1 H, olefinic), 6.1 (m, 1 H, COCH=CH), 7.2 (m, 1 H, COCH=CH). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.42; H, 8.34.

Reaction of Phthalimide with Crotylindium (2b). The reaction was similarly carried out at room temperature for 16 h. Aqueous workup and purification on preparative TLC (silica gel, 30% AcOEt in hexane) gave a diastereomeric mixture of **15** in 44% yield.

3-(3-Buten-2-yl)-3-hydroxyphthalimidine (15): mp 110–120 °C; IR (KBr) 3275, 1700, 1660, 1610, 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.85 and 1.2 (each d, J = 4 Hz, total 3 H, Me), 2.6–3.1 (m, 1 H, CH), 3.2 (b s, 1 H, OH), 4.9–5.25 (m, 2 H, olefinic), 5.3 (b s, 1 H, NH), 5.5–6.3 (m, 1 H, olefinic), 7.3–7.8 (m, 4 H, Ar); MS (70 eV) m/z 185 ($M^+ - H_2O$). Anal. Calcd for $C_{12}H_{13}NO$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.45; H, 6.46; N, 6.82.

Reaction of Chlorotributylstannane with Allylic Indium Reagents 2. General Procedure. To an allylic indium reagent **2** prepared from In (1 mmol) and an allylic halide (1.5 mmol) in DMF (1 mL) was added chlorotributylstannane (1 mmol) at room temperature. After the reaction was complete (1–7 h), hydrochloric acid (1%, 10 mL) was added and the product extracted with ether. The extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography on silica gel (hexane–CH_2Cl_2 gradient) to give the allylic tributylstannane **16**. The structure was confirmed on the basis of the spectral data. The isomeric ratio was estimated by ^1H and ^{13}C NMR spectroscopy. Results are summarized in Table III.

Allyltributylstannane (16a):[18] ^1H NMR (200 MHz, $CDCl_3$) δ 0.70–1.08 (m, 15 H, Me and CH_2), 1.15–1.72 (m, 12 H, CH_2), 1.79 (d, J = 8 Hz, 2 H, CH_2), 4.59–5.00 (m, 2 H, olefinic), 5.81–6.18 (m, 1 H, olefinic).

(*E*)- and (*Z*)-2-hexenyltributylstannane (16d):[19] ^1H NMR (200 MHz, $CDCl_3$) δ 0.76–1.04 (m, 18 H, Me and CH_2), 1.15–1.61 (m, 14 H, CH_2), 1.71 (m, 2 H, CH_2), 1.97 (m, 2 H, CH_2), 5.00–5.68 (m, 2 H, olefinic); ^{13}C NMR ($CDCl_3$) 124.3, 125.7, 128.2, 129.2 (olefinic).

(*E*)-Cinnamyltributylstannane (16e):[18] ^1H NMR (200 MHz, $CDCl_3$) δ 0.70–1.02 (m, 15 H, Me and CH_2), 1.17–1.69 (m, 12 H, CH_2), 1.97 (d, J = 8 Hz, 2 H, CH_2), 6.21 (d, J = 15 Hz, 1 H, olefinic), 6.40 (dt, J = 15, 8 Hz, 1 H, olefinic), 7.06–7.44 (m, 5 H, Ph).

(*E*)- and (*Z*)-3,7-dimethyl-2,6-octadienyltributylstannane (16g):[19] ^1H NMR (200 MHz, $CDCl_3$) δ 0.78–1.00 (m, 15 H, Me and CH_2), 1.20–1.70 (m, 14 H, CH_2), 1.57 (s, 3 H, Me), 1.61 (s, 3 H, Me), 1.69 (s, 3 H, Me), 2.02 (m, 4 H, CH_2), 5.12 (m, 1 H, olefinic), 5.34 (b t, J = 8 Hz, 1 H, olefinic); ^{13}C NMR ($CDCl_3$) 122.8, 123.2, 124.6, 129.0, 129.4, 131.0, 131.2 (olefinic).

(18) Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774.
(19) Takuwa, A.; Soga, O.; Mishima, T.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 1261.

Facial Differentiation in Diels–Alder Reactions to Dissymmetric Cyclohexa-1,3-dienes

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Reactions of **2a–c** with maleic anhydride (MA) and benzoquinone (BQ) show strong preference for addition to the "carbonyl" face of the diene. For dimethyl acetylenedicarboxylate (DMAD), attack from this face decreases with successive methylidene substitution while for *N*-phenyl-1,2,4-triazolinedione (PTAD) the reverse occurs. The consequence of orbital tilting and transition-state steric and torsional interactions cannot alone account for the facial selectivity for the reactions with DMAD and PTAD. Unfavorable orbital interaction of the closed shells of the carbonyl(s) and methylidene(s) syn to the incoming orthogonal π orbital of DMAD is considered to be important.

Introduction

The pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCUD, 1) framework has proved to be both of theoretical interest,[1] because of the strain contained in the pentacyclic ring system and the stereochemical relationship of the cofacial carbonyl groups, and of synthetic value as a route for the preparation of linearly fused tricyclopentanoids.[2] The diene analogue, hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (**2a**) is of interest for similar reasons but in addition offers an attractive framework for the study of π-facial selectivity that complements the results for the well-studied diene, isodicyclopentadiene.[3] X-ray crystal structure analyses of this diketone[4] and a hemiacetal derivative[5] show the diene component to be in a planar arrangement in both compounds. The diene **2a**[5] showed a marked preference for alkene addition from the carbonyl face of the diene. A selection of these addition reactions was independently reported somewhat later[6] where it was concluded that the carbonyl groups were not in any way responsible for influencing the facial selectivity since the diol resulting from $NaBH_4$ reduction of the carbonyl groups in **2a** also underwent addition of acrylonitrile from the carbonyl face. This is despite the fact that we had previously reported additions[5] of azo and alkyne dienophiles to **2a** which show variation in facial selectivity inconsistent with the conclusions of Pandey et al.[6]

We have been interested in examining in detail the effect of the carbonyl substituents on the facial selectivity of the Diels–Alder reactions. To this end we now report a series

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(3) Watson, W. H. *Stereochemistry and Reactivity of Systems Containing π Electrons*; Verlag Chemie International: Deerfield Beach, FL, 1983; pp 41–75. Paquette, L. A.; Vanucci, C.; Rogers, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 5792. See also: Paquette, L. A.; Gugelchuk, M. *J. Org. Chem.* **1988**, *53*, 1835.
(4) Dhaneshwar, N. N.; Tavale, S. S.; Guru Row, T. N.; Zope, U. R.; Pandey, B.; Ayyangar, N. R. *Acta Crystallogr.* **1988**, *C44*, 2191.
(5) Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *J. Org. Chem.* **1987**, *52*, 4726.
(6) Pandey, B.; Zope, U. R.; Ayyanger, N. R. *Synth. Commun.* **1989**, *19*, 585.

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1 2

a: X=Y=O
b: X=O, Y=CH_2
c: X=Y=CH_2

of reactions where the carbonyl oxygens of diene **2a** have been selectively replaced by methylidene groups (**2b** and **2c**), thereby retaining the π-electron configuration but replacing the lone pairs of the carbonyl oxygens with hydrogen atoms in the expectation that this would result in an increase in steric hindrance to carbonyl face addition and encourage reaction from the cyclobutane face of the diene. We also wished to examine whether the selectivity observed in these reactions with alkenes and alkynes could be reproduced by molecular mechanics calculations and have carried out a series of calculations on the adducts of **2a–c** and modeled the transition state for reactions leading to these adducts.

Results and Discussion

The methylidene derivatives **2b** and **2c** required for this study were prepared from the diketone **2a** using the Wittig procedure which had been successfully applied to the closely related PCUD (**1**) system.[7] In the presence of 1 equiv of ylide a 4:1 mixture of **2b**:**2c** was obtained, while with 2 equiv of ylide only the dimethylidene product **2c** was isolated.[8] In contrast the Peterson reaction, which had also successfully given both the mono- and dimethylidene derivatives for the PCUD system,[9] gave on reaction with **2a** only low yields (ca. 9%) of the monomethylidene **2b**.

