9 (CH), 130.1, 129.7, 128.6, 128.5, 126.7, 122.2, 116.2 (C), 89.2 (CH), 60.1 (C), 30.4 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 23.2 (CH_3). IR

1782, 1650, 1401, 1175, 1036 cm^{-1}. Mass spectrum (CI) m/z 348 ($M+H^+$, 92%), 210 (49), 198 (29), 105 (100). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.14; H, 6.14; N, 3.87.

(2'R, 3R, 4R)-3'-Benzoyl-2'-phenyl-3-methylspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (17a).

Mp 155-6°C, $[\alpha]_D^{27}$ + 79.1 (c 0.30 $CHCl_3$). ^1H NMR δ 7.32-6.98 (m, 10H), 6.60 (s, 1H, H2'), 5.92 (m, 1H, H1), 5.67 (m, 1H, H2), 3.01 (m, 1H, H3α), 2.76 (m, J = 6.4, 14 Hz, 1H, H5α), 2.50 (m, 1H, H6α), 2.41 (m, 1H, H6β), 2.30 (m, J = 6.4, 14 Hz, 1H, H5α), 1.30 (d, J = 7.2 Hz, 3H). [minor isomer (from NMR on the mixture) 6.75 (s, 1H, H2'), 5.82 (m, 1H, $=CH_2$), 5.48 (m, 1H, $=CH_2$), 1.25 (d, J = 7.6 Hz, 3H)]. ^{13}C NMR δ 174.4 (CO), 169.93 (CO), 137.0, 136.8, 130.0, 129.6, 129.4, 128.6, 128.4, 126.5, 126.2 (=CH), 126.1 (=CH), 89.8 (CH), 65.4 (C), 38.0 (CH), 30.2 (CH_2), 23.0 (CH_2), 16.4 (CH_3). IR 1798, 1647, 1223, 1165, 1051, 729, 700 cm^{-1}. Mass spectrum (CI) m/z 348 (14%, $M+H^+$), 302 (33), 242 (33), 210 (38), 197 (100), 182 (82). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.37; H, 6.06; N, 3.94.

(2'R, 3R, 4R)-3'-Benzoyl-2'-phenyl-3-methoxyspiro[cyclohex-1-ene-4,4'-oxazolidin]-5'-one (17b).

Mp 118-20°C, $[\alpha]_D^{25}$ (on 82:18 mixture) + 56.6 (c 0.45 $CHCl_3$). ^1H NMR (on mixture) δ 7.32-6.89 (m, 10H), 6.61 (s, 1H, H2') [minor isomer, 6.52 (s, 1H, H2')], 5.97 (m, 1H, H1), 5.90 (m, 1H, H2), 4.15 (br s, 1H, H3α), [minor isomer, 5.03 (br s, 1H, H3β)], 3.55 (s, 3H, OCH_3) [minor isomer, 3.62 (s, 3H. OCH_3)], 2.50 (m, 2H, H5β/6α), 2.34 (m, 2H, H5α/H6β). ^{13}C NMR (of mixture, in part) δ 172.4 (CO), 170.4 (CO), 137.5, 136.6, 130.1, 129.7, 128.5, 128.0, 127.2, 126.8, 123.2 (=CH), 122.5 (=CH), 90.4 (CH), 75.2 (CH), 65.5 (C), 57.7 (CH_3), 28.8 (CH_2), 23.1 (CH_2). IR 1775, 1636, 1395, 1335, 1168, 1083, 680 cm^{-1}. Mass spectrum (CI) m/z 364 (100%, $M+H^+$), 332 (37). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.54; H, 6.12; N, 3.95.

(2'R, 3R, 4R) and (2'R,3S, 4R) -3'-Benzoyl-2'-phenyl-3-methoxyspiro[cyclohexan-1-one-4,4'-oxazolidin]-5'-one (19) and (20).

The two diastereoisomers were separated by fractional recrystallization from ethyl acetate/hexane.
20: Mp 135-8°C, $[\alpha]_D^{20}$ + 80 (c 0.3 $CHCl_3$). ^1H NMR δ 7.3-6.88 (m, 10H), 6.55 (s, 1H, H2'), 4.14 (dd, J = 5.6, 12 Hz, 1H, H3α), 3.52 (s, 3H, OCH_3), 3.00 (m, 4H), 2.65 (m, 2H). [NOE cross peak was observed betwwen H2' and H3α]. ^{13}C NMR δ 207.3 (CO), 174.5 (CO), 171.3 (CO), 136.6, 136.1, 130.2, 129.9, 128.7, 128.4, 127.0, 126.1, 91.4 (CH), 80.8 (CH), 64.9 (C), 57.8 (CH_3), 42.3 (CH_2), 36.51 (CH_2), 28.84 (CH_2). IR 1790, 1705, 1648, 1300, 1222, 1162, 1100, 1025, 695 cm^{-1}. Mass spectrum (CI) 380 (10%, $M+H^+$), 348 (14), 229 (33), 198 (75), 122 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58, N, 3.69. Found: C, 69.18; H, 5.77, N, 3.44.

