Carbohydrate Research, 204 (1990) 11–25
Elsevier Science Publishers B.V., Amsterdam

Determination of the *gauche* effect of 3-acetamido- and 3-acetoxy-piperidine and -tetrahydropyran by ^{1}H-n.m.r. spectroscopy*

Bruno Bernet†, Umberto Piantini, and Andrea Vasella†
Organisch-Chemisches Institut der Universität Zürich, Winterthurerstr. 190, CH-8057 Zürich (Switzerland)

(Received September 22nd, 1989; accepted for publication, December 6th, 1989)

ABSTRACT

The A-values of the acetamido and the acetoxy group were determined by low-temperature ^{1}H-n.m.r. spectroscopy. The limiting values for the relevant vicinal coupling constants of the newly prepared *trans*- (**22**) and *cis*-5-acetoxy-2-(1-hydroxy-1-methylethyl)tetrahydropyran (**24**) were obtained at room temperature. The attractive *gauche* effect of AcNH-3 and AcO-3 in piperidines, piperidinium trifluoroacetates, and tetrahydropyrans was investigated by ^{1}H-n.m.r. spectroscopy both at low temperature (integrals) and at room temperature (band widths and coupling constants). The results obtained at low temperature are more reliable. The position of the conformational equilibrium of *N*-(3-piperidyl)acetamide (**11**), *N*-(1-methyl-3-piperidyl)acetamide (**12**), and *N*-(tetrahydropyran-3-yl)acetamide (**17**) [but not of 3-acetoxy-1-methylpiperidine (**8**) and 3-acetoxytetrahydropyran (**15**)] depends strongly upon the nature of the solvent and, in apolar solvents, upon the concentration.

INTRODUCTION

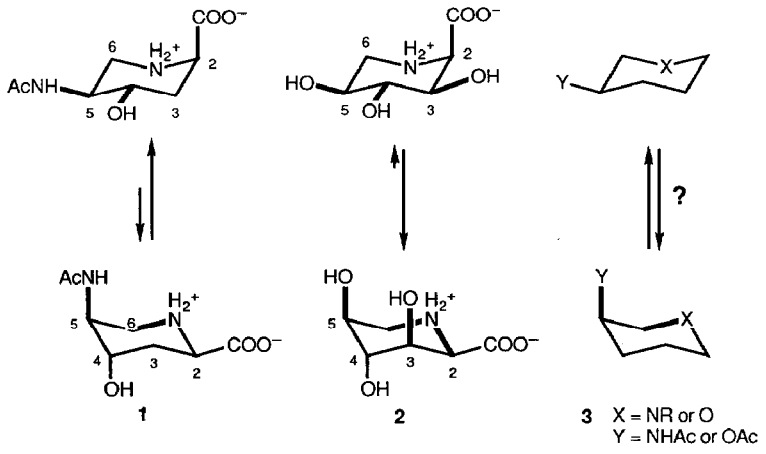
The large coupling constants ($J_{3a,4}$ 8.5, $J_{4,5} = J_{5,6a}$ = 8.0 Hz) in the ^{1}H-n.m.r. spectrum of the weak competitive inhibitor **1** of bacterial sialidases revealed a 2:1 equilibrium between the $^2C_5$ and $^5C_2$ conformers[1]. In contrast, the trihydroxypipecolic acid **2** is characterized by small coupling constants ($J_{2,3}$ 2.5, $J_{5,6}$ 2.7, and $J_{5,6'}$ 2.6 Hz) which indicate a clear preference for the $^5C_2$ conformation[2]. This situation may be rationalized by the preferred equatorial arrangement of the carboxy group in pipecolic acids[3] and by *gauche* effects[4–10]. In **2**, each chair conformer exhibits two attractive *gauche* effects (indicated with bold lines in **1–3**). Thus, the position of the conformational equilibrium of **2** is determined mainly by the carboxy group. In **1**, each chair conformer shows one attractive *gauche* effect ($^2C_5$: C-4-OH and C-5-NHAc; $^5C_2$: C-6-$\overset{+}{N}H_2R$ and C-5-NHAc). The position of the conformational equilibrium of **1**, favouring the $^2C_5$ (axial carboxy group) over the $^5C_2$ (equatorial carboxy group) conformer, raises the question of the relative importance of these *gauche* effects.

It is not known if the *gauche* effect between the acetamido group and C–N or C–O

* Presented at EUROCARB V, the Vth European Symposium on Carbohydrates, Prague, Czechoslovakia, August 21–25, 1989.

† Authors for correspondence.

0008-6215/90/$ 03.50

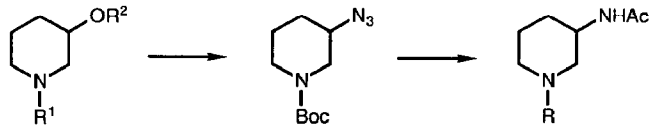


bonds is attractive or not. Therefore, this effect has been investigated using piperidyl and tetrahydropyranyl acetamides and acetates of the type **3**.

RESULTS AND DISCUSSION

The piperidyl acetamides were prepared from the commercially available 3-hydroxypiperidine (**4**). Protection of the amino function of **4**, mesylation, and substitution of the mesyloxy group by the azido group gave **9** which, on hydrogenation in the presence of acetic anhydride, led to the protected acetamide **10**. Deprotection of **10** with trifluoroacetic acid gave the secondary amine **11** (ref. 11) which was stable at room temperature, but decomposed at higher temperatures. Under the conditions of the Eschweiler–Clarke reaction, **10** was transformed into the crystalline *N*-methylamine **12** (ref. 12, 13). Similarly, the acetamide **17** was obtained from 3-hydroxytetrahydropyran[14] (**13**). Treatment of **17** with an excess of methyl iodide in the presence of sodium hydride led to the *N*-methylacetamide **18**. Acetylation of the alcohols **7** and **13** gave the acetates **8** (ref. 13) and **15** (ref. 15), respectively. In order to prepare the acetates **22** and **24**, commercially available **19** was treated with an excess of methylmagnesium bromide. The resulting enol ether **20** (ref. 16) was hydroboronated ($BH_3{\cdot}SMe_2$), yielding, after chromatography, the diols **21** and **23** in reasonable yields and in the ratio of ~2:3. These compounds were best acetylated with acetic anhydride and NEt_3 in the presence of small amounts of 4-dimethylaminopyridine. The relative configurations of **21–24** were deduced from the $^3J_{H,H}$ values (see below and Experimental) and from the chemical shifts of the resonance of C-3 (see Table V) which, in the case of the *cis*-substituted alcohols **23** and **24**, occurs at higher field (γ-effect). The coupling constants agree well with $^2C_5$ conformations of **21–24**.

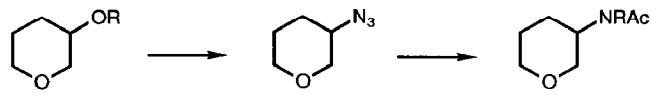
The low-temperature ^{1}H-n.m.r. method[17] requires neither an exact determination of coupling constants nor conformationally locked reference compounds and is suitable for the conformational analysis of cyclic acetamides and acetates. CD_2Cl_2 as an apolar, and CD_3OD as a polar, protic solvent were used for these measurements. Thus, the



4 $R^1 = R^2 = H$
5 $R^1 = Boc$, $R^2 = H$
6 $R^1 = Boc$, $R^2 = Ms$
7 $R^1 = CH_3$, $R^2 = H$
8 $R^1 = CH_3$, $R^2 = Ac$

9

10 R = Boc
11 R = H
12 $R = CH_3$



13 R = H
14 R = Ms
15 R = Ac

16

17 R = H
18 $R = CH_3$

A-value of the acetamido group and of the acetoxy group* were determined† at < 200 K (see Table I). The A-value of the acetamido group is similar to that of the amino group (1.44 kcal/mol) as determined by low-temperature ^{15}N-n.m.r. spectroscopy[19], and almost twice as large as that of the acetoxy group.