In compounds **2a–c** the methylidene and/or carbonyl groups are held in conformationally rigid 5-membered rings[10] and exhibit π-transannular interactions in a manner similar to that described for other polycyclic bifunctional molecules.[11] The resultant bichromophoric interaction will be reflected in changes in the ^{13}C NMR chemical shifts. The chemical shift of the carbonyl carbon in going from **2a** to **2b** increases from 210.2 to 215.2 ppm. The quaternary olefin chemical shift in going from **2b** to **2c** increases from 151.5 to 155.6 ppm but the exocyclic carbon decreases from 105.1 to 102.6 ppm. Similar changes in chemical shift are also observed in the Diels–Alder adducts of **2a–c** and parallel those reported for the related PCUD (**1**) series.[11b] Photoelectron spectroscopy and theoretical studies[7,12] of **1c** confirm that the methylidene groups undergo through-space and through-bond interactions. The ^1H NMR spectra for the series of compounds **2a–c** also show significant chemical shift variations: the cyclobutane hydrogens in **2a** are observed at 3.35 ppm; in **2b** at 3.23 and 3.01 ppm and in **2c** at 2.93 ppm. Thus replacement of the carbonyl oxygens by methylidene groups results in a large (0.42 ppm) upfield shift for the spatially distant cyclobutane face protons. This is consistent with a through-space orbital interaction of the σ-antibonding orbitals of the carbonyl groups(s) with the cyclobutane C–H bonds and such orbital mixing is indeed observed in the molecular orbital calculations described below.

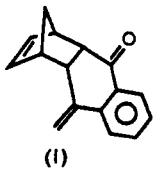
Table I. Product Ratios[a] for the Diels–Alder Reactions[b] of 2a–c

dienophile	% reaction at the "carbonyl face" 2a	2b	2c
maleic anhydride	100	100	85
benzoquinone	100	100	100
dimethylacetylene dicarboxylate (DMAD)	55	25	10
phenyl-1,2,4-triazolinedione (PTAD)	64	78	93

[a] Product ratios from 300 -MHz ^1H NMR of crude reaction mixtures. Estimated error of 2.5%. [b] All reactions carried out in benzene at 80 °C except those involving PTAD (0–5 °C in CH_2Cl_2) and DMAD with **2c** (110 °C in toluene).

Diels–Alder Reactions. Diels–Alder reactions were carried out using the dienes **2b** and **2c** and dienophiles which the eariler study[5] of **2a** had shown to be representative of the larger number originally studied. Only symmetrical dienophiles were employed in order to avoid the formation of different regioisomers in reactions of the dissymetric monomethylidene diene **2b**. Compounds **2b** and **2c** were generally less reactive than **2a** and required longer reaction times. A summary of the product ratios of the facial isomers[13] for the reactions of **2a–c** with maleic anhydride (MA), benzoquinone (BQ), dimethyl acetylenedicarboxylate (DMAD), and *N*-phenyltriazolinedione (PTAD) is given in Table I. The stereochemistry of the adducts was determined using nuclear Overhauser effect difference (NOED) spectroscopy; in particular the products resulting from carbonyl face attack on the dienes showed mutual NOE enhancements between the olefinic and cyclobutane ring protons as has previously been described[5]

(7) Shen, K.-W.; Kuebler, N. A. *Tetrahedron Lett.* **1973**, *24*, 2145.
(8) Attempts were made to carry out photochemical intramolecular [$_\pi$2 + $_\pi$2] cycloadditions by irradiating **2b** and **2c**. Compound **2c** was found to be inert to extensive irradiation in both benzene and acetone. The monomethylene **2b**, however, reacted to give a quantitative yield of (i) which is the product of opening of the cyclobutane ring. A closely related cycloreversion has recently been reported in the literature: Pandey, B., Zope, U. R.; Ayyangar, N. R. *J. Chem. Soc., Chem. Commun.* **1990**, 107.

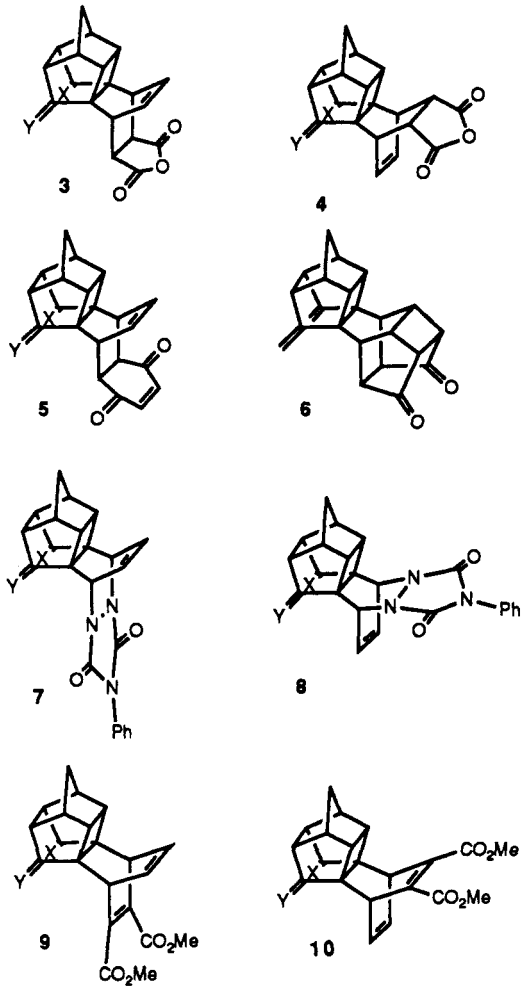


(i)

(9) Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1983**, *48*, 5392.
(10) The experimentally measured distance between the carbonyl groups in **2a** is 2.563 and 3.856 Å for the C–C and O–O distances, respectively. This data was extracted from the coordinates given in ref 4. The corresponding AM1 calculated distances for C–C and O–O are as follows: For **2a**: 2.562 and 3.932 Å. For **2b**: 2.549 and 3.944 Å. For **2c**: 2.559 and 4.014 Å.
(11) (a) Chow, T. J.; Wu, T.-K.; Shih, H.-J. *J. Chem. Soc., Chem. Commun.* **1989**, 490. (b) Bishop, R.; Lee, G.-H. *Aust. J. Chem.* **1987**, *40*, 249. (c) Bishop, R. *Aust. J. Chem.* **1984**, *37*, 319.
(12) Marchand, A. P.; Huang, C.; Kaya, R.; Baker, A. D.; Jemmis, E. D.; Dixon, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 7095.
(13) Product ratios were determined by careful 300-MHz ^1H NMR analysis of the crude reaction mixtures by integration of the olefinic proton signals of the adducts and by careful analysis of other selected signals such as the bridgehead methylenes. In all cases crude recovered material was quantitative. In all cases the ^1H NMR of the crude reaction mixtures exhibited no evidence for products other than starting material and the facial stereoisomers. No attempts were made to optimize the isolated yields of the adducts, the primary objective being the measurement of the ratio of facial stereoisomers and the isolation of the individual compounds for characterization. No evidence for interconversion of product stereoisomers was observed. The reaction of **2a** with MA and **2c** with DMAD, as being representative reactions, were carefully monitored by NMR, and the ratio of facial stereoisomer(s) did not change as the reaction progressed. Reactions with PTAD are such that even at −78 °C the reaction was too fast to monitor. Four representative pure products (**3c**, **5b**, **7c**, **10c**) were resubjected to the reaction conditions and found not to undergo isomerization and were recovered unchanged. We have, however, observed interconversion of isomeric products from reactions involving nitrosobenzene as the dienophile (unpublished results).

for the reactions of **2a**. Proton–carbon correlation spectroscopy (HETCOR) was used to unambiguously assign the ^{13}C NMR spectra for the adducts.

