Tetrahedron Vol. 44, No. 14, pp. 4605 to 4618, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
Pergamon Press plc

INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN-DIENE. COMPARISON OF REACTIVITY AND STEREOSELECTIVITY WITHIN A SET OF STRUCTURALLY RELATED SUBSTRATES OF POTENTIAL USE IN GIBBERELLIN TOTAL SYNTHESIS

Giovanni Appendino[1], Jan Hoflack and Pierre J. De Clercq[2*]

State University of Gent, Department of Chemistry,
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 Gent (Belgium)

and

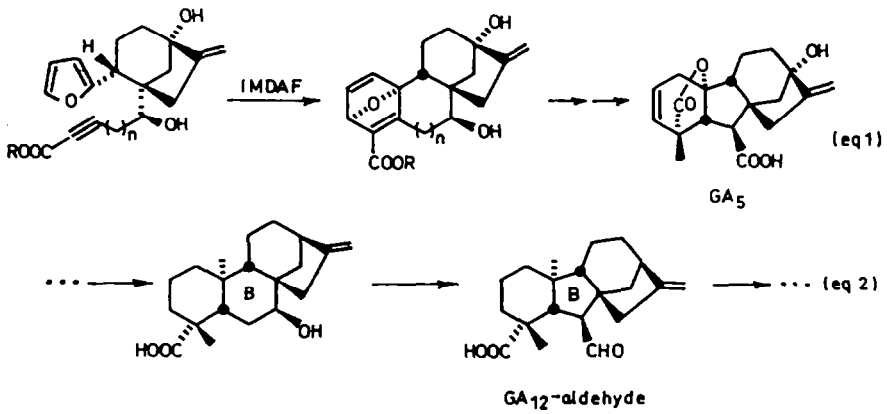
Giacomo Chiari and Mariano Calleri

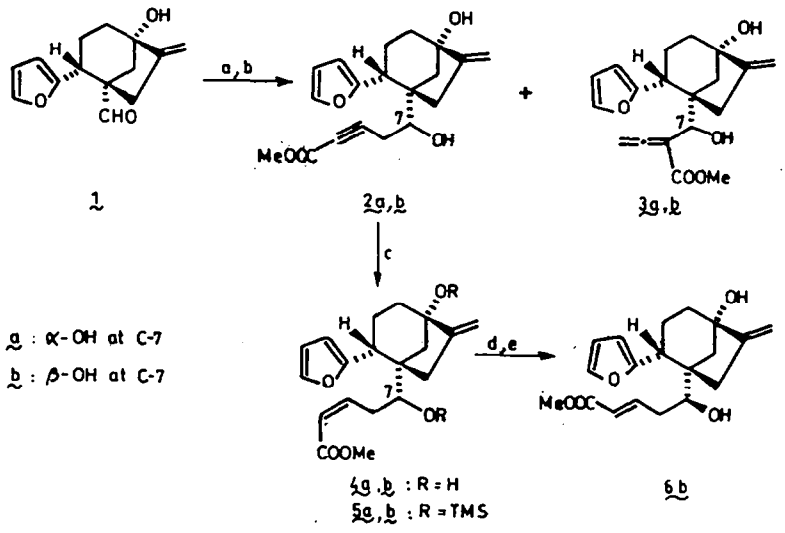
Dipartimento di Scienze della Terra,
Via San Massimo, 24, I-10123 Torino (Italy)

(*Received in UK 28 March 1988*)

Abstract - The reactivity and stereoselectivity of the intramolecular cycloaddition of a set of structurally related Diels-Alder precursors 2-6 is studied. The kinetically controlled cycloaddition of acetylene 2 yields in refluxing benzene a mixture of 7 and 8, in which the latter predominates. The allene-derivative 3b was found to cycloadd at room temperature at the unactivated π-bond to yield a single adduct 9b. The structural elucidation of adducts 7b, 8a and 9b was solved by X-ray diffraction. Olefin 4 gives the adduct 12 as sole diastereomeric adduct. A model is proposed for rationalizing the observed stereochemical outcome.

The application of intramolecular Diels-Alder strategy with furan-diene (IMDAF)[3] recently resulted in an expeditious total synthesis of (±)-GA_5 (eq 1, n = 0)[4]. As a further development we have been investigating the potential of a biomimetic variant of this route (eq 1, n = 1)[5]. An important step in the biosynthesis of the plant growth hormonal gibberellins indeed involves the ring contraction of the six-membered B-ring of the ent-kaurene skeleton into a five-membered ring as illustrated for GA_{12}-aldehyde (eq 2)[6].





[a] $(CH_2-C\equiv C-COO)Li_2$, see table 1; [b] CH_2N_2; [c] Lindlar, EtOAc, H_2; [d] Et_3N, Me_3SiCl, DMF; [e] LiSEt, THF, rt; HCl

Scheme 1

During these synthetic studies a series of Diels-Alder precursors 2-6 were obtained, which differ only in the structure of the dienophilic side-chain (scheme 1). These constitute an ideal set for the purpose of gaining more insight into the reactivity and stereoselectivity of this reaction type. In this paper we wish to report on the result of these studies, including structural aspects of the obtained adducts, as revealed by the X-ray diffraction study of adducts 7b, 8a and 9b, by force field calculations and by some diagnostic ^1H NMR spectral data.

The synthesis of Diels-Alder precursors 2-6 (scheme 1)

Starting from the known aldehyde 1[7], reaction with the dianion of 2-butynoic acid[8], followed by diazomethane treatment, invariably led to a mixture of acetylenes 2a and 2b, next to allenes 3a and 3b, the diastereomers with β-oriented hydroxy group at C-7 predominating (table 1). The assigned stereochemistry at C-7 follows from the X-ray structural determination of adducts 7b, 8a and 9b, and is also in line with previous results[4,7b,9]. On a preparative scale method 3 (table 1) gave, after HPLC purification, the acetylenes 2a and 2b, and the allene 3b, in yields of 6 %, 18 % and 4 %, respectively, next to starting material (38 %).

Table 1. *Condensation of aldehyde 1 with the dianion of 2-butynoic acid*

entry	reaction conditions[a]	yield[b]	ratio[c] 2a	2b	3a	3b
1	LTMP[d], 3 equiv, THF-HMPA (5.5:1), -100°C	67 %	8	61	7	24
2	LTMP[d], 3 equiv, THF, -100°C	50 %	28	57	5	10
3	n-BuLi-TMEDA[e], 4 equiv, THF-pentane (1:3), -60°C	58 %	19	54	9	18

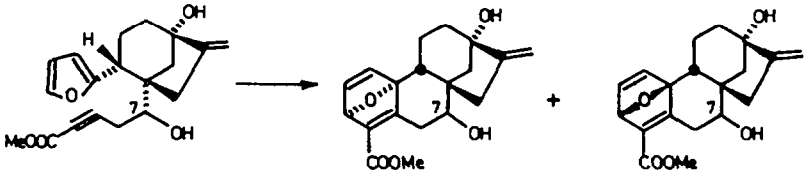
[a] base, molar equivalents of dianion, solvent, temp; [b] combined yield; [c] determined by HPLC; [d] lithium 2,2,6,6-tetramethylpiperidide; see ref. 8a; [e] N,N,N',N'-tetramethylethylene diamine; see ref. 8b.

The effective isolation of pure allene 3b proved elusive since it was found to cycloadd spontaneously during the isolation procedure (vide infra). The partial catalytic hydrogenation of 2a and 2b gave the desired Z-olefins 4a and 4b, respectively (90 % yield). The conversion of 4b to the (E)-derivative 6b proceeded via lithium ethyl thiolate induced isomerization on the

corresponding silylated 5b (68 % overall yield from 4b)[10]. The same procedure applied on unprotected 4b gave, however, lactone 17b in 58 % isolated yield.

Intramolecular cycloaddition of acetylenes 2a and 2b (scheme 2)

The Diels-Alder reaction of acetylenes 2a and 2b in refluxing benzene is slow and not very stereoselective. In the case of 2a, a 82 % conversion is realized after 7 days, leading to adducts 7a and 8a in 12 % and 70 % isolated yield, respectively (ratio 15:85). A similar result is obtained for 2b, leading to adducts 7b and 8b in a ratio 16:84 (80 % conversion). In order to improve on the reactivity and stereoselectivity, the cycloaddition of 2b was performed in water in the presence of β-cyclodextrin[11] : at 65°C, after 4 days, adducts 7b and 8b were isolated in 25 % and 67 % yields, respectively (ratio 27:73), while at 45°C yields of 6 % and 75 % (ratio 8:92), respectively, were obtained after 9 days. A similar enhancement of rate was observed in the five-membered ring case (eq 1, n = 0), but in the latter case the adduct with α-oxygen bridge was found to be kinetically preferred[4].



2a,b 7a,b 8a,b

a : α-OH at C-7 ; b : β-OH at C-7

Scheme 2

The structures of the obtained adducts were unambiguously solved via the X-ray diffraction studies of 7b and 8a (figures 1 and 2)[12]. Whereas in the case of 7b the B-ring is forced to adopt a high energy quasi 1,3-diplanar conformation, a flattened chair conformation is available for the same ring in 8a. In both cases the C-ring adopts a strained chair conformation. The endocyclic torsion angles of the B-ring in the solid-state conformations of adducts 7b and 8a are shown in figures 3 and 4, respectively.

