^1H–^1H Long range couplings in fused cyclopropanes. NMR spectral assignment and conformation of 17,18-cyclosteroids

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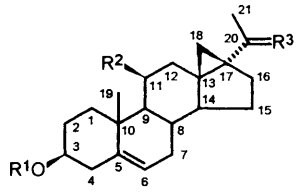
^1H–^1H NMR couplings through four bonds ($^4J_{H-H}$) involving cyclopropane hydrogens were calculated for model compounds by semiempirical methods and used for the ^{13}C and ^1H NMR spectral assignment of 17,18-cyclosteroids. The couplings ($^4J_{HH}$) between cyclopropyl and non-cyclopropyl hydrogens follow an angular dependence which resembles that of allylic couplings. Solution conformations of rings C-D and the side-chain of 17,18-cyclopregnanes were determined from semiempirical molecular orbital calculations, three and four bond ^1H–^1H coupling constants and NOE measurements.

The introduction of cyclopropane rings on steroid structures has been used extensively for enhancing or modifying biopharmacological activities of natural and synthetic compounds.[1] In certain aspects, cyclopropane rings may mimic double bonds, *e.g.* altering the polarization of neighbouring carbonyl groups by conjugation with the advantage of a diminished reactivity towards addition reactions and with different conformational requirements (conjugation requires a bisected conformation between the σ and π systems instead of the coplanar relationship needed for two π systems).[2] Cyclopropane rings, either as spiro or fused substituents, may also induce conformational changes in neighbouring rings and/or lock certain conformations.[3]

Kirk and Rajagopalan[4] isolated 17,18-cyclosteroids as byproducts in the hydrolysis of 18-iodo-20-ketopregnanes. The strain introduced in these systems by the fused three membered ring acts as a spring loaded mechanism to activate C(13)–C(17) bond cleavage and as such they have been proposed as biosynthetic intermediates in the pathway leading to ring D aromatic withanolides in plants.[5] In a previous publication, this reactivity of 17,18-cyclopregnanes was exploited using them as synthetic precursors of 17(13→18)-*abeo*pregnanes.[6]

From the structural point of view, these compounds are characterized by an extremely rigid molecular framework due to the combination of three fused rings of six, five and three members sharing a common carbon atom (C-13), which leads to a well defined arrangement of the hydrogen atoms and the steroid side-chain. It is interesting to accurately characterize this arrangement and to obtain information regarding bond strength and extent of conjugation with a 20-keto group, which could help in taking better advantage of the subjacent reactivity in these systems. In this publication the solution conformation of two 20-keto-17,18-cyclopregnanes (**1**, **2**) and a 20-hydroxy-17,18-cyclopregnane (**3**) are studied using NMR data as well as semiempirical calculations. Due to the fact that several of the carbons involved had no hydrogens, the use of vicinal coupling constants that may be related to dihedral angles by the Altona equation[7] was of limited help. However ^1H–^1H long range couplings involving the cyclopropyl hydrogens were clearly observed, and could be measured (or estimated) by means of 2D NMR methods. Although no empirical equations are available for relating these coupling constants to geometrical parameters, they may be calculated theoretically within the framework of molecular orbital theory.[8] In a recent publication the NMR data and ring A conformation of several cyclosteroids and



1 R1 = Ac, R2 = H, R3 = O
2 R1 = H, R2 = OH, R3 = O
3 R1 = Ac, R2 = H, R3 = H,OH

cyclopropanosteroids have been described, however no information was provided with respect to long range couplings of cyclopropyl hydrogens.[9]

Results and discussion

Assignment of ^1H and ^{13}C NMR spectra

In order to analyse the ^1H–^1H coupling data, full ^1H and ^{13}C NMR spectral assignments were required for all compounds and are shown in Tables 1 and 2 respectively. This was accomplished by a combination of 1D and 2D methods as suggested by several authors.[10] The basic strategy was to measure the ^{13}C NMR and DEPT spectrum and assign as many resonances as possible. This can be done with relative ease with the exception of a few carbons, by analogy with related compounds. The next step was to measure the HETCOSY spectrum with ^1H–^1H decoupling to obtain the individual chemical shifts of the hydrogens, particularly those appearing in the heavily overlapped region between 0.8 and 2.4 ppm. Assignments were then verified with the correlations found in COSY-45 and DQF-COSY spectra and corrected when needed. Finally, vicinal ^1H–^1H couplings were measured from the normal ^1H NMR spectrum and the phase sensitive DQF-COSY. As the ^1H resonances involved lie largely in the region between 0.8 and 2.4 ppm, most of these data were obtained from the cross peaks of the phase sensitive DQF-COSY spectra. It should be noted that despite the heavy overlap of signals in the region mentioned above, at 200 MHz the coupled hydrogens analysed have $\Delta\nu/J$ larger than 4 (in most cases larger than 6); this allows the direct use of couplings measured from DQF-COSY spectra without corrections.[10b]