The alkene dienophiles, MA and BQ, reacted with the enone (**2b**) with complete selectivity from the carbonyl face of the molecule giving adducts **3b** and **5b**, respectively. This is identical with the selectivity found in reactions of diketone (**2a**). The introduction of a single methylidene group (**2b**) does not provide sufficient steric hindrance to force competitive reaction of these alkene dienophiles from the cyclobutane bearing face of the molecule. For the reaction with the acetylenic dienophile DMAD, however, the single exocyclic methylidene group had a significant influence on the selectivity; only 25% of the reaction with **2b** occurred at the carbonyl bearing face to give **9b**, in contrast to the 55% of **9a** for **2a**. However, in the opposite sense the azo dienophile, PTAD, reacts to a greater extent from the carbonyl face of **2b** to give 78% of **7b** compared with the reaction with **2a** giving 64% of **7a**.



a: X=Y=O
b: X=O, Y=CH_2
c: X=Y=CH_2

While the reaction of the ketones **2a** and **2b** with MA occurred exclusively from the carbonyl face the reaction with the dimethylidene compound **2c** is less facially selective with 85% reaction from the carbonyl face to give **3c** and 15% of cyclobutane face adduct **4c**. Benzoquinone on the other hand reacts exclusively from the carbonyl bearing face for **2a**, **2b**, and **2c**. A solution of the adduct of BQ with **2c** on standing in sunlight on a laboratory bench underwent a [$_\pi$2 + $_\pi$2] cycloaddition to produce the bis-cage product **6**.

Table II. Calculated (MMX) Energy Differences ($\Delta E_{(carbonyl-cyclobutane)}$, kJ mol^{-1}) between Adducts Resulting from Carbonyl Face and Cyclobutane Face Reaction and Calculated Percent Carbonyl Face Reaction at 80 °C of 2a–c with Selected Dienophiles

	$E_{carbonyl} - E_{cyclobutane}$, kJ mol^{-1} (calculated percentage carbonyl face reaction at 80 °C)		
dienophile	2a	2b	2c
MA	13.6 (1%)	-9.5 (97%)	-17.6 (100%)
BQ	5.6 (13%)	-11.0 (98%)	-19.1 (100%)
DMAD	1.9 (34%)[a]	0.8 (43%)[a]	3.2 (27%)[a]
PTAD	9.7 (2%)	-4.0 (83%)	-17.1 (100%)

[a] BAKMDL (MM2) energy difference between the average Boltzmann energy of significant conformers at 80 °C.

The reaction of **2c** with MA is the first example where an alkene dienophile has been observed to react to any extent at all from the cyclobutane bearing face and is considered to be a result of the greater steric barrier that the two exocyclic methylidene groups provide to the incoming dienophile. This steric congestion caused by the hydrogens in the reaction of DMAD[14] with **2c** is also reflected in the lower reactivity compared to **2b** and **2a**. This reaction only proceeded in a reasonable time at a temperature of 110 °C. The facial selectivity for the addition of DMAD to **2c** continues the trend established by the reaction with **2a** and **2b**: only 10% of the reaction now occurs from the carbonyl bearing face giving **9c** as the minor product; the cyclobutane face product, **10c**, now dominates (90%). The facial selectivity for reaction of PTAD with **2c** continues the opposite trend to DMAD, in this case 93% of the reaction occurs from the carbonyl face to give **7c** as the major product with **8c** the minor product (7%).

In summary the results for **2a–c** shown in Table I show the alkene dieneophiles MA and BQ to react from the carbonyl bearing face of the molecule. While DMAD has a high sensitivity to the introduction of the methylidene groups with the reaction from the carbonyl face disfavored by the introduction of each successive exocyclic methylidene, PTAD shows the opposite trend with an *increasing* selectivity on the face syn to exocyclic methylidene substitution as each carbonyl oxygen is selectively replaced. All the additions to **2a**, **2b**, and **2c** gave the products of Alder addition, this is consistent with obvious steric constraints and supported undoubtedly by secondary orbital interactions.[15]

Early kinetic and thermodynamic investigations of π-facial selectivity led to the proposal[16] that product stability was important in influencing π-facial preference although this has been shown to be of limited generality.[17] In order to investigate any relationship of product stability to the reactions of **2a–c** the MMX[18] steric energy was calculated for each of the possible products resulting from reaction of **2a–c** with each of the four dienophiles employed.[19] The calculated steric energy differences between the facial

(14) The exocyclic π systems in **2a–c** are remote from the diene and changes in these groups have a minor effect on the frontier orbitals of the diene. This is confirmed by AM1 calculations. The eigenvalues for the HOMO and LUMO for **2a–c** and a CaChe diagram of the wavefunction for these orbitals for **2a** is included in the supplementary material.

(15) Ginsberg, D. *Tetrahedron* **1983**, *39*, 2095.

(16) Hagenbuch, J.-P.; Vogel, P.; Pinkerton, A. A.; Schwarzenbach, D. *Helv. Chim. Acta* **1981**, *64*, 1818.

(17) Mahaim, C.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 866.

(18) The calculations were performed using MMX 88 and associated parameters as available from Serena Software, 489 Serena Lane, Bloomington, IN 47401.

(19) For DMAD the MM2 force-field as implemented in the BAKMDL (1989) program was used in order to allow conformational searching of the methoxycarbonyl groups.

Table III. Energy Differences between Transition States ($E_{carbonyl} - E_{cyclobutane}$, kJ mol^{-1}) Calculated Using MMX Transition-State Parameters and Predicted Percentage Reaction at the Carbonyl Face for the Diels–Alder Reactions

	$E_{carbonyl} - E_{cyclobutane}$, kJ mol^{-1} (calculated percentage carbonyl face reaction at 80 °C)		
dienophile	**2a**	**2b**	**2c**
MA			
MMX parameters	−15.6 (100%)	−6.9 (92%)	−3.3 (75%)
fixed model[a]	−20.7 (100%)	−19.7 (100%)	−13.9 (99%)
BQ			
MMX parameters	−18.2 (100%)	−11.5 (98%)	−3.2 (75%)
fixed model[a]	−22.0 (100%)	−19.2 (100%)	−14.3 (99%)
DMAD[b]			
fixed model[a]	−17.8 (100%)	−4.9 (84%)	+7.9 (8%)

[a] Calculated using a fixed model based on AM1 transition-state calculations for acetylene and cyclohexadiene. [b] Difference is between average Boltzmann energy of significant conformers at 110 °C.

isomers as reported in Table II clearly show that product stability does not account for the experimentally observed selectivities. For example the results in Table II indicate the adducts with **2a** which would result from addition at the cyclobutane bearing face are the thermodynamically more stable. Failure to observe the formation of these products is consistent with the experimentally observed irreversibility (and exothermicity) of these reactions and militates against the hypothesis that product stability[16] is an important factor in determining π-facial selectivity.

The product stability calculations show a remarkable sensitivity to the nature of the exocyclic π-system. In particular dipole interactions of the carbonyl group(s) with the dienophile fragment are important in destabilizing the syn adduct. This sensitivity of product stability to substitution makes this system an interesting case to study since such effects should be exhibited in some manner at the various transition-state geometries.

Houk[20] has proposed in his study of isodicyclopentadiene that steric and torsional interactions resulting from bending at the "transition state" account for the endo facial selectivity of these reactions with alkene dienophiles. His molecular mechanics calculations, based on a fixed model derived from a MNDO calculation for the "transition state" for ethylene and butadiene, were successful in predicting the variation of selectivity with a variety of alkene dienophiles.

As an estimate of the effect of steric and torsional interactions at the transition state MMX calculations[18] were performed of the steric energy at an approximate C_s transition structure for the reactions of **2a–c** with MA and BQ at each face (Table III).[21] With the alkene dienophiles, MA and BQ, this method predicts a strong preference for reaction from the carbonyl bearing face of the molecule (Table III), but this preference falls off somewhat as the carbonyls are replaced with methylidene groups. These calculations are consistent with the experimental observations (see Table I). This trend in facial selectivity can be understood in terms of the steric barrier the methylidene hydrogens offer to incoming alkene dienophiles.

