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High-Pressure and Thermally Induced Asymmetric Diels-Alder Cycloadditions of Heterosubstituted Dienes to Homochiral α,β-Didehydro Amino Acid Derivatives

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Abstract: An amino pentenoate and an unsaturated oxazolone have shown to be suitable homochiral dienophiles to be reacted with electron-rich heterosubstituted dienes. High-pressure and thermal activation have been studied for these cycloadditions. The adducts obtained are polyfunctional building blocks useful for the synthesis of enantiopure cyclohexane amino acids and related products.

INTRODUCTION

Carbocyclic amino acids constitute a class of compounds which are receiving great attention in this decade due to the biological activity shown by themselves or incorporated in conformationally constrained peptides. Thereby, the development of efficient and stereoselective methods to produce such products in enantiopure form is crucial. As a part of our research in the asymmetric synthesis of these amino acids, we have reported recently synthetic routes to different cyclopropane derivatives based on diastereoselective 1,3-dipolar cycloadditions of diazomethane to suitable chiral precursors.[1,2,3]

Now in this paper we describe the results obtained from the Diels-Alder reactions between heterosubstituted dienes and chiral didehydroamino acid derivatives. The enantiopure adducts obtained contain, in addition to the hexagonal backbone, several functional groups and four stereogenic centers with unambiguous configuration. These products must be, therefore, potent and versatile building blocks to be used in the synthesis of several cyclohexane amino acids.

The synthetic approaches to these products published up to the present are mainly based on Diels-Alder cycloadditions to achiral ylidene 5(4*H*)-oxazolones (azlactones) affording racemic adducts.[4-6] Two synthesis of enantiopure products have been achieved by using microbial transformations[7] and chiral auxiliaries,[8] respectively, as convenient methods to induce asymmetry. More recently, the cycloadditions of **5** to non-heterosubstituted dienes have also been reported.[9]

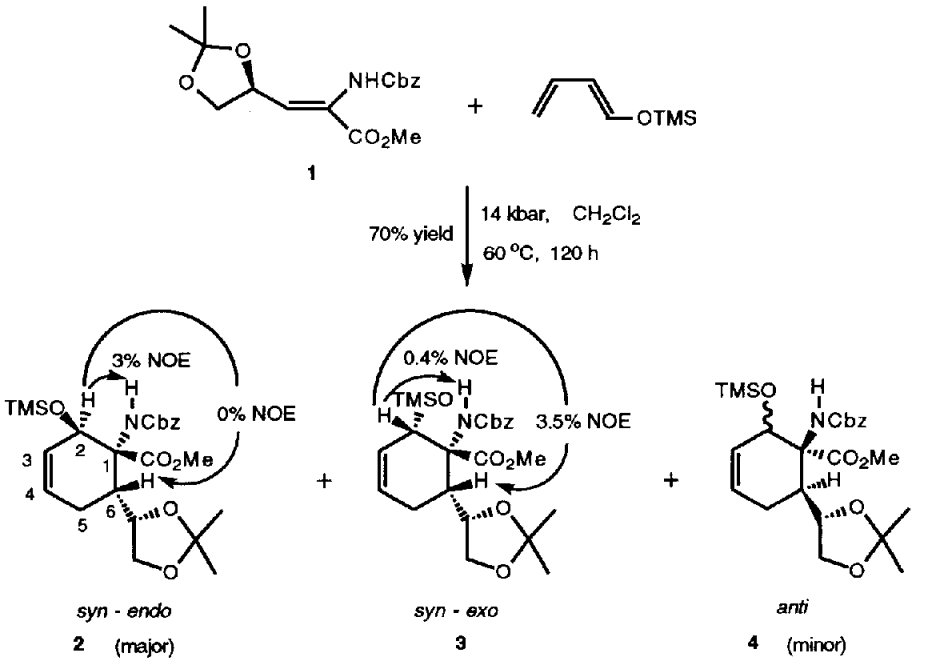
We have combined for the first time the use of the intrinsically chiral dienophiles **1**[10] and **5**,[11] both being easily available from D-mannitol, and 1-trimethylsilyloxy-1,3-butadiene (1-TMSO-butadiene) and Danishefsky's diene to afford highly functionalized cyclohexane derivatives in an efficient and

stereocontrolled manner. High-pressure activation of these processes has been investigated in some cases, the results being compared with those of the thermal reactions.

RESULTS AND DISCUSSION

1. *Reaction of pentenoate 1 with 1-TMSO-butadiene.*

Although pentenoate **1** was shown to be a good dipolarophile adding diazomethane at 0°C quantitatively,[2,3] its dienophilicity under thermal activation conditions was very low. Thus, it remained unaltered in the presence of excess cyclopentadiene in a wide range of temperatures, even in the presence of usual catalysts such as lithium perchlorate, chlorodiethylaluminium, or titanium tetrachloride. It was also recovered when treated with 1-TMSO-butadiene.

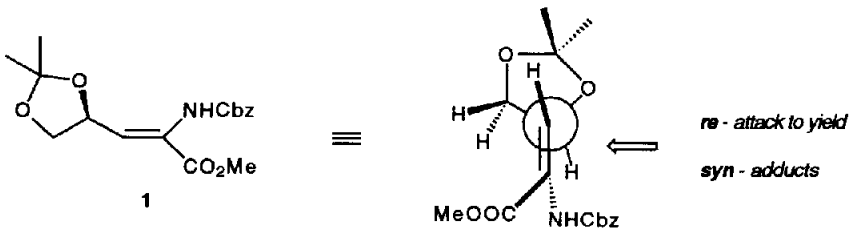


Scheme 1

Nevertheless, reaction of this diene with **1**, in dichloromethane, under 14 kbar pressure, at 60°C for 120 h, afforded a 6:3:1 mixture of adducts **2-4** (Scheme 1) along with 40% starting material (70% yield based on converted **1**). These products could be chromatographically isolated and characterized by their physical constants and spectroscopic data. Stereochemistry of major isomers **2** and **3** was determined on the basis of differential NOE experiments and previous results of other related cycloadditions.[2,3,12,13] Thus, 3% NOE was observed between *H-2* and N*H* protons in isomer **2** while no NOE enhancement was produced for *H-2* and *H-6* according to a 1,3-*trans* disposition for these protons as corresponds to an *endo*-adduct. *Exo* stereochemistry was assigned to **3** since 3.5% NOE was now observed for protons *H-2/H-6*, in agreement with a 1,3-*cis* relationship.