The data thus obtained were used to assign axial and

Table 1 ^{1}H chemical shifts (in ppm downfield from Me_4Si) and geminal couplings (absolute values in Hz) for compounds **1**–**3** in deuterochloroform

	1		**2**		**3**	
H	δ	$^2J_{HH}$	δ	$^2J_{HH}$	δ	$^2J_{HH}$
1α	1.18	nd	1.13	13.3	1.16	13.7
1β	1.93		2.06		1.91	
2α	1.90	15.0	1.85	12.8	1.88	11.7
2β	1.61		1.59		1.63	
3β	4.64		3.51		4.64	
4α	2.41	nd	2.36	nd	2.33	nd
4β	2.30		2.29		2.33	
6	5.38		5.38		5.38	
7α	1.67	17.0	1.69	18.7	1.62	19.5
7β	2.08		2.24		2.08	
8β	1.31		1.78		1.25	
9α	1.12		1.11		1.10	
11α	1.89	13.2	4.45		1.86	15.6
11β	1.35		—		1.64	
12α	1.56	nd	1.74	13.5	1.79	11.7
12β	1.76		1.97		1.43	
14α	1.57		1.58		1.51	
15α	1.74	11.6	1.76	12.2	1.61	11.7
15β	0.84		0.90		0.71	
16α	2.20	11.6	2.21	12.7	1.72	13.6
16β	1.96		2.00		1.29	
18*endo*	1.24	4.6	1.43	4.0	0.54	4.5
18*exo*	0.95		1.14		−0.08	
19	1.03		1.24		0.99	
20	—		—		3.55	
21	2.20		2.19		1.27	
Acetate	2.06		—		2.02	

nd: not detected.

Table 2 ^{13}C chemical shifts for compounds **1**–**3** in deuterochloroform (in ppm downfield from Me_4Si)

C	**1**[a]	**2**	**3**[b]
1	37.1	37.4	37.2
2	27.8	31.4	27.9
3	73.8	71.3	74.0
4	38.1	41.4	38.2
5	139.5	141.1	139.5
6	121.9	120.1	122.4
7	31.6	31.7	31.6
8	36.8	31.1	36.4
9	49.9	53.9	50.3
10	36.7	36.6	36.7
11	26.1	68.3	25.5
12	29.3	37.9	30.3
13	43.1	38.4	35.3
14	50.3	51.9	50.9
15	24.7	24.0	23.9
16	29.2	29.0	25.6
17	46.1	40.9	37.1
18	19.1	19.9	14.7
19	19.5	21.9	19.5
20	207.5	207.8	71.2
21	28.8	28.8	20.7

[a] C-3 acetate: 21.5 and 170.3 ppm. [b] C-3 acetate: 21.4 and 170.6 ppm.

equatorial hydrogens and to corroborate the above assignments. Assignment of the individual hydrogens at C-18 as *exo* and *endo*, was not possible by the above methods. For compounds **1** and **2**, NOESY spectra did not show conclusive evidence, as the expected correlations for the pairs 18*endo*-H/15β-H, 18*endo*-H/16β-H and 18*exo*-H/12β-H were partially or totally obscured by other trivial correlations (*e.g.* 1α-H/1β-H). Hence a different approach was followed in this case (see below). In particular, in the case of compound **1**, differentiation of the pairs C-9/C-14 and C-12/C-16 is not straightforward due to their similar chemical shifts. However, in the 11β-hydroxy derivative **2**, the 9α-H may be easily assigned to the resonance at 1.11 ppm (from its correlation with H-11α in the COSY spectrum) leaving H-14 at 1.58 ppm; these ^{1}H resonances are almost unaffected by the 11β-hydroxy group and have almost the same chemical shifts in compound **1**. In a similar way, comparison of the ^{13}C NMR spectra of **1** and **2** shows a pronounced downfield shift of the C-12 signal in the latter compound, leaving the C-16 resonance almost unchanged; the C-16 signal is clearly distinguishable by the chemical shifts of the attached hydrogens which remain unchanged and well differentiated from the hydrogens at position 12 in both compounds.

