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Diastereofacial Selectivity in 1,3-Dipolar Cycloadditions. Reactions of Diazomethane with endo,cis-5,6-Disubstituted Bicyclo[2.2.2]oct-2-enes.[1]

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Key Words 1,3-Dipolar cycloadditions, Facial selectivity, Diazomethane, Bicyclo[2 2 2]oct-2-enes

Abstract *The reaction of diazomethane with endo,cis-5,6-diacetoxy, dimesyloxy, bis(methoxycarbonyl) and dihydroxybicyclo[2 2 2]oct-2-ene derivatives, respectively, afforded either only the anti adduct or a mixture of anti and syn adducts wherein the anti diastereoisomer was highly dominant (≥10 1) The observed facial selectivity provides convincing evidence that direct through space interactions between the attacking 1,3-dipole and acetoxy, hydroxy etc substituents are, as a whole, repulsive Steric "non-bonded" repulsions and dipole-dipole interactions override possible stabilizing interactions, e g orbital interactions and hydrogen bonding effects*

INTRODUCTION

The >98% syn selectivity of the reaction of diazomethane with cis-3,4-diacetoxy-, dimesyloxy- and dialkoxycyclobutene (Figure 1) no doubt provides one of the most interesting and intriguing examples of facial selectivity in the field of 1,3-dipolar cycloadditions [2] When one attempts to find out a theoretical rationale for this experimental finding the problem of separating intramolecular from intermolecular effects arises In fact, the substituents at positions 3 and 4 of the cyclobutene certainly do act both via direct through space intermolecular interactions (steric, electrostatic, secondary orbital interactions etc) with the incoming reactant and by perturbing the π-bond through intramolecular hyperconjugative σ-π interactions On the basis of theoretical investigations we have recently concluded that intramolecular hyperconjugative interactions play a major role in favoring syn attack by inducing in these compounds a significant out-of-plane anti bending of the olefinic hydrogens [2,3] However, owing to the very high selectivity observed, one may well argue that also intermolecular interactions, as a whole, favor syn attack For example, London dispersion forces in Diels-Alder reactions[4] as well as secondary orbital interactions in both Diels-Alder[5] and 1,3-dipolar cycloadditions[6] (Figure 2) have been advanced as stabilizing through space interactions[7] favoring syn attack Thus, in order to clarify on an experimental basis what is the role of intermolecular interactions, it was mandatory to study the reaction of diazomethane with appropriate dipolarophiles in which the substituents could fully exploit their direct through space effect without strongly perturbing the π-bond intramolecularly Endo,cis-5,6-disubstituted bicyclo[2 2 2]oct-2-enes, e g **1**, **3** and **4**, lend themselves as appealing substrates to study this problem for the following reasons i) Owing to the symmetry of the parent compound there is not any carbon-skeleton imposed facial diastereotopicity ii) Ab-initio calculations show that the substituents at positions 5 and 6 do not appreciably impair the two faces of the double bond at least as far as the planarity of this bond is concerned [8] Substituents are located in a homoallylic position and consequently there is not any hyperconjugative interaction between the π-bond and σ_{C-X} bonds iii) The substituents can efficiently interact (directly through space) with

the incoming 1,3-dipole In fact when attractive interactions between substituents and the attacking 1,3-dipole can be at work they actually show them up clearly in the observed diastereoselectivity. For example, in the reaction of nitrones with the endo,cis-5,6-dihydroxybicyclo[2 2.2]oct-2-ene,i e. **1a**, syn[9] attack is highly dominant as a result of hydrogen bonding involving the oxygen atom of the 1,3-dipole and one of the hydroxy group (Figure 3) [8]

In this paper we describe our findings in the reactions of diazomethane with endo,cis-5,6-disubstituted bicyclo[2.2 2]oct-2-enes bearing substituents, such as acetoxy and mesyloxy groups, which are the most efficient groups in promoting syn attack to cis 3,4-disubstituted cyclobutenes Moreover, we extended this study also to the reaction of diazomethane with dihydroxybicyclooctenes in order to find out whether hydrogen bonding plays some role in guiding facial selectivity in the cycloadditions of diazomethane or not.

RESULTS AND DISCUSSION

Bicyclooctenes

Bicyclooctenes used in this study are reported in Scheme 1. Osmylation reactions of compounds **5** and **7**, respectively, were carried out under catalytic conditions in acetone·water 4.3[10] to produce mixtures of two dihydroxyderivatives In the case of **5** the disubstituted double bond is at least twice as reactive as the trisubstituted one Only products arising from "bottom side" attack, i e anti to the ethano bridge, were isolated The attack by OsO_4 to **7** took place only at the disubstituted double bond with formation of a mixture of the two diastereoisomers **4a** and **8a** ,with the former highly dominant The observed selectivity clearly reflects the tendency of the mildly electrophilic osmium tetroxide to attack the more electron-rich and less crowded double bond on its sterically less encumbered face Facial selectivity of osmylation reactions of **5** and **7** is similar to that found in the reaction of **7** with 1,3-dipoles In fact, only bottom side attack was observed in the reactions of diphenylnitrile imide, phenyl azide and nitrile oxides with **7**.[11] The dominant anti 1,3-dipolar cycloaddition to **7** was tentatively explained[11] on the basis of a higher extension of HOMO and LUMO (as a result of orbital mixing, Fukui's model)[12] on the face anti to the ethano bridge However, we feel that steric effects (as stated above) provide a much more straightforward rationalization of the observed facial selectivity not only in osmylation reactions of **5** and **7** but also in 1,3-dipolar cycloadditions of **7**

As for the conformational isomerism of the substituents on bicyclooctenes, X-ray data[13a], and MO (MNDO) calculations[13b] indicate that they prefer a conformation of the type **9** (Scheme 1) with the R groups located away from the double bond This conformation is very similar to that adopted by the same substituents in cis-3,4-disubstituted cyclobutenes [2,3] Thus, steric hindrance to syn attack in bicyclooctenes should resemble, more or less closely, that present in cyclobutenes

The IR spectra of a very dilute (CCl_4) solution of the dihydroxyderivatives **1a**, **3a** and **4a** displayed a strong band in the region of OH absorptions (at 3559, 3496, and 3527 cm^{-1}, respectively).Only in the case of **4a** a weak absorption at 3620 cm^{-1} was also present In contrast, the exo derivative **2** showed two strong bands at 3631 (free OH) and 3529 (bonded OH) cm^{-1} These findings suggest that the dominant conformation of **1a**, **3a** and **4a** features both OH groups involved in hydrogen bonding, i e a conformation of the type **10** or **11** [14] Aside from hydrogen bonding effects these conformations are also favored by a lessening of repulsions between the electrons of the oxygen lone pairs and those of the π bond [14] Regardless of which factor determines the observed conformational preference of the two OH groups in **1a**, **3a** and **4a**, at least one of them is properly oriented to be involved in hydrogen bonding with the attacking 1,3-dipole However, if the reaction can not take advantage of hydrogen bonding steric hyndrance to syn attack in **10** and **11** may even be slightly larger than in **9** and a higher anti selectivity can be anticipated for the former compounds than for the latter one

Cycloadditions

It is known that the double bond of bicyclo[2.2 2]oct-2-ene exhibits a very low reactivity in 1,3-dipolar cycloadditions [15,16] Actually, the reaction of diazomethane with the π bond of **1a** is so slow that no adducts of

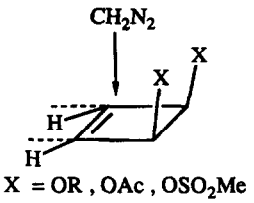


FIGURE 1

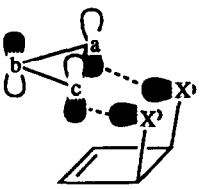


FIGURE 2

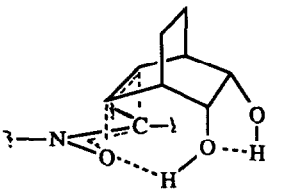
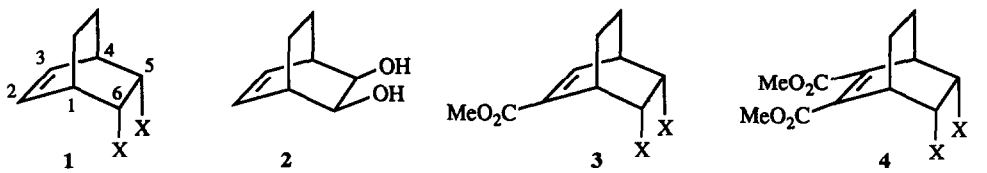
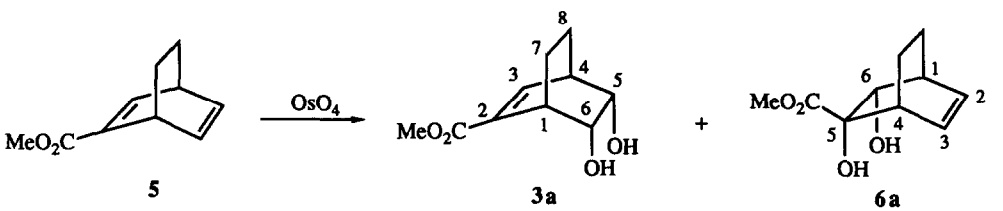
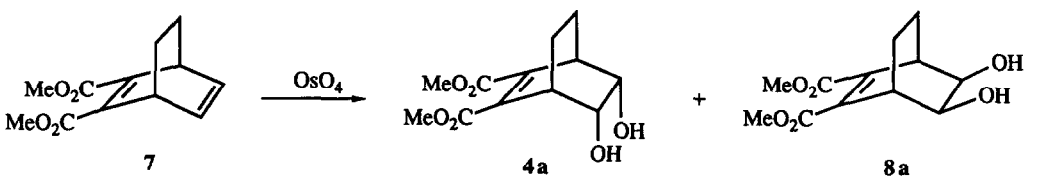