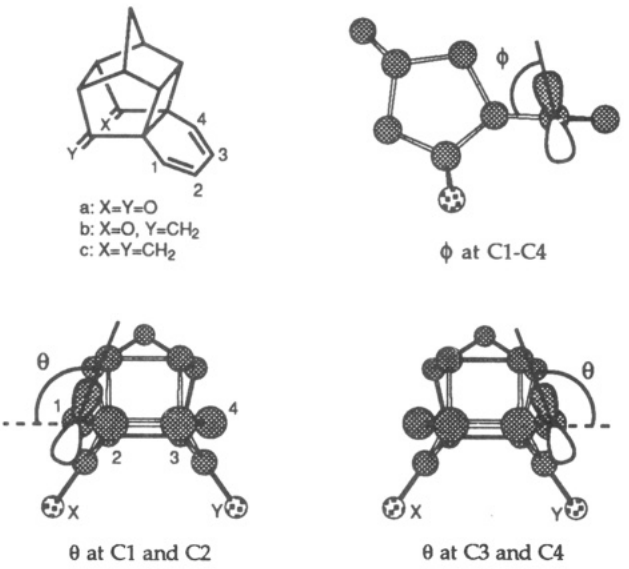


Figure 1. Definition of atom labeling and the tilting angles θ and ϕ for Table IV.

Table IV. AM1 Tilting Angles, Orbital Energies, and Coefficients for the Ψ(1) Butadiene-like MO of 2a–c (See Figure 1 for Definition of Atom Numbering and Tilting Angles)

compd	Ψ(1) orbital energy (eV)	angles (deg) and AO coefficients	C1	C2	C3	C4
2a	−11.8542					
		θ	112.2	71.9	71.9	112.2
		ϕ	71.4	102.6	102.6	71.4
		coeff	0.279	0.376	0.376	0.279
2b	−11.3346					
		θ	98.4	83.5	82.8	107.5
		ϕ	96.9	86.2	90.5	84.8
		coeff	0.275	0.402	0.358	0.196
2c	−11.1663					
		θ	101.4	83.6	83.6	101.4
		ϕ	93.5	87.4	87.4	93.5
		coeff	0.256	0.424	0.424	0.256

These calculations do not take account for mixing of reactant orbitals but reflect steric factors associated with the interaction of the polycyclic framework and substituents with the bicyclic Diels–Alder transition structures and account in broad terms for the facial selectivity observed in the reaction of **2a–c** with the alkene dienophiles.

There is, however, another explanation for the observed selectivity that warrants consideration. On the basis of ab initio and semiempirical calculations, Gleiter and Paquette[22] reported that for isodicyclopentadiene mixing of high lying σ-orbitals with the lowest occupied π-orbital (π_s) resulted in disrotatory tilting of the π-lobes. The faces of the diene are thus differentiated and antibonding interactions between the HOMO of the dienophile and the π_s orbital of the diene were considered greater when reaction occurs from the exo face of isodicyclopentadiene, consistent with the observed endo preference.[23]

In order to establish the importance of σ–π interactions in **2a–c**, AM1[24] calculations were carried out. Analysis of

(20) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971.
(21) The MMX88 transition state parameters[18] used for the alkene dienophiles closely reproduce the C_s transition structure for reaction between ethylene and butadiene calculated by high level ab initio calculations (for example: Bernardi, F.; Bottoni, A.; Field, M. J.; Guest, M. F.; Hillier, I. H.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1988**, *110*, 3050) and are likely to give a good approximation to the geometry of the transition states in the reactions of **2a–c**.
(22) Bohm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *J. Am. Chem. Soc.* **1980**, *102*, 7218. Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328.
(23) The model is based on ground-state calculations and takes no account of the approach of the dienophile which introduces steric and electronic perturbation to the system.
(24) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

the calculated molecular orbitals does indeed show extensive mixing between the high-lying σ-orbitals of the cyclobutane fragment and the lowest occupied π-orbital ($\Psi(1)$) of the diene fragment and this results in rotation of the p_z lobes for the butadiene-like $\Psi(1)$ as shown schematically in Figure 1 and Table IV. Negligible mixing occurs in the butadiene-like π-HOMO $\Psi(2)$. While the calculated AO coefficients at the reacting carbons (C1 and C4) are similar for all three dienes (**2a–c**), the inward tilting on the top face of the diene of the terminal p_z lobes (as shown by the value of θ in Table IV) at these reacting termini is greatest in the diketone **2a** and least in the dimethylidene **2c**. This inward orbital tilting of the terminal p_z lobes for **2a–c** could be considered to favor reaction at the carbonyl face with most dienophiles since antibonding interaction between the $\Psi(1)$ of the diene and the HOMO of the incoming dienophile will be greatest from the cyclobutane face. The experimental observations of carbonyl face addition are consistent with this since the only significant cyclobutane face reaction with alkenes is found in the reaction of MA with **2c**, the diene with the least terminal p-lobe tilting and consequently the least differentiation in π-electron density. Thus for alkene dienophiles σ–π interactions and torsional and steric analysis give parallel predictions and the relative importance of each factor cannot be established.

The acetylenic dienophile DMAD however shows a greater sensitivity in selectivity in reactions with **2a–c** than the reactions of MA and BQ and is therefore an important case for applying the steric MMX transition-state model. MMX "transition state" parameters are not available for Diels–Alder reactions involving alkynes so a "rigid model"[25] was developed for these reactions similar to the MNDO-based model employed by Houk for his study of isodicyclopentadiene[20] and Mehta for norbornyl-fused *p*-benzoquinones.[26] An AM1 calculated transition structure for the addition of 1,3-cyclohexadiene and acetylene was established.[27] With the appropriate bicyclic atoms of this transition structure fixed, the additional cage and dienophile components were appended, and molecular mechanics calculations were used to give a measure of the steric effect of the added structure on the relative energies of the diastereofacial transition structures. These calculations do not incorporate the effect of electronic interactions of the peripheral structure on the transition state, and therefore any deviation between the model and experimental observations will point to the importance of electronic effects in the peripheral structure on the course of reaction. The relative steric interactions at a geometry approximating the "transition state" for reaction at each face of **2a–c** with alkyne dienophiles from the rigid model described above were calculated using the MODEL/BAKMDL program,[28] and the results are summarized in Table III.[29] To allow for the conformationally flexible methoxy carbonyl groups in the DMAD transition states a conformational search at the fixed transition state geometry was carried out using the BAKMDL program to determine the most significant conformations at the reaction temperature. The energy difference between the two faces is the difference between the average Boltzmann energy of the most significant conformers at the reaction temperature.

The extent of the DMAD reaction predicted from the carbonyl face (Table III) is consistent with the experimental results only for the dimethylidene diene **2c**. For the carbonyl containing dienes (**2a, 2b**) the carbonyl face addition is greatly overestimated by this fixed "steric only" model. It is not unreasonable that there may be electronic interactions between the incoming acetylene and the π- and σ-orbitals of the carbonyl and methylidene groups, and this introduces an electronic interaction not incorporated in molecular mechanics calculations.

There is no similar model available for the reactions of PTAD. Our preliminary results from a computational study of the additions of azo compounds to dienes, along with experimental evidence,[30] indicate that the symmetrical models for acetylenes and alkenes transition states may be inappropriate for azo dienophiles. The experimentally observed selectivity in the addition reactions of PTAD suggests the importance of filled shell interactions along with steric effects in controlling the facial selectivity.

Conclusions

Reaction of **2a–c** with MA and BQ which occurs, except for **2c**, exclusively from the "carbonyl" face of the diene is consistent with both transition-state calculations and with predicted $\Psi(1)$/HOMO dienophile antibonding interactions. The reaction of MA with **2c**, the diene with the least terminal p-lobe tilting and consequently the least differentiation in facial π-electron density, occurs in part from the cyclobutane face consistent with the importance of orbital influence on facial selectivity. However transition-state calculations which reflect steric interactions also parallel this experimental observation. In contrast, for DMAD carbonyl face attack decreases substantially with successive methylidene substitution. DMAD shows a greater sensitivity in selectivity than the reactions of MA and BQ, and the extent of the DMAD reaction from the carbonyl face predicted by transition-state calculations is consistent with the experimental results only for **2c**. This indicates for **2c** that any effects of $\Psi(1)$/HOMO dienophile antibonding interactions, which would in any case be smallest for **2c**, are swamped by steric factors. In **2a** and **2b** both transition-state calculations and $\Psi(1)$/HOMO dienophile antibonding interactions would favor carbonyl face addition. The observation of extensive top (cyclobutance) face addition in these cases suggests the importance of closed shell interactions between the dienes **2a** and **2c** and the incoming acetylenic dienophile. The

(25) With the atoms associated with bond forming and bond breaking held in the transition-state calculations (AM1) on model systems, the steric energy differences between the two faces can be evaluated in a molecular mechanics calculation.