Syn-facial diastereoselection was assumed to be predominant in this reaction by analogy with the stereoselectivity of the cycloaddition of diazomethane to **1**,[2,3] as a result of the preferential attack on the less

hindered *re* face of the double bond, by considering a preferred conformation such as that represented below.. *Syn*-stereoselectivity had also been found to govern the Diels-Alder additions of several dienes to similar chiral pentenoates.[12,13]



2. ***Diels-Alder reactions of oxazolone 5.***

In contrast with the behaviour observed for pentenoate **1**, unsaturated oxazolones are reported to be good dienophiles. Kraus *et al.* described in 1989 the first Diels-Alder reaction of such dienophiles to occur between 2-phenyl-4-arylidene-5(4*H*)-oxazolone and Danishefsky's diene at 160 °C, affording a single adduct although *endo/exo* stereochemistry was not determined.[4] Later, Cativiela *et al.* reported the addition of the same diene to 2-phenyl-4-benzylidene-5(4*H*)-oxazolone at 110 °C to give a mixture of *endo /exo* isomers in 45:55 ratio.[6] *Exo* adduct was also predominant in both catalyzed or uncatalyzed reactions of **5** with cyclopentadiene.[9]

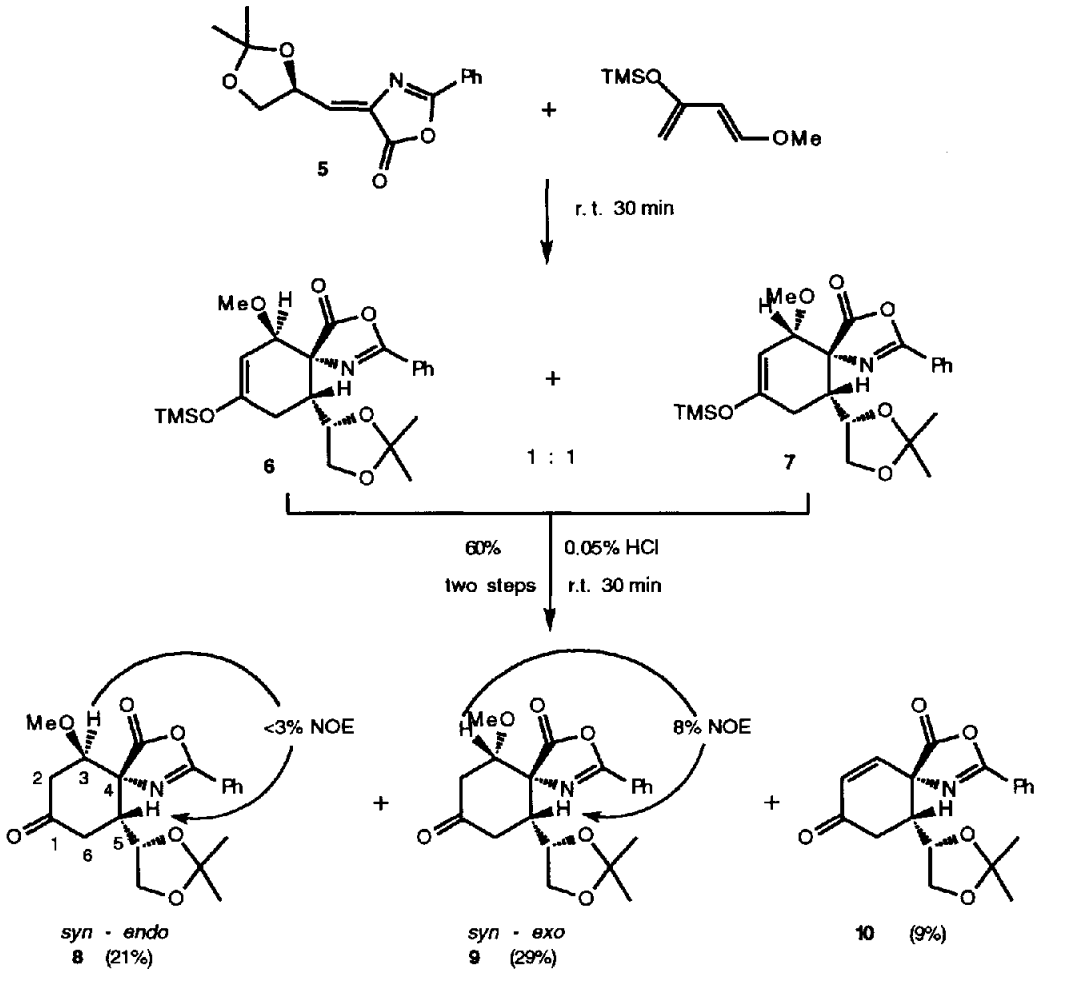
In our case, the double bond of **5** is not conjugated to an aromatic substituent, being more reactive. Thus, the cycloadditions to Danishefsky's diene and 1-TMSO-butadiene could be carried out under much milder conditions.

(a) Cycloaddition of 5 to Danishefsky's diene.