Table 3 Relevant NOESY correlations for cyclopropylalcohol **3**

H	Correlates with H	H–H distance[a]/Å
12β (1.43 ppm)	18-*exo* (−0.08 ppm)	2.50
15β (0.71 ppm)	18-*endo* (0.54 ppm)	2.40
16β (1.29 ppm)	18-*endo* (0.54 ppm)	2.76
20 (3.55 ppm)	18-*exo* (−0.08 ppm)	2.65[b]

[a] From AM1 calculations. [b] In conformer 1 (Table 4).

Table 4 Relative energies of the rotamers around the C(17)–C(20) bond for compounds **1**–**3** from AM1 calculations

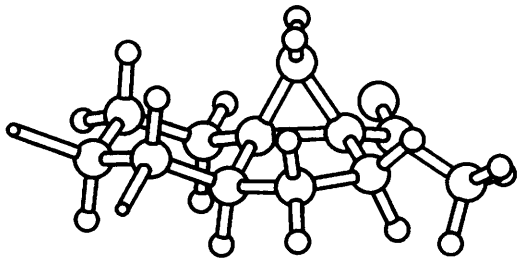
Comp.	Conformer	C(16)–C(17)–C(20)–O(20) (deg)	Relative energy (kcal mol^{-1})[a]
1	1	30.7	0.491
	2	−177.8	0.000
	3	−5.0	1.017
2	1	31.7	0.164
	2	179.8	0.000
	3	−4.1	0.758
3	1	46.3	0.950
	2	−157.1	0.000
	3	−68.7	0.990

[a] 1 cal = 4.184 J.

To study the conjugation effect of the C-20 carbonyl on the chemical shifts of the cyclopropyl hydrogens and carbons, ketone **1** was reduced with sodium borohydride to the alcohol **3**. Stereochemistry at C-20 of the major product was assigned as *R*, according to the recent work of Lautens and Delanghe.[11] In the case of alcohol **3**, difficulties arose in the NMR spectra (Tables 1 and 2), with the carbons and hydrogens at positions 12, 15 and 16 which could not be unambiguously assigned by the procedures outlined above (assignment of C-9 and C-14 was based on the corresponding ^{1}H chemical shifts by comparison with **1** and **2**). However, the NOESY spectra allowed the assignment of both hydrogens at position 18. The relevant observed correlations are presented in Table 3 together with the calculated distances between the hydrogen pairs (AM1). The NOE correlation between H-18 at −0.08 ppm and H-20, provided conclusive evidence to assign that resonance to the 18-*exo* hydrogen. The H-18 resonating at lower field (0.54 ppm) had NOE correlations with H-15 and H-16. Final assignment of these nuclei and of the 18*exo*-H and 18*endo*-H in all compounds was confirmed by analysing the long range couplings between the cyclopropyl hydrogens at C-18 and the hydrogens at positions 12, 14, 16 and 20, the latter for compound **3** (see below).

Molecular orbital calculations

The molecular modelling studies were carried out using the AM1 semiempirical method (AMPAC 5.0, Semichem, USA). Only minor differences were observed in the optimized geometries when the PM3 method was used. Calculations on the three 17,18-cyclopregnanes (**1**–**3**), showed that the cyclopropyl ring plane forms a *ca.* 120° angle with the



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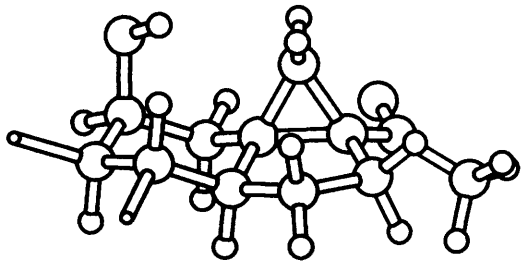

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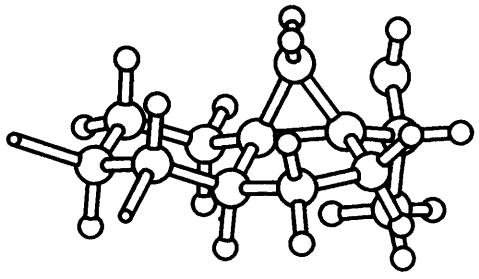