The conformations of the 3-hydroxypiperidines **4** and **7** at room temperature have been investigated by i.r.[20-21] and n.m.r.[22-24] spectroscopy. Various amounts (38–72%) of the axial conformers were found. These results depend strongly upon the experimental method and were rationalized by assuming the formation of intramolecular hydrogen bonds in the axial conformer. Considerable amounts of the axial conformers were detected by ^{1}H-n.m.r. spectroscopy of the acetates **8** (26%)[22] and **15** (43–60%)[15] and of 3-chlorotetrahydropyran (24%)[25]. Since only 10–15% of cyclohexyl acetate exists in the axial conformation (see Table I) and since **8** and **15** cannot form hydrogen bonds, the stronger preference for the axial conformation of the heterocyclic acetates must be due to the attractive *gauche* effect.

Monosubstituted acetamides prefer almost completely the (*E*) conformation [ΔE (E/Z) = 2.8 kcal/mol for *N*-methylacetamide[26]]. The barrier for the nitrogen inversion in piperidine (6.1 kcal/mol) is much lower than that for ring reversal (10.4 kcal/mol)[27]. The coalescence due to ring reversal is observed at 220–235 K and that due to nitrogen inversion at 160–170 K. Thus, the integration of the appropriate signals in the ^{1}H-n.m.r. spectra of the acetamides and acetates at 200–180 K allows the unequivocal determination of the equilibrium established by ring reversal. In the low-temperature ^{1}H-n.m.r. spectra of the acetates **8** and **15** and of the amides **11** and **12**, the signals of H-3 of the

* According to Hirsch[18], the A-value of the acetoxy group is 0.36–1.6 kcal/mol.
† The signals of all measured acetamides and acetates coalesce between 220 and 235 K. For the calculation of $\Delta G = -RT \ln K$, $T = 220$ K was used.

TABLE I

A-Values of the acetamido and the acetoxy group determined by low-temperature ^{1}H-n.m.r. spectroscopy (400 MHz, <200 K, 0.07M solutions)

Substituent	*Solvent*	K = *[ax]/[eq]*	*A-Value (kcal/mol)*
NHAc	CD_2Cl_2	0.026	1.6
	CD_3OD	0.017	1.8
OAc	CD_2Cl_2	0.11	0.95
	CD_3OD	0.15	0.85

axial and equatorial conformer are well separated (see Table II). As expected, the signal of H-3 of the axial conformer is sharper and found at lower field. In the spectra of **17**, the H-3 and H-6*e* signals of each conformer overlap, whereas the signals of H-2*a* are well separated. The signal of H-2*a* of the axial conformer occurs as a doublet at 3.53 p.p.m. and that of the equatorial conformer as a triplet at 2.83 p.p.m. Thus, the percentage of axial and equatorial conformers of the above-mentioned acetamides and acetates can be determined easily and reproducibly (see Table II). In the low-temperature ^{1}H-n.m.r. spectrum of **18**, only signals of the (*E*) and (*Z*) equatorial conformers are observed. Their ratio (9:11) is the same as at room temperature. This finding indicates that the (bulky) *N*-methylacetamido group (A-value unknown) may be useful for the preparation of anancomeric[28] compounds.

In CD_2Cl_2, the equilibrium constants K = [ax]/[eq] for the acetamides **11**, **12**, and **17** decrease with increasing concentration. The equilibrium constants of the acetates **8** and **15** shows no dependence upon concentration. The different behaviour is due to the concentration-dependent formation of intermolecular hydrogen bonds by the acetamides[29], which favours the equatorial conformers and is evidenced by the concentration dependence of the chemical shifts of the H–N signals of **12** and **17** (see Table III). This dependence is more pronounced for the equatorial conformers and indicates their higher tendency to participate in intermolecular hydrogen bonding. Also, in the i.r. spectrum of **17**, the intensity of the associated H–N band at 3320 cm^{-1} increases with increasing concentration (free H–N band at 3440 cm^{-1}). Whereas the conformational equilibrium constants for the acetates **8** and **15** increase slightly upon addition of CD_3OD, those of the acetamides **11**, **12**, and **17** decrease strongly. The increased population of the equatorial conformation for the acetamides is rationalized by the better solvation of the equatorial conformers.

The protonation of piperidines by weak acids (pH of the resulting solution > 0) is a reversible process[30]. Thus, the protonation of **8** and **12** with trifluoroacetic acid led to mixtures of diastereoisomers at equilibrium. The piperidinium salts of **8**, **11**, and **12** have a stronger preference for the axial conformation than the free bases. This situation agrees with the findings of Terui and Tori[23] who observed that 42% of **8**, but ~66% of its hydroiodide, exist in the axial conformation.

The values for the attractive *gauche* effect were obtained by subtraction of the

TABLE II

Attractive *gauche* effects of the acetates **8** and **15** and of the acetamides **11**, **12**, and **17** determined by low-temperature ^{1}H-n.m.r. spectroscopy (400 MHz, < 200 K)

Compound	*Solvent*	*Concentration (mol/L)*	*Chemical shifts of H-3 (δ)*		*Axial conformer (%)*	K = *[ax]/[eq]*	*ΔG° at 220 K (kcal/mol)*[a]	*Attractive* gauche *effect (kcal/mol) (ΔG° − A-value)*[a]
			ax. conformer	*eq. conformer*				
8	CD_2Cl_2	0.07	4.82	4.58	41	0.7	0.15	0.8
	5:2 CD_2Cl_2–CD_3OD	0.05	4.82	4.54	48	0.9	0.05	0.8
	5:2 CD_2Cl_2–CD_3OD–10μL CF_3COOH	0.05	5.03	4.77	85	5.65	−0.75	1.6
15	CD_2Cl_2	0.07	4.68	4.58	68[b]	2.15	−0.35	1.3
	5:2 CD_2Cl_2–CD_3OD	0.05	4.65	4.58	74[b]	2.85	−0.45	1.3
11	CD_2Cl_2	0.03	3.89	3.59	51	1.05	0	1.6
	CD_2Cl_2	0.09	3.88	3.59	42	0.7		
	CD_2Cl_2	0.20	3.88	3.56	40	0.65		
	CD_2Cl_2	0.30	3.88	3.56	31	0.45		
	5:1 CD_2Cl_2–CD_3OD	0.05	3.92	3.61	5	0.05	1.3	0.5
	5:1 CD_2Cl_2–CD_3OD–10 μL CF_3COOH	0.05	4.02	3.75	15	0.2	0.7	1.1
12	CD_2Cl_2	0.01	3.98	3.68	76	3.15		
	CD_2Cl_2	0.06	3.98	3.68	69	2.25	−0.35	1.95
	CD_2Cl_2	0.13	3.95	3.68	59	1.45		
	CD_2Cl_2	0.26	3.95	3.68	52	1.1		
	5:2 CD_2Cl_2–CD_3OD	0.07	3.82	3.65	7	0.1	1.2	0.7
	5:2 CD_2Cl_2–CD_3OD–10 μL CF_3COOH	0.07	4.03	3.84	35	0.55	0.25	1.55
17[c]	CD_2Cl_2	0.01	3.49	2.83	61	1.55		
	CD_2Cl_2	0.07	3.53	2.83	54	1.2	−0.1	1.7
	CD_2Cl_2	0.17	3.53	2.83	51	1.05		
	CD_2Cl_2	0.28	3.53	2.83	45	0.8		
	5:2 CD_2Cl_2–CD_3OD	0.05	3.47	3.00	24	0.3	0.55	1.35

[a] Determined only for 0.05–0.07M solutions. [b] The signals of H-2*a* were integrated (partial overlap of the signals of H-3). [c] The signals of H-2*a* were integrated and their *δ* values are listed in the Table (overlap of H-3 and H-6*e*).