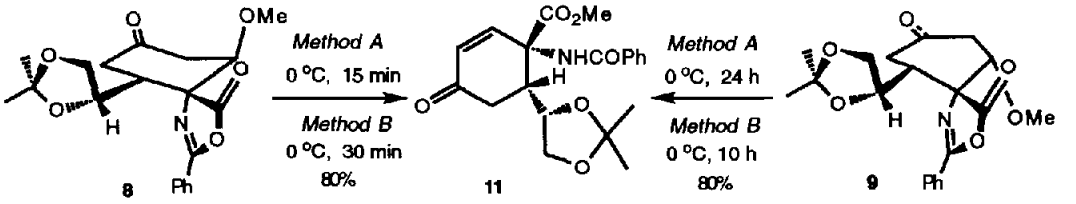
Cycloaddition of homochiral **5** to Danishefsky's diene was performed at room temperature for 30 minutes yielding a 1:1 mixture of adducts **6** and **7**,[14] which was hydrolyzed (0.05% HCl at room temperature, 30 min) giving a mixture of ketones **8** (21%), **9** (29%), and conjugated **10** (9%), in 60% combined yield for the two steps (Scheme 2).[15]

The ketones **8** and **9** are new products which were isolated and characterized. *Endo/exo* assignment was made from differential NOE values observed for proton *H-5* when *H-3* was selectively irradiated, being less than 3% in *endo*-adduct **8** and 8% in *exo*-adduct **9**.[16] *Syn* stereochemistry was unambiguously elucidated by X-ray structural analysis of a single crystal of compound **9** (Figure 1). A *chair-like* conformation for the cyclohexane ring bearing both the methoxyl and the dioxolane substituents in equatorial disposition was found for this molecule in solid state.

Ketone **10** was probably produced from **8** through concomitant elimination of methanol during hydrolysis of the silyl enol ether. The relative ease to underwent methanol elimination in basic medium, according to an E_2-type mechanism, was evidenced by treatment of each isomeric methoxy ketones **8** and **9** with DBU in methanol at 0 °C (Scheme 3). The same conjugated ketone **11** was obtained in 80% yield in both cases confirming the same facial diastereoselection in the production of the primary adducts **6** and **7**. Nevertheless, while reaction from **9** needed more than 10 hours for completion, the process from **8** was achieved in 15 minutes. Similarly, treatment of **8** with catalytic sodium methoxide in methanol at °C for 30 minutes led to **11** in 82% yield while reaction of **9** with one equivalent of the same base at 0 °C required 10 hours to afford **11** in 78% yield.

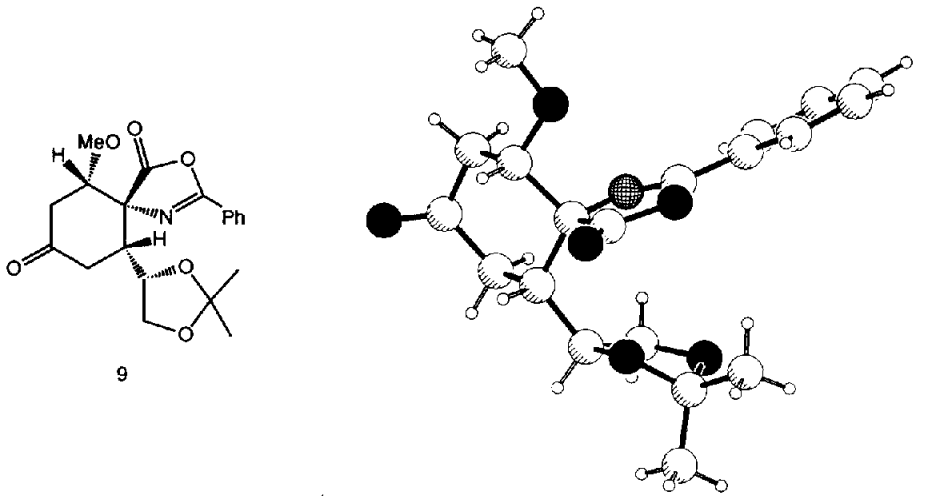


Scheme 2



Method A: 1 eq DBU, MeOH. *Method B*: NaOMe (a) catalytic amount for **8** or (b) 1 eq for **9**, MeOH.

Scheme 3



9

Fig. 1 Structure of ketone 9 as determined by X-ray structural analysis.

These kinetic findings agree with the *endo/exo* stereochemistry previously assigned to these products. The methoxyl group is axial in a *chair-like* conformation for **8** whereas this disposition can be reached in a *boat-like* conformation for **9**, considering the dioxolane ring to be equatorial in both cases.