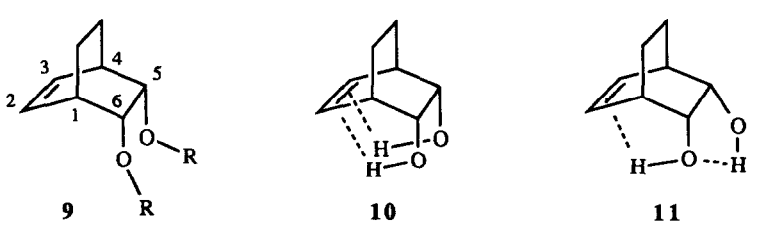
FIGURE 3



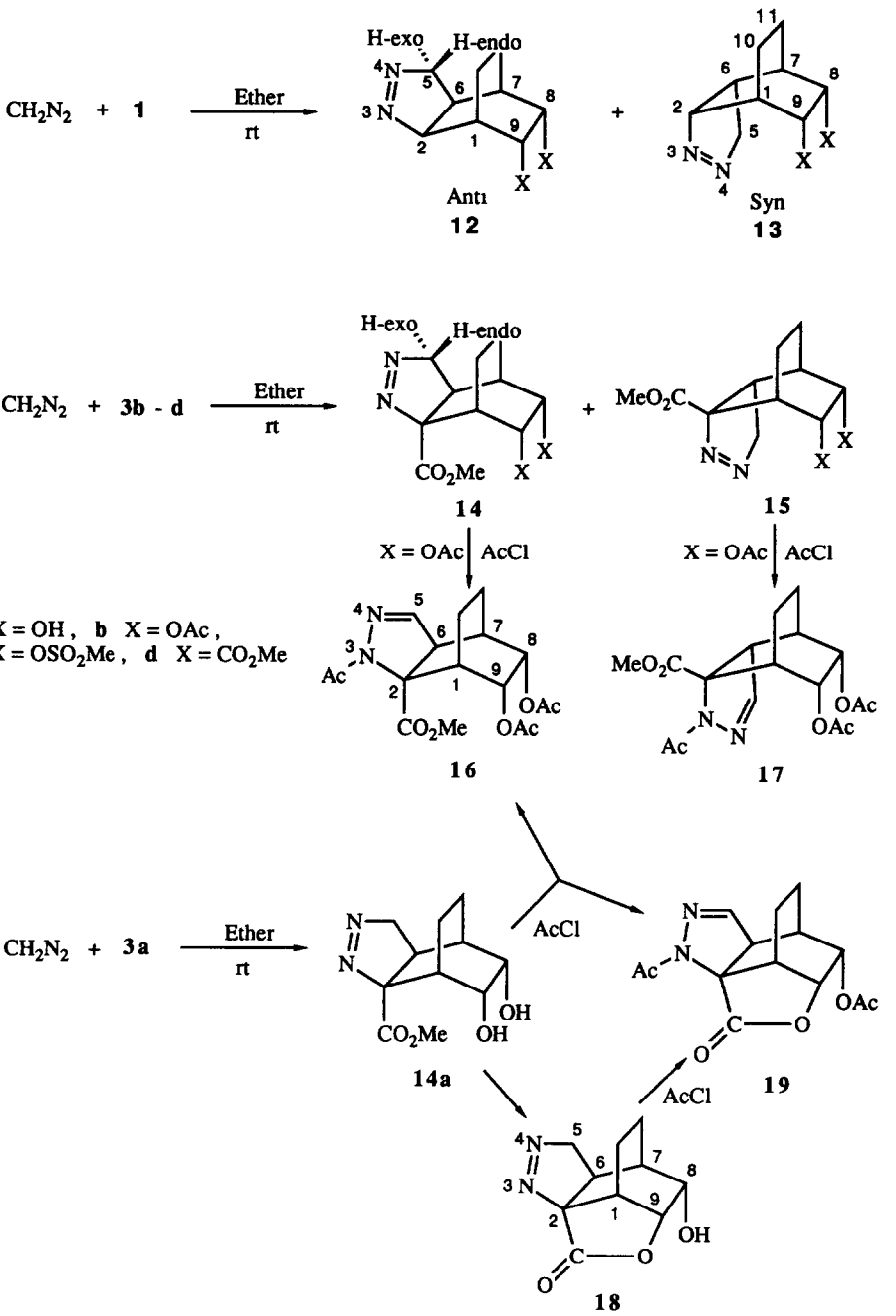
a X = OH , **b** X = OAc , **c** X = OSO_2Me , **d** X = CO_2Me







SCHEME 1


CH2N2 + 1
Ether
rt
H-exo
H-endo
Anti
12
Syn
13
CH2N2 + 3b - d
14
15
X = OAc
AcCl
a X = OH, b X = OAc,
c X = OSO2Me, d X = CO2Me
16
17
CH2N2 + 3a
14a
19
18

SCHEME 2

the type **12** (or **13**) (Scheme 2) were formed (at least in isolable amounts) and the monomethyl derivative of **1a** was isolated in good yields after one month Also in the reaction of **2** with diazomethane the methylation reaction, although slower than that of **1a**, was again preferred over cycloaddition

In the case of **1b** and **1c** very long reaction times (two months at rt) allowed us to isolate a single monoadduct, i e **12b** and **12c** respectively, in low yields (25%) (Scheme 2) Symmetry of the carbon skeleton of the bicyclooctane moiety in these adducts, and in all of the adducts which we will be dealing with, precludes the possibility of using the vicinal coupling constants $J_{1,2}$ and $J_{6,7}$ as a stereochemical probe However, the anti structure **12b** could firmly be established by transforming **12b** into the dihydroxyderivative **12a** whose anti stereochemistry was safely inferred from LIS experiments In fact in the presence of increasing amounts of $Eu(fod)_3$ the signals of H-2 and H-6 moved to lower fields more rapidly not only than H-5-endo and H-5-exo but also than H-1 and H-7, respectively This observation is consistent with the anti structure **12a** but not with the syn one **13a** A syn structure would have required the presence of a long range coupling constant (^4J) between H-2 and H-9 as well as between H-6 and H-8 (owing to the presence of a W coupling pathway) Such a splitting was missing in the ^1H NMR spectra of adducts **12** [17a] The very similar chemical shifts of H-5-endo and H-5-exo in adducts **12** also supports their anti structure [17b] It is interesting to notice that in **12b** and **12c** the 1-pyrazoline nucleus brings about a different deshielding of the two bridgehead protons, H-1 and H-7, with H-1 resonating at lower fields than H-7 by >1 0 ppm This effect can be attributed both to the electron attracting effect of the azo group directly attached to position 1 and to the proximity of the lone pair on N-3 to H-1

We carefully looked for (by chromatographic and ^1H NMR techniques) the syn adduct in the reactions of **1b** and **1c** but we did not manage to find any evidence of its presence Even if small amounts of the syn adduct might well have escaped detection, the high anti selectivity (> 95%) observed for **1b** and **1c** is totally at variance with the > 98% syn selectivity of the cycloaddition of diazomethane to diacetoxy and dimesyloxycyclobutene Through space interaction between the acetoxy or mesyloxy groups and the attacking diazomethane is, as a whole, repulsive Consequently we conclude that the syn orienting effect of these groups in cyclobutenes does not stem from this kind of interaction