TABLE III

Chemical shifts (δ scale) of the signal for H–N of **12** and **17** in CD_2Cl_2 At <200 K (400 MHz)

Compound		*Concentration (mol/L)*			
		0.015	*0.07*	*0.14*	*0.28*
12	axial conformer	6.92 (b)	7.14	7.13	7.05
	equatorial conformer	6.92 (b)	7.14	7.43	7.53
17	axial conformer	6.88	7.23	7.23	7.58
	equatorial conformer	6.34	7.12	7.23	7.77

A-values from the ΔG° values (see Table II). The concentration dependence of the position of the conformational equilibrium of the acetamides in CD_2Cl_2 makes it difficult to determine exactly the attractive *gauche* effect that involves the acetamido group. Thus, the decrease of the conformational equilibrium constants observed for the acetamides **11**, **12**, and **17**, on changing the solvent from CD_2Cl_2 to CD_2Cl_2–CD_3OD mixtures, is caused to a larger extent by stronger hydrogen bonds than by a weaker attractive *gauche* effect. Nevertheless, the following conclusions may be drawn. In apolar solvents, the attractive *gauche* effect is stronger for the acetamides than for the corresponding acetates, for which, moreover, it depends only weakly upon the solvent. The piperidinium salts show a larger effect than the piperidines.

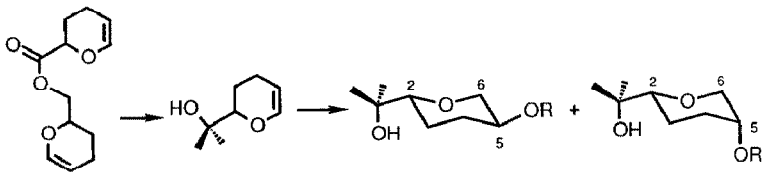
Low-temperature ^{1}H-n.m.r. spectroscopy has the disadvantage that only few solvents are suitable, whereas room-temperature n.m.r. spectroscopy is used widely for the determination of the conformational equilibria in a range of solvents. At room temperature, the coupling constants and signal widths are averaged values resulting from all conformers. Provided that only chair conformations are involved in the equilibria, the following equations* are valid:

$$W_{H\text{-}3} = xW_{H\text{-}3a} + (1 - x)W_{H\text{-}3e}$$
$$J_{2trans,3} = xJ_{aa} + (1 - x)J_{ee}$$
$$J_{2cis,3} = xJ_{ae} + (1 - x)J_{ea}.$$

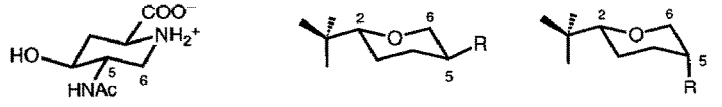
The limiting values W_a, W_e, J_{aa}, J_{ee}, J_{ae}, and J_{ee} were obtained from the conformationally locked hydroxyacetates **22** ($W_{H\text{-}3a}$ 31, J_{aa} 10.5, J_{ae} 5.0 Hz) and **24** ($W_{H\text{-}3e}$ 8.5, J_{ee} 2.1, J_{ea} 1.5 Hz). Similar values as for **22** and **24** are obtained from **25** (ref. 31) ($J_{5,6a}$ 11.8, $J_{5,6e}$ 4.7 Hz), **26** (ref. 25) ($W_{H\text{-}5}$ 31, $J_{5,6a}$ 10.8, $J_{5,6e}$ 4.7 Hz), **27** (ref. 15) ($W_{H\text{-}5}$ 31 Hz), **28** (ref. 25) ($J_{5,6e}$ 2.2, $J_{5,6a}$ 1.9 Hz), and **29** (ref. 15) ($W_{H\text{-}5}$ 8.8 Hz).

In the 400-MHz n.m.r. spectra of the acetates **8** and **15** and of the acetamides **11**, **12**, and **17**, the signals of H-2*trans*, H-2*cis*, and H-3 were well separated for most compounds (see Table IV). The $J_{2trans,3}$ and $J_{2cis,3}$ values were derived from the sharp signals of H-2*trans* and H-2*cis*, respectively, by first-order interpretation. This proce-

* *cis* and *trans* denote the relation of H-2x to H-3.



19 20 **21** R = H **22** R = Ac **23** R = H **24** R = Ac



25 **26** R = Cl **27** R = OAc **28** R = Cl **29** R = OAc

dure avoids the difficulties encountered[24] in the extraction of these coupling constants from the broadened signals of H-3. The best criteria for the determination of the equilibria of ring reversal are the width of the signal of H-3 and/or $J_{2trans,3}$; $J_{2cis,3}$ is not suitable for this purpose, as the difference between the limiting values J_{ae} and J_{ea} is only 3.5 Hz. The percentage of the axial conformers of the acetates and acetamides calculated from $J_{2trans,3}$ is mostly larger than that derived from the band width of the signal of H-3. A comparison of the results with those obtained by the low-temperature n.m.r. method confirms the dependence on concentration and solvent of the equilibrium constants of the acetamides, the weak solvent dependence of the acetates, and the stronger preference for the equatorial conformer of the piperidinium salts. In agreement with earlier findings[15], the conformational equilibrium constant of the acetate **15** shows only a weak dependence upon the solvent (K = 1.0–1.2), with the exception of water (K = 2.5)*. In contrast with this behaviour, the conformational equilibrium constant of the corresponding acetamide **17** depends strongly upon the solvent. The equilibrium constant does not correlate with the polarity of the solvent†, but with its capacity to solvate a polar substituent. Thus, acetone, acetonitrile, and methyl sulfoxide solvate the equatorial conformer better than the axial one and, hence, shift the equilibrium towards the equatorial conformer. Again, water is an exception, favouring the axial conformer to a higher degree than methanol. The azide **16** (K = 0.5) has a weaker preference for the axial conformation than the acetamide **17** (K = 2.0), presumably due to a weaker *gauche* effect.

The differences between the results derived from $J_{2trans,3}$ and the band width of the signal of H-3 may stem from the limiting values which are derived from more or less closely related model compounds. The results obtained at room temperature show a

* The n.m.r. spectrum of **15** in 2:1 CD_3OD–D_2O is characterized by broad, unresolved signals. This may be taken as evidence for an aggregation, causing its unexpected behaviour in water.

† The solvents are arranged in the Table according to increasing polarity[32].