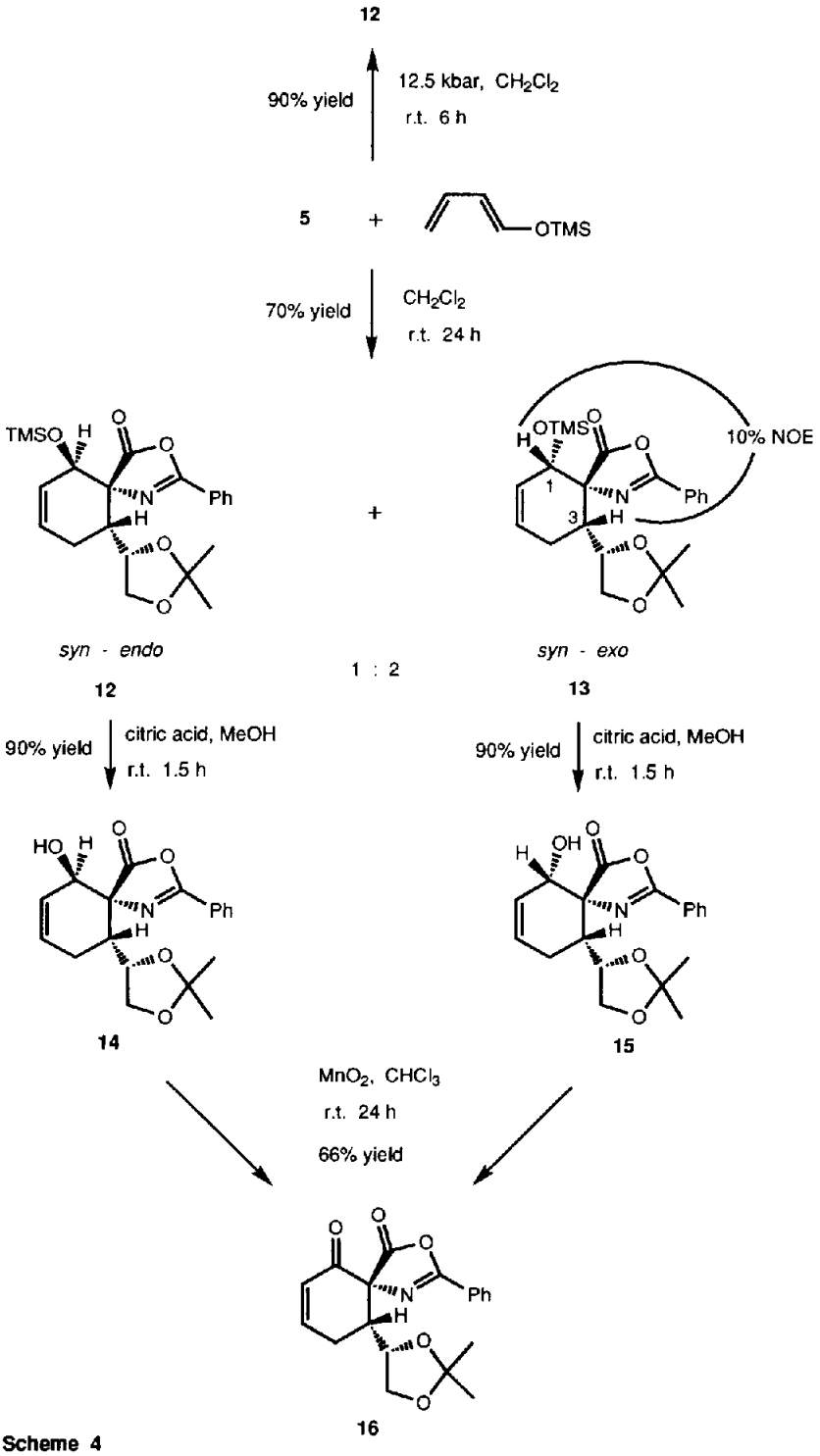
(b) Cycloaddition of 5 to 1-TMSO-butadiene.

Dienophile **5** was also reacted with 1-TMSO-butadiene in dichloromethane solution at room temperature for 24 hours to afford a 1: 2 mixture adducts **12** and **13** in 70% yield (Scheme 4). These new products were isolated by flash column chromatography and characterized. Each one was treated with citric acid in absolute methanol at room temperature for 1.5 hours, giving the allylic alcohols **14** and **15**, respectively, in almost quantitative manner. Tetrabutylammonium fluoride was not convenient to remove the silyl ether since the diol function was also partially deprotected.

Subsequently, both alcohols **14** and **15** were transformed into enone **16** by reaction with manganese dioxide in chloroform, at room temperature for 24 hours (66% yield). This fact showed that **14** and **15**, and consequently **12** and**13**, are *endo/exo* isomers as a result of the same facial diastereoselection. *Syn* orientation was assigned by comparison with the stereochemistry observed for adducts **6** and **7** from reaction of **5** with Danishefsky's diene, which had been unambiguously determined as mentioned above. *Exo* stereochemistry was assigned to **13** due to 10% NOE observed for *H-1* and *H-3* in adduct **13**, while no NOE enhancement was observed for the equivalent protons in **12**.

Interestingly, pressurization of dienophile **5** with 1-TMSO-butadiene (12.5 kbar, room temperature, 6 hours) afforded only *syn-endo* isomer **12** in 90% yield (Scheme 4). High-pressure condition was shown indeed to be better than thermal activation in order to produce Diels-Alder adducts in more efficient and stereoselective manner. Moreover, *endo/exo* selectivity of this cycloaddition was converse with respect to that of the thermal counterpart, in agreement with the general rule that *endo* adducts are favoured under high-pressure conditions.[17]

The use of these two different reaction activations offers, thereby, alternative ways to obtain *syn-endo* **12** or *syn-exo* **13** in good yields.


12
90% yield
12.5 kbar, CH_2Cl_2
r.t. 6 h
5
+
OTMS
70% yield
CH_2Cl_2
r.t. 24 h
TMSO
H
O
O
N
Ph
H
O
O
+
OTMS
H
10% NOE
1
3
syn - endo
12
1 : 2
syn - exo
13
90% yield
citric acid, MeOH
r.t. 1.5 h
90% yield
citric acid, MeOH
r.t. 1.5 h
HO
OH
14
15
MnO_2, $CHCl_3$
r.t. 24 h
66% yield
16

Scheme 4

CONCLUSION

The homochiral dienophiles **1** and, especially, **5** have shown to be able to produce Diels-Alder adducts by reaction with electron-rich heterosubstituted dienes. These adducts present a cyclohexane moiety, several chemical functions, and four stereocenters. Therefore, these compounds are valuable synthetic intermediates to be used in the preparation of polyfunctional cyclohexane amino acids and other related compounds. Active investigation in this field is being carried out in our laboratory.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh) unless otherwise stated. Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale) from $CDCl_3$ solutions.