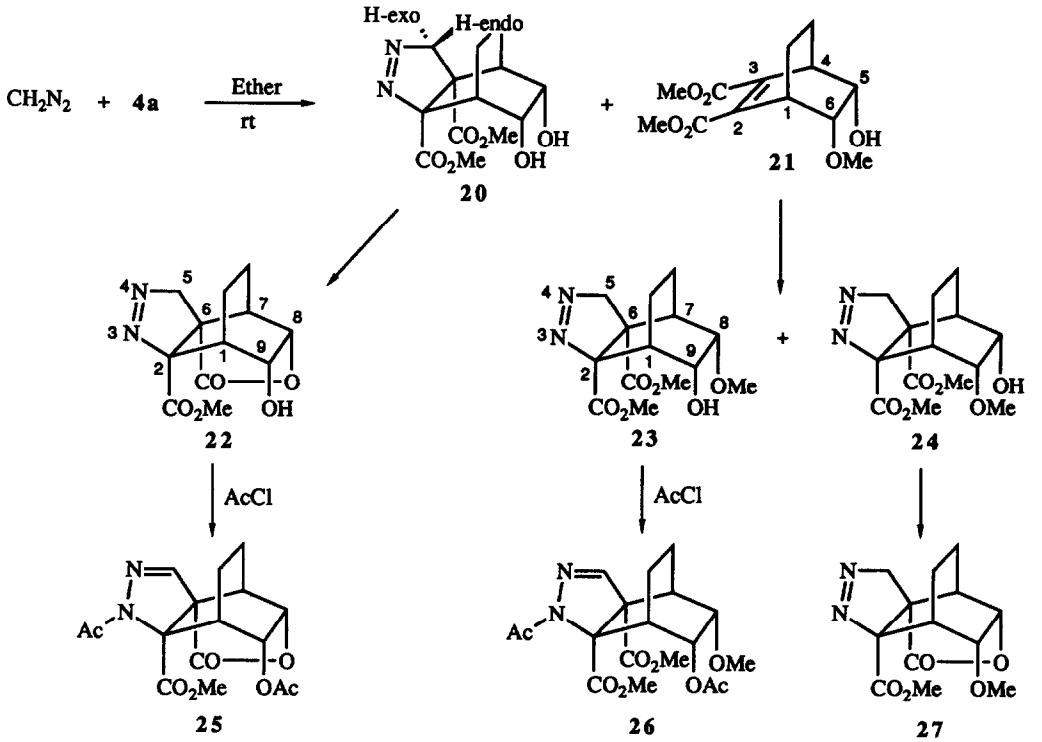
To properly substantiate this conclusion we deemed it necessary to extend our study to more reactive bicyclooctenes such as **3** and **4** in which the carbon carbon double bond is activated by the presence of methoxycarbonyl groups

The dihydroxybicyclooctene **3a** reacted readily (≤ 6 h) with excess diazomethane to afford only the anti adduct **14a** whose structure relies firmly on its very easy lactonization reaction to give **18** (Scheme 2) Even if small amounts of the syn adduct could have gone undetected this result provides reliable evidence against the presence in the transition state of relevant stabilizing hydrogen bonding interactions between diazomethane and the OH groups

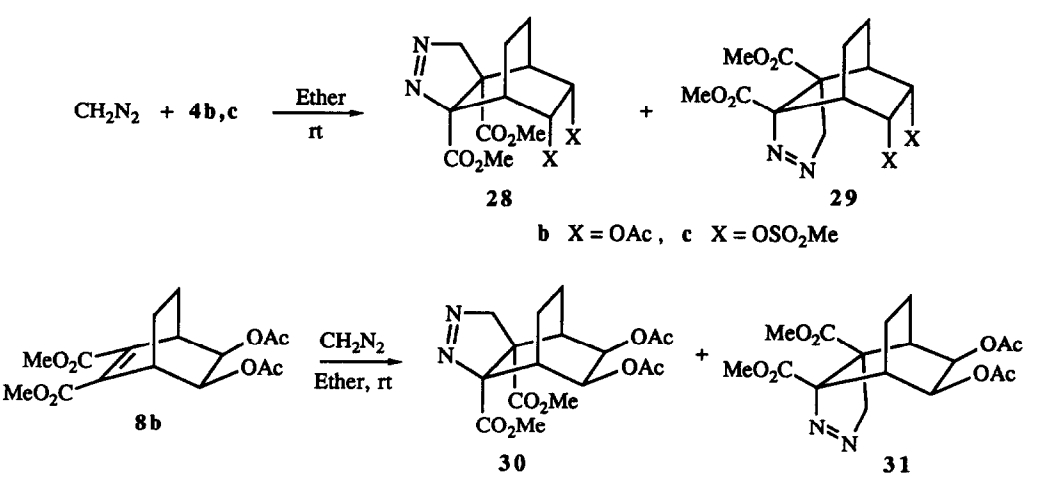
Compound **3b** and **3c** also reacted readily with diazomethane to produce mixtures of anti and syn adducts, i e **14** and **15,** (Scheme 2) wherein the anti adduct was highly dominant (**14** : **15** ≥ 10 1) In the case of **3b** (X = OAc) the syn adduct **15b** could be isolated in a pure state and fully characterized Differentiating features between the ^1H NMR of the syn adduct **15b** and that of the anti adduct **14b** are i) the presence in **15b** of a long range coupling constant between H-6 and H-8 ($^4J_{6,8}$ = 1 0 Hz) ii) a shift to lower fields of H-5-endo in **15b** as a result of proximity of the lone pairs of the acetoxy groups [17b] Chemical correlation between **14a** and **14b** is described in Scheme 2 Acetylation of hydroxy groups in **14a** and **18** is accompanied by tautomerization of the 1-pyrazoline moiety to a 2-pyrazoline structure which in turn is acetylated Likewise treatment of **14b** and **15b** with acetyl chloride led to 1-acetyl-2-pyrazolines **16** and **17**,respectively In the reaction of **3c** (X = OSO_2Me) the syn adduct was detected by ^1H NMR analysis of the crude reaction mixture

Only one adduct was isolated from the reaction of **3d** (X = CO_2Me) with diazomethane, i e the anti adduct **14d**

Introduction of a second methoxycarbonyl group on the bicyclooctene double bond, i e passing to compounds **4**, brought about a decrease in 1,3-dipolar cycloaddition rate as compared to compounds **3** However, compounds **4** were more reactive than their unsubstituted counterparts, i e compounds **1** The lower reactivity of **4** than **3** can be ascribed to steric congestion which in **4** impedes adoption of a coplanar



SCHEME 3



SCHEME 4

conformation by the second methoxycarbonyl group with the result that it can not fully exploit its activating conjugating effect Steric shielding to 1,3-dipolar attack increases and is not efficiently counteracted by an increase in the "electronic" reactivity of the double bond.[18]

In the reaction of **4a** with diazomethane methylation and cycloaddition compete to produce a mixture of **21** (22%) and **22** (18%) (after 60 h with a 33% recovery of **4a**) and minor amounts of **23** and **27** (Scheme 3) These latter compounds were also produced in the reaction of **21** with diazomethane The lactone ring in **22** and **27** proves beyond all doubt that their precursors (neither isolated nor detected) are anti adducts, i e **20** and **24**, respectively. Lactonization reaction involves the methoxycarbonyl group at position 6 and the hydroxy group at position 8 both in **20** and **24** [19a] In fact in **22** (**27**) the proton attached to the carbon atom which bears the OH (OMe) group[19b] is coupled to that one of the two bridgehead protons (H-1 and H-7) which resonates at lower fields, namely H-1 (see above).The anti structure **23** was assigned on the basis of LIS experiments which showed that the signals of the two protons at position 5 moved to lower fields much less rapidly than H-1 and H-7. In **23** the proton coupled to OH is also coupled to H-1 thus unambiguously establishing the regiochemistry of this adduct

Only the anti adduct, i e **28b** (X = OAc), could be detected in the cycloaddition of diazomethane to **4b** whereas the ^{1}H NMR spectrum of the crude product from the reaction of **4c** (X = OSO_2Me) displayed signals that could be attributed to **29c** (**28c**.**29c** = 95:5) (Scheme 4) The structure of **28b** was unambiguously established by a single crystal X-ray analysis [20]

Finally, we studied the reaction of diazomethane with **8b** in order to rule out a possible through bond effect of the substituent on facial selectivity of bicyclooctene derivatives Compound **8b** reacted faster than **4b** (≤ 24 h to reach 100% conversion as compared to ≥10 days for **4b**)[21] to produce almost equimolar amounts of **30** and **31** (Scheme 4)

This latter finding and planarity of the double bond in 5,6-disubstituted bicyclooctenes[8] allows us to confidently feel that the observed facial selectivity in the reactions of bicyclooctenes stems from direct through space interaction effects

CONCLUSION

The reaction of diazomethane with endo,cis-5,6-disubstituted bicyclo[2.2 2]oct-2-enes bearing substituents such acetoxy, mesyloxy and methoxycarbonyl groups afforded anti adducts in ≥ 90% relative yield Anti approach is favored by ≥ 1 3 kcal mol^{-1} over syn approach This finding provides conclusive evidence that direct through space interactions between these substituents and the attacking 1,3-dipole are as a whole repulsive Thus, even for the "small" diazomethane steric non bonded interactions clearly win over through space stabilizing interactions such as that involving the diazomethane LUMO and the lone pairs of the substituents [22,23] Only anti adducts were isolated in the reactions of diazomethane with endo,cis-5,6-dihydroxybicyclo[2 2 2]oct-2-ene derivatives, stabilizing hydrogen bonding effects do not play any relevant role in directing facial selectivity in these reactions

Facial selectivity of the reactions of bicyclooctenes strikingly contrasts with that of the reactions of cyclobutenes bearing the same substituents [2] For example only syn adducts were detected in the reactions of diazomethane with cis-3,4-diacetoxy and cis-3,4- dimesyloxycyclobutene The electronic effect which gives rise to such a high syn selectivity in the reaction of cyclobutenes must be particularly strong (> 3 0 kcal mol^{-1}) as it also has to overcome a counteracting steric effect. Cyclobutenes are rigid molecules with two stereogenic centers whose C-X bonds are ideally disposed to be involved in σ-π hyperconjugation with the π bond If the syn directing electronic effect of electron attracting substituents (acetoxy, mesyloxy, alkoxy, chlorine etc) mostly stems from σ-π hyperconjugation effects, it must certainly be at its maximum in cyclobutenes thus explaining why in these substrates it emerges so clearly. Indeed, cyclobutenes provide a rare but unambiguous example of facial selectivity control by hyperconjugation (or, put in other words, by pyramidalization induced by hyperconjugation) in the presence of opposing steric bias