(26) Mehta, G.; Padma, S.; Pattabhi, V.; Pramanik, A.; Chandrasekhar, J. *J. Am. Chem. Soc.* **1990**, *112*, 2942.

(27) The geometry of the bicyclooctadiene product from the reaction of acetylene and 1,3-cyclohexadiene was first optimized using AM1 parameters as implemented in the MOPAC program (MOPAC 4.0 is available from the Quantum Chemistry Program Exchange (QCPE)). Additional calculations were carried out for structures where the σ-bonds which develop in the forward reaction were systematically extended while maintaining C_s symmetry. An approximate symmetrical "transition state" geometry was thereby established and refined using the gradient minimization (McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1971**, *94*, 2625) procedure in the MOPAC program. A vibrational analysis showed a single negative eigenvalue demonstrating that the structure represents a saddle point on the AM1 potential surface. The transition-state geometry is similar to that calculated by our recent high level ab initio calculations for the Diels–Alder reaction between acetylene and butadiene (Coxon, J. M.; Grice, S. T.; Maclagan, R. G. A. R.; McDonald, D. Q. *J. Org. Chem.* **1990**, *55*, 3804) with a forming σ-bond distance of 2.086 Å and the calculated energy of activation for the forward reaction is 150.0 kJ mol^{-1}. A full description of the transition state geometry for 1,3-cyclohexadiene/acetylene and ethene is available as supplementary material.

(28) A copy of the extensively rewritten Still MODEL program, version 2.94, was provided by Professor Kosta Steliou of the University of Montreal.

(29) A similar rigid model based on an AM1 calculation of the TS between ethylene and cyclohexadiene was applied to the reactions of alkenes. The results (Table III) were quantitatively the same as those obtained with the transition state parameterized model.

(30) Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376.

precise nature of these interactions is the subject of a more detailed investigation.

Experimental Section

General. NMR spectra were recorded on a spectrometer equipped with a 5-mm probe operating at 299.930 and 75.426 MHz for ^1H and ^{13}C, respectively. Difference NOE spectra were obtained in an arrayed experiment with the decoupler offset 10 000 Hz and then cycled with low power over the multiplet peaks of the desired proton for irradiation, a procedure based on that of Kinns and Sanders.[31] Heteronuclear proton–carbon correlated spectra were recorded using a sequence that ensures full ^1H–^1H decoupling.[32] All dienophiles were obtained commercially. The addition reactions were followed by TLC analysis and after the stated reaction period the crude reaction mixtures were analyzed by 300-MHz NMR spectroscopy to determine the product ratios. The crude addition products were then separated and purified by either recrystallization or radial chromatography on silica. Melting points are uncorrected.

10-Methylidenehexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-dien-3-one (2b) and 3,10-Dimethylidenehexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene (2c). To 50 mL of dry dimethyl sulfoxide (DMSO) was added under nitrogen 136 mg (4.54 mmol) of an 80% suspension of NaH in mineral oil. The mixture was stirred at 60 °C for 2 h. The resulting solution was cooled to room temperature, and 1.62 g (4.54 mmol) of methyltriphenylphosphonium bromide was added. A dark yellow solution formed immediately and the mixture was stirred at room temperature for 2 h after which time 1.0 g (4.45 mmol) of the diketone **2a** was added. The reaction mixture was stirred and kept for 3 days in an oil bath at 60 °C. The solution was then cooled and poured into 50 mL of water. The combined DMSO/water layer was extracted with 100-, 75-, and 50-mL portions of pentane. The extracts were combined, washed with a 1:1 water/DMSO mixture (2 × 50 mL) and with water (2 × 50 mL), dried ($MgSO_4$), and evaporated to yield 510 mg of a white solid. The crude solid was absorbed onto a column of 30 g of alumina, and elution with petroleum ether gave **2c** (101 mg, 10.3%), which was recrystallized from ethanol to give waxy white needles: mp 85–86 °C; IR (KBr) 3000, 1700, 1100, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 10.7 Hz, H15b), 1.67 (d, J = 10.7 Hz, H15a), 2.50 (m, H1, H12), 2.85 (m, H2, H11), 2.93 (m, H13, H14), 4.46 (d, J = 1.3 Hz, C=CH_2, syn), 4.71 (d, J = 1.3 Hz, C=CH_2, anti), 5.44 (m, H5, H8), 5.88 (m, H6, H7); ^{13}C NMR ($CDCl_3$) δ 35.0 (C15), 46.7 (C1, C12), 50.4 (C4, C9), 52.9 (C2, C11), 55.8 (C13, C14), 102.6 (C=CH_2), 123.0 (C6, C7), 125.1 (C5, C8), 155.6 (C3, C10); HRMS-CI required for $C_{17}H_{17}$ (M^+ + 1) 221.1330, found 221.1327. Further elution with a 3:20 mixture of ether–petroleum ether gave **2b** (398 mg, 40.2%): mp 59–61 °C; IR (KBr) 3010, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (d, J = 11.0 Hz, H15b), 1.84 (d, J = 11.0 Hz, H15a), 2.61 (m, H2), 2.74 (m, H1, H12), 3.03 (m, H14), 3.13 (m, H11), 3.23 (m, H13), 4.60 (d, J = 1.3 Hz, C=CH_2, anti), 4.86 (s, C=CH_2, syn), 5.41 (m, H5, H8), 5.93 (m, H6, H7); ^{13}C NMR ($CDCl_3$) δ 37.3 (C15), 43.1 (C12), 48.0 (C1), 49.6 (C9), 50.1 (C14), 52.0 (C4), 53.8 (C11), 54.7 (C2), 56.9 (C13), 105.1 (C=CH_2), 120.6 (C8), 123.4 (C6), 123.9 (C5), 124.5 (C7), 151.5 (C10), 215.2 (C3); HRMS required for $C_{16}H_{14}O$ 222.1044, found 222.1039. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.84; H, 6.45. A repeat of this procedure but with 2 equiv of base and phosphonium salt on 3.0 g of diketone gave 1.55 g of a crude waxy material. Chromatography on alumina (60 g) gave on elution with petroleum ether 1.2 g (40.7%) of **2c**, which was identical in all respects with the material obtained above.

Diels–Alder Addition Reactions to the Monomethylidene Diene 2b. (i) A solution of **2b** (200 mg) and MA (89 mg) in benzene (20 mL) was heated under reflux for 2 days. The solvent was removed under reduced pressure to give **10-methylidene-15-oxaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-3,14,16-trione (3b)**, which was recrystallized from ethanol as white needles (230 mg): mp 240–241 °C; IR 2970, 1840, 1810, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (d, J = 11.3 Hz, H20b), 1.86 (d, J = 11.3 Hz, H20a), 2.34 (m, H7), 2.56 (m, H4), 2.63 (m, H5, H6), 2.71 (m, H8), 3.10 (m, H9), 3.28 (m, H1), 3.41 (m, H12), 3.46 (dd, J = 3.1, 8.9 Hz, H13), 3.85 (dd, J = 3.3, 8.9 Hz, H17); 4.87 (s, C=CH_2, syn), 4.94 (s, C=CH_2, anti), 6.51 (m, H18, H19); ^{13}C NMR ($CDCl_3$) δ 32.2 (C1), 34.9 (C12), 39.0 (C20), 39.4 (C17), 39.9 (C7), 40.9 (C13), 42.6 (C8), 46.7 (C5), 47.6 (C6), 52.5, 53.1 (C11, C2), 54.8 (C4), 55.3 (C9), 105.0 (C=CH_2), 132.9, 133.4 (C18, C19), 155.7 (C10), 172.4, 172.6 (C14, C16) (C3 was not observed); HRMS required for $C_{20}H_{16}O_4$ 320.1049, found 320.1046. Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.98; H, 5.04. Found: C, 74.94; H, 4.98.