High-pressure induced cycloaddition of 1-trimethylsilyloxy-1,3-butadiene to pentenoate 1: Adducts 2, 3, and 4. 1-Trimethylsilyloxy-1,3-butadiene (1.2 g, 8.3 mmol) and pentenoate **1** (1.0 g, 3.0 mmol) in dichloromethane (1.0 ml) were introduced, by means of a syringe, into a 3 ml pyrex glass cell (1.5 mm wall-thickness) fitted with a 1 mm inner diameter capillary orifice. The cell was immersed into hexane, used as piezotransmitter liquid wich was contained in the high pressure apparatus, closed on the bottom side with a steel stopper. Then the mobile piston was inserted and the whole assembly was placed between the pistons of a hydraulic press. The reaction was performed at 14 Kbar and 60 °C for 120 h. After decompression the solvent was removed and the residue chromatographed using mixtures of hexane-ethyl acetate, to afford 395 mg of recovered **1** and cycloadducts **2**, **3** and **4** (567 mg, 70 % combined yield based on converted **1**).This mixture of adducts was analyzed by ^{1}H-NMR showing a 6/3/1 ratio. Further chromatography led to obtain the adducts in pure form.

Methyl (*1S,2R,6R*)-1-benzyloxycarbonylamino-6-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-trimethylsilyloxy-3-cyclohexen-1-carboxylate, 2. Oil, $[\alpha]_D$-134.9 (c=2.43, $CHCl_3$); IR (film) 3381, 3037, 1750 1736 cm^{-1}; MS, m/e 462 (M-15, 1), 408 (4), 308 (3), 225 (21), 209 (7), 142 (100), 101 (15), 91 (75), 73 (28), 43 (14); 250-MHz ^{1}H-NMR 0.05 (s, 9H), 1.24 (s, 3H), 1.30 (s, 3H), 2.18 (m, 1H), 2.33 (m, 1H), 2.59 (m, 1H), 3.64 (t, J=7.5 Hz, 1H), 3.73 (s, 3H, OMe), 4.09 (t, J=7.5 Hz, 1H), 4.59 (d, J=5.0 Hz, 1H), 4.73 (m, 1H), 4.96-5.10 (complex absorption, 2H), 5.22 (broad s, 1H), 5.65 (m, 1H), 5.93 (m, 1H), 7.31 (broad s, 5H); 62.5-MHz ^{13}C-NMR 0.2 (3C), 21.5, 25.1, 26.2, 34.7, 52.0, 64.3, 66.5, 68.2, 68.5, 74.4, 109.0, 124.4, 128.0, 128.2, 128.4 (2C), 131.3, 136.5, 155.2, 170.9, 175.8. Anal. Calcd. for $C_{24}H_{35}O_7NSi$: C, 60.43; H, 7.40; N, 2.94. Found: C, 60.29; H, 7.47; N, 2.97.

Methyl (*1S,2S,6R*)-1-benzyloxycarbonylamino-6-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-trimethylsilyloxy-3-cyclohexen-1-carboxylate, 3. Oil, $[\alpha]_D$ -44.3 (c= 1.31, $CHCl_3$); IR (film) 3409, 3036, 1722 cm^{-1}; MS, m/e 462 (M-15, 1), 142 (37), 91 (100), 73 (28), 43 (21); 250-MHz ^{1}H-NMR 0.01 (s, 9H), 1.24 (s, 3H), 1.30 (s, 3H), 2.15 (m, 1H), 2.41 (m, 1H), 3.09 (m, 1H), 3.58 (dd, J=8.2 Hz, J'=6.7 Hz, 1H), 3.67 (s, 3H, OMe), 3.92 (dd, J=8.2 Hz, J'=7.3 Hz, 1H), 4.15 (m, 1H), 5.04 (broad s, 2H), 5.44 (d, J=10.1 Hz, 1H), 5.77 (m, 1H), 6.49 (s, 1H), 7.24-7.36 (complex absorption, 5H); 62.5-MHz ^{13}C-NMR -0.1 (3C), 24.0, 25.0, 26.0, 38.2, 52.4, 66.0, 66.6, 66.9, 69.7, 73.4, 108.7, 127.2, 128.2, 128.3 (2C), 128.5 (2C), 136.3, 153.9, 171.0.

Methyl 1-benzyloxycarbonylamino-6-[(4S)-4-(2,2-dimethyl-1,3-dioxolo)]-2-trimethylsilyloxy-3-cyclohexen-1-carboxylate, 4. Oil, MS, m/e 419 (M-59($COOCH_3$), 1), 354 (1), 308 (1), 252 (1), 151 (1), 142 (100), 107 (11), 91 (36), 73 (34), 43 (21); 250-MHz ^{1}H-NMR 0.06 (s, 9H), 1.24 (s, 3H), 1.32 (s, 3H), 2.18 (m, 1H), 2.43-2.52 (complex absorption, 2H), 3.49 (t, J=7.5 Hz, 1H), 3.68 (s, 3H, OMe), 3.96 (m, 1H), 4.46 (m, 1H), 5.04-5.09 (complex absorption, 2H), 5.32 (dd, J=10.1 Hz, J'=2.1 Hz, 1H), 5.39 (broad s, 1H), 5.79 (m, 1H), 7.27-7.36 (complex absorption, 5H); 62.5-MHz ^{13}C-NMR -0.1 (3C), 26.1, 26.8, 42.9, 52.3, 63.9, 66.6, 68.5, 72.7, 107.3, 126.2, 127.9, 128.4 (2C), 129.5, 136.5, 156.1, 171.9, 175.8.

Cycloaddition of Danishefsky's diene to unsaturated oxazolone 5: Ketones 8 and 9.