EXPERIMENTAL

Melting points were uncorrected. Elemental analyses were made on a Carlo Erba CHN analyser, model 1106. Infrared spectra were recorded as either Nujol suspensions or films on a Perkin-Elmer 157 spectrophotometer. Infrared spectra of **1a**, **2**, **3a** and **4a**, respectively, were recorded in dilute CCl_4 solutions ($\approx 10^{-3}$ M) on a PE 983 spectrophotometer. NMR spectra were recorded either on a Bruker WP80SY (at 80 MHz) or on a Bruker AE 300 (at 300 MHz) spectrometers with tetramethylsilane as internal standard for $CDCl_3$ solutions unless otherwise stated Protons were correlated by decoupling experiments ^1H NMR spectra were evaluated as first order spectra. Lanthanide-induced shifts (LIS) were measured in $CDCl_3$ solutions with $Eu(fod)_3$ as shift reagent ΔM values (shifts for the 1.1 mole ratio) were evaluated by extrapolation from measurements carried out in the range of 1:0 03 to 1 0 2 mole ratios of substrate and shift reagent. Mass spectra were measured on a Finnigan MATT 8222 using chemical ionization (CI) mode. GC analyses were carried out with a Dani 6500, PTV injector, CP-SIL-19 CB (25 m) capillary column and carrier H_2. Thin-layer chromatograms were done on plates precoated with silicagel 60 GF_{254} (Merck) Spots were visualized either by spraying with 3% chromic oxide in sulphuric acid (50%) followed by heating at 120 °C or under UV light Column chromatography was performed with Silicagel 60 (70-230 mesh) Merck eluting with cyclohexane-ethyl acetate mixtures Bicyclooctenes **1a**, **2**[24a] and bicyclo[2 2 2]octa-2,5-diene **7**[24b] were prepared according to literature procedures

Bicyclo[2.2.2]oct-2-enes 1b and 1c

Derivatives **1b** and **1c** were obtained from **1a** in good yields by standard methods **1b** colorless prisms from cyclohexane, mp 101-102 °C, ^1H NMR δ 1 15-1 80 (m, 4H, H-7 and H-8), 2 03 (s, 6H, Me), 2 88 (m, H-1 and H-4), 5 05 (bs, H-5 and H-6), 6 35 (m, H-2 and H-3) Anal Calcd for $C_{12}H_{16}O_4$· C, 64 3, H, 7 2 Found C, 63 9, H, 7 2 **1c**: colorless prisms from dichloromethane, mp 166-167 °C, ^1H NMR δ 1 42 (m, 4H, H-7 and H-8), 3 06 (s, 6H, $MeSO_2$), 3 06 (m, H-1 and H-4), 4 84 (bs, H-5 and H-6), 6 33 (m, H-2 and H-3) Anal Calcd for $C_{10}H_{16}O_6S_2$ C, 40 5; H, 5 4 Found C, 40 3, H, 5 4

2-Methoxycarbonylbicyclo[2.2 2]octa-2,5-diene 5

To a solution of 1,3-cyclohexadiene (3.5 g) and methyl propiolate (3 7 g) in anhydrous benzene (50 mL) anhydrous aluminum trichloride (≈ 3 0 g) was added portionwise under stirring at 0 °C The reaction mixture was stirred overnight at room temperature, poured into ice water and washed with a solution of sodium bicarbonate After usual workup the yellow residue was column chromatographed to give **5** as a colorless oil ^1H NMR δ 1 31 (m, 4H, H-7 and H-8), 3 73 (s, CO_2Me), 3 75 (m, H-4), 4 20 (m, H-1), 6 33 (m, H-5 and H-6), 7 30 (dd, H-3, $J_{1,3}$ = 2 0 Hz and $J_{3,4}$ = 6 0 Hz)

Catalytic osmylation of 5 Synthesis of 3a-c and 6a,b

To a solution of **5** (453 mg, 2 76 mmol) in acetone/water (4 3, 14 mL) N-methyl morpholine -N-oxide H_2O (7 92 mmol) and 1 mL of a 2 5% solution of osmium tetraoxide in tert-butyl alcohol were added The reaction mixture was left stirring at room temperature for 43 h before being diluted with a 10% solution of sodium sulfite This new solution was stirred for 10 minutes before adding a 10% solution of sulfuric acid (dropwise) until the solution was neutral to litmus paper Then the reaction mixture was extracted several times with ethyl acetate, the organic layers were washed once with saturated brine, dried with sodium sulfate and filtered The solvent was removed under reduced pressure and the oily residue column chromatographed (cyclohexane/AcOEt, 1 1, as eluant) to give in order of elution **6a** (139 mg, 23%) and **3a** (257 mg, 42%) **3a** colorless needles, mp 61-63 °C, ^1H NMR δ 1 18 and 1 44 (m, 4H, H-7 and H-8), 2 93 (bd, H-4), 3 30 (bs, H-1), 3 43 (broad, OH), 3 73 (s, CO_2Me), 3 88 (bs, H-5 and H-6), 7 25 (dd, H-3, $J_{1,3}$ = 1 5 Hz and $J_{3,4}$ = 6 3 Hz) ΔM 3 20 and 4 20 (H-7 and H-8), 8 94 (H-4), 10 80 (H-1), 3 98 (CO_2Me), 11 85 (H-5 and H-6), 7 85 (H-3) Anal Calcd for $C_{10}H_{14}O_4$ C, 60 6, H, 7 1 Found C, 60 5, H, 7 0 **6a** colorless oil, ^1H NMR δ

0 75-1 90 (m, 4H, H-7 and H-8), 2 73 (m, H-1 and H-4) 3.65 (broad, OH), 3.74 (s, CO_2Me), 4 26 (d, H-6, $J_{1,6}$ = 2 5 Hz), 6 22 (m, H–2 and H–3) Anal Found· C, 60 3; H, 7 3. Compounds **3a** and **6a**, respectively, were dissolved in acetyl chloride and left standing at rt for 48 h The solvent was removed under reduced pressure and the residue column chromatographed to give **3b** and **6b**, respectively, in ≥ 90% yields **3b:** colorless prisms from petroleum ether, mp 72-73 °C, IR ν_{max} 1740, 1702 and 1630 cm^{-1}, ^1H NMR δ 1.27 and 1 59 (two m, 4H, H-7 and H-8), 1 93 and 1 95 (two s, OAc), 2 95 (bd, H-4), 3 40 (bs, H-1), 3 77 (s, CO_2Me), 5.02 (m, H-5 and H-6), 7 27 (dd, H-3, $J_{1,3}$ = 1 5 Hz and $J_{3,4}$ = 6 8 Hz) Anal Calcd for $C_{14}H_{18}O_6$ C, 59 6, H, 6 4 Found C, 59 4, H, 6.2 **6b** colorless needles from cyclohexane-petroleum ether, mp 95-97 °C, ^1H NMR δ 0.90-2 10 (m, 4H, H-7 and H-8), 1 88 and 2 00 (two s, OAc), 2 81 (m, H-1 and H-4), 3.71 (s, CO_2Me), 5 81 (d, H-6, $J_{1,6}$ = 3 0 Hz), 6 25 (m, H-2 and H-3) Anal Found. C, 59 3, H, 6.6

To a solution of **3a** (0 594 g, 3 0 mmol) and triethylamine in anhydrous dichloromethane (25 mL) at 0 °C was added a solution of methanesulfonyl chloride (6 6 mmol) in dichloromethane (5 mL) dropwise under stirring The reaction mixture was left stirring at 0 °C for 1 h and at rt for 2 h before being washed twice with saturated brine and once with water Usual workup and column chromatography (cyclohexane/AcOEt, 1 1, as eluant) afforded pure **3c** (0 584 g, 55%) which was recrystallized from cyclohexane/AcOEt to give colorless platelets, mp 124 °C IR ν_{max} 1706, 1625, 1350 and 1170 cm^{-1} ^1H NMR δ 1 37 and 1 62 (two m, 4H, H-7 and H-8), 3 08 (s, 6H, $MeSO_2$), 3 25 (bd, H-4), 3 63 (m, H-1), 3 81 (s, CO_2Me), 4 94 (m, H-5 and H-6), 7 34 (dd, H-3, $J_{1,3}$ = 1 5 Hz and $J_{3,4}$ = 7 5 Hz) Anal Calcd for $C_{12}H_{18}O_8S_2$· C, 40 7, H, 5 1 Found. C, 40 9, H, 5 3

Catalytic osmylation of 7 Synthesis of 4a-c and 8a,b.