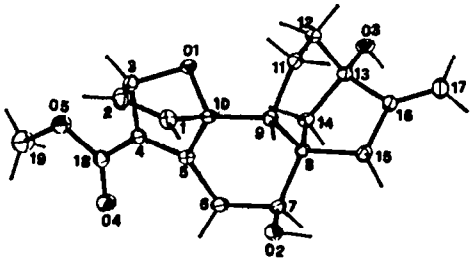


Figure 1. Stereoview of 7b

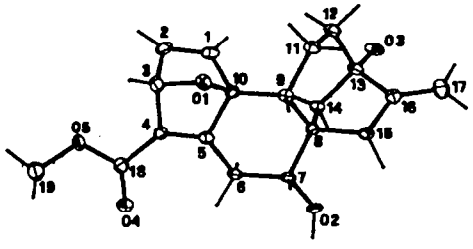
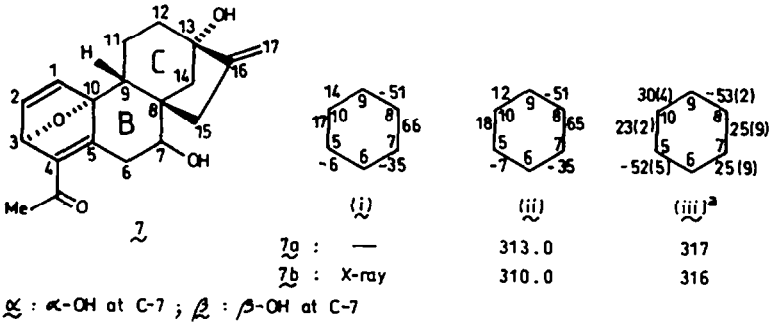


Figure 2. Stereoview of 8a

The preferred conformations of 7a, 7b, 8a and 8b were determined by force field calculations using Allinger's MM2 program[13]. For that purpose, preliminary geometries were first generated by an enhanced version of the program SCA[14]. Cartesian coordinates obtained for these geometries were then used as input files for further manipulation by MacroModel[15]. In practice we have found this combination to be a very efficient and reliable way for the finding of minimum-energy conformations of polycyclic derivatives (see experimental).

In the case of 7b the lowest energy conformer possesses a geometry almost identical with that found in the crystalline state (figure 3). Interestingly, at least two other conformations,

involving twist-boat forms for the central B-ring, were found, which are only slightly higher in energy than the preferred one (conformational energy difference : 6 kJoule/mol). The same qualitative result was found for the epimer 7a (figure 3). Both 8a and 8b yield a miminum-energy conformation almost identical to that found in the crystalline state of 8a (figure 4). No other minimum-energy conformations expected to be populated (within 10 kJoule/mol range) were found.



[a] "average" conformation : 2 minimum-energy forms in each case posses geometries with torsion angles within indicated limits (between parentheses).

Figure 3. Endocyclic torsion angles for the B-ring of adduct 7; (i) : X-ray geometry of 7b, (ii) and (iii) : MM2 low-energy conformations for 7a and 7b with corresponding steric energies (kJoul/mol)

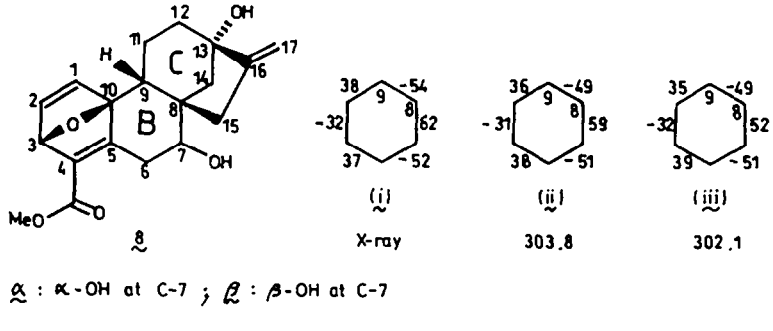


Figure 4. Endocyclic torsion angles for the B-ring of adduct 8; (i) : X-ray geometry of 8a; preferred MM2 conformations for 8a (ii) and for 8b (iii) with steric energies (kJoul/mol)

It is interesting here to compare the experimental vicinal coupling constant values in the (C-6,C-7)-fragment with the corresponding calculated values for the minimized conformations of 7a, 7b, 8a and 8b, that are shown in figures 3 and 4. As is apparent from table 2, a very fine agreement is observed between calculated and experimental values, also further indicating that the minimum-energy forms, which were found next to the lowest-energy form in the case of 7a and 7b, are not substantially populated in solution.

Although the distinction between structures 7 and 8 was unambiguously solved via X-ray diffraction, some very diagnostic ^{1}H NMR spectral differences between both adduct types are summarized in table 3. The products included in the table are the mono-acetylated derivatives at C-7 of adducts 7a, 7b, 8a and 8b. The following features deserve comment. (1) The down-field resonance of H-1 in adducts 8, compared to adducts 7 ($\Delta\delta$0.4 ppm). This effect is even further enhanced by derivatizing the C-13 hydroxy group with trichloroacetyl isocyanate[17] (TAI); whereas induced shift differences are rather small, even on proximate hydrogens (e.g., 0.00 to 0.14 for H-17), a 0.17 ppm downfield shift is observed for H-1 in the mono-acetylated derivatives of 8a and 8b upon TAI acylation. A perspective drawing of the preferred conformation of 8a (acetylated

at C-13) illustrates the relative proximity of the centers at hand (figure 5); in the indicated conformation for the acyl-residue, the distance between H-1 and the carbonyl oxygen is 3.20 Å[15].

Table 2. Comparison between experimental and calculated vicinal coupling constant values (^{1}H NMR, Hz) in the C-6,C-7 fragment of adducts 7, 8 and 12[a]

adduct	experimental[b] $^3J(H\text{-}7,H_2\text{-}6)$	calculated[c] $^3J(H\text{-}7,H_\alpha\text{-}6)$	$^3J(H\text{-}7,H_\beta\text{-}6)$
7a	8.6, 8.6	9.3 (5.7-4.7)	7.4 (1.4-1.7)
7b	5.5, 1	4.9 (9.4)	1.7 (5.7)
8a	5.0, 10.0	4.9	11.2
8b	2.6, 3.2	2.5	3.5
12a	11.5, 3.6	11.4	3.9
12b	2.0, 3.7	2.1	4.2

[a] atomnumbering as in figures 3, 4 and 9; [b] in chloroform-d_1 (7b, 12a, 12b); in pyridine-d_5 (7a), in DMSO-d_6 (8a, 8b); [c] see text, according to ref. 16; for 7, see figure 3 : conformation ii and conformation iii between parentheses; for 8, see figure 4 : conformation ii for 8a and conformation iii for 8b; for 12, see figure 9.

Table 3. Diagnostic ^{1}H NMR parameters for the distinction between 7-acetoxy adducts 7 and 8[a]

adduct	chemical shift (ppm) H-1 (+ TAI)[b]	H-2 (+ TAI)[b]	$\lvert^5J(H2,H9)\rvert$	$\lvert^2J(H_2\text{-}6)\rvert$
7-acetoxy-7a	6.70 (+0.01)	7.19 (+0.02)	< 0.4 Hz	20.8 Hz
7-acetoxy-7b	6.76 (0.00)	7.18 (+0.01)	< 0.4 Hz	21.1 Hz
7-acetoxy-8a	7.27 (+0.17)	7.17 (0.00)	1.0 Hz	16.5 Hz
7-acetoxy-8b	7.16 (+0.17)	7.28 (0.00)	0.9 Hz	18.2 Hz

[a] chloroform-d_1, 200 MHz; [b] shift difference upon addition of trichloroacetyl isocyanate.

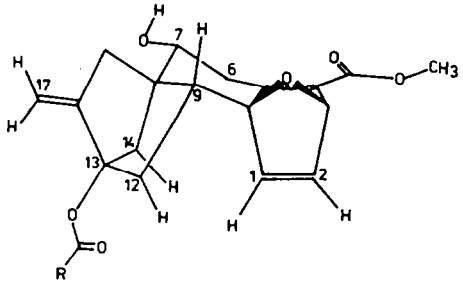


Figure 5. Stereodrawing of the preferred conformation of adduct 8a

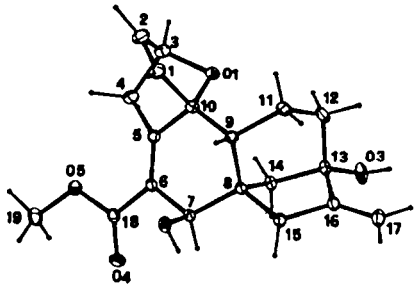
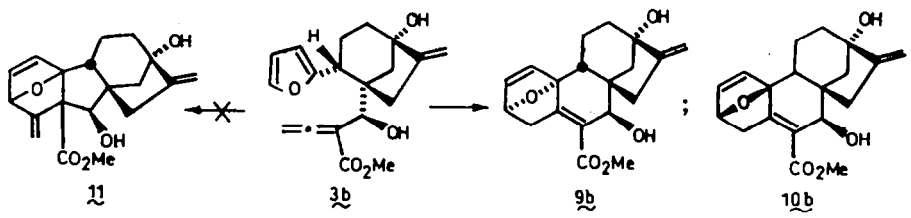


Figure 6. Stereoview of 9b

(2) The presence of a long range coupling between H-2 and H-9 (∿ 1.0 Hz) in adducts 8, which is far less pronounced in adducts 7 (0.4 Hz). The magnitude of this pseudo-homoallylic coupling[18] indicates a coplanar and anti-orientation of H-2 and H-9 in adducts 8 as illustrated in figure 5.
(3) Very large geminal coupling constant values for the allylic hydrogens at C-6 in adducts 7, compared to adducts 8. The observed values, i.e. ∿ 21 Hz, are among the largest ever reported in methylene groups[19], indicating a large π-contribution to the geminal coupling constant[20]. According to Barfield and Grant the magnitude and sign of this contribution depends on the dihedral angle between the methylene group and the adjacent π-bond and has the largest negative effect when the π-bond bisects the H-C-H angle[20a]. Whereas the latter situation is accomodated in the preferred conformation of adducts 7a and 7b, i.e., the endocyclic torsion angle at C-5,C-6 = -6°, the same dihedral angle in the preferred form of 8a and 8b is quite larger, i.e., = 37°, and the corresponding geminal coupling constant smaller (16-18 Hz).