Danishefsky's diene (1.6 g, 9.1 mmol) was added to a stirred solution of oxazolone **5** (500 mg, 1.8 mmol) in dry dichloromethane (25 mL) under argon and the mixture was stirred at room temperature for 30 min. After completion the solvent was removed and a 0.05 % HCl-THF solution (20 mL) was added to the residue. The reaction mixture was stirred for 30 min, the solvent was eliminated and the mixture was diluted with dichloromethane (15 ml). This solution was extracted with satured aqueous sodium carbonate (2x20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed (3:1 hexane-ethyl acetate) to afford three fractions: (a) ketone **8** (140 mg, 21% yield, two steps), (b) ketone **9** (70 mg) and (c) 170 mg of a 2:1 mixture of **9/10** (after ^{1}H-RMN analysis). Compound **9:** 187 mg, 28% yield, two steps. Compound **10**: 53 mg, 9% yield.

***(3R,4S,5R)*-5-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-4-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-3-methoxycyclohexan-1-one, 8.** Oil, o.t. 210 °C (0.5 mbar); $[\alpha]_D$ -46.6 (c=3.97, $CHCl_3$); IR(film) 1813, 1722, 1658 cm^{-1}; MS, m/e 358 (M-15, 1), 315 (18), 257 (6), 214 (26), 186 (8), 105 (100), 85 (9), 77 (26), 43 (18); 250-MHz ^{1}H-NMR 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.32 (m,1H), 2.53 (m, 1H), 2.74-3.0 (complex absorption, 3H), 3.31 (s, 3H, OMe), 3.60 (t, J=7.6 Hz, 1H), 4.00-4.13 (complex absorption, 2H), 4.72 (m, 1H), 7.45-7.63 (complex absorption, 3H), 8.03-8.06 (complex absorption, 2H); 62.5-MHz ^{13}C NMR 24.9, 25.0, 35.7, 41.8, 42.0, 58.2, 67.6, 73.8, 76.4, 78.3, 110.5, 125.5, 128.1 (2C), 128.8, 133.0 (2C), 161.6, 205.3. Anal. Calcd. for $C_{20}H_{23}O_6N$: C, 64.40, H, 6.22, N, 3.76. Found: C, 64.45, H, 6.25 , N, 3.70.

***(3S,4S,5R)*-5-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-4-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-3-methoxycyclohexan-1-one, 9.** Crystals, m.p. 148-150 °C (from ethyl acetate/pentane); $[\alpha]_D$ +78.5 (c=0.56, $CHCl_3$); IR (KBr) 1827, 1722, 1658 cm^{-1}; MS, m/e 373 (M, 1), 358 (M-15, 2), 315 (25), 257 (4), 214 (21), 187 (8), 134 (4), 105 (100), 97 (5), 85 (9), 77 (25), 72 (5), 69 (5), 43 (21); 250-MHz ^{1}H-NMR 1.18 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.51-2.73 (complex absorption, 3H), 2.85 (d, J=8.8 Hz, 2H), 3.26 (s, 3H, OMe), 3.72-3.80 (complex absorption, 3H), 3.96 (m, 1H), 7.45-7.61 (complex absorption, 3H), 8.01-8.05 (complex absorption, 2H); 62.5-MHz ^{13}C NMR 24.7, 25.5, 39.4, 40.9, 42.9, 57.7, 66.5, 74.3, 74.8, 81.3, 109.3, 125.7, 128.2 (2C), 128.7 (2C), 132.9, 178.7, 205.2. Anal. Calcd. for $C_{20}H_{23}O_6N$: C, 64.40, H, 6.22, N, 3.76. Found: C, 64.33, H, 6.24, N, 3.76.

X-Ray Structure determination for compound 9. Atomic coordinates, bond lenghts and angles , and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. Details of the crystals, collection and processing, and refinement are as follow. *Crystal data.* $C_{20}H_{23}NO_6$, M = 373.39, monoclinic, space group $P2_1$ (No. 4), a = 6.922 (1) A, b = 8.646 (4) A, c = 16.293 (3) A, β = 91.31 (1)° (from least squares fitting of setting angles for 25 reflections 8.8° < θ < 15.6°), V = 974.8 A^3, Z = 2, D_c =

1.272 g cm^{-3}, μ = 0.94 cm^{-1}; radiation: graphite monochromated Mo-Kα (λ = 0.71069 A), colourless prismatic crystal 0.43 x 0.25 x 0.22 mm. *Data collection and processing.* Data were collected on an Enraf-Nonius CAD4 in ϖ-2θ scan, T = 293 °K, data collection range $2 < 2\theta < 50^{o}$ ($-8 < h < 8$, $0 < k < 10$, $0 < l < 19$). 1837 Unique reflections of which 1110 were observed ($I > 2\sigma(I)$). No significant variation in intensity of one standard reflection was observed. *Structure solution and refinement.* The structure was solved by direct methods using the SHELXS-86 program.[18] Full matrix least-squares refinement on F^2 for all reflections was carried out using the SHELXL-93 program,[19] number of variables: 244, hydrogen atoms in calculated positions with isotropic thermal parameters fixed at 1.5 (methyl groups) or 1.2 (the rest) times U_{eq} of the corresponding carbon atoms. R(F) = 0.0397, $R_w(F^2)$ = 0.0809 for the observed reflections.