An identical procedure to that reported above for **5** was followed for the cis-dihydroxylation of **7** (4 00 g) to afford **4a** (2 74 g, 73%) and **8a** (0 119 g, 3%) Compounds **4a** and **8a** were transformed into **4b** and **8b** (≥90% yield) by treatment with acetyl chloride and **4a** into **4c** (51%) by treatment with methanesulfonyl chloride and triethylamine **4a** colorless oil, IR ν_{max} 3440, 1715 and 1640 cm^{-1}; ^1H NMR δ 1 15-1 75 (m, 4H, H-7 and H-8), 3 02 (broad , OH), 3 21 (m, H-1 and H-4), 3 80 (s, 6H, CO_2Me), 3 92 (m, H-5 and H-6) Anal Calcd for $C_{12}H_{16}O_6$ C, 56 2, H, 6 3 Found C, 56.5, H, 6 1 **8a** colorless oil, ^1H NMR δ 1 23 and 2 09 (two m, 4H, H-7 and H-8), 2 80 (very broad, OH), 3 13 (m, H-1 and H-4), 3 79 (m, H-5 and H-6), 3 82 (s, 6H, CO_2Me) ΔM 4 97 (H-7 and H-8 anti to OH groups), 8 80 (H-7 and H-8 syn to OH groups), 8 53 (H-1 and H-4), 11 50 (H-5 and H-6), 1 20 (CO_2Me) Anal Found C, 56 0, H, 6 1 **4b:** colorless platelets from cyclohexane, mp 113-114 °C, IR ν_{max} 1725 and 1635 cm^{-1}, ^1H NMR δ 1 15-1 80 (m, 4H, H-7 and H-8), 1 95 (s, 6H, OAc), 3 27 (m, H-1 and H-4), 3 79 (s, 6H, CO_2Me), 4 99 (m, H-5, and H-6) Anal Calcd for $C_{16}H_{20}O_8$ C, 56 5; H, 5 9 Found C, 56 2, H, 5 8 **8b:** colorless glassy solid, IR ν_{max} 1735 and 1640 cm^{-1}· ^1H NMR δ 1 25 (m, 4H, H-7 and H-8), 2 00 (s, 6H, OAc), 3 16 (m, H-1 and H-4), 3 75 (s, 6H, CO_2Me), 4 72 (m, H-5 and H-6) Anal Found C, 56 6, H, 6 0 **4c** colorless prisms from AcOEt, mp 149-150 °C, IR ν_{max} 1721, 1706, 1635, 1350 and 1160 cm^{-1}, ^1H NMR δ 1 57 (m, 4H, H-7, and H-8), 3 18 (s, 6H, $MeSO_2$), 3 51(m, H-1 and H-4), 3 85 (s, 6H, CO_2Me), 4 98 (m, H-5 and H-6) Anal Calcd for $C_{14}H_{20}O_{10}S_2$ C, 40 8, H, 4 85 Found C, 41 0, H, 4 9

Reaction of diazomethane with bicyclooctenes General procedure

The reactions of diazomethane with bicyclooctenes (200-500 mg) were carried out in ether at room temperature (≈20-23 °C) by using a large excess of a concentrated solution of the 1,3-dipole The sparingly soluble dimesyloxy derivatives were dissolved in DMF or dichloromethane and to that solution was added an ethereal solution of diazomethane When the dipolarophile had totally been consumed (as judged from TLC) the solvent was evaporated and the reaction products separated by column chromatography The adducts of diazomethane to bicyclooctenes proved stable under reaction and workup conditions with the exception of anti adducts to **3a** and **4a** which underwent a lactonization reaction. The presence of a 1-pyrazoline ring in the adducts was clearly disclosed by a weak N N absorption at 1530-1550 cm^{-1} in their IR spectra This

absorption was missing in the IR spectra of 1-acetyl-2-pyrazoline derivatives formed during acetylation processes. The spectra of the latter compounds displayed C H, C N and MeCON absorptions at ≈3060, 1600 and 1670 cm^{-1}, respectively

Reaction of diazomethane with 1a-c and 2

Endo,cis-5-hydroxy-6-methoxybicyclo[2.2.2]oct-2-ene [75%, IR (CCl_4, 5.0 10^{-3} M) ν_{max} 3524 cm^{-1}, ^1H NMR δ 1.26 (m, 4H, H-7 and H-8), 2 74 (m, H-1 and H-4), 3 00 (d, OH, $J_{5,OH}$ = 7.0 Hz), 3.40 (s, OMe), 3.40 (m, H-6), 3.85 (ddd, H-5, $J_{5,6}$ = 7 0 Hz and $J_{4,5}$ = 3 0 Hz), 6 20 (m, H-2 and H-3) Anal. Calcd for $C_9H_{14}O_2$ C, 70.1, H, 9.15 Found C, 70 4, H, 9.45] and exo,cis-5-hydroxy-6-methoxybicyclo[2 2.2]oct-2-ene [73%, IR (CCl_4, 8 0 10^{-3} M) ν_{max} 3524 cm^{-1}; ^1H NMR δ 1.03 and 1.85 (two m, 4H, H-7 and H-8), 2 68 (m, H-1 and H-4), 3 16 (dd, H-6, $J_{1,6}$ = 3 5 Hz and $J_{5,6}$ = 9 0 Hz), 3.45 (s, OMe), 3.61 (dd, H-5, $J_{4,5}$ = 3.0 Hz), ≈ 3 5 (broad, OH), 6 22 (m, H-2 and H-3) ΔM 5 1 (H-7 and H-8 anti to OH), 10 0 (H-7 and H-8 syn to OH), 8 2 (H-4), 11.3 (H-1), 13.3 (H-6), 11.95 (H-5), 14 5 (OMe), 3.9 (H-2 and H-3). Anal. Found C, 70.4; H, 8.95] were isolated as colorless oils from the reaction of **1a** and **2**, respectively, with diazomethane after 30-45 days GC analysis (after 17 h) of a reaction carried out with an equimolar mixture of **1a** and **2** showed that **1a** is methylated ≈2 5 times faster than **2**

A 25% (25%) yield of **12b** (**12c**) was obtained from the reaction of **1b** (**1c**) after 37 (45) days with a 60% (63%) recovery of **1b** (1c). **12b:** colorless prisms from benzene/cyclohexane, mp 153-154 °C, IR ν_{max} 1735 and 1545 cm^{-1}, ^1H NMR δ 1 40 (m, 4H, H-10 and H-11), 1 71 (m, H-7, $J_{6,7}$ = 2.0 Hz and $J_{7,8}$ = 2.7 Hz), 2 49 (m, H-6, $J_{2,6}$ = 11 0 Hz, $J_{5\text{-endo},6}$ = 3 3 Hz, and $J_{5\text{-exo},6}$ = 10 0 Hz), 3 02 (m, H-1, $J_{1,2}$ ≈ 2 0 Hz and $J_{1,9}$ = 4.0 Hz), 4 50 (ddd, H-5-exo, $J_{2,5\text{-exo}}$ = 2 2 Hz and $J_{5\text{-exo},5\text{-endo}}$ = 18 0 Hz), 4.67 (ddd, H-5-endo, $J_{2,5\text{-endo}}$ = 3.3 Hz), 4.72 (m, H-2), 4.98 (dd, H-8, $J_{8,9}$ = 8 4 Hz), 5 25 (dd, H-9) Anal. Calcd for $C_{13}H_{18}N_2O_4$ C, 58.6; H,6.8, N, 10.5 Found: C, 58 6; H, 6 8; N, 10 5 **12c:** colorless needles, mp 160-161°C; IR ν_{max} 1550, 1355 and 1172 cm^{-1}, ^1H NMR δ 1 15-1 55 (m, 4H, H-10 and H-11), 1.97 (m, H-7, $J_{6,7}$ = 2 5 Hz and $J_{7,8}$ = 2.6 Hz), 2 58 (m, H-6, $J_{2,6}$ = 10 0 Hz, $J_{5\text{-endo},6}$ = 3 0 Hz, and $J_{5\text{-exo},6}$ = 9.8 Hz), 3 12 and 3 18 (two s, $MeSO_2$) 3.25 (m, H-1, $J_{1,2}$ = 2 5 Hz and $J_{1,9}$ = 4 0 Hz), 4 54 (ddd, H-5-exo, $J_{2,5\text{-exo}}$ = 2 0 Hz and $J_{5\text{-exo},5\text{-endo}}$ = 18.5 Hz), 4.71 (ddd, H-5-endo, $J_{2,5\text{-endo}}$ = 3 0 Hz), 4 78 (m, H-2), 4 83 (dd, H-8, $J_{8,9}$ = 8 3 Hz), 5 10 (dd, H-9) Anal Calcd for $C_{11}H_{18}N_2O_6S_2$ C, 39 05 H, 5 3, N, 8 3 Found C, 39 05, H, 5 4, N, 8 3

Compound **12b** was reduced with excess $LiAlH_4$ in ether at rt to give **12a** (40% yield) **12a**. glassy solid purified by column chromatography; ^1H NMR δ 1 25 (m, H-10 and H-11), 1.60 (m, H-7, $J_{7,8}$ = 2.5 Hz), 2 50 (m, H-6), 2 50 (broad, OH), 2 97 (m, H-1, $J_{1,9}$ = 4.0 Hz), 3.95 (dd, H-8, $J_{8,9}$ = 8.0 Hz), 4 16 (dd, H-9), 4 55 (m, H-5-endo and H-5-exo, $J_{2,5\text{-endo}} \approx J_{5\text{-endo},6}$ = 3.0 Hz, $J_{2,5\text{-exo}}$ = 2 0 Hz, $J_{5\text{-exo},5\text{-endo}}$ = 18 5 Hz, and $J_{5\text{-exo},6}$ = 10 0 Hz, these coupling constants were evaluated from the spectrum in the presence of $Eu(fod)_3$), 4 80 (m, H-2) ΔM: 3 26 (H–10 and H–11), 12 40 (H–7), 14 67 (H–6), 11 60 (H–1), 15.00 (H–8), 15 90 (H–9), 2 30 (H–5–exo), 5 35 (H–5–endo), 11 80 (H–2) Anal Calcd for $C_9H_{14}N_2O_2$ C, 59 3; H, 7 7, N, 15 4 Found C, 59 0, H, 7 4, N, 15 1

Reaction of diazomethane with 3a-d.