Scheme 3

Intramolecular cycloaddition of allene 3b (scheme 3)

In contrast to the above acetylene cases, the allene derivative 3b was found to cycloadd very readily. Upon concentration of a pure HPLC fraction spontaneous cycloaddition to yield a single diastereomer was observed. X-ray diffraction analysis showed it to be the α-adduct 9b (figure 6)[12]. The observed chemoselective addition on the unactivated π-bond of the allene moiety is worth noting. Based on FOT theory alone product 11 would have been expected[21]. On the other hand, as is illustrated in figure 7 for the formation of an endo-adduct with α-oxygen bridge, the transition state geometry involved in the formation of 11 is destabilized by repulsive nonbonded interactions, especially between H-3 and the exo-methylene group[22].

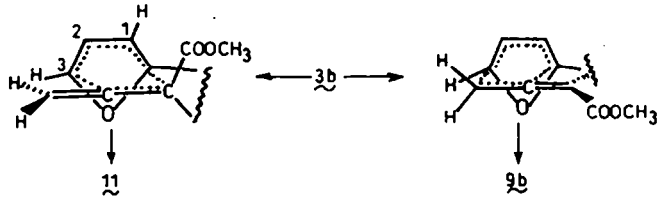
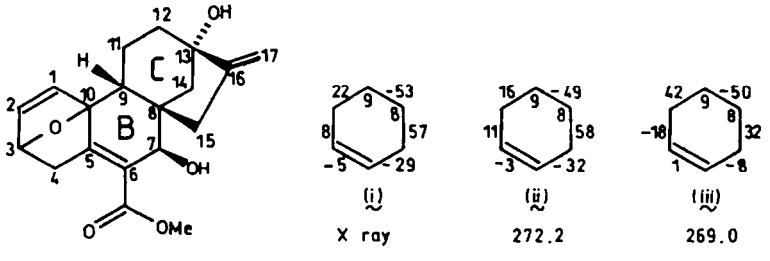


Figure 7. Transition state geometries for the cycloaddition of allene 3b

Intramolecular Diels-Alder reactions involving allene-dienophiles are not common[23,24]. The present example, involving the room temperature cycloaddition of the unactivated π-bond of an allene moiety, is analogous to the recently reported facile intramolecular cycloadditions of allene carboxanilides[25].



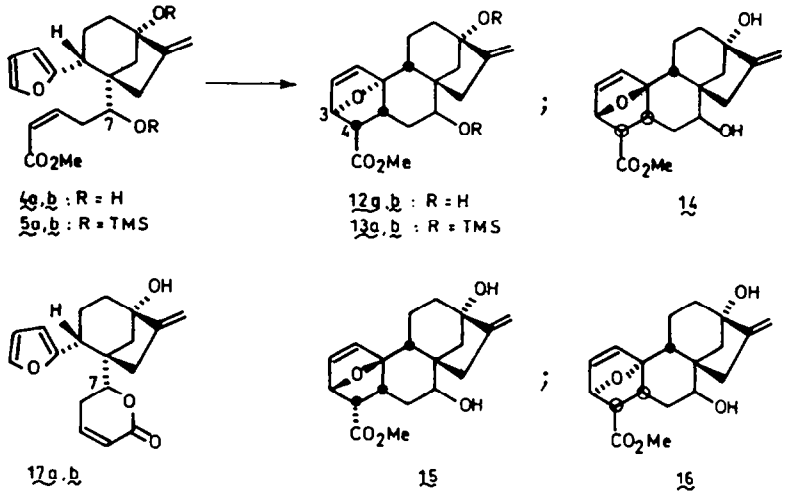
9b : α-oxygen bridge at C-3 ; 10b : β-oxygen bridge at C-3

Figure 8. Endocyclic torsion angles for the B-ring of adducts 9b and 10b; (i) : X-ray geometry of 9b; MM2 preferred conformations for 9b (ii) and for 10b (iii) with steric energies (kJoul/mol)

The preferred conformations of adducts 9b and 10b were also determined by force field calculations (see experimental). The preferred geometry of the B-ring in these adducts is shown in figure 8. Again, the calculated conformation of 9b is very close to the one observed in the crystalline state. As in the acetylene-derived adducts the C-ring adopts a distorted chair conformation in both 9b and 10b.

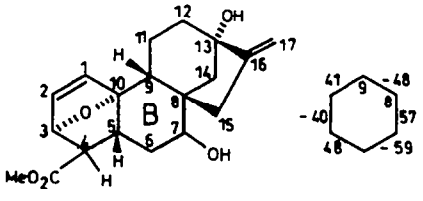
Intramolecular cycloaddition of (Z)-olefins 4a,b (scheme 4) and (E)-olefin 6b (scheme 5)

The (Z)-olefin 4b yields after 40 h refluxing in benzene a single diastereomeric adduct 12b (95 % conversion). Again, an acceleration in rate was observed when the reaction was conducted in water in the presence of β-cyclodextrin[11] : after 12 h at 50°C pure adduct 12b was isolated in 92 % yield. Under the same conditions 4a led to 12a as the sole reaction product in 78 % isolated yield.



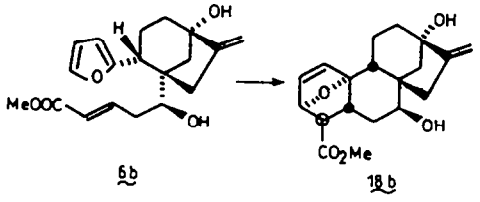
Scheme 4

In view of the reversible nature of the cycloaddition, especially when involving olefin dienophiles[24b], the sole formation of exo-adduct 12 is not surprising. Force field calculations indicate a somewhat flattened chair conformation for the central B-ring (figure 9). The exo-diastereomer 14 and the two endo-adducts 15 and 16 were found to be much higher in energy; in view of the constraints imposed by the bridged systems at C-5,C-10 and at C-8,C-9, a boat-type conformation must be involved for the B-ring of 14 and 16, while 15 was found to be at least 25 kJoule/mol less stable than 12.



12a : β-H at C-4 , α-OH at C-7 245.7
12b : β-H at C-4 , β-OH at C-7 243.6
18b : α-H at C-4 , β-OH at C-7 238.6

Figure 9. Endocyclic torsion angles for the B-ring of the MM2 preferred conformation of adducts 12a, 12b and 18b with corresponding steric energies (kJoul/mol)[a]



Scheme 5

The structural assignment of the observed adduct as 12(a,b) is straightforward. The absence of visible coupling between H-3 and H-4 indicates a relation as in 12 or 14[26]. Distinction between the latter follows from chemical correlation. The conjugate hydride addition (sodium borohydride, MeOH) to adduct 7b yields a mixture of two reduction products (ratio 1:9), which

were shown to be identical with 12b and 18b, respectively, hence proving the α-stereochemistry in the latter. Adduct 18b is the sole reaction product isolated from the intramolecular cycloaddition of (E)-olefin 6b (benzene, 80°C; isolated after 4 days, see kinetics). The geometry of the B-ring in the preferred conformation of 18b as deduced by force field calculations is also shown in figure 9. Again, as in the case of adducts 7-8, a nice correspondance is observed between the calculated and experimental coupling constants related to the (C-6,C-7)-fragment of 12a and 12b (table 2).

Kinetics (table 4)

The Diels-Alder reactions of 2a, 2b, 4a, 4b, 5a, 5b and 6b were conducted in benzene at 80°C. The rates were monitored via HPLC and reflect the disappearance of starting furan. No rate data are available for the cycloaddition of 2a due to the precipitation of the formed adducts in the reaction medium, and for the cycloaddition of 4a, since substantial amounts of lactone 17a were formed after 4 days (19 %). In contrast only trace amounts of the corresponding lactone 17b (< 5 %) were observed during reaction of 4b. In contrast to the cycloaddition of 4b, which yields an equilibrium mixture the reaction of the other olefins run to completion (after 30 h (5a,5b) and 4 days (6b); > 95 %). Within the same epimeric series the (E)-olefin 6b reacts 4 times faster than the (Z)-isomer 4b; the latter is about 7 times more reactive than the acetylene precursor 2b. These results are qualitatively in line with the expectations[27].

Table 4. Observed first-order rate constants and half-live values for the cycloadditions of 2b, 4b, 5a,b and 6b

substrate	$k_{obsd} \cdot 10^5 (s^{-1})^a$	$t_{1/2}$ (hrs)
2b	0.20[b]	92.6
4b	1.4	13.7
5a	3.0	6.4
5b	6.7	2.9
6b	6.5	3.0

[a] based on the disappearance of starting material (see experimental), estimated error of 10 %; [b] sum of rate constants for the formation of 7b and 8b.

The enhanced reactivity of 5b compared to 5a (factor ∿ 2) translates into a small difference (ca 2 kJoule/mol) in transition state energies, that corresponds to the calculated difference in steric energies of 12a and 12b (figure 9). It is interesting to note that derivatizing the hydroxy groups at C-7 and C-13 (cf. 4b → 5b) results in a rate enhancement of 4. This effect, which is not easy to rationalize, may be due to relief of ground state strain in 5b (as compared to 4b) while proceeding to the transition state.

Model for diastereoselectivity

In order to account for the observed diastereoselectivity in the kinetically controlled cycloadditions of 2 and 3, we consider transition states in which the asynchronicity of the Diels-Alder reaction is reflected[28]. In view of the highest coefficient in the LUMO of the dienophile (cf. C-5)[29], these transition states correspond to geometries where the formation of the (C-5,C-10)-bond is more advanced than that of the (C-3,C-4)-bond (figure 10).