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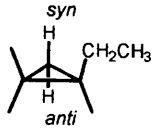
Fig. 1 Ball and stick representation of the most stable conformations of rings C, D, cyclopropane and side chain of compounds **1–3** (conformer 2 in Table 4), as predicted by AM1 calculations (AMPAC 5.0)

cyclopentane ring plane, and that the latter is distorted from its normal 13β,14α-half chair conformation to a 15β-envelope (Fig. 1). Three rotamers around the C(17)–C(20) bond are obtained for each compound within the AM1 calculations; in the 20-keto derivatives (**1**, **2**) the lowest energy corresponds as expected to the one with the C=O bond bisecting the C(13)–C(18) bond (Table 4). It is noteworthy that in compound **2**, the 11β-hydroxy substituent renders a conspicuous destabilizing effect on the preferential rotamer, probably owing to a through-space interaction. In the preferred conformations the C(17)–C(20) bond is slightly shortened as compared with the other two rotamers, and a concomitant lengthening of the carbonyl C=O bond is observed. This result supports the assumption quoted above on the role played by conjugation with the cyclopropane ring. An interaction that could also be important in defining the preferred conformation is a throughspace interaction between the carbonyl C=O bond and the highly polarizable cyclopropane C–C bonds which should be similar to that recently described in a different type of compound.[12] The latter possibility is strongly supported upon comparison of the energies of the three rotamers of alcohol **3**, where despite the essentially non-existent conjugative effect, the energy of the preferred conformation (which allows through-space interaction between the C–O bond and the cyclopropane C–C bond) is notably lower.

Further, in all three rotamers of each compound (**1–3**) the C(13)–C(17) optimized bond length is slightly larger than the C–C bond length in an isolated cyclopropane (*e.g.* **4**). This trend



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is in line with the strain introduced by the fusion of the three and five membered rings which drives the spring loaded mechanism to activate C(13)–C(17) bond cleavage.[5,6]

^1H–^1H spin–spin coupling constants were calculated for rings C, D and cyclopropane using the following approaches: vicinal couplings were calculated using the Altona equation[7] on the AM1 optimized structures for 20-keto derivatives **1** and **2**. Values thus obtained are shown in Table 5 compared with the experimental data. A fair agreement is observed for most couplings; the differences in the predicted and experimental 15-H,16-H couplings in both steroids may originate in different phenomena (or a combination of them), namely, (*i*) a slight distortion of that part of the D ring with respect to the AM1 geometry; (*ii*) existence of a 'mobile' part of the molecule involving C-15 and C-16; (*iii*) proximity effects either with the methylene-18 bridge or with the side-chain methyl, similar to those defining notably different *exo–exo* and *endo–endo* couplings in norbornane.[13] The marked increase in $J_{15\beta,16\alpha}$ when going from **1** to **2**, supports this possibility.

Long range couplings were calculated within the molecular orbital framework using three different semiempirical ground state wavefunctions and the Fermi contact term was calculated using the polarization propagator approach at the RPA level,[14] namely, RPA-INDO,[8a] RPA-MNDO[8b] and RPA-AM1.[8c] Although they are not explicitly shown in this work, RPA-INDO and RPA-MNDO couplings involving either the *exo*- or *endo*-H atoms of the cyclopropane ring, are in poorer agreement with experimental values than those obtained with the RPA-AM1 method. Coupling constants' calculations were carried out as follows: starting from the fully optimized AM1 geometries of **1–3**, simplified model compounds were built by deletion of carbons C-1 to C-6 and C-19, and their attachments; methylene-7 and C-10 were then replaced by hydrogen atoms with the corresponding C–H bond lengths taken from the standard geometrical model.[15] This simplification was required due to limitations in the number of atoms that may be handled by the program (*ca.* 30). The couplings involving the cyclopropyl hydrogens are shown in Table 6 and they correspond in each case to the rotamer with the preferred conformation (see Table 4 and Fig. 1). No substantial differences were found for couplings calculated in the different rotamers.