All of the three dipolarophiles had totally been consumed after ≈ 6 h Several experiments were carried out with **3a** In the first one we managed to isolate **14a** as colorless oil in 59% yield by column chromatography and to record its IR and ^1H NMR spectra [IR ν_{max} 3400, 1730 and 1688 cm^{-1}, ^1H NMR δ 0 90-1 50 (m, H-10 and H-11), 1 60 (m, H-7), 2 95 (m, H-6), 3 43 (m, H-1), 3 70 (s, CO_2Me), 3 80 (dd, H-8, $J_{7,8}$ = 2 6 Hz and $J_{8,9}$ = 8 0 Hz), 4 06 (dd, H-9, $J_{1,9}$ = 4.0 Hz), 4 70 (m, H-5-endo and H-5-exo) ΔM ≈ 4 0 (H-10 and H-11), 8 90 (H-7), 10 50 (H-6), 9.15 (H-1), 0 0 (CO_2Me), 11 20 (H-8), 12 30 (H-9), 2 20 (H-5-exo), 3 90 (H-5-endo)] When we tried to repeat this experiment the only product, that we were able to isolate by column chromatography, was the lactone **18** as a glassy solid. **18:** IR ν_{max} 3430, 1755 and 1545 cm^{-1}, ^1H NMR δ 1 15-1 80 (m, H-10 and H-11), 1 60 (broad, OH), 2 12 (m, H-7, $J_{6,7}$ = 4 0 Hz and $J_{7,8}$ = 2 0 Hz), 2 50 (m,

H-6, $J_{5\text{-endo},6}$ = 10.5 Hz and $J_{5\text{-exo},6}$ = 7 5 Hz), 3 38 (ddd, H-1, $J_{1,9}$ = 5 5 Hz and $J_{1,10}$ ≈ 3 0 Hz), 4.07 (dd, H-8, $J_{8,9}$ = 5 5 Hz), 4 53 (dd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18.9 Hz), 4 91 (dd, H-5-endo), 4 92 (dd, H-9) Assignment of H-5-exo and H-5-endo is tentative

Treatment of **18** with excess acetyl chloride for 24 h led to **19** in 90% yield. **19:** colorless needles from methanol, mp 209-213 °C, IR ν_{max} 3060, 1812, 1743, 1670 and 1598 cm^{-1}, ^1H NMR δ 1 61 (m, 4H, H-10 and H-11), 2 13 (s, OAc), 2 39 (s, NAc), 2 39 (m, H-7), 3 48 (m, H-1), 3 70 (bd, H-6, $J_{6,7}$ = 4.0 Hz), 4 78 (dd, H-8, $J_{7,8}$ = 1 7 Hz and $J_{8,9}$ = 6 0 Hz), 5 03 (dd, H-9, $J_{1,9}$ = 6 0 Hz), 6 82 (bs, H-5) Anal. Calcd for $C_{14}H_{16}N_2O_5$ C, 57 5, H, 5 5, N, 9.6 Found C, 57 1; H, 5 6, N, 9 7.

In a third experiment the solvent was removed from the reaction mixture under reduced pressure and the crude residue was treated with a large excess of acetyl chloride at rt for 24 h Acetyl chloride was evaporated under reduced pressure and the residue subjected to column chromatography (cyclohexane/AcOEt, 1:1, as eluant) to give in order of elution **16:** colorless prisms from cyclohexane-petroleum ether, mp 137-138 °C, IR ν_{max} 3060, 1745, 1670 and 1608 cm^{-1}, ^1H NMR δ 1 25-1 70 (m, 4H, H-10 and H-11), 1.96 and 2 05 (two s, OAc), 2 00 (m, H-7), 2 30 (s, NAc), 3 59 (m, H-1), 3 75 (s, CO_2Me),4 02 (bs, H-6), 4 95 (dd, H-8, $J_{7,8}$ = 2 5 Hz and $J_{8,9}$ = 8.3 Hz), 5 26 (dd, H-9, $J_{1,9}$ = 4.0 Hz), 6 81 (bs, H-5) Anal Calcd for $C_{17}H_{22}N_2O_7$ C, 55 7, H, 6 05, N, 7 65 Found C, 55.4, H, 6 3, N, 7 4

From the reaction of **3b** we isolated **14b** (higher R_f on TLC, cyclohexane/AcOEt, 7 3, as eluant) in 81% yield and **15b** in 8% yield.Treatment of **14b** and **15b** with acetyl chloride (at rt, 24 h and 4 days, respectively) afforded **16** (95%) and **17** (30%), respectively **14b:** colorless needles from cyclohexane, mp 119-121 °C, IR ν_{max} 1752, 1740 and 1550 cm^{-1}, ^1H NMR δ 1 01, 1 28, 1 32, and 1 62 (four m, 4H, H-10 and H-11), 1 52 (m, H-7, $J_{7,8}$ = 2 4 Hz and $J_{6,7}$ = 1.5 Hz), 1 98 and 2 04 (two s, OAc), 3 08 (m, H-6, $J_{5\text{-endo},6}$ = 2 3 Hz and $J_{5\text{-exo},6}$ = 8 3 Hz), 3 62 (m, H-1), 3 76 (s, CO_2Me), 4 74 (dd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 4 Hz), 4 84 (dd, H-5-endo), 4 87 (dd, H-8, $J_{8,9}$ = 8 4 Hz), 5.25 (dd, H-9, $J_{1,9}$ = 4 1 Hz) Anal Calcd for $C_{15}H_{20}N_2O_6$ C, 55 55, H, 6 2, N, 8 6 Found C, 55 7, H, 6 1, N, 8 9 **15b** glassy solid, IR ν_{max} 1740 and 1545 cm^{-1}, ^1H NMR δ ($CDCl_3$) 1 56 (m, 4H, H-10 and H-11), 1 99 and 2 03 (two s, OAc), 2 07 (m, H-7), 2 63 (m, H-6, $J_{5\text{-endo},6}$ = 4 0 Hz and $J_{5\text{-exo},6}$ = 10 0 Hz), 3 44 (m, H-1), 3 81 (s, CO_2Me), 4 64 (dd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 3 Hz), 4 93 (m, H-8 and H-9), 5.17 (dd, H-5-endo), δ (C6D6) 0 80-1 50 (m, 4H, H-10 and H-11), 1 72 (m, H-7, $J_{6,7}$ = 3.0 Hz), 1 69 and 1 72 (two s, OAc), 2 30 (m, H-6), 3 24 (s, CO_2Me), 3 58 (m, H-1), 4 38 (dd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ =18.1 Hz and $J_{5\text{-exo},6}$ = 10 0 Hz), 4.70 (ddd, H-8, $J_{6,8}$ = 1 0 Hz, $J_{7,8}$ = 3 0 Hz, and $J_{8,9}$ = 9 0 Hz), 4 92 (dd, H-5-endo, $J_{5\text{-endo},6}$ = 4 0 Hz), 4 92 (dd, H-9, $J_{1,9}$ = 3 0 Hz), CI (isobutane) mass spectrum, m/e 325 (MH^+, 5%), 297 ([MH^+ - N_2], 100%) Anal Found C, 55 9, H, 6 5, N, 8 8 **17** colorless needles from cyclohexane, mp 150-152 °C, ^1H NMR δ 1 54 (m, 4H, H-10 and H-11), 1 97 and 2 03 (two s, OAc), 2 27 (s, NAc), 2 30 (m, H-7), 3 31 (m, H-6), 3 40 (m, H-1), 3 75 (s, CO_2Me), 5 04 (m, H-8 and H-9), 6 86 (d, H-5, $J_{5,6}$ = 1.0 Hz) Anal Found C, 55 5, H, 6 3, N, 7 9