TABLE IV

Conformational equilibria of the acetates **8** and **15** and of the acetamides **11**, **12**, and **17** determined by room-temperature ^{1}H-n.m.r. spectroscopy (400 MHz, 298 K, 0.07M solutions)

Compound	*Solvent*	*Chemical shifts (δ scale)*			*J Values (Hz)*		*Band width (Hz) of H-3 signal*	*Axial conformer (%)*		K = *[ax]/[eq]*[a]
		H-2 trans	*H-2* cis	*H-3*	$J_{2trans,3}$	$J_{2cis,3}$		*from* $J_{2trans,3}$	*from width H-3*	
8	CD_2Cl_2	2.05	2.63	4.79	[b]	3.15	23.4		34	0.5
	CD_3OD	2.22	2.67	4.83	[b]	[b]	22.1		48	0.9
	CD_3OD–10 μL CF_3COOH[c]	3.22	3.57	5.18	1.95	2.2	8.5	80[d]	–	4.0
15	C_6D_6	3.45	3.59	4.73	6.2	3.3	20.3	51	48	1.0
	$CDCl_3$	3.57	3.75	4.80	5.8	3.1	19.1	56	53	1.2
	Pyridine-d_5	3.56	3.77	4.83	6.1	3.2	20.2	52	48	1.0
	CD_2Cl_2	3.47	3.70	4.72	5.95	3.2	19.9	54	49	1.1
	$(CD_3)_2SO$	3.39	3.65	4.62	6.0	3.2	19.9	54	49	1.1
	CD_3OD	3.52	3.74	4.72	5.8	3.1	19.4	56	52	1.2
	1:2 CD_3OD–D_2O	3.64	3.70	4.74	4.3	2.6	15.5	74	69	2.5
	D_2O	3.72	3.72	4.79	[b]	[b]	14.2		74	2.8
11	$CDCl_3$	2.62	2.99	3.95	6.6	3.0	27.0[e]	46	53	1.0
	CD_2Cl_2	2.63	2.94	3.82	6.5	3.5	28.5[e]	48	47	0.9
	CD_3OD	2.52	3.16	3.82	9.9	4.0	28.6	7	11	0.1
	CD_3OD–10 μL CF_3COOH	2.81	3.39	3.98	10.5	3.9	28.4	14[f]	15[f]	0.2
12	CD_2Cl_2	2.20	2.35	3.93	[b]	[b]	27.2[e]		52	1.1
	CD_3OD	2.05	2.82	3.88	[b]	[b]	27.9		14	0.2
	CD_3OD–10 μL CF_3COOH[c]	2.66	3.57	3.99	11.7	2.1	32.1	81[d]	–	4.3
	[g]	3.12	3.64	4.09	3.0	[b]	7.0	19[d]	–	
17	C_6D_6	3.14	3.51	3.95	5.6	3.05	27.2[e]	58	52	1.2
	$CDCl_3$	3.48	3.73	4.00	4.4	2.7	25.5[e]	73	60	2.0
	$CDCl_3$(0.28M)	3.43	3.72	3.95	5.1	2.85	26.2[e]	64	57	1.5
	Acetone-d_6	3.12	3.74	3.78	7.7	3.85	23.3	33	34	0.5
	Pyridine-d_5	3.01	3.71	3.89	7.8	3.8	32.1[e]	32	31	0.5
	CD_2Cl_2	3.35	3.70	3.87	5.75	3.2	27.6[e]	57	51	1.2
	CD_2Cl_2(0.28M)	3.33	3.71	3.87	5.9	3.2	28.8[e]	55	49	1.1
	CD_3CN	3.26	~3.84	~3.84	8.1	[b]	[b]	28		0.4
	$(CD_3)_2SO$	3.03	~3.65	~3.65	8.1	[b]	[b]	28		0.4
	CD_3OD	3.21	~3.80	~3.80	9.1	[b]	[b]	17		0.2
	D_2O	3.35	~3.80	~3.80	7.65	[b]	[b]	34		0.5
16[h]	$CDCl_3$	3.37	3.85	3.60	7.6	3.0	[b]	35		0.5

[a] Averaged value obtained from $J_{2trans,3}$ and $W_{H\text{-}3}$. [b] Coupling constant or band width not determined due to signal overlap or poor resolution. [c] Data of major diastereoisomer. [d] Obtained by integration of the signals for NMe or OAc or NAc. [e] $J_{3,NH}$ is assumed to be 8 Hz. [f] Using J_{aa} 11.7, J_{ee} 3.0, and $W_{H\text{-}3}$ 32.1 Hz (from **12**). [g] Data for minor diastereoisomer. [h] At 200 MHz.

TABLE V

^{13}C-N.m.r.-data (50 MHz, $CDCl_3$)

Compound	*Chemical shifts (δ scale)*						
	C-2	*C-3*	*C-4*	*C-5*	*C-6*	*Ac*	*Other*
4	53.11	65.79	32.80	23.71	45.35	–	–
8	58.93	69.18	28.41	22.24	55.17	170.33, 21.14	N-Me: 46.06
5	50.58	66.07	32.49	28.37	43.92	–	Boc: 155.19 79.70, 28.37
6	48.0[a]	75.36	30.40	21.61	43.5[a]	–	Boc: 154.65, 80.14,28.29; Ms: 38.75
9	47.66	56.44	29.56	22.64	43.63	–	Boc: 154.58, 79.96, 28.32
10	48.40	45.26	29.63	22.37	43.92	169.50, 23.35	Boc: 155.13, 79.87, 28.33
11[b]	51.45	47.72	31.45	25.87	46.41	172.60, 22.68	–
12	59.77	44.89	28.28	22.93	55.33	169.27, 21.85	NMe: 46.22
15	69.30	67.77	27.85	22.67	67.52	170.08, 20.68	–
16	70.10	56.15	28.41	23.70	67.77	–	–
17	70.94	44.81	28.34	23.04	67.87	169.51, 23.04	–
20[c]	143.72	100.76	22.60[d]	20.31[d]	81.60	–	CMe_2OH: 71.71, 25.79, 24.18
21[c]	72.71	65.75	32.41	24.52	83.46	–	CMe_2OH: 71.76, 26.08, 24.09$_2$
22[c]	72.49	64.06	29.47	19.52	83.87	–	CMe_2OH: 71.70, 26.14, 24.24
23[c]	69.18	68.01	28.84	24.32	83.65	170.09, 20.86	CMe_2OH: 71.44, 25.88, 24.07
24[c]	69.77	67.10	27.15	21.15	83.73	170.60, 20.45	CMe_2OH: 71.63, 25.80, 24.00

[a] Broad signal. [b] In CD_3OD. [c] The same numbering as for **4** was used. [d] Attribution may be interchanged.

mean deviation of 5–10%. In contrast, the relative amounts of axial and equatorial conformers are determined in a highly reproducible way by the integration method in the low-temperature n.m.r. spectra (mean deviation < 2%). The differences between the results obtained at low and at room temperature may be caused by entropy effects. The spread of values obtained at room temperature and the broadening of signals below 270 K did not allow entropy effects to be determined in a meaningful manner.

EXPERIMENTAL

General methods. — Solvents were distilled before use. Solutions were concentrated at or below 45° in a Büchi rotary evaporator. Continuous extraction was carried out in a Kutscher–Steudel apparatus. If not stated otherwise, qualitative t.l.c. was performed on Silica Gel F_{254} (Merck) with detection by treatment with iodine or phosphomolybdic acid (10% in ethanol). Flash chromatography was carried out on silica gel (Merck 60, 40–63 μm). Melting points were determined with a Büchi 510 apparatus. ^{1}H-n.m.r. spectra were recorded with a Bruker AM-400 or Varian XL-200 spectrometer, and ^{13}C-n.m.r. spectra at 50 MHz with a Varian XL-200 spectrometer. The chemical shifts

are given in p.p.m. relative to that of Me_4Si, and the *J* values (first-order interpretation) in Hz. The attributions were ascertained by selective decoupling experiments and by spin-saturation-transfer experiments[33]. I.r. spectra were recorded on 3% solutions in chloroform with a Perkin–Elmer 298 spectrometer. Mass spectra (e.i., 70 eV; c.i., isobutane) were determined using a Varian 112S spectrometer.