Long range couplings of cyclopropyl hydrogens

Several strong correlations involving the cyclopropyl hydrogens were observed in the DQF-COSY spectra of compounds **1–3**. Weaker correlations corresponding to smaller couplings (*ca.* 1 Hz) could be observed with the delayed COSY technique (Table 6).[16]

The spatial relationships between the hydrogen pairs which present significant four-bond couplings, do not correspond to the usual W-type arrangement found in systems with 'normal' sp^3 carbon atoms, but instead closely resemble the relationship found in allylic systems.[17] Thus the C(17)–C(18) bond mimics a double bond with its plane perpendicular to the cyclopropane ring. This is in agreement with the requirements for conjugation of a cyclopropane and a π system when compared to conjugation between two π systems.[2] For the discussion that follows the cyclopropane bond plane denotes a plane containing the cyclopropane bond and perpendicular to the cyclopropyl ring plane.

In order to study the angular dependence of $^4J_{HH}$ couplings

Table 5 Observed and calculated[7] three-bond ^1H–^1H coupling constants (in Hz) for rings C and D of compounds **1** and **2**

	1			**2**		
H,H	Angle[a] (deg)	$^3J_{HH}$(calc.)	$^3J_{HH}$(obs.)	Angle[a] (deg)	$^3J_{HH}$(calc.)	$^3J_{HH}$(obs.)
8β,9α	−178.5	12.1	11.0	179.3	12.6	11.3
8β,14α	178.2	12.1	11.0	−178.3	12.1	10.3
9α,11α	60.1	3.2	no	59.5	1.7	2.5
9α,11β	178.2	11.8	13.2	—	—	—
11α,12α	−57.2	3.6	no	−54.6	2.6	2.6
11α,12β	61.1	2.8	no	63.5	4.5	3.6
11β,12α	−174.1	13.2	13.2	—	—	—
11β,12β	−55.8	3.7	3.6	—	—	—
14α,15α	−35.1	7.1	7.0	−34.4	7.2	7.2
14α,15β	−154.9	10.2	11.6	−154.1	10.1	10.3
15α,16α	25.9	9.2	7.0	25.5	9.2	7.2
15α,16β	−94.6	0.9	< 1	−94.8	0.9	< 1
15β,16α	145.7	9.3	8.0	145.3	9.2	11.5
15β,16β	25.2	9.2	7.7	24.9	9.3	7.8

no: not observed. [a] Geometrical data for conformer 2 (Table 4) from AM1 calculations.

Table 6 Observed (absolute value) and calculated (RPA-AMI)[8c] four-bond ^1H–^1H coupling constants (Hz) for cyclopropyl hydrogens of compounds **1**–**3**

	1			**2**			**3**		
H,H	Angle[a] (deg)	$^4J_{HH}$(calc)	$^4J_{HH}$(obs)[b]	Angle[a] (deg)	$^4J_{HH}$(calc)	$^4J_{HH}$(obs)[b]	Angle[a] (deg)	$^4J_{HH}$(calc)	$^4J_{HH}$(obs)[b]
18*exo*,12α	130.6	−2.35	1.6	130.8	−2.39	2.0	132.4	−2.43	1.9
18*exo*,12β	19.7	−0.40	no	19.3	−0.38	*c*	21.3	−0.43	no
18*exo*,14α	64.5	−1.24	*c*	64.9	−1.26	lr	66.6	−1.21	lr
18*exo*,16α	−54.5	−0.59	no	−54.0	−0.64	no	−52.5	−0.70	no
18*exo*,16β	77.8	−1.01	lr	78.1	−1.03	*c*	78.3	−1.13	lr
18*endo*,12α	−107.6	−1.04	*c*	−107.5	−1.07	lr	−107.6	−1.10	lr
18*endo*,12β	141.5	−0.87	no	141.1	−0.86	no	141.3	−0.85	no
18*endo*,14α	−162.9	−2.14	*c*	−162.4	−2.14	lr	−163.7	−2.18	lr
18*endo*,16α	178.7	−1.92	2.0	179.0	−1.94	2.0	−179.7	−1.96	1.9
18*endo*,16β	−49.0	−0.12	no	−48.9	−0.18	no	−49.0	−0.23	no

no: not observed. lr: correlation observed only in delayed COSY experiment (J < 1.5 Hz). [a] Improper torsion angles in conformer 2 (Table 4) defined as H(18)–C(18)···C(*n*)–H(*n*). [b] Couplings measured in cross peaks of DQF-COSY spectrum; absolute values are given. [c] Partially overlapped correlations in delayed COSY experiment.

involving a cyclopropyl and an exocyclic hydrogen, RPA-AM1 calculations were carried out in model compound **4**. Starting from the AM1 optimized geometry, other structures were obtained through rigid rotations of the ethyl group around the C_{cyclo}–CH_2 bond. Calculated couplings are presented in Fig. 2. The spatial relationship between *anti* and exocyclic methylene hydrogens is analogous to that analysed for allylic systems,[17] and the results obtained predict minima which are only slightly shifted with respect to the latter system [Fig. 2(*b*)].