(ii) A solution of **2b** (200 mg) and BQ (98 mg) in benzene (20 mL) was heated under reflux for 2 days. Removal of the solvent gave **10-methylideneoctacyclo[10.6.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,18}]heneicosa-15,19-diene-3,14,17-trione (5b)**, which was recrystallized from ethanol as yellow needles (211 mg): mp 313–316 °C dec; IR (KBr) 2950, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, J = 11.0 Hz, H21b), 1.83 (d, J = 11.0 Hz, H21a), 2.29 (m, H6), 2.51 (m, H4), 2.56 (m, H7), 2.61 (m, H8), 2.85 (m, H5), 3.08 (m, H9), 3.35 (m, H13), 3.39 (m, H1), 3.47 (m, H12), 3.69 (m, H18), 4.92 (s, C=CH_2, syn), 4.94 (s, C=CH_2, anti), 6.41 (m, H19, H20), 6.66 (m, H15, H16); ^{13}C NMR ($CDCl_3$) δ 34.5 (C1), 37.7 (C12), 38.9 (C21), 40.0 (C6), 42.6 (C5), 43.5 (C18), 44.6 (C13), 46.5 (C8), 47.8 (C8), 53.0, 53.9 (C11, C2), 55.1 (C4), 55.4 (C9), 104.8 (C=CH_2), 134.2, 133.7 (C19, C20), 141.2 142.0 (C15, C16), 155.7 (C22), 198.5, 198.7 (C14, C17), 217.3 (C3); HRMS required for $C_{22}H_{18}O_3$ 330.1256, found 330.1253. Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.97; H, 5.50. Found: C, 80.27; H, 5.90.

(iii) To an ice-cooled solution of **2b** (300 mg) in CH_2Cl_2 (15 mL) was slowly added dropwise a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (236 mg) in CH_2Cl_2 (15 mL). The solution was stirred at 0–5 °C for 1 h after which time a faint red color was persistent, and analysis by TLC showed no starting material remained. The solvent was removed at room temperature under reduced pressure to give a solid residue which was adsorbed onto silica on a radial chromatograph. Elution with a 1:1 mixture of ether–petroleum ether gave **10-methylidene-15-phenyl-13,15,17-triazaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{3,17}]eicos-18-ene-3,14,16-trione (8b)**, which was recrystallized from ethanol as colorless prisms (85 mg): mp 243–244 °C; IR (KBr) 3020, 1790, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (d, J = 11.2 Hz, H20b), 1.99 (d, J = 11.2 Hz, H20a), 2.57 (m, H4), 2.82 (m, H8), 2.87 (m, H5), 3.11 (m, H9, H7), 3.34 (m, H6), 4.53 (s, C=CH_2, syn), 4.85 (s, C=CH_2, anti), 5.01 (dd, J = 2.2, 5.0 Hz, H1), 5.10 (dd, J = 2.2, 4.8 Hz, H12), 6.57 (m, H18, H19), 7.37 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 38.1 (C7), 40.4 (C20), 43.3 (C5), 45.1 (C6), 47.7 (C8), 50.7 (C1), 53.2 (C12), 54.0 (C4), 54.5 (C9), 55.6, 55.8 (C2, C11), 105.7 (C=CH_2), 118.6, 125.5, 128.4, 129.1, 131.3 (C18, C19 and phenyl), 146.8 (C10), 211.6 (C3); HRMS required for $C_{24}H_{19}N_3O_3$ 397.1426, found 397.1431. Anal. Calcd for $C_{24}H_{19}N_3O_3$: C, 72.52; H, 4.82; N, 10.55. Found: C, 72.58; H, 4.83, N, 10.72. Further elution with ether gave **10-methylidene-15-phenyl-13,15,17-triazaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{3,17}]eicos-18-ene-3,14,16-trione (7b)**, which was recrystallized from ethanol as white cubes (210 mg): mp 296–298 °C; IR (KBr) 3000, 1760, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62, (d, J = 11.2 Hz, H20b), 1.91 (d, J = 11.2 Hz, H20a), 2.42 (m, H6), 2.66 (m, H7, H8), 2.73 (m, H4, H5), 3.19 (m, H9), 5.00 (s, C=CH_2, anti), 5.13 (dd, J = 2.2, 5.1 Hz, H1), 5.17 (s, C=CH_2, syn), 5.23 (dd, J = 2.2, 5.1 Hz, H12), 6.68 (m, H18, H19), 7.39 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 38.2 (C7), 40.0 (C20), 42.5 (C5), 44.7 (C6), 47.3 (C8), 49.8 (C1), 50.2, 51.3 (C2, C11), 52.4 (C12), 54.3 (C4), 105.0 (C=CH_2), 118.6, 125.5, 128.1, 129.7, 129.9, 131.4 (C18, C19, and phenyl), 146.7 (C10), 155.6, 155.7 (C14, C16), 211.1 (C3); HRMS required for $C_{24}H_{19}N_3O_3$ 397.1426, found 397.1429. Anal. Calcd for $C_{24}H_{19}N_3O_3$: C, 72.52; H, 4.82; N, 10.55. Found: C, 72.53; H, 4.84; N, 10.60.

(iv) A solution of **2b** (200 mg) and dimethyl acetylenedicarboxylate (128 mg) in benzene was heated under reflux for 8 days, after which time the solvent was removed under reduced pressure to leave an oily residue which was adsorbed onto silica on a radial chromatograph. Elution with a 1:5 mixture of ether–petroleum ether gave **dimethyl 10-methylidene-3-oxoheptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-13,14-dicarboxylate (10b)**, which was recrystallized from ethanol as white prisms (98 mg): mp 147–148 °C; IR (KBr) 2860, 1750, 1715, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (d, J = 10.9 Hz, H17b), 1.77 (d, J = 10.9 Hz, H17a), 2.42 (m, H4, H6), 2.64 (m, H7, H8), 2.71 (m, H5), 2.99 (m, H9), 3.81 (6 H, s, OCH_3), 3.95 (dd, J = 1.9,

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(32) Perpic-Dumont, M.; Reynolds, W. F.; Enriquez, R. G. *Magn. Reson.* **1988**, *26*, 358.

3.3 Hz, H1), 4.05 (dd, J = 1.9, 4.0 Hz, H12), 4.58 (s, C=CH_2, syn), 4.75 (s, C=CH_2, anti); 6.53 (m, H15, H16); ^{13}C NMR ($CDCl_3$) δ 38.6 (C6), 39.2 (C1), 40.2 (C17), 41.8 (C12), 43.2 (C5), 45.3 (C7), 47.7 (C8), 52.4 (OCH_3), 53.2 (C5), 53.8 (C9), 59.1, 60.1 (C2, C11), 104.5 (C=CH_2), 132.7, 133.1 (C15, C16), 142.6, 143.4 (C13, C14), 149.6 (C10), 166.2, 166.5 (C=O), 214.6 (C3); HRMS required for $C_{22}H_{20}O_5$ 364.1311, found 364.1307. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.50; H, 5.54. Found: C, 72.41; H, 5.42. Further elution with a 2:5 mixture of ether–petroleum ether gave **dimethyl 10-methylidene-3-oxoheptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-13,14-dicarboxylate (9b)**, which was recrystallized from ethanol as colorless plates (32 mg): mp 180–182 °C; IR (KBr) 2860, 1740, 1710, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 11.0 Hz, H17b), 1.77 (d, J = 11.0 Hz, H17a), 2.19 (m, H6), 2.36 (m, H4), 2.47 (m, H7), 2.55 (m, H5), 2.60 (m, H8), 2.92 (m, H9), 3.67, 3.74 (s, 6 H, OCH_3), 3.88 (m, H1), 4.08 (m, H12), 4.70 (s, C=CH_2, syn), 5.05 (s, C=CH_2, anti); 6.62 (m, H15, H16); ^{13}C NMR ($CDCl_3$) δ 38.5 (C6), 39.7 (C1), 40.0 (C17), 42.0 (C12), 42.9 (C5), 45.7 (C7), 47.4 (C8), 52.5 (OCH_3), 52.9 (C4), 54.3 (C9), 59.3, 59.7 (C2, C11), 105.9 (C=CH_2), 134.9, 135.0 (C15, C16), 141.9, 144.8 (C13, C14), 148.9 (C10), 166.2, 166.4 (C=O) (C3 not observed); HRMS required for $C_{22}H_{20}O_5$ 364.1311, found 364.1310. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.50; H, 5.54. Found: C, 72.51; H, 5.37.