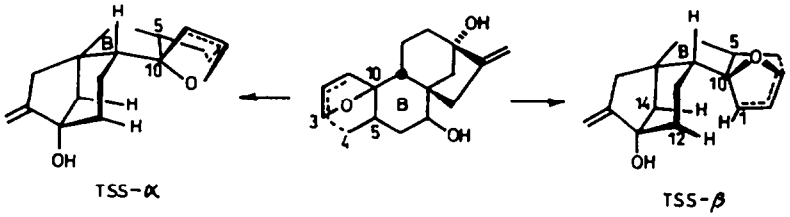


Figure 10. Transition state geometries for α- and β-adduct formation

The eventual stereochemical outcome in favor of adducts with α- or β-oriented oxygen bridge would be essentially determined by two factors : (1) the difference in conformational energy of the B-ring in both transition states; (2) the rate retardment in the formation of β-adduct, as compared with the α-adduct, caused by nonbonded interaction between H-1 and the two α-oriented hydrogens at C-12 and C-14 in TTS-β. In cases where no substantial difference in conformational energy of the B-ring between the α- and β-adduct is expected, the stereochemical outcome would be determined primarily by the above nonbonded interactions[30], and would be in favor of α-adduct formation. This is indeed observed in the five-membered ring case (eq 1, n = 0) and also for the cycloaddition of 3b. In contrast to the olefin case (4-6) where both effects would favor α-adduct formation, in the acetylene 2, the two effects oppose each other, the net result being a 85:15 predominance of β-adduct 8 in refluxing benzene. The presence of the above mentioned nonbonded interactions in 8a is revealed by the X-ray diffraction analysis : the interatomic distances between H-1 and H-12, and H-1 and H-14 are 2.25 Å and 2.43 Å, respectively (sum of effective van der Waals radii : 2.4 Å). The same distances in the calculated preferred conformation of 8a, 8b and 9b equal 2.24 and 2.36 Å, 2.23 and 2.35 Å, and 2.21 and 2.15 Å, respectively.

The synthetic potential of adducts 8b and 12b is currently under investigation.

Acknowledgments. We are indebted to the "Nationaal Fonds voor Wetenschappelijk Onderzoek" and the "Ministerie voor Wetenschapsbeleid" for financial support to the laboratory. J.H. thanks the I.W.O.N.L. for a scholarship.

EXPERIMENTAL[31]

M.ps. are uncorrected. IR spectra were recorded on a Beckman IR-4230 spectrometer (cm^{-1}), mass spectra on a AEI MS-50 spectrometer. The ^1H NMR spectra were recorded at 200 MHz (WP-Brucker) or at 360 MHz (WH-Brucker) with TMS as internal standard in chloroform-d unless otherwise stated. Rf values are quoted for Merck silicagel 60 GF_{254} plates of thickness 0.25 mm. HPLC preparations were performed on Waters M 6000 A (RI) for semi-preparative purposes or on Kontron 420/Sicon Analytic LCD 201 (RI) for analytical purposes.

(5R)-5-[(1S)-2exo-(Furan-2-yl)-5-hydroxy-6-methylene-bicyclo[3.2.1]oct-1-yl]-5-hydroxy-pent-2-ynoic acid methyl ester (2a), (5S)-... (2b), and (4S)-4- (1S)-2exo-Furan-2-yl)-5-hydroxy-6-methylene-bicyclo[3.2.1]oct-1-yl]-4-hydroxy-3-methoxycarbonyl-1,2-butadiene (3a) and (4R)- ... (3b).
Method a (cf. table 1, entry 1). To a cooled solution (-78°C) of 2,2,6,6-tetramethylpiperidine (383 mg, 2.71 mmol) in dry THF (5 mL) were added n-butyllithium (1.57 mL of a 1.64 M solution in hexanes, 2.58 mmol) and HMPA (0.5 mL). After stirring at -78°C for 30 min, the solution was brought to -100°C and treated dropwise with a solution of 2-butynoic acid (108 mg, 1.29 mmol) in HMPA (0.5 mL). After stirring for 1 h at -80°C, a solution of aldehyde 1 (100 mg, 0.431 mmol) in THF (0.6 mL) was added dropwise at -100°C. After stirring for 30 min at -100°C, the reaction mixture was brought to -60°C and quenched by the addition of wet ether (6 mL). After extraction (3 x) with saturated sodium bicarbonate (5 mL), the combined extracts were acidified with 10 % HCl, and the aqueous phase further extracted with ether, washed with brine and dried (magnesium sulfate). After treatment of this solution with diazomethane at 0°C, the solution was concentrated in vacuo, the residue dissolved in dichloromethane and filtered through a short silica gel (3 g) column. After concentration in vacuo, the residual oil (67 % yield) was found by NMR to consist of a mixture of 2a, 2b, 3a and 3b, in the proportion of 8:61:7:25, respectively, as determined by HPLC (eluent : ethyl acetate-isooctane, 1:1).
Method b (cf. table 1, entry 3). To a solution of n-butyllithium (2.26 mL of a 1.64 M solution in hexanes, 3.70 mmol) in pentane was added tetramethylethylenediamine (0.14 mL, 0.924 mmol) at 0°C. After stirring for 1 h at 0°C, a solution of 2-butynoic acid (156 mg, 1.85 mmol) in THF (1 mL) and pentane (1.63 mL) was added dropwise at -60°C. After stirring for 2 h at -60°C, a solution of the aldehyde 1 (100 mg, 0.431 mmol) in THF (0.2 mL) was added dropwise. After stirring for 2 h at -60°C, the reaction mixture is worked up as described above. The residual oil (40 %) was found to consist of the same mixture as above, in the proportion of 26:57:5:12. The same procedure carried out on aldehyde 1 (1 g, 4.3 mmol) gave, after HPLC purification 85 mg of 2a (6 % yield), 256 mg of 2b (18 %) and 57 mg of 3b (4 %). From the neutral phase of the reaction there was obtained, after purification on silica gel, 380 mg of unreacted aldehyde 1 (38 %).
For 2a : m.p. 115-116°C (ether). Rf 0.17 (toluene-ether, 3:2). IR (KBr) : 3400, 2235, 1710, 1680, 1630, 1610. NMR (200 MHz) : 7.35 (1H, dd : 1.9, 0.8 Hz), 6.34 (1H, dd + LR : 3.2, 1.9 Hz), 6.17 (1H, dd : 3.2, 0.8 Hz), 5.10 (1H, br t : 2.5 Hz), 4.95 (1H, br t : 2.0 Hz), 3.75 (3H, s), 3.68 (1H, dd : 9.3, 3.4 Hz), 3.21 (1H, br d : 6.3 Hz) ppm. MS : m/z 330 (M+., 10), 312 (5), 304 (8), 298 (8), 215 (14), 193 (17), 181 (30), 165 (23), 124 (100), 91 (68), 77 (59), 55 (44), 41 (62).
For 2b : m.p. 49-51°C (ether-hexane). Rf 0.11 (toluene-ether, 3:2). IR (KBr) : 3400, 2230, 1705, 1630 (br). NMR (200 MHz) : 7.32 (1H, dd : 1.9, 0.8 Hz), 6.32 (1H, dd : 3.2, 1.9 Hz), 6.13 (1H, dd : 3.2, 0.8 Hz), 5.08 (1H, br t : 2.5 Hz), 4.92 (1H, br t : 2.0 Hz), 3.75 (3H, s), 3.61 (1H, dd : 9.5, 2.7 Hz), 2.85 (1H, br d : 6.5 Hz) ppm. MS : m/z 330 (5), 312 (3), 298 (7), 286 (7), 268 (12), 253 (12), 240 (44), 202 (29), 168 (27), 165 (31), 115 (50), 91 (94), 77 (83), 44 (85), 41 (100).

For 3a (from combined HPLC analyses) : NMR (360 MHz) : 7.37 (1H, dd : 1.75, 0.5 Hz), 6.35 (1H, dd : 3.25, 1.75 Hz), 6.23 (1H, br d : 3.0 Hz), 5.36 (1H, ABd : 14.0, 2.0 Hz), 5.30 (1H, ABd : 14.0, 1.75 Hz), 5.07 (1H, t : 2.25 Hz), 4.93 (1H, br t : 2.0 Hz), 4.53 (1H, br t : 1.5 Hz), 3.69 (3H, s), 3.35 (1H, br d : 6.5 Hz) ppm.
For 3b (contaminated with 9b, see text) NMR (300 MHz) : 7.27 (1H, m), 6.27 (1H, dd : 3.0, 1.75 Hz), 6.06 (1H, br d : 3.25 Hz), 5.27 (2H), 5.06 (1H), 4.89 (1H), 4.33 (1H), 3.76 (3H, s), 3.05 (1H) ppm.