1-tert-*Butoxycarbonyl-3-hydroxypiperidine* (**5**). — A solution of **4** (1.0 g, 9.9 mmol) and di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) in $CHCl_3$ (100 mL) was heated at 100° for 90 min. Concentration and bulb-to-bulb distillation (130°, 0.02 Torr) then gave **5** as an oil (1.872 g, 94%) which crystallized from hexane at −20°; m.p. 68-69°; R_F 0.33 (1:1 hexane–AcOEt); ν_{max} 3600 w, 3440 wb, 2980 m, 2940 m, 2860 m, 1670 s, 1465 m, 1420 s, 1390 m, 1365 s, 1345 w, 1165 s, 1145 s, 1060 m, 1020 w, 1000 w, 985 w, 970 m, 945 w, 920 w, 900 w, 880 m, and 860 w cm^{-1}. ^{1}H-n.m.r. data (200 MHz, $CDCl_3$): δ 3.85–3.65 (m, 2 H), 3.63–3.43 (m, 1 H, H-3), 3.25–2.95 (m, 2 H), 2.0–1.65 (m, 3 H, 1 H exchangeable with D_2O), 1.63–1.3 (m, 2 H), and 1.46 (s, 9 H, ^{t}Bu). C.i.-mass spectrum: *m/z* 202 (100, $M^+ + 1$), 146 (88), 102 (45), and 84 (16).

Anal. Calc. for $C_{10}H_{19}NO_3$ (201.26): C, 59.7; H, 9.5; N, 6.9; Found: C, 60.0; H, 9.4; N, 6.7.

1-tert-*Butoxycarbonylpiperid-3-yl methanesulfonate* (**6**). — A solution of **5** (2.5 g, 12 mmol) and NEt_3 (2.6 mL, 10 mmol) in CH_2Cl_2 (63 mL) at 0–5° was treated with methanesulfonyl chloride (1.16 mL, 14.5 mmol). After 30 min, the mixture was diluted with CH_2Cl_2, washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent left **6** as a viscous oil (3.433 g, 99%), R_F 0.47 (19:1 CH_2Cl_2–EtOH); ν_{max} 3000 w, 2980 m, 2950 m, 2865 w, 1685 s, 1465 m, 1420 m, 1390 m, 1365 s, 1340 s, 1265 m, 1165 s, 1095 w, 1065 w, 1010 w, 1000 w, 970 s, 960 s, 945 s, 930 w sh, 900 s, 860 m, and 830 w cm^{-1}. ^{1}H-n.m.r. data (200 MHz, $CDCl_3$): δ 4.76–4.66 (m, 1 H, H-3), 3.70–3.55 (m, 2 H), 3.50–3.30 (m, 2 H), 3.05 (s, 3 H, OMs), 2.0–1.5 (m, 4 H), and 1.46 (s, ^{t}Bu). C.i.-mass spectrum: *m/z* 280 (16, $M^+ + 1$), 224 (79), 128 (100), and 84 (11).

Anal. Calc. for $C_{11}H_{21}NO_5S$ (279.36): C, 47.3; H 7.6; N, 5.0; S, 11.5. Found: C, 47.2; H, 7.7; N, 5.1; S, 11.3.

3-Azido-1-tert-*butoxycarbonylpiperidine* (**9**). — A solution of **6** (3.4 g, 12.2 mmol) and sodium azide (2.04 g, 31.1 mmol) in *N,N*-dimethylformamide (35 mL) was heated at 100° for 90 min, then diluted with Et_2O, washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and bulb-to-bulb distillation (80°, 0.02 Torr) then afforded **9** as a colourless oil (2.589 g, 92%), R_F 0.40 (19:1 CH_2Cl_2–EtOH); ν_{max} 2980 m, 2950 m, 2870 m, 2100 s, 1685 s, 1465 s, 1420 s, 1390 m, 1365 s, 1345 m, 1310 m, 1160 m sh, 1150 s, 1095 w, 1075 w, 1030 w, 1000 m, 940 w, 900 w, 875 m, and 860 m cm^{-1}. ^{1}H-n.m.r. data (200 MHz, $CDCl_3$): δ 3.95–3.72 (m, 1 H), 3.7–3.4 (m, 2 H), 3.25–3.0 (m, 2 H), 2.07–1.92 (m, 1 H), 1.86–1.68 (m, 1 H), 1.68–1.45 (m, 2 H), and 1.47 (s, 9 H, ^{t}Bu). C.i.-mass spectrum: *m/z* 227 (89, $M^+ + 1$), 184 (24), 171 (100), 128 (19), 127 (25), 84 (41).

Anal. Calc. for $C_{10}H_{18}N_4O_2$ (226.28): C, 53.1; H, 8.0; N, 24.8. Found: C, 53.2; H, 8.1; N, 24.5.

N-(1-tert-*Butoxycarbonyl-3-piperidyl)acetamide* (**10**). — A mixture of **9** (2.589 g, 11.4 mmol) and Pd–C (5%, 250 mg) in 4:1 AcOEt–Ac_2O (25 mL) was hydrogenated for

14 h. The catalyst was removed, the filtrate was stirred with 2M $NaHCO_3$ for 2 h and extracted with Et_2O, and the extract was washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and bulb-to-bulb distillation (150°, 0.01 Torr) then afforded **10** as a colourless oil (2.645 g, 95%), R_F 0.25 (AcOEt); ν_{max} 3440 w, 3360 wb, 3000 m, 2980 m, 2940 m, 2860 m, 1675 s, 1505 m, 1475 m, 1465 m, 1420 s, 1395 m, 1365 s, 1310 w, 1270 s, 1170 m, 1150 s, 1040 w, 1025 w, 1005 w, 970 w, 905 w, 875 w, and 860 w cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 5.7 (bm, 1 H, H-N), 4.1–3.85 (m, 1 H, H-3), 3.63–3.45 (m, 1 H), 3.4–3.2 (m, 3 H), 1.98 (s, 3 H, NAc), 1.95–1.4 (m, 4 H), and 1.47 (s, 9 H, ^{t}Bu). C.i.-mass spectrum: *m/z* 243 (61, $M^+ + 1$), 187 (100), and 143 (79).

Anal. Calc. for $C_{12}H_{22}N_2O_3$ (242.33): C, 59.5; H, 9.2; N, 11.6. Found: C, 59.2; H, 9.4; N, 11.3.

N-*(3-Piperidyl)acetamide*[11] (**11**). — A solution of **10** (340 mg, 1.4 mmol) in trifluoroacetic acid (3 mL) was stirred for 40 min at room temperature, then concentrated at room temperature. Column chromatography of the residue on alumina B III (Woelm, 12 g, 19:1 CH_2Cl_2–MeOH) gave **11**, isolated as a colourless oil (144 mg, 72%), R_F 0.7; ν_{max} 3440 m, 3340 mb, 2990 m, 2950 s, 2860 m, 2830 m, 2740 w, 1660 s, 1510 s, 1440 m, 1370 m, 1340 w, 1310 m, 1115 m, 1015 m, 980 w, 930 w, 890 w, and 860 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 6.2–5.9 (bs, 1 H, H-NAc), 3.9–3.77 (m, 1 H, H-3), 2.95 (dd, 1 H, $J_{2a,2e}$ 12.5, $J_{2e,3}$ 3.6 Hz, H-2*e*), 2.82–2.65 (m, 2 H, 2 H-6), 2.53 (dd, 1 H, $J_{2a,2e}$ 12.5, $J_{2a,3}$ 7.0 Hz, H-2*a*), 2.1–1.8 (m, 1 H, H-N), 1.94 (s, 3 H, NAc), 1.77–1.58 (m, 2 H), and 1.58–1.4 (m, 2 H).