19: Mp 205-8°C, $[\alpha]_D^{20}$ +127.7 (c 0.23 $CHCl_3$). ^1H NMR δ 7.32-6.89 (m, 10H), 6.54 (s, 1H, H2'), 4.79 (dd, J = 5.2, 11.6 Hz, 1H, H3β), 3.53 (s, 3H, OCH3), 3.36, (dd, J = 5.2, 11.6 Hz, 1H, H2α), 3.18 (m, 1H, H2β), 3.14 (dd, J = 5.2, 11.6 Hz, 1H, H6α), 2.97 (m, 1H, H6β), 2.59 (m, 1H, H5β), 2.44 (m, 1H, H5α). [NOE cross peak was observed between H2' and OCH_3] ^{13}C NMR δ 206.5 (CO), 170.7 (CO), 169.8 (CO), 136.1, 136.1,

129.99, 129.96, 128.7, 128.6, 126.9, 125.7, 90.8 (CH), 75.2 (CH), 65.5 (C), 57.3 (CH_3), 41.7 (CH_2), 36.7 (CH_2), 27.9 (CH_2). Mass spectrum (FAB positive) m/z 380 (34%, $M+H^+$), 348 (54), 316 (39), 288 (100).

(1S)-1-(1-Benzenecarboxamido-3,4-dimethyl-cyclohex-3-enyl)methanol (13)

A mixture (97 : 3) of 11 and 12 (100mg, 0.3 mmol) in dry methanol (10ml) was treated with $NaBH_4$ (20 mg). After 16 hrs at room temperature the solution was then treated with acetone (2ml) at 0°C for 10 min. The solvent was then evaporated and water was added and the alcohol was extracted into CH_2Cl_2(2x). Short-path column chromatography on silica gel gave (13) (32mg, 41%) ^1H NMR δ 7.72-7.41 (m, 5H), 6.17 (br s, 1H, OH), 5.14 (br s, 1H, NH), 3.79 (m, 2H, CH_BH_AOH), 2.22-2.0 (m, 5H), 1.78 (m, 1H), 1.67 (br s, 6H). Mass spectrum (CI) m/z 260 (53%, M + H^+), 138 (100), 122 (95), 105 (63).

(1S,2S,4S)-2-(2-Benzenecarboxamidobicyclo[2.2.2.)]oct-5-enyl)methanol (6).

This compound was prepared from a mixture (76 : 24) of 3 and 4 (200mg, 0.6mmol) by treatment with $NaBH_4$ as described above. Purification of the crude reaction product by column chromatography gave 6 (40mg, 50%). ^1H NMR δ 7.68-7.4 (m, 5H), 6.45 (t, J = 7.2Hz, 1H, H6), 6.32 (t, J = 7.2Hz, 1H, H5), 5.94 (br s, 1H, NH), 5.64 (dd, J = 2.4, 9.2 Hz, 1H, OH), 4.10 (dd, J = 2.4, 12, Hz, 1H, CH_ACH_BOH), 3.68 (dd, J=9.2, 12 Hz, 1H, CH_ACH_BOH), 3.32 (m, 1H, H1), 2.68 (m, 1H, H3β), 1.94 (m, 1H, H4), 1.71-1.23 (m, 5H). ^{13}C NMR δ 168.1 (CO), 135.7, 134.8, 132.9, 131.7, 128.7, 126.9, 68.9, 62.6, 42.3, 34.4, 30.0, 23.4, 20.6.

References

1. Pyne, S. G.; Dikic, B.; Gordon, P. A.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1991**, 1505.
2. Pyne, S. G.; Dikic, B.; Gordon, P. A.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 1505.
3. Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327.
4. (a) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305. (b) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380. (c) Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, *33*, 4691. (d) Roush, W. R., Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.
5. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (7): ^1H NMR δ 5.24 (d, J = 11.2 Hz, 1H) (minor isomer, 5.05 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H) (minor isomer, 4.56, d, J = 11.2 Hz, 1H). 14 : ^1H NMR δ 4.79 (d, J = 11.2 Hz, 1H), (minor isomer, 4.87, d J = 11.2 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), (minor isomer, 4.63, d, J = 11.2 Hz, 1H).
6. Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc.* **1965**, *87*, 4388.
7. (a) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537. (b) Berson, J. A.; Hamlet, Z.; Meuller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. (c) Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548. (d) Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Feuno, T. *J. Am. Chem. Soc.* **1972**,

94, 3634. (e) Quick, J. *J. Org. Chem.* **1978**, *43*, 2275. (f) Mellor, J. M.; Webb, C. F., *J. Chem. Soc. Perkin II*, **1974**, 17. (g) Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Syn Commun.* **1988**, *18*, 1453.

8. For exo diastereoselective Diels-Alder reactions of (i) cyclic enals see: Rehnberg, N.; Sundin, A,; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5477. Kim, K. S.; Cho, I. H.; Joo, Y. H.; Yoo I. Y.; Song, J. H.; Ko, J. H. *Tetrahedron Lett.* **1992**, *33*, 4029. (ii) Exocyclic methylene dienophiles see: Dehydro amino acids see: Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Tetrahedron Lett.* **1980**, *21*, 4101. Crossley, M. J.; Hambley, T. W.; Stamford, A. W. *Aust. J. Chem.* **1990**, *43*, 1827. Cativiela, C.; Lopez, P.; Mayoral, J. A. *Tetrahedron: Asymmetry*, **1990**, *1*, 379. Cativiela, C.; Lopez, P.; Mayoral, J. A. *Tetrahedron: Asymmetry*, **1991**, *2*, 1295. Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453.
9. For other, unrelated exo selective Diels-Alder reaction see: Lamy-Schelkens, H.; Giomi, D.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 5887. Ward, D. E.; Gai, Y. *Tetrahedron Lett.* **1992**, *33*, 1851. Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784.
10. Girard, C.; Conia, J-M. *J. Chem. Res* (S) **1978**, 182; Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3205.
11. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

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