(5R)-5-[(1S)-2exo-(Furan-2-yl)-5-hydroxy-6-methylene-bicyclo[3.2.1]oct-1-yl]-5-hydroxy-(Z)-pent-2-enoic acid methyl ester (4a) and (5S)-... (4b).
After saturation of a suspension of palladium on barium sulfate (5 %, 2.2 g) in dry ethyl acetate (200 mL) and quinoline (8.8 mL) with hydrogen (10 mL), a solution of acetylene 2b (5.0 g) in ethyl acetate (100 mL) was added. The reaction mixture was hydrogenated at rt under normal pressure until hydrogen uptake ceased (1 equiv). After filtration, the filtrate was washed (3 x) with 2 N HCl, brine, and concentrated in vacuo, yielding the Z-olefin 4b (4.9 g, 96 % yield) as an amorphous solid. Under identical conditions, the reduction of acetylene 2a (1.23 g) gave 1.126 g of Z-olefin 4a (91 %) as an amorphous solid.
For 4a : Rf 0.40 (ether). IR (film) : 3400, 1705 (br), 1630. NMR (200 MHz) : 7.27 (1H, dd : 1.9, 0.8 Hz), 6.35 (1H, dt : 11.5, 7.0 Hz), 6.33 (1H, dd : 3.2, 1.9 Hz), 6.19 (1H, dd : 3.2, 0.8 Hz), 5.89 (1H, dt : 11.5, 2.7 Hz), 5.06 (1H, t : 2.5 Hz), 4.51 (1H, t : 2.0 Hz), 3.71 (3H, s), 3.43 (1H, dd : 10.5, 2.7 Hz), 3.22 (1H, br d : 7 Hz), 2.91 (1H, dddd : 15.0, 10.5, 8.0, 1.5 Hz), 2.69 (1H, dddd : 15.0, 7.5, 2.7, 1.5 Hz), 2.57 (1H, dt : 17.0, 2.5 Hz) ppm.
For 4b : Rf 0.33 (ether). IR (film) : 3400, 1705 (br), 1640. NMR (200 MHz) : 7.29 (1H, dd : 1.9, 0.8 Hz), 6.35 (1H, ddd : 11.5, 9.0, 7.0 Hz), 6.30 (1H, dd : 3.2, 1.9 Hz), 6.12 (1H, dd : 3.2, 0.8 Hz), 5.93 (1H, dt : 11.5, 1.3 Hz), 5.08 (1H, br t : 2.5 Hz), 4.93 (1H, br t : 2.0 Hz), 3.73 (3H, s), 3.42 (1H, dd : 9.7, 3.0 Hz), 2.96 (1H, br d : 6 Hz) ppm.

The bis-trimethylsilylated derivatives of 4a and 4b.
To a solution of Z-olefin 4b (0.32 g, 0.96 mmol) in DMF (7 mL) were added at 0°C triethylamine (1.34 mL, 9.6 mmol) and trimethylsilylchloride (0.575 g, 5.33 mmol). After stirring for 10 min at 0°C and 1 h at rt, the reaction mixture was quenched by the addition of wet ether. The organic phase was washed with brine, dried (potassium carbonate), and concentrated in vacuo (DMF traces) to yield 0.466 g of 5b (97 % yield) as an oil. In an identical way 4a was converted to the silyl derivative 5a (95 %).
For 5a : Rf 0.52 (hexane-ethyl acetate, 9:1). NMR (200 MHz, $CDCl_3$) : 7.33 (1H), 6.32 (1H), 6.30 (1H), 6.07 (1H), 5.85 (1H), 5.07 (1H), 4.90 (1H), 3.74 (3H), 3.67 (1H, dd : 7.5, 4.5 Hz), 3.08 (1H) ppm.
For 5b : Rf 0.49 (hexane-ethyl acetate, 9:1). NMR (200 MHz) : 7.34 (1H), 6.38 (1H), 6.32 (1H), 6.13 (1H), 5.84 (1H), 5.04 (1H), 4.87 (1H), 3.72 (3H), 3.55 (1H, dd : 6.5, 4.0 Hz) ppm.

(5S)-5-[(1S)-2exo-(Furan-2-yl)-5-hydroxy-6-methylene-bicyclo[3.2.1]oct-1-yl]-5-hydroxy-(E)-pent-2-enoic acid methyl ester (6b).
To a solution of the silyl derivative 5b (0.396 g, 0.83 mmol) in THF (6 mL) was added lithium ethyl thiolate (52 mg, 0.83 mmol). After stirring for 150 min at rt, ether (20 mL) was added, the organic phase washed with brine and concentrated in vacuo to yield 353 mg of bis-trimethylsilylated 6b (89 % yield) as an oil. ^1H NMR analysis showed the absence of starting Z-olefin 5b. To a solution of the above derivative (353 mg) in THF (10 mL) were added 2 N HCl (4 mL). After 5 min saturated sodium bicarbonate solution (6 mL) was added, and the organic phase washed with brine, dried and concentrated in vacuo. After purification on silica gel (eluent : ether-hexane, 4:1) 220 mg of 6b were obtained as a gum (79 % yield). In contrast to Z-olefins 4a and 4b, the E-olefin 6b slowly cycloadds on storage at low temperature.
For 6b : Rf 0.07 (toluene-ether, 3:2). IR (film) : 3400, 1710, 1650. NMR (200 MHz) : 7.31 (1H, dd : 1.9, 0.8 Hz), 7.12 (1H, ddd : 15.5, 8.1, 6.3 Hz), 6.30 (1H, dd : 3.2, 1.9 Hz), 6.10 (1H, dd : 3.2, 0.8 Hz), 5.90 (1H, dt : 15.5, 1.1 Hz), 5.08 (1H, t : 2.5 Hz), 4.92 (1H, t : 2.0 Hz), 3.48 (1H, dd : 9.5, 2.5 Hz), 3.74 (3H, s), 2.95 (1H, br d : 5.5 Hz), 2.76 (1H, dt : 17.0, 2.5 Hz) ppm. MS : m/z 332 (1), 300 (11), 282 (6), 215 (11), 193 (11), 191 (16), 188 (14), 175 (15), 147 (20), 129 (21), 117 (24), 108 (72), 95 (82), 94 (80), 91 (55), 41 (100).
For bis-trimethylsilylated 6b : Rf 0.50 (hexane-ethyl acetate, 9:1). NMR (200 MHz) : 7.35 (1H), 6.96 (1H), 6.35 (1H), 6.10 (1H), 5.87 (1H), 5.05 (1H), 4.85 (1H), 3.74 (3H), 3.52 (1H, dd : 9.5, 2.5 Hz), 2.93 (1H), 2.75 (1H) ppm.

(6R)-6-[(1S)-2exo-(Furan-2-yl)-5-hydroxy-6-methylene-bicyclo[3.2.1]oct-1-yl]-5,6-hydro-pyran-2-one (17b).
When the above procedure for the preparation of 6b is applied to the unprotected olefin 4b, lactone 17b is obtained in 58 % yield. Thus, to a solution of lithium ethyl thiolate (2.5 mg, 0.036 mmol) in dry THF (2 mL), was added 4b (40 mg, 0.12 mmol), and the solution stirred for 1 h under nitrogen - the reaction was worked up by the addition of a few drops of 0.1 N HCl at 0°C and extracted with ether. After washing with saturated sodium bicarbonate and brine, concentration of the organic phase in vacuo gave 21 mg of lactone 17b.
For 17b : m.p. 78-79°C (ether). Rf 0.18 (toluene-ether, 3:2). IR (KBr) : 3400, 1700, 1650. NMR (200 MHz) : 7.25 (1H, dd : 1.9, 0.8 Hz), 6.83 (1H, dd : 9.5, 6.5, 2.0 Hz), 6.26 (1H, dd : 3.9, 1.9 Hz), 6.11 (1H, d : 3.5 Hz), 5.92 (1H, ddd : 9.5, 3.0, 1.0 Hz), 5.07 (1H, t : 2.5 Hz), 4.88 (1H, t : 2.0 Hz), 4.16 (1H, dd : 12.6, 3.5 Hz), 2.90 (1H, br d : 6.0 Hz), 2.82 (1H, dt : 16.5, 2.5 Hz), 2.56 (1H, dddd : 18.0, 6.5, 3.5, 1.0 Hz) ppm.

(3R)-6t,9-Dihydroxy-8-methylene-(11at)-5,6,7,8,9,10,11,11a-octahydro-3r,11bc-epoxido-6ac,9c-methano-cyclohepta [a]naphtalene-4-carboxylic acid methyl ester (7a) and (3S)-6c,9-Dihydroxy-8-methylene-(11ac)-5,6,7,8,9,10,11,11a-octahydro-3r,11bc-epoxido-6at,9t-methano-cyclohepta [a]naphtalene-4-carboxylic acid methyl ester (8a).

A solution of acetylene 2a (330 mg) in dry benzene (10 mL) was refluxed under nitrogen for 7 days, during which time adducts 7a and 8a partly precipitated. After 90 h the collected precipitate was washed with ether, yielding 113 mg of pure 8a. After a further 77 h, the new precipitate (110 mg) was shown by NMR to consist of a 8:1 mixture of 8a and 7a, respectively. After concentration of the filtrate in vacuo, the residue was purified by column chromatography on silica gel (eluent : hexane-ethyl acetate, 7:3) to give a further 20 mg of 8a and 28 mg of 7a. Combined yield of adducts 7a and 8a : 82 %, ratio 1:5.8, respectively. Both pure adducts are quasi insoluble in regular organic solvents at rt, except DMSO and pyridine. Suitable crystals for the X-ray diffraction analysis of 8a were obtained from the slow evaporation of a saturated solution in hot methanol.

For 7a : m.p. 120-122°C (acetone). Rf 0.21 (ethyl acetate-hexane, 2:3). IR (KBr) : 3370, 1740, 1695 (s), 1650, 1633, 1625. NMR (360 MHz, pyridine-d_5) : 7.26 (1H, dd : 5.2, 2.0 Hz), 6.89 (1H, d : 5.2 Hz), 5.76 (1H, d : 2.0 Hz), 5.54 (1H, q : 2.3 Hz), 4.14 (1H, t : 8.6 Hz), 3.63 (3H, s), 3.55 (1H, dt : 16.9, 2.8 Hz), 3.42 (1H, ABd : 21, 8.6 Hz), 3.27 (1H, ABd : 21, 8.6 Hz) ppm. MS : m/z 330 (1), 312 (17), 298 (15), 280 (17), 183 (8), 181 (10), 175 (13), 165 (17), 151 (18), 136 (28), 124 (30), 115 (24), 103 (32), 91 (42), 77 (40), 55 (45), 44 (100), 41 (76).