N-*(1-Methyl-3-piperidyl)acetamide*[12,13] (**12**). — A solution of **10** (430 mg, 1.77 mmol) in 2:3 formic acid–36% formalin (1.5 mL) was stirred for 8 h at 100°, then diluted with 0.5M NaOH and continuously extracted with AcOEt overnight. Removal of the solvent and chromatography (99:1 CH_2Cl_2–MeOH) of the residue on alumina B III (25 g) afforded **12** (95 mg, 34%) which crystallized from Et_2O–hexane. For analysis, a sample was sublimed at 75° and 0.5 Torr and had m.p. 81° (lit.[12] m.p. 85–86°; lit.[13] m.p. 75–77°); R_F 0.7 (19:1 CH_2Cl_2–MeOH); ν_{max} 3430 w, 3000 s, 2940 s, 2860 m, 2800 m, 2740 w, 1660 s, 1500 s, 1465 m, 1445 m, 1375 m, 1310 w, 1290 m, 1265 m, 1165 m, 1140 m, 1100 m, 1035 m, 1025 m, 1010 m, 970 w, 900 w, 870 w, and 850 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 6.25–5.95 (bs, 1 H, H-N), 3.97–3.87 (m, 1 H, H-3), 2.45–2.0 (m, 4 H), 2.14 (s, 3 H, NMe), 1.88 (s, 3 H, NAc), 1.75–1.58 (m, 1 H), and 1.58–1.35 (m, 3 H). C.i.-mass spectrum: *m/z* 157 (100, $M^+ + 1$), 98 (10), and 97 (14).

3-Acetoxy-1-methylpiperidine[13] (**8**). — A solution of **7** (120 mg, 1.04 mmol), NEt_3 (100 μL, 1.38 mmol), 4-dimethylaminopyridine (1 mg), and Ac_2O (132 μL, 1.4 mmol) in CH_2Cl_2 (5 mL) was stirred for 20 min at room temperature, then diluted with AcOEt, washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Bulb-to-bulb distillation then afforded **8** as a colourless oil (145 mg, 88%), R_F 0.75 (alumina, CH_2Cl_2); ν_{max} 2950 s, 2830 m, 2795 s, 1725 s, 1465 m, 1445 m, 1375 m, 1365 m, 1310 w, 1170 w, 1150 m, 1135 m, 1125 w, 1100 m, 1085 m, 1065 m, 1040 s, 1020 m, 1010 m, 1000 w, 980 w, 965 m, 920 w, 870 w, and 860 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 4.78 (tt, 1 H, J 8.0 and 3.9 Hz, H-3), 2.63 (dd, 1 H, $J_{2a,2e}$ 11.0, $J_{2e,3}$ 3.2 Hz, H-2*e*), 2.48–2.38 (m, 1 H, H-6*e*), 2.22 (s, 3 H, NMe), 2.2–2.1 (m, 2 H), 2.00 (s, 3 H, OAc), 1.82–1.68 (m, 2 H), 1.62–1.5 (m, 1 H), and

1.44–1.33 (m, 1 H). C.i.-mass spectrum: *m/z* 158 (82, $M^+ + 1$), 98 (78), 97 (100), 67 (87), and 65 (85).

Tetrahydropyran-3-yl methanesulfonate (**14**). — A solution of **13** (ref. 14) (3.96 g, 38.8 mmol) and NEt_3 (8.1 mL, 58.6 mmol) in CH_2Cl_2 (30 mL) at 0–5° was treated with a solution of methanesulfonyl chloride (3.35 mL, 43.1 mmol) in CH_2Cl_2 (10 mL). After 30 min, the mixture was diluted with CH_2Cl_2, washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Treatment with decolourizing charcoal and removal of the solvent left **14** as a viscous oil (6.64 g, 95%), R_F 0.49 (AcOEt); ν_{max} 3020 w, 2960 m, 2860 m, 1465 w, 1440 w, 1415 w, 1360 s, 1335 s, 1170 s, 1125 w, 1105 s, 1095 s, 1065 m, 1035 w, 1015 w, 1005 m, 975 s, 955 s, 925 s, 875 s, and 840 m cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 4.77–4.67 (m, 1 H, H-3), 3.86 (ddd, 1 H, $J_{2a,2e}$ 12.0, $J_{2e,3}$ 3.3, $J_{2e,4e}$ 1.1 Hz, H-2*e*), 3.75–3.60 (m, 3 H), 3.07 (s, 3 H, OMs), 2.2–1.8 (m, 3 H), and 1.8–1.5 (m, 1 H).

3-Azidotetrahydropyran (**16**). — A solution of **14** (6.01 g, 33.3 mmol) and sodium azide (6.5 g, 0.1 mol) in *N,N*-dimethylformamide (45 mL) was heated for 4 h at 100° then diluted with Et_2O, washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and bulb-to-bulb distillation (74°, 15 Torr) then afforded **16** as a colourless oil (2.746 g, 65%), R_F 0.70 (AcOEt); ν_{max} 3000 w, 2940 m, 2850 m, 2100 s, 1465 w, 1435 w, 1310 w, 1090 m, 1065 w, 1030 w, 1010 w, 970 w, 935 w, 910 w, 875 m, and 860 w cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 3.85 (ddd, 1 H, $J_{2a,2e}$ 11.0, $J_{2e,3}$ 3.3, $J_{2e,4e}$ 1.6 Hz, H-2*e*), 3.73 (dt, 1 H, $J_{6a,6e}$ 11.5, $J_{6e,5a} = J_{6e,5e} = 3.7$ Hz, H-6*e*), 3.60–3.38 (m, 2 H, H-3,6*a*), 3.37 (dd, 1 H, $J_{2a,2e}$ 11.0, $J_{2a,3}$ 7.6 Hz, H-2*a*), 2.15–1.95 (m, 1 H), and 1.92–1.5 (m, 3 H).

N-*(Tetrahydropyran-3-yl)acetamide* (**17**). — A mixture of **16** (2.53 g, 19.9 mmol) and Pd–C (5%, 200 mg) in 5:1 AcOEt–Ac_2O (48 mL) was hydrogenated for 14 h. The catalyst was removed, the filtrate was stirred with 2M $NaHCO_3$ for 2 h and then extracted with Et_2O, and the extract was washed with 2M $NaHCO_3$ and brine, and dried ($MgSO_4$). The aqueous layer was extracted continuously with AcOEt overnight. Removal of the solvent from the combined organic layers and crystallization of the residue from CH_2Cl_2–hexane afforded **17** (1.65 g, 58%), m.p. 83°, R_F 0.2 (19:1 CH_2Cl_2–MeOH); ν_{max} 3440 m, 3330 wb, 2950 m, 2930 m, 2910 w, 2880 m, 2750 w, 1665 s, 1510 s, 1465 m, 1445 m, 1440 m, 1370 m, 1335 w, 1310 m, 1300 w, 1270 m, 1160 w, 1105 m, 1095 m, 1065 m, 1035 w, 1015 w, 975 w, 920 w, 900 w, 875 w, 860 w, and 855 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 6.0–5.75 (bs, 1 H, H–NAc), 3.91–3.82 (m, 1 H, H-3), 3.70 (ddd, 1 H, $J_{2a,2e}$ 11.2, $J_{2e,3}$ 3.2, $J_{2e,4e}$ 0.7 Hz, H-2*e*), 3.67–3.52 (m, 2 H, 2 H-6), 3.35 (dd, 1 H, $J_{2a,2e}$ 11.2, $J_{2a,3}$ 5.75 Hz, H-2*a*), 1.92 (s, 3 H, NAc), 1.90–1.77 (m, 1 H), 1.77–1.67 (m, 1 H), and 1.67–1.50 (m, 2 H). C.i.-mass spectrum: *m/z* 144 ($M^+ + 1$).