Methyl (*1R,6R*)-1-benzamido-6-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-4-oxo-2-cyclohexen-1-carboxylate, 11. *Method A* from **8** is described (Scheme 3). DBU (82 mg, 0.5 mmol) was added to a solution of compound **8** (200 mg, 0.5 mmol) in MeOH (15 ml) and the mixture was stirred for 15 min at 0°C. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane-ethyl acetate as eluent to yield enone **11** (165 mg, 82 % yield) as a solid. Crystals, m.p 168-170 °C (from ethyl acetate/pentane); $[\alpha]_D$ +74.4 (c=0.86, $CHCl_3$); IR (KBr) 3332, 1729, 1686, 1665, 1525, cm^{-1}; MS, m/e 358 (M-15, 1), 105 (100), 77 (52), 51 (10), 43 (27); 250-MHz ^{1}H-NMR 1.38 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.47-2.59 (complex absorption, 2H), 2.79 (m, 1H), 3.73 (dd, J=8.8 Hz, J'=5.8 Hz, 1H), 3.80 (s, 3H, OMe), 4.09 (dd, J=8.8 Hz, J'=7.3 Hz, 1H), 4.52 (t, J=6.6 Hz, 1H), 6.05 (d, J=10.2 Hz, 1H), 7.38-7.53 (complex absorption, 3H), 7.69 (d, J=10.2 Hz, 1H), 7.76 (complex absorption, 2H), 8.40 (broad s, NH, 1H); 62.5-MHz ^{13}C-NMR 24.7, 25.8, 32.5, 42.8, 53.3, 61.0, 68.8, 73.8, 110.7, 127.0, 127.8, 128.6, 131.9, 133.2, 147.5, 167.6, 171.6, 197.3. Anal. Calcd. for $C_{20}H_{23}O_6N$: C, 64.40, H, 6.22, N, 3.76. Found: C, 64.26, H, 6.19, N, 3.57.

Cycloaddition of 1-trimethylsilyloxy-1,3-butadiene to oxazolone 5: Adducts 12 and 13.

(a) Thermal cycloaddition. 1-Trimethylsilyloxy-1,3-butadiene (2.2 mL, 12.8 mmol) was added to a stirred solution of oxazolone **5** (700 mg, 2.6 mmol) in dry dichloromethane (25 mL) under argon and the mixture was stirred at room temperature for 20 h. After completion the solvent was removed and the residue was chromatographed (85:15 hexane-ethyl acetate) to afford the cycloadducts **12** (254 mg, 24% yield) and **13** (465 mg, 45% yield).

(b) High-pressure induced cycloaddition. 1-Trimethyllsilyloxy-1,3-butadiene (370 mg, 2.7 mmol) and azalactone **5** (400 mg, 1.4 mmol) in dichloromethane (0.9 mL) were reacted at 12.5 Kbar for 6 h. After decompression the solvent was removed and the residue was chromatographed (85:15 hexane-ethyl acetate) to afford 50 mg of recovered **5** and cycloadduct **12** (480 mg, 91% yield).

(*1R,2S,3R*)-3-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-1-trimethylsilyloxy-5-cyclohexene, 12. Crystals, m.p. 97-99 °C (from ethyl acetate/pentane); $[\alpha]_D$ -120.6 (c=0.68, $CHCl_3$); IR (film) 1820, 1658 cm^{-1}; MS, m/e 415 (M, 1), 400 (M-15,1), 314 (4), 143 (13), 142 (100), 105 (66), 77(23), 73(39), 43(16); 250-MHz ^{1}H-NMR -0.03 (s, 9H), 1.23 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.09 (m, 1H), 2.71 (dd, J=5.5 Hz, J'=2.9 Hz, 1H), 2.79 (dd, J=5.5 Hz, J'=2.6 Hz, 1H), 3.66 (m. 1H), 4.24-4.38 (complex absorption, 2H), 4.46 (broad s, 1H), 5.51 (m, 1H), 5.90 (m, 1H), 7.42-7.58 (complex absorption, 3H), 7.92-7.97 (complex absorption, 2H); 62.5-MHz ^{13}C NMR -0.1 (3C), 23.3, 25.8, 26.5, 42.7, 69.2, 69.9, 74.1, 75.1, 107.9, 125.6, 125.9, 127.8 (2C), 127.9, 128.7 (2C), 133.6, 160.7, 175.6. Anal. Calcd. for $C_{22}H_{29}O_5NSi$: C, 63.67; H, 7.04; N, 3.38. Found: C, 63.54; H, 7.18; N, 3.41.

(*1S,2S,3R*)-3-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-1-trimethylsilyloxy-5-cyclohexene, 13. Crystals, m.p. 95-97 °C (from ethyl acetate/pentane); $[\alpha]_D$ +153.4 (c=1.63, $CHCl_3$); IR (film) 1820, 1658 cm^{-1}; MS, m/e 415 (M, 1), 400 (M-15,1), 314 (4), 143 (13), 142 (100), 105 (54), 77(20), 73(32), 43(13); 250-MHz ^{1}H-NMR 0.0 (s, 9H), 1.14 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.30-2.36 (complex absorption, 2H), 2.61 (m, 1H), 3.73-3.85 (complex absorption, 2H), 3.95 (dd, J=14.1 Hz, J'=6.2 Hz, 1H), 4.70 (broad s, 1H), 5.57 (dd, J=10.0 Hz, J'=1.7 Hz, 1H), 5.88 (m, 1H), 7.41-7.56 (complex absorption, 3H), 7.98-8.02 (complex absorption, 2H); 62.5-MHz ^{13}C NMR -0.2 (3C), 24.7, 25.6 (2C), 40.9, 66.9, 72.9, 74.6, 75.5, 108.6, 125.9, 127.1 (2C), 127.9 (2C), 128.1, 128.4, 132.3, 161.0, 180.2. Anal. Calcd. for $C_{22}H_{29}O_5NSi$: C, 63.67; H, 7.04; N, 3.38. Found: C, 63.60; H, 7.14; N, 3.41.

(*2S,3R*)-3-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-5-cyclohexen-1-one, 16, through alcohols 14 and 15. A solution of citric acid (185 mg, 0.96 mmol) in methanol (8 ml) was added to a stirred solution of trimethylsilyloxy ether **13** (200 mg, 0.48 mmol) in methanol (12 ml). The mixture was stirred at room temperature for thirty minutes. The solution was diluted with methylene chloride washed with satured aqueous sodium carbonate and extracted. After evaporation of the solvent, the alcohol **15** was obtained as a viscous yellow oil (152 mg, 93% yield). Further purification was performed by chromatography (hexane-ethyl acetate) to give 140 mg of pure **15**.