For 8a : no m.p. below 250°C (MeOH). Rf 0.21 (hexane-ethyl acetate, 2:3). IR (KBr) : 3380, 1700 (s), 1670, 1650. NMR (360 MHz, DMSO-d_6) : 7.30 (1H, br d : 5.3 Hz), 7.20 (1H, d : 5.3 Hz), 5.41 (1H, d : 1.8 Hz), 5.12 (1H, d : 5.1 Hz), 4.97 (1H, br s), 4.77 (1H, br s), 3.67 (3H, s), 3.57 (1H, dt : 17.1, 2.6 Hz), 3.49 (1H, dt : 10.5 Hz), 3.38 (1H, dd : 16.7, 4.9 Hz), 2.21 (1H, dq : 17.1, 2.2 Hz) ppm. MS : m/z 330 (1), 312 (5), 298 (6), 280 (9), 207 (11), 181 (22), 165 (21), 136 (25), 124 (47), 115 (29), 91 (36), 77 (38), 44 (100).

(3R)-6c,9-Dihydroxy-8-methylene-(11at)-5,6,7,8,9,10,11,11a-octahydro-3r,11bc-epoxido-6ac,9c-methano-cyclohepta [a]naphtalene-4-carboxylic acid methyl ester (7b) and (3S)-6t,9-Dihydroxy-8-methylene-(11ac)-5,6,7,8,9,10,11,11a-octahydro-3r, 11bc-epoxido-6at,9t-methano-cyclohepta [a]naphtalene-4-carboxylic acid methyl ester (8b).

A suspension of 2b (1.10 g, 3.33 mmol) in water (37.8 mL) was sonicated for 10 min until a milky emulsion resulted. After addition of β-cyclodextrin hydrate (3.78 g, 3.33 mmol), the mixture was stirred at 45°C for 9 days (complete by TLC). The reaction was worked up by the addition of ethyl acetate (100 mL) and water (20 mL). The aqueous phase was extracted thoroughly with ethyl acetate (5 x 60 mL). The organic extracts were washed with brine, dried and concentrated in vacuo. The solid residue was washed with ether (3 x), leaving 730 mg of pure 8b as a white powder. After concentration of the ether phase, the residue was purified by chromatography on silica gel yielding a further 90 mg of 8b and 66 mg (6 % yield) of 7b. The combined yield of 8b is 75 %. Pure 7b and 8b are scarcely soluble in organic solvents, except DMSO and pyridine. Suitable crystals of 8b for X-ray diffraction analysis were obtained from the slow evaporation of a saturated hot acetone solution.

For 7b : m.p. 165-167°C (acetone). Rf 0.38 (ethyl acetate-hexane, 5:1). IR (KBr) : 3450, 1680, 1635. NMR (360 MHz, DMSO-d_6) : 7.19 (1H, dd : 5.1, 2.0 Hz), 6.82 (1H, d : 5.1 Hz), 5.49 (1H, d : 2.0 Hz), 4.91 (1H, br q : 1.8 Hz), 4.76 (1H, br q : 1.8 Hz), 4.92 (1H, d : 3.4 Hz), 4.73 (1H, s), 3.67 (3H, s), 3.66 (1H, br d : 5.5, 1 Hz), 3.17 (1H, dd : 21.3, 5.4 Hz), 2.76 (1H, br d : 7.2 Hz) ppm. MS : m/z 330 (3), 312 (2), 298 (12), 286 (3), 240 (46), 202 (36), 181 (34), 165 (48), 124 (55), 121 (57), 115 (71), 105 (87), 95 (67), 91 (95), 77 (100).

For 8b : m.p. 219-221°C (acetone). Rf 0.29 (ethyl acetate-hexane, 5:1). IR (KBr) : 3330, 1705, 1655 cm^{-1}. NMR (360 MHz, DMSO-d_6) : 7.29 (1H, ddd : 5.4, 1.9, 1.1 Hz), 7.19 (1H, d : 5.4 Hz), 5.40 (1H, d : 1.9 Hz), 4.96 (1H, br q : 2.5 Hz), 4.79 (1H, br q : 1.9 Hz), 4.92 (1H, s), 4.91 (1H, d : 3.6 Hz), 3.65 (3H, s), 3.58 (1H, q : 3.0 Hz), 3.31 (1H, dd : 17.5, 2.6 Hz), 2.22 (1H, dd : 17.5, 3.2 Hz) ppm. MS : m/z 330 (1), 312 (13), 280 (32), 262 (18), 253 (13), 240 (23), 221 (18), 212 (26), 196 (52), 181 (42), 165 (50), 128 (44), 115 (66), 91 (60), 77 (76), 44 (100).

(3S)-6t,9-Dihydroxy-8-methylene-(11at)-4,6,7,8,9,10,11,11a-octahydro-3r,11bc-epoxido-6ac,9c-methano-cyclohepta [a]naphtalene-5-carboxylic acid methyl ester (9b).

During the isolation of allene 3b, spontaneous cycloaddition to 9b was observed upon concentration of a pure HPLC fraction (vide supra). Reaction was complete at rt in the solid state fater 4 days. Suitable crystals for X-ray diffraction analysis were obtained by slow crystallziation from a hot MeOH solution.

For 9b : m.p. : 216°C. IR (KBr) : 3400 (br), 1680, 1630, 1610 cm^{-1}. NMR (360 MHz, DMSO-d_6) : 6.70 (1H, dd : 5.5, 1.8 Hz), 5.99 (1H, d : 5.5 Hz), 5.10 (1H, dd : 4.0, 1.8 Hz), 4.92 (1H, br s), 4.79 (1H, br s), 4.11 (1H, s), 3.66 (3H, s), 2.38 and 2.27 (1H, AB : 16 Hz) ppm.

(3R)-6c,9-Dihydroxy-8-methylene-(4at,11at)-4,4a,5,6,7,8,9,10,11,11a-decahydro-3r,11bc-epoxido-6ac,9c-methano-cyclohepta [a]naphtalene-4c-carboxylic acid methyl ester (12a) and (3R)-6t,... (12b).

A suspension of Z-olefin 4b (840 mg, 2.53 mmol) and β-cyclodextrin hydrate (2.872 g, 2.53 mmol) in water (30 mL) was stirred at 50°C for 12 h. The residue, obtained after work-up (cf. 7b, 8b), was purified by column chromatography on silica gel (eluent : methylene chloride-ethyl acetate, 4:1) to yield 770 mg (92 %) of 12b as a powder. In the same way, there was obtained from 4a (36 mg, 0.11 mmol) 28 mg of the adduct 12a (78 % yield).

For 12a : m.p. 173-174°C (ether). Rf 0.09 (hexane-ethyl acetate, 2:3). IR (KBr) : 3400, 1730, 1660, 1630, 1615. NMR (200 MHz) : 6.37 (1H, dd : 5.7, 1.9 Hz), 6.02 (1H, d : 5.7 Hz), 5.13 (1H, d : 1.9 Hz), 5.06 (1H, br t : 2.5 Hz), 4.91 (1H, br t : 1.8 Hz), 3.71 (3H, s), 3.57 (1H, dd : 11.5, 3.6 Hz), 2.62 (1H, d : 8.2 Hz) ppm. MS : m/z332 (16), 314 (2), 300 (3), 282 (3), 255 (2), 215 (16), 145 (19), 129 (24), 121 (35), 117 (24), 115 (25), 108 (36), 107 (38), 97 (39), 95 (53), 94 (100), 91 (52), 81 (45), 79 (42), 77 (44), 69 (37), 55 (35), 41 (64).

For 12b : m.p. 83-84°C (ether). Rf 0.11 (ethyl acetate-isooctane, 3:2). IR (KBr) : 3400, 1725, 1660. NMR (200 MHz) : 6.36 (1H, dd : 5.6, 1.7 Hz), 6.08 (1H, d : 5.6 Hz), 5.12 (1H, d : 1.7 Hz), 5.05 (1H, td : 2.5, 0.5 Hz), 4.91 (1H, br t : 2 Hz), 3.70 (3H, s), 3.64 (1H, dd : 3.7, 2.0 Hz), 2.61 (1H, d : 8.5 Hz), 2.22 (1H, dd : 10, 1.5 Hz) ppm. MS : m/z 332 (4), 232 (3), 215 (5), 165 (14), 129 (26), 128 (24), 115 (38), 95 (51), 94 (59), 91 (65), 77 (61), 55 (58), 43 (62), 41 (100).

The sodium borohydride reduction of adduct 7b.
A solution of adduct 7b (36 mg, 0.11 mmol) in dry MeOH (1 mL) was treated with an excess sodium borohydride (65 mg). After stirring for 4 h at rt, the reaction was worked up by the addition of saturated ammonium chloride. After extraction with ethyl acetate, the organic phase was dried and concentrated in vacuo, yielding 26 mg (78 %) of a 9:1 mixture of 18b and 12b, respectively (^{1}H NMR). Pure 18b was further obtained by HPLC purification (eluent : hexane-ethyl acetate, 1:1).
For 18b : m.p. 180-181°C (ether). Rf 0.23 (ether). IR (KBr) : 3465, 3390, 1710. NMR (200 MHz) : 6.28 (1H, dd : 5.7, 1.5 Hz), 6.17 (1H, d : 5.7 Hz), 5.11 (1H, dd : 4.7, 1.5 Hz), 5.04 (1H, t : 2.5 Hz), 4.92 (1H, br t : 2 Hz), 3.64 (4H, m), 2.73 (1H, dd : 4.7, 3.0 Hz) ppm. MS : m/z 332 ($M^{+\cdot}$, 7), 314 (1), 296 (1), 214 (12), 120 (42), 106 (45), 93 (62), 92 (100), 90 (62), 80 (67), 78 (67), 76 (75).