Anal. Calc. for $C_7H_{13}NO_2$ (143.18): C, 58.7; H, 9.2; N, 9.8. Found: C, 58.8; H, 9.0; N, 10.0.

N-*Methyl*-N-*(tetrahydropyran-3-yl)acetamide* (**18**). — A mixture of **17** (864 mg, 6.04 mmol), methyl iodide (1 mL, 16 mmol), and NaH (230 mg, 9.4 mmol) in *N,N*-dimethylformamide (5 mL) was stirred for 2 h at room temperature. After the addition of methanol (2 mL), the mixture was diluted with 2M $NaHCO_3$ and continuously extracted with AcOEt overnight. Concentration and removal of the solvent (1 h, 40°, 0.5 Torr) left an oily residue (1.2 g) which, on bulb-to-bulb distillation (120° and 0.5 Torr),

afforded a 10:1 mixture of **18** and **17** (631 mg). Flash chromatography (49:1 CH_2Cl_2–MeOH) on SiO_2 (20 g) yielded **18** as a viscous oil (600 mg, 64%), R_F 0.26 (19:1 CH_2Cl_2–MeOH); ν_{max} 3000 m, 2970 m, 2950 m, 2860 m, 1630 s, 1475 s, 1455 m, 1440 m, 1405 m, 1385 w, 1370 w, 1360 w, 1315 m, 1180 w, 1090 s, 1065 w, 1035 w, 1015 m, 965 w, 915 m, 870 w, and 860 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 4.45–4.38 (m, 0.55 H, H-3), 3.85–3.65 (m, 2.45 H), 3.37 (t, 0.45 H, *J* 10.6 Hz) and 3.28 (t, 0.55 H, *J* 10.6 Hz, H-2a), 3.30–3.20 (m, 1 H), 2.83 (s, 1.65 H) and 2.75 (s, 1.35 H, NMe), 2.07 (s, 1.35 H) and 2.01 (s, 1.65 H, NAc), and 1.87–1.65 (m, 4 H). C.i.-mass spectrum: *m/z* 158 (60, $M^+ + 1$), 57 (100), and 43 (17).

*2-(1-Hydroxy-1-methylethyl)-3,4-dihydro-2*H*-pyran*[16] (**20**) — To a cooled solution (< 5°) of methylmagnesium iodide (147 mmol, prepared from 3.58 g of Mg and 20.9 g of methyl iodide) in Et_2O (70 mL) was added a solution of **19** (Fluka, 15 g, 66.9 mmol) in Et_2O (15 mL) dropwise during 30 min. The mixture was allowed to attain room temperature, stirred for 15 min, and treated with 0.5M $NaHCO_3$ (300 mL). The precipitate was collected and washed with Et_2O and water, and the combined filtrate and washings were diluted with Et_2O, washed with brine, and dried ($MgSO_4$). Et_2O was distilled off through a Vigreux column. The residue (15.1 g) was chromatographed (8:1 hexane–AcOEt) on SiO_2 (400 g) to afford **20** (5.74 g, 60%, after bulb-to-bulb distillation at 140°/90 Torr), R_F 0.31 (4:1 hexane–AcOEt); ν_{max} 3585 w, 3060 w, 2980 m, 2935 m, 2875 w, 2850 w, 1650 m, 1465 w, 1450 w, 1435 w, 1390 m, 1375 m, 1350 w, 1325 m, 1295 w, 1155 m, 1125 w, 1085 m, 1065 s, 1045 m, 1020 w, 1000 w, 970 m, 945 m, 905 m, and 885 w cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 6.41 (bd, 1 H, $J_{5,6}$ 5.5 Hz, H-6), 4.74–4.65 (m, 1 H, H-5), 3.57 (dd, 1 H, *J* 11.8 and 1.8 Hz, H-2), 2.25 (s, 1 H, HO, exchangeable with D_2O), 2.2–1.8 (m, 2 H), 1.75–1.4 (m, 2 H), 1.23 (s, 3 H, CH_3), and 1.19 (s, 3 H, CH_3). Eluted second was 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (5.929 g, 78%), R_F 0.17.

trans- (**21**) *and* cis-*5-hydroxy-2-(1-hydroxy-1-methylethyl)tetrahydropyran* (**23**). — To a cooled solution (< 5°) of borane–methyl sulfide complex (Fluka, 1.65 g, 21.7 mmol) in tetrahydrofuran (10 mL) was added dropwise during 10 min a solution of **20** (3.72 g, 26.2 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 45 min at < 5° and then for 75 min at room temperature. The gas evolution increased at higher temperature. 2M NaOH (60 mL) and aqueous 30% H_2O_2 (20 mL) were added portionwise during 10 min. The mixture (< 5°) was allowed to attain room temperature and stirring was continued for 4 h. After dilution with M $NaHCO_3$, continuous extraction with AcOEt overnight, and concentration of the extract, the residue (7 g) was dissolved in CH_2Cl_2 (5 mL) and treated with 1:1 Et_2O-hexane (25 mL). The precipitate (dimethyl sulfone) was removed, the filtrate was concentrated, and flash chromatography (1:1 hexane–AcOEt) of the residue on SiO_2 (50 g) gave a complex mixture (330 mg) of products, **21** (865 mg, 21%), a 1:1 mixture (114 mg, 3%) of **21** and **23**, and **23** (1.48 g, 35%). After crystallisation from Et_2O–hexane at −20°, **21** had m.p. 64°, R_F 0.21 (AcOEt): ν_{max} 3610 m, 3580 m, 3450 wb, 3000 s, 2980 s, 2960 s, 2860 s, 1465 m, 1455 w, 1440 m, 1390 m, 1375 m, 1365 m, 1330 m, 1315 m, 1160 s, 1150 s, 1095 s, 1065 s, 1045 s, 1005 m, 995 m, 985 w, 965 m, 955 s, 920 m, 900 m, and 865 m cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 4.05 (ddd, 1 H, *J* 10.5, 4.9 and 2.3 Hz, H-6*e*), 3.8–3.6 (m, 1 H, H-5),

3.2–2.95 (m, 2 H, H-2,6*a*), 2.6–2.4 (bs, 1 H, HO, exchangeable with D_2O), 1.85–1.3 (m, 5 H, 1 H exchangeable with D_2O), 1.19 (s, 3 H, CH_3), and 1.15 (s, 3 H, CH_3). C.i.-mass spectrum: *m/z* 143 ($M^+ - OH$).

Compound **23** had R_F 0.12 (AcOEt); ν_{max} 3590 m, 3450 mb, 2980 s, 2960 s sh, 2890 m, 2860 m, 1445 m, 1380 s, 1330 m, 1160 s, 1100 s, 1060 s, 1035 m, 1025 m, 1000 m, 975 s, 960 s, 950 m, 905 s, 865 m, and 820 w cm^{-1}. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 3.98 (bd, 1 H, *J* 12.0 Hz, H-6*e*), 3.76 (bs, 1 H, H-5), 3.61 (bd, 1 H, *J* 12.0 Hz, H-6*a*), 3.14 (dd, 1 H, *J* 11.0 and 2.2 Hz, H-2), 2.8–2.1 (bs, 2 H, 2 HO, exchangeable with D_2O), 2.05–1.5 (m, 4 H), 1.21 (s, 3 H, CH_3), and 1.18 (s, 3 H, CH_3). C.i.-mass spectrum: *m/z* 143 ($M^+ - OH$).