In the reaction of **3c** with diazomethane only one spot was detected by TLC Column chromatography allowed us to isolate the reaction product in 96% yield Its ^1H NMR spectrum showed that it consisted of two adducts, i e **14c** and **15c** (**14c** : **15c** = 10 1) IR ν_{max} 1730, 1550, 1375, and 1175 cm^{-1} **14c** ^1H NMR δ 1 04, 1 30, and 1 66 (three m, 4H, H-10 and H-11), 1.98 (m, H-7, $J_{6,7}$ ≈ 2 5 Hz and $J_{7,8}$ = 2 5 Hz), 3 10 and 3 13 (two s, $MeSO_2$), 3 10 (m, H-6, $J_{5\text{-endo},6}$ = 2 5 Hz and $J_{5\text{-exo},6}$ = 8 0 Hz), 3 83 (m, H-1), 3 83 (s, CO_2Me), 4 78 (dd, H-8, $J_{8,9}$ = 8 5 Hz), 4 79 (dd, H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 0 Hz), 4 86 (dd, H-5-endo), 5 05 (dd, H-9, $J_{1,9}$ = 4 3 Hz) **15c** ^1H NMR δ 2 31 (m, H-7), 2 63 (m, H-6, $J_{5\text{-endo},6}$ = 3 0 Hz, $J_{5\text{-exo},6}$ = 9 5 Hz, and $J_{6,7}$ ≈ 2 5 Hz), 3 09 and 3 15 (two s, $MeSO_2$), 3 84 (s, CO_2Me), 4 63 (dd, H-5-exo, $J_{5\text{-exo},5\text{-endo}}$ = 18 5 Hz), 5 35 (dd, H-5-endo), the other signals are buried under those of **14c** Compounds **14c** and **15c** could not be isolated in a pure state and a ≈ 9.1 mixture of **14c** and **15c**(mp 152-154 °C), obtained by crystallization from ethyl acetate of the crude product, was subjected to elemental analysis Anal Calcd for $C_{13}H_{20}N_2S_2O_8$ C, 39 4, H, 5 05, N, 7.1 Found C, 39.1; H, 5 0, N, 7 3

Adduct **14d** was obtained in 97% yield from **3d** **14d** colorless prisms from cyclohexane, mp 98-100 °C, IR ν_{max} 1743, 1725 and 1545 cm^{-1}, ^1H NMR δ 0 93, 1 21, 1 38, and 1 77 (four m, 4H, H-10 and H-11),

2 01 (m, H-7), 2 65 (dd, H-8, $J_{8,9}$ = 11 8 Hz and $J_{7,8}$ = 1 75 Hz), 3 18 (m, H-6, $J_{5\text{-endo},6}$ = 1.9 Hz, $J_{5\text{-exo},6}$ = 8 0 Hz, and $J_{6,7}$ = 2 5 Hz), 3 32 (dd, H-9, $J_{1,9}$ = 3 6 Hz), 3 59, 3.61,and 3 64 (three s, CO_2Me), 3.65 (m, H-1), 4 78 (dd, H-5-exo, $J_{5\text{-exo},5\text{-endo}}$ = 18 0 Hz), 4 92 (dd, H-5-endo). Anal Calcd for $C_{15}H_{20}N_2O_6$ C, 55 55, H, 6 2; N, 8 6. Found. C, 55 9; H, 6.4; N, 8.6.

Reaction of diazomethane with 4a- c

The reaction of **4a** with diazomethane was interrupted after 63 h and the residue from evaporation of the solvent column chromatographed (cyclohexane/AcOEt, 1 1, as eluant) to give in order of elution **21** and **22** (22 5% and 18.5% yield, respectively) and the starting compound (32% recovery) along with minor amounts of two other adducts. Compound **21** was characterized as its acetyl derivative colorless oil; IR ν_{max} 1725 and 1638 cm^{-1}, ^1H NMR δ 1 52 (m, 4H, H-7 and H-8), 2 07 (s, OAc), 3 19 (m, H-4), 3.35 (s, OMe), 3.47 (m, H-1), 3 62 (dd, H-6, $J_{1,6}$ = 2 9 Hz and $J_{5,6}$ = 7 8 Hz), 3 82 (s, 6H, CO_2Me), 4.93 (dd, H-5, $J_{4,5}$ = 2.5 Hz) Anal Calcd for $C_{15}H_{20}0_7$ C, 57 7, H, 6.5 Found C, 57 95, H, 6 7 **22**. colorless prisms from AcOEt, mp 180 °C dec.; IR ν_{max} 3420, 1778, 1725, and 1550 cm^{-1}, ^1H NMR δ 1 28, 1 59, and 1.82 (three m, 4H, H-10 and H-11), 2.42 (m, H-7), 3 18 (m, H-1), 3 73 (s, CO_2Me), 4 03 (ddd, H-9, $J_{9,OH}$ = 10.5 Hz, $J_{1,9}$ = 1.0 Hz, and $J_{8,9}$ = 6 5 Hz), 4 73 (d, OH), 4 79 (dd, H-8, $J_{7,8}$ = 6 5 Hz), 4 80 and 4 91 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ =18 0 Hz) Anal Calcd for $C_{12}H_{14}N_2O_5$ C, 54 1, H, 5 3; N, 10 5. Found C, 54 5, H, 5 4, N, 10 2 Treatment of **22** with acetyl chloride (48 h) afforded quantitatively **25**. **25**: colorless needles, mp 207-208 °C, IR ν_{max} 3085, 1788, 1750, 1730, 1663, and 1598 cm^{-1}; ^1H NMR δ 1 68 (m, 4H, H-10 and H-11), 2 15 (s, OAc), 2 34 (s, NAc), 2 71 (m, H-7), 3 40 (m, H-1), 3.69 (s, CO_2Me), 4 99 (m, H-8 and H-9), 6 81 (s, H-5) Anal Calcd for $C_{16}H_{18}N_2O_7$· C, 54 85, H, 5 2, N, 8 0 Found C, 54 6, H, 5 15, N,7 9

Compound **21** was reacted with diazomethane and after seven days we managed to isolate (by column chromatography in order of elution) lactone **27** (45% yield) and adduct **23** (15% yield) along with starting material (15% recovery) Compounds **23** and **27** were identical in every respect to the minor adducts isolated in the reaction of **4a**. Compound **23** was transformed into **26** (80% yield) by treatment with acetyl chloride. **23** glassy solid, ^1H NMR δ 0.80-1 80 (m, 4H, H-10 and H-11), 2 23 (m, H-7), 3 37 (dd, H-8, $J_{7,8}$ = 2 0 Hz and $J_{8,9}$ = 8 0 Hz), 3 43 (s, OMe), 3 47 (m, H-1), 3 69 and 3 72 (two s, CO_2Me), 3 90 (d, OH, $J_{9,OH}$ = 8 0 Hz),4 20 (ddd, H-9, $J_{1,9}$ = 4 0 Hz), 4 85 and 5.05 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 0 Hz) ΔM ≈ 4 80 (H-10 and H-11), 10 90 (H-7), 10 76 (H-8), 9.98 (OMe), 8 20 (H-1), 2 40 (CO_2Me), 10 76 (H-9), 5 97 and 6 04 (H-5-endo and H-5exo) **26**· glassy solid, IR ν_{max} 3060, 1755, 1725, 1680, and 1605 cm^{-1}, CI (isobutane) mass spectrum, m/e 397 (MH^+), ^1H NMR δ 1 20-1 70 (m, 4H, H-10 and H-11), 2.10 (s, OAc), 2 28 (s, NAc), 2 48 (m, H-7), 3 26 (s, OMe), 3.43 (m, H-1), 3 51 (dd, H-8, $J_{7,8}$ = 2.0 Hz and $J_{8,9}$ = 9 0 Hz), 3.62 and 3 71 (two s, CO_2Me), 5.23 (dd, H-9, $J_{1,9}$ = 4 0 Hz), 6 75 (s, H-5). Anal Calcd for $C_{18}H_{24}N_2O_8$ C, 54 5, H, 6 1, N, 7 1 Found C, 54 5, H, 6 3, N, 7 0 **27** colorless needles from cyclohexane, mp 150 °C dec ; IR ν_{max} 1788, 1742, and 1542 cm^{-1}, ^1H NMR δ 1 25, 1 55, and 1 89 (three m, 4H, H-10 and H-11), 2 38 (m, H-7), 3 47 (s, OMe), 3 72 (s, CO_2Me), 3 60 (dd, H-9, $J_{1,9}$ = 2 0 Hz and $J_{8,9}$ = 7 0 Hz), 3 70 (m, H-1), 4 73 (dd, H-8, $J_{7,8}$ = 5 5 Hz), 4 92 and 5 08 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 0 Hz) Treatment of **27** with acetyl chloride led to a monoacetyl 2-pyrazoline colorless prisms from chloroform, mp 265 °C dec , IR ν_{max} 3070, 1780, 1703, 1665, and 1602 cm^{-1}, ^1H NMR δ 1 60 (m, 4H, H-10 and H-11), 2 35 (s, NAc), 2 68 (bd, H-7), 3 45 (s, OMe), 3 70 (s, CO_2Me), H-1 and H-9 are buried under these two latter signals, 4 90 (dd, H-8, $J_{7,8}$ = 5 5 Hz and $J_{8,9}$ = 6 5 Hz), 6 80 (s, H-5) Anal Calcd for $C_{15}H_{18}N_2O_6$ C, 55 9, H, 5 6, N, 8 7 Found C, 56 2, H, 5 4, N, 8 9