Diels–Alder Additions to the Dimethylidene Diene (2c). (i) A solution of 200 mg of **2c** and MA (89 mg) in 20 mL of benzene was heated under reflux for 3 days. Removal of the solvent under reduced pressure gave a solid residue, which was adsorbed onto silica on a radial chromatograph. Elution with a 1:10 mixture of ether in petroleum ether gave **3,10-dimethylidene-15-oxaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-14,16-dione (3c)**, which was recrystallized from ethanol as white needles (210 mg): mp 253–255 °C; IR (KBr) 3020, 1880, 1790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 11.0 Hz, H20b), 1.69 (d, J = 11.0 Hz, H20a), 2.35 (m, H6, H7), 2.39 (m, H5, H8), 2.80 (m, H4, H9), 3.32 (m, H1, H12), 3.48 (m, H13, H17), 4.69 (s, C=CH_2, syn), 4.79 (s, C=CH_2, anti), 6.52 (m, H18, H19); ^{13}C NMR ($CDCl_3$) δ 34.7 (C1, C12), 36.9 (C20), 40.8 (C13, C17), 45.2 (C6, C7), 46.5 (C5, C8), 52.0 (C2, C11), 53.0 (C4, C9), 102.5 (C=CH_2), 133.5 (C18, C19), 152.3 (C3, C10), 173.0 (C14, C16); HRMS required for $C_{21}H_{18}O_3$ 318.1260, found 318.1253. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.21; H, 5.70. Found: C, 79.49; H, 5.50. Further elution with a 3:20 mixture of ether–petroleum ether gave **3,10-dimethylidene-15-oxaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-14,16-dione (4c)**, which was recrystallized from ethanol as colorless prisms (23 mg): mp 285–287 °C; IR (KBr) 3020, 1890, 1790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 11.0 Hz, H20b), 1.69 (d, J = 11.0 Hz, H20a), 2.50 (m, H5, H8), 2.65 (m, H7, H8), 2.76 (m, H4, H9), 3.33 (m, H1, H12), 3.69 (d, J = 1.6 Hz, H13, H17), 4.42 (s, C=CH_2, syn), 4.65 (s, C=CH_2, anti), 6.36 (m, H18, H19); ^{13}C NMR ($CDCl_3$) δ 35.4 (C1, C12), 38.5 (C20), 43.0 (C13, C17), 43.3 (C6, C7), 46.6 (C5, C8), 51.9 (C4, C9), 55.0 (C2, C11), 102.7 (C=CH_2), 131.4 (C18, C19), 152.2 (C3, C10), 172.8 (C14, C16); HRMS required for $C_{21}H_{18}O_3$ 318.1260, found 318.1262.

(ii) A solution of **2c** (200 mg) and BQ (105 mg) in benzene was heated under reflux for 3 days. Removal of the solvent under reduced pressure gave **3,10-dimethylideneoctacyclo-[10.6.2.1^{5,8}.0^{2,6}.0^{4,9}.0^{7,11}.0^{13,18}]heneicosa-15,19-diene-14,17-dione (5c)**, which was recrystallized from ethanol to give yellow prisms (188 mg): mp 256–257 °C; IR (KBr) 2950, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 10.6 Hz, H21b), 1.66 (d, J = 10.6 Hz, H21a), 2.20 (m, H6, H7), 2.37 (m, H5, H8), 2.78 (m, H4, H9), 3.36 (m, H1, H12, H13, H18), 4.78 (s, C=CH_2), 6.42 (m, H19, H20), 6.66 (s, H15, H16); ^{13}C NMR ($CDCl_3$) δ 36.9 (C21), 38.0 (C1, C12), 44.7 (C13, C18), 45.2 (C6, C7), 46.6 (C5, C8), 53.2 (C4, C9), 102.2 (C=CH_2), 134.1 (C19, C20), 141.8 (C15, C16), 153.2 (C3, C10), 199.4 (C14, C17); HRMS required for $C_{23}H_{20}O_2$ 328.1463, found 328.1457. Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.11; H, 6.14. Found: C, 84.51; H, 6.19. A solution of **5c** (100 mg) in chloroform (5 mL) was exposed to sunlight for 12 days. Removal of the solvent gave a quantitative yield of **3,16-dimethylidenedecacyclo-[16.2.1.0^{2,17}.0^{4,15}.0^{4,20}.0^{5,9}.0^{6,13}.0^{7,12}.0^{10,14}.0^{15,19}]heneicosane-8,11-dione (6)**, which was recrystallized from ethanol as white prisms (85 mg): mp >260 °C dec; IR (KBr) 2985, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 10.8 Hz, H21b), 1.78 (d, J = 10.8 Hz, H21a), 2.27 (m, H5, H14), 2.48 (m, H1, H18), 2.73 (m, H9, H10, H19, H20), 2.84 (m, H2, H17), 3.00 (m, H7, H12), 3.48 (m, H6, H13), 4.55 (s, C=CH_2, syn), 4.71 (s, C=CH_2, anti); ^{13}C NMR ($CDCl_3$) δ 34.5 (C6, C13), 34.8 (C5, C14), 36.8 (C21), 44.3 (C9, C10), 45.2 (C19, C20), 45.5 (C7, C12), 45.9 (C4, C15), 46.3 (C1, C18), 52.8 (C2, C17), 102.0 (C=CH_2), 153.6 (C3, C16), 211.2 (C8, C11); HRMS required for $C_{23}H_{20}O_2$ 328.1463, found, 328.1458. Anal. Calcd for $C_{23}H_{20}O_2 \cdot C_2H_5OH$: C, 80.17; H, 7.00. Found: C, 80.07; H, 6.77.

(iii) To an ice-cooled solution of **2c** (400 mg) in CH_2Cl_2 (15 mL) was slowly added dropwise a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (315 mg) in CH_2Cl_2 (15 mL). The solution was stirred at 0–5 °C for 1 h after which time a faint red color was persistent. The solvent was removed at room temperature under reduced pressure to give a solid residue, which was adsorbed onto silica on a radial chromatograph. Elution with a 1:5 mixture of ether–petroleum ether gave **3,10-dimethylidene-15-phenyl-13,15,17-triazaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-14,16-dione (7c)**, which was recrystallized from ethanol as colorless needles (585 mg): mp 203–204 °C; IR (KBr) 2990, 1780, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 10.9 Hz, H20b), 1.76 (d, J = 10.9 Hz, H20a), 2.34 (m, H6, H7), 2.50 (m, H5, H8), 2.91 (m, H4, H9), 4.89 (s, C=CH_2, syn), 5.00 (s, C=CH_2, anti), 5.11 (m, H1, H12), 6.69 (m, H18, H19), 7.40 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 36.9 (C20), 43.4 (C6, C7), 46.2 (C5, C8), 50.5 (C2, C11), 52.6 (C1, C12), 52.9 (C4, C9), 103.7 (C=CH_2), 125.5 (C18, C19), 128.1, 129.0, 130.0, 132.5 (phenyl), 150.4 (C3, C10), 155.6 (C14, C16); HRMS required for $C_{25}H_{21}O_2N_3$ 395.1634, found 395.1635. Anal. Calcd for $C_{25}H_{21}O_2N_3$: C, 75.72; H, 5.36; N, 10.63. Found: C, 75.72; H, 5.36; N, 10.63. Further elution with a 3:10 mixture of ether–petroleum ether gave **3,10-dimethylidene-15-phenyl-13,15,17-triazaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-14,16-dione (8c)**, which was recrystallized from ethanol to give colorless prisms (23 mg): mp 237–239 °C; IR (KBr) 2980, 1740, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, J = 10.9 Hz, H20b), 1.83 (d, J = 10.9 Hz, H20a), 2.57 (m, H5, H8), 2.83 (m, H4, H9), 3.02 (m, H6, H7), 3.02 (m, H6, H7), 4.38 (s, C=CH_2, syn), 4.73 (s, C=CH_2, anti), 5.06 (m, H1, H12), 6.53 (m, H18, H19), 7.47 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 38.6 (C20), 43.7 (C6, C7), 46.5 (C5, C8), 52.5 (C1, C12), 53.3 (C4, C9), 53.6 (C2, C11), 103.4 (C=CH_2), 125.5 (C18, C19), 128.2, 128.9, 129.0, 129.1 (phenyl), 150.7 (C3, C10), 155.6 (C14, C16); HRMS required for $C_{25}H_{21}O_2N_3$ 395.1643, found 395.1625.