The mono-acetylation of adducts 7a, 8a, 7b, 8b.
A solution of the diol (50-100 mg, 0.15-0.30 mmol) in dry methylene chloride (ca 10 mL/mmol) containing pyridine (50 equiv) and acetic anhydride (25 equiv) was stirred at rt for 12 h. The reaction was quenched by the addition of ice and MeOH. After stirring for a further 20 min, methylene chloride (15 mL/mmol) was added and the organic phase washed with sodium bicarbonate, dilute HCl and brine. After drying, the residue, obtained upon concentration in vacuo, was purified by column chromatography on silica gel (hexane-ethyl acetate, 1:1) to give the 7-acetoxy derivatives of 7a, 8a and 7b in nearly quantitative yield (94-97 %). In the case of 8b there was obtained a 1:3 mixture of monoacetate and starting diol 8b.
For 7-acetoxy-7a : oil. Rf 0.25 (hexane-ethyl acetate, 1:1). NMR (200 MHz) : 7.19 (1H, dd+LR : 5.2, 2.0 Hz), 6.70 (1H, d : 5.2 Hz), 5.57 (1H, d : 2.0 Hz), 5.08 (1H, t : 2.5 Hz), 5.00 (1H, t : 8.5 Hz), 4.92 (1H, t : 2.0 Hz), 3.15 (1H, dd : 20.8, 8.5 Hz), 3.74 (3H, s), 2.90 (1H, dd : 20.8, 8.5 Hz), 2.65 (1H, dt: 17.0, 2.5 Hz), 2.26 (1H, br d : 6.5 Hz), 2.11 (3H, s) ppm.
For 7-acetoxy-7b : oil. Rf 0.65 (hexane-ethyl acetate, 1:5). NMR (200 MHz) : 7.18 (1H, ddd : 5.1, 1.8, 0.4 Hz), 6.76 (1H, d : 5.1 Hz), 5.60 (1H, d : 1.8 Hz), 5.05 (1H, t : 2.5 Hz), 4.99 (1H, dd : 6.4, 1.1 Hz), 4.90 (1H, t : 2.0 Hz), 3.74 (3H, s), 3.46 (1H, dd : 21.1, 6.4 Hz), 2.73 (1H, br d : 7.0 Hz), 2.61 (1H, br d : 21.1, 1.1 Hz) ppm.
For 7-acetoxy-8a : m.p. 162-163°C (ether). Rf 0.19 (hexane-ethyl acetate, 1:1). IR (KBr) : 3300, 1740, 1720, 1700, 1670. NMR (200 MHz) : 7.27 (1H, ddd : 5.4, 1.9, 1.0 Hz), 7.17 (1H, d : 5.4 Hz), 5.55 (1H, d : 1.9 Hz), 5.11 (1H, t : 2.5 Hz), 4.98 (1H, dd : 11.0, 4.9 Hz), 4.95 (1H, t : 2.0 Hz), 3.74 (3H, s), 3.65 (1H, dd : 16.5, 5.0 Hz), 2.62 (1H, dt : 17.0, 2.5 Hz), 2.09 (3H, s) ppm.
For 7-acetoxy-7b : m.p. 190-191°C (ether). Rf 0.49 (ethyl acetate-hexane, 5:1). NMR (200 MHz) : 7.28 (1H, ddd : 5.5, 1.9, 0.9 Hz), 7.16 (1H, d : 5.5 Hz), 5.56 (1H, d : 2.0 Hz), 5.09 (1H, t : 2.5 Hz) 4.94 (1H, t : 2.0 Hz), 4.99 (1H, dd : 3.2, 2.5 Hz), 3.73 (3H, s), 3.59 (1H, dd : 18.2, 2.5 Hz), 2.31 (1H, dd : 18.2, 3.2 Hz), 2.05 (3H, s) ppm.

Kinetic measurements
The cycloaddition reaction of 2a, 2b, 4a, 4b, 5a, 5b and 6b was performed with 100 mg samples in dilute benzene solution (1.5 % for the olefins 4-6; 0.8 % for acetylene 2b) at the reflux temperature of benzene (80°C). The reaction was followed over 2-3 half-lives, except in the case of 2b (0.6 half-life) by injecting 60 µl aliquots at regular time intervals (6-7 times); in the diol cases (2b, 4a, 4b, 6b) direct injection from benzene solution, for the silylated derivatives (5a,5b), the samples were first freed from benzene and injected in the eluent of the analysis (hexane-ethyl acetate, 20:1). The concentration of starting material was determined by measuring the peak heights (HPLC; eluent : hexane-ethyl acetate, 2:3) in the linear region of the calibration curve. All reactions showed good first-order kinetic behavior. The $t_{1/2}$ and first-order rate constants were obtained from the raw data after least-squares treatment.
- The cycloaddition of acetylenes 2a and 2b was interrupted after 7 days. No reproducible results were obtained in the case of 2a due to the precipitation of the formed adducts during the reaction.
- The cycloaddition of olefins 4a (and 4b) was interrupted after 4 days. Purification of the residue on silica gel (eluent : hexane-ethyl acetate, 1:1) gave, next to starting material and adduct 12a (and 12b), also pure lactone 17a (and traces of 17b).
For 17a : oil. Rf 0.19 (hexane-ethyl acetate, 2:3). IR (film) : 3400, 1705. NMR (200 MHz) : 7.33 (1H, dd : 1.9, 0.8 Hz), 6.84 (1H, ddd : 9.5, 6.3, 2.0 Hz), 6.30 (1H, dd : 3.2, 1.9 Hz), 6.15 (1H, dd : 3.2, 0.8 Hz), 5.99 (1H, ddd : 9.5, 2.7, 0.9 Hz), 5.11 (1H, t : 2.5 Hz), 4.98 (1H, t : 2.1 Hz), 4.38 (1H, dd : 12.8, 3.9 Hz), 3.41 (1H, br d), 2.63 (1H, dt : 17.8, 2.5 Hz) ppm.
- The cycloaddition of bis-trimethylsilylated derivatives 5a and 5b was interrupted after 29 hrs, yielding only adducts 13a and 13b, respectively (^{1}H NMR).
For 13a : NMR (200 MHz) : 6.39 (1H, dd : 5.5, 1.5 Hz), 6.05 (1H, d : 5.5 Hz), 5.17 (1H, d : 1.5 Hz), 5.05 (1H, m), 4.88 (1H, m), 3.75 (3H, s), 3.55 (1H, dd : 11.0, 3.5 Hz), 2.81 (1H, dt : 16.5, 3.0 Hz), 2.63 (1H, d : 8.5 Hz) ppm.
For 13b : NMR (200 MHz) : 6.33 (1H, dd : 5.5, 1.6 Hz), 6.18 (1H, d : 5.5 Hz), 5.10 (1H, d : 1.6 Hz), 5.10 (1H, m), 4.84 (1H, br m), 3.70 (3H, s), 3.53 (1H, dd : 3.8, 1.8 Hz), 2.58 (1H, d: 8.5 Hz) ppm.

Molecular Modelling

Calculations of optimized geometries and steric energies were performed using a combination of the SCA program (enhanced graphics version)[14] and MacroModel[15]. The present version of SCA runs on IBM compatible PC's and generates, starting from a graphically entered 2D-structural diagram of a polycyclic molecule (5-, 6-, and 7-membered composite rings), all reasonable conformations including approximate conformational energies. For each conformation, the corresponding cartesian coordinates of all entered atoms are deduced, which can be used, either for the graphic display of the various forms, or for entering direct input files for Allinger's MMP2 program or for further manipulation by MacroModel. The latter programs run on a Microvax-II configuration, with Tektronix 4207 graphics terminal and Tektronix 4957 data tablet.The following features of MacroModel have been used : (1) calculation of steric energies using Allinger's MM2 force field and block diagonal Newton Raphson minimization until RMS 0.1 or better was reached; (2) a further torsional search around the appendages (i.e., noncyclic bonds), in particular the hydroxyl groups at C-13 and at C-7, and the methoxycarbonyl group at C-4 (or C-6 in the case of 9b and 10b); (3) the calculation of vicinal coupling constants (H NMR), according to ref. 16.

X-ray analyses of 7b, 8a, and 9b.

The intensities of the measured reflections (table 5) were collected on a Nicolet R3 4 circles diffractometer using MoKα graphite monochromatized radiation. The structure was solved by direct methods and refined by the program SHELXTL with anisotropic thermal parameters for the non-hydrogen atoms and constrained distances for hydrogen atoms.[32] Relevant crystal data are included in Table 5, atomic coordinates in Table 6.

Table 5. Crystal data of 7b, 8a, and 9b

	7b	8a	9b
space group	monoclinic, $P_c 2_1/c$	orthorhombic $P_c b2_1a$	triclinic $P\bar{1}$
a =	10.536(2)Å	7.735(5)Å	8.472(3)Å
b =	12.737(2)	13.366(7)	9.806(4)
c =	12.887(2)	16.036(8)	10.546(3)
α =	90°	90°	79.92(3)°
β =	108.39(1)	90	71.05(2)
γ =	90	90	71.59(3)
V =	1641.0(5)Å^3	1660.7(9)Å^3	783.7(5)Å^3
D_x =	1.34 g cm^{-3}	1.28 g cm^{-3}	1.40 g cm^{-3}
Reflections measured	1816	1520 (2 octants)	2458
Reflections observed $I \geq 3\sigma$ (I)	1701	764	2353
$2\Theta_{max}$	45°	40°	50°
R value	0.040	0.027	0.056

