130. Conformations of the Ten-membered Ring in 5,10-Secosteroids I.¹) X-Ray and NMR. Analysis of (*E*)-3*β*-Hydroxy-5,10-seco-1(10)-cholesten-5-one Esters

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Dedicated to Professor *Vladimir Prelog* on the occasion of his seventieth birthday

(22. III. 76)

Summary. X-ray structure determination of the *p*-bromobenzoate **2b** of one of the (*E*/*Z*)-isomeric 3*β*-hydroxy-5,10-seco-1(10)-cholesten-5-ones confirmed the (*E*)-configuration proposed previously and showed the cyclodecenone ring to adopt an extended *crown* conformation of type $\mathbf{A_1}$ (Fig. 9). Analysis of the ^{1}H- and ^{13}C-NMR. spectra of acetate **2a** revealed that in solution the ten-membered ring of this steroid exists in at least two distinct forms, the predominant (about 85%) corresponding to the solid-state conformation of **2b** ($=\mathbf{A_1}$), and the minor most likely to $\mathbf{B_2}$ (Fig. 9). From NMR. data the energy difference between the two species and the relevant activation energy were estimated. A number of conformational force field calculations using a simplified partial structural model was performed; but the computed energy differences between the various possible conformations do not reproduce the effective situation, neither in solution nor in the crystal lattice, indicating that additional effects such as the transannular interaction of the double bond with the carbonyl group may strongly influence the thermodynamic stability of the system. The conformations deduced were used to rationalize the stereochemical course of different chemical reactions of **2a**.

Introduction. – (*E*)- and (*Z*)-cyclodecenones annelated to the residual *C-D* ring system of steroids are formed by fragmentation of 5α- and 5*β*-hydroxy compounds under the conditions of the lead tetraacetate [2] [3] and hypoiodite reaction [4] [5]. In a previous paper of this series [6] the configuration around the double bond of the two isomers **2a** and **3**, obtained from 5α- and 5*β*-cholestan-3*β*,5-diol 3-acetate (**1a** and **1b**), was deduced from the NMR. spectra as well as from the chemical reactivity of the two compounds. *Akhtar & Marsh* [7] reached the same conclusion concerning the configuration of **2a** by interpreting UV. and IR. data. Additional chemical evidence for the proposed structures accumulated in recent years [1] [8–10].

Extending the conformational concepts developed by *Prelog & Dunitz* [11] [12] for the cyclodecane system to **2a**, two possible conformations ($\mathbf{A_1}$ and $\mathbf{A_2}$, *cf.* Fig. 9) were

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¹) Part XI of the series: Synthesis, Structure and Reactions of Secosteroids Containing a Medium-sized Ring. – For part X *cf.* [1].

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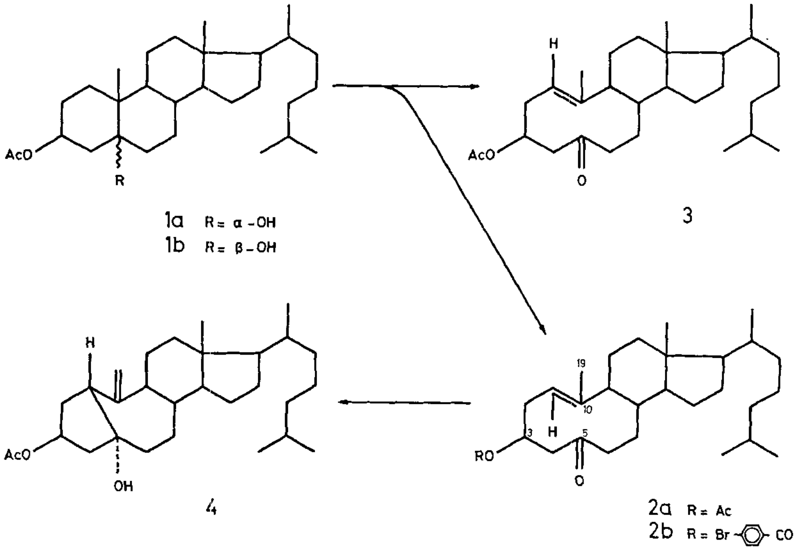
originally discussed [6]5)). In addition two further conformations (B_1 and B_2, *cf.* Fig. 9 had to be considered in connection with the ground-state form of (*E*)-cyclodecene ir its complexe with silver nitrate, and in view of the easy thermal cyclization of **2a** tc the *B*-homo-*A*-norsteroid **4** [8].

Scheme 1



The present work appears to settle these configurational and conformational problems. The results are used to interpret the stereochemistry of a few known chemical transformations of compound **2a**.

1. Determination of the Solid State Conformation of (*E*)-3β-(*p*-Bromobenzoyloxy)-5,10-seco-1(10)-cholesten-5-one (2b) by X-ray Analysis. – 1.1. *Experimental*6)). *Crystal data.* $C_{34}H_{49}O_3Br$, $M = 585.7$. Monoclinic, $a = 14.828$ (14), $b = 6.966$ (7), $c = 15.503$ (26) Å, $\beta = 102.20$ (5)°, $U = 1565.3$ Å^3, $Z = 2$, $D_c = 1.243$, $D_m = 1.242$ g/cm^3, F(000) = 624. Mo*Kα* radiation, $\lambda = 0.71069$ Å; μ(Mo*Kα*) = 15.1 cm^{-1}. Space group $P2_1$ from systematic absences.

Crystal Structure Determination. Colourless crystals of (*E*)-3β-(*p*-bromobenzoyloxy)-5,10-seco-1(10)-cholesten-5-one (**2b**) were grown from acetone solution (m.p. 169°, $[\alpha]_D^{20} = +21 \pm 2°$ ($c = 0.75$, $CHCl_3$)). Preliminary unit cell and space group data were determined from *Weissenberg* and precession photographs taken with Cu*Kα* radiation; cell constants were refined by least-squares methods from 2 θ values for 11 reflections measured on a diffractometer with Mo*Kα* radiation [14].

Crystallographic measurements. A *Picker*-FACS-I automatic diffractometer was used for data collection with Mo*Kα* radiation and a graphite monochromator. The intensities of 3012 inde-

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5) For reasons of stability, conformation A_2 was preferred. *Akhtar & Marsh* [7], on the ground of the transannular electronic transition involving the double bond and the carbonyl group, considered only conformation A_1. The same type of interaction is also responsible for the solvent effect described by *Kosower et al.* [13] in the case of cyclodecenone. This effect is also observed with the pair **2** and **3**.

6) All crystallographic calculations were performed on an *IBM*-370/155 computer using programs written by one of us (*H.C.M.*).

pendent reflections with $\theta \leqslant 25°$ were measured by a $(2\theta - \theta)$ step scan with stationary background counts at the extrema [14]; the 2411 reflections with $I \geqslant 2\sigma(I)$ were considered observed. Data reduction included adjustment of intensities to fluctuations in the standard reflections, and corrections for *Lorentz* and polarisation factors, but not for absorption.

Structure analysis. x- and z-coordinates of the bromine atom were found from a *Harker* synthesis at $v = 1/2$. Four cycles of (structure factor)-(*Fourier* calculations) with automatic peak search located 31 of the 38 non-hydrogen atoms in the molecule. The seven atoms C(21) to C(27) in the side chain were not resolved. In order to find these, positional and isotropic thermal parameters for the 31 atoms found were subjected to two cycles of block-diagonal leastsquares refinement (BDLS.). The $R(= \Sigma||F_{obs}| - |F_{calc}||/\Sigma|F_{obs})$ index for the 1667 most reliable reflections ($F_{obs} \geq 4\sigma(F_{obs})$) was lowered from 0.248 to 0.216, but a subsequent *Fourier* synthesis located only three of the seven missing atoms. Automatic peak search on a weighted [15] *beta* synthesis [16] with cut-off [17], on the other hand, revealed correct positions of all seven atoms unequivocally. Refinement was started by two cycles of BDLS. with isotropic thermal parameters, and R dropped from 0.22 to 0.16. Four further cycles of BDLS. with anisotropic temperature parameters brought R to 0.085. At this stage the weighting scheme was changed from $\sqrt{w} = 1/\sigma(F_{obs})$ to a *Hughes* [18] type scheme after careful analysis of the $w\Delta^2$ values ($\Delta = |F_{obs}| - |F_{calc}|$). Another two cycles of BDLS. lowered R to 0.076. Finally, three cycles of full matrix LS. were calculated with nineteen atoms refined per cycle and including the anomalous scattering contribution [19] for the bromine atome [20] ($\Delta f' = -0.3$, $\Delta f'' = 2.6$). The final value of R was 0.073 for all 2411 observed reflections and 0.060 for the 1832 most reliable ones with $F_{obs} \geq 3\sigma(F_{obs})$. Hydrogen atoms were excluded from both refinement and structure factor calculations. The r.m.s. ratio between shifts and e.s.d.'s was 0.32 for the last two LS. cycles including all 343 parameters, and only one parameter, y(C(26)), had a shift larger than its e.s.d. The actual weighting scheme for the final LS. cycles was $\sqrt{w} = 1$ for $4.68 \leqslant F_{obs} \leqslant 21.04$, $\sqrt{w} = F_{obs}/4.68$ for $F_{obs} < 4.68$, and $\sqrt{w} = 21.04/F_{obs}$ for $F_{obs} > 21.04$. The quantity minimized was $\Sigma w\Delta^2$.