(iv) A solution of **2c** (500 mg) and dimethyl acetylenedicarboxylate (325 mg) in toluene (30 mL) was heated under reflux for 14 days. The solvent was removed under reduced pressure, and the residue was adsorbed onto silica on a radial chromatograph. Elution with a 1:5 mixture of ether–petroleum ether gave **3,10-dimethylideneheptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-13,14-dicarboxylate (10c)**, which was recrystallized from ethanol as colorless plates (398 mg): mp 154–155 °C; IR (KBr) 2990, 1730, 1715, 1670, 1640; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 10.7 Hz, H17b), 1.69 (d, J = 10.7 Hz, H17a); 2.33 (m, H6, H7), 2.42 (m, H5, H8), 2.70 (m, H4, H9), 3.81 (s, 6 H, OCH_3), 4.01 (dd, J = 2.9, 4.2 Hz, H1, H12), 4.44 (s, C=CH_2, syn), 4.65 (s, C=CH_2, anti), 6.48 (m, H15, H16); ^{13}C NMR ($CDCl_3$) δ 38.5 (C17), 42.1 (C1, C12), 44.1 (C6, C7), 46.7 (C5, C8), 51.8 (C4, C9), 52.3 (OCH_3), 57.8 (C2, C11), 102.2 (C=CH_2), 132.6 (C15, C16), 143.5 (C13, C14), 153.7 (C3, C10), 166.7 (C=O); HRMS required for $C_{23}H_{22}O_4$ 362.1518, found 362.1510. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.21; H, 6.12. Found: C, 76.09; H, 6.07. Further elution with a 1:5 mixture of ether–petroleum ether gave a 5:1 mixture of **10c** and **3,10-dimethylideneheptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-13,14-dicarboxylate (9c)**, which was not obtained in a pure form. Repeated recrystallization of this mixture from ethanol gave samples enriched in **9c** (2:5 mixture of **9c**:**10c**), which has the following spectral parameters: ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 10.8 Hz, H17b), 1.69 (d, J = 10.8 Hz, H17a), 2.19 (m, H6, H7), 2.37 (m, H5, H8), 2.70 (m, H4, H9), 3.76 (s, 6 H, OCH_3), 4.22 (m, H1, H12), 4.65 (s, 4 H, C=CH_2), 6.48 (m, H15, H16); ^{13}C NMR ($CDCl_3$) δ 38.1 (C17), 42.4 (C1, C12), 44.2 (C6, C7), 46.1 (C5, C8), 52.1 (C4, C9), 52.2 (OCH_3), 57.8 (C2, C11), 102.7 (C=CH_2), 135.4 (C15, C16), 143.5 (C13, C14), 153.2 (C3, C10), 166.7 (C=O).

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Supplementary Material Available: Summaries of AM1 calculations of transition states for reactions of cyclohexadiene with acetylene and ethylene; and AM1 calculated cartesian coordinates and eigenvalues/eigenvectors for the HOMOs and LUMOs of **2a**, **2b**, and **2c** (20 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of the Antisecretory Prostaglandin Enisoprost

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An efficient 11-step synthesis of the antisecretory prostaglandin enisoprost starting with (*Z*,*Z*)-1,5-cyclooctadiene has been developed. The key steps in the synthesis are a selective ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene, a zinc chloride catalyzed rearrangement of a furanylcarbinol, and a coupling reaction of a suitably substituted cyclopentenone with a dilithiocyanocuprate reagent derived from 4-methyl-1-octyn-4-ol.

Introduction

A 13-step synthesis of the antisecretory prostaglandin enisoprost was previously reported by Collins et al.[1] in 1983. The reported synthesis involved coupling of enone **6** with a cuprate reagent[2] derived from a suitably substituted vinylstannane and cuprous pentyne to give enisoprost **10** in 60% yield after removal of protecting groups and chromatographic purification.

Further development work on the synthesis of enisoprost has resulted in an improved method for preparing the key enone precursor **6** as outlined in Scheme I. Use of the *trans*-vinyl iodide **9** in place of the corresponding vinylstannane derivative and use of dilithiocyanocuprate[3] coupling technology resulted in an 85% isolated yield of enisoprost **10** as outlined in Scheme II.

Direct conversion of the terminal acetylene **8b** into protected enisoprost via a one-pot process has also been accomplished as outlined in Scheme II. This latter modification greatly simplified the process and resulted in a 71% isolated yield of enisoprost **10**.

Results and Discussion

Among the disadvantages of the reported synthesis of enisoprost were the 5% overall yield for the nine-step route used to prepare the hydroxycyclopentenone **5** and the need to chromatograph three of the intermediates in the sequence. The reported synthesis also utilized a Lindlar reduction of an acetylenic intermediate to generate a *cis*-olefin. Upon attempted scale-up, we found that the Lindlar reduction was always accompanied by the formation of 2–4% of the corresponding *trans*-olefin.[4] This impurity in turn was carried through the remaining steps of the synthesis to give 2–4% of the corresponding $\Delta^{4,5}$-trans analogue of enisoprost in the final product. In order to overcome these problems, we developed an improved synthesis of intermediate **5**.

Previous work by Piancatelli[5a–d] and Floyd[6a,b] suggested that rearrangement of a suitably substituted furanylcarbinol derivative might be a much more efficient method for preparing intermediate **5**. Tolstikov et al.[7] reported that selective ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene produced the half aldehyde–half acid **2a**, which could be converted into the half aldehyde–half ester **2b** via a two-step reaction sequence. Schreiber[8] subsequently reported a modified ozonolysis procedure for preparing half aldehyde–half esters directly via a one-pot ozonolysis of cyclic olefins. We felt that it should be possible to prepare the half aldehyde–half ester **2b** directly by ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene. Subsequent reaction of **2b** with 2-furanylmagnesium chloride would give the substituted furanylcarbinol **3** required for further elaboration into enisoprost.

Optimum yields of **2b** were obtained by carrying out the ozonolysis of (*Z*,*Z*)-1,5-cyclooctadiene to ~65–70% conversion. In this manner, **2b** could be obtained in isolated yields of 40–50% along with approximately 2–5% of the corresponding dialdehyde. Reaction of crude **2b** with 2-furanylmagnesium chloride[9] produced the furanylcarbinol **3** in good yield. Crude **3** was refluxed in aqueous dioxane in the presence of 3 equiv of zinc chloride for 18–24 h to produce a mixture of **4a** and **4b**.[10] The crude product

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(9) Furanylmagnesium chloride was prepared in situ by adding *n*-BuLi to a solution of furan in THF at −10 °C. The mixture was stirred at 0 °C for 30 min followed by the addition of anhydrous $MgCl_2$. The mixture was warmed to room temperature to effect transmetallation of the initially formed furanyllithium intermediate.
(10) Varying amounts of intermediate **5** and its corresponding acid were also present in the crude reaction mixture.

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