Table 6. Atomic coordinates (x 10^4) for non-hydrogen atoms

	7b			8a			9b		
	x	y	z	x	y	z	x	y	z
O(1)	13293(2)	4447(1)	7905(1)	3936(3)	710(2)	5956(1)	-159(2)	1614(1)	841(1)
O(2)	12370(2)	7915(1)	6584(2)	6236(3)	353(2)	9139(1)	840(1)	2996(1)	4605(1)
O(3)	8620(2)	4723(1)	7638(1)	-287(3)	62(2)	9304(1)	-5890(2)	3630(1)	3455(1)
O(4)	13295(2)	4670(2)	4353(1)	8049(3)	2942(2)	6825(2)	745(2)	6261(1)	2739(1)
O(5)	14222(2)	3255(1)	5329(1)	6559(3)	3401(2)	5702(1)	2528(1)	5285(1)	858(1)
C(1)	14845(2)	5762(2)	8178(2)	2082(4)	1627(3)	6741(2)	2235(2)	356(2)	1529(2)
C(2)	15433(2)	4901(2)	8011(2)	2459(5)	2164(3)	6087(2)	2715(3)	386(2)	220(2)
C(3)	14302(3)	4168(2)	7401(2)	4172(5)	1754(3)	5772(2)	1405(2)	1635(2)	-239(2)
C(4)	13661(2)	4635(2)	6259(2)	5574(4)	2016(3)	6415(2)	1785(2)	3015(2)	-8(2)
C(5)	13042(2)	5511(2)	6426(2)	5174(4)	1472(2)	7075(2)	1116(2)	2957(2)	1509(1)
C(6)	12165(2)	6285(2)	5662(2)	5884(4)	1402(3)	7935(2)	764(2)	3927(2)	2388(1)
C(7)	11482(2)	7054(2)	6222(2)	5718(4)	345(3)	8289(2)	-317(2)	3724(2)	3805(1)
C(8)	11113(2)	6549(2)	7170(2)	3899(4)	-61(2)	8213(2)	-1612(2)	2887(1)	3913(1)
C(9)	12397(2)	6241(2)	8099(2)	3320(4)	-121(3)	7288(2)	-633(2)	1409(2)	3338(2)
C(10)	13324(2)	5568(2)	7683(2)	3562(4)	862(2)	6836(2)	553(2)	1569(2)	1932(2)
C(11)	12069(2)	5755(2)	9077(2)	1519(4)	-595(3)	7205(2)	-1876(2)	502(2)	3456(2)
C(12)	10890(2)	4990(2)	8749(2)	222(4)	-269(3)	7871(2)	-3560(2)	1380(2)	3128(2)
C(13)	9724(2)	5432(2)	7821(2)	1042(4)	-218(3)	8733(2)	-4334(2)	2838(2)	3756(2)
C(14)	10198(2)	5585(2)	6825(2)	2544(4)	521(3)	8704(2)	-2995(2)	3700(2)	3193(2)
C(15)	10238(2)	7275(2)	7623(2)	3758(4)	-1119(3)	8607(2)	-2748(2)	2700(2)	5363(2)
C(16)	9400(2)	6548(2)	8073(2)	1951(4)	-1182(3)	8954(2)	-4418(2)	2576(2)	5232(2)
C(17)	8524(3)	6823(2)	8559(3)	1288(6)	-1894(3)	9417(2)	-5752(2)	2320(2)	6224(2)
C(18)	13690(2)	4217(2)	5220(2)	6871(4)	2807(3)	6352(2)	1321(2)	5270(2)	2032(1)
C(19)	14267(4)	2748(3)	4332(3)	7733(6)	4243(3)	5608(2)	3234(2)	6513(2)	546(2)

REFERENCES AND NOTES

1. Present address : Dipartimento di Scienza e Tecnologia del Farmaco, Torino (Italy).
2. Senior Research Associate of the National Fund for Scientific Research (Belgium).
3. For recent reviews on the IMDA reaction, see : A.G. Fallis, Can. J. Chem., 62, 183 (1984); E. Ciganek, Organic Reactions, 32, 1 (1984). For a recent review on the use of furan as intermediate in organic synthesis including IMDA, see : B.H. Lipshutz, Chem. Rev., 86, 795 (1986).
4. W.M. Grootaert and P.J. De Clercq, Tetrahedron Lett., 27, 1731 (1986).
5. For a preliminary report, see : J. Hoflack, G. Appendino, and P.J. De Clercq, Abstract presented at the Belgian Organic Synthesis Symposium-1, Namur (1986).
6. J.R. Hanson and J. Hawker, J. Chem. Soc., Chem. Commun., 208 (1971); J.E. Graebe, P. Hedden and J. MacMillan, ibid., 161 (1975).
7. (a) W.M. Grootaert, R. Mijngheer, and P.J. De Clercq, Tetrahedron Lett., 23, 3287 (1982); (b) W.M. Grootaert and P.J. De Clercq, ibid., 23, 3291 (1982).
8. (a) B.S. Pitzele, J.S. Baran, and D.H. Steinman, J. Org. Chem., 40, 269 (1975); (b) C. Celia Shen and C. Ainsworth, Tetrahedron Lett., 83 (1979).
9. M. Van Meerssche, J.P. Declercq, W.M. Grootaert, and P.J. De Clercq, Bull. Soc. Chim. Belges, 91, 819 (1982).
10. H.-J. Gais, Angew. Chem., 96, 142 (1984).
11. D.C. Rideout and R. Breslow, J. Am. Chem. Soc., 102, 7816 (1980). For an example of an IMDAF reaction, catalyzed by ß-cyclodextrin, see : D.D. Sternbach and D.M. Rossana, J. Am. Chem. Soc., 104, 5853 (1982).
12. (a) The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Date Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation. (b) Supplementary data available : atomic coorinates and isotropic thermal parameters for hydrogen and non-hydrogen atoms; bond lengths and bond angles; anisotropic thermal parameters; observed and calculated structure factors. See : Tetrahedron 40(2), ii (1984). (c) For all further informations concerning X-ray analyses contact G.C.
13. For reviews, see : N.L. Allinger, Adv. Phys. Org. Chem., 13, 1 (1976); U. Burkert, N.L. Allinger, "Molecular Mechanics"; American Chemical Society; Washington, DC, 1982. The version of the MM2 program used is that available on MacroModel, (version 1.5), which corresponds to Allinger's August 1985 parameter set.
14. J. Hoflack and P.J. De Clercq, unpublished results : a full graphics oriented version (for use on IBM compatible PC's) of the program described in : P.J. De Clercq, Tetrahedron, 40, 3717, 3729 (1984).
15. MacroModel, version 1.5, kindly provided to us by Professor C. Still (Columbia University, New York).
16. C.A.G. Haasnoot, F.A.A.M. de Leeuw, and C. Altona, Tetrahedron, 36, 2783 (1980).
17. Z. Samek and M. Budesinsky, Collect. Czechoslov. Chem. Commun., 44, 558 (1979).
18. S.H. Grover and J.B. Stothers, J. Am. Chem. Soc., 91, 4331 (1969); see, also : M.J. Anteunis and R. Camerlynck, J. Chem. Soc., Perkin II, 1434 (1975).
19. R.C. Cookson, T.A. Crabb, J.J. Frankel, and J. Hudec, Tetrahedron, suppl. 7, 355 (1966); R.Cahill, R.C. Cookson, and T.A. Cragg, Tetrahedron, 25, 4681, 4711 (1969).
20. (a) M. Barfield and D.M. Grant, J. Am. Chem. Soc., 85, 1899 (1963); (b) G.E. Maciel, J.W. McIver, Jr., N.S. Ostlund, and J.A. Pople, J. Am. Chem. Soc., 92, 4151 (1970); (c) D. Montecalvo and M. St.-Jacques, J. Org. Chem., 40, 940 (1975).
21. D. Pasto, Tetrahedron, 40, 2805 (1984). See, also : E. Sonveaux, J. Andre, J. Delhalle, and J. Eripiat, Bull. Soc. Chim. Belges, 94, 831 (1985); E. Han, I. Lee, B. Chang, Bull. Korean Chem. Soc., 4, 197 (1983).
22. J.-L. Gras, J. Chem. Res. (S), 300 (1982); J.-L. Gras and A. Guerin, Tetrahedron Lett., 26, 1781 (1985).
23. (a) S. Nelson, J. Gillespie, P. Hintz, and E. Seppanen, J. Am. Chem. Soc., 95, 8380 (1973); (b) G. Himbert and D. Fink, Tetrahedron Lett., 26, 4363 (1985); (c) K. Hayakawa, M. Yodo, S. Ohsuki and K. Kanematsu, J. Am. Chem. Soc., 106, 6735 (1984); and references cited therein.
24. For IMDAF reactions involving allene-dienophiles, see : (a) K. Hayakawa, Y. Yamaguchi, and K.Kanematsu, Tetrahedron Lett., 26, 2689 (1985); (b) P. Missiaen and P. De Clercq, Bull. Soc. Chim. Belges, 96, 105 (1987).
25. G. Himbert and L. Henn, Ang. Chemie, Int. Ed. Engl., 21, 620 (1982); G. Himbert, K. Diehl, and G. Maas, J. Chem. Soc., Chem. Commun., 900 (1984); see also reference 23b.
26. W.L. Nelson and D.R. Allen, J. Heterocyclic Chem., 9, 561 (1972). See, also : P.J. De Clercq and L.A. Van Royen, Synthet. Commun., 9, 771 (1979), and note 18 therein.
27. J. Sauer, Ang. Chem., 79, 76 (1967); J. Sauer and R. Sustmann, Ang. Chem., 92, 773 (1980).
28. M.J.S. Dewar and A.B. Pierini, J. Am. Chem. Soc., 106, 203 (1984); M.J.S. Dewar, J. Am. Chem. Soc., 106, 209 (1984). See, also : F.K. Brown and K.N. Houk, Tetrahedron Lett., 26, 2297 (1985); Y.-T. Lin and K.N. Houk, Ibid., 26, 2717 (1985), and examples cited therein.
29. Also in the allene 3b; see reference 21.
30. See, e.g. : R.K. Boeckman, S.S. Ko, J. Am. Chem. Soc., 104, 1033 (1982); W.R. Roush, A.I. Ko, and H.R. Gillis, J. Org. Chem. 45, 4267 (1980).
31. We thank Dr. O. Weissbach of the Beilstein-Institut (Frankfurt am Main) for the preferred nomenclature of the compounds mentioned in this section.
32. G.M. Sheldrick "SHELXTL", revision 3, "An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data", Univ. of Göttingen, 1981.