The predicted shifts in the position of the $^4J_{HH}$ minima in Fig. 2 may be related to the fact that cyclopropyl hydrogens lie towards one side of the cyclopropane bond plane. No data are available for the angular dependence of $^4J_{HH}$ of the *syn*-H in allylic systems, however the calculations described and experimental results for the cyclopropane case, show a similar angular dependence for the *syn*-H although with larger observed (and predicted) absolute $^4J_{HH}$ values [Fig. 2(*a*)]. The asymmetry observed in the curves in Fig. 2 for angles smaller and larger than 180° is a result of the cyclopropane bond not being symmetric with respect to the bond plane defined above. The most pronounced minimum corresponds to the exocyclic H being on the same side as the rest of the cyclopropane ring.

The above calculations indicate that significant couplings should be observed for the pairs 18*exo*-H/12α-H and 18*endo*-H/16α-H. The experimental data from the DQF COSY spectra indicate that these couplings are *ca.* 2 Hz and allow the assignment of the individual signals of H-18 *exo* and *endo* with the latter being the most deshielded in all cases. The couplings observed for alcohol **3** also allowed the unambiguous assignment of 12α-H/12β-H (from the observed coupling to 18*exo*-H), C-15/C-16 and 16α-H/16β-H (observed coupling to 18*endo*-H) in agreement with the observed NOESY correlations. The predicted couplings between both hydrogens at position 18 and 14-H could not be measured in the DQF-COSY spectra and only weak correlations were observed in the delayed COSY spectra for the pair 18*endo*-H/14-H which corresponds with the larger coupling predicted by the theoretical calculations. This would indicate that, as already mentioned, the AM1 predicted geometry may be slightly distorted with respect to the C15–C16 portion of the molecule.

Conclusions

Four bond couplings between cyclopropyl and exocyclic hydrogens can be predicted by theoretical methods at the RPA-AM1 level with reasonable accuracy and their angular dependence used for spectral and stereochemical assignments. This may lead to the future development of Karplus type equations for these systems if enough experimental data becomes available. The theoretically derived curves in Fig. 2 may be used as a first approximation in this respect.

Experimental

Molecular orbital calculations were carried out on Sun Sparcstation 10 and Sparcstation 20 computers. ^1H and ^{13}C

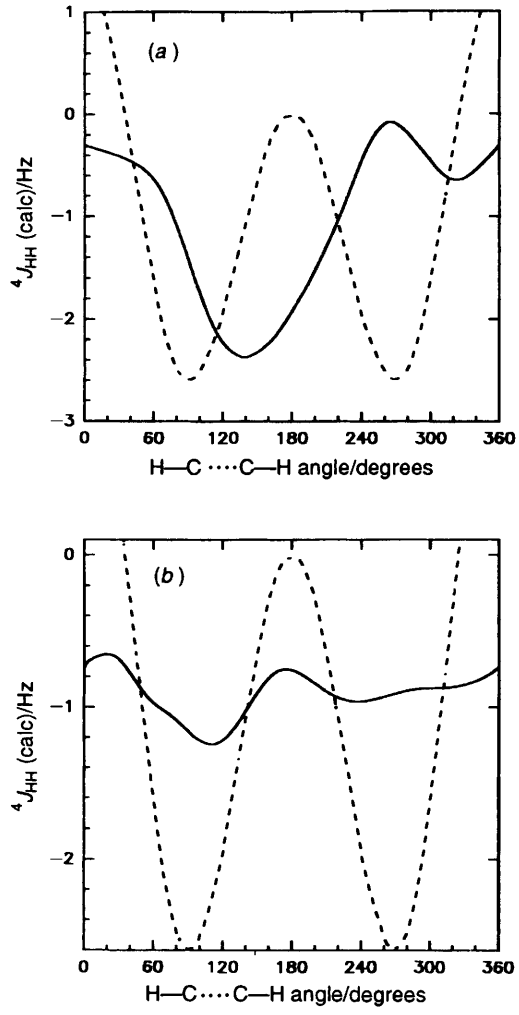

Fig. 2 Theoretically calculated (RPA-AM1) angular dependence of $^4J_{HH}$ between the exocyclic CH_2 and *syn* (*a*) and *anti* (*b*) cyclopropyl hydrogens in alkylcyclopropane **4**. The dotted line corresponds to the coupling in allylic systems according to Garbisch.[17]