1.2. *Results and discussion.* The structure was refined excluding hydrogen atoms. Final atomic coordinates and thermal parameters with their standard deviations are given in Table 1. The molecular structure of **2b** is illustrated in Fig. 1 with the atomic numbering scheme and the bond lengths. More precise values of the bond lengths with their standard deviations and selected transannular distances in the ten-membered ring are shown in Table 2. Bond angles are illustrated in Fig. 2 and shown in Table 3, and torsion angles in Fig. 3 and Table 4. Fig. 4 is a stereo plot [21] of the molecule.

The ten-membered ring is in the extended *crown* conformation of approximate symmetry 2/m (C_{2h}). Similar shapes have been reported for the ten-membered ring in both the 1:1 silver nitrate adduct of germacatriene [22] and elephantol *p*-bromobenzoate [23] but these cannot be used for comparison because the torsion angle τ(C(3)-C(4)-C(5)-C(6)) is fixed near the antiperiplanar partial conformation in both compounds. The same is true for a derivative of (*E*,*E*)-cyclodeca-1,6-diene the crystal structure of which has been studied recently [24]. The geometry of the double bond C(1)=C(10) in **2b** deviates only slightly from planarity, in contrast to other (*E*)-cyclodecene structures. While corresponding torsion angles have values of *e.g.* 163° in elephantol-*p*-bromobenzoate [23], 151° in (*E*)-cyclodec-5-en-1-yl-(*p*-nitrobenzoate) [25], [26], and 138° in the 1:2 silver nitrate adduct of (*E*)-cyclodecene [27], the torsion angle τ(C(2)-C(1)-C(10)-C(9)) is 175° in **2b**. The geometrical prerequisite for this is the short transannular distance C(1) . . . C(5) of only 2.84 Å, considerably less than the sum of the *van der Waals* radii. Apart from the absence of steric hindrance between the two sp²-carbon atoms C(1) and C(5), the short transannular distance probably indicates a transannular attraction of the C=C and C=O double bonds by a π-inter-

Table 1. *(E)-3β-Hydroxy-5,10-seco-1(10)-cholesten-5-one* p-*Bromobenzoate. Final positional and thermal parameters* ($*10^4$)[a]) *for the non-hydrogen atoms*

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{23}	β_{31}
Br	3183 (1)	8430 (5)	5209 (1)	51 (1)	258 (3)	105 (1)	−4 (3)	−19 (4)	69 (1)
O(3)	7474 (4)	8297 (18)	4347 (4)	37 (3)	291 (21)	47 (3)	−4 (20)	−18 (20)	32 (5)
O(3′)	7921 (4)	8633 (19)	5820 (4)	49 (3)	370 (24)	47 (4)	0 (24)	−80 (25)	13 (6)
O(5)	10389 (5)	8941 (13)	4770 (5)	55 (4)	290 (32)	50 (4)	27 (16)	−36 (17)	7 (6)
C(B1)	4458 (6)	8484 (26)	5196 (7)	51 (5)	153 (19)	71 (6)	−15 (34)	22 (37)	36 (10)
C(B2)	4715 (6)	8466 (30)	4387 (7)	51 (5)	286 (25)	59 (6)	49 (37)	34 (41)	40 (9)
C(B3)	5654 (6)	8375 (27)	4371 (7)	48 (5)	235 (25)	58 (6)	8 (34)	33 (35)	19 (9)
C(B4)	6316 (5)	8518 (25)	5155 (6)	46 (4)	177 (19)	47 (5)	20 (32)	−21 (31)	38 (8)
C(B5)	6034 (6)	8523 (28)	5963 (6)	63 (5)	269 (26)	50 (5)	−10 (40)	−55 (37)	44 (9)
C(B6)	5113 (7)	8425 (30)	5977 (7)	69 (6)	322 (29)	60 (6)	−25 (44)	27 (41)	63 (10)
C(3′)	7322 (7)	8500 (24)	5175 (7)	58 (5)	173 (20)	57 (6)	10 (37)	−33 (35)	36 (10)
C(1)	9247 (7)	6263 (17)	3259 (7)	50 (5)	189 (24)	49 (6)	−29 (20)	−34 (20)	15 (9)
C(2)	8335 (7)	6585 (20)	3481 (7)	50 (5)	326 (36)	45 (6)	−44 (24)	−73 (25)	44 (9)
C(3)	8435 (7)	7995 (15)	4254 (7)	44 (5)	200 (38)	60 (6)	2 (18)	−17 (20)	44 (9)
C(4)	8853 (7)	9916 (19)	4102 (8)	46 (5)	221 (29)	64 (7)	20 (21)	−9 (24)	35 (10)
C(5)	9873 (7)	9730 (16)	4144 (8)	50 (5)	156 (25)	67 (7)	−4 (20)	−62 (23)	34 (10)
C(6)	10259 (7)	10602 (18)	3389 (8)	47 (5)	232 (29)	64 (6)	11 (20)	7 (23)	38 (10)
C(7)	11128 (7)	9611 (21)	3197 (8)	42 (5)	365 (36)	78 (8)	−56 (25)	−142 (30)	55 (10)
C(8)	11029 (5)	8416 (26)	2369 (6)	38 (4)	269 (24)	53 (5)	34 (32)	−18 (34)	33 (7)
C(9)	10502 (6)	6499 (17)	2407 (7)	38 (5)	235 (27)	56 (6)	−11 (20)	−30 (23)	24 (9)
C(10)	9514 (6)	6789 (16)	2512 (7)	42 (5)	221 (25)	44 (5)	−7 (19)	−24 (21)	26 (8)
C(11)	10522 (7)	5146 (20)	1641 (8)	54 (5)	329 (37)	66 (7)	−22 (25)	−61 (28)	63 (10)
C(12)	11501 (8)	4737 (20)	1523 (8)	61 (6)	264 (33)	67 (7)	10 (25)	−31 (26)	48 (11)
C(13)	12017 (7)	6623 (17)	1418 (7)	51 (5)	246 (28)	54 (6)	31 (21)	19 (23)	53 (9)
C(14)	12004 (7)	7816 (16)	2246 (7)	44 (5)	267 (33)	50 (6)	−4 (19)	−2 (21)	18 (9)
C(15)	12691 (7)	9525 (23)	2183 (10)	44 (6)	348 (37)	94 (9)	−32 (26)	−18 (33)	55 (12)
C(16)	13420 (7)	8518 (32)	1766 (8)	56 (5)	328 (32)	89 (7)	33 (41)	−23 (47)	72 (10)
C(17)	13065 (7)	6519 (19)	1493 (7)	47 (5)	310 (34)	47 (6)	40 (23)	32 (24)	23 (9)
C(18)	11553 (8)	7670 (23)	529 (8)	60 (6)	486 (51)	54 (6)	96 (29)	85 (29)	20 (11)
C(19)	8848 (7)	7741 (20)	1715 (8)	46 (6)	362 (38)	55 (6)	54 (22)	24 (24)	3 (10)
C(20)	13423 (7)	5712 (22)	663 (8)	48 (5)	394 (45)	59 (6)	27 (26)	−33 (29)	46 (10)
C(21)	13084 (8)	3715 (38)	351 (9)	78 (7)	558 (67)	87 (8)	0 (46)	−155 (51)	74 (13)
C(22)	14498 (8)	5801 (25)	851 (9)	55 (6)	471 (50)	85 (8)	89 (30)	97 (35)	68 (12)
C(23)	14981 (9)	4636 (33)	1600 (13)	56 (7)	660 (72)	151 (14)	148 (39)	358 (58)	72 (16)
C(24)	16014 (11)	4282 (36)	1431 (14)	66 (8)	666 (94)	146 (14)	104 (46)	257 (62)	49 (17)
C(25)	16492 (11)	2856 (25)	1941 (15)	68 (9)	350 (59)	151 (15)	90 (35)	12 (43)	55 (19)
C(26)	16164 (10)	1029 (28)	2068 (11)	76 (9)	454 (53)	101 (11)	10 (37)	84 (40)	58 (16)
C(27)	17521 (8)	2818 (22)	1811 (11)	58 (7)	416 (53)	108 (10)	15 (27)	−61 (35)	43 (13)

[a]) Numbers in brackets are estimated standard deviations, obtained from the inverted matrix after the final least-squares calculation. The anisotropic temperature factor is of the form $\exp[-(\beta_{11} h^2 + \beta_{22} k^2 + \beta_{33} l^2 + \beta_{12} hk + \beta_{23} kl + \beta_{31} lh)]$.