trans-*5-Acetoxy-2-(1-hydroxy-1-methylethyl)tetrahydropyran* (**22**). — A mixture of **21** (250 mg, 1.56 mmol), NEt_3 (390 μL, 2.8 mmol), Ac_2O (190 μL, 2.03 mmol), and 4-dimethylaminopyridine (2 mg) in CH_2Cl_2 (5 mL) was stirred for 2 h at room temperature, then diluted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated. The residue was eluted (4:1 hexane–AcOEt) from SiO_2 (2 g), and the eluate was concentrated and dried (30 min at 12 Torr and 5 min at 0.5 Torr) to afford **22** as a colourless oil (303 mg, 96%), R_F 0.54 (AcOEt); ν_{max} 3570 w, 3005 m, 2980 m, 2960 m, 2865 s, 1730 s, 1470 w, 1440 w, 1390 m, 1370 s, 1330 m, 1170 m, 1150 m, 1100 s, 1045 s, 960 m, 920 m, 890 w, and 865 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 4.78–4.70 (m, 1 H, width 31 Hz, H-5), 4.08 (ddd, 1 H, $J_{6a,6e}$ 10.5, $J_{5,6e}$ 5.0, $J_{4e,6e}$ 2.3 Hz, H-6*e*), 3.21 (t, 1 H, $J_{6a,6e} = J_{5,6a} = 10.5$ Hz, H-6*a*), 3.10 (dd, 1 H, $J_{2,3a}$ 10.9, $J_{2,3e}$ 2.1 Hz, H-2), 2.40 (s, 1 H, HO, exchangeable with D_2O), 2.22–2.16 (m, 1 H), 2.04 (s, 3 H, OAc), 1.78–1.73 (m, 1 H), 1.58–1.44 (m, 2 H), 1.18 (s, 3 H, CH_3), and 1.15 (s, 3 H, CH_3). C.i.-mass spectrum: *m/z* 185 (100, $M^+ - OH$), 143 (15, $M^+ - OAc$).

cis-*5-Acetoxy-2-(1-hydroxy-1-methylethyl)tetrahydropyran* (**24**). — As described for **22**, **24** (99%) was obtained from **23**; R_F 0.39 (AcOEt); ν_{max} 3570 w, 3010 m, 2980 m, 2940 m, 2860 w, 1730 s, 1440 w, 1380 s, 1345 w, 1330 m, 1300 w, 1165 s, 1140 m, 1120 s, 1095 m, 1070 m, 1055 m, 1025 s, 1000 w, 965 m, 910 m, 870 w, and 845 w cm^{-1}. ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 4.80–4.78 (m, 1 H, width 7.6 Hz, H-5), 4.08 (dt, 1 H, $J_{6a,6e}$ 12.8, $J_{5,6e} = J_{4e,6e} = 2.1$ Hz, H-6*e*), 3.61 (dd, 1 H, $J_{6a,6e}$ 12.8, $J_{5,6a}$ 1.5 Hz, H-6*a*), 3.14 (dd, 1 H, $J_{2,3a}$ 11.1, $J_{2,3e}$ 2.1 Hz, H-2), 2.47 (s, 1 H, HO, exchangeable with D_2O), 2.10 (s, 3 H, OAc), 2.07–2.01 (m, 1 H), 1.79–1.60 (m, 2 H), 1.52–1.48 (m, 1 H), 1.20 (s, 3 H, CH_3), and 1.17 (s, 3 H, CH_3). C.i.-mass spectrum: *m/z* 185 ($M^+ - OH$).

ACKNOWLEDGMENTS

We thank the Swiss National Science Foundation, F. Hoffmann-La Roche, AG, Basel, and Sandoz AG, Basel, for generous support.

REFERENCES

1 K. Clinch, A. Vasella, and R. Schauer, *Tetrahedron Lett.*, 28 (1987) 6425–6429.
2 B. P. Bashial, H.-F. Chow, L. E. Fellows, and G. W. J. Fleet, *Tetrahedron*, 43 (1987) 415–422.
3 D. E. Caddy and J. P. Utley, *J. Chem. Soc., Perkin Trans.* 2, (1973) 1258–1262.
4 A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer–Verlag, Berlin, 1983, pp. 32–36 and 75–77.

5 E. Juaristi, *J. Chem. Educ.*, 56 (1979) 438–441.
6 E. L. Eliel and E. Juaristi, *J. Am. Chem. Soc.*, 100 (1978) 6114–6119.
7 N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, 34 (1978) 2953–2959.
8 N. S. Zefirov, *Tetrahedron*, 33 (1977) 3193–3202.
9 S. Wolfe, *Acc. Chem. Res.*, 5 (1972) 102–111.
10 M. Tichy, S. Vasickova, S. V. Arakelian, and J. Sicher, *Collect. Czech. Chem. Commun.*, 35 (1970) 1522–1535.
11 A. M. Crider, R. Lamey, H. G. Floss, and J. M. Cassady, *J. Med. Chem.*, 23 (1980) 848–851.
12 I. W. Mathison, J. G. Beasley, K. C. Fowler, and E. R. Peters, *J. Med. Chem.*, 12 (1969) 928–931.
13 J. G. Cannon and L. D. Milne, *J. Heterocycl. Chem.*, 13 (1976) 685–689.
14 H. C. Brown, J. V. N. V. Prasad, and S.-H. Zee, *J. Org. Chem.*, 50 (1985) 1582–1589.
15 C. B. Anderson, D. T. Sepp, M. P. Geis, and A. A. Roberts, *Chem. Ind. (London)*, (1968) 1805–1806.
16 J. Colonge, J. Buendia, and H. Guignard, *Bull. Soc. Chim. Fr.*, (1969), 956–962.
17 H. Günther, *NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart, 1983, pp. 241–245.
18 J. A. Hirsch, *Top. Stereochem.*, 1 (1967) 214.
19 G. W. Buchanan and V. L. Webb, *Tetrahedron Lett.*, 24 (1983) 4519–4520.
20 S. Vasickova, A. Vitek, and M. Tichy, *Collect. Czech, Chem. Commun.*, 38 (1973) 1791–1803.
21 H. S. Aaron and C. P. Ferguson, *J. Am. Chem. Soc.*, 98 (1976) 7013–7017.
22 R. E. Lyle, D. H. McMahon, W. E. Krueger, and C. K. Spicer, *J. Org. Chem.*, 31 (1966) 4164–4167.
23 Y. Terui and K. Tori, *J. Chem. Soc., Perkin Trans. 2*, (1975) 127–133.
24 J. J. van Luppen, J. A. Lepoivre, R. A. Dommisse, and F. C. Alderweireldt, *Org. Magn. Reson.*, 18 (1982) 199–206.
25 C. B. Anderson and M. P. Geis, *Tetrahedron*, 31 (1975) 1149–1154.
26 G. Csismadia, M. R. Peterson, C. Kozmutza, and M. A. Robb, in S. Patai (Ed.), *The Chemistry of Acid Derivatives, Supplement B*, Wiley, New York, 1979, p. 31.
27 F. A. L. Anet and I. Yavari, *J. Am. Chem. Soc.*, 99 (1977) 2794–2796.
28 M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chem. Belg.*, 75 (1966) 396–412.
29 D. Hadzi and S. Detoni, in S. Patai (Ed.), *The Chemistry of Acid Derivatives, Supplement B*, Wiley, New York, 1979, p. 243.
30 J.-J. Delpuech and M.-N. Deschamps, *Nouv. J. Chim.*, 2 (1978) 563–568.
31 B. I. Glänzer and A. Vasella, unpublished results.
32 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH Verlagsgesellschaft mbH, Weinheim, 1988, p. 352.
33 S. Forsen and R. A. Hoffman, *J. Chem. Phys.*, 39 (1963) 2892–2901.