Using the same experimental procedure for trimethylsilyloxy ether **12** (100 mg, 0.24 mmol), alcohol **14** was produced (74 mg, 90% yield).

***(1R,2S,3R)*-3-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-5-cyclohexen-1-ol , 14.** Oil, IR (film) 3592-3198 (broad), 1813, 1651 cm^{-1}; MS, m/e 299.1 (M-44, 2), 241 (1), 199 (19), 118 (16), 105 (100), 101 (14), 77 (79), 51 (21), 43 (60), 41 (12); 250-MHz ^{1}H-NMR 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.39 (m, 1H), 2.48 (m, 1H), 2.57 (m, 1H), 2.65 (d, J=5.1 Hz, 1H), 3.70 (t, J=7.7 Hz, 1H), 4.11-4.33 (complex absorption, 3H), 5.77 (dd, J=10.2 Hz, J'=2.9 Hz, 1H), 6.03 (m, 1H), 7.42-7.59 (complex absorption, 3H), 7.93-7.97 (complex absorption, 2H); 62.5-MHz ^{13}C NMR 23.9, 25.2, 26.1, 40.6, 68.5, 73.6, 75.0, 108.5, 124.3, 125.5, 127.8, 127.9, 128.7 (2C), 129.8, 132.8, 161.3, 177.2.

(*1S,2S,3R*)-3-[(*4S*)-4-(2,2-dimethyl-1,3-dioxolo)]-2-spiro{4'[2'-phenyl-5'(4'*H*)-oxazolone]}-5-cyclohexen-1-ol, 15. Oil, $[\alpha]_D$ +194.8 (c=2.32, $CHCl_3$); IR (film) 3557-3240 (broad), 1813 , 1651 cm^{-1}; MS, m/e 299.1 (M-44, 2), 241 (1), 224 (1), 199(16), 118 (16), 105 (98), 101 (16), 77 (100), 73 (13), 59 (11), 51 (32), 43 (91), 41 (18); 250-MHz ^{1}H-NMR 1.17 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.08 (broad d, J=10.9 Hz, OH), 2.22-2.29 (complex absorption, 2H), 2.57 (m, 1H), 3.69-3.83 (complex absorption, 2H), 3.94 (dd, J=13.9 Hz, J'=6.2 Hz, 1H), 4.55 (m, 1H), 5.61 (dd, J=10.2 Hz, J'=2.2 Hz, 1H), 5.86 (m, 1H), 7.40-7.56 (complex absorption, 3H), 7.97-8.00 (complex absorption, 2H); 62.5-MHz ^{13}C-NMR 24.6, 25.1, 25.5, 41.1, 66.7, 72.1, 74.1, 75.2, 108.7, 125.6, 127.6, 128.0 (2C), 128.1, 128.6 (2C), 132.8, 162.4, 179.6.

Manganese dioxide (291 mg, 3.3 mmol) was added to a stirred solution of alcohol **15** (115 mg, 0.33 mmol) in cloroform (15 ml). The black mixture was stirred at room temperature for 24 hours. The suspension was filtered through celite and the solvent was removed. The residue was chromatographed with ethyl acetate-hexane using Florisil as stationary phase[20] to afford pure ketone **16** (75 mg, 66% yield). This ketone was also obtained (23 mg, 62% yield) from alcohol **14** (38 mg, 0.11 mmol) by using the same experimental procedure.

Ketone 16: Crystals, m.p 151-153°C (from ethyl acetate/pentane) $[\alpha]_D$ +228.1 (c=0.57, $CHCl_3$); IR (KBr) 1827, 1679, 1651 cm^{-1}; MS, m/e 341 (M, 1), 326 (M-15, 1), 283 (19), 240 (1), 196 (3), 187 (2), 174 (3),105 (100), 77 (31), 68 (20), 51 (5), 43 (13); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.52-2.56 (complex absorption, 2H), 2.73 (dd, J=13.9 Hz, J'=6.9 Hz, 1H), 3.58 (m, 1H), 3.73 (t, J=8.1 Hz, 1H), 3.88 (dd, J=13.2 Hz, J'=6.6 Hz, 1H), 5.97 (d, J=10.2 Hz, 1H), 7.00 (m, 1H), 7.16-7.35 (complex absorption, 3H), 7.75-7.78 (complex absorption, 2H); 62.5-MHz ^{13}C NMR 25.0, 25.5, 25.8, 42.8, 67.5, 74.6, 76.5, 109.1, 125.4, 127.3, 128.2 (2C), 133.2, 151.6, 163.2, 175.1, 189.2. Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.92, H, 5.62, N, 4.11. Found: C, 66.90, H, 5.60, N, 4.19.

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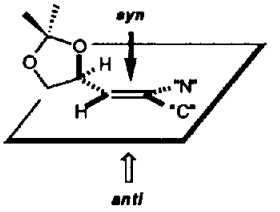
    Syn/anti is a notation used in these works to distinguish the two facial diastereoisomers and is also applied in the present paper. Thus, *syn* facial diastereoselection is referred to the attack of the diene on the π-face of the double bond marked by the black arrow, assuming a conformation for the dioxolane ring as represented in the figure. *Anti* orientation is stated by the white arrow to occur by the opposite side of the plane. Although we reported in reference 12a that such a conformation involves, indeed, an energy maximum, this representation is useful to unify the nomenclature.



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14. Adducts **6** and **7** are unstable oils which were hydrolyzed without purification. Ratio of both stereoisomers was shown to be 1:1 after ^{1}H NMR analysis.
15. Unsaturated **10** could not be isolated but identified from the **9/10** mixture that shows characteristic doublets for the olefinic protons at δ 6.87 and 7.89 (J = 7.9 Hz).
16. These values are approximate since absorption corresponding to *H-5* is very close to those of $H\text{-}6_a$ and $H\text{-}6_b$.
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20. This compound was unstable when chromatographed on silica gel.

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