NMR spectra were measured at 200.13 and 50.32 MHz respectively in a Bruker AC-200 NMR spectrometer in deuteriochloroform (with tetramethylsilane as internal standard) using standard Bruker software. All spectra were recorded at 303 K. Typical conditions for ^{13}C NMR spectra were 20 000 transients, 16 K data points, 4.4 μs pulses (45° flip angle), 11 000 Hz spectral width, 0.74 s aquisition time. An exponential multiplication (LB = 1.0 Hz) was applied to improve peak shape. For ^1H NMR spectra a 3000 Hz spectral width was used and a 2.2 s aquisition time with a 16 K data table.

The double quantum filtered COSY spectra (DQF-COSY) were measured in the phase sensitive mode (TPPI) with the Bruker standard pulse sequence. A total of 512 data points for the t_1 dimension and 2048 data points for the t_2 dimension were used over a 1000 Hz spectral width. The t_1 dimension was zero-filled to 1 K, Lorentzian–Gaussian multiplication was used on t_2 and unshifted squared sine-bell on t_1, before Fourier transformation. Digital resolution in the transformed spectra was 0.98 Hz/pt. Spectra were not symmetrized.

The delayed COSY-45 experiments were recorded in the absolute value mode with a standard pulse sequence[16] and a 0.125 s delay. A total of 256 data points for the t_1 dimension and 1024 data points for the t_2 dimension were used. The FIDs were Fourier transformed on a 1 K × 1 K data matrix using unshifted sine-bell window functions in both dimensions. Transformed spectra were symmetrized.

NOESY spectra were measured in the phase sensitive mode (TPPI) with the standard Bruker sequence and a 1.0 s mixing time. A total of 256 data points for the t_1 dimension and 1024 data points for the t_2 dimension were used. The FIDs were Fourier transformed on a 1 K × 1 K data matrix using exponential window functions in both dimensions. Transformed spectra were symmetrized after phasing. Phasing was performed in such a way that diagonal signals were pure positive absorption and positive NOE crosspeaks were pure negative absorption peaks. Correlations *via* spin–spin couplings (dispersive signals) were not observed.

^1H–^{13}C shift correlation spectra (HETCOSY) were measured in the absolute value mode with ^1H–^1H decoupling in F_1 with the standard Bruker sequence. A total of 256 data points for the t_1 dimension (1000 Hz spectral width) and 2048 data points for the t_2 dimension (5500 Hz spectral width) were used. The FIDs were Fourier transformed on a 1 K × 2 K data matrix using shifted squared sine-bell window functions in both dimensions.

3β-Acetoxy-17,18-cyclopregn-5-en-20-one (**1**) and 3β,11β-dihydroxy-17,18-cyclopregn-5-en-20-one (**2**) were prepared from pregnenolone acetate and the 11β-hydroxy derivative respectively *via* the corresponding 18-iodo-20-ketopregnanes.[6]

3β-Acetoxy-20β-hydroxy-17,18-cyclopregn-5-ene 3

Ketone **1** (0.209 g) was dissolved in dry methanol (20 cm^3), cooled to 0 °C and sodium borohydride (0.120 g, 3.2 mmol) added. The reaction mixture was stirred at 0 °C for 1 h, acidified (pH 5–6) with hydrochloric acid (1 mol dm^{-3}), and then neutralized with 10% aqueous sodium hydrogen carbonate. The solution was concentrated under reduced pressure to a volume of 6 cm^3, diluted with water and extracted with dichloromethane. Evaporation of the solvent followed by flash chromatography on silica gel with hexane-ethyl acetate 8:2 as eluent afforded *alcohol* **3** (0.164 g, 78%) homogeneous by TLC; mp 132–136 °C (from EtOAc-hexane); *m/z* (EI) 340 ($M^+ - H_2O$, 0.5%), 298 (M − HOAc, 47), 280 (M − HOAc − H_2O, 15), 265 (9), 253 (34), 147 (25), 133 (37), 119 (20), 105 (40), 91 (55) and 43 (100).

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