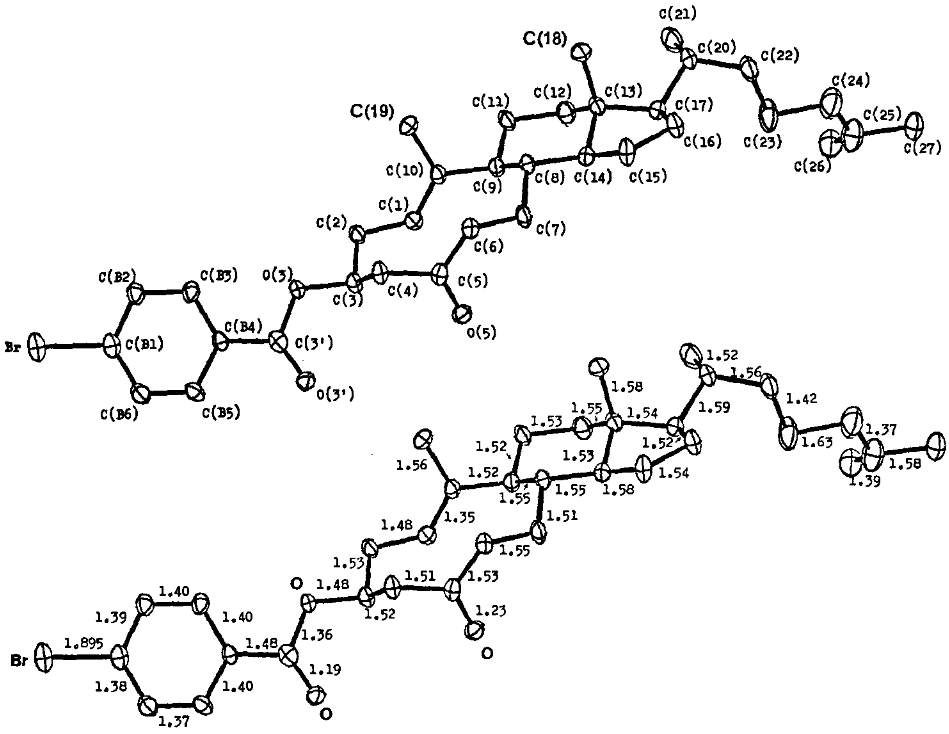

Fig. 1. *Molecular structure of* **2b**, atom numbering scheme (above) and bond lengths (below) (more precise values and e.s.d.'s in Table 2)

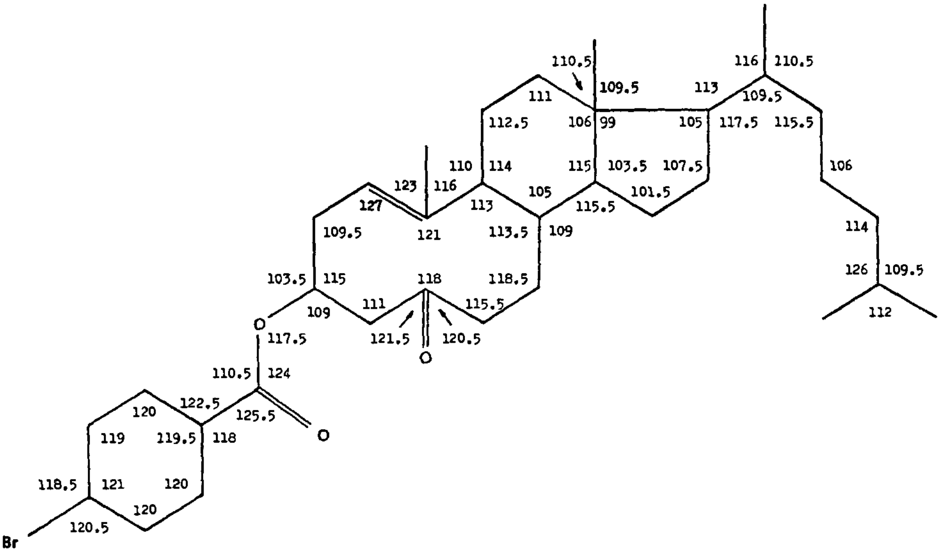

Fig. 2. *Bond angles* (more precise values and e.s.d.'s in Table 3)

Table 2. *Intramolecular distances* (*Å*)

(a) *Bond distances*

C (1)—C(10)	1.350 (15)
C (1)—C (2)	1.482 (14)
C (2)—C (3)	1.532 (16)
C (3)—C (4)	1.515 (16)
C (3)—O (3)	1.477 (12)
C (4)—C (5)	1.506 (15)
C (5)—C (6)	1.532 (17)
C (5)—O (5)	1.230 (14)
C (6)—C (7)	1.546 (15)
C (7)—C (8)	1.511 (18)
C (8)—C (9)	1.555 (20)
C (8)—C(14)	1.555 (14)
C (9)—C(10)	1.521 (13)
C (9)—C(11)	1.521 (17)
C(10)—C(19)	1.558 (15)
C(11)—C(12)	1.528 (16)
C(12)—C(13)	1.546 (18)
C(13)—C(14)	1.533 (16)
C(13)—C(17)	1.536 (14)
C(13)—C(18)	1.582 (17)
C(14)—C(15)	1.583 (18)
C(15)—C(16)	1.541 (19)
C(16)—C(17)	1.517 (24)
C(17)—C(20)	1.593 (17)
C(20)—C(21)	1.524 (29)
C(20)—C(22)	1.561 (17)
C(22)—C(23)	1.472 (25)
C(23)—C(24)	1.628 (22)
C(24)—C(25)	1.370 (29)
C(25)—C(26)	1.392 (26)
C(25)—C(27)	1.580 (21)
O (3)—C (3′)	1.356 (13)
C (3′)—O (3′)	1.193 (13)
C (3′)—C(B4)	1.485 (13)
C(B4)—C(B5)	1.402 (13)
C(B5)—C(B6)	1.372 (14)
C(B6)—C(B1)	1.384 (15)
C(B1)—C(B2)	1.386 (15)
C(B2)—C(B3)	1.399 (13)
C(B3)—C(B4)	1.395 (13)
Br—C(B1)	1.895 (9)

(b) *Selected transannular distances*

C(1)..C(4)	2.98 (2)
C(1)..C(5)	2.84 (2)
C(1)..C(6)	3.36 (2)
C(5)..C(2)	3.17 (2)
C(5)..C(10)	3.21 (2)
C(6)..C (9)	3.29 (2)
C(6)..C(10)	3.08 (2)
C(7)..C(10)	3.11 (2)

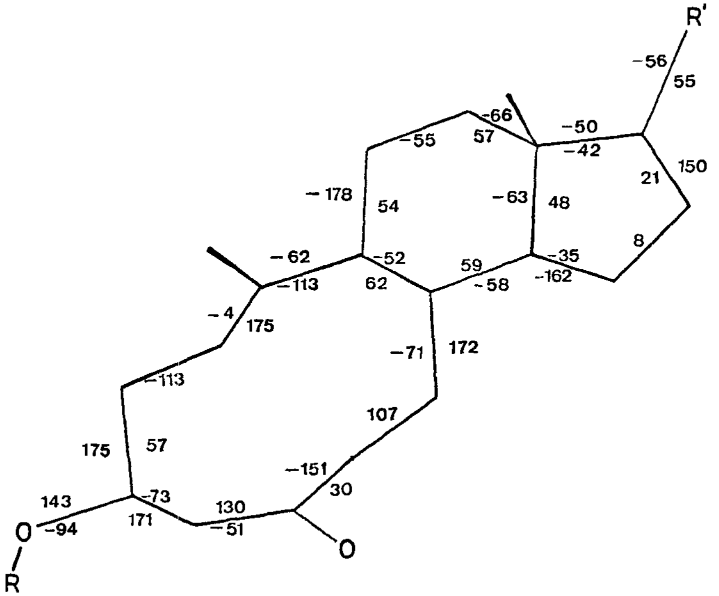

Fig. 3. *Selected torsion angles characterizing the secosteroid skeleton of* **2b** (further values in Table 4)

Table 3. *Intramolecular angles (deg.)*

C(10)—C (1)—C (2)	127.2	C(13)—C(14)—C(15)	103.5
C (1)—C (2)—C (3)	109.7	C(14)—C(15)—C(16)	101.6
C (2)—C (3)—C (4)	114.8	C(15)—C(16)—C(17)	107.6
C (2)—C (3)—O (3)	103.5	C(16)—C(17)—C(13)	105.3
O (3)—C (3)—C (4)	108.9	C(16)—C(17)—C(20)	113.2
C (3)—C (4)—C (5)	111.0	C(13)—C(17)—C(20)	117.4
C (4)—C (5)—C (6)	117.8	C(17)—C(20)—C(21)	115.8
C (4)—C (5)—O (5)	121.6	C(17)—C(20)—C(22)	109.7
O (5)—C (5)—C (6)	120.6	C(21)—C(20)—C(22)	110.5
C (5)—C (6)—C (7)	115.5	C(20)—C(22)—C(23)	115.6
C (6)—C (7)—C (8)	118.4	C(22)—C(23)—C(24)	105.8
C (7)—C (8)—C (9)	113.6	C(23)—C(24)—C(25)	114.0
C (7)—C (8)—C(14)	109.1	C(24)—C(25)—C(26)	126.2
C(14)—C (8)—C (9)	105.2	C(24)—C(25)—C(27)	109.5
C (8)—C (9)—C(10)	113.2	C(26)—C(25)—C(27)	112.3
C (8)—C (9)—C(11)	114.1	C (3)—O (3)—C (3′)	117.7
C(11)—C (9)—C(10)	110.2	O (3)—C (3′)—O (3′)	123.9
C (9)—C(10)—C (1)	121.2	O (3)—C (3′)—C(B4)	110.4
C (9)—C(10)—C(19)	115.7	O (3′)—C (3′)—C(B4)	125.7
C(19)—C(10)—C (1)	123.0	C (3′)—C(B4)—C(B3)	122.4
C (9)—C(11)—C(12)	112.7	C(3′)—C(B4)—C(B5)	118.0
C(11)—C(12)—C(13)	111.0	C(B3)—C(B4)—C(B5)	119.4
C(12)—C(13)—C(14)	106.1	C(B4)—C(B5)—C(B6)	120.0
C(12)—C(13)—C(17)	117.9	C(B5)—C(B6)—C(B1)	120.2
C(12)—C(13)—C(18)	110.5	C(B6)—C(B1)—C(B2)	120.9
C(14)—C(13)—C(17)	98.8	C(B1)—C(B2)—C(B3)	118.8
C(14)—C(13)—C(18)	113.6	C(B2)—C(B3)—C(B4)	120.1
C(17)—C(13)—C(18)	109.6	C(B6)—C(B1)—Br	120.6
C (8)—C(14)—C(13)	115.1	C(B2)—C(B1)—Br	118.4
C (8)—C(14)—C(15)	115.6		

Table 4. *Torsion angles (deg.) not shown in Fig. 3*

C (7)—C (8)—C (9)—C(11)	171	C(22)—C(23)—C(24)—C(25)	165
C(14)—C (8)—C (9)—C(10)	179	C(23)—C(24)—C(25)—C(26)	–48
C (7)—C (8)—C(14)—C(13)	179	C(23)—C(24)—C(25)—C(27)	173
C (9)—C (8)—C(14)—C(15)	180	C (3)—O (3)—C (3′)—O (3′)	–8
C (8)—C (9)—C(10)—C(19)	– 67	C (3)—O (3)—C (3′)—C(B4)	172
C(11)—C (9)—C(10)—C (1)	–118	O (3)—C (3′)—C(B4)—C(B3)	1
C(11)—C(12)—C(13)—C(17)	–167	O (3)—C (3′)—C(B4)—C(B5)	–174
C(12)—C(13)—C(14)—C(15)	–170	O (3′)—C (3′)—C(B4)—C(B3)	–179
C(17)—C(13)—C(14)—C (8)	–175	O (3′)—C (3′)—C(B4)—C(B5)	6
C(18)—C(13)—C(14)—C (8)	– 59	C (3′)—C(B4)—C(B5)—C(B6)	176
C(18)—C(13)—C(14)—C(15)	68	C(B3)—C(B4)—C(B5)—C(B6)	1
C(12)—C(13)—C(17)—C(16)	156	C(B4)—C(B5)—C(B6)—C(B1)	5
C(12)—C(13)—C(17)—C(20)	– 77	C(B5)—C(B6)—C(B1)—C(B2)	–6
C(14)—C(13)—C(17)—C(20)	169	C(B5)—C(B6)—C(B1)—Br	178
C(18)—C(13)—C(17)—C(16)	– 77	Br —C(B1)—C(B2)—C(B3)	176
C(13)—C(17)—C(20)—C(22)	–178	C(B6)—C(B1)—C(B2)—C(B3)	0
C(16)—C(17)—C(20)—C(21)	179	C(B1)—C(B2)—C(B3)—C(B4)	7
C(17)—C(20)—C(22)—C(23)	– 62	C(B2)—C(B3)—C(B4)—C(B5)	–8
C(21)—C(20)—C(22)—C(23)	67	C(B2)—C(B3)—C(B4)—C(3′)	178
C(20)—C(22)—C(23)—C(24)	–158		

action of the type reported for (*E*)-cyclodec-5-enone [13] and a number of sesquiterpenes [28]. The interdependence of transannular C ... C distances, torsion angles and the steric requirements of type III[7]) atoms in ten-membered rings is illustrated in Fig. 5. In cyclodecane [26] (not illustrated) the transannular distance is 3.29 Å between two methylene groups with a torsion angle of 152°. In cyclodecane-1,6-dione (**A**) [29] the CH_2 ... CO distance is 3.13 Å with $\tau = 157°$. In 2-oxacyclodecane-1,6-dione (**B**) [30] the CH_2 ... CO distance is reduced to 3.04 Å and the O ... CO distance is only 2.83 Å. The resultant torsion angles are 174° and −155°, and the geometry of the central moiety of **B** is closely similar to that of compound **2b** (= **C**).

The six-membered ring in **2b** assumes the normal chair conformation with an average bond angle of 110.7° and an average torsion angle of 56.7°. The conformation of the five-membered ring is intermediate between a C(13) envelope and a C(16) halfchair, with *Romers* ring parameters [31] $\varphi_m = 48°$ and $\Delta = 15.4°$.

The conformation of the side chain C(20) to C(27) is not unusual. Bond lengths and angles in this part of the molecule are unreliable reflecting the effect of either

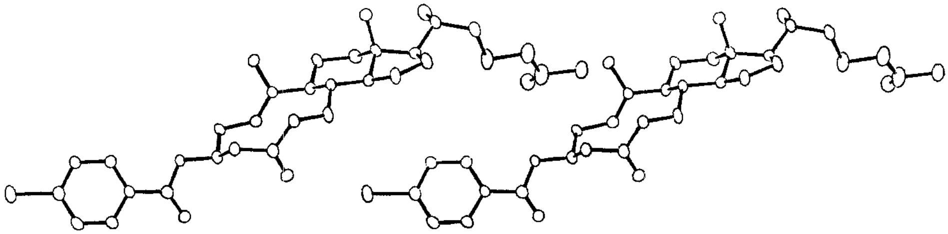

Fig. 4. *Stereo plot of* **2b**

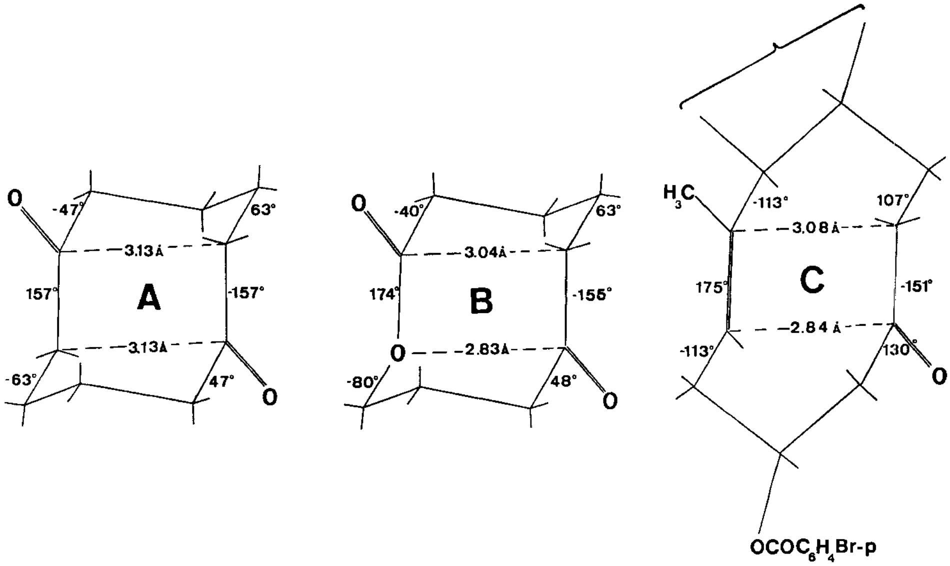

Fig. 5. *Transannular distances and torsion angles in cyclodecane-1,6-dione* (**A**) [29], *2-oxacyclodecane-1,6-dione* (**B**) [30] *and the ten-membered ring of* **2b** (= **C**)

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[7]) For the nomenclature of the stable cyclodecane conformation: *cf.* [26].

floppiness in the chain or disorder or both. Similar difficulties have been reported in e.g. the crystal structure analysis of 4,4-dichloro-2a-aza-*A*-homocholestan-3-one [32]. Since our main objective was to establish the conformation of the ten-membered ring no attempt was made to account for these effects.

2. Conformations of the Ten-membered Ring of (*E*)-3β-Acetoxy-5,10-seco-1(10)-cholesten-5-one (2a) in Solution. NMR. Analysis. – 2.1. *General remarks.* In this NMR. study the acetate **2a** was investigated instead of the *p*-bromobenzoate **2b**. This replacement was necessary because of the coincidence of the chemical shifts of the two protons at C(1) and C(3) in the spectrum of **2b**. The coupling constants of these protons were of great importance for the following conformational analysis. We assume that this change of substituents does not significantly alter the conformation of the ten-membered ring. Both compounds exhibit negative *Cotton* effects of similar magnitude for the keto group in position 5. This may be considered a good indication for similar conformations of the cyclodecenone ring in the two compounds.

No detailed comparisons have been made so far between the conformations of medium sized ring ketones in solid state and in solution[8]. A discussion of conformations of medium sized monocyclic carbonyl compounds in solution has been published recently by *Anet et al.* For cyclodecanone these authors propose a *boat-chair-boat* conformation with pseudorotation of the CO group [35] [36].

2.2. *Experimental.* Noise decoupled ^{13}C-NMR. spectra were recorded at 25.2 MHz and ^{1}H-NMR. spectra at 100 MHz on a *Varian* XL-100 spectrometer equipped with a *Fourier* transform accessory. Deuterions of the deuteriated solvents (chloroform and toluene) were used for a 15.4 MHz ^{2}H-lock during ^{13}C-work. In toluene solutions the temperature dependence of ^{1}H- and ^{13}C-NMR. spectra of **2a** was studied between −60° and +90°. At temperatures above 50° the thermal cyclization of **2a** to the *B*-homo-*A*-nor-compound **4** [8] is fast enough to reduce the resolution of ^{13}C-NMR. spectra between 0 and 60 ppm from TMS. due to a large number of additional resonances. At the same time the signal to noise ratio of the whole spectrum is reduced; the temperature dependence was therefore mainly studied at chemical shift values larger than 60 ppm.

2.3. *Results.* Due to the long accumulation times required, resonances of the cyclization product **4** were found in the ^{13}C-NMR. spectrum of **2a** (labelled R in Fig. 6). Apart from these signals, in both, the ^{13}C- and ^{1}H-NMR. spectra two sets of lines (I and II) were observed, with the following properties: a) formation of **4** does not alter the intensity ratio of the two sets of lines; b) the two sets exhibit a temperature dependence characteristic for two conformations (I and II) in thermal equilibrium.

In the ^{1}H-NMR. spectrum of **2a** in toluene (Fig. 7) the relative intensities of resonances in sets I and II are $P_I = 0.86 \pm 0.02$ and $P_{II} = 0.14 \pm 0.02$. The large uncertainty is due to broad and partially overlapping lines of the only resolved resonances H–C(1) and H–C(3) of set I and II. The three *m* at low field are attributed to H–C(1) and H–C(3) of both conformations and have relative intensities of approximately 3:1:3. Therefore the weakest *m* corresponds to the resonances of *both* H–C(1)

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[8] In the work of *Mabry et al.* [33], *e.g.*, only the general structure has been analysed by NMR., the conformation of the ten-membered Germacranolide-type ring was determined by X-ray. For the general problem *cf.* [34].

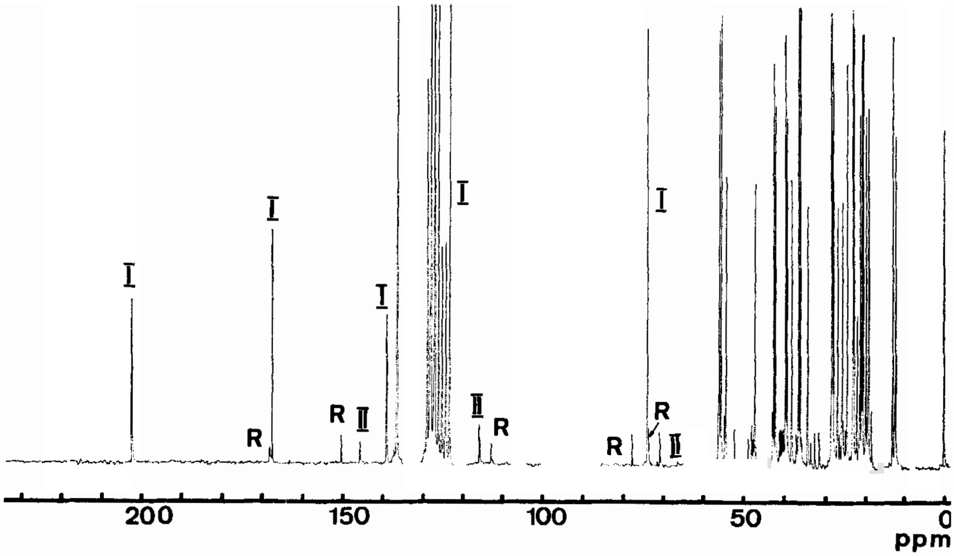

Fig. 6. *^{13}C-NMR. spectrum of* **2a** *in toluene.* Resonances of the two conformations are labeled I and II. Resonances of the cyclization product are labelled R.

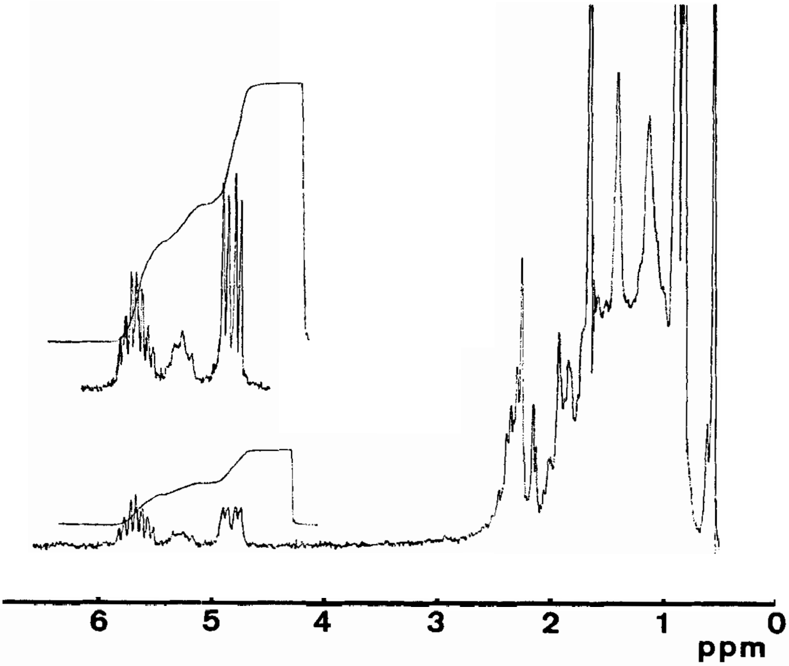

Fig. 7. *^{1}H-NMR. spectrum of* **2a** *in deuteriated toluene.* Bottom trace: single resonance spectrum; upper trace: resonances of the low field protons H—C(1) and H—C(3) while the protons of H_3C—C(10) are decoupled

and H–C(3) of conformation II. Based on its coupling pattern, the *q* at 4.8 ppm with relative intensity 3 is assigned to H–C(1) of conformation I.

The ^{1}H-NMR. spectrum of **2a** in $CDCl_3$ (Fig. 8) has been discussed partly in a preceding paper of this series [6]. The intensity ratio of the two low field *m* is approximately 4:3 as is expected, if both low field protons of conformation II and H–C(3) of conformation I had similar chemical shifts in $CDCl_3$. The ^{1}H-NMR. data are collected in Table 5.

Some ^{13}C chemical shifts of set I and II are listed in Table 6. They will be discussed in detail in a subsequent publication.

2.4. *Discussion.* According to the NMR. spectra of **2a** the ten-membered ring of the compound must adopt at least two different conformations in solution.

The ^{1}H-NMR. pattern of H–C(3) of the main component of **2a** (*cf.* Table 5 and Fig. 7) in the temperature region of very slow exchange may be characterized as a triplet of triplets with coupling constants of approximately 5 and 10 Hz. This is typical for an axial proton with two *vicinal* methylene groups, equivalent with respect to their coupling behaviour. Consequently the acetoxy group of the main component is equatorial.

Unfortunately the resonance pattern of H–C(3) in the less stable conformation is not resolved. However, the width of the *m* estimated from (180°–90°) pulse experiments to be 25–30 Hz, is again compatible with an equatorial acetoxy group. Therefore an equatorial substituent at C(3) is assumed for all the conformations to be discussed.

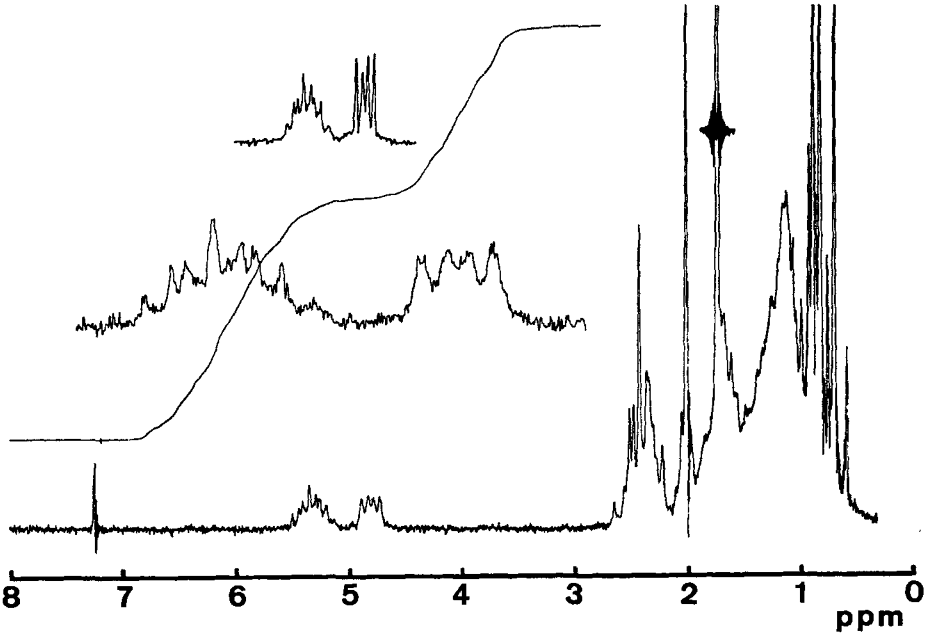

Fig. 8. *^{1}H-NMR. spectrum of* **2a** *in deuteriated chloroform.* Bottom trace: single resonance spectrum; center trace: single resonance showing relative intensities of low field multiplets; top trace: low field protons, during decoupling of the protons of H_3C—C(10)

Table 5. *^{1}H-NMR. Chemical Shifts of H—C(1) and H—C(3) in* **2a**

Solvent	δ (ppm) of set I		δ (ppm) of set II	
	H—C(1)	H—C(3)	H—C(1)	H—C(3)
Chloroform	4.82	5.35	5.10 – 5.40	
Toluene	4.80	5.60	5.20 – 5.30	

Table 6. *Some ^{13}C-NMR. Chemical Shifts of* **2a** *in Toluene*[a] *at +30°*

Carbon atom	C(1)	C(3)	C(5)	C(10)	C(19)	C(Ac)[c]
δ (Set I)	123.9	74.5	203.8	139.8	12.9	168.5
δ (Set II)	116.6	71.3		146.5	19.5[b]	169.2

[a] In ppm from TMS.
[b] Tentative assignment; chloroform solution.
[c] Carbonyl C-atom of the acetoxy group.

With this limitation in mind and following the arguments used above, it seems reasonable to consider for **2a** the four conformations **A**$_1$, **A**$_2$, **B**$_1$ and **B**$_2$ (Fig. 9). They reflect the four possibilities of orienting the olefinic methyl group and the carbonyl group in 5 above (position *b*) or below (position *a*) the mean plane of the ten-membered ring[9][10].

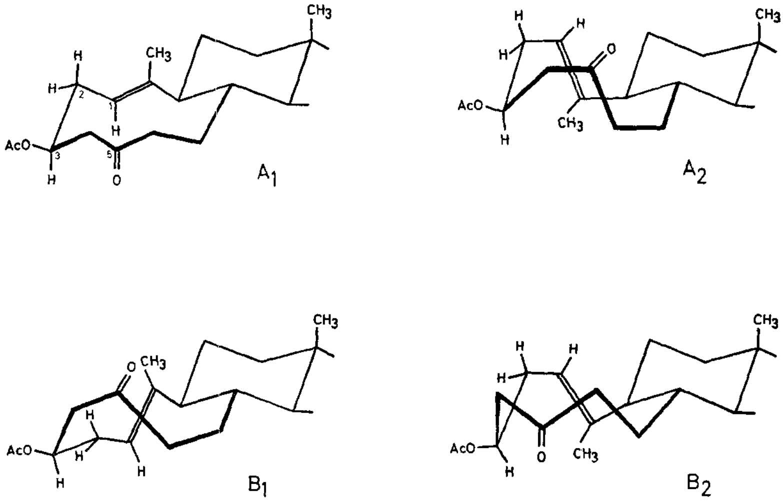

Fig. 9. *Conformations* **A**$_1$, **A**$_2$, **B**$_1$ *and* **B**$_2$

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[9] In position *b* the olefinic methyl group is on the same side of the defined plane as $H_3C(18)$ of the steroid.

[10] Other conformations distinctly different from the four proposed lead to stronger steric interactions.

Table 7. *Theoretical and Experimental Coupling Constants* J *of H–C(1)*

Theoretical J[a]		Experimental J	
Conformations **A**$_1$ and **B**$_1$[b]	Conformations **A**$_2$ and **B**$_2$[c]	Resonances (Set I)[d]	Resonances (Set II)[e]
$J_1 = 11.6$ Hz	$J_1 = 6.6$ Hz	$J_1 \geqslant 11$ Hz	*t*-like structure
$J_2 = 3.6$ Hz	$J_2 = 4.8$ Hz	$J_2 \leqslant 5$ Hz	*t*-like structure

[a] According to *Karplus* rule [37].
[b] The dihedral angles of H–C(1) with the protons at C(2) are: $\phi_1 = 180°$, $\phi_2 = 60°$.
[c] The dihedral angles of H–C(1) with the protons at C(2) are: $\phi_1 = 0°$, $\phi_2 = 120°$.
[d] $J_1 + J_2 = 16$ Hz.
[e] $J_1 + J_2 = 14$ Hz.

Two classes of possible conformations may be distinguished according to the chemical shifts of the olefinic proton (*cf.* [6]): in class **A** H–C(1) is in the shielding region of the keto group, in class **B** it is not affected.

Another parameter for the characterization of the possible conformations of **2a** is the dihedral angle (or the coupling constant) between H–C(1) and the protons on C(2). This angle does not fix the position of C(6), which is however restricted by the geometric relations giving rise to the H–C(3) coupling pattern discussed before. The four conformations are characterized as follows:

A$_1$ (crown *conformation = solid-state conformation*). H–C(1) is in the shielding region of the keto group. The dihedral angle H–C(1)/H$_b$–C(2) is 180°. C(6) and the olefinic methyl group are in position *b*.

A$_2$ (*ground-state cyclodecane conformation* [6]). H–C(1) is in the shielding region of the keto group. However, the olefinic methyl group and C(6) are now in position *a*. The dihedral angle H–C(1)/H$_b$–C(2) is 0°.

B$_1$ (*ground-state conformation of* (E)-*cyclodecene-AgNO*$_3$*-complex* [27]). The olefinic methyl group at C(10) ($H_3C(19)$) is in the shielding region of the keto group and H–C(1) is not influenced by the latter. The dihedral angle H–C(1)/H$_b$–C(2) is 180°. C(6) is below, the olefinic methyl group above the plane of the ring.

B$_2$ (*conformation proposed in* [8]). As in **B**$_1$ the olefinic methyl group is in the shielding region of the ketone. The dihedral angle H–C(1)/H$_b$–C(2) is 0°. C(6) is in position *b* and $H_3C(19)$ in *a*.

Major Conformation of **2a** (Resonances of Set I). The chemical shift of H–C(1) in $CHCl_3$ is $\delta = 4.82$ ppm (Table 5). Accordingly, H–C(1) must be shielded by the carbonyl group. Both conformations **A**$_1$ and **A**$_2$ are compatible with this, as well as with the fact, that the Eu(fod)$_3$ induced shift of the signal of H-C(1) ($\Delta = +0.78$ ppm) is much larger than the one for the protons of the olefinic methyl group ($\Delta = +0.37$ ppm) (measured in $CDCl_3$ with an arbitrary amount of Eu(fod)$_3$). Neglecting the coupling with the methyl group, H–C(1) couples with the two protons at C(2) (*cf.* Fig. 7). The resonances of the latter are not resolved. Therefore the two *vicinal* coupling constants $^3J_1$ and $^3J_2$ have to be taken from the signal of H–C(1), *i.e.* $^3J_1 + {}^3J_2 = 16$ Hz with $^3J_1 \geqslant 11$ Hz and $^3J_2 \leqslant 5$ Hz.

Theoretical and experimental coupling constants of the four proposed conformations and for the two sets of resonances are collected in Table 7. According to the

Karplus equation for *vicinal* coupling in analogous allylic systems [37], $J \geqslant 11$ Hz is compatible only with a dihedral angle of about 180°. Therefore conformation $\mathbf{A}_2$ can be excluded and $\mathbf{A}_1$ (crown) *has to be the predominant conformation of* **2a** *in solution.*

There are additional arguments in favour of this assignment: Upon addition of Eu(fod)$_3$ the NMR. pattern (CDCl$_3$) of the two H–C(4) of **2a** are well resolved: H$_{ax}$–C(4) (ax/ax coupling) resonates at much higher field than H$_{eq}$–C(4) (ax/eq coupling). If we assume that the europium reagent interacts mainly with the keto group, only conformation $\mathbf{A}_1$ would be in agreement with such a behaviour. The fact, that addition of benzene to a CDCl$_3$ solution of **2a** shifts the proton *geminal* to the acetoxy group (H–C(3)) from 5.38 to 5.60 ppm is again in favour of conformation $\mathbf{A}_1$[11] (in $\mathbf{A}_2$ an upfield shift would be expected [38]).

Minor conformation of **2a** (Resonances of Set II). H–C(1) and H–C(3) appear both between 5.20 and 5.40 ppm as a poorly resolved *m* (Fig. 7). Such a value for the olefinic proton excludes conformations $\mathbf{A}_1$ and $\mathbf{A}_2$. Knowledge of the coupling between H–C(1) and the two H–C(2) would make distinction between conformations $\mathbf{B}_1$ and $\mathbf{B}_2$ possible. But even addition of the europium reagent and experiments at 270 MHz did

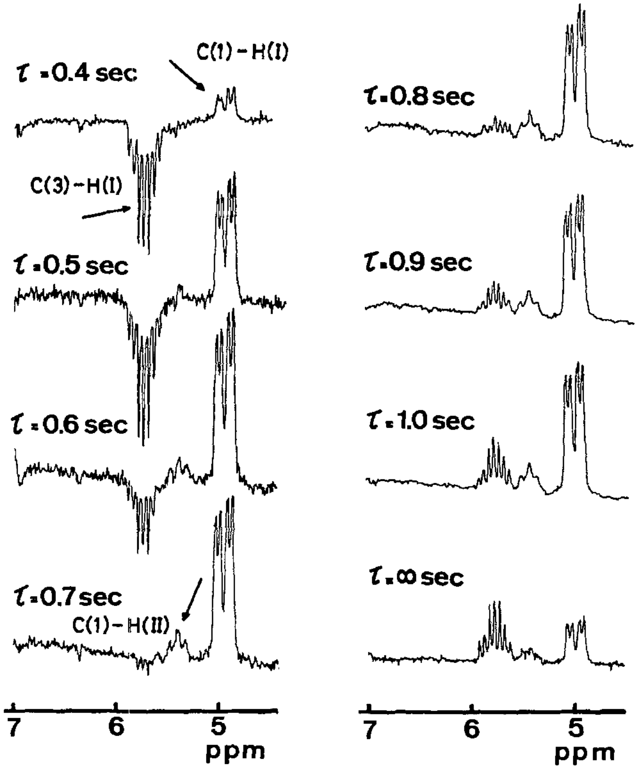

Fig. 10. *(180°–τ–90°)* ^{1}*H-NMR.* Fourier *transform spectra of* **2a** *in toluene.* Trace at $\tau = 0.7$ s shows well resolved triplet at 5.4 ppm assigned to H–C(1) of conformation II

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[11] Steroids with an acetoxy group in 3 position and no additional carbonyl group showed no similar shift.

not yield better resolution. One may all the same speculate on the conformation corresponding to this second set of resonances. The *m* of H–C(3) which couples with the four protons of the adjacent methylene groups must have a similar pattern in all the proposed conformations. The signals of the minor conformation above room temperature are broadened by slow exchange. The pattern of H–C(3) ('triplet of triplets') vanishes faster at elevated temperatures than the much simpler signal of H–C(1). The broadened *t* apparent in the insert of Fig. 7 should therefore be due to the resonance of H–C(1).

This assignment has been confirmed by (180°–τ–90°) FT. experiments [39], where the inverted (negative) signal relaxes towards a positive value as a function of the delay time τ. For the delay time τ_0 defined by the equation $T_1 = \tau_0/\ln 2$, where T_1 is the longitudinal relaxation time of the nucleus, the signal amplitude becomes zero. For nuclei in different chemical surroundings τ_0 usually is not the same. Two overlapping proton resonances may thus be resolved by setting $\tau = \tau_0$ for one of the protons if the two relaxation times are sufficiently different. Fig. 10 shows (180°–τ–90°) ^{1}H-NMR. spectra for a number of τ-values. The H-C(3) relaxes slower than the H–C(1) of set I. For a value of $\tau = 0.7$ s the H–C(3) multiplet is nearly zero and the H–C(1) of set I has relaxed to a positive signal. At this value of τ the multiplet (set II) at 5.4 ppm shows maximum resolution, indicating that the H–C(3) in both conformations have similar longitudinal relaxation times; the well resolved *t* is assigned to H–C(1) of set II. A *t* structure is not compatible with conformation $\mathbf{B}_1$ which should exhibit a similar *m* pattern for H–C(1) as in conformation $\mathbf{A}_1$ (*cf.* Table 7), but would be in agreement with conformation $\mathbf{B}_2$.

The theoretical (*Karplus*) sum of the *vicinal* coupling constants of conformation $\mathbf{B}_2$ (= 11.4 Hz) has to be compared with the experimental sum of 14 Hz. Steric interaction between the keto group in position 5 and $H_3C(19)$ might lead to a slight distortion of conformation $\mathbf{B}_2$, increasing both dihedral angles ϕ_1 and ϕ_2 (*cf.* Table 7). Such distortion would increase the smaller coupling constant J_2 much faster than it would decrease J_1. According to these arguments, *a* $\mathbf{B}_2$*-like conformation should make the main contribution to the set II of resonances.*

2.5. *Estimation of Activation Energy and Energy Difference of Conformations* $\mathbf{A}_1$ *and* $\mathbf{B}_2$. In order to determine the activation energy between the two plausible conformations of **2a** the temperature dependence of the ^{13}C-NMR. spectra was studied. As **2a** is not stable at higher temperatures, the study of the exchange is restricted to the slow and medium exchange region. Due to the ratio of the populations of the two conformations, $P_I/P_{II} = 6:1$, conformation $\mathbf{B}_2$ can be observed only in a narrow temperature range. The experimental data therefore do not allow more than a rough estimate of the activation energy. The equilibrium constant $K = P_I/P_{II}$ did not change between +30° and −30°. The estimated *Arrhenius* activation energy for II → I amounts to: $E_A = 12.7 \pm 3.0$ kcal/mol[12]).

According to the equilibrium constant $K = P_I/P_{II} = 6$, conformation $\mathbf{B}_2$ has a slightly higher energy than conformation $\mathbf{A}_1$. Assuming exchange between two isolated states, the energy difference would be about 1 kcal/mol.

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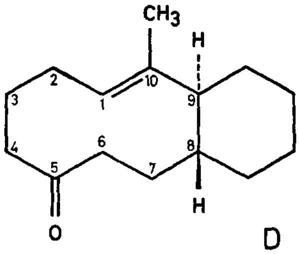
[12]) For the theory of exchange phenomena *cf.* [40]. In the slow exchange region the equation for the average lifetime τ_m of a particle in the conformation m was used: $\tau_m^{-1} = \pi \Delta\nu_m$ with $\Delta\nu_m$ = exchange broadening.



D

Fig. 11. *Partial structural model* **D**, *basis for force field calculations*

3. Conformational Force Field Calculations. For an energetical interpretation of the results of the NMR. and crystal structure analyses a number of conformational force field calculations was performed. Because of computational limitations, only a partial structural model **D** (Fig. 11) could be considered, which however comprises most features characteristic for the conformational problem.

(*E*)-Cyclodecene is known to possess a considerable number of energetically similar conformations [25] [41]. This might be expected also for **D** despite the influence of the fused and relatively rigid six-membered ring. For a rigorous conformational analysis of **D** it would have been desirable to take all conformations similar to those of (*E*)-cyclodecene [25] [41] [42] and to select the ones which allow the incorporation of the six-membered ring in the required fashion, *i.e.* those with a torsion angle τ (C(7)–C(8)–C(9)–C(10)) of about 60°. However, because of their approximate character we restricted the calculations to the four conformational types corresponding to $\mathbf{A}_1$, $\mathbf{A}_2$, $\mathbf{B}_1$ and $\mathbf{B}_2$.

The force field used for the calculations is that developed by *Ermer & Lifson* for nonconjugated olefins and saturated hydrocarbons [41]. Because no optimized force field parameters for the keto group are available it was approximated by the fictituous group $\genfrac{}{}{0pt}{}{\text{C}}{\text{C}}\!\!>\!\text{C=C}$ with a divalent C-atom substituting for the O-atom. The neglect of partial atomic charges for the polar $>$C=O group is justified, because in the course of the derivation of our force field charges were found unnecessary and omitted [41].

The conformation corresponding to $\mathbf{A}_2$ was calculated to possess the lowest enthalpy (vibrational contributions included). The ones corresponding to $\mathbf{A}_1$, $\mathbf{B}_1$ and $\mathbf{B}_2$ were less stable by 2.7, 3.0, and 4.0 kcal/mol, respectively. The preference of $\mathbf{A}_1$ and $\mathbf{B}_2$ in solution inferred from the NMR. analysis is thus not reproduced by our model force field calculations for gaseous **D**. Only the calculated relative enthalpies of the conformations corresponding to $\mathbf{A}_1$ and $\mathbf{B}_2$ agree with the NMR. data.

Fig. 12 gives a comparison of the calculated minimum energy geometry of our model compound **D** in the *crown* conformation corresponding to $\mathbf{A}_1$, and the geometry of the *p*-bromobenzoate **2b** as observed by X-ray. Even with a better energetical description of the carbonyl group and a calculation for a more complete molecular model we could not expect a very good agreement of the two geometries. Indeed, the flexibility of the ten-membered ring makes its geometry very sensitive to even small perturbations, *e.g.* substituent effects or crystal packing forces. A few tentative conclusions might nevertheless be drawn from Fig. 12. The average absolute deviation of the observed and calculated (C–C–C) angles is 1.8°, that of the (C–C–C–C) torsion

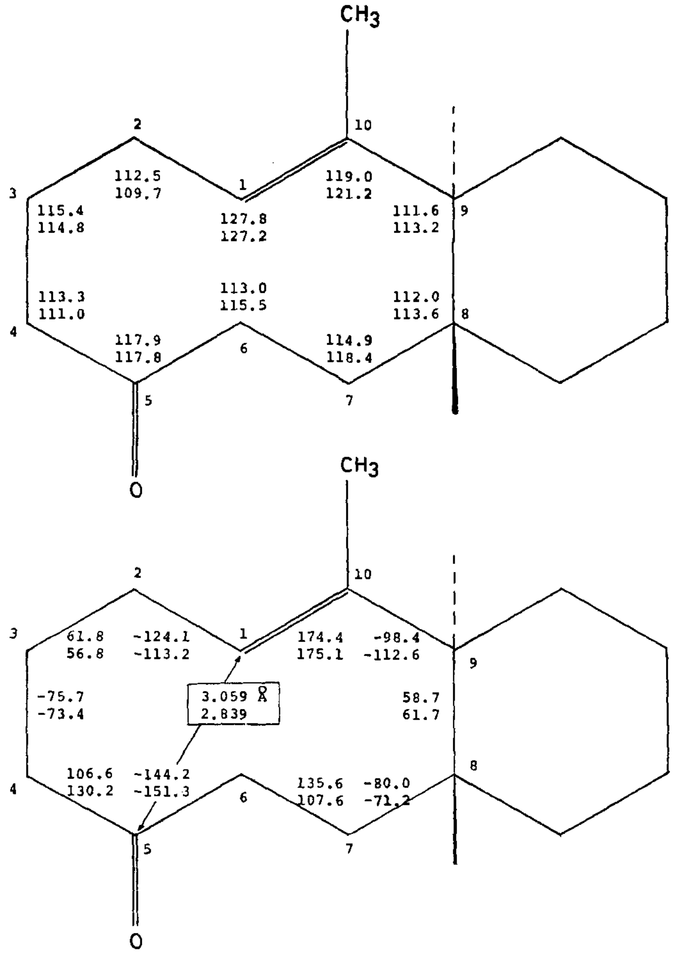


Fig. 12. *Calculated ring geometry of* **D** (*upper values*), *and observed geometry* (*X-ray*) *of the* p-*bromobenzoate* **2b** (*lower values*). Top formula: (C—C—C) angles; bottom formula: (C—C—C—C) torsion angles

angles 10.4°. The poor agreement of the torsion angles is largely due to the big discrepancies of the two torsion angles around C(4)–C(5) and C(6)–C(7) which essentially correspond to a rotation of the C(4)–C(5)–C(6)–C(7) segment around an axis through C(4) and C(7) in such a way as to increase the transannular distance C(1) ... C(5). The difference in the torsion angle around C(5)–C(6) affects this distance in the same way, while the differences in the torsion angles around C(1)–C(2) and C(9)–C(10) (which are also fairly large) correspond to a rotation of the segment C(2)–C(1)=C(10)–C(9) around the C(2)–C(9) axis so as to shorten the calculated distance C(1) ... C(5). The net result is that this distance is calculated to be longer by 0.22 Å than the one observed for **2b** (3.06 and 2.84 Å, respectively). The reason for these differences might well be sought in a transannular attraction of the C=O and C=C double bonds which is not represented in our force field. π-interactions of this type have been observed *e.g.* in (*E*)-cyclodec-5-enone [13] for analogous cases *cf.* [43]. Therefore one might expect an out-of-plane deformation of the C–CO–C group such that C(5) would move towards C(1). The observed deviation of C(5) from the plane defined by C(6), O, and C(4) is in the expected direction, although small (0.01 Å).

4. General Discussion. – In spite of predominantly negative predictions based on general stability considerations of simple cyclodecane and cyclodecene derivatives, as well as on approximative force field calculations (chap. 3), the *crown* conformation $\mathbf{A}_1$ was shown by X-ray analysis (chap. 1) to represent the ten-membered ring of **2b** in the crystal lattice. To some extent specific solid state phenomena such as crystal packing forces might be responsible for this preference.

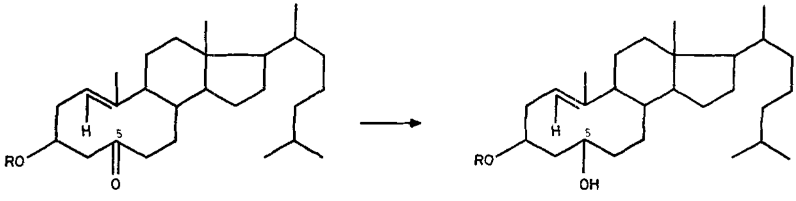
Considering the small energy differences between the various possible conformations, one would hesitate to apply the X-ray data of the cyclodecenone part of **2b** to describe its behaviour in solution. The results of the NMR. study of **2a** (chap. 2) showing that the predominant conformation in chloroform and toluene is *again* $\mathbf{A}_1$ are therefore of particular interest.

The conformation $\mathbf{B}_2$, postulated for the minor component of **2a** in solution, represents according to calculations the least stable of the discussed set of four. The relative rigidity of the system (attachment to ring *C* and the predominantly equatorially oriented substituent at C(3)), and the transannular electronic interaction between the double bond and the carbonyl group could eventually account for the higher than expected stability of $\mathbf{B}_2$.

One can now try to correlate the two deduced conformations with the stereochemical course of different chemical transformations described for compounds of type **2**[13]), at the risk of such contemplation being somewhat speculative.

4.1. *Reduction of the 5-Oxo Group* [10]. **2a** and the corresponding free alcohol **2c** are reduced by sodium borohydride (in dioxane/methanol or 2-propanol) and lithium aluminium hydride (in diethyl ether) to only one of the two possible isomeric 5-hydroxy compounds **5a** and **5c**, respectively (*Scheme 2*). The (5*S*) configuration has been tentatively assigned to both **5a** and **5c** [44].

Scheme 2



2a R = Ac
2c R = H

5a R = Ac
5c R = H

In the two conformations $\mathbf{A}_1$ and $\mathbf{B}_2$ postulated for the acetate **2a** in solution, a preferential attack at the carbonyl C(5)-atom from the less hindered front side can be

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[13]) For preliminary discussions *cf.* [8] and [10].

expected (*cf.* Fig. 13). Consequently the (5*S*)-alcohol of type **5** should be formed in both cases.

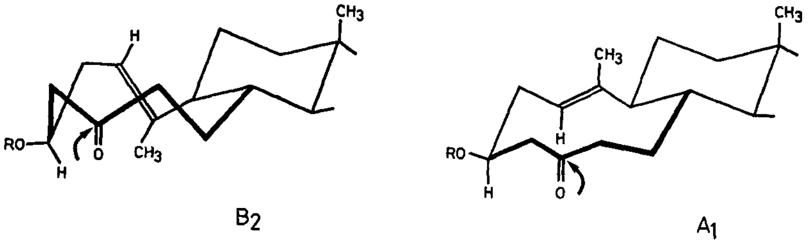
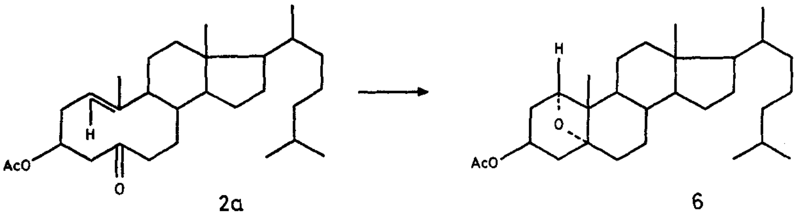


Fig. 13

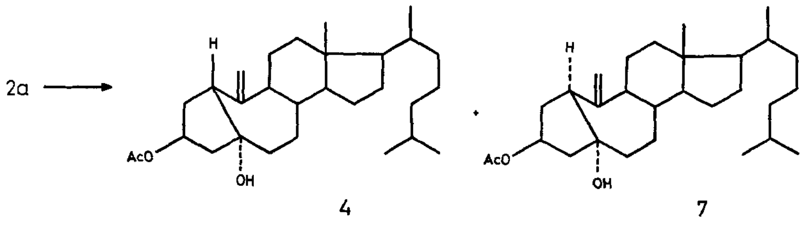
4.2. *Intramolecular* Paterno-Büchi *Reaction* [9]. UV.-irradiation of **2a** in dioxane yields a mixture of cyclized compounds, from which the crystalline oxetane **6** (*Scheme 3*) has been isolated as the major component[14]. A conformation corresponding to a slightly distorted variant of $\mathbf{A_1}$ could explain the formation of a compound exhibiting the natural steroid skeleton (= **6**), if a 'stereochemical memory' for the intermediate diradical species is postulated.

Scheme 3



4.3. *Acid Catalysed Cyclization* [6]. Under the influence of acids, **2a** is cyclized to a 9:1 mixture of the two isomeric compounds **4** and **7** (*Scheme 4*). As has been stressed in [8], the *trans*-compound **4** can be stereochemically correlated with $\mathbf{B_2}$ and the *cis*-isomer **7** with $\mathbf{A_1}$.

Scheme 4



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[14] Better results are obtained in acetone (unpublished experiments of *Lj. Lorenc*).

4.4. *Thermal Cyclization* [8]. As mentioned before (chap. 2) **2a** is readily cyclize to **4** (*Scheme 1*), already by moderate heating of its solutions. An intramolecula synchronous (symmetry allowed) process (*cf.* Fig. 14) can only be formulated if **B** is the involved conformation.

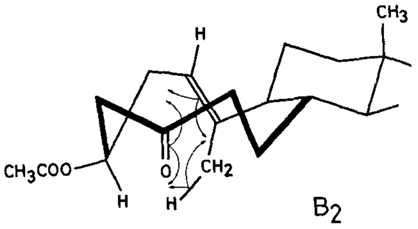
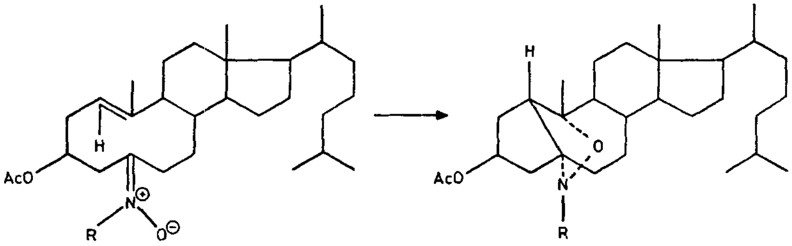


Fig. 14.

4.5. *1,3 Dipolar Additions* [45] [6]. Finally there has to be mentioned the therma cyclization of nitrones of type **8** to isoxazolidines **9** (*Scheme 5*). In this case again onl a distorted conformation of type **B$_2$** can explain the stereochemical course of th 1,3 dipolar addition.

Scheme 5



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