It took ≥ 15 days to reach 100% conversion in the reactions of diazomethane with **4b** and **4c** with formation of the sole anti adduct, i e **28b** (as judged by TLC and ^1H NMR analysis, 96% yield), and of a mixture of **28c** and **29c** (**28c** **29c** ≈ 95 5, 67%yield), respectively **28b**: colorless prisms from ethyl acetate, mp 150-153 °C, IR ν_{max} 1750 and 1560 cm^{-1}, ^1H NMR δ 0 88-1 80 (m, 4H, H-10 and H-11), 2 01 and 2 06 (two s, OAc), 2 28 (m, H-7), 3 62 and 3 75 (two s, CO_2Me), 3 64 (m, H-1), 4 81 (dd, H-8, $J_{7,8}$ = 2 0 Hz and $J_{8,9}$ = 9 0 Hz), 4.86 and 5 10 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 18 5 Hz), 5 24 (dd, H-9,

$J_{1,9}$ = 4.0 Hz). Anal. Calcd for $C_{17}H_{22}N_2O_8$. C, 53.4; H, 5.8, N, 7.3 Found: C, 53.7, H, 5.5, N, 7 3. Treatment of **28b** with excess acetyl chloride (15 days at rt) led to the related 1-acetyl-2-pyrazoline [colorless needles from methanol, mp 216-219 °C; IR ν_{max} 3070, 1760, 1742, 1730, 1678, and 1603 cm^{-1}; ^1H NMR δ 1.50 (m, 4H, H-10 and H-11), 2 02 and 2 05 (two s, OAc), 2.28 (s, NAc), 2 45 (m, H-7), 3.56 (m, H-1), 3 63 and 3 82 (two s, CO_2Me), 4.88 (dd, H-8, $J_{7,8}$ = 2.2 Hz and $J_{8,9}$ = 9.0 Hz), 5 27 (dd, H-9, $J_{1,9}$ = 4 0 Hz), 6 77 (s, H-5)]. **28c:** colorless prisms from ethyl acetate, mp 218-219 °C, IR ν_{max} 1760, 1715, 1560, 1350, and 1170 cm^{-1}, ^1H NMR δ 1 06, 1.27, 1 48, and 1 73 (four m, 4H, H-10 and H-11), 2.50 (m, H-7), 3 08 and 3 22 (two s, $MeSO_2$), 3 63 and 3.74 (two s, CO_2Me), 3 72 (m, H-1), 4 72 (dd, H-8, $J_{7,8}$ = 1 8 Hz and $J_{8,9}$ = 9 0 Hz), 4.88 and 5 14 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 19 0 Hz), 5 15 (dd, H-9, $J_{1,9}$ = 5.5 Hz). Anal Calcd for $C_{15}H_{22}N_2O_{10}S_2$ C, 39 6, H, 4 8, N, 6.2 Found: C, 40 0; H, 4 8, N, 6 2 **29c** (not isolated in a pure state). ^1H NMR δ 3.11 and 3 14 (two s, $MeSO_2$), 3 67 and 3 73 (two s, CO_2Me), 5 58 (d, H-5-endo, $J_{5\text{-endo},5\text{-exo}}$ = 18 5 Hz), the signals of protons H-7 (2 52), H-1 (3 58), H-5-exo (4 78), H-8 (4 85) and H-9 (4 93) are partly overlapped by signals of the protons of **28c**

*Reaction of diazomethane with exo,cis-5,6-diacetoxybicyclo[2 2.2]oct-2-ene **8b***

The reaction went to completion within 24 h to give a mixture of two adducts, i e **30** and **31** (but we do not know which is which). Column chromatography (cyclohexane/AcOEt, 3 2, as eluant) led to isolation of two fractions in 48% and 52% relative yield (total yield = 95%). First fraction. colorless solid, mp 181-184 °C, IR ν_{max} 1750, 1730, and 1555 cm^{-1}, ^1H NMR δ 1 15-2 30 (m, 4H, H-10 and H-11), 2 00 and 2 08 (two s, OAc), 2 04 (m, H-7), 3 47 (m, H-1), 3 66 and 3.74 (two s, CO_2Me), 4 38 (dd, H-8, $J_{7,8}$ = 2 0 Hz and $J_{8,9}$ = 8 7 Hz), 4 93 (dd, H-9, $J_{1,9}$ = 4.0 Hz), 4 93 and 5 27 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 19 0 Hz) Anal Found C, 53 4, H, 5 9, N, 7 3 Second fraction colorless glassy solid, mp ~ 110-120 °C, IR ν_{max} 1750, 1730, and 1560 cm^{-1}, ^1H NMR δ 0 90, 1 30, and 1 25 (three m, 4H, H-10 and H-11), 2 03 and 2 10 (two s, OAc), 2 18 (m, H-7), 3 28 (m, H-1), 3 70 and 3.78 (two s, CO_2Me), 5.01 and 5 09 (AB system, H-5-endo and H-5-exo, $J_{5\text{-endo},5\text{-exo}}$ = 19 0 Hz), 5 09 (ddd, H-9, $J_{1,9}$ = 4 0 Hz, $J_{8,9}$ = 8 5 Hz, and J = 1 3 Hz), 5 42 (ddd, H-8, $J_{7,8}$ = 2 0 Hz and J = 2 0 Hz) Anal Found C, 53 5, H, 5 8, N, 7 4

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13 (a) The structure of **1c**, determıned by a sıngle crystal X-ray analysıs (Bovıo,B., prıvate communıcatıon), exhıbıts the followıng dıhedral angles· C_1C_6OS = -96 1° and C_4C_5OS = 150.6° (b) Geometry optımızatıon of endo,cıs-5,6-dımethoxybıcyclo[2 2.2]oct-2-ene, as a model compound for **1b**, by MNDO method (Dewar, M. J. S.; Theıl, W *J Am Chem Soc* **1977**, *99*, 4899) led to the followıng dıhedral angles for the most stable conformatıon C_1C_6OC = - 94.5° and C_4C_5OC = 139.7°. A conformatıon wıth one of the methyl groups below the double bond (C_1C_6OC = -114.4° and C_4C_5OC = -41 1°) ıs 2 3 kcal mol^{-1} hıgher ın energy than the most stable conformatıon.

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16 For an excellent revıew on 1,3-dıpolar cycloadditıons of dıazoalkanes see Regıtz, M.; Heydt, H *Dıazoalkanes* ın *1,3-Dıpolar Cycloadditıon Chemistry*, Padwa, A ,Ed , Wiley-Interscience New York, 1984, Vol 1, p 393.

17 (a) Whıle the presence of a long range couplıng constant between H-2 (H-6) and H-9 (H-8) unequıvocally supports a syn structure ıts absence does not ıtself provıde a defınıtıve proof of an antı structure. A slıght dıstortıon of the W couplıng pathway may make the relatıng couplıng constant dısappear. For example, the W coupling pathway between H-2 (H-6) and one of the protons H-10 (H-11) does not gıve rıse to a measurable splıttıng ın compounds **12** and **14**. (b) A substantıal (by ≥ 0.4 ppm) shıft to lower fıelds of H-5-endo and a smaller (by ≤ 0 16 ppm) shıft to hıgher fıelds of H-5-exo was observed ın syn adducts wıth respect to antı adducts

18 Huısgen, R *1,3- Dıpolar Cycloadditıons - Introductıon, Survey, Mechanısm* ın *1,3-Dıpolar Cycloadditıon Chemıstry*, Padwa, A , Ed ; Wıley-Interscıence. New York, 1984, p 141

19 (a) Cross lactonızatıon, e.g, between posıtıons 2 and 8, ıs less lıkely as shown by IR absorptıons of these lactones (≥ 1780 cm^{-1}) whıch are consıstent wıth a fıve membered rıng structure. (b) Thıs proton (ı e H-9) ıs easıly ıdentıfied as ıt resonates at hıgher fıelds (by ≥ 0.7 ppm) than H-8 deshıelded by the lactone oxygen. Moreover, H-9 ın **22** exhıbıts couplıng to OH.

20 Bovıo, B., Unıversıta' dı Pavıa, prıvate communıcatıon

21 The endo substıtuents ın **4b** not only hınder the 1,3-dıpolar attack on the syn face but also gıve rıse to a decrease ın reactıvıty of the carbon carbon double bond Thıs effect can tentatıvely be traced back to a donor effect of the substıtuents owıng to the ınteractıon between theır lone paırs and the π bond thus decreasıng the propensıty of thıs bond to suffer attack by the "electron-rıch" dıazomethane Paddon-Row, M N , Patney, H K., Warrener, R N *J Org Chem* **1979**, *44*, 3908. Houk, K N ; Rondan, N.G , Wu, Y D , Metz, J T. Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

22 Also dıpole-dıpole ınteractıons should slıghtly dısfavor syn attack ın **1b,c** owıng to the fact that thıs attack leads to the more polar adduct.

23 It should be emphasızed that facıal selectıvıty observed ın the reactıons of bıcyclooctenes conforms to Hehre's model whıch predıcts that nucleophıles (dıazomethane ıs an "electron-rıch" 1,3-dıpole)[16] wıll attack double bonds antı wıth respect to lone paır contaınıng substıtuents However, the same author has shown that thıs effect can be overrıdden by steric factors when the double bond and the heteroatoms are embedded ın a rıgıd bıcyclıc skeleton (Khan, S. D., Pau, C F , Chamberlaın, A R , Hehre, W. J *J Am Chem Soc* **1987**, *109*, 650) In our case steric effects and Hehre's effect work ın the same dırectıon thus precludıng any relıable conclusıon about the role of thıs